Selective catalytic oxidations by palladium and manganese

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Chapter 2

Pd-catalysed selective *anti*-Markovnikov oxidation of allylic esters

The Pd(II)-catalysed *anti*-Markovnikov oxidation of allylic esters to aldehydes at room temperature provides a viable alternative to valuable cross aldol products. High regioselectivity towards the aldehyde product was achieved using the ester protecting group for the allylic alcohol. Remarkably, rapid isomerisation, catalysed by palladium, between linear and branched allylic ester regioisomers, together with the much higher rate of oxidation of the branched isomer, results in the same aldehyde product forming selectively both form the linear and branched allylic esters.

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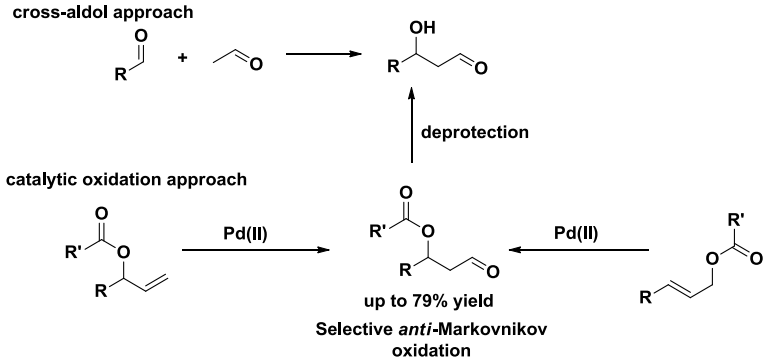
2.1 Introduction

The Pd(II)-catalysed *anti*-Markovnikov oxidation of allylic esters to aldehydes at room temperature provides a viable alternative to valuable cross aldol products. High regioselectivity towards the aldehyde product was achieved using the ester protecting group for the allylic alcohol. Remarkably, rapid isomerization, catalysed by palladium, between linear and branched allylic ester regioisomers, together with the much higher rate of oxidation of the branched isomer, results in the same aldehyde product forming selectively both form the linear and branched allylic esters.

The Pd(II)-catalysed oxidation of alkenes to carbonyl compounds, usually referred to as the Wacker or Wacker-Tsuji reaction,[1,2] is arguably one of the best-known reactions catalysed by palladium. It is an important catalytic process, industrially for the production of ethanal and synthetically for the conversion of olefins to ketones.[3,4] The oxidation of terminal alkenes typically proceeds with selective formation of methylketones.[5] The *anti*-Markovnikov (AM) Wacker oxidation of terminal olefins to aldehydes remains, however, a major challenge.[6] Under certain conditions, AM selectivity is obtained with styrenes,[7,8.9,10] Michael-type acceptor alkenes[11] and certain olefins, such as 2-vinyl-furanosides, bearing a directing functional group.[12] Indeed, high aldehyde selectivity in the catalytic oxidation of phthalimide protected allylic amines was reported by our group to yield a key intermediate in the preparation of β-amino acids.[13] On the other hand Sigman and co-workers have reported the regioselective oxidation of protected allylic amines controlled by various palladium catalysts to yield the corresponding methyl ketones.[14]

In 1986, Pd(II)-catalysed aldehyde selective oxidation of styrene with O_2 and CuCl in *t*-BuOH at 30 ^{o}C was reported by Feringa.[7] Later, Wenzel reported good selectivity (6:1) for aldehyde formation from allyl acetate (56% combined yield of aldehyde and ketone), in *t*-BuOH with $PdCl_2/CH_3CN/CuCl/NaCl$ at 50^{o}C.[15] More recently aldehyde selective oxidation of styrenes was reported by Grubbs and co-workers using the catalyst $[PdCl_2(CH_3CN)_2]$, *p*-benzoquinone as oxidant and *t*-BuOH as solvent at 85^{o}C.[10] However, a more general *anti*-Markovnikov alkene oxidation of non-aryl alkenes under mild conditions remains a challenge, despite the tremendous value in extending this reaction to other substrate classes, in particular allylic alcohols and esters.



Scheme 1. Synthesis of β-Hydroxy aldehydes by cross aldol reactions compared with Pd(II) catalysed oxidation of allylic esters.

β-Hydroxy aldehydes are usually prepared by the cross-aldol reaction between aldehydes or an aldehyde and a ketone.[16] The direct catalytic formation of an aldehyde via selective attack at the terminal carbon of an α-olefin would be a highly valuable alternative. However, the selective *anti*-Markovnikov oxidation of allylic alcohols to β-hydroxy aldehydes has proven to be very difficult due to formation of the ketone products and competing olefin isomerisation.[17]

Here, we demonstrate the aldehyde selective catalytic oxidation of ester protected allylic alcohols with as low as 0.5 mol% of $[PdCl_2(PhCN)_2]$ and *p*-benzoquinone (BQ) as oxidant in *t*-BuOH under ambient conditions. Importantly, the same *anti*-Markovnikov oxidation products were obtained selectively from both branched and linear allylic esters (Scheme 1) due to rapid isomerization between allylic esters under the reaction conditions (*vide infra*).

2.2 Results and discussion

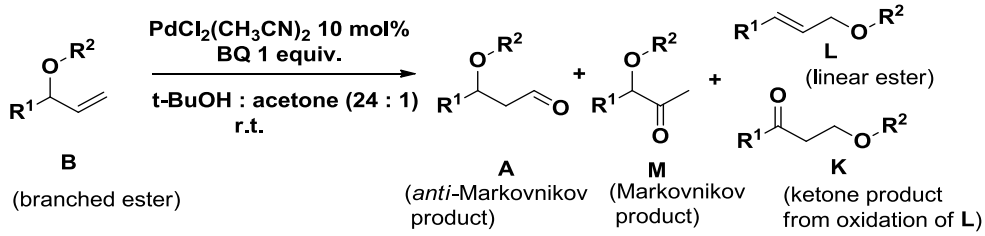
Initial attempts at AM oxidation of ester protected allylic alcohols, under conditions used earlier by our group for the AM oxidation of phthalimide protected allylic amines,[13] provided the Markovnikov product primarily (see Section 2.3.3, Table 4). A broad screening of reaction conditions (see Section 2.3.3, table 6), indicated that *t*-BuOH and the stoichiometric oxidant *p*-benzoquinone offered the highest AM selectivity. The methyl ketone was the main product obtained in the oxidation of unprotected allylic alcohol with $[PdCl_2(CH_3CN)_2]$ and *p*-benzoquinone in acetone/*t*-BuOH (Table 1, entry 1). Protection of oct-1-en-3-ol with 2-methoxyethoxymethyl and benzyl groups did not realize an improvement in regioselectivity (Table 1, entries 2 and 4). Furthermore the trimethylsilyl protected allyl alcohol was found to be unstable with deprotection observed under the reaction conditions (Table 1, entry 3).

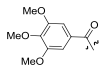
In sharp contrast, a wide range of allylic esters were found to give good aldehyde selectivity under the present reaction conditions (Table 1, entries 5-12).[18] Aryl ester protected but-3-en-2-ol provided a > 5:1 ratio of aldehyde to ketone (Table 1, entries 5, 6, 7 and 10). 2-Furoyl protected but-3-en-2-ol and oct-1-en-3-ol gave a > 7:1 ratio of aldehyde and ketone (Table 1, entries 8 and 11). Similar aldehyde selectivity was obtained using the thiophene-2-carboxyl and acetyl protecting groups (Table 1, entries 9 and 12). The 2-furoyl protecting group provided high selectivity for the aldehyde products and was focused upon in the optimization of reaction conditions (Tables S3, S4 and S5).

In the absence of water, conversion was not observed and although the selectivity was not affected significantly when water was present in near stoichiometric amounts addition of excess water led to a reduction in selectivity (Section 2.3.3, Table 5). The solidification of *t*-BuOH at ambient temperatures was found to be problematic and although the use of higher temperatures (Section 2.3.3, Table 5) avoided this, the selectivity was reduced also. The solidification of *t*-BuOH could be avoided conveniently by addition of co-solvents, other than water, also, (*e.g.*, acetone, dichloromethane, diethyl ether and pentane, Section 2.3.3, Table 7) with acetone giving the highest selectivities (Section 2.3.3, Table 6, entry 5). The use of high substrate concentrations (0.5 M), together with the fact that water does not need to be added to the reaction

indicates, tentatively, that the source of the oxygen in the aldehyde and ketone products originates from the solvent *t*-BuOH.

Table 1. Effect of protecting group on the oxidation of allylic alcohols



Entry	R^1	R^2 [b]	Conv. [a], [b]	**A : M : (L+K)**
1[c]	C_5H_{11}	H	full	11 : 89 : 0
2	C_5H_{11}	MEM	full	15 : 85 : 0
3[d]	C_5H_{11}	TMS	full	---
4	Me		full	20 : 80 : 0
5	Me		full	79 : 14 : 7
6	Me		full	79.5 : 11.5 : 9
7	Me		full	75 : 13.5: 11.5
8	Me		full	83 : 11 : 6
9	Me		full	85: 10 : 5
10	Me		full	74.5 : 13.5 :12
11	C_5H_{11}		full	87 : 6 :7
12	C_5H_{11}		full	86 : 7 :7

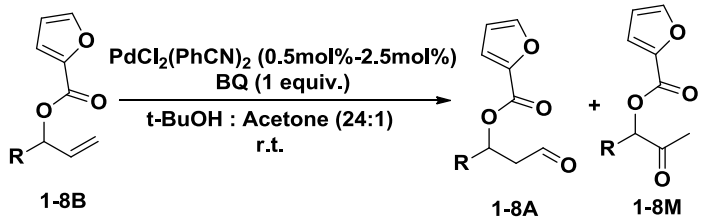
[a] 0.025 M in substrate, conversion and selectivity determined by ^{1}H NMR spectroscopy. [b] reaction mixtures were stirred at r.t. until completion was indicated by TLC unless stated otherwise. [c] unidentified side products observed. [d] deprotection was observed under reaction conditions.

A range of palladium complexes were tested for *anti*-Markovnikov selectivity under optimized reaction conditions (Chapter 4, Table 1). $[PdCl_2(PhCN)_2]$ showed higher selectivity in the oxidation of **2B** to the corresponding aldehyde **2A** (Chapter 4, Table 1) and shorter reaction times in general compared with, *e.g.*, $[PdCl_2(CH_3CN)_2]$.[19]

A key challenge in the palladium catalysed oxidation of alkenes is the often high catalyst loadings employed.[1,3] In the present system, as little as 0.5-2.5 mol% catalyst is sufficient, providing excellent aldehyde selectivity (A:M ratios were 7:1 – 20:1) when substrate concentrations from 0.1 M to 0.5 M in *t*-BuOH/acetone are used (Table 2). 2-Furoyl protected allylic alcohols (**1-8B**) were tested under the optimized reaction conditions; 0.5-2.5 mol% of $[PdCl_2(PhCN)_2]$, 1 equiv. of *p*-benzoquinone and *t*-BuOH/acetone at room temperature (Table 2).

Most aliphatic allylic esters underwent oxidation with high selectivity for the formation of aldehydes in > 70% yield (Table 2, entries 1-4). Ester protected 4-methylhex-1-en-3-ol (**5B**) provided good selectivity also, albeit in a yield of only 45% of aldehyde **5A** due to the formation of the corresponding linear allylic ester **5L** (Table 2, entry 5 and *vide infra*).

Table 2. Pd(II)-catalysed oxidation of branched allylic esters[a], [b]



Entry	R	compound	Conv.	**A** : **M**	**A,** Isolated yield
1[c]	H	**1B**	full	11 : 1	**1A**, 78%
2[d]	CH_3	**2B**	full	7 : 1	**2A**, 71 %
3[d]	C_2H_5	**3B**	full	20 :1	**3A**, 79 %
4[e]	C_5H_{11}	**4B**	full	20 : 1	**4A,** 73%
5[e], [f]		**5B**	95%	20 : 1	**5A**, 45%
6[c]		**6B**	full	20 : 1	**6A**, 71%
7[e], [f]	Ph	**7B**	full	20 : 1	**7A**, 52%
8[e], [g]	Bn	**8B**	95%	20 : 1	**8A**, 64%

[a] Reactions were performed at 1 mmol (substrate) scale. 0.5 M in substrate unless noted otherwise, conversion and selectivity determined by ^{1}H NMR spectroscopy. [b] reaction mixtures were stirred at r.t. until completion (by TLC). [c] 0.5 mol% $PdCl_2(PhCN)_2$ [d] 1 mol% $PdCl_2(PhCN)_2$. [e] 2.5 mol% $PdCl_2(PhCN)_2$. [f] unless stated otherwise, the major side product was the corresponding linear allylic ester. [g] 0.1 M substrate concentration.

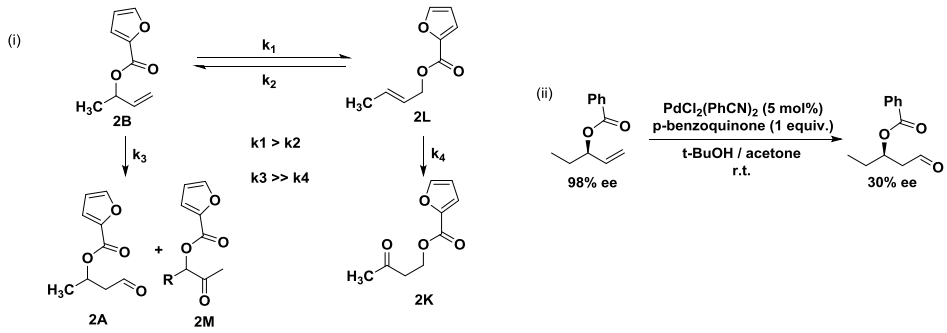
By contrast, the benzyl methyl ether substituted allylic ester provided high selectivity and yield of the aldehyde product (Table 2, entry 6). The phenyl and benzyl substituted allylic esters provided the aldehyde in slightly lower yield (52% and 64%, Table 2, entries 7 and 8, respectively); again primarily due to rearrangement and not ketone formation (*vide infra*).

When *p*-benzoquinone was omitted from the reaction mixture the linear allylic ester (*e.g.,* **2L**) was the main species present within several minutes (Scheme 2). This indicates that it is the thermodynamically most stable regioisomer and that under the reaction conditions an equilibrium, *e.g.*, **2B** and **2L**, is established. Such a rearrangement, catalysed by palladium, has been noted previously by Henry, Oehlschlager and others.[20] In the presence of *p*-benzoquinone, the rearrangement occurred also but was slower (ca. 30 min). [26,27] Using the (*S*)-enantiomer of benzoate protected pent-1-en-3-ol,[21] the *anti*-Markovnikov product, which was obtained with 30% ee, (see section 2.3.7), showing partial retention of configuration. This indicated that the rate of oxidation was of a similar order of magnitude as the rate of isomerisation to the corresponding linear allylic ester (Scheme 2).

From a mechanistic perspective the rearrangement could suggest the involvement of (π-allyl)-palladium complexes. However, it should be noted that, in the presence of

deuterated acetic acid, neither the oxidised nor the rearrangement products of an acetyl protected allylic ester contained the $CD_3C(=O)$- moiety.[22]

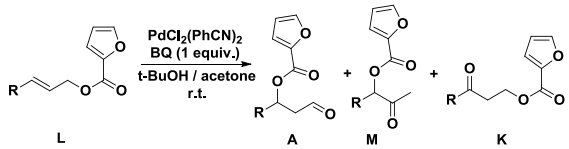
Importantly, despite the relatively rapid reversible rearrangement to the linear allylic ester, in the presence of *p*-benzoquinone, all substrates examined gave the branched aldehyde as the main product under optimised reaction conditions. This, together with the low amounts of the ketone (**2K**), resulting from oxidation of the linear allylic ester, indicates that k3>>k4 and that the Curtin-Hammett principle [23] applies (Scheme 2).



Scheme 2. (i) Isomerization equilibrium and oxidation of linear an branched alkenes. The mechanism is consistent with (ii) the partial loss of e.e. benzyl protected substrate and (Table 3) the conversion of linear allylic esters (e.g. 2L) to branched ester protected β-hydroxy aldehydes.

The observation of isomerization to predominantly the linear isomer under the reaction conditions encouraged us to examine the possibility of using linear allylic esters as starting material to obtain the protected β-hydroxy aldehydes **A**. Indeed, several examples of linear alcohols **L** (Table 3) demonstrated that this alternative substrate class could be used with selectivities and yields being essentially the same as those obtained from the corresponding branched allylic esters (Table 3). An exception was 2-furoyl protected 3-phenyl-prop-2-ene-ol **8L**, which showed lower conversion and yield and required higher catalyst loadings than the corresponding branched allylic ester **8B**.

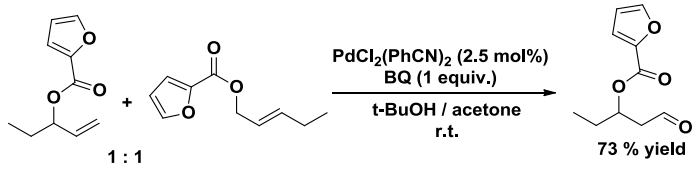
Table 3. Oxidation of linear allylic esters



Entry	R	compound	Conv.[a][b]	**A** : **M**	**A**, isolated yield
1[c]	CH_3	**2L**	full	7 : 1	**2A**, 70%
2[d]	C_2H_5	**3L**	full	16 : 1	**3A**, 74%
3[d]	C_5H_{11}	**4L**	95%	15 : 1	**4A**, 72%
4[c]		**6L**	full	20 : 1	**6A**, 71%
5[e], [f]	Bn	**8L**	85%	10 : 1	**8A**, 43%

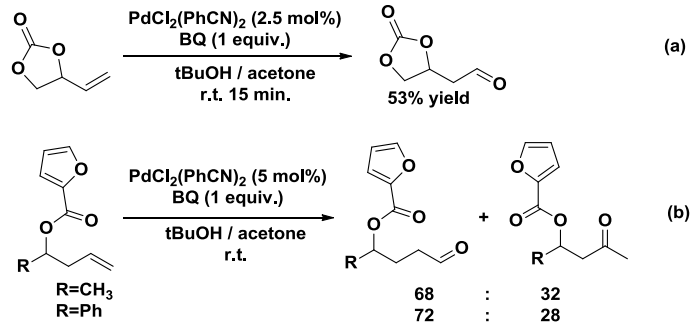
[a] Reactions were performed at 1 mmol scale, 0.5 M in substrate. Conversion and selectivity determined by ^{1}H NMR spectroscopy. [b] reaction mixtures were stirred at r.t. until completion as indicated by TLC unless stated otherwise. [c] 2.5 mol % $PdCl_2(PhCN)_2$. [d] 1 mol% $PdCl_2(PhCN)_2$. [e] 10 mol % $PdCl_2(PhCN)_2$. [f] 0.1 M substrate concentration.

A major advantage of the isomerisation between branched and linear allylic esters is that even substrate mixtures provide only a single major product, *i.e.* the aldehyde, in this Pd(II) catalysed oxidation (Scheme 3).



Scheme 3. Oxidation of a mixture of linear and branched allylic esters.

The ester group at the allylic position of the alkenes was found to be key to *anti*-Markovnikov selectivity when compared with other protecting groups (Table 1). This protecting group class was previously found to be important in the rearrangement of allylic esters with palladium(II) complexes also.[20] However, we have found that the rearrangement can be blocked by the use of cyclic protecting groups, *i.e.* in 4-vinyl-1,3-dioxolan-2-one and the corresponding aldehyde was obtained with high selectivity while only trace ketone formation and no rearrangement was observed (Scheme 4a). Furthermore, the reaction proceeded at a much faster rate than with acyclic allylic esters, possibly due to the absence of the competing rearrangement. In this case, competing decarboxylation[28] was observed also, which leads to a decreased yield. It is notable that, as for isomerization, the decarboxylation is much faster in the absence of *p*-benzoquinone.



Scheme 4. Oxidation of 4-vinyl-1,3-dioxolan-2-one and homoallylic esters.

Finally, the AM selectivity observed for ester protected homoallylic esters, which cannot undergo isomerisation to the linear allylic esters, was found to be surprisingly high under the reaction conditions optimised for allylic esters (Scheme 4b).

In summary, we have developed the first highly selective catalytic *anti*-Markovnikov oxidation of allylic esters, which provides a facile route to the synthesis of protected β-hydroxy aldehydes from terminal alkenes with high selectivity, high yield and, importantly, with low Pd catalyst loadings. Furthermore, the aldehyde products can be obtained by using either the branched or linear protected allylic esters under the same reaction conditions, which provides a new synthetic approach for the preparation of β-hydroxy aldehydes from linear allylic esters or even the mixtures of terminal and internal alkenes. Future studies will focus on the catalytic use of *p*-benzoquinone using a 'redox

coupling with oxygen approach,[24] as applied recently in the Pd catalysed oxidation of internal alkenes.[25]

2.3 Experimental Section

General procedure for the catalytic oxidation of branched allylic esters (Table 2): $[PdCl_2(PhCN)_2]$ and *p*-benzoquinone were dissolved in a mixture of *t*-BuOH and acetone (v : v / 24 : 1). The branched allylic ester **B** (0.5 M) was added to the mixture under N_2 and stirred at room temperature until the reaction was complete; by T.L.C. analysis. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash silica-gel chromatography yielded the desired aldehyde **A**.

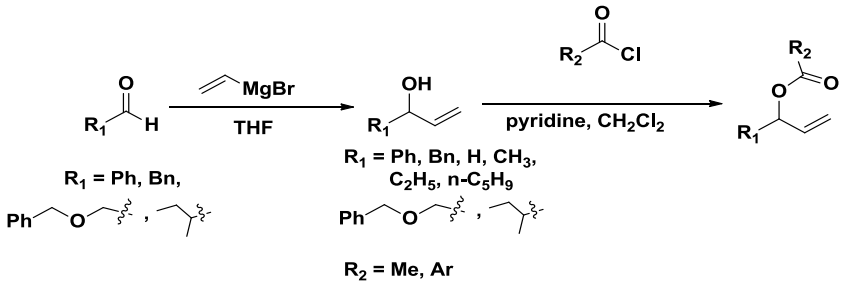
Note. All reagents are of commercial grade and used as received unless stated otherwise.

2.3.1 General Procedures and methods

Chromatography: Merck silica gel type 9385 230-400 mesh, T.L.C.: Merck silica gel 60, 0.25 mm, with visualization by UV and cerium/molybdenum or potassium permanganate staining. Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: 7.26 for ^{1}H, 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q =quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. ^{13}C spectra were assigned based on APT ^{13}C-NMR spectroscopy. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques.

2.3.2 Preparation of substrates

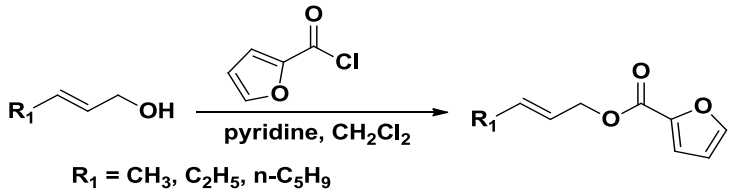
Preparation and protection of branched allylic esters



A dry Schlenk tube was charged with aldehyde (10 mmol) and dry THF (40 mL) and cooled to 0°C. Vinylmagnesium bromide (12 mL, 1.0 M in THF) was added dropwise to the mixture. Upon complete conversion (2 h), the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash silica-gel chromatography (pentane / ether) yielded the desired allylic alcohol.

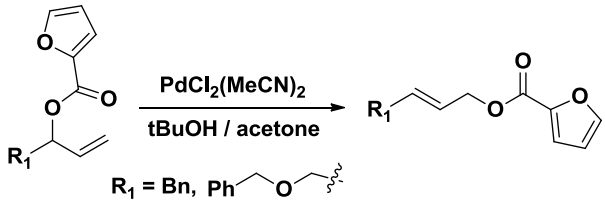
The allylic alcohol (10 mmol) and pyridine (20 mmol) were dissolved in CH_2Cl_2 (5.0 mL). The reaction mixture was cooled to 0 °C and charged dropwise with the acid chloride (10.3 mmol). Upon complete addition, the reaction mixture was allowed to warm to r.t. and conversion verified by TLC. The mixture was diluted with EtOAc (100 mL) and washed with aqueous 1N HCl (30 mL), water (30 mL) and brine (30 mL). The solution was concentrated under reduced pressure. Purification by flash silica-gel chromatography (pentane / ether) yielded the desired allylic ester.

Protection of linear allylic alcohols



Linear allylic alcohols were protected as for branched allylic alcohols where the corresponding allylic alcohols were available from commercial sources.

Preparation of protected linear allylic esters from their corresponding branched allylic esters

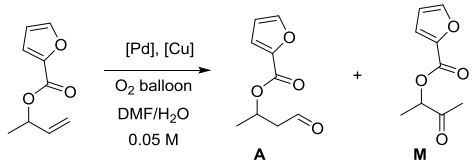


A solution of the allylic ester (5 mmol) in *t*-BuOH (9.52 mL) and acetone (0.48 mL) under argon was treated with $[PdCl_2(MeCN)_2]$ (10 mol%). The solution was stirred overnight after which conversion had reached in excess of 50 %. The solution was concentrated *in vacuo*. Purification by flash silica-gel chromatography (pentane / ether) yielded the linear allylic ester.

2.3.3 Optimisation of conditions for catalysed oxidation reactions

Table 4. Selectivity and conversion achieved in the oxidation of allylic esters with oxygen as terminal oxidant

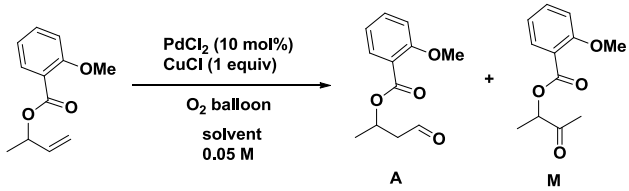
a)



Entry	Conditions	Reaction time	**A : M**[a]	Comments
1	$PdCl_2$ (10 mol%), CuCl (100 mol%), DMF:H_2O 7:1	3 days	1 : 5.5	73% isolated yield
2	$PdCl_2$ (10 mol%), $CuCl_2$ (50 mol%), DMF:H_2O 4:1	3 days	0 : 100	Reaction stops at 62% conv.
3	Na_2PdCl_4 (10 mol%), CuCl (100 mol%), DMF:H_2O 1:1	5 days	0 : 100	----

[a] Determined by ^{1}H-NMR spectral analysis of the crude reaction mixture.

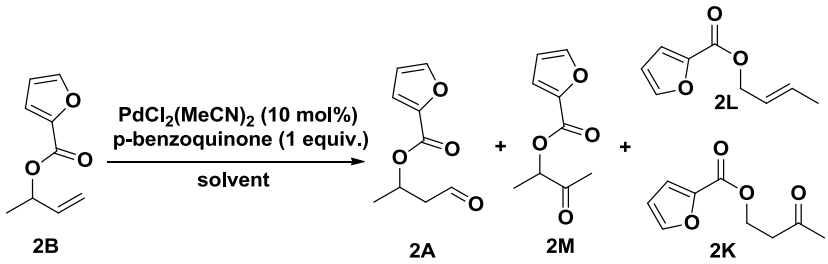
b)



Entry	Solvent	**A : M**[a]	Comments
1	DMF:H_2O 7:1	1 : 3	Full conv. after 2 days; 79% yield
2	DMF:H_2O 1:1	0 : 100	82% yield
3	DMF:H_2O 7:1 + 2 eq. HMPA	0 : 100	85% yield
4	DMF	--	No reaction, SM recovered
5	Acetonitrile	--	No reaction, SM recovered
6	DMF:H_2O 5:1	1 : 4.2	Full conv.
7	DMF:H_2O 15:1	1 : 3.7	Slower reaction; Full conv. not reached
8	*t*-BuOH:H_2O 9:1	1.8 : 1	85% yield of combined yield (**A** and **M**)

[a] Determined by ^{1}H-NMR analysis of the crude reaction mixture.

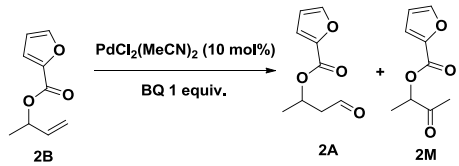
Table 5. Selectivity and conversion achieved in the oxidation of allylic esters with different amount of water



Entry	Solvent[c]	Conv.[b]	**2A : 2M : (2L+2K)**
1	*t*-BuOH / 100 eq. H_2O	full	71 : 24 : 5
2	*t*-BuOH / 3 eq. H_2O	full	75 : 17 :8
3[a]	*t*-BuOH / 3 eq. H_2O	full	68 : 19 : 13
4	*t*-BuOH / 1.1 eq. H_2O	full	75 : 15 : 10
5	*t*-BuOH / acetone (24 : 1)[d]	full	83 : 11 : 6

[a] at 40 °C [b] reaction mixtures were stirred at r.t. until completion (by TLC) unless stated otherwise [c] keep the substrate concentrate at 0.025 M [d] volume ratio.

Table 6. Screening of solvent, temperature, reaction time and added water in the oxidation of 2B with 10 mol% [$PdCl_2(MeCN)_2$].



entry	time	H_2O Equiv.	solvent	Temp.	result[a]
1	5 h	3.0	t-amyl alcohol	r.t.	Low conversion
2	20 h	3.0	t-amyl alcohol	r.t.	Full conv. A: M / 2.5 : 1
3	18 h	1.1	t-amyl alcohol	r.t.	Full conv. A:M / 3.2:1
4	18 h	1.1	*t*-BuOH : t-amyl alcohol 24 : 1	r.t.	Full conv. A:M / 3.3:1
5	3 h	100	*t*-BuOH	r.t.	Full conv. A:M / 2.2:1
6	5 h	3.0	*t*-BuOH	r.t.	Full conv. A:M / 4.4:1 side products less than 10%
7	5.5 h	3.0	*t*-BuOH (0.025 M)	r.t.	Full conv. A:M / 4.4:1 more than 10% side product
8	3 h	3.0	*t*-BuOH	40 °C	Full conv. A:M / 3.5:1
9	5.5 h	1.1	*t*-BuOH	r.t.	Full conv. A : M / 4.9 :1 10% side product
10	20 h	1.1	*t*-BuOH (5 mol% Pd)	r.t.	Full conv. A : M / 4.2 :1 17% side product
11	20 h	1.1	*t*-BuOH (1 mol% Pd)	r.t.	Full conv. A : M / 4.8 :1 10% side product
12	5.5 h	3.0	*t*-BuOH : *i*-PrOH 24 : 1	r.t.	Full conv. A : M / 4.4 : 1
13	5.5 h	3.0	*t*-BuOH : EtOH 24 : 1	r.t.	Full conv. A : M / 3.5 : 1
14	4 h	1.0	*t*-BuOH : *i*-PrOH 24 : 1	r.t.	Full conv. A : M / 5 : 1 14.5% side product
15	4 h	1.0	*t*-BuOH : acetone 24 : 1	r.t.	Full conv. A : M / 6.3 : 1 9% side product
16	5 h	1.0	*t*-BuOH : acetone 4 : 1	r.t.	Full conv. A : M / 6.3 : 1 9% side product
17	4h	1.0	*t*-BuOH : butanone 4 : 1	r.t.	Full conv. A : M / 6.0 : 1 7% side product
18	4h	1.0	*t*-BuOH : butanedione (4 equiv.)	r.t.	Full conv. A : M / 6.4 : 1 Less than 5% side product
19	4.5 h	1.1	Acetone	r.t.	55% conv. Only rearrangement product (*i.e.* the linear alkene)

[a] side product = corresponding linear alkene and oxidised linear alkene

Table 7. Oxidation of 2B with co-solvents, at r.t. using 10 mol% $[PdCl_2(CH_3CN)_2]$

entry	time	solvent	result[a]
1	6 h	*t*-BuOH : *t*-BuCN (24 : 1)	74% conv. 40% side product 26% aldehyde 8% ketone
2	6 h	*t*-BuOH : CH_2Cl_2 (24 : 1)	Full conv. A : M / 6.3 : 1 5% side product
3	6 h	*t*-BuOH : Diethyl ether (24 : 1)	90% con. 10% side product A : M / 6.5 : 1
4	5h	*t*-BuOH : Pentane (24 : 1)	Full conv. A : M / 5.7 : 1 6% side product
5	6h	*t*-BuOH : Acetone (24 : 1)	Full conv. A : M / 7.5 : 1 6% side product

[a] side product = corresponding linear alkene and oxidized linear alkene.

2.3.4 General procedures for catalysed oxidation of allylic esters

Oxidation of branched allylic esters (Table 2, Scheme 4)

$[PdCl_2(PhCN)_2]$ (0.005 mmol to 0.025 mmol) and *p*-benzoquinone (1 mmol) were dissolved in a 2 ml mixture of *t*-BuOH and acetone (v : v / 24 : 1). The branched allylic ester (1 mmol, 0.5 M) was added to the mixture under N_2 and stirred at room temperature until the reaction was complete by T.L.C. analysis. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash silica-gel chromatography yielded the desired aldehyde.

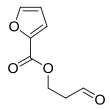
Oxidation of linear allylic esters (Table 3)

$[PdCl_2(PhCN)_2]$ (0.005 mmol to 0.05 mmol) and linear allylic alcohol (0.5 mmol, 0.5 M) were dissolved in the 1 ml mixture of *t*-BuOH and acetone (v : v / 24 : 1). *p*-Benzoquinone (0.5 mmol) was added in the solution. The reaction mixture was protected by nitrogen and stirred at room temperature until the reaction was complete. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by silica-gel flash chromatography yielded the desired aldehyde.

Oxidation of a mixture of linear and branched allylic esters (Scheme 3)

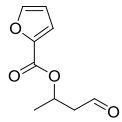
$[PdCl_2(PhCN)_2]$ (0.025 mmol) and linear allylic alcohol (0.5 mmol, 0.25 M) were dissolved in the 2 ml mixture of *t*-BuOH and acetone (v : v / 24 : 1). After stirring for 30 min, *p*-benzoquinone (1 mmol) was added to the solution. After the *p*-benzoquinone had dissolved, the branched allylic ester (0.5 mmol, 0.25 M) was added. The reaction mixture was kept under N_2 and stirred at room temperature until the reaction was complete. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash silica-gel chromatography (9 : 1 / pentane : ether eluent) yielded the desired aldehyde.

2.3.5 Characterisation of products and substrates



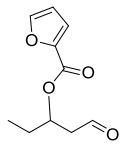
3-Oxopropyl furan-2-carboxylate 1A (Table 2, entry 1) Isolated by flash column chromatography on silica gel (pentane/ether = 9:1, Rf = 0.6). The title compound was obtained as a colourless oil (78% yield). HRMS (ESI+) calc. for $C_8H_9O_4$ $(M+H)^+$ 168.0500, found 169.0494;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.58 (s, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.51 (m, 1H), 4.64 (t, *J* = 6.17 Hz, 1H), 2.90 (dt, *J* = 1.35 Hz, 6.16, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 158.3, 146.5, 144.1, 118.3, 111.8, 58.3, 42.7.



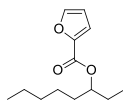
4-Oxobutan-2-yl furan-2-carboxylate 2A (Table 2, entry 2) Isolated by flash column chromatography on silica gel (pentane/ether = 9:1, Rf = 0.5).The title compound was obtained as a colourless oil (71% yield). HRMS (ESI+) calc. for $C_9H_{11}O_4$ $(M+H)^+$ 183.0651, found 183.0651;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.57 (s, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.50 (m, 1H), 5.6 (m, 1H), 2.87 (ddd, *J* = 16.94 Hz, 7.08 Hz, 2.32 Hz, 1H), 2.70 (ddd, *J* = 16.94 Hz, 5.43 Hz, 1.46 Hz, 1H), 1.45 (d, *J* = 6.37 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 157.9, 146.4, 144.4, 118.2, 111.8, 66.6, 49.5, 20.2.



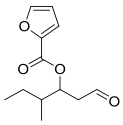
1-Oxopentan-3-yl furan-2-carboxylate 3A (Table 2, entry 3) Isolated by flash column chromatography on silica gel (pentane/ether = 8.5:1.5, Rf = 0.55).The title compound was obtained as a colourless oil (79% yield). HRMS (ESI+) calc. for $C_{10}H_{13}O_4$ $(M+H)^+$ 197.0808, found 197.0808;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.56 (s, 1H), 7.15 (d, *J* = 3.49 Hz, 1H), 6.49 (m. 1H), 5.46(m. 1H), 2.80 (ddd, *J* = 16.8 Hz, 7.26 Hz, 2.56 Hz, 1H), 2.73 (ddd, *J* = 16.8 Hz, 5.06 Hz, 1.5 Hz, 1H), 1.77 (m. 1H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 158.1, 146.4, 144.3, 118.1, 111.8, 70.9, 47.6, 27.3, 9.4.



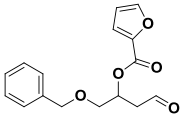
1-Oxooctan-3-yl furan-2-carboxylate 4A (Table 2, entry 4) Isolated by flash column chromatography on silica gel (pentane/ethyl acetate = 8.5:1.5, Rf = 0.45).The title compound was obtained as colourless oil (73% yield). HRMS (ESI+) calc. for $C_{13}H_{19}O_4$ $(M+H)^+$ 239.1277, found 239.1277;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.57 (s, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.51 (m. 1H), 5.53 (m. 1H), 2.79 (ddd, *J* = 16.75 Hz, 7.13 Hz, 2.59 Hz, 1H), 2.74 (ddd, *J* = 16.75 Hz , 5.12 Hz , 1.6 Hz, 1H), 1.74 (m, 2H), 1.30 (m, 6H), 0.87 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 158.1, 146.4, 144.3, 118.2, 111.8, 69.9, 48.1, 34.2, 31.4, 24.8, 22.4, 13.9.



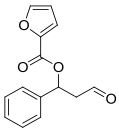
4-Methyl-1-oxohexan-3-yl furan-2-carboxylate 5A (Table 2, entry 5) Isolated by flash column chromatography on silica gel (pentane/ether = 8:2, Rf = 0.45).The title compound was obtained as a colourless oil (45% yield). HRMS (ESI+) calc. for $C_{12}H_{17}O_4$ $(M+H)^+$ 225.1121, found 225.1120;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.58 (s, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.50 (m. 1H), 5.54 (m. 1H), 2.72 (m, 2H), 1.88-1.16 (m, 3H), 0.94 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 199.6, 158.1, 146.5, 118.1, 118.1, 111.8, 72.9, 72.3, 45.8, 44.8, 38.5, 38.1, 25.3, 24.9, 14.3, 14.1, 11.5, 11.3.



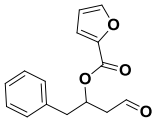
1-(Benzyloxy)-4-oxobutan-2-yl furan-2-carboxylate 6A (Table 2, entry 6) Isolated by flash column chromatography on silica gel (pentane/ether = 7.5:2.5, Rf = 0.4).The title compound was obtained as a colourless oil (71% yield). HRMS (ESI+) calc. for $C_{16}H_{17}O_5$ $(M+H)^+$ 289.1070, found 289.1070;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.59 (s, 1H), 7.35-7.27 (m. 5H), 7.18 (d, *J* = 3.5 Hz , 1H), 6.51 (m, 1H), 5.67 (m, 1H), 4.61-4.53 (dd, *J* = 22.8 Hz, 12.1 Hz, 2H), 3.75-3.67 (ddd, *J* = 22.5 Hz ,10.5 Hz, 4.7 Hz, 2H), 2.90 (dd, *J* = 6.2 Hz, 1.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 157.8, 146.6, 144.1, 137.5, 128.4, 127.8, 127.6, 118.5, 111.9, 73.3, 70.2, 68.5, 45.0, 29.6.



3-Oxo-1-phenylpropyl furan-2-carboxylate 7A (Table 2, entry 7) Isolated by flash column chromatography of silica gel (pentane/ether = 8:2, Rf = 0.5).The title compound was obtained as a colourless oil (52% yield). HRMS (ESI+) calc. for $C_{14}H_{13}O_4$ $(M+H)^+$ 245.0808, found 245.0810;

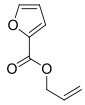
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.58 (s, 1H), 7.45-7.30 (m. 5H), 7.21 (d, *J* = 3.5 Hz, 1H), 6.51 (m, 1H), 3.23 (ddd, *J* = 17.0 Hz, 8.3 Hz, 2.2 Hz, 1H), 2.99 (ddd, *J* = 17.0 Hz, 4.9 Hz, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 157.5, 146.6, 144.2, 138.6, 128.8, 128.6, 126.3, 118.5, 111.9, 70.9, 49.7.



4-Oxo-1-phenylbutan-2-yl furan-2-carboxylate 8A (Table 2, entry 8) Isolated by flash column chromatography on silica gel (pentane/ether = 7:3, Rf = 0.4).The title compound was obtained as a colourless oil (64% yield). HRMS (ESI+) calc. for $C_{15}H_{15}O_4$ $(M+H)^+$ 259.0970, found 259.0965;

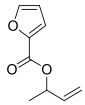
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.58 (s, 1H), 7.32-7.23 (m. 5H), 7.15 (d, *J* = 3.5 Hz, 1H), 5.72 (m, 1H), 3.14 (dd, *J* = 13.7 Hz, 6.0 Hz, 1H), 3.00 (dd, *J* =13.8 Hz, 6.9 Hz , 1H), 2.78 (ddd, *J* = 17.07 Hz, 7.4 Hz, 2.3 Hz, 1H), 2.72 (ddd, *J* = 17.0 Hz, 5.0 Hz, 0.9 Hz, 1H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ198.9, 157.8, 146.5, 144.2, 136.0, 129.5, 128.6, 127.0, 118.3, 111.8, 70.3, 46.9, 40.2.



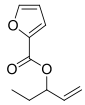
Allyl furan-2-carboxylate 1B (Table 2, entry 1) Isolated by flash column chromatography on silica gel (8 : 2 / pentane : ether eluent). The title compound was obtained as a colourless oil (91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.46 (m, 1H), 5.97 (m, 1H), 5.37 (d, *J* = 7.17 Hz, 1H), 5.25 (d, *J* = 10.41 Hz, 1H), 4.76 (d, *J* = 5.7 Hz, 2H)



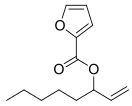
But-3-en-2-yl furan-2-carboxylate 2B (Table 2, entry 2) Isolated by flash column chromatography on silica gel (7.5 : 2.5 / pentane : ether eluent). The title compound was obtained as a colourless oil (93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 6.44 (m, 1H), 5.87 (m, 1H), 5.51 (m, 1H), 5.29 (d, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 1.36 (d, *J* = 6.5 Hz, 3H).



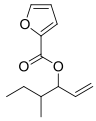
Pent-1-en-3-yl furan-2-carboxylate 3B (Table 2, entry 3) Isolated by flash column chromatography on silica gel (8.5 : 1.5 / pentane : ether eluent). The title compound was obtained as a colourless oil (90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.13 (d, *J* = 3.5 Hz, 1H), 6.45 (m, 1H), 5.82 (m, 1H), 5.36 (m, 1H), 5.30 (d, *J* = 7.2 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 1.73 (m., 2H), 0.91 (t, *J* = 7.4 Hz, 3H).



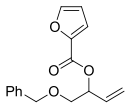
Oct-1-en-3-yl furan-2-carboxylate 4B (Table 2, entry 4) Isolated by flash column chromatography on silica gel (8 : 2 / pentane : ether eluent). The title compound was obtained as a colourless oil (94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.09 (d, *J* = 3.5 Hz, 1H), 6.40 (m, 1H), 5.79 (m, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 1.64 (m, 2H), 1.28 (m, 6H), 0.78 (m, 3H)



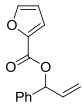
4-Methylhex-1-en-3-yl furan-2-carboxylate 5B (Table 2, entry 5) Isolated by flash column chromatography on silica gel (9 : 1 / pentane : ether eluent). The title compound was obtained as a colourless oil (88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.49 (m, 1H), 5.86 (m, 1H), 5.39 (d, *J*=7.2 Hz, 1H), 5.41-5.20 (m, 3H), 1.74-1.69 (m,1H), 1.57-1.50 (m,1H), 1.25-1.15 (m,1H), 0.97-0.82 (m, 6H).



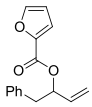
1-(Benzyloxy)but-3-en-2-yl furan-2-carboxylate 6B (Table 2, entry 6) Isolated by flash column chromatography on silica gel (8.5 : 1.5 / pentane : ether eluent). The title compound was obtained as a colourless oil (85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.33-7.21 (m, 6H), 6.52 (m,1H), 5.93 (m,1H), 5.74 (m,1H), 5.44 (d, *J* = 7.2 Hz, 1H), 5.31 (d, *J* = 10.5 Hz, 1H), 4.61 (dd, *J* = 2.2 Hz, 22.7 Hz, 2H) , 3.73-3.64 (m, 2H).



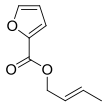
1-Phenylallyl furan-2-carboxylate 7B (Table 2, entry 7) Isolated by flash column chromatography on silica gel (8 : 2 / pentane : ether eluent). The title compound was obtained as a colourless oil (85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.46-7.32 (m, 5H), 7.24 (d, *J* = 3.5 Hz, 1H), 6.50 (m, 1H), 6.14 (m, 1H), 5.43 (d, *J* = 7.2 Hz, 1H), 5.33(d, *J* = 10.5 Hz, 1H).



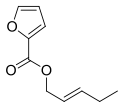
1-Phenylbut-3-en-2-yl furan-2-carboxylate 8B (Table 2, entry 8) Isolated by flash column chromatography on silica gel (9 : 1 / pentane : ether eluent). The title compound was obtained as a colourless oil (87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.31-7.17 (m, 6H), 6.49 (m, 1H), 5.91 (m, 1H), 5.71 (m, 1H), 5.33 (d, *J* = 7.2 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 3.13 (dd, *J* = 7.1 Hz, 13.7 Hz, 1H), 3.02 (dd, *J* = 6.3 Hz, 13.7 Hz, 1H)



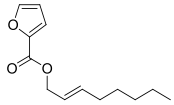
(E)-but-2-en-1-yl furan-2-carboxylate 2L (Table 3, entry 1) Isolated by flash column chromatography on silica gel (8.5 : 1.5 / pentane : ether eluent). The title compound was obtained as a colourless oil (93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.11 (d, *J* = 3.5 Hz, 1H), 6.43 (m, 1H), 5.80 (m, 1H), 5.59 (m, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 1.66 (d, *J* = 6.4 Hz, 1H).



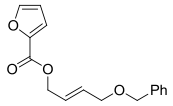
(E)-pent-2-en-1-yl furan-2-carboxylate 3L (Table 3, entry 2) Isolated by flash column chromatography on silica gel (9 : 1 / pentane : ether eluent). The title compound was obtained as a colourless oil (91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.14 (d, *J* = 3.5 Hz, 1H), 6.46 (m, 1H), 5.83 (m, 1H), 5.56 (m, 1H), 4,72 (d, *J* = 6.3 Hz, 2H), 2.02 (m, 2H), 0.97 (m, 3H).



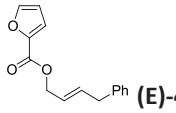
(E)-oct-2-en-1-yl furan-2-carboxylate 4L (Table 3, entry 3) Isolated by flash column chromatography on silica gel (8 : 2 / pentane : ether eluent). The title compound was obtained as a colourles oil (95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.48 (m, 1H), 5.83 (m, 1H), 5.62 (m, 1H), 4.73 (d, *J* = 6.4 Hz, 2H), 2.03 (m, 2H), 1.27 (m, 6H), 0.86 (m, 3H).



(E)-4-(benzyloxy)but-2-en-1-yl furan-2-carboxylate 6L (Table 3, entry 4) Isolated by flash column chromatography of silica gel (9.5 : 0.5 to 8.5 : 1.5 / pentane : ether eluent). The title compound was obtained as a colourless oil (61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.30-7.21 (m, 5H), 7.15 (d, *J* = 3.5 Hz, 1H), 6.46 (m, 1H), 5.92 (m, 2H), 4.78 (d, *J* = 4.3 Hz, 2H), 4.48 (s, 2H), 4.02 (d, *J* = 3.5 Hz, 2H).

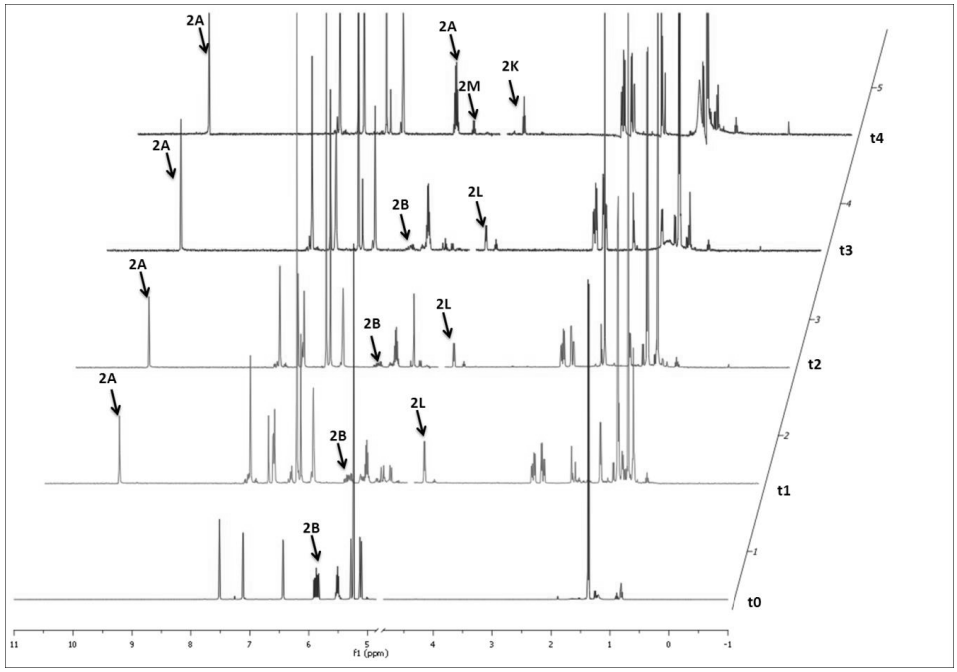


(E)-4-phenylbut-2-en-1-yl furan-2-carboxylate 8L (Table 3, entry 5) Isolated by flash column chromatography on silica gel (9.7 : 0.3 to 8.5 : 1.5 / pentane : ether eluent). The title compound was obtained as a colourless oil (56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.32-7.18 (m, 6H), 6.51 (m, 1H), 6.02 (m, 1H), 5.73 (m, 1H), 4.79 (d, *J* = 6.3 Hz, 2H)), 3.42 (d, *J* = 6.7 Hz, 2H).

2.3.6 Offline ^{1}H NMR spectroscopic analysis

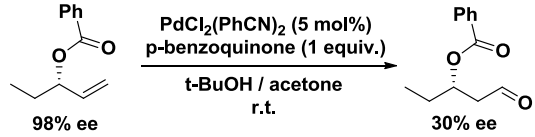
Reaction progress in the oxidation of allylic ester **2B** (Scheme 2i) was studied by off-line ^{1}H NMR spectroscopy.

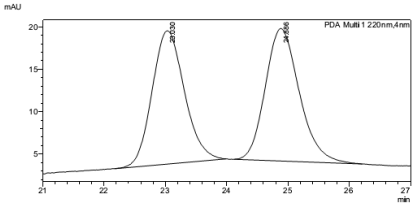


t0 = 0 h (only starting material **2B**), t1 = 1 h (starting material **2B**, linear allylic ester **2L**, aldehyde **2A**), t2 = 5 h (starting material **2B**, linear allylic ester **2L**, aldehyde **2A**), t3 = 16 h (starting material **2B**, linear allylic ester **2L**, aldehyde **2A**), t4 = 36 h (aldehyde **2A**, ketone **2M**, ketone **2K**)

2.3.7 Oxidation of enantiopure protected allylic alcohol

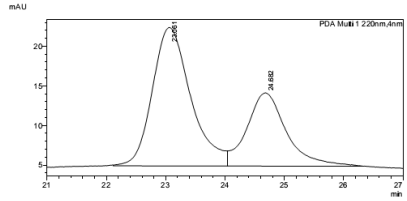
Retention of configuration in the oxidation of enantiopure benzyl protected pent-1-ene-3-ol determined by chiral HPLC (ODH – *i*-PrOH/Heptane, 1:99).





PDA Ch1 220nm

Peak#	Ret. Time	Area	Area%
1	23.030	575326	48.847
2	24.886	602482	51.153
Total		1177808	100.000



PDA Ch1 220nm

Peak#	Ret. Time	Area	Area%
1	23.061	786389	64.859
2	24.682	426064	35.141
Total		1212454	100.000

HPLC chromatogram of benzyl protected 3-hydroxypentanal prepared by oxidation of (left) racemic benzyl protected 3-hydroxypentanal and (right) (*S*)-benzyl-pent-1-ene-3-ol ester.

2.4 Bibliography

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[18] Although the *anti*-Markovnikov oxidation products of the branched allylic esters were the major products, other products including the Markovnikov oxidation products,

rearrangement to the linear allylic esters and the latter's oxidation product were obtained (Table 2, entries 1-8).

[19] Several other palladium complexes such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ provided no conversion (see also see Chapter 4, Table 1), while $PdCl_2$ provided primarily the linear allylic ester (**L**). Oxidants, other than benzoquinone (see Chapter 4, Table 1), and other solvents (Section 3.3.3) provided lower reactivity and selectivity.

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[22] Addition of acetic acid, although not affecting the selectivity of the reaction, increased the rate of reaction modestly.

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