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Catalytic Oxidation of Homoallylalcohols to α-Alkoxytetrahydrofurans by a Pd-Nitro Complex and Molecular Oxygen

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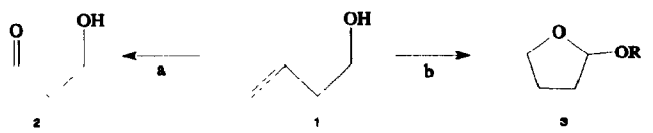
Abstract: Various homoallylalcohols were highly regioselective oxidized with molecular oxygen at the terminal carbon to afford cyclic acetals (α-alkoxytetrahydrofurans) using $PdNO_2Cl(CH_3CN)_2$ as a catalyst in the presence of $CuCl_2$ and t-butanol or isopropanol.

Catalytic oxidation of substituted olefins with molecular oxygen has attracted considerable attention[1] in order to avoid oxygen atom donors like hypochlorite, iodosylbenzene and peroxides and to have direct access to epoxides[2], alcohols and phenols[3], aldehydes[4] and ketones[5]. Considerable activity is devoted to mimicking oxygenases using O_2 as oxidant.[6,7] Furthermore the indirect use of oxygen in Wacker type oxidations with $PdCl_2$ of olefins to ketones (scheme 1, route a) has extensively been studied.[8] More recently palladium(II) catalyzed intramolecular cyclizations of hydroxyalkenes provide an atractive means of olefin functionalization.[9] For instance the oxidative formation of cyclic acetals, which are good precursors for lactones[10], the cyclization of a diol as a short way to both natural and unnatural Frontalin and the formation of aminoalcohols[12] illustrate nicely their potential in the synthesis of natural products. Control of the stereoselectivity might be achieved by the presence of stereogenic centers in the hydroxy alkenes.

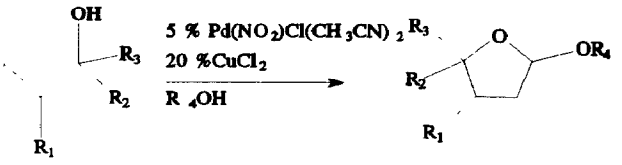
Earlier[4,13] we reported the use of a Pd-nitro complex capable of converting α-alkenes into aldehydes (60-70 % selectivity) or methyl ketones (> 90 % selectivity) by using molecular oxygen.[4] Now we wish to report the effective oxidation of 1-alken-4-ols to α-alkoxytetrahydrofurans (up to 100 % selectivity and high yields) by $PdNO_2Cl(CH_3CN)_2$ in the presence of $CuCl_2$, O_2 in t-butanol (t-BuOH) or isopropanol (IPA), (scheme 1, path b). In addition the first selective oxidation of homoallylalcohols without the necessity of directing substituents at the allylic position is described.[10]



Scheme 1 a. Wacker type oxidation to methylketones
b. oxidative cyclization to alkoxytetrahydrofurans

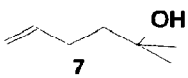
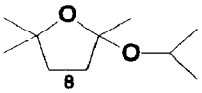
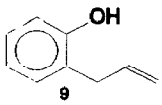
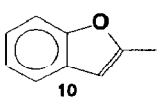
It appears that competing Wacker type oxidation to methylketones can be largely avoided.

The oxidation reactions were performed at 30°C using an in situ prepared Palladium-nitro catalyst under an O_2 atmosphere (Scheme 1, route b). The results of the oxidation reactions are given in table 1.

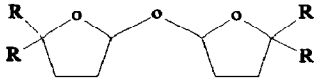


Scheme 2

TABLE: 1[a]

Entry	Homoallylalcohol 4			Solvent	React. time.	Product 5 GC Yield/%
	R_1	R_2	R_3	(R_4OH)	(h)	(isolated Yield/%)
1	H	H	H	IPA	3	26[b] (2 70%)
2	H	H	H	t-BuOH	16	94[b] (30)
3	H	CH_3	CH_3	IPA	2	100[b] (50)
4	H	CH_3	CH_3	t-BuOH	2	100[b] (80)
5	H	CH_3	CH_3CH_2	IPA	100	95 (55)
6	H	CH_3	CH_3CH_2	t-BuOH	40	100 (70)
7	H	Phenyl	Phenyl	IPA	16	80 (70)
8	H	Phenyl	Phenyl	t-BuOH	4	75 (32)
9	CH_3	CH_3	CH_3	IPA	1	99 (60)
10	CH_3	CH_3	CH_3	t-BuOH	2	96 (70)
11	 7			IPA	1	56 (40)  8
12	 9			t-BuOH	2.5	66 (60)  10

a: In a typical procedure the catalyst was made in situ by dissolving 5 mol% $PdNO_2Cl(CH_3CN)_2$, 20 mol% $CuCl_2$ in IPA or t-BuOH and stirred under oxygen at 55°C for 2 hours. After cooling the reaction mixture to 30°C, 1 g. of substrate together with an internal standard (isooctane) was added. The reaction was monitored with GC. Most reactions were completed within 4 hours. Work up was done by filtration (Al_2O_3) of the catalyst followed by extraction with pentane/water and molecular distillation under reduced pressure. All products showed IR, ^1H, ^{13}C-NMR, MS data in accordance with the structures; 2-t-butoxytetrahydrofuran was prepared independently[14]. b: during isolation the product partly dimerizes to bisdihydrofuran 6.



6 (R=H,CH_3)

Most oxidations are highly selective at the terminal carbon. Thus the oxidation of 3-buten-1-ol in t-BuOH yields α-t-butoxytetrahydrofuran and all tertiary homoallylalcohols are oxidized to α-alkoxytetrahydrofurans. It should be noted that, except for t-homoallylalcohols, selectivities are higher in t-butanol as solvent. (c.f. ref. 13 for the t-butanol effect) When the carbon chain of the hydroxyalkene is lengthened by one carbon there is no selective oxidation at the terminal carbon. The formation of a six membered ring is less favourable than the formation of a five membered ring. Therefore, 2-methyl-5-hexen-2-ol and 2-allylphenol are not oxidized to α-alkoxypyrans but only partly converted into the corresponding furans (table 1, entries 11, 12).

The catalyst is still active after one run. The activity of the catalyst was investigated in several subsequent runs using 3,4-dimethyl-1-penten-4-ol as the substrate. Typically 1 g. of substrate was added to the catalytic system (3 mol % of catalyst) and after complete conversion another gram of substrate was added and this was repeated once more. The observed conversions were 100% and 95% after the second and third run respectively showing that the catalyst is still active. However, small amounts of unidentified side products were formed after more than three runs. For comparison a number of oxidation reactions with $PdCl_2(CH_3CN)_2$, $CuCl_2$ in t-BuOH using molecular oxygen were performed. A selective oxidation of 4-methyl-1-penten-4-ol to 5,5-dimethyl-2-t-butoxytetrahydrofuran was observed but the oxidation of 3,4-dimethyl-1-penten-4-ol was very slow and did not give complete conversion.

Nokami and co-workers[10] found that a substituent on the allylic position (R_1 = alkyl, alkoxy, alkoxycarbonyl, sulfonyl) is necessary to achieve selective oxidation (scheme 1, path b) using a Wacker type system ($PdCl_2$, p-benzoquinone in wet DMF). The absence of a substituent on the allylic position (4, R_1=H) afforded a methylketone (scheme 1, path a). Inomata and co-workers[15] found that a coordinating group is necessary to afford selective oxidation, i.e. a tosyl group was used on the allylic position (4, R_1=Ts) with a $PdCl_2$, $CuCl_2$, N,N,N',N'-tetramethylurea, ethyl acetate based system in methanol under nitrogen to oxidize homoallylalcohols to cyclic acetals.

Our results clearly show that a substituent at the allylic position or a "directing group" is not required for the highly selective oxidation of homoallylic alcohols to α-alkoxytetrahydrofurans with O_2 as the oxidant using a Palladium-nitro catalyst.

In a further extension the oxidative cyclization of allyl-substituted-α-hydroxyesters (4, R_3=CO_2Et) was investigated. The results of this investigation are summarized in table2. The starting materials are readily available by allylation of α-hydroxyesters.[16]

TABLE 2[a]

Entry	Homoallylalcohol 4[b]			Solvent	React. time. (h)	Product 5 Yield (%)
	R^1	R^2	R^3			
1	H	CH_3	COOEt	IPA	2	60
2[c]	H	CH_3	COOEt	t-BuOH	18	63
3[d]	H	Phenyl	COOEt	IPA	2	70
4	H	Phenyl	COOEt	t-BuOH	20	>90

a: Typical procedure, see footnote table 1. b: racemate. c: 1 mol% of catalyst. d: 4 mol % of catalyst.

All homoallyl esters are oxidized to the α-alkoxytetrahydrofurans and only small amounts of methylketones are formed. However, the reactions in t-BuOH are significantly slower, but also more selective compared to the reactions in IPA. Ester substituted α-alkoxytetrahydrofurans are attractive precursors for substituted lactones and carbohydrate derivatives.

The oxidative cyclization by a palladium-nitro based catalyst proved to be an attractive synthetic reaction because: (1) less catalyst is required compared to related Wacker systems, (2) a very high selectivity and (3) good yields for a broad range of substrates are obtained. The availability of enzymatic methods for the preparation of optically active allylsubstituted α-hydroxyesters[16] makes this catalytic oxidation reaction particularly attractive for the asymmetric synthesis of substituted tetrahydrofurans.

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