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Palladium-Catalyzed Reactions of Enol Ethers: Access to Enals, Furans, and Dihydrofurans

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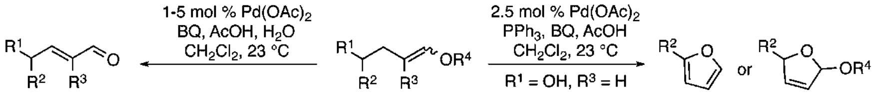
ABSTRACT

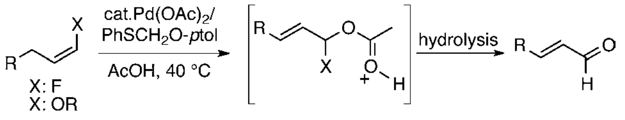


The palladium-catalyzed oxidation of alkyl enol ethers to enals, which employs low loadings of a palladium catalyst, is described. The mild oxidation conditions tolerate a diverse array of functional groups, while allowing the formation of di-, tri-, and tetrasubtituted olefins. The application of this methodology to intramolecular reactions of alkyl enol ethers containing pendant alcohols provides furan and 2,5-dihydrofuran products.

Investigations into allylic oxidation reactions of terminal olefins has dramatically increased over the past several years.[1] In contrast, recent literature reports of allylic oxidation reactions of internal olefins have not been as prevalent.[2] Our laboratory recently discovered that allylic oxidations of *cis*-vinyl silanes proceed with low catalyst loadings with high regio- and diastereoselectivity.[2c] Shortly thereafter, we began to investigate allylic oxidation reactions of alternative disubstituted olefins.

Initial expansion of this reaction began with investigating vinyl fluorides as substrates. Exposure of *cis*-vinyl fluoride to our standard allylic oxidation conditions provided the corresponding α,β-unsaturated aldehyde (Scheme 1). Although α,β-unsaturated aldehydes are synthetically useful compounds,[3] the inconvenience of preparing stereo- and regiochemically pure vinyl fluorides lessens the utility of this transformation.[4] We surmised that formation of the enal occurs by elimination of fluoride from the allyl acetate compound.[5] If this hypothesis is accurate, then the vinyl fluorine substrate could be replaced by more synthetically accessible substrates, such as vinyl ethers, which are easily accessed in a single step via Wittig olefination of the corresponding aldehyde.

Scheme 1. Proposed Conversion of Vinyl Fluorides to Enals



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[1] For selected examples, see: (a) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824. (b) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116. (c) Lin, B. -L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264. (d) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481. (e) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771. (f) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (g) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (h) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448.

[2] For selected examples, see: (a) Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 5518. (b) Pilarski, L. T.; Janson, P. G.; Szabó, K. J. *J. Org. Chem.* **2011**, *76*, 1503. (c) Check, C. T.; Henderson, W. H.; Wray, B. C.; Vanden Eynden, M. J.; Stambuli, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 18503. (d) Shi, E.; Shao, Y.; Chen, S.; Hu, H.; Liu, Z.; Zhang, J.; Wan, X. *Org. Lett.* **2012**, *14*, 3384. (e) Alam, R.; Pilarski, L. T.; Pershagen, E.; Szabó, K. J. *J. Am. Chem. Soc.* **2012**, *134*, 8778.

[3] For recent selected examples, see: (a) Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872. (b) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (c) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 1512. (d) Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466. (e) Albrecht, L.; Ransborg, L. K.; Gschwend, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 17886. (f) Maji, B.; Ji, L.; Wang, S.; Vedachalam, S.; Ganguly, R.; Liu, X. -W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8276. (g) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433. (h) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (i) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. (j) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345. (k) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076.

[4] Zhang, H.; Zhou, C.-B.; Chen, Q.-Y.; Xiao, J.-C.; Hong, R. *Org. Lett.* **2010**, *13*, 560 and references cited therein.

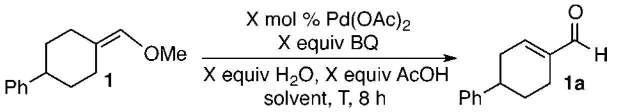
10.1021/ol3028994

The palladium-promoted preparation of α,β-unsaturated aldehydes is described throughout the literature. Seminal reports by Saegusa detailed the synthesis of α,β-unsaturated ketones from silyl enol ethers using 50 mol % $Pd(OAc)_2$ and 50 mol % benzoquinone (BQ) in acetonitrile, with only a single example of an enal.[6] Despite the high loading of palladium, the utility of the Saegusa reaction is demonstrated by its continued exploitation in natural product synthesis.[7] Following this report, Larock reported the use of DMSO as a ligand, which allowed catalyst loadings to decrease to 10 mol %,[8a] while Tsuji reported the formation of enals from silyl enol ethers using 5 mol % Pd and 2 equiv of diallyl carbonate.[8b] In 1992, Takayama reported the conversion of methyl enol ethers to α,β-unsaturated aldehydes.[9] However, this method required the use of 50−100 mol % of $Pd(OAc)_2$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ under basic conditions. An attempt to lower the catalyst loading to 10 mol % of $Pd(OAc)_2$ provided only a 49% yield of the unsaturated aldehyde. More recently, the conversion of aldehydes to α,β-unsaturated aldehydes was reported simultaneously by two different groups, using 5−10 mol % of palladium salt.[10] Unfortunately, overoxidation of the resulting enals to the corresponding dienes limited the substrate scope of the reaction. Despite the number of catalytic methods to produce enals or enones from enol ethers, conditions have not been discovered that employ low catalyst loadings, while still maintaining a broad reaction scope. Herein, we report the preparation of α,β-unsaturated aldehydes from alkyl enol ethers using uncoventionally low loadings of $Pd(OAc)_2$. In addition to this work, a new method that produces furans and dihydrofurans from intramolecular reactions of alkyl enol ethers is reported.

Initial investigations commenced with exposing a diastereoemeric mixture of (4-methoxymethylene)cyclohexyl benzene (**1**) in AcOH with BQ in the absence of $Pd(OAc)_2$ to ensure that the reaction does not proceed in the absence of catalyst (Table 1, entry 1). Addition of 5 mol % of $Pd(OAc)_2$ in the presence of an external sulfur ligand ((phenyl(2-*p*-tolyloxy)ethyl)sulfane) with BQ at 40 °C provided the desired enal in 39% yield (entry 2). Removal of the ligand had no effect on the reaction outcome (entry 3). Most surprising was that the addition of water to the catalyst system dramatically increased the reaction yield to 87% (entry 4). More importantly, when the catalyst loading was lowered to 2 mol %, the reaction yield remained at 85% (entry 5). Two other interesting observations were made: (i) no reaction occurred when starting from an aldehyde; (ii) the vinyl ether slowly hydrolyzes under the reaction conditions, which makes the aldehyde the major side product in the reaction.

In order to avoid employing neat acetic acid, a solvent screen was conducted (entries 6−10). Several solvents allowed the reaction to proceed in good to high yields. Although acetone and dioxane were competent solvents for this reaction, we employed dichloromethane because acetone and dioxane are more difficult to keep dry.

Table 1. Screening of Reaction Conditions[a]



entry	$Pd(OAc)_2$ (mol %)	*T* (°C)	BQ	H_2O	AcOH	solvent	yield (%)
1	0	40	2	0	–	AcOH	0
2	5	40	2	0	–	AcOH	39[b]
3	5	40	2	0	–	AcOH	38
4	5	23	1.2	1.1	–	AcOH	87
5	2	23	1.2	1.1	–	AcOH	85
6	2	23	1.2	1.1	4	DCM	81
7	2	23	1.2	1.1	4	toluene	74
8	2	23	1.2	1.1	4	acetontrile	42
9	2	23	1.2	1.1	4	dioxane	77
10	2	23	1.2	1.1	4	acetone	78

[a] Yields are determined by GC using an internal standard. All table values are equivalents unless noted. [b] 5 mol % of (phenyl(2-*p*-tolyloxy)-ethyl)sulfane was added to the reaction.

With optimized conditions in hand, we proceeded to examine the scope of this process (Table 2). Alkyl substrates (entries 1−3) gave good yields, and the mild conditions allowed tolerance of silyl ethers, acetate esters, and vinyl silanes (entries 4−6). Methylene cyclohexanes (entries 7 and 8) proceeded to give high yields of the enal products, along with the nitrogen containing substrates in the form of phthalimide and succinimide (entries 9 and 10). Tri- and tetrasubstituted enals could be formed in good yields, albeit at higher temperatures and/or cataylst loadings (entries 11 and 12). Methyl enol ether (**13**), derived from citronellal, produced the desired enal product in 72% yield. This compound is an intermediate in Mori's synthesis of stellettadine A.[11] Boc-protected indolyl enol ether (**14**) also gave a good yield of the corresponding enal product. Because of the success of converting enol ethers to enals with low loadings of palladium, we investigated potential intramolecular reactions with alcohol nucleophiles, which may proceed via a similar mechanism.

Our initial screenings for the formation of dihydrofurans started with enol ether (**15**), which quickly aromatizes via

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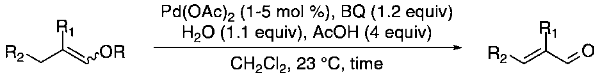
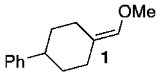
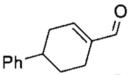
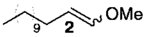
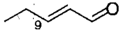
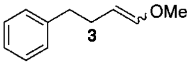
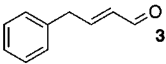
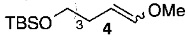
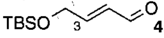
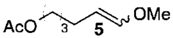
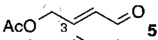
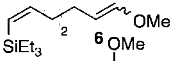
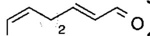
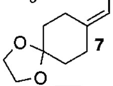
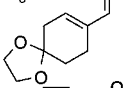
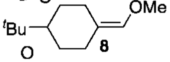
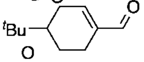
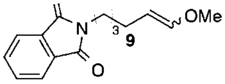
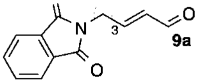
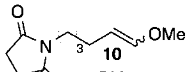
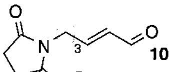
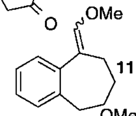
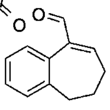
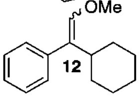
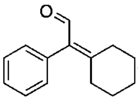
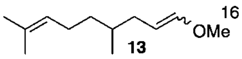
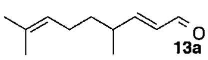
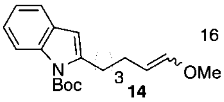
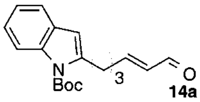
(10) (a) Gao, W.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. *Chem. Sci.* **2012**, *3*, 883. (b) Diao, T.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887.

(11) Takikawa, H.; Nozawa, D.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 657.

Table 2. Conversion of Enol Ethers to Enals[a]

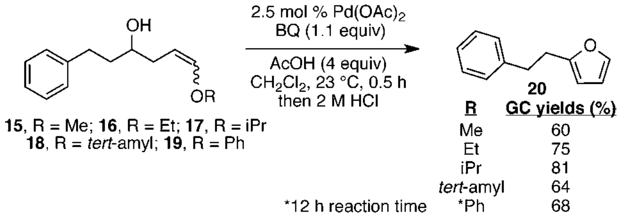


entry	enol ether	time (h)	Pd(mol %)	product	yield(%)
1	 **1**	8	2	 **1a**	80
2	 **2**	4	2	 **2a**	65
3	 **3**	4	1	 **3a**	63
4	 **4**	8	2.5	 **4a**	57
5	 **5**	12	1	 **5a**	79
6	 **6**	24	4	 **6a**	67
7	 **7**	18	2.5	 **7a**	76
8	 **8**	6	2	 **8a**	90
9	 **9**	7	2.5	 **9a**	72
10	 **10**	8	2.5	 **10a**	72
11	 **11**	16	5	 **11a**	73[b]
12	 **12**	96	10	 **12a**	57[c]
13	 **13**	16	5	 **13a**	72
14	 **14**	16	5	 **14a**	44

[a] Yields are an average of two one mmol reactions. [b] Reaction was conducted in neat AcOH at 40 °C. [c] Reaction was conducted in neat AcOH at 23 °C.

an acid catalyzed elimination of the resulting 2,5-dihydrofuran cyclic acetal. As a result, the crude reaction mixtures were treated with 2 M HCl to aid in the isolation of C2-substituted furan.[12] Unlike the reactions of enol ethers that produced α,β-unsaturated aldehydes, the yields of reactions of 4-hydroxy-1-enol ethers were controlled by the alkyl group on the enol. The optimal group was the enol ether containing isopropyl, which gave an 81% yield of desired furan (Scheme 2). Smaller groups, such as methyl (60% yield) or ethyl (75% yield), and larger groups such as *tert*-amyl (64% yield of furan) failed to give higher yields of furan.

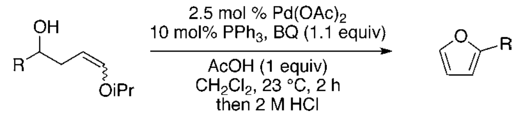
Scheme 2. Effect of Alkyl Enol Identity on Furan Yield

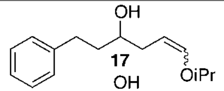
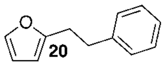
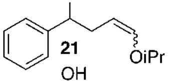
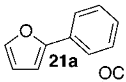
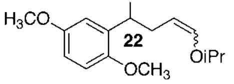
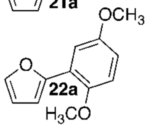
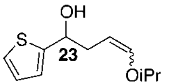
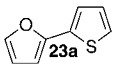
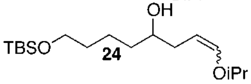
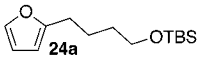


R	GC yields (%)
Me	60
Et	75
iPr	81
tert-amyl	64
*Ph	68

The phenyl vinyl ether was also used, but the reaction was sluggish and only gave a 68% yield of furan. Although the reactions are conducted under mildly acidic conditions, there does not appear to be a trend between the rate of hydrolysis of enol ethers and the yield of furans in the reaction.[13]

Table 3. Conversion of Enol Ethers to Furans[a]



entry	enol ether	product	yield(%)
1	 **17**	 **20**	82
2	 **21**	 **21a**	75
3	 **22**	 **22a**	89
4	 **23**	 **23a**	72
5	 **24**	 **24a**	78[b]

[a] Yields are an average of two 1 mmol reactions. [b] Reaction conducted for 6 h.

Further optimization for the formation of furans showed that the amount of acetic acid could be lowered from 4 to 1 equiv and that a catalytic quantity of triphenylphosphine was beneficial for the yield of the reaction. The requirement of external phosphine likely extended the reaction time, as 2 h were required for the reaction to reach completion. Good yields of 2-substituted furans could be obtained from 4-hydroxy-1-enol ethers containing alkyl (entries 1 and 5), aromatic (entries 2 and 3), and heteroaromatic (entry 4) substituents (Table 3).

The optimized reaction conditions are only mildly acidic, thereby allowing 2,5-dihydrofuran products to be isolated in good yields (Table 4). Reactions with secondary

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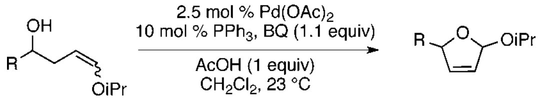
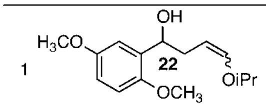
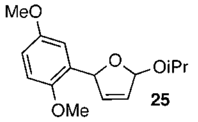
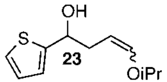
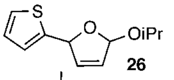
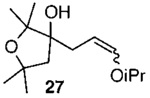
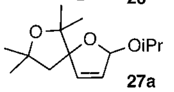
(12) For some recent methods to prepare furans, see: (a) Kramer, S.; Madsen, J. L. H.; Rottlander, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758. (b) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624. (c) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500.

(13) (a) Jones, D. M.; Wood, N. F. *J. Chem. Soc.* **1964**, 5400. (b) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228.

Table 4. Conversion of Enol Ethers to 2,5-Dihydrofurans[a]



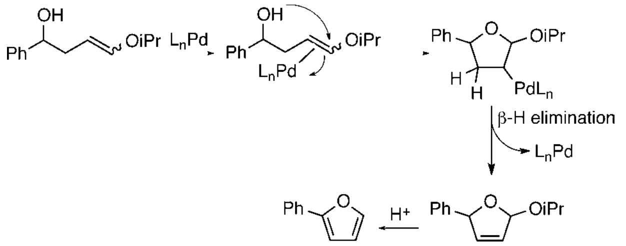
entry	enol ether	product	yield(%)
1	 22	 25	75[b]
2	 23	 26	89[b]
3	 27	 27a	72[c]

[a] Yields are an average of two 1 mmol reactions. [b] Product isolated as a 1:1 mixture of diastereomers. [c] Product isolated as a 3:1 mixture of diastereomers.

alcohols must be closely monitored in order to quench the reaction after cyclization is complete, which minimizes the amount of furan product formed. 4-Hydroxy enol ethers containing tertiary alcohols also underwent cyclization to the 2,5-dihydrofuran (entry 3). Reissig had previously shown that alkyl enol ethers could be converted to 2,5-dihydrofurans using 50 mol % of palladium under basic conditions.[14]

A proposed mechanism for the formation of 2,5-dihydrofurans and furans is shown in Scheme 3. Initial coordination of the enol ether to palladium is followed by attack of the alcohol onto the coordinated enol, which forms the corresponding alkylpalladium complex. β-Hydride elimination from the alkylpalladium complex would produce the 2,5-dihydrofuran and regenerate the catalyst. The furan product is then obtained by aromatization of the dihydrofuran compound during an acidic aqueous workup.

Scheme 3. Proposed Reaction Pathway for Furan and Dihydrofuran Formation



In conclusion, we have demonstrated an efficient conversion of alkyl enol ethers to α,β-unsaturated aldehydes. The catalyst loadings are significantly lower in most cases than previously reported Saegusa-type oxidations of enals, while the mild reaction conditions tolerate a broad array of functional groups. The formation of dihydrofurans and furans expands the utility of alkyl enol ethers in transition metal catalysis.

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Supporting Information Available. Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Hölemann, A.; Reissig, H.-U. *Synthesis* **2004**, 1963.

The authors declare no competing financial interest.