5-Alkoxy-2(5H)-furanones in asymmetric synthesis

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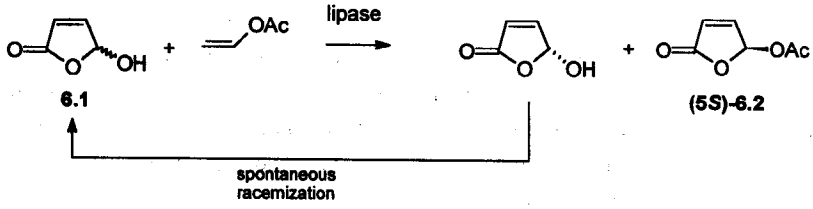
Chapter 6

Asymmetric synthesis of 5-alkoxy-2(5*H*)-furanones

6.1 Introduction

5-Alkoxy-2(5*H*)-furanones are versatile chiral synthons. They have been used in a number of total syntheses of enantiomerically pure natural products as described in Chapter 1. Although the chiral auxiliary based method has been used most frequently to obtain enantiomerically pure 5-alkoxy-2(5*H*)-furanones, other routes towards these starting materials in enantiomerically pure form are highly wanted. In chapter 1.6 the synthesis of enantiomerically pure 5-acyloxy-2(5*H*)-furanones via lipase mediated acylation of racemic 5-hydroxy-2(5*H*)-furanone was described. Because of the facile racemization of the starting material, combined with the enantioselectivity of the enzymatic conversion, a second order asymmetric transformation takes place, resulting in good yields (up to 90%) and excellent e.e.'s (>99%) of the product (Scheme 6.1).[1] Preliminary results on palladium catalyzed conversions of these optically active 5-acyloxy-2(5*H*)-furanones to 5-alkoxy-2(5*H*)-furanones will be described in section 6.7.



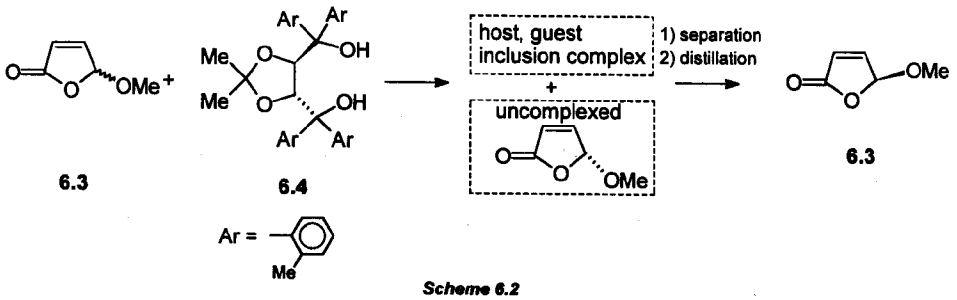
Scheme 6.1

Another way to obtain optically active 5-alkoxy-2(5*H*)-furanones is by chemical kinetic resolution. The cinchona alkaloid catalyzed addition of aromatic thiols to 5-alkoxy-2(5*H*)-furanones results in kinetic resolution of the furanone. When quinidine was used as catalyst in the reaction of 5-methoxy-2(5*H*)-furanone with 4-t-butylthiophenol, 5-methoxy-2(5*H*)-furanone was recovered in 21% yield and with 91% e.e.[2] A second approach, which involves resolution of 5-alkoxy-2(5*H*)-furanones via complexation with a chiral host will be described in the next sections.

6.2 Host-guest chemistry

An elegant method to resolve a racemic mixture is by forming host-guest inclusion complexes with a chiral host (Scheme 6.2).[3] Liberation of the guest from the complex gives enantiomerically enriched guest compounds. Several 5-alkoxy-2(5*H*)-furanones have been

resolved by the host-guest complexation method, using tartaric acid derived hosts, such as **6.4**.[4]

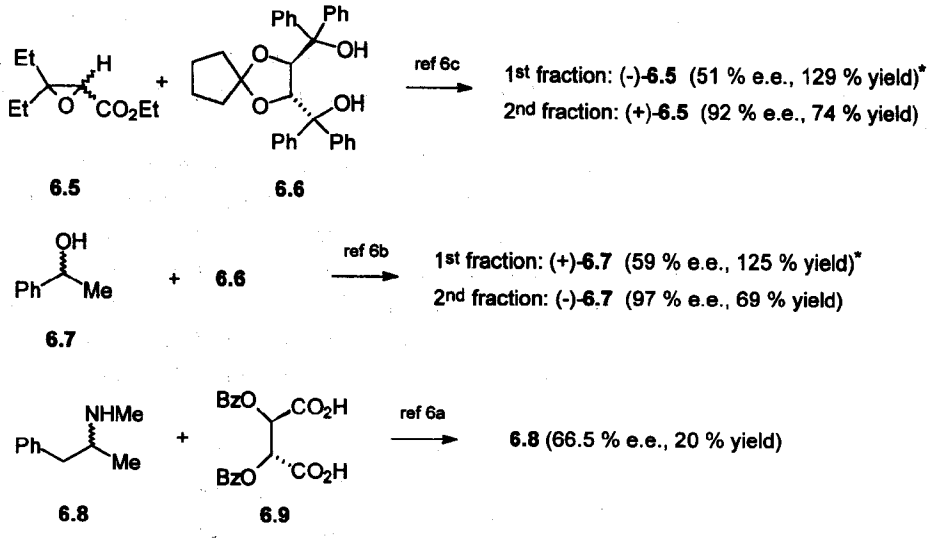


Scheme 6.2

Single crystal X-ray analysis of a 1:1 host-guest complex of **6.3** and **6.4**, revealed that the main interaction between the host and the guest molecules is a hydrogen bond between a hydroxyl group of the host and the carbonyl group of the guest molecule. Two methods were used for the resolution; crystallization of a mixture of host and guest from a mixture of hexane/toluene afforded crystalline 1:1 inclusion complexes. Isolation of the crystals by filtration and removal of the guest from the crystals by distillation gave enantiomerically enriched 5-methoxy-2(5*H*)-furanone. Alternatively, when a suspension of the host and guest in water are mixed in the presence of a small amount of phase transfer catalyst, the host-guest complex is precipitated. After isolation and subsequent liberation of the guest from this complex by distillation, the 5-methoxy-2(5*H*)-furanone is obtained with high optical purity. The two methods are not always complementary and for some combinations of host and guest only one of the two methods is effective.[4]

6.3 Resolution by fractional distillation from host-guest complexes

Simple fractional distillation of a mixture of host and guest is a conceivable method to perform a resolution.[5] When the interactions between host and guest are strong enough, mixing will result in formation of an inclusion complex. One enantiomer of the guest will have better interactions with the chiral host and is stronger bound. The other enantiomer can be removed from the complex by careful distillation, leaving the chiral host-guest complex between the host and the 'right' enantiomer intact. At more elevated temperatures the better fitting enantiomer can be distilled from the complex. This method allows resolution of a racemate, without isolation of the chiral host-guest complex. Furthermore, the host is recovered unchanged afterwards and can be reused. Few examples are known (Scheme 6.3), wherein a chiral host and a racemic guest are mixed, either in the solid state, or as a suspension in hexane, followed by fractional distillation of the guest compound.[6]



** maximum yield of one enantiomer is 100 % at 100 % e.e.*

Scheme 6.3

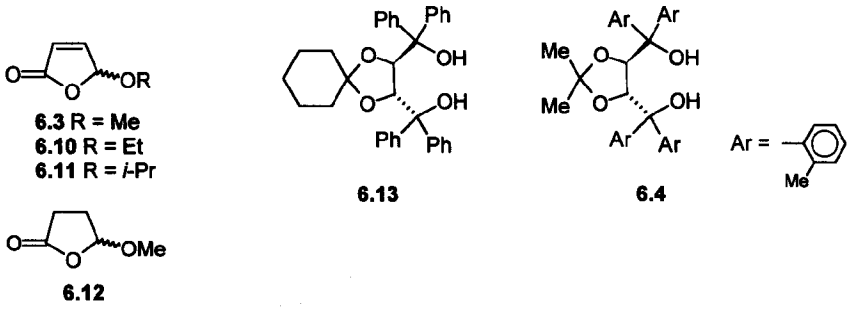
Three conditions have to be met in order to obtain successful resolution with this method: (i) the host and guest must form a stable inclusion complex (ii) there must be a high degree of chiral discrimination in formation of the host-guest complex (iii) the guest has to be volatile enough, in order to be distilled at temperatures below the melting point of the host-guest complex.

6.4 Resolution of 5-alkoxy-2(5*H*)-furanones by fractional distillation from host-guest complexes

It appeared to us that the experimentally simple fractional distillation method would be applicable for the resolution of a racemic mixture of 5-alkoxy-2(5*H*)-furanones, in addition to the two methods described in section 6.2. To examine whether this method could be applied to 5-alkoxy-2(5*H*)-furanones we tried to resolve racemic 5-methoxy-2(5*H*)-furanone (**6.3**) by mixing it thoroughly (using a pestle and mortar) with 1 equivalent of **6.4**. Subsequent bulb-to-bulb distillation of the uncomplexed enantiomer (75°C, 10 mmHg) gave a first fraction of enantiomerically enriched **6.3** (45% yield, 46% e.e.). Distillation of the

residue (150°C, 10 mmHg) afforded a second fraction of **6.3**, which was enriched in the other enantiomer (46% yield, 47% e.e.). This result encouraged us to investigate the method more thoroughly and it was found that dissolving a 1:2 mixture of host and guest in ether, followed by concentration in vacuo, provided a crystalline solid. Subsequent bulb-to-bulb distillation (75°C, 10 mmHg) afforded a first fraction of **6.3** (48% yield, 51% e.e.). Distillation of the residue at 150°C, 10 mmHg gave a second fraction of **6.3** (43% yield, 52% e.e.).

The enantiomeric purities of the products depended on the ratio of host and guest and the best result was obtained for a 1:4 ratio (see Table 6.1, entry 4), furnishing 5-methoxy-2(5*H*)-furanone (**6.3**) in 74% e.e. after one distillation. It should be noted that the results of these experiments are not very reproducible and the optimal results of several runs are presented here; usually deviations from these optimal yields and e.e.'s are less than 10 %. It appears that the crystallization of the complex after evaporation of ether (method A) is a critical process, leading to the variations in the results. Also incomplete heat transfer during



Scheme 6.4

Table 6.1: Optical resolution of 5-methoxy-2(5*H*)-furanone (**6.3**) by fractional distillation from a host-guest complex with chiral host **6.4**

Entry	ratio	Method	fraction 1 (Yield[b] (%), T(°C),P(mmHg))	e.e.[a] (%) (config.)	fraction 2 (Yield (%), T(°C),P(mmHg))	e.e.[a] (%) (config.)
1	1:1	B	45 (75^{10})	46 (*R*)	46 (150^{10})	47 (*S*)
2	1:1	A	13 ($66^{0.1}$)	66 (*R*)	84 ($150^{0.1}$)	17 (*S*)
3	1:2	A	48 (75^{10})	51 (*R*)	43 (150^{10})	52 (*S*)
4	1:4	A	80 (80^{10})	14 (*R*)	19 (150^{10})	74 (*S*)
5	3:4 (6.3 of 52 % e.e.)	A	35 (75^{10})	13 (*R*)	50 (150^{10})	81 (*S*)

[a] *e.e. was determined by GC on a capillary column coated with CP-cyclodextrin-B-2,3,6-M-19*
Method A: host and guest were dissolved in ether (3mL /mmol) and concentrated in vacuo.
Method B: host and guest were mixed by grounding with a pestle and mortar.
[b] *Based on maximum 50 % yield at 100 % e.e.*

fractional distillation may cause irregularities.

In Table 6.1 results of the resolution of 5-methoxy-2(5*H*)-furanone (**6.3**) with chiral tartaric acid derived host **6.4** are shown. Repeating the fractional distillation with partially enriched 5-methoxy-2(5*H*)-furanone (**6.3**, 52 % e.e.) allows a further increase of the enantiomeric purity of the substrate (Table 6.1, Entry 5). Thus when a solution of **6.3** (52% e.e) and **6.4** in ether in a molar ratio of 4:3 was concentrated in vacuo, a crystalline material was obtained. Distillation at 75°C, 10 mmHg afforded **6.3** (35% yield, 13% e.e.) and distillation of the residue at 150°C, 10 mmHg gave a second fraction of **6.3** (50% yield, 81% e.e.). Repetition of this process did unexpectedly not result in an increase in enantiomeric excess of the furanone **6.3**.

5-Isopropoxy-2(5*H*)-furanone (**6.11**) could be resolved with host **6.13** using the fractional distillation method as described before (Table 6.2, Entry 1). Dissolving host and guest (ratio 1:2) in ether followed by concentration in vacuo gave a crystalline material. Bulb-to-bulb distillation (70°C, 0.1 mmHg) afforded a first fraction of enantiomerically enriched **6.11** (65% yield, 23% e.e.). Distillation of the residue at 150°C, 0.1 mmHg furnished a second fraction of the other enantiomer of **6.11** (27% yield, 75% e.e.).

Despite the successful resolution of 5-ethoxy-2(5*H*)-furanone (**6.10**) employing either the crystallization or suspension method,[4] the fractional distillation method was not successful for this substrate. Butenolide **6.10** was obtained with a maximum e.e. of 14 % (Table 6.2, Entry 2).

5-Methoxy-2(3*H*)-dihydrofuranone (**6.12**) could be resolved by the same method to give at 75°C, 10 mmHg a first fraction of **6.12** (32% yield, 50% e.e.) and at 150°C, 10 mmHg a second fraction of **6.12** (30% yield, 42% e.e.) (Table 6.2, Entry 3)

Table 6.2: Optical resolution of 5-alkoxy-2(5*H*)-furanones **6.10-6.12** by fractional distillation from a host-guest complex with chiral hosts **6.3** or **6.13**

Entry	Host	Guest	ratio	fraction 1 (Yield(%), T(°C),P(mmHg))	e.e.[a] (%) (config.)	fraction 2 (Yield(%), T(°C),P(mmHg))	e.e.[a] (%) (config.)
1	**6.13**	**6.11**	1:2	65 ($65^{0.1}$)	23 (*R*)	27 ($150^{0.1}$)	75 (*S*)
2	**6.4**	**6.10**	1:2	32 (90^{10})	3 (*S*)	25 (150^{10})	14 (*R*)
3	**6.4**	**6.12**	1:2	32 (75^{10})	50	30 (150^{10})	42

[a] *e.e. was determined by GC on a capillary column coated with CP-cyclodextrin-B-2,3,6-M-19*

Absolute configurations of 5-alkoxy-2(5*H*)-furanones were derived from the signs of optical rotation, and determined via a new circular dichroism method developed in our group.[7] Retention times for 5-alkoxy-2(5*H*)-furanones on chiral GC (cylodextrin column) are given in Table 6.4 (Experimental section).

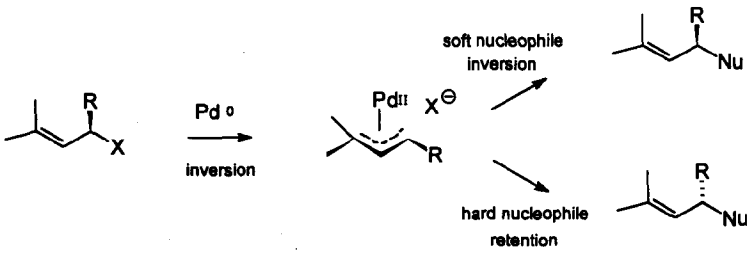
6.5 Discussion

It can be concluded that the method described here for the resolution of racemic furanones is straightforward. Although in these preliminary experiments selectivities are moderate to good, it is one of the few examples of the separation of enantiomers by fractional distillation from an in situ prepared complex with a chiral host. The method requires only dissolving the host and the guest in ether, and subsequent evaporation of the solvent leaves the crystalline host-guest complex, together with the uncomplexed enantiomer of the guest. Fractional distillation of this mixture first gives the uncomplexed guest molecules, while at higher temperatures the enantiomer is released from the host-guest complex. The chiral host can be easily recovered and reused.

Mixing of the host and the guest seems to be crucial for the success of this method. By simply grounding the solid host with the liquid guest it is difficult to achieve efficient mixing of both compounds, thus giving rise to only a partial conversion to the inclusion complex. Better mixing can be achieved by dissolving both host and guest molecules in ether and evaporating the solvent. Usually this gives immediately a crystalline complex of the host and the guest. It appears that both enantiomers of **6.3** can form the inclusion compound with host **6.4**. Because the best resolution is achieved by using a 1:4 ratio of host and guest, it is assumed that the *S* enantiomer forms a slightly more stable inclusion complex. In a dynamic crystallization procedure (thermodynamic control) the equilibrium will be shifted to the more stable complex with the *S* enantiomer. The procedure described here, however, is probably under kinetic control. When the supply of both enantiomers is higher, more of the complex with the *S* enantiomer is formed. The right combination of host and guest molecules apparently is crucial for an effective resolution and slight changes in the host molecules might lead to even better results.

6.6 Nucleophilic substitution reactions of allyl palladium complexes

Palladium catalyzed nucleophilic substitution reactions of allylic substrates have become important reactions in organic chemistry.[8] A variety of allylic substrates and nucleophiles have been applied in this reaction. The proposed mechanism is shown in Scheme 6.5.[9]



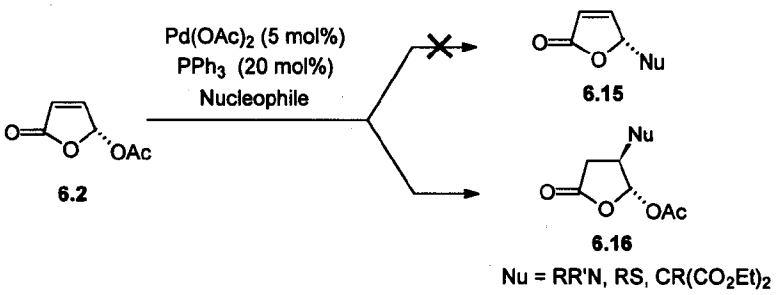
Scheme 6.5

Oxidative addition of a Pd^0-complex to a substrate with a leaving group at the allylic position, results in inversion of configuration, to give the Pd^{II}-species. Nucleophilic substitution of this intermediate can occur with inversion (soft nucleophiles) or with retention of configuration (hard nucleophiles). Examples of soft nucleophiles that react with inversion, are amines, thiols, and anions of β-dicarbonyl compounds. Hard nucleophiles are typically organometallic compounds such as alkylzinc, alkylmagnesium, or organotin reagents.

Especially palladium catalyzed enantioselective carbon-carbon bond forming reactions have been successfully developed in recent years.[10] Many chiral ligands based on, in particular, phosphines or amines have been designed. Enantiomeric excesses of the addition products often exceed 98 %. Trost et al.[11] have recently developed elegant deracemization procedures, by converting symmetric diacyloxy substrates with a chiral palladium catalyst to chiral monosubstituted products with high e.e.'s. Although heteroatom nucleophiles were amongst the first nucleophiles[12] that were used in palladium catalyzed allylic substitution reactions, relatively few reports concerning these nucleophiles have appeared,[13] probably because non-carbon nucleophiles usually give a reversible reaction.

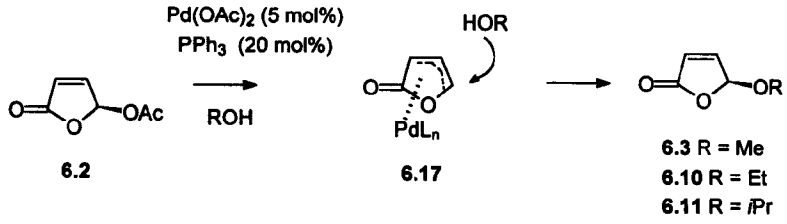
6.7 Palladium catalyzed substitution reactions of 5-acetoxy-2(5*H*)-furanone

5-Acyloxy-2(5*H*)-furanones (**6.2**) are intriguing substrates to undergo palladium catalyzed nucleophilic substitution reactions. They can be prepared in enantiomerically pure form via a lipase mediated acylation of 5-hydroxy-2(5*H*)-furanone, or via lipase catalyzed transesterification of 5-acyloxy-2(5*H*)-furanone (Scheme 6.1).[1] Both enantiomers are accessible following one of these routes. To investigate if optically active 5-acetoxy-2(5*H*)-furanone (**6.2**) can be converted into optically active 5-substituted 2(5*H*)-furanones **6.15** via a palladium catalyzed reaction, several nucleophiles were tested, but initially without success (Scheme 6.6).



Scheme 6.6

It is evident that the substrate puts a limitation on the type of nucleophile that may be applied. The α,β-unsaturated lactone is a good Michael acceptor for amines, thiols, and enolates (Chapter 2). Michael additions to 5-acetoxy-2(5*H*)-furanone to give products **6.16** take place much faster than formation of an allyl palladium complex, inhibiting a palladium catalyzed conversion of the substrate. For example, reaction of **6.2** with sodium diethyl malonate in THF in the presence of $Pd(OAc)_2$ (5 mol %) and PPh_3 (20 mol %) resulted in clean conversion to the Michael addition product **6.16** (Nu = $CH(CO_2Et)_2$). Oxygen nucleophiles, however, are less reactive as Michael donors and can therefore be applied in palladium catalyzed nucleophilic substitution reactions of 5-acetoxy-2(5*H*)-furanone (Scheme 6.7). Presumably allyl palladium complex **6.17** is initially formed via acetate cleavage. Nucleophilic attack of the alcohol to **6.17** furnishes 5-alkoxy-2(5*H*)-furanones **6.3**, **6.10**, or **6.11**, depending on the alcohol used. In Table 6.2 the results of some typical experiments with three different alcohols are given. Conversions and e.e.'s were obtained by GC.



Scheme 6.7

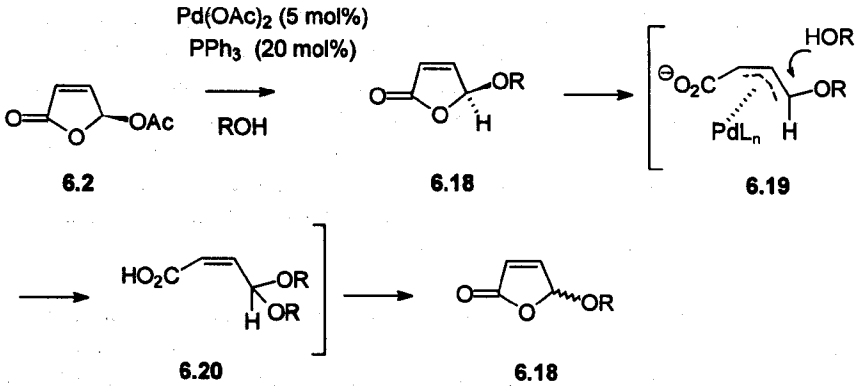
Table 6.3: Palladium catalyzed conversion of (5 *S*)-acetoxy-2(5*H*)-furanone (**6.2**) to 5-alkoxy-2(5*H*)-furanones at room temperature.

Entry	ROH	time (min)	product	conversion %	e.e. of **6.2** [a]	e.e. of product [c]
1	MeOH	30	**6.3**	10	>95	27 [b]
2	MeOH	90	**6.3**	80	>95	75 [b]
3	MeOH	150	**6.3**	100	-	87 [b]
4	MeOH	1200	**6.3**	100	-	0 [b]
5	EtOH	90	**6.10**	5	>95	n.d
6	EtOH	210	**6.10**	65	>95	92
7	EtOH	1200	**6.10**	100	-	15
8	*i*PrOH	210	**6.11**	1	>95	n.d.
9	*i*PrOH	1200	**6.11**	16	>95	>95
10	*i*PrOH	2640	**6.11**	50	>95	>95

[a] *Starting material **6.2** with an e.e. of >95% was used.* [b] *The starting material contained 5 % of racemic **6.3**.* [c] *Conversions and e.e.'s were determined by GC.*

From the preliminary experiments the following conclusions can be drawn:
Regioselectivity of nucleophilic additions to allyl palladium complex **6.17** is always good, giving only substitution products at C_5.
Sterically more demanding alcohols react slower than less bulky ones (iPrOH vs MeOH).
Retention of configuration is observed in the overall conversion of 5-acetoxy-2(5*H*)-furanone (**6.2**) to 5-alkoxy-2(5*H*)-furanones. (+)-(5*S*)-Acetoxy-2(5*H*)-furanone furnishes (+)-(5*S*)-alkoxy-2(5*H*)-furanones. The absolute configuration of 5-alkoxy-2(5*H*)-furanones is related to the sign of optical rotation. The absolute configurations of various 5-alkoxy-2(5*H*)-furanones have been determined by a simple circular dichroism method.[7]
Partial racemization of the products takes place, because the products are not stable under the reaction conditions. As long as 5-acetoxy-2(5*H*)-furanone (**6.2**) is present in the reaction mixture this racemization is negligable.
Additional solvents cause a strong decrease of reaction rate. This is not shown in Table 6.2, but it was found that the reaction described in Scheme 6.7, with EtOH as nucleophile, gave conversions < 10 % after 1 day, when THF, DMF, or MeCN was used as solvent.
A rise in temperature causes an increase of the reaction rate. Reaction of racemic 5-acetoxy-2(5*H*)-furanone (**6.2**) with EtOH as depicted in Scheme 6.7, catalyzed by $Pd(OAc)_2$ and PPh_3 at 70°C, showed complete conversion to **6.10** after 180 min.

The observed partial racemization may be caused by ring opening of the furanone as depicted in Scheme 6.8. The product still contains an acyloxy-allyl moiety and is reactive towards Pd^0-species, forming **6.19**. The intermediate allyl palladium compound **6.19** reacts with the alcohol to give achiral acetal **6.20**. Ring closure then furnishes racemic 5-alkoxy-2(5*H*)-furanone **6.18**.



6.2 **6.18** **6.19** **6.20** **6.18**

Scheme 6.8

6.8 Summary and conclusions

Palladium catalyzed nucleophilic substitution reactions of 5-acyloxy-2(5*H*)-furanones offer many possibilities. Although some nucleophiles are not suitable for this type of reaction, a number of others, in particular poor Michael donors, are. Only oxygen nucleophiles have been successfully applied so far, but it is likely, that for example enamines, tin enolates or allyl tin reagents are good candidates for this reaction. Variation of the catalytic system will probably lead to better yields and more controlable reactions. The availability of 5-acyloxy-2(5*H*)-furanones in enantiomerically pure form via enzymatic resolutions, in combination with the proper nucleophilic reagents, allows the preparation of 5-substituted 2(5*H*)-furanones in enantiomerically pure form. This would be a welcome addition to the methodology described in Chapter 5.

Acknowledgments: Chiu Leung is acknowledged for performing the initial experiments on host-guest resolution of 5-alkoxy-2(5*H*)-furanones, and also for his contributions to the palladium catalyzed substitution reactions of 5-acetoxy-2(5*H*)-furanone. Hanneke van der Deen is gratefully acknowledged for the preparation of optically active 5-acyloxy-2(5*H*)-furanone.

6.9 Experimental

For general experimental details, see Chapter 2. 5-Alkoxy-2(5*H*)-furanones **6.3**,[14] **6.10**,[14] and **6.11** were prepared by refluxing 5-hydroxy-2(5*H*)-furanone in the appropriate alcohol. 5-Methoxy-2(3*H*)-dihydrofuranone (**6.12**) was prepared from **6.3** by reduction with H_2 over Pd/C.[15] Chiral host-compounds **6.4** and **6.13** were prepared following the procedure of Seebach.[16] Optically active (5*S*)-acetoxy-2(5*H*)-furanone (**6.2**) was prepared by Hanneke van der Deen.[1] Enantiomeric purities of 5-alkoxy-2(5*H*)-furanones were determined by GC on a cyclodextrin column, see Chapter 5, and table 6.4.

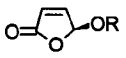
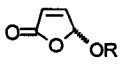
Resolution of 5-alkoxy-2(5*H*)-furanones by mixing with a chiral host, general procedure: To 1 mmol of host **6.4** was added 1 mmol of a 5-alkoxy-2(5*H*)-furanone and the resulting sticky solid material was grinded with a pestle and mortar. The resulting amorphous solid was transferred to a distillation flask and a first fraction of the 5-alkoxy-2(5*H*)-furanone was obtained by bulb-to-bulb distillation at the given temperature and pressure (Table 6.1). A second fraction of the 5-alkoxy-2(5*H*)-furanone was obtained by distillation at higher temperatures. E.e.'s of both fractions were determined by chiral GC-analysis. Absolute configurations were determined from the sign of rotation, and correlated to the retention times on chiral GC.

Resolution of 5-alkoxy-2(5*H*)-furanones by dissolving with a chiral host in ether, general procedure: To a solution of 1 mmol of host **6.4** or **6.13** in 5 mL of ether was added a 5-alkoxy-2(5*H*)-furanone and the resulting cloudy solution was concentrated in vacuo. Bulb-to-bulb distillation of the solid residue at the given temperature and pressure (Tables 6.1 and 6.2) afforded a first fraction of the 5-alkoxy-2(5*H*)-furanone. A second fraction of the 5-alkoxy-2(5*H*)-furanone was

obtained by distillation at higher temperatures. E.e.'s of both fractions were determined by chiral GC-analysis.

Palladium catalyzed conversion of 5-acetoxy-2(5*H*)-furanone to 5-alkoxy-2(5*H*)-furanones, general procedure: To a solution of 0.5 mmol of 5-acetoxy-2(5*H*)-furanone in the appropriate alcohol (2 mL) was added triphenylphosphine (0.1 mmol), followed by $Pd(OAc)_2$ (0.025 mmol). The reaction mixture turned immediately bright yellow, and then gradually darker. It was stirred for the indicated time at room temperature. Conversions and e.e's were determined by GC. Aliquots were taken at intervals by bringing a drop of the reaction mixture in 1 mL of ether and subsequent filtration over silica gel.

Table 6.4: Retention times of 5-alkoxy-2(5*H*)-furanones, 5-acetoxy-2(5*H*)-furanone, and 5-methoxy-2(3*H*)-dihydrofuranone on chiral GC; CP cyclodextrin B-2,3,6-M-19 column.

			 (5*S*)	 (5*R*)
Entry	R	substrate	GC temperature (°C) R_f (min)	R_f (min)
1	Me	**6.3**	105	14.9	15.3
2	Et	**6.10**	125	12.6	13.1
3	*i*Pr	**6.11**	130	11.9	12.4
4	MeCO	**6.2**	125	20.5	21.5
5	Me (dihydro)	**6.12**	105	15.5[a]	16.2[a]

[a]*For this substrate, the absolute configuration was not determined.*

6.10 References

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