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Palladium Catalyzed Stereospecific Allylic Substitution of 5-Acetoxy-2(5*H*)-furanone and 6-Acetoxy-2*H*-pyran-3(6*H*)-one by Alcohols

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Abstract:

Enantiomerically pure 5-acetoxy-2(5*H*)-furanone and 6-acetoxy-2*H*-pyran-3(6*H*)-one are converted into 5-alkoxy-2(5*H*)-furanones and 6-alkoxy-2*H*-pyran-3(6*H*)-ones by a palladium catalyzed allylic substitution. The reactions proceed with nearly complete retention of configuration, resulting in products with ee's of 95%.

The 2(5*H*)-furanone and 3(6*H*)-pyranone structures are frequently found in natural products.[1] These have a broad range of biological activities. In addition furanones and pyranones have served as intermediates in synthesis of a variety of products.[2] In recent years especially chiral alkoxy-furanones and alkoxy-pyranones have attracted considerable attention. Using *d*- or *l*-menthol and *d*-pantholactone as chiral auxiliaries, the corresponding 5-menthyloxy-2(5*H*)-furanones[3] and 6-pantholactoxy-2*H*-pyran-3(6*H*)-one[4] are readily accessible and have been used as multifunctional chiral synthons in a variety of asymmetric transformations, including routes to β-lactams, amino alcohols, decalins and lignans.[5]

A catalytic route to chiral non-racemic 5-alkoxy-2(5*H*)-furanones, not relying on a stoichiometric use of chiral auxiliaries, would be a valuable extension and considerably enhance their practicality in asymmetric synthesis.

We now report a new methodology for the preparation of optically active 5-alkoxy-2(5*H*)-furanones and 6-alkoxy-2*H*-pyran-3(6*H*)-ones by palladium catalyzed allylic substitutions of (*S*)-(+)-5-acetoxy-2(5*H*)-furanone and (*R*)-(-)-6-acetoxy-2*H*-pyran-3(6*H*)-one. Despite the widespread use of palladium catalyzed nucleophilic substitutions of allylic

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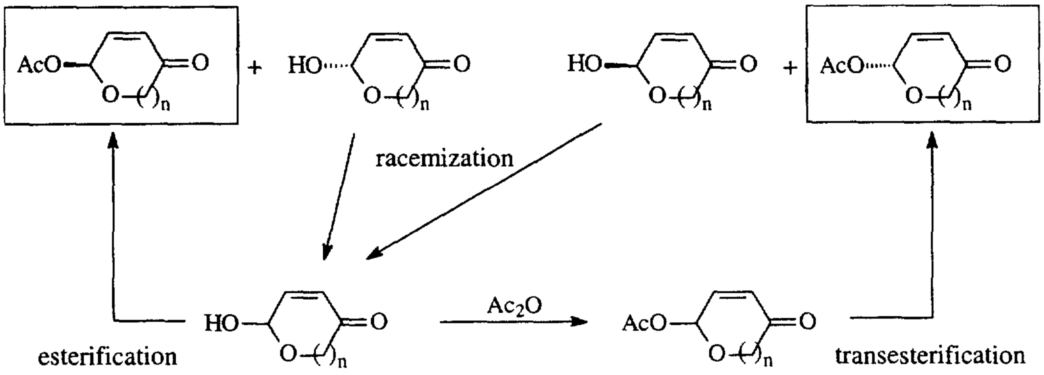
substrates in organic synthesis[6] only a few examples have been reported of the use of alcohols,[7] probably because they are generally considered poor nucleophiles. Recently the use of alcohols in palladium catalyzed allylic substitutions of acyloxypyrrolinones was reported.[8]

During our previous investigations we have found a simple and efficient enzymatic methodology to obtain enantiomerically pure acyloxy-furanones and acyloxy-pyranones. For instance both enantiomers of 5-acetoxy-2(5*H*)-furanone (**3**) can be obtained by the same enzyme (lipase R) using either an esterification or a transesterification (scheme 1).[9]



1 (n=0)
2 (n=1)

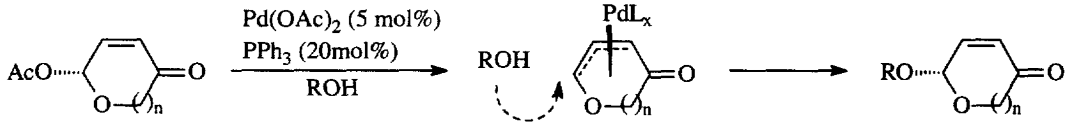
3 (n=0)
4 (n=1)

Scheme 1

Although 5-acetoxy-2(5*H*)-furanone is a valuable chiral synthon, as demonstrated in the total synthesis of (-)-acetomycin,[10] the high sensitivity of the 5-acyl-substituent in subsequent C-C bond formation is an important incentive for the alkoxy-furanone and alkoxy-pyranone formation described here.

When a solution of (*S*)-(+)-**3** (ee > 98%) in MeOH is stirred at room temperature for 3 h in the presence of 5 mol% $Pd(OAc)_2$ and 20 mol% PPh_3, complete conversion to (*S*)-(+)-5-methoxy-2(5*H*)-furanone (**7a**) with 95% ee is observed (scheme 2, table 1, entry 1). Enantiomerically pure **3** is thus converted into the corresponding 5-methoxy-2(5*H*)-furanone with nearly complete retention of configuration, presumably via allylpalladium intermediate **5**. The absolute configurations of 5-alkoxy-2(5*H*)-furanones have been determined by a simple circular dichroism method.[11]

Other alcohols like EtOH and i-PrOH can be used as nucleophile resulting in the corresponding furanones **7b** and **7c** with high ee. In these substitutions the nucleophile is used as the solvent. Addition of other solvents leads into a strong decrease in reaction rate. For instance it was found that the substitution of **3** with EtOH in THF, DMF or MeCN as the solvent gave conversions < 10% after 24 h at room temperature. The reactions with EtOH and i-PrOH at room temperature are much slower than with MeOH (entries 3, 4 and 7) and it is evident that sterically more demanding alcohols react slower than less bulky ones. An increase in temperature leads to much faster substitution (entries 5 and 8), but prolonged reaction times (entries 6 and 9) resulted in depletion of ee.



3 (n=0)
4 (n=1)

5 (n=0)
6 (n=1)

7 (n=0)
8 (n=1)

a: R = Me
b: R = Et
c: R = i-Pr

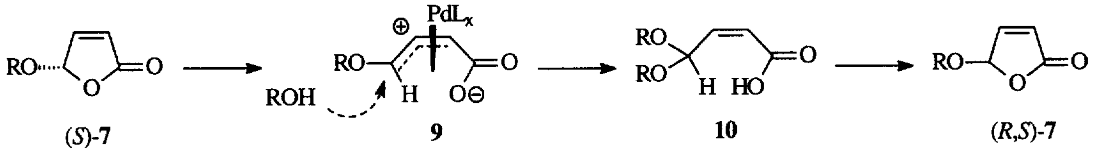
Scheme 2

table 1: Alkoxy-furanones and Alkoxy-pyranones Obtained by Palladium Catalyzed Substitution.

Entry	Starting material	ROH	Product	Temperature (°C)	Time (min.)	Conversion[a] (%)	Ee of product[b] (%)
1	**3**	MeOH	**7a**	20	180	100	95
2	**3**	MeOH	**7a**	20	210	100	89
3	**3**	EtOH	**7b**	20	210	65	92
4	**3**	EtOH	**7b**	20	1200	100	15
5	**3**	EtOH	**7b**	40	15	100	96
6	**3**	EtOH	**7b**	40	30	100	69
7	**3**	i-PrOH	**7c**	20	2640	50	95
8	**3**	i-PrOH	**7c**	40	120	81	95
9	**3**	i-PrOH	**7c**	40	180	100	91
10	**4**	MeOH	**8a**	20	60	100	95
11	**4**	MeOH	**8a**	20	120	100	95
12	**4**	EtOH	**8b**	20	15	100	96
13	**4**	EtOH	**8b**	20	60	100	96
14	**4**	i-PrOH	**8c**	20	30	80	96
15	**4**	i-PrOH	**8c**	20	60	100	96

a) Conversions are measured with a Hewlet Packard 5890 GC, equipped with a 30.0 m x 250 μm x 1.00 μm capillary column coated with dimethylpolysiloxane, using n-decane as internal standard. b) Ee's are measured with a Hewlet Packard 6890 GC system equipped with a CP cyclodextrine-B-2,3,6-M-19 capillary column (50.0 m x 250 μm x 0.25μm) (**7a**, **7b**, **7c**) or a FS lipodex C capillary column (50.0 m x 250 μm x 0.25 μm) (**8a**, **8b**, **8c**).

The observed partial racemization at longer reaction times (entry 2, 4, 6) might be due to ring opening of the furanone as is shown in scheme 3. The 5-alkoxy-substituted furanones **7** still contain an acyloxy-allyl moiety and can therefore undergo ring-opening, albeit at a lower rate than elimination of the acyloxy-moiety in **3**, to form allyl-Pd intermediate **9**. Subsequent reaction with the alcohol provides achiral acetal **10** which upon ring closure furnishes racemic 5-alkoxy-2(5*H*)-furanone (**7**). Alternatively depletion of the ee might be caused by loss of the stereochemical integrity of allyl palladium intermediates formed from (*S*)-**7**, by the intermediacy of a furan-derivative (homoenolization of **7**), or by racemization due to the nature of the acid-labile acetal group.



Scheme 3

Next the palladium catalyzed allylic substitution of (*R*)-(+)-6-acetoxy-2*H*-pyran-3(6*H*)-one (**4**) was examined.[12] Much to our delight using catalytic amounts of $Pd(OAc)_2$ in the presence of PPh_3 (20 mol%) highly chemo-and stereospecific substitution was observed. For MeOH, EtOH and i-PrOH 100% conversion and ee > 95% was reached within 1 h at room temperature (table 1, entries 10-15). Notable features of the allylic substitutions of pyranone **4** compared to furanone **3** are the much shorter reaction times needed to reach full conversion and the fact that no racemization is observed at longer reaction times.

In conclusion we have shown that enantiomerically pure 5-acetoxy-2(5*H*)-furanone (**3**) and 6-acetoxy-2*H*-pyran-3(6*H*)-one (**4**) can be converted to 5-alkoxy-2(5*H*)-furanones (**7a-c**) and 6-alkoxy-2*H*-pyran-3(6*H*)-ones (**8a-c**), respectively, with nearly complete retention of configuration. By combination of the lipase catalyzed (trans)esterification and the palladium catalyzed allylic substitution a chemoenzymatic route to optically active alkoxy-furanones and alkoxy-pyranones is available.

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