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# An Acid-Catalyzed Formal Allylic C−H Oxidation of Aryl Cycloalkenes with *N*-Propylthiosuccinimide

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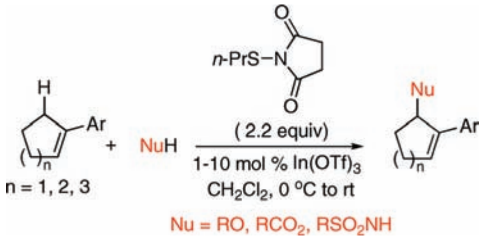
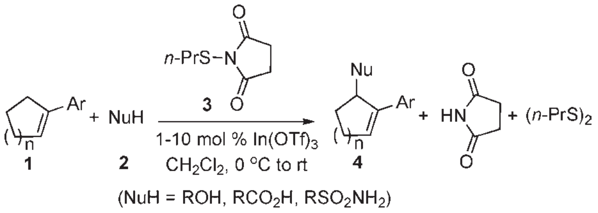
## ABSTRACT



**A mild acid-catalyzed formal allylic C−H oxidation of aryl cycloalkenes with *N*-propylthiosuccinimide in the presence of various nucleophiles to generate allylic ethers, esters, and sulfonamides is described. A possible reaction mechanism has been proposed.**

Allylic C−H oxidation of olefins provides an important approach to introduce functionality into molecules. Various processes have been developed,[1] including Pd(II)-catalyzed allylic acetoxylation[2] and amination,[3−5] Cu-catalyzed allylic oxidation with peresters,[6] and selenium based allylic oxidations.[7,8] During our studies on the reactivity of sulfenamides[9] toward olefins, we have found that aryl cycloalkenes can be oxidized at the allylic positions regioselectively with *N*-propylthiosuccinimide **3** and various nucleophiles in the presence of a catalytic amount of acid to form allylic ethers, esters, and sulfonamides

**Scheme 1**



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(1) For leading reviews, see: (a) Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1972**, 1. (b) Rawlinson, D. J.; Sosqovsky, G. *Synthesis* **1973**, 567. (c) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.

(2) For leading references on Pd(II)-catalyzed acetoxylation, see: (a) Tsuji, J.; Sakai, K.; Nagashima, H.; Shimizu, I. *Tetrahedron Lett.* **1981**, *22*, 131. (b) McMurry, J. E.; Kočovský, P. *Tetrahedron Lett.* **1984**, *25*, 4187. (c) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (d) Grennberg, H.; Simon, V.; Bäckvall, J. E. *J. Chem. Soc., Chem. Commun.* **1994**, 265. (e) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (f) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (g) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (h) Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 5518. (i) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Bras, J. L.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771.

(3) For leading references on Pd(II)-catalyzed amination, see: (a) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (b) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (c) Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707. (d) Shimizu, Y.; Obora, Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372.

(4) For leading reviews on generation of $\pi$-allyl Pd complexes from olefins with PdX$_2$, see: (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Åkermark, B.; Zetterberg, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E-i., Ed.; John Wiley & Sons, Inc.: New York, 2002; p 1875.

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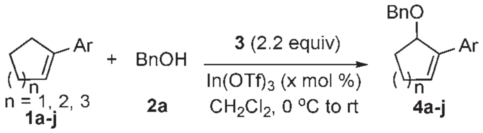
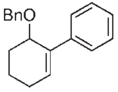
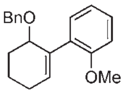
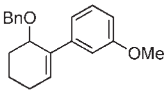
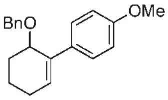
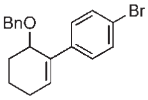
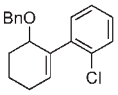
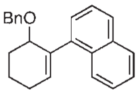
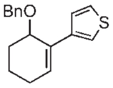
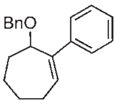
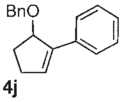
(Scheme 1). Herein we wish to report our preliminary results on this subject.

Initial studies with 1-phenylcyclohexene and BnOH showed that In(OTf)$_3$ gave overall the best result among various Lewis acids examined. TsOH was also capable of catalyzing the reaction but with low activity, thus requiring a long reaction time. While TfOH was found to be an active catalyst, the resulting product decomposed quickly under the reaction conditions due to TfOH's strong acidity. Among the solvents tested, $CH_2Cl_2$ was found to be the solvent of choice. Treating 1-phenylcyclohexene (**1a**) with BnOH (2.0 equiv), *N*-propylthiosuccinimide **3** (2.2 equiv), and In(OTf)$_3$ (5 mol %) in $CH_2Cl_2$ at rt for 1.5 h gave allylic benzyl ether **4a** in 81% yield (Table 1, entry 1). Various substituted 1-phenylcyclohexenes (**1b**−**f**) could also be oxidized (Table 1, entries 2−6), and more electron-rich substrates were found to be more reactive. Other aryl cycloalkenes such as 1-naphthyl (**1g**), 1-(3-thiophenyl)-cyclohexene (**1h**), 1-phenylcycloheptene (**1i**), and 1-phenylcyclopentene (**1j**) were found to be suitable substrates for the reaction (Table 1, entries 7−10). For more reactive substrates, the catalyst loading was decreased to 1 mol % to minimize any byproduct (Table 1, entries 2−4, 9, 10).

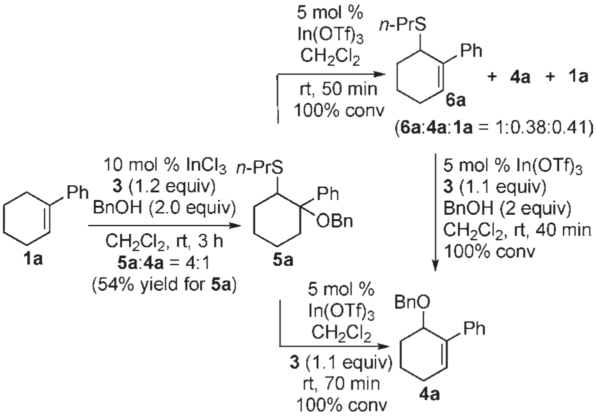
**Table 1.** Allylic Oxidation of Aryl Cycloalkenes



| entry[a] | 4a − 4j | x | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 |  **4a** | 5 | 1.5 | 81 |
| 2 |  **4b** | 1 | 2 | 73 |
| 3 |  **4c** | 1 | 6 | 74 |
| 4 |  **4d** | 1 | 2 | 73 |
| 5 |  **4e** | 5 | 4 | 74 |
| 6 |  **4f** | 5 | 4 | 66 |
| 7 |  **4g** | 5 | 6 | 60 |
| 8 |  **4h** | 5 | 3.5 | 49 |
| 9 |  **4i** | 1 | 6 | 63 |
| 10[c] |  **4j** | 1 | 24 | 63 |

[a] The reaction was carried out with **1** (1.0 mmol), **3** (2.2 mmol), BnOH (2.0 mmol), and In(OTf)$_3$ (*x* mol %) in $CH_2Cl_2$ (5 mL) at rt unless otherwise stated. [b] Isolated yield. [c] At 0−4 °C.

**Scheme 2**



Various other nucleophiles were also investigated with 1-phenylcyclohexene (**1a**). As shown in Table 2, other alcohols, carboxylic acids, and sulfonamides could be employed to give the corresponding allyl ethers, esters, and sulfonamides in 52−83% yields.

When a weaker Lewis acid $InCl_3$ was used as a catalyst, compound **5a** was formed as the major product along with allyl ether **4a** (Scheme 2). Compound **5a** was then isolated and subjected to various reaction conditions. When **5a** was

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(5) For a recent book on Pd, see: Tsuji, J. *Palladium Reagents and Catalysts: New Perspective for the 21st Century*; John Wiley & Sons Ltd.: 2004.

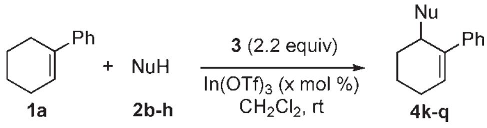
(6) For a leading review on Cu-catalyzed allylic oxidation, see: Andrus, M. B.; Lashley, J. C. *Tetrhedron* **2002**, *58*, 845.

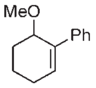
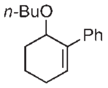
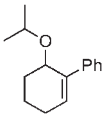
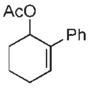
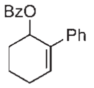
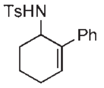
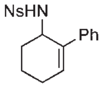
(7) For a leading reference on allylic oxidation with $SeO_2$, see: Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(8) For leading references on oxyselenenylation−elimination reactions of olefins to generate allylic ethers, see: (a) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429. (b) Wirth, T.; Häuptli, S.; Leuenberger, M. *Tetrahedron: Asymmetry* **1998**, *9*, 547. (c) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4645. (d) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169. (e) Browne, D. M.; Niyomura, O.; Wirth, T. *Phosphorus, Sulfur, and Silicon* **2008**, *183*, 1026. (f) Oshida, M.; Nakamura, T.; Nakazaki, A.; Kobayashi, S. *Chem. Pharm. Bull.* **2008**, *56*, 404. (g) Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649.

(9) For a leading review on sulfenamides, see: Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.

**Table 2.** Allylic Oxidation of 1-Phenylcyclohexene with Various Nucleophiles



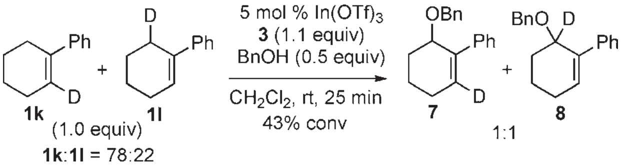
| entry[a] | NuH | 4k – 4q | x | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | MeOH<br>**2b** |  <br>**4k** | 5 | 6 | 80 |
| 2 | *n*-BuOH<br>**2c** |  <br>**4l** | 5 | 6 | 83 |
| 3 | *i*-PrOH<br>**2d** |  <br>**4m** | 5 | 22 | 68 |
| 4 | AcOH<br>**2e** |  <br>**4n** | 1 | 2 | 67 |
| 5 | BzOH<br>**2f** |  <br>**4o** | 1 | 4.5 | 52 |
| 6 | $TsNH_2$<br>**2g** |  <br>**4p** | 1 | 4 | 69 |
| 7[c] | $NsNH_2$<br>**2h** |  <br>**4q** | 10 | 29 | 54 |

[a] The reaction was carried out with **1a** (1.0 mmol), **3** (2.2 mmol), NuH (2.0 mmol), and $In(OTf)_3$ (*x* mol %) in $CH_2Cl_2$ (5 mL) at rt unless otherwise stated. [b] Isolated yield. [c] The reaction was carried out with $NsNH_2$ (1.2 mmol) in 1,4-dioxane (5 mL).

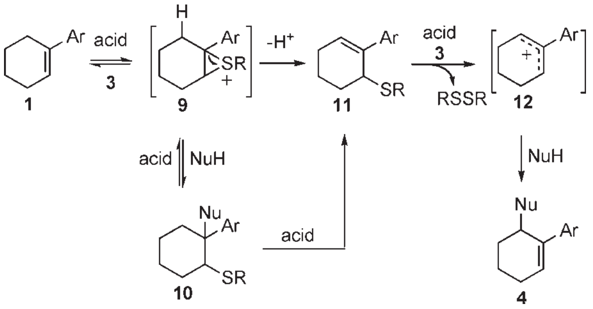
treated with $In(OTf)_3$ (5 mol %), allyl sulfide **6a** was formed along with allyl ether **4a** and 1-phenylcyclohexene (**1a**). However, when *N*-propylthiosuccinimide **3** was added, allyl ether **4a** was formed predominately. When allyl sulfide **6a** was treated with $In(OTf)_3$ (5 mol %), *N*-propylthiosuccinimide **3**, and BnOH, it was converted to allyl ether **4a** cleanly. All these results suggest that compounds **5a** and **6a** are likely to be the intermediates involved in the reaction pathway.

To further probe the reaction mechanism, deuterium-labeled 1-phenylcyclohexene was prepared and investigated for the reaction. It was found that compound **1k** was slowly converted to **1l** under the acidic reaction conditions (Scheme 3). Therefore, the reaction was then carried out for a partial conversion to determine the ratio of the remaining **1k** and **1l** in addition to the ratio of products **7** and **8**. As shown in Scheme 3, when deuterium-labeled 1-phenylcyclohexene (**1k:1l** = 78:22) was treated with 5 mol % $In(OTf)_3$, 1.1 equiv of **3**, and 0.5 equiv of BnOH in $CH_2Cl_2$ at rt for 25 min, compounds **7** and **8** were obtained as a 1:1 mixture with the remaining **1k** and **1l** being 72:28 (only a slight decrease from the initial 78:22).

**Scheme 3**



**Scheme 4.** A Proposed Reaction Pathway



Based on the aforementioned observations, a plausible reaction mechanism for the allylic C−H oxidation is proposed in Scheme 4. Thiiranium **9** generated from **1** undergoes an elimination to form allyl sulfide **11**[10−13] or a nucleophilic opening to form compound **10**, which is then converted to allyl sulfide **11** directly or via thiiranium **9**. At the end, allyl cation **12** generated from **11** by acid and *N*-propylthiosuccinimide **3** reacts with the nucleophile to form product **4**. The involvement of allyl cation **12** is supported by the fact that a 1:1 mixture of **7** and **8** was obtained in Scheme 3.

In summary, we have developed a mild and efficient acid-catalyzed formal allylic C−H oxidation of aryl cycloalkenes with N-propylthiosuccinimide. Various nucleophiles including alcohols, carboxylic acids, and sulfonamides can be employed to give corresponding allyl ethers, esters, and

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(10) For leading reviews on thiiranium ions, see: (a) Mueller, W. H. *Angew. Chem., Int. Ed.* **1969**, *8*, 482. (b) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462.

(11) For a leading review on seleniranium ions, see: Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740.

(12) For leading references on acid-promoted addition of RS or RSe to olefins with RS−N or RSe−N reagents, see: (a) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. (b) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231. (c) Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1280.

(13) For a leading reference on the generation of allylic sulfide with PhSCl, see: Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

sulfonamides. Importantly, the reaction occurs selectively at one allylic carbon. Mechanistic studies show that the sulfenamide plays an important role in converting the allyl sulfide intermediate into the products. Further efforts will be devoted to the development of a more effective system to expand the substrate scope and to reduce sulfur reagents to catalytic amounts as well as an asymmetric process possibly with chiral counteranions.

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**Supporting Information Available.** Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.