ORGANIC LETTERS

2009
Vol. 11, No. 15
3294−3297

Pyridine *N*-Oxides as Ligands in Cu-Catalyzed *N*-Arylation of Imidazoles in Water

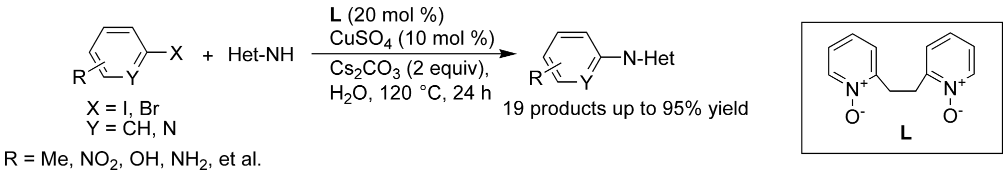
Lei Liang,[†] Zhengkai Li,[†] and Xiangge Zhou*,[†,‡]

Institute of Homogeneous Catalysis, College of Chemistry, Sichuan University, Chengdu 610064, China, and State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China

zhouxiangge@scu.edu.cn

Received May 18, 2009

ABSTRACT



***N*-Arylation of imidazoles with aryl halides catalyzed by a combination of copper(II) sulfate and 1,2-bis(2-pyridyl)-ethane-*N*,*N′*-dioxide in water afforded up to 95% yield.**

N-Arylimidazoles play an important role in a wide range of pharmaceuticals, natural products, and biologically active compounds[1] and have been exploited as precursors of versatile *N*-heterocyclic carbenes,[2] efficient ligands for transition-metal catalysis[3] or ionic liquids.[4] Traditionally, these moieties are prepared by nucleophilic aromatic substitution of imidazoles by activated aryl halides or the classical Ullmann-type coupling reactions.[5] In both cases, the reactions suffered from several drawbacks such as harsh reaction conditions (Ullmann reaction requires high temperature, extended reaction time), stoichiometric amounts of copper reagents, and low tolerance of functional groups, which limited their applications. A breakthrough has been made by Buchwald and co-workers who discovered that the Cu-catalyzed *N*-arylation of nitrogen-containing heterocycles with aryl halides could be achieved in good yields under mild conditions in the presence of bidentate *N*,*N*-ligands.[6] Following these pioneering works, a number of Cu-catalyzed

---

[†] Sichuan University.

[‡] Nanjing University.

(1) For recent reviews, see: (a) Wiglenda, T.; Ott, I.; Kircher, B.; Schumacher, P.; Schuster, D.; Langer, T.; Gust, R. *J. Med. Chem.* **2005**, *48*, 2126. (b) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196. (c) De Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1. (d) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Wiglenda, T.; Gust, R. *J. Med. Chem.* **2007**, *50*, 1475. (f) Kison, C.; Opatz, T. *Chem.—Eur. J.* **2009**, *15*, 843.

(2) (a) Vargas, V. C.; Rubio, R. J.; Hollis, T. K.; Salcido, M. E. *Org. Lett.* **2003**, *5*, 4847. (b) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(3) (a) Beller, M.; Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A. *Adv. Synth. Catal.* **2004**, *346*, 1742. (b) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2983. (c) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918.

(4) (a) Baltus, R. E.; Culbertson, B. H.; Dai, S.; Luo, H.; DePaoli, D. W. *J. Phys. Chem. B* **2004**, *108*, 721. (b) Suárez-Pantiga, S.; Rubio, E.; Alvarez-Rúa, C.; González, J. *Org. Lett.* **2009**, *11*, 13.

(5) For reviews of copper-catalyzed cross-coupling reactions, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(6) See the important references: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (c) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (d) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779. (e) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190. (f) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78.

10.1021/ol9010773 CCC: $40.75

coupling reactions with various ligands have been reported.[7] Nevertheless, room for exploration of an efficient ligand-assisted catalytic system, especially in the aqueous phase, still remains.[8]

On the other hand, amine as well as its *N*-oxide derivatives have long been recognized as ligands in coordination chemistry (Figure 1),[9] and pyridine *N*-oxides, well-known for their superior solubilities in water, can be viewed as neutral structural analogues of the widely popular anionic phenolate systems.[10] However, application of *N*-oxides in metal-mediated cross-coupling reactions has not yet been reported.

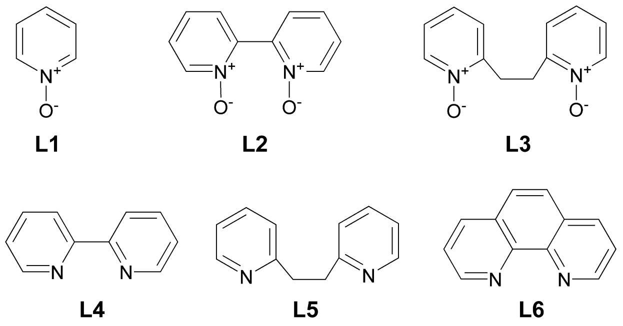


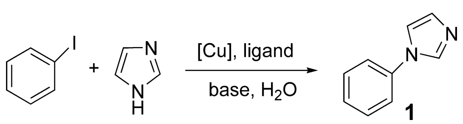
Figure 1. Amine and *N*-oxide ligands employed in this work.

In general, many achievements of synthesis in organic solvents inherently have the problem of pollution. Considering the requirement of green chemistry, the development of a more environmentally benign reaction would be desirable.[11] Thus, synthesis of organic molecules in water is an extensively investigated topic which entails the additional challenges of water tolerance for the catalyst[12] and the associated problem of substrate solubilities and reactivities. In this aspect, the development of less expensive and more sustainable catalysts in water remains an elusive goal in modern synthetic chemistry.

In continuation of our endeavors to develop environmentally friendly protocols, herein we disclose *N*-arylation of imidazoles with aryl halides catalyzed by readily available $CuSO_4$ with pyridine *N*-oxide ligands in water.

Iodobenzene and imidazole were initially chosen as models for the coupling reaction in water. The standardized protocol was carried out by using imidazole (1.1 equiv), iodobenzene (1 equiv), base (2 equiv), Cu source (10 mol %), and ligand (20 mol %) in water at 120 °C for 24 h. The results are shown in Table 1.

Table 1. Screening Reaction Conditions for *N*-Arylation of Imidazole with Iodobenzene[a]



entry	Cu source	ligand	base	yield[b] (%)
1	$CuSO_4{\cdot}5H_2O$	**L1**	Cs_2CO_3	26
2	$CuSO_4{\cdot}5H_2O$	**L2**	Cs_2CO_3	78
3	$CuSO_4{\cdot}5H_2O$	**L3**	Cs_2CO_3	91
4	$CuSO_4{\cdot}5H_2O$	**L3**	Cs_2CO_3	69[c]
5	$CuSO_4{\cdot}5H_2O$	**L4**	Cs_2CO_3	8
6	$CuSO_4{\cdot}5H_2O$	**L5**	Cs_2CO_3	5
7	$CuSO_4{\cdot}5H_2O$	**L6**	Cs_2CO_3	6
8	$CuSO_4{\cdot}5H_2O$	**L3**	K_2CO_3	12
9	$CuSO_4{\cdot}5H_2O$	**L3**	K_3PO_4	34
10	$CuSO_4{\cdot}5H_2O$	**L3**	KOH	66
11		**L3**	Cs_2CO_3	0
12	$CuSO_4{\cdot}5H_2O$		Cs_2CO_3	9
13	CuI	**L3**	Cs_2CO_3	73
14	$CuCl_2$	**L3**	Cs_2CO_3	77
15	$Cu(OAc)_2$	**L3**	Cs_2CO_3	16
16	Cu_2O	**L3**	Cs_2CO_3	12
17	$CuClO_4$	**L3**	Cs_2CO_3	36
18	$CuSO_4{\cdot}5H_2O$	**L3**	Cs_2CO_3	87[d]
19	$CuSO_4{\cdot}5H_2O$	**L3**	Cs_2CO_3	50[e]

[a] Unless otherwise noted, the reactions were carried out with imidazole (1.10 mmol), iodobenzene (1.00 mmol), Cs_2CO_3 (2.00 mmol), $CuSO_4$ (10 mol %), and **L3** (20 mol %) in water (3 mL) at 120 °C for 24 h. [b] Determined by GC/MS. [c] The reaction was performed with $CuSO_4$ (5 mol %) and **L3** (10 mol %) in water (3 mL) at 120 °C for 36 h. [d] $(n\text{-Bu})_4NBr$ (32.2 mg, 0.1 mmol) was added as PTC. [e] The reaction temperature was 100 °C.

Among the ligands used, pyridine *N*-oxides were more beneficial to the catalysis than their pyridine analogues, and **L3** exhibited much higher catalytic ability than the other two *N*-oxide ligands (Table 1, entries 1−7). The excellent solubility in water and the flexibility of ligand structure probably contributed the high efficiency of **L3**. Different copper sources have also been examined, and the catalysis by $CuSO_4$, CuI, or $CuCl_2$ with **L3** afforded the *N*-arylated product in good yields of 91%, 73%, and 77%, respectively (Table 1, entries 3, 13, and 14). However, the employment of $Cu(OAc)_2$, Cu_2O, and $CuClO_4$ resulted in lower yields of

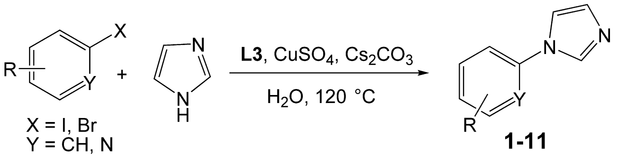
---

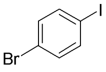
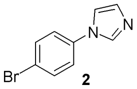
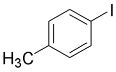
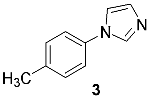
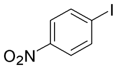
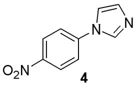
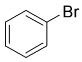
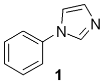
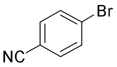
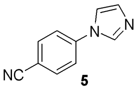
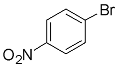
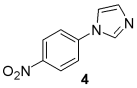
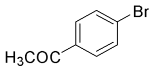
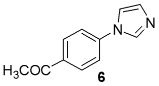
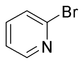
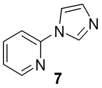
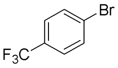
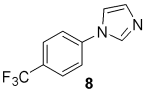
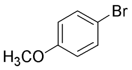
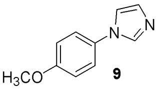
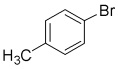
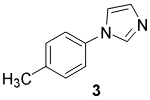
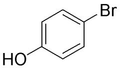
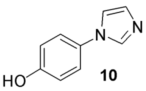
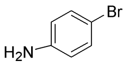
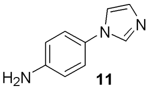
[7] (a) Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096. (c) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (e) Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 4367. (f) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (g) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241. (h) Xie, Y.-X.; Pi, S.-F.; Wang, J.; Yin, D.-L.; Li, J.-H. *J. Org. Chem.* **2006**, *71*, 8324. (i) Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135. (j) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737. (k) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (l) Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2007**, *348*, 2197. (m) Ma, H.; Jiang, X. *J. Org. Chem.* **2007**, *72*, 8943. (n) Cheng, D.; Gan, F.; Qian, W.; Bao, W. *Green Chem.* **2008**, *10*, 171.

[8] For reviews of Cu-catalyzed cross-coupling reactions with the participation of water or in water, see: (a) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107. (b) Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289. (c) Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997. (d) Zhu, X.; Ma, Y.; Su, L.; Song, H.; Chen, G.; Liang, D.; Wan, Y. *Synthesis* **2006**, 3955. (e) Yadav, L. D. S.; Yadav, B. S.; Rai, V. K. *Synthesis* **2006**, 1868. (f) Röttger, S.; Sjöberg, P. J. R.; Larhed, M. *J. Comb. Chem.* **2007**, *9*, 204. (g) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Green Chem.* **2007**, *9*, 219. (h) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467. (i) Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2007**, *63*, 10425. (j) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J* **2007**, *13*, 5100.

[9] For overviews, see: (a) Karayannis, N. M. *Coord. Chem. Rev.* **1973**, *11*, 93. (b) Albini, A. *Synthesis* **1993**, 263.

Table 2. *N*-Arylation of Imidazole with Aryl Halides Catalyzed by $CuSO_4$/**L3** in Water[a]



entry	ArX	product	yield [%] [b]
1		 **2**	90
2		 **3**	78
3		 **4**	95
4		 **1**	85
5		 **5**	82
6		 **4**	89
7		 **6**	69
8		 **7**	74
9		 **8**	88
10		 **9**	32[c]
11		 **3**	47[c]
12		 **10**	38
13		 **11**	46

[a] Unless otherwise noted, the reactions were carried out with imidazole (1.10 mmol), aryl halide (1.00 mmol), Cs_2CO_3 (2.00 mmol), $CuSO_4$ (10 mol %), and **L3** (20 mol %) in water (3 mL) at 120 °C for 24 h. [b] Determined by GC/MS and confirmed by isolated yield after column chromatography. [c] The reaction time was 48 h.

16%, 12%, and 36% (Table 1, entries 15, 16, and 17). Investigation of a variety of bases revealed that Cs_2CO_3 was better than the others including K_2CO_3, K_3PO_4, and KOH (Table 1, entries 8, 9, and 10). Control experiments confirmed that no product was detected in the absence of copper salt, while only 9% yield was obtained by using copper sulfate as catalyst (Table 1, entries 11 and 12). Furthermore, addition of phase-transfer reagents such as $(n\text{-Bu})_4NBr$ into the catalytic system seemed to have no positive effect on the result (Table 1, entry 18). Temperatures lower than 120 °C will dramatically decrease the reaction rate and entire conversion (Table 1, entry 19). In summary, the optimal conditions for the *N*-arylation process in water consist of the combination of $CuSO_4$ (10 mol %), **L3** (20 mol %), and Cs_2CO_3 (2 equiv) at 120 °C for 24 h in the air. The scope of aryl halides was carried out by using imidazole as the nucleophile. The results are listed in Table 2.

In general, most of the substituted aryl iodides and electron-deficient aryl bromides afforded the *N*-arylimidazole products with moderate to excellent yields ranging from 69% to 95%. As usual, the coupling reaction between imidazole and aryl iodides provided slightly superior yields than those with aryl bromides, and aryl bromides bearing electron-donating groups afforded much lower yields even with an extended reaction time of 48 h (Table 2, entries 10 and 11). It is noteworthy that the reaction was highly chemoselective; for example, reaction between *p*-bromoiodobenzene and imidazole gave 1-(4-bromophenyl)-1*H*-imidazole as the major product (Table 2, entry 1).

Furthermore, the catalytic system exhibited tolerance with aryl halides bearing nitrile, nitro, acetyl, ether, hydroxyl, or amino groups without formation of diaryl ether, diarylamine, or other coupling side products (Table 2, entries 5−7, 10, 12, and 13). Figure 2 shows the X-ray structure of the coupling product **11** between imidazole and 4-bromoaniline.

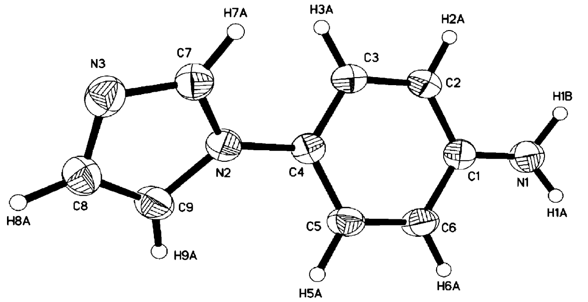
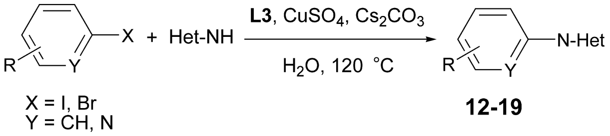


Figure 2. X-ray structure of the coupling product **11**.

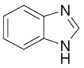
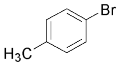
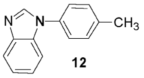
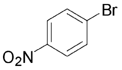
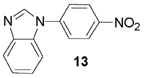
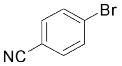
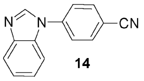
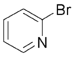
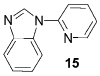
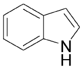
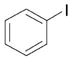
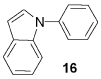
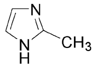
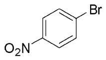
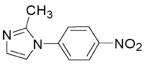
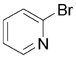
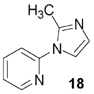
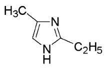
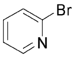
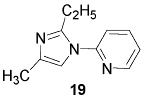
In an endeavor to expand the scope of the methodology, this new catalytic system was applied to a variety of imidazole derivatives, and the results are shown in Table 3.

To our delight, most of the imidazole derivatives and indoles exclusively afforded the corresponding products in moderate to excellent yields (64−90%) under the optimized reaction conditions. Notably, 2-methylimidazole could undergo the selective *N*-arylation with 4-nitrobromobenzene or 2-bromopyridine to afford corresponding coupling products in 85% or 72% yields (Table 3, entries 6 and 7). Another

Table 3. *N*-Arylation of Imidazoles with Aryl Halides Catalyzed by $CuSO_4$/**L3** in Water[a]



12-19

entry	Het-NH	ArX	product	yield [%][b]
1			 12	71
2			 13	87
3			 14	82
4			 15	78
5			 16	90
6			 17	85
7			 18	72
8			 19	64

[a] Unless otherwise noted, the reaction was carried out with nitrogen nucleophile (1.10 mmol), aryl halide (1.00 mmol), Cs_2CO_3 (2.00 mmol), $CuSO_4$ (10 mol %), and **L3** (20 mol %) in water (3 mL) at 120 °C for 24 h. [b] Isolated yield after column chromatography.

more bulkier *N*-nucleophile, 2-ethyl-4-methylimidazole, was coupled with 2-bromopyridine to give 1-(2-pyridyl)-2-methyl-4-ethylimidazole **19** in 64% yield (Table 3, entry 8), and all of the coupling products were well characterized and confirmed (see the Supporting Information).

In summary, we have developed a simple, highly efficient, economical, and environmentally friendly protocol for the *N*-arylation of imidazoles with aryl iodides and bromides promoted by a ligand-assisted copper catalyst in water. This method avoids the use of toxic organic solvents and stringent inert conditions. In addition, the catalytic system can be easily generated using a mixture of the inexpensive $CuSO_4$ and **L3**. Overall, we believe that this catalytic system could provide an avenue toward the Cu-catalyzed methods that have scarcely been adopted in the aqueous phase. Further investigation to broaden the scope of this catalytic system to other coupling reactions is currently ongoing in this laboratory.

Acknowledgment. This project was sponsored by the Natural Science Foundation of China (Nos. 20672075, 20771076) and the Sichuan Provincial Foundation (08ZQ026-041). We also thank the Analytic and Testing Centre of Sichuan University for the NMR spectral determination.

Supporting Information Available: Synthetic procedures, characterization, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9010773

---

(10) For recent examples and catalytic applications, see: Nienkemper, K.; Kotov, V. V.; Kehr, G.; Erker, G.; Fröhlich, R. *Eur. J. Inorg. Chem.* **2006**, 366, and references cited therein.

(11) (a) *Organic Synthesis in Water*; Grieca, P. A., Ed.; Blackie A & P: London, 1998. (b) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *101*, 825. (c) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2741. (d) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (e) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725. (f) DeSimone, J. M. *Science* **2002**, *297*, 799. (g) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807. (h) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (i) Blackmond, D. G.; Armstrong, A.; Coomber, V.; Wells, A. *Angew. Chem. Int. Ed.* **2007**, *119*, 3872. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798. (j) Minakata, S.; Komatsu, M. *Chem. Rev.* **2008**, *101*, 825. (k) Teo, Y.-C.; Chua, G.-L. *Chem.—Eur. J.* **2009**, *15*, 3072. (l) Teo, Y.-C. *Adv. Synth. Catal.* **2009**, *351*, 720.

(12) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221.