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Wacker-type oxidative functionalization of β-substituted unsaturated sulfoxides

Sadagopan Raghavan *, V. Krishnaiah, Kailash Rathore

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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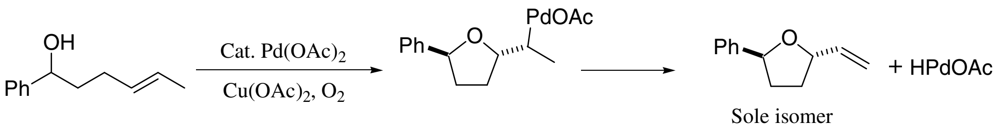
ABSTRACT

The Wacker-type oxidation is an important procedure catalyzed by palladium complexes. A mild and general method for the preparation of β-substituted-δ-oxosulfoxides from the corresponding β-substituted-γ,δ-unsaturated sulfoxides is described. The products are versatile synthetic intermediates for the preparation of *syn*- and *anti*-1,3-diol and 1,3-aminoalcohol derivatives.

A large number of dense vicinally functionalized compounds are present in Nature. The method of choice to introduce vicinal functionality is through nucleophilic attack, either inter- or intramolecular, initiated by the addition of an electrophile to an alkene.[1] The palladium catalyzed oxidative functionalization of unsaturated alcohols to 2-vinyltetrahydrofurans was first described by Hosokowa and co-workers[2] using catalytic $Pd(OAc)_2$ in the presence of stoichiometric $Cu(OAc)_2$ under an oxygen atmosphere, Eq. 1.



(1)

In continuation of our interest in utilizing the sulfinyl group as an intramolecular nucleophile for the hetero-functionalization of alkenes[3] activated by electrophiles,[4] we were attracted to the possibility of using catalytic amounts of a Pd^{2+} salt in a Wacker-type reaction to prepare an alkene diol from an allyl alcohol, Scheme 1. By way of 1,2-asymmetric induction, the new carbinol stereocenter was expected to be introduced with good diastereoselectivity. In addition, the alkene diol was envisioned to be further transformed by reaction with NBS into a bromotriol via intramolecular sulfinyl group participation.

We describe herein the results of our investigation on the Wacker-type reaction of β-substituted-γ,δ-unsaturated sulfoxides. Reaction of allyl alcohol[5] **1** with stoichiometric amounts of $Pd(OAc)_2(CH_3CN)_2$ in anhydrous THF[6] in the presence of potassium carbonate and water (2 equiv) yielded the keto alcohol **2** in 75% yield and none of the expected diol[7] **3**. Interestingly, **2** was obtained in a better yield using only catalytic amounts of $PdCl_2$ in the presence of stoichiometric amounts of CuCl in aq DMF[8] under an oxygen atmosphere.[9] It is noteworthy that the sulfoxide configuration is retained in the product.[10] The reaction probably proceeds via intermediate **I** formed by chelation of $PdCl_2$ to sulfur and the alkene,[11] followed by intermolecular attack of water[12] to afford intermediate **II**, which then undergoes dehydropalladation to yield HPdCl and enol **4** which tautomerizes to keto alcohol **2**, Scheme 2.

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* Corresponding author. Tel.: +91 040 27191643; fax: +91 040 27160512.
E-mail addresses: sraghavan@iict.res.in, purush101@yahoo.com (S. Raghavan).

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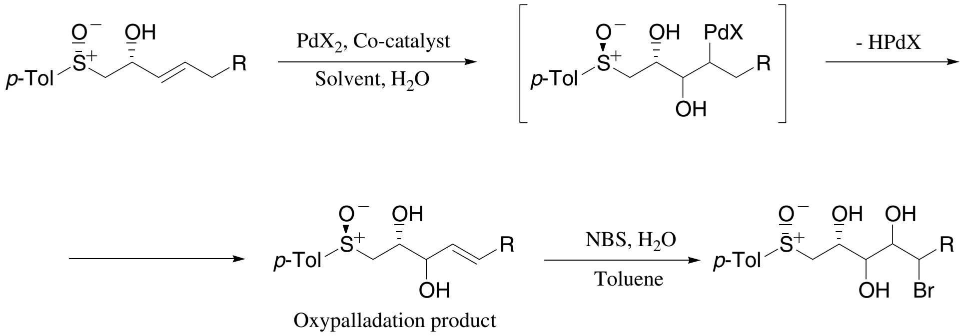
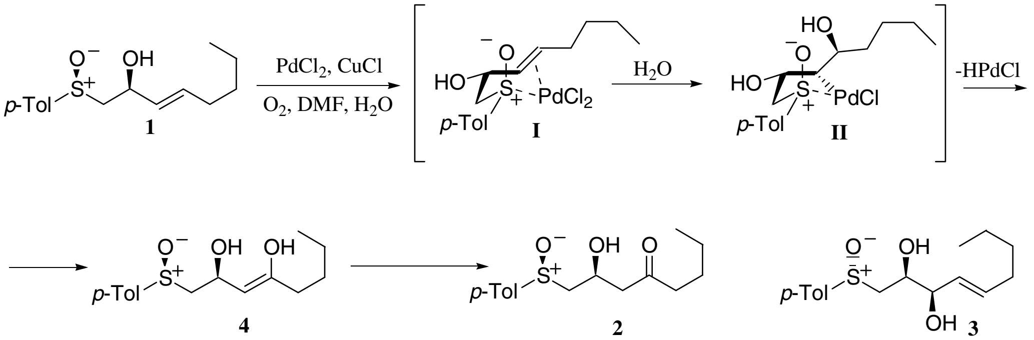


Scheme 1.



Scheme 2.

The generality of the reaction was explored, and the results are tabulated in Table 1. A perusal of the Table reveals that the reaction outcome is not affected by (a) the relative configurations at sulfur and carbon (compare entries 1, 2 and 4, 5), (b) protecting the hydroxy group (entry 3), and (c) double bond geometry[13] (compare entries 1 and 4). Terminal alkenes[14] cleanly afforded the corres-

Table 1
Oxidative functionalization of alkenes with catalytic PdCl$_2$[a]

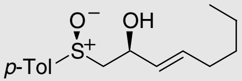
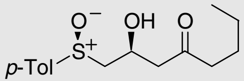
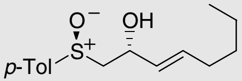
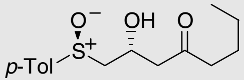
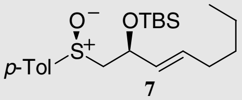
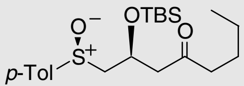
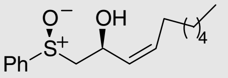
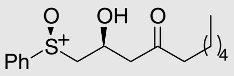
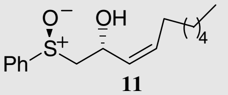
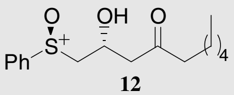
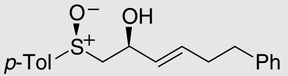
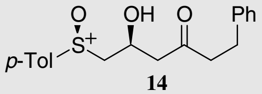
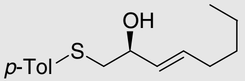
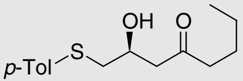
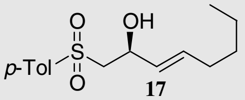
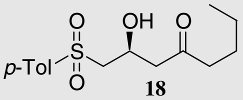
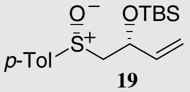
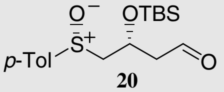
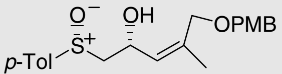
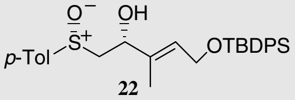
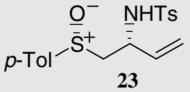
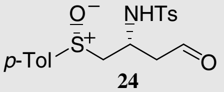
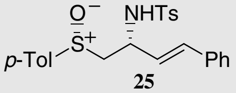
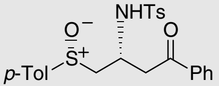
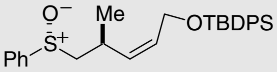
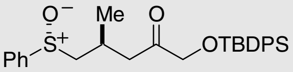
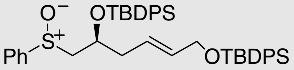
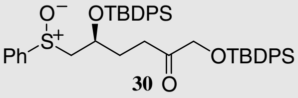
Entry	Alkene	Aldehyde/ketone	Yield (%) Time (h)
1	 **1**	 **2**	95 (12)
2	 **5**	 **6**	95 (12)
3[b]	 **7**	 **8**	65 (12)
4	 **9**	 **10**	78 (6)
5	 **11**	 **12**	80 (6)
6	 **13**	 **14**	89 (12)

Table 1 (*continued*)

Entry	Alkene	Aldehyde/ketone	Yield (%) Time (h)
7	 **15**	 **16**	76 (8)
8	 **17**	 **18**	83 (8)
9	 **19**	 **20**	85 (5)
10	 **21**	–	
11	 **22**	–	
12	 **23**	 **24**	84 (5)
13	 **25**	 **26**	85 (12)
14[c]	 **27**	 **28**	81 (12)
15[d,e]	 **29**	 **30**	73 (12)

[a] All reactions were carried out on 0.5 mmol scale using 10 mol % of $PdCl_2$ and 1 equiv of CuCl in aq DMF under an oxygen atmosphere at 65 °C for 5–12 h.

[b] 25% of **2** was also isolated.

[c] Racemic substrate was used.

[d] The sulfoxide **30** was characterized as the corresponding sulfone.

[e] The reaction did not proceed to completion even after 12 h and some unreacted starting material was recovered; yield is based on recovered starting material.

ponding aldehydes as the sole products[15] without any trace of the methyl ketone (entries 9 and 12). The reaction did not proceed when attempted on tri-substituted alkenes[16] employing the standard reaction conditions. Over extended periods of time, at higher temperatures and/or using stoichiometric amounts of $PdCl_2$, decomposition was observed. Steric factors are probably responsible for the lack of reactivity of tri-substituted alkenes. A sulfide and a sulfone are suitable substrates and afford keto alcohols in good yields (entries 7 and 8). Interestingly there was no poisoning of the catalyst by the sulfide and the sulfone which are also capable of complexing palladium chloride. The β-protected amino sulfoxide[17] yielded the expected amino ketone derivative without incident (entry 13). That a heteroatom at the β-position to the sulfoxide is not required was shown from the result of the reaction of a β-methyl substituted alkene[18] (entry 14). Finally a mixture of β-siloxy-δ,ω-unsaturated sulfoxide[19] was subjected to the standard reaction conditions to furnish an ω-keto alcohol which was characterized after oxidation to the sulfone (entry 15). The reaction conditions are mild, and protecting groups are tolerated.

The β-hydroxy δ-ketosulfoxide can be reduced to the corresponding *syn*- or *anti*-1,3-diols following literature procedures to furnish important intermediates in the synthesis of polyhydroxylated natural products.[20] The β-amino protected-δ-ketosulfoxide can likewise be reduced selectively to furnish *syn*- or *anti*-1,3-aminoalcohol derivatives. 1,3-Aminoalcohols are structural subunits present in many synthetic[21] and natural products[22] possessing potent biological activity. Their potential as chiral auxiliaries and ligands in asymmetric synthesis is well recognized.[23] In this context, it is noteworthy that β-hydroxy-δ-ketosulfoxides are obtained readily using the present methodology in comparison to the methodology reported by Solladie and co-workers using a β-dioxolane protected β-keto ester as starting material.[24]

In summary, we have described a novel, general and mild method for the preparation of β-substituted-δ-oxosulfoxide derivatives from mono- and di-substituted alkenes. These are useful synthons for the preparation of polyhydroxylated and aminoalcohol subunit-containing natural products.

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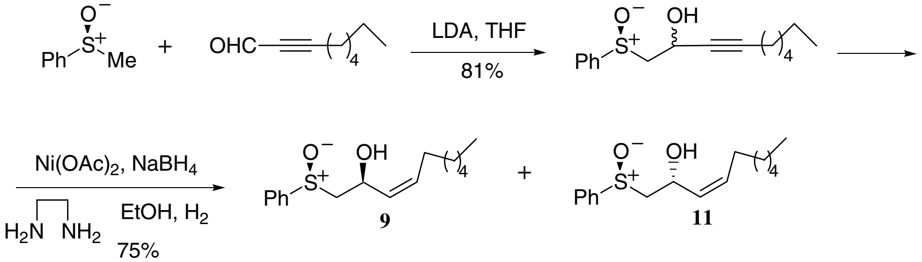
2. Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonoda, A. *Tetrahedron Lett.* **1976**, *17*, 1821–1824.
3. Mono-, cis-, trans di-substituted and tri-substituted alkenes have been shown to be suitable substrates for heterofunctionalization.
4. For the use of NBS as an electrophile, see: (a) Raghavan, S.; Rasheed, M. A.; Joseph, S. C.; Rajender, A. *Chem. Commun.* **1999**, 1845; (b) Raghavan, S.; Ramakrishna Reddy, S.; Tony, K. A.; Naveen Kumar, Ch.; Varma, A. K.; Nangia, A. *J. Org. Chem.* **2002**, *67*, 5838; (c) Raghavan, S.; Rajender, A.; Joseph, S. C.; Rasheed, M. A.; Ravi Kumar, K. *Tetrahedron: Asymmetry* **2004**, *15*, 365.; For the use of Hg(OC(O)CF$_3$)$_2$ as an electrophile, see: (d) Raghavan, S.; Ramakrishna Reddy, S. *Tetrahedron Lett.* **2004**, *45*, 5593.
5. Raghavan, S.; Krishnaiah, V. *Tetrahedron Lett.* **2006**, *47*, 7611.
6. Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.
7. Diol **3** was expected based on Pd^{2+} attacking the same face of the alkene as Br$^+$ attacks **1**.
8. (a) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9; (b) *Typical experimental procedure:* A flask containing a suspension of palladium(II) chloride (9 mg, 0.05 mmol) and copper(I) chloride (50 mg, 0.5 mmol) in *N,N*-dimethylformamide (1 mL) and water (1 mL) was stirred under an oxygen atmosphere for 1 h. Alkene **1** (67 mg, 0.5 mmol) in *N,N*-dimethylformamide (0.5 mL) and water (0.5 mL) was added, and the reaction mixture was stirred at 65 °C for 12 h. The reaction mixture was diluted with ether and the organic layer washed with water, brine; dried over Na$_2$SO$_4$, and evaporated. Purification by column chromatography on silica gel yielded hydroxy ketone **2** (67 mg) in 95% yield.
9. Reactions attempted in the absence of copper catalyst as reported in the literature failed to afford the desired product, see: (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892; (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778; (c) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036; (d) Ronn, M.; Backvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749; (e) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.
10. The coupling constants for the protons directly bonded to the carbon in the β-hydroxy sulfoxide moiety are diagnostic for assigning the relative configuration, see: Carreno, M. C.; Garcia Ruano, T. L.; Martin, A. M.; Pedregal, C.; Rodrigues, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120. Also the sign of optical rotation remained unchanged in the product indicating retention of sulfur configuration.
11. The same product **2** is expected when the PdCl$_2$ chelates to the other face of the alkene to yield an intermediate diastereomeric to **I**.
12. *anti* Oxypalladation assumed though *syn* oxypalladation cannot be ruled out. For a leading reference on the mechanism of Pd^{2+} catalyzed oxypalladation see: (a) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. Asian J.* **2008**, *3*, 473; (b) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036.
13. The cis di-substituted alkenes were prepared by the following sequence of reactions: (i) reaction of the lithio anion of (*S*)-methyl phenylsulfoxide with a 1-formyl alkyne to furnish an approximately equimolar mixture of propargylic alcohols, followed by (ii) stereoselective *cis* reduction using nickel boride to furnish readily separable allyl alcohols.



14. For the preparation of the alkene in entry 9 see: (a) Raghavan, S.; Mustafa, S. *Tetrahedron Lett.* **2008**, *49*, 3216; (b) The details of the preparation of the alkene in entry 12 will be disclosed elsewhere.
15. Methyl ketones are expected from terminal alkenes. Reversal of the regioselectivity has been observed in alkenes containing heteroatoms which probably coordinate with palladium intermediates, for example, see: (a) Bose, A. K.; Krishnan, L.; Wagle, D. R.; Manhas, M. S. *Tetrahedron Lett.* **1986**, *27*, 5955; (b) Lai, J.-Y.; Shi, X.-x.; Dai, L.-x. *J. Org. Chem.* **1992**, *57*, 3485; (c) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758; Also see (d) Ho, T.-L.; Chang, M. H.; Chen, C. *Tetrahedron Lett.* **2004**, *44*, 6955 for the abnormal Wacker oxidation of 1,5-dienes.
16. For the preparation of tri-substituted alkenes in entries 10 and 11 see: Raghavan, S.; Sreekanth, T. *Tetrahedron Lett.* **2008**, *49*, 1169.
17. For the preparation of the alkene in entry 13 see: Raghavan, S.; Rajender, A. *Tetrahedron Lett.* **2004**, *45*, 1919.
18. For the preparation of the alkene in entry 14 see: Ref. 4b.
19. For the preparation of alkene in entry 15 see: Raghavan, S.; Ramakrishna Reddy, S. *J. Org. Chem.* **2003**, *68*, 5754.
20. (a) Solladie and co-workers have utilized β-hydroxy-δ-ketosulfoxides as intermediates in a number of synthesis; see: Hanquet, G.; Colobert, F.; Lanners, S.; Solladie, G. *ARKIVOC* **2003**, *vii*, 328.; (b) Solladie, G.; Colobert, F.; Denni, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3081; (c) Solladie, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 7774; (d) Solladie, G.; Huser, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2679; (e) Solladie, G.; Dominguez, C. *J. Org. Chem.* **1994**, *59*, 3898.
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