

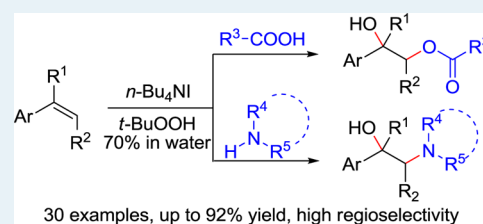
Metal-Free, $n\text{-Bu}_4\text{NI}$ -Catalyzed Regioselective Difunctionalization of Unactivated Alkenes

Qicai Xue,[†] Jin Xie,[†] Pan Xu,[†] Kaidong Hu,[†] Yixiang Cheng,[†] and Chengjian Zhu^{*,†,‡}[†]State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, People's Republic of China[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, People's Republic of China

Supporting Information

ABSTRACT: A new synthetic approach toward difunctionalization of alkenes has been developed under metal-free conditions. Various carboxylic acids and amines could react smoothly with alkenes to give dioxygenation and oxyamidation products, respectively. This organocatalytic process delivers 2-hydroxy alcohols directly from simple alkenes with high levels of region control.

KEYWORDS: alkene, dioxygenation, oxyamidation, metal-free, regioselective



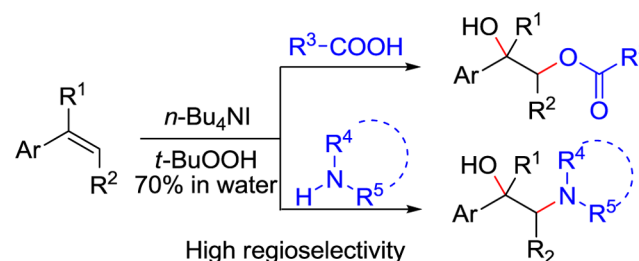
INTRODUCTION

Direct difunctionalization of alkenes has attracted considerable attention, providing the most attractive strategy for the assembly of functionalized organic compounds. In recent years, a number of transition-metal-catalyzed difunctionalizations of alkenes have been reported, such as dioxygenation,¹ oxyamidation,² oxyphosphorylation,³ and diamination.⁴ However, the cost, toxicity and environmental impact of these catalysts have hindered its further application. In this context, the development of a metal-free difunctionalization procedure provides a challenging and highly attractive target. Despite some remarkable progress that has been made, this area is considerably less established than their metal-based counterparts,^{5–7} and regioselective difunctionalization of alkenes is still a challenge. Recently, the catalytic system “ $n\text{-Bu}_4\text{NI}$ –TBHP” has been a focus of interest because of high efficiency, lower toxicity, and environmental friendliness,⁸ and some excellent results about C–O⁹ and C–N¹⁰ bond formations have been achieved. Herein, we report a protocol for an $n\text{-Bu}_4\text{NI}$ -catalyzed regioselective difunctionalization of alkenes using TBHP as an oxidant (Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of α -methylstyrene **1a** with 4-chlorobenzoic acid **2a** was selected as a model reaction. The dioxygenation product **3a** could be formed under the catalysis of $n\text{-Bu}_4\text{NI}$ (Table 1, entry 1). Encouraged by this result, we investigated the reaction conditions in detail, and the results are summarized in Table 1. Among the catalysts screened, $n\text{-Bu}_4\text{NI}$ showed the best catalytic efficiency (Table 1, entry 1). The use of $n\text{-Bu}_4\text{NBr}$, KI, or I₂ instead of $n\text{-Bu}_4\text{NI}$ decreased the yields dramatically (Table 1, entries 2–4). Subsequently, various oxidants were evaluated in this process. The starting material **1a**

Scheme 1. Difunctionalization of Alkenes



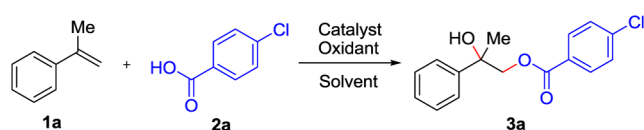
was rapidly consumed when K₂S₂O₈ was used as an oxidant; only a trace amount of product **3a** was detected (Table 1, entry 5). Other oxidants such as O₂, H₂O₂, and DTBP gave unsatisfactory results (Table 1, entries 6–8). To maximize the yields, different solvents were also tested. The results showed that n -hexane is a highly effective solvent, affording the product **3a** with the highest isolated yield (Table 1, entry 12). In addition, control experiments demonstrated that no **3a** could be identified when either $n\text{-Bu}_4\text{NI}$ or TBHP was absent (Table 1, entries 13 and 14).

With the optimized reaction conditions established (Table 1, entry 12), the scope of our protocol was investigated (Table 2). First, a variety of alkenes were tested. Under the optimized conditions, α -methylstyrene and 1,1-diphenylethylene were converted to dioxygenation products in good isolated yields (Table 2, **3a** and **3b**). Styrene substrates bearing electron-withdrawing groups were converted into the corresponding products with higher yields than electron-donating groups

Received: April 1, 2013

Revised: May 16, 2013

Published: May 20, 2013

Table 1. Optimization of Reaction for the Alkene Dioxygenation^a


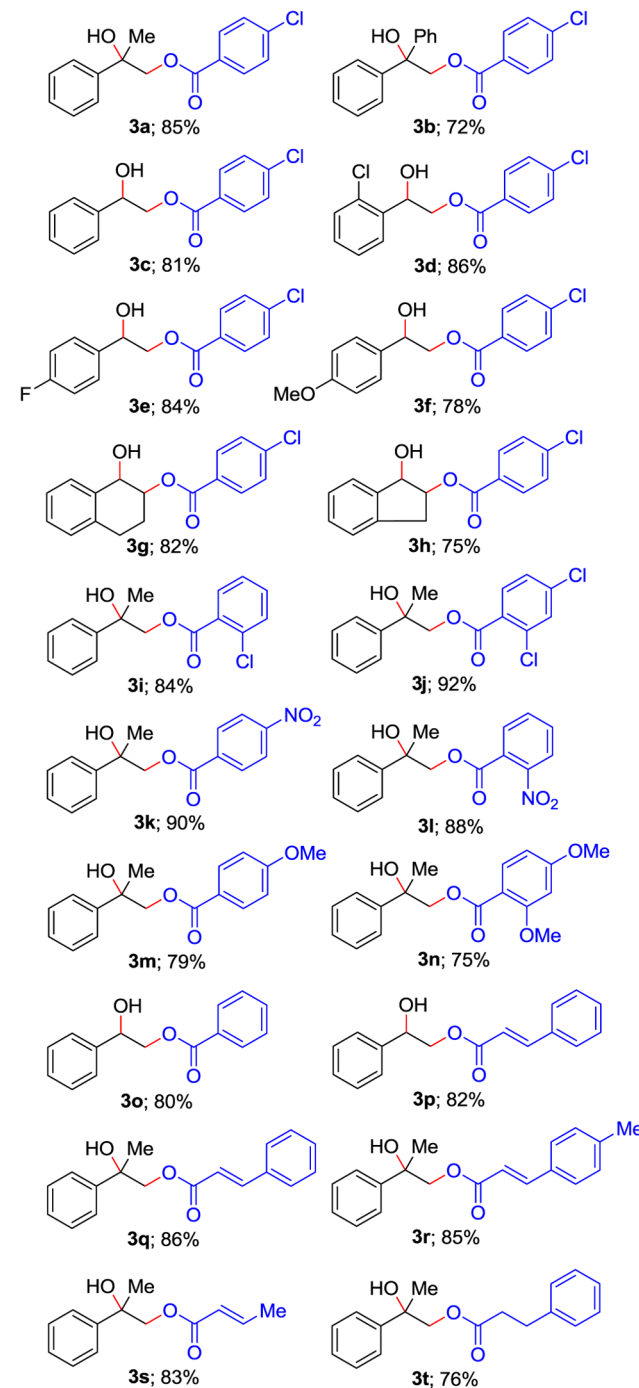
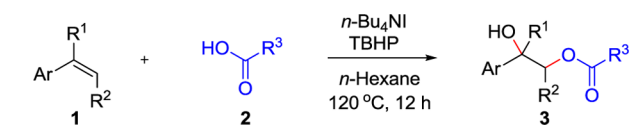
entry	catalyst	oxidant	solvent	yield (%) ^b
1	<i>n</i> -Bu ₄ NI	TBHP ^c		75
2	<i>n</i> -Bu ₄ NBr	TBHP		trace
3	KI	TBHP		12
4	I ₂	TBHP		23
5	<i>n</i> -Bu ₄ NI	K ₂ S ₂ O ₈		trace
6	<i>n</i> -Bu ₄ NI	O ₂ ^d		N.D. ^e
7	<i>n</i> -Bu ₄ NI	H ₂ O ₂ ^c		N.D.
8	<i>n</i> -Bu ₄ NI	DTBP ^c		trace
9	<i>n</i> -Bu ₄ NI	TBHP	benzene	55
10	<i>n</i> -Bu ₄ NI	TBHP	DCE ^c	73
11	<i>n</i> -Bu ₄ NI	TBHP	EA ^c	78
12	<i>n</i> -Bu ₄ NI	TBHP	<i>n</i> -hexane	85
13	<i>n</i> -Bu ₄ NI	TBHP	<i>n</i> -hexane	trace
14	<i>n</i> -Bu ₄ NI	TBHP ^f	<i>n</i> -hexane	trace
15	<i>n</i> -Bu ₄ NI	TBHP ^f	<i>n</i> -hexane	85

^aReaction conditions: **1a** (0.6 mmol), **2a** (0.3 mmol), catalyst (10 mol %), oxidant (0.9 mmol), 120 °C, 12 h. ^bIsolated yield. ^cTBHP, *tert*-butyl hydroperoxide 70% in water; H₂O₂ 30% in water; DTBP, di-*tert*-butyl peroxide; DCE, 1,2-dichloroethane; EA, ethyl acetate. ^dUnder an oxygen atmosphere (1.0 atm). ^eNot detected. ^fTBHP 5.5 M in decane.

(Table 2, **3c–f**). 1,2-Dihydronaphthalene and 1*H*-indene were still very effective in our catalytic system and can give good results (Table 2, **3g** and **3h**). When styrene was replaced by tetraphenylethylene, allylbenzene, or cyclohexene, no difunctionalization product was detected. Subsequently, different aromatic acids were examined in this *n*-Bu₄NI-catalyzed reaction. In general, both electron-deficient and electron-rich aromatic acids were suitable for this protocol, and the corresponding dioxygenation products were obtained in good to excellent yields (Table 2, **3i–n**). To our delight, it was found that cinnamic acid derivatives were still very effective in our catalytic system and can give good results (Table 2, **3p–r**). When crotonic acid or aliphatic acid was employed, the reaction could proceed smoothly, leading to the desired product with high yield (Table 2, **3s** and **3t**).

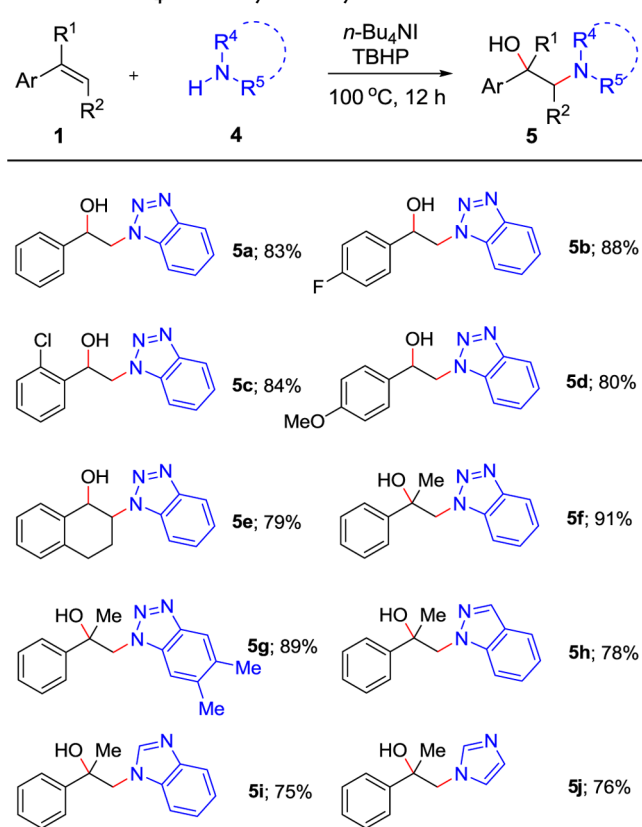
The success of dioxygenation of alkenes encouraged us to further explore the scope of this protocol. Interestingly, we found that the reaction of styrene with benzotriazole **4a** at 100 °C for 12 h proceeded smoothly to afford the oxyamido product **5a** with high efficiency (optimization of reaction conditions; see the Supporting Information). Encouraged by this result, the scope of oxyamidation of alkenes was investigated. As shown in Table 3, a variety of alkenes were tolerated in this process, affording the desired products in good yields (Table 3, **5a–f**). Notably, electron-withdrawing as well as electron-donating groups on the aromatic rings were compatible in the oxyamidation of alkenes. Furthermore, different benzotriazoles could react with alkenes in the presence of *n*-Bu₄NI to give the desired products in 89–91% yields (Table 3, **5f** and **5g**). Moreover, indazole, benzimidazole and imidazole were also tolerated in this protocol, furnishing the desired products in good yields (Table 3, **5h–j**).

To probe the mechanism of alkene dioxygenation, several control experiments were conducted (Scheme 2). The reaction

Table 2. The *n*-Bu₄NI-Catalyzed Dioxygenation of Alkenes^a


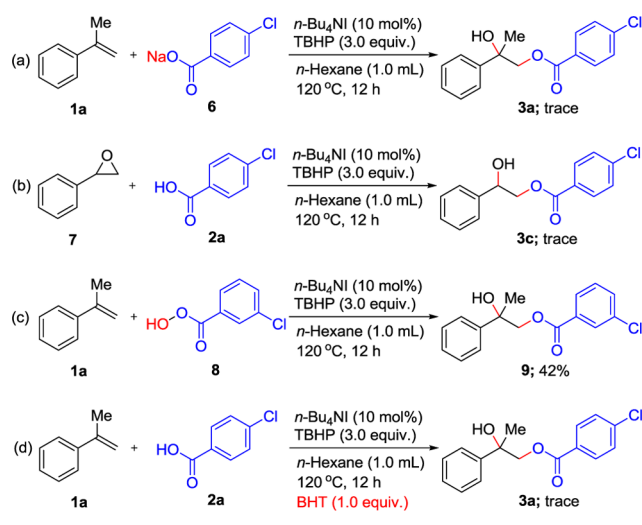
^aReaction conditions: **1** (0.6 mmol), **2** (0.3 mmol), *n*-Bu₄NI (10 mol %), TBHP 70% in water (0.9 mmol), *n*-hexane (1.0 mL), 120 °C, 12 h. Yields are for the isolated products.

of α-methylstyrene **1a** and sodium *p*-chlorobenzoate **6** did not result in the formation of **3a** (Scheme 2a). Interestingly, styrene oxide was rapidly consumed in this process; only a trace amount of **3a** was detected (Scheme 2b). The above results indicate that the carboxylate anion and epoxy compound were

Table 3. *n*-Bu₄Ni-Catalyzed Oxyamidation of Alkenes^a

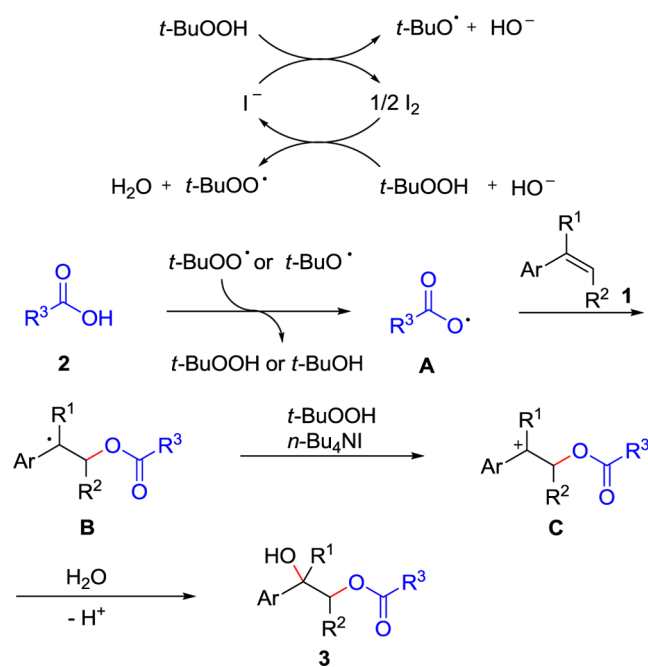
^aReaction conditions: **1** (0.6 mmol), **4** (0.3 mmol), *n*-Bu₄Ni (10 mol %), TBHP 70% in water (0.9 mmol), 100 °C, 12 h. Yields are for the isolated products.

Scheme 2. Investigation into the Reaction Mechanism



not involved in this dioxygenation process. Furthermore, 3-chloroperoxybenzoic acid, a known acyloxy radical donor, was also tolerated in this protocol (Scheme 2c).^{9a} Adding a radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction system, the formation of the dioxygenation product was completely suppressed (Scheme 2d).

On the basis of the above results, a plausible mechanism for *n*-Bu₄Ni-catalyzed dioxygenation of alkenes is proposed in Scheme 3. Initially, *n*-Bu₄Ni reacts with TBHP to give the *tert*-butoxyl and *tert*-butylperoxy radicals. Subsequently, these

Scheme 3. Proposed Reaction Mechanism for *n*-Bu₄Ni-Catalyzed Dioxygenation of Alkenes

radicals abstract hydrogen atoms from the acid, **2**, to afford radical **A**,^{9a,11} then it reacts with **1** to form intermediate **B**. Oxidation of radical **B** forms the benzyl cation **C**.¹² Finally, the benzyl cation **C** reacts with water to form the desired product **3** (for the study of HRMS on the mechanism, see the Supporting Information). However, to disclose the exact mechanics of this transformation, further studies are needed.

CONCLUSIONS

In summary, we have successfully developed a novel *n*-Bu₄Ni-catalyzed operationally simple method for difunctionalization of alkenes. Various dioxygenation and oxyamidation products were obtained in good to excellent yields using TBHP (70% in water) as an inexpensive and environmentally friendly oxidant. This metal-free process makes use of simple, inexpensive starting materials and demonstrates excellent regioselectivity in all cases. Further studies concerning the detailed mechanism are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: cjzhu@nju.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21172106, 21074054), the National Basic Research Program of China (2010CB923303), and the Research Fund for the Doctoral Program of Higher Education

of China (20120091110010) for their financial support. J. Xie thanks the academic scholarship for doctoral candidates of MOE.

REFERENCES

- (1) For select reviews, see: (a) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. For selected dioxygenation, see: (c) Wang, W.; Wang, F.; Shi, M. *Organometallics* **2010**, *29*, 928. (d) Wang, A.; Jiang, H.; Chen, H. J. *Am. Chem. Soc.* **2009**, *131*, 3846. (e) Li, Y.; Song, D.; Dong, V. M. J. *Am. Chem. Soc.* **2008**, *130*, 2962. (f) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076.
- (2) For selected oxyamidation, see: (a) de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 906. (b) Mancheno, D. E.; Thornton, A. R.; Stoll, A. H.; Kong, A.; Blakey, S. B. *Org. Lett.* **2010**, *12*, 4110. (c) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866. (d) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690.
- (3) Wei, W.; Ji, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9097.
- (4) For selected diamination, see: (a) Iglesias, Á.; Pérez, E. G.; Muñoz, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8109. (b) Sequeira, F. C.; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365. (c) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523. (d) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590.
- (5) Hydroxamic acid as reactant: (a) Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2012**, *3*, 1672. (b) Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402. (c) Giglio, B. C.; Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 13320. (c1) Schmidt, V. A.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4491.
- (6) Peroxide-mediated reactions: (a) Jones, K. M.; Tomkinson, N. C. O. *J. Org. Chem.* **2012**, *77*, 921. (b) Kang, Y.; Gade, L. H. *J. Org. Chem.* **2012**, *77*, 1610. (c) Picon, S.; Rawling, M.; Campbell, M.; Tomkinson, N. C. O. *Org. Lett.* **2012**, *14*, 6250. (d) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M. *J. Am. Chem. Soc.* **2010**, *132*, 14409. (e) Rawling, M. J.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2013**, *11*, 1434.
- (7) $\text{PhI}(\text{OAc})_2$ as reactant: (a) Liu, Q.; Zhao, Q. Y.; Liu, J.; Wu, P.; Yi, H.; Lei, A. *Chem. Commun.* **2012**, *48*, 3239. (b) Fujita, M.; Wakita, M.; Sugimura, T. *Chem. Commun.* **2011**, *47*, 3983. (c) Kang, Y.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. (d) Zhong, W.; Yang, J.; Meng, X.; Li, Z. *J. Org. Chem.* **2011**, *76*, 9997. (e) Röben, C.; Souto, J. A.; González, Y.; Lishchynskiy, A.; Muñoz, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9478. (f) Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071. (g) Santoro, S.; Santi, C.; Sabatini, M.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2008**, *350*, 2881.
- (8) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177.
- (9) For selected examples, see: (a) Shi, E.; Chen, S.; Chen, S.; Hu, H.; Chen, S.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384. (b) Feng, J.; Liang, S.; Chen, S.; Zhang, J.; Fu, S.; Yu, X. *Adv. Synth. Catal.* **2012**, *354*, 1287. (c) Huang, J.; Li, L.; Li, H.; Husan, E.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 10204. (d) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (e) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085. (f) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376.
- (10) For selected examples, see: (a) Xue, Q.; Xie, J.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 3700. (b) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (c) Mai, W.; Wang, H.; Li, Z.; Yuan, J.; Xiao, Y.; Yang, L.; Mao, P.; Qu, L. *Chem. Commun.* **2012**, *48*, 10117. (d) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979. (e) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (f) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333.
- (11) Silbert, L. S. *J. Am. Oil Chem. Soc.* **1969**, *46*, 615.
- (12) (a) Li, Y.; Li, B.; Lu, X.; Lin, S.; Shi, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (b) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073.