Nickel-Catalyzed sp^3 C–H Bond Activation from Decarboxylative Cross-Coupling of α,β-Unsaturated Carboxylic Acids with Amides

Jia-Xiang Zhang,[a] Yan-Jing Wang,[b] Nai-Xing Wang,*[a] Wei Zhang,[a] Cui-Bing Bai,[a] Yi-He Li,[a] Jia-Long Wen[a]

[a] Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. of China

[b] College of Sciences, Beijing University of Chemical Technology, Beijing 100029, P. R. of China
Fax +86(10)62554670; E-mail: nxwang@mail.ipc.ac.cn

Received: 10.03.2014; Accepted after revision: 07.04.2014

Abstract: Nickel-catalyzed functionalization of C(sp^3)–H bonds adjacent to a nitrogen atom in amides through decarboxylative cross-coupling of α,β-unsaturated carboxylic acids is reported. A possible reaction mechanism is proposed that involves radical intermediate species.

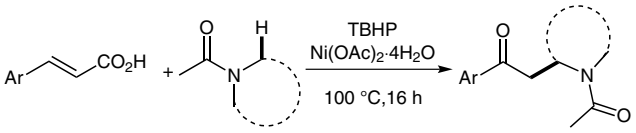
Key words: C–H bonds activation, nickel, cross-coupling, amides, radical reaction

The development of methodologies for the efficient functionalization of C–H bonds has become a hot topic in organic synthesis.[1] One related area is decarboxylative cross-coupling, which can afford the desired negative synthon for use in organic synthesis. In this approach, stable and inexpensive carboxylic acids can be used in place of expensive and unstable organometallic reagents. Moreover, decarboxylative carbon–heteroatom cross-coupling is a powerful method for the construction of C–C bonds and C–H bond functionalization.[2,3] Particularly, transition-metal-catalyzed activation of C(sp^3)–H bonds adjacent to a heteroatom (often nitrogen or oxygen) has attracted considerable attention, and remarkable progress has been made in this field.[4–7]

In many oxidative coupling reactions, precious metals such as palladium, rhodium, and ruthenium salts are used as catalysts;[8] however, the use of copper and iron salts has also been developed.[9,10] Recently, nickel-catalyzed oxidative C–H functionalizations have been attracting increasing attention.[11] For example, Veiros reported the first C–H activation of an acetonitrile ligand on a nickel center.[11d] Lei's group has demonstrated a nickel-catalyzed oxidative arylation of C(sp^3)–H bonds adjacent to the oxygen atom of cyclic ethers.[11e]

However, the activation of C(sp^3)–H bonds adjacent to the nitrogen atom of amides has scarcely been investigated.[12] Amides are important resources in organic synthesis, and oxidative cross-coupling strategies that employ amides as raw material could provide an important new synthetic tool.[13]

In this study, we report on the nickel-catalyzed functionalization of C(sp^3)–H bonds adjacent to the nitrogen atom in amides through decarboxylative cross-coupling of α,β-unsaturated carboxylic acids. To the best of our knowledge, we present a precedent for a new oxidative functionalization of C(sp^3)–H bonds in amides, which is related with decarboxylative cross-coupling (Scheme 1).



Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, naphthyl, furan, thiophene

17 examples
up to 80% yield

Scheme 1 Functionalization of sp^3 C–H bonds adjacent to a nitrogen atom in amides

Initially, cinnamic acid and *N*,*N*-dimethylacetamide (DMA) were chosen as model substrates. The optimization of reaction conditions is shown in the Table 1. It was found that cinnamic acid did not react with DMA without the catalyst or additive oxidant (entries 1 and 2); thus, catalysts and additive oxidants were essential for the reactions. The reaction of DMA and TBHP was also conducted with a range of temperatures (entries 3–8) and it was found that the yield could be increased to 80% by performing the reaction at 100 °C. The yield was not improved further by performing the reaction at higher temperatures (entries 7 and 8). Moderate yield was obtained through the use of DTBP (entry 9). When other oxidizing agents such as *N*-bromosuccinimide (NBS) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were used, no product was obtained (entries 10 and 11). Furthermore, only trace amounts of product was obtained by using $K_2S_2O_8$ as the oxidant in the reaction (entry 12). A range of transition-metal salts were tested as catalysts for the reactions, and it was found that $Ni(OAc)_2{\cdot}4H_2O$ was most efficient (entries 13–20). The optimized reaction conditions were thus established to involve heating TBHP as oxidizing agent and 10 mol% $Ni(OAc)_2{\cdot}4H_2O$ as catalyst to 100 °C (entry 6).

To expand the scope of the system, a range of α,β-unsaturated carboxylic acids were tested as substrates, and we were pleased to find that the corresponding products were all obtained in moderate to good yield (Figure 1). It is noteworthy that α,β-unsaturated carboxylic acids substituted with electron-donating groups gave better yields. The aryl group also affected the reaction yields. Several α,β-unsaturated carboxylic acids connected to furan and

SYNLETT 2014, 25, 1621–1625
Advanced online publication: 14.05.2014
DOI: 10.1055/s-0033-1341279; Art ID: st-2014-w0210-l

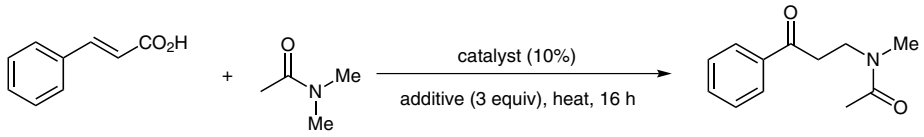
thiophene structures generated the corresponding products with moderate yields.

Other amides could also be used as reactants, including 1-(pyrrolidin-1-yl)ethanone, *tert*-butyl pyrrolidine-1-carboxylate, 1-(piperidin-1-yl)ethanone, and *N*,*N*-dimethylformamide. Some other types of amides such as *N*-methylformamide and *N*-methylacetamide were tested as the substrates; however, only trace amounts of products were found (Scheme 2). The unsymmetrical amide *N*-methyl-2-pyrrolidinone (NMP) was also a suitable substrate for the reaction; in this case, the major product was **q**, with only trace amounts of the alternative product **r** being observed (Scheme 2). It is notable that the selectivity toward the CH_2 group adjacent to the nitrogen atom in the ring predominated over the *N*-methyl group for NMP. All of the new products were characterized by NMR and HRMS analysis.

In the ^{1}H NMR spectra of purified products **a**–**j** and **p**, some peaks appeared as a set of two peaks instead of a single peak; signal duplication was also observed for the corresponding ^{13}C NMR spectra. Such extra peaks are generated because the nitrogen atom in these compounds is bonded to three different groups, and C–N bond rotation leads to the emergence of rotamers[8] and consequent splitting in the NMR spectra.[14,15] It was found that when the substituent on the nitrogen atom was smaller, splitting of the NMR spectra was more obvious compared with the NMR spectra of **a** and **p**. When the nitrogen atom was fixed within a cyclic structure, the rotation of the C–N bonds was reduced, and the splitting in the corresponding NMR spectrum was weakened (see the NMR spectra of **k**–**o**, Primary Data).

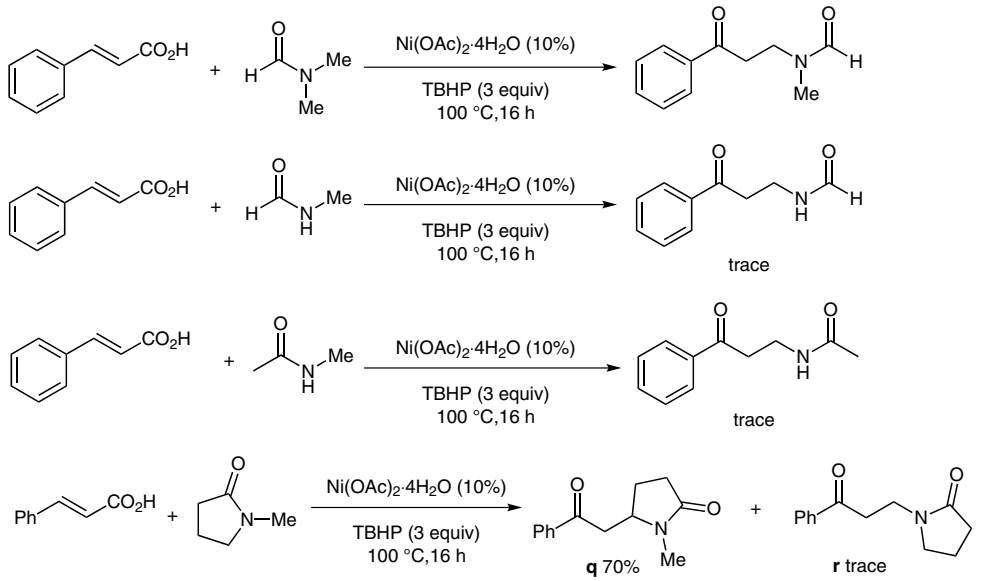
The reaction yield dropped in the presence of butylated hydroxytoluene (BHT). Moreover, no product was ob-

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Additive[b]	Temp. (°C)	Yield (%)
1	–	–	100	0
2	–	TBHP	100	0
3	$Ni(OAc)_2·4H_2O$	TBHP	25	0
4	$Ni(OAc)_2·4H_2O$	TBHP	60	45
5	$Ni(OAc)_2·4H_2O$	TBHP	90	75
6	$Ni(OAc)_2·4H_2O$	TBHP	100	80
7	$Ni(OAc)_2·4H_2O$	TBHP	120	78
8	$Ni(OAc)_2·4H_2O$	TBHP	150	70
9[c]	$Ni(OAc)_2·4H_2O$	DTBP	100	50
10	$Ni(OAc)_2·4H_2O$	NBS	100	0
11	$Ni(OAc)_2·4H_2O$	DDQ	100	0
12	$Ni(OAc)_2·4H_2O$	$K_2S_2O_8$	100	trace
13	$NiCl_2·6H_2O$	TBHP	100	70
14	$NiSO_4·6H_2O$	TBHP	100	60
15	$Cu(OAc)_2$	TBHP	100	50
16	$Cu(OAc)_2·H_2O$	TBHP	100	55
17	$Co(OAc)_2·4H_2O$	TBHP	100	45
18	$Zn(OAc)_2·2H_2O$	TBHP	100	40
19	$Pb(OAc)_2·3H_2O$	TBHP	100	43
20	$Mn(OAc)_2·4H_2O$	TBHP	100	45

[a] Reaction conditions: cinnamic acid (0.148 g, 1 mmol), catalyst (0.1 mmol, 10 mol%), additive (3 mmol).
[b] TBHP = *tert*-butyl hydroperoxide (70% in water).
[c] DTBP = di-*tert*-butylperoxide.



Scheme 2 Reactions of cinnamic acid reacted with some types of amides

served in the presence of radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). These results indicate that the reaction likely follows a radical addition–elimination process in the activation of C–H bonds mediated by TBHP.[16–18]

A possible reaction mechanism is proposed in Scheme 3. Thus, the reaction of *N*,*N*-dimethylacetamide with the initiator TBHP affords radical **A**, which adds to the α-position of the double bond of salts of Ni(II) carboxylate to produce intermediate **B**. A hydroxyl radical, generated from homolysis of TBHP, then adds to B to generate the aryl α-hydroxylalkylated product and eliminate carbon dioxide and Ni(II). Finally, the desired product is generated upon oxidation.

In conclusion, we have developed the nickel-catalyzed activation of C(sp^3)–H bonds adjacent to a nitrogen atom in

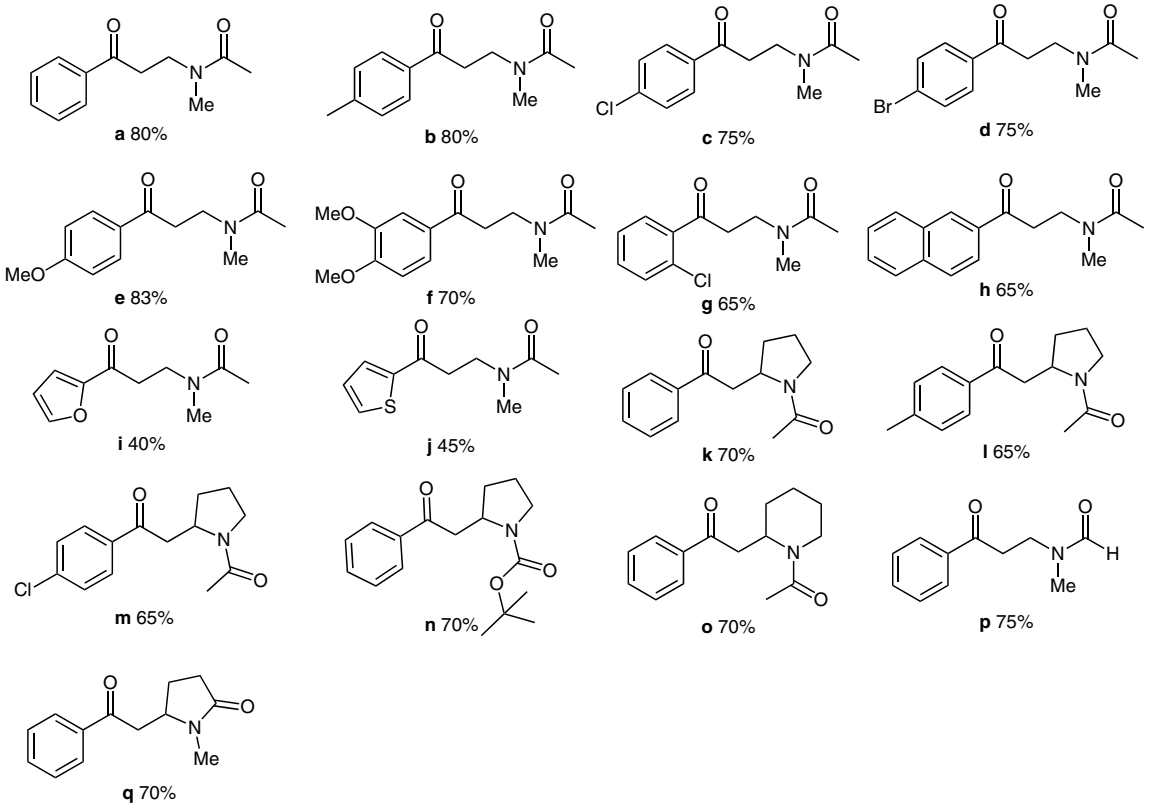
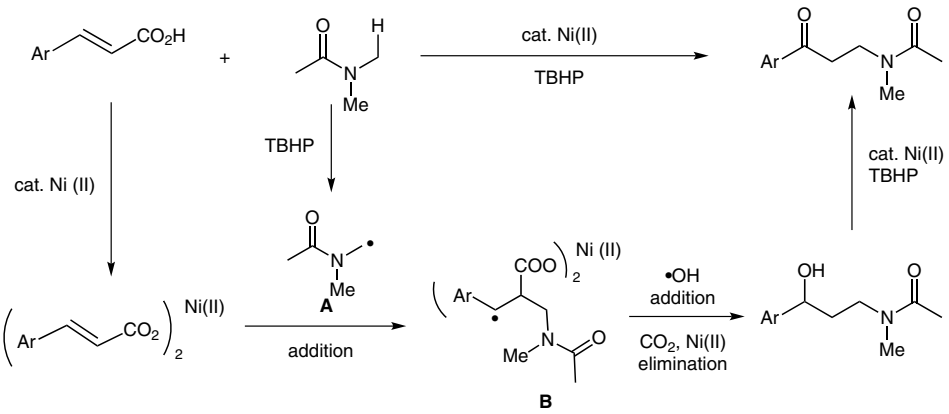


Figure 1 Products obtained



Scheme 3 Proposed reaction mechanism

amides with decarboxylative cross-coupling of α,β-unsaturated carboxylic acids.[19] This work provides a useful approach for the synthesis of amide derivatives. It is noteworthy that novel types of β-carbonylamides containing pyrrolidine and piperidine structure can be synthesized by using this methodology.

Acknowledgment

This work was supported financially by the Natural Science Foundation of China (21172227) and by the National 973 Program Foundation (No. 2010CB732202).

Primary Data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0058th.

References and Notes

(1) (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1683.

(2) (a) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935.

(3) (a) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (b) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372. (c) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 5284.

(4) (a) Zhang, Y.-H.; Li, C.-J. *Angew. Chem. Int. Ed.* **2006**, *45*, 1949. (b) Li, Z.-P.; Yu, R.; Li, H.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7497. (c) Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 14218. (d) Richter, H.; Mancheño, O. G. *Eur. J. Org. Chem.* **2010**, 4460.

(5) (a) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (b) Chu, L.-L.; Zhang, X.-G.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 2197.

(6) (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4348. (b) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (c) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (e) Gooßen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 3043. (f) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738. (g) Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 5259.

(7) (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (b) You, S.-L.; Dai, L.-X. *Angew. Chem.* **2006**, *118*, 5372. (c) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852. (d) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440.

(8) (a) Yang, Y.-Z.; Cheng, K.; Zhang, Y.-H. *Org. Lett.* **2009**, *11*, 5606. (b) Wei, Y.; Kan, J.; Wang, M.; Su, W.-P.; Hong, M.-C. *Org. Lett.* **2009**, *11*, 3346. (c) Zhang, X.-G.; Fan, S.-L.; He, C.-Y.; Wan, X.-L.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506. (d) Gandeepan, P.; Parthasarathy, K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8569. (e) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337. (f) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 5198. (g) Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, *127*, 6632. (h) Deng, G.-J.; Zhao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 6278.

(9) (a) Gao, Y. X.; Wang, G.; Chen, L.; Xu, P. X.; Zhao, Y. F.; Zhou, Y. B.; Han, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052. (c) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (d) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (e) Cheng, K.; Huang, L. H.; Zhang, Y. H. *Org. Lett.* **2009**, *11*, 2908. (f) Huang, L. H.; Cheng, K.; Yao, B. B.; Zhao, J. L.; Zhang, Y. H. *Synthesis* **2009**, 3504. (g) Sun, H. Y.; Zhang, Y. H.; Guo, F. F.; Zha, Z. G.; Wang, Z. Y. *J. Org. Chem.* **2012**, *77*, 3563.

(10) (a) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6505. (b) Guo, X.-W.; Yu, R.; Li, H.-J.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387. (c) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (d) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wünsch, B.; Itami, K. *Chem. Asian J.* **2009**, *4*, 1416.

(11) (a) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890. (b) Yin, W.-Y.; He, C.; Chen, M.; Zhang, H.; Lei, A.-W. *Org. Lett.* **2009**, *11*, 709. (c) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 2202. (d) Oertel, A. M.; Ritleng, V.; Chetcuti, M. J.; Veiros, L. F. *J. Am. Chem. Soc.* **2010**, *132*, 13588. (e) Liu, D.; Liu, C.; Li, H.; Lei, A.-W. *Angew. Chem. Int. Ed.* **2013**, *52*, 4453.

(12) (a) Tang, R.-Y.; Xie, Y.-X.; Xie, Y.-L.; Xiang, J.-N.; Li, J.-H. *Chem. Commun.* **2011**, *47*, 12867. (b) Shepherd, N. E.; Tanabe, H.; Xu, Y.-J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666. (c) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2012**, *18*, 10092. (d) Dai, C.-H.; Meschini, F.; Narayanam, J. M. R.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 4425. (e) Li, G.-C.; Qian, S.-Y.; Wang, C.-X.; You, J.-S. *Angew. Chem. Int. Ed.* **2013**, *52*, 7837.

(13) (a) Li, H.-M.; Xie, J.; Xue, Q.-C.; Cheng, Y.-X.; Zhu, C.-J. *Tetrahedron Lett.* **2012**, *53*, 6479. (b) Xu, K.; Hu, Y.-B.; Zhang, S.; Zha, Z.-G.; Wang, Z.-Y. *Chem. Eur. J.* **2012**, *18*, 9793. (c) Wang, G.; Yu, Q.-Y.; Chen, S.-Y.; Yu, X.-Q. *Org. Biomol. Chem.* **2014**, *12*, 414.

(14) (a) Deng, S.-J.; Taunton, J. *J. Am. Chem. Soc.* **2002**, *124*, 916. (b) Ohnishi, Y.; Sakai, M.; Nakao, S.; Kitagawa, O. *Org. Lett.* **2011**, *13*, 2840.

(15) (a) Li, X.-B.; Curran, D. P. *Org. Lett.* **2010**, *12*, 612. (b) Hu, D. X.; Grice, P.; Ley, S. V. *J. Org. Chem.* **2012**, *77*, 5198.

(16) (a) Zhao, L. X.; Shang, X. J.; Cui, Z. L.; Liu, Z. Q. *Org. Lett.* **2012**, *14*, 3219. (b) Cui, Z. L.; Shang, X. J.; Shao, X. F.; Liu, Z. Q. *Chem. Sci.* **2012**, *3*, 2853.

(17) Russell, G. A.; Ngoviwatchai, P. *J. Org. Chem.* **1989**, *54*, 1836.

(18) (a) Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486. (b) Xiang, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 11986. (c) Xiang, J.; Jiang, W.; Gong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 4123. (d) Li, Z.; Jiang, Y. Y.; Fu, Y. *Chem. Eur. J.* **2012**, *18*, 4345.

(19) **Typical Procedure:** To a mixture of cinnamic acid (0.148 g, 1 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (25 mg, 0.1 mmol), and *N*,*N*-dimethylacetamide (2 mL), *tert*-butyl hydroperoxide (0.39 g, 3 mmol, 70% in water) was added at r.t. dropwise. The resulting mixture was heated to 100 °C for 16 h, then the mixture was added to dichloromethane (40 mL) and washed with water and saturated brine. The organic solution was dried with anhydrous magnesium sulfate and the desired product was separated on a silica gel column (petroleum ether–EtOAc).

