

Tetrabutylammonium Iodide Catalyzed Synthesis of Allylic Ester with *tert*-Butyl Hydroperoxide as an Oxidant

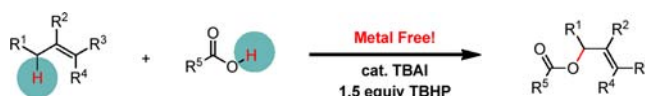
Erbo Shi,[†] Ying Shao,[‡] Shulin Chen,[†] Huayou Hu,[¶] Zhaojun Liu,[†] Jie Zhang,[†] and Xiaobing Wan^{*,†}

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China, Key Laboratory of Fine Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China, and Key Laboratory for Chemistry of Low-Dimensional Materials, School of Chemistry and Chemical Engineering, Huaiyin Normal University, Huaian 223300, P. R. China

wanxb@suda.edu.cn

Received May 17, 2012

ABSTRACT



A metal-free C–H oxidation for the construction of allylic esters has been developed. The use of a commercially available and inexpensive catalyst and oxidant, and readily available starting materials, coupled with the operational simplicity of the reaction, renders the methodology a useful alternative to other approaches typically employed in the synthesis of allylic esters.

The selective oxidation of allylic C–H bonds, for the construction of highly valuable α -functionalized alkenes, has drawn much attention in recent years. This atom-

economical process avoids prefunctionalization of C–H bonds, thus making synthetic schemes shorter, cleaner, and more efficient.¹ To date, several transition metal catalyzed allylic C–H oxidations have developed.² Allylic esters are ubiquitous structural motifs and occur in many natural products.³ They also serve as important building blocks in organic synthesis⁴ and have been traditionally synthesized by acylation of the corresponding allylic alcohols.⁵ Recently, a palladium-catalyzed atom-economical synthesis of allylic esters from carboxylic acids and

[†] Soochow University.

[‡] Changzhou University.

[¶] Huaiyin Normal University.

(1) For recent reviews on this topic, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Li C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (d) Dobreiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Copéret, C. *Chem. Rev.* **2010**, *110*, 656. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Mkhaliid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (i) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (j) Gunay, A.; Theopold, K. H. *Chem. Rev.* **2010**, *110*, 1060. (k) Balcells, D.; Colt, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749. (l) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (m) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (n) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (o) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (p) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

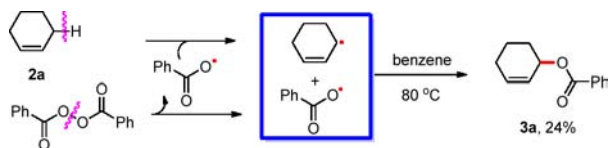
(2) For selected examples, see: (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (c) Grennberg, H.; Bäckvall, J.-E. *Chem.—Eur. J.* **1998**, *4*, 1083. (d) Macsari, I.; Szabo, K. J. *Tetrahedron Lett.* **1998**, *39*, 6345. (e) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845. (f) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (g) Chen, H.; Cai, C.; Liu, X.; Li, X.; Jiang, H. *Chem. Commun.* **2011**, *47*, 12224.

(3) For selected examples, see: (a) Quang, D. N.; Hashimoto, T.; Stadler, M.; Asakawa, Y. *J. Nat. Prod.* **2004**, *67*, 1152. (b) Ankisetty, S.; ElSohly, H. N.; Li, X.-C.; Khan, S. I.; Tekwani, B. L.; Smillie, T.; Walker, L. *J. Nat. Prod.* **2006**, *69*, 692. (c) Saito, T.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2009**, *11*, 5274. (d) Chang, C.-L.; Zhang, L.-J.; Chen, R. Y.; Kuo, L.-M. Y.; Huang, J.-P.; Huang, H.-C.; Lee, K.-H.; Wu, Y.-C.; Kuo, Y.-H. *J. Nat. Prod.* **2010**, *73*, 1482.

(4) For selected examples, see: (a) Nicolaou, K. C.; Winssinger, N.; Hughes, R.; Smethurst, C.; Cho, S. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1084. (b) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; White, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 8217. (c) Schlummer, S.; Vetter, R.; Kuder, N.; Henkel, A.; Chen, Y.-X.; Li, Y.-M.; Kuhlmann, J.; Waldmann, H. *ChemBioChem* **2006**, *7*, 88. (d) Jogalekar, A. S.; Kriel, F. H.; Shi, Q.; Cornett, B.; Cicero, D.; Snyder, J. P. *J. Med. Chem.* **2010**, *53*, 155. (e) Reddy, N. K.; Vijaykumar, B. V. D.; Chandrasekhar, S. *Org. Lett.* **2012**, *14*, 299. (f) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860. (g) Williams, F. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 4459.

monosubstituted olefins by C–H bond oxidation has constituted a significant breakthrough in this area.⁶ The coupling of allenes⁷ or terminal alkynes⁸ with carboxylic acids has also provided a powerful protocol for the formation of allylic esters. Both of these elegant reactions proceeded via a π -allyl metal intermediate, generated in situ from the reaction between a C–H bond and transition metal catalyst.

Scheme 1. Allylic Ester Synthesis via Radical Coupling



The Kharasch–Sosnovsky reaction,⁹ a Cu-catalyzed esterification of an allylic C–H bond with *tert*-butyl peresters, is a classical method of allylic ester synthesis. We herein describe a new, highly selective radical coupling strategy to construct allylic esters. Compared with *tert*-butyl peresters, carboxylic acids are commercially available or easily prepared. Free radical chemistry has advanced tremendously since its discovery in 1900;¹⁰ however, the highly selective coupling of different radical species still remains a challenge in radical chemistry.¹¹

To test our hypothesis, benzoyl peroxide, a well-known precursor to acyloxy radicals,¹² was coupled with cyclohexene. This formed the desired allylic ester **3a** in 24% yield (Scheme 1, GC yield). In spite of the low yield obtained, we

(5) (a) Xiang, J.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4117. (b) Meyer, M. E.; Ferreira, E. M.; Stoltz, B. M. *Chem. Commun.* **2006**, 1316. (c) Mohan, K. V. V. K.; Narender, N.; Kulkarni, S. J. *Green Chem.* **2006**, *8*, 368. (d) Zhang, L.; Luo, Y.; Fan, R.; Wu, J. *Green Chem.* **2007**, *9*, 1022.

(6) (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabakaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhofer, K. J.; Prabakaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (e) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448. (f) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547. (g) Vermeulen, N. A.; Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 11323. (h) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (i) Stang, E. M.; White, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 2094. (j) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584. (k) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824. (l) Takenaka, K.; Akita, M.; Tanigaki, Y.; Takizawa, S.; Sasai, H. *Org. Lett.* **2011**, *13*, 3506.

(7) (a) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809. (b) Kim, I. S.; Krische, M. J. *Org. Lett.* **2008**, *10*, 513.

(8) (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386. (b) Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746. (c) Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.* **2012**, *3*, 789.

(9) (a) Kharasch, M. S.; Sosnovsky, G. N.; Yang, C. *J. Am. Chem. Soc.* **1959**, *81*, 5819. For reviews, see: (b) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845. (c) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567.

(10) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; Wiley: 2001.

(11) (a) Studer, A. *Chem.—Eur. J.* **2001**, *7*, 1159. (b) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. (c) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267.

(12) (a) Nozaki, K.; Bartlett, P. D. *J. Am. Chem. Soc.* **1946**, *68*, 1686. (b) Nozaki, K.; Bartlett, P. D. *J. Am. Chem. Soc.* **1946**, *68*, 2377.

Table 1. Optimization of Reaction Conditions^a

entry	catalyst	oxidant	yield ^b
1	Bu ₄ NI	TBHP	87%
2	Bu ₄ NI	NaClO	N.D. ^c
3	Bu ₄ NI	H ₂ O ₂	N.D.
4	Bu ₄ NI	O ₂	N.D.
5	Bu ₄ NI	BQ	N.D.
6	Bu ₄ NI	Di- <i>tert</i> -butyl peroxide	N.D.
7	Bu ₄ NI	–	N.D.
8	–	TBHP	N.D.
9	Bu ₄ NCl	TBHP	N.D.
10	Bu ₄ NBr	TBHP	N.D.
11	Bu ₄ NOH	TBHP	N.D.
12	Bu ₄ NI	TBHP	71% ^d
13	Bu ₄ NI	TBHP	50% ^e

^a Reaction conditions: 0.5 mmol of 4-chlorobenzoic acid **1b**, 2.0 mmol of cyclohexene **2a**, 20 mol % catalyst, 1.5 equiv of TBHP (70% aqueous solution) in 2.0 mL of benzene at 80 °C for 8 h. ^b Isolated yield. ^c Not detected. ^d 1.0 mmol of cyclohexene **2a** was used. ^e 5 mol % catalyst was used.

were encouraged by the initial result as it proved the feasibility of coupling of acyloxy and allylic radicals. To determine the utility of the transformation, commercially inexpensive and abundant carboxylic acids were investigated as potential acyloxy radical donors. Extending our recent studies involving tetrabutylammonium iodide (TBAI) catalyzed chemical reactions,¹³ we envisioned converting carboxylic acids and alkenes to the corresponding allylic ester using a similar, metal-free approach. 20 mol % TBAI/1.5 equiv of TBHP (*tert*-butyl hydroperoxide) in benzene at 80 °C was found by screening to give a high yield (87%) of the desired allylic ester **3b** without requiring an inert atmosphere (Table 1, entry 1).

Table 1 reveals the effect of different catalysts and oxidants on the efficiency of the allylic C–H oxidation process. The choice of oxidant was critical to the conversion, as no desired allylic ester **3b** was detected when any oxidant other than TBHP was employed (entries 2–6).

(13) Recently, we and others reported Bu₄NI-catalyzed reaction using TBHP; see: (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem.—Eur. J.* **2011**, *17*, 4085. (b) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827. (c) Chen, S.; Xu, Y.; Wan, X. *Org. Lett.* **2011**, *13*, 6152. (d) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231. (e) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (f) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754. (g) Ma, L.; Zhang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (h) Tang, R.-Y.; Xie, Y.-X.; Xie, Y.-L.; Xiang, J.-N.; Li, J.-H. *Chem. Commun.* **2011**, *47*, 12867. (i) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979. (j) Kloeckner, U.; Weckenmann, N. M.; Nachtsheim, B. J. *Synlett* **2012**, *23*, 97. (k) Zhu, C.; Wei, Y. *ChemSusChem* **2011**, *4*, 1082. (l) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841. (m) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561. (n) He, T.; Li, H.; Li, P.; Wang, L. *Chem. Commun.* **2011**, *47*, 8946. (o) Feng, J.; Liang, S.; Chen, S.-Y.; Zhang, J.; Fu, S.-S.; Yu, X.-Q. *Adv. Synth. Catal.* **2012**, *354*, 1287.

No significant amount of **3b** was observed in the absence of TBAI or TBHP (entries 7–8). In addition, Bu_4NCl , Bu_4NBr , and Bu_4NOH failed to catalyze the formation of the desired **3b**, indicating that the use of iodide is also critical for this transformation (entries 9–11).

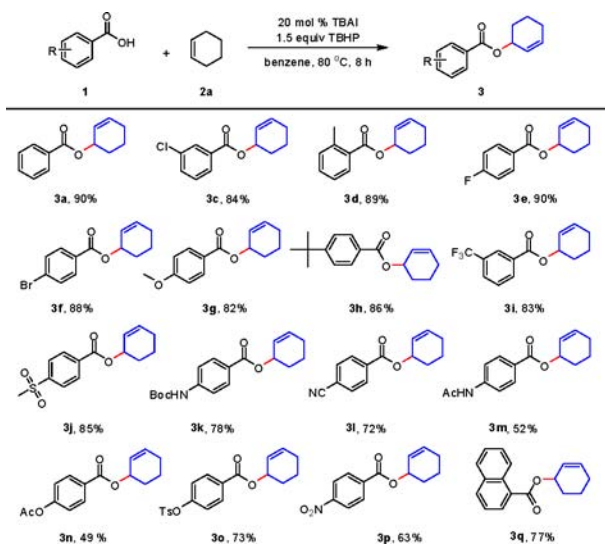


Figure 1. Scope of aryl carboxylic acids. (a) Reaction conditions: 0.5 mmol of aryl carboxylic acids **1**, 2.0 mmol of cyclohexene **2a**, 20 mol % TBAI, 1.5 equiv of TBHP (70% aqueous solution) in 2.0 mL of benzene at 80 °C for 8 h.

With optimized conditions in hand, a series of substituted aryl carboxylic acids were investigated, as shown in Figure 1. Both electron-donating and -withdrawing aryl carboxylic acids could be successfully converted to the corresponding allylic esters in moderate to excellent yields. In addition, a high level of functional group tolerance was observed, with halides, ethers, sulfones, Boc-protected amines, nitriles, amides, tosylates, and nitro groups being unaffected by the reaction.

To highlight the utility of this transformation, other types of carboxylic acids were subjected to the standard reaction conditions. These results are presented in Figure 2. A variety of heteroaryl acids, including thiophene, furan, benzofuran, indazole, and phthalimide, were coupled with cyclohexene **2a**, providing the corresponding allylic esters in good yields. Treatment of α,β -unsaturated carboxylic acids, such as crotonic acid and *trans*-cinnamic acid, with cyclohexene **2a** afforded the anticipated cross-coupling products **4f** and **4g** in 76% and 87% yield, respectively. It is noteworthy that protected amino acids were also suitable reaction partners under the standard conditions (products **4h–4j**). A series of aliphatic carboxylic acids also provided the expected allylic esters **4k–4n** in high yields, when subjected to the standard reaction conditions.

To further explore the potential of our methodology, a variety of alkenes were investigated as shown in Figure 3. In contrast to the transition metal catalyzed reaction,⁶ even multiply substituted alkenes reacted successfully in the allylic ester synthesis. Cyclopentene reacted well with

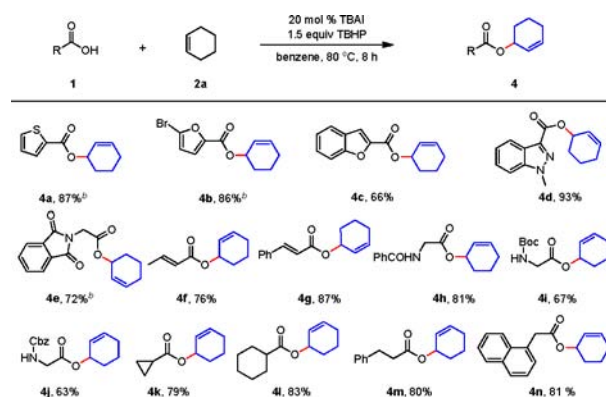


Figure 2. Scope of carboxylic acids. (a) Reaction conditions: 0.5 mmol of carboxylic acids **1**, 2.0 mmol of cyclohexene **2a**, 20 mol % TBAI, 1.5 equiv of TBHP (70% aqueous solution) in 2.0 mL of benzene at 80 °C for 8 h. (b) 50 mol % TBAI was used.

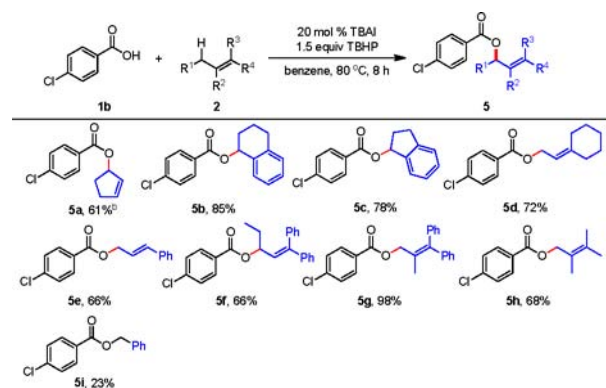
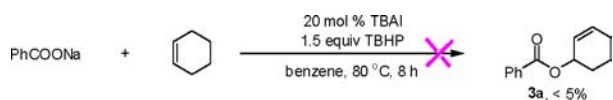


Figure 3. Scope of alkenes. (a) Reaction conditions: 0.5 mmol of 4-chlorobenzoic acid **1b**, 2.0 mmol of alkenes **2**, 20 mol % TBAI, 1.5 equiv of TBHP (70% aqueous solution) in 2.0 mL of benzene at 80 °C for 8 h. (b) 50 mol % TBAI was used.

4-chlorobenzoic acid **1b** to afford **5a** in good yield. Notably, benzylic C–H bonds could also be oxidized to the corresponding benzylic esters under the optimized conditions, leading to **5b**, **5c**, and **5i** in low to good yields. When terminal alkenes were subjected to the reaction conditions, including vinylcyclohexane and allylbenzene, linear allylic esters **5d** and **5e** were obtained selectively in 72% and 66% yields, respectively. A trisubstituted alkene was also transformed into the desired product **5f** in satisfactory yield when reacted with **1b**. Even tetrasubstituted alkenes provided the anticipated allylic esters in good yields (products **5g** and **5h**). To the best of our knowledge, this is the first reported example of allylic C–H oxidation using tetrasubstituted alkenes as reactants.

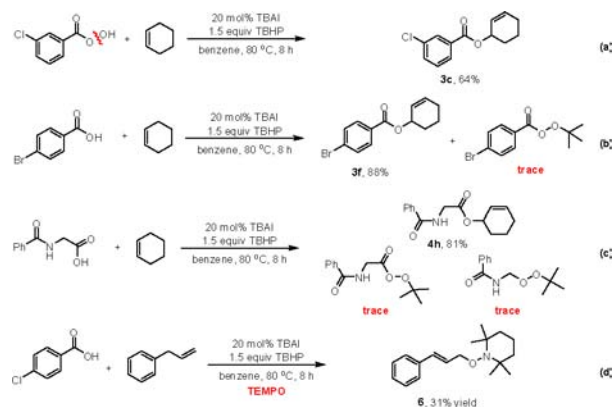
Further experiments were conducted to elucidate the mechanism of the allylic C–H oxidation. The reaction of sodium benzoate and cyclohexene did not result in the formation of allylic ester **3a**, indicating that the reaction of

Scheme 2. Investigation into the Reaction Mechanism



a carboxylate anion and allyl cation were not involved in the allylic ester synthesis (Scheme 2).

Scheme 3. Investigation into the Reaction Mechanism



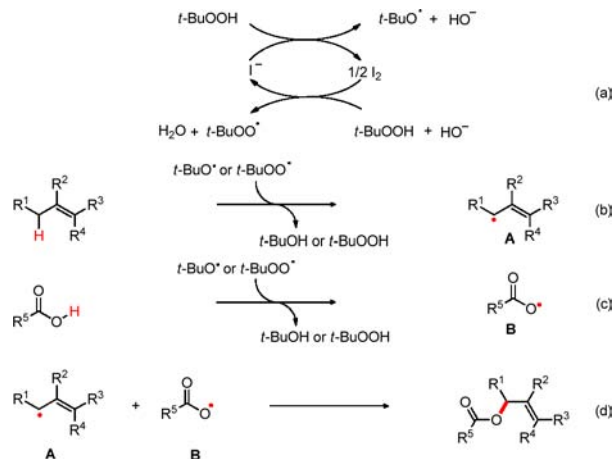
3-Chloroperoxybenzoic acid, a known acyloxy radical donor,¹⁴ was also a suitable reaction partner for the transformation (Scheme 3a). Notably, a *tert*-butyl perester, from the coupling of the acyloxy and *tert*-butoxyl radicals, was detected by LC-MS in the reaction mixture (Scheme 3b). When hippuric acid was used as a reactant, both the *tert*-butyl perester and decarboxylation product were observed as byproducts (Scheme 3c). When TEMPO, a well-known radical-trapping reagent, was introduced to the reaction mixture, the formation of the desired allylic ester was completely suppressed. Compound **6**, an adduct of TEMPO and the allylic radical, was isolated from this test in a yield of 31% (Scheme 3d). Based upon the above results, we prefer that the reaction involves the coupling of acyloxy and allylic radicals in the catalytic cycle of the allylic ester synthesis.

(14) Groenhof, A. R.; Ehlers, A. W.; Lammertsma, K. *J. Phys. Chem. A* **2008**, *112*, 12855.

(15) Silbert, L. S. *J. Am. Oil Chem. Soc.* **1969**, *46*, 615.

On the basis of these results, a plausible catalytic cycle is presented in Scheme 4. Initially, TBHP decomposes to generate the *tert*-butoxyl and *tert*-butylperoxy radicals (Scheme 4a). These radicals subsequently abstract hydrogen atoms from the alkene and carboxylic acid¹⁵ to provide both the allylic radical **A** and acyloxy radical **B**, respectively (Scheme 4b and c). Finally, the coupling of **A** and **B** forms the desired allylic ester (Scheme 4d).

Scheme 4. Proposed Catalytic Cycle



In summary, we have successfully developed the first metal-free allylic ester synthesis allowing for the selective coupling of acyloxy and allylic radicals using TBAI and TBHP. This radical process is free from both metal and photolysis conditions and makes use of commercially available, inexpensive, and abundant starting materials. Further investigations of both intramolecular and asymmetric versions of the reaction are currently underway in our laboratory.

Acknowledgment. A project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and NSFC (21072142). Prof. Dr. H. Hu is grateful to Jiangsu Province NSF (No.: BK2011408) and Jiangsu Province Department of Education (No. 10KJB150002) for their financial support.

Supporting Information Available. Experimental details, ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.