Tetrahedron 64 (2008) 5794–5799

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Ether-directed diastereoselectivity in catalysed Overman rearrangement: comparative studies of metal catalysts

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ARTICLE INFO

Article history:
Received 12 December 2007
Received in revised form 9 March 2008
Accepted 27 March 2008
Available online 3 April 2008

ABSTRACT

Ether-directed diastereoselectivity in Overman rearrangement of δ-methoxy and δ-TBDMSO substituted allylic trichloroacetimidates has been explored using $PtCl_2$, $PtCl_4$, AuCl and $AuCl_3$ catalysts in comparison with commonly used Pd(II) catalysts. For both substrates the use of $PtCl_2$ catalyst gave notably improved *anti*/*syn*-ratio of 1,2-aminoalcohol derivatives (*anti*/*syn*=11:1 for δ-methoxy; 6:1 for δ-TBDMSO) compared to all metal catalysts known to promote Overman rearrangement. Formation of 2-trichloromethyloxazoline was observed as a dominant side reaction in the metal catalysed rearrangement of δ-methoxy substituted allylic trichloroacetimidates considerably reducing the yield of the desired product. This side reaction was suppressed when δ-TBDMS-ether was used as a directing group.

1. Introduction

The rearrangement of *O*-allyltrichloroacetimidates to *N*-allyltrichloroacetamides, first discovered by Overman, is a useful approach for the synthesis of nitrogen containing compounds.[1] The rearrangement can be performed thermally at elevated temperatures or catalysed by 'soft' metal salts at very mild reaction conditions. Recently developed chiral cobalt oxazoline palladacycle (COP-Cl) catalysts provide a possibility to achieve enantioselective rearrangement of prochiral *O*-allyltrichloroacetimidates.[2] Substrate controlled stereochemical induction has been intensively studied for catalytic rearrangement of *O*-allyltrichloroacetimidates bearing a metal chelating group adjacent to the double bond.[3,4] High diastereoselectivity has been reported in Pd(II) catalysed rearrangement of trichloroacetimidates with δ-*tert*-butoxycarbonylamino group giving access to orthogonally protected *anti*-1,2-diamines.[3] Recent investigations by Jamieson and Sutherland as well as others have been devoted to the δ-ether directed 1,2-stereoinduction in the Pd(II) catalysed rearrangement of trichloroacetimidates leading preferentially to *anti*-1,2-aminoalcohol derivatives (Fig. 1).[4] It has been shown that *anti*/*syn*-selectivity in rearrangement of allylic trichloroacetimidates is largely influenced by the δ-oxygen substituent R^1. Rearrangement proceeds with low stereoselectivity when the oxygen substituent R^1 is a bulky TBDMS group (*anti*/*syn*=2:1).[4a] Medium *anti*-stereoselectivity was observed when δ-hydroxy, δ-methoxy or δ-ethoxy substituted *O*-allyltrichloroacetimidates were used as substrates (*anti*/*syn*=4:1, 5:1 and 7:1, respectively). MOM group substitution at the δ-oxygen provided a very strong directing effect to give *anti*-1,2-aminoalcohol derivatives in high diastereomeric excess (*anti*/*syn*=10–15:1, depending on the solvent).[4a,c]

In the proposed stereoinduction model, palladium coordinates with both the oxygen atom and the double bond, selecting the diastereotopic face of the double bond that leads to the complex with minimised 1,3-allylic strain (Fig. 1).[4d] The addition of trichloroacetimidate occurs from the uncomplexed face of the activated alkene according to a cyclisation induced rearrangement (CIR) mechanism.[1d]

Recently, we have reported Pt(II), Pt(IV), Au(I) and Au(III) as new catalysts for the Overman rearrangement.[5] In this publication, we present our investigation of these metals as catalysts for the ether-directed diastereoselective rearrangement in comparison with commonly used Pd(II) catalysts. δ-Methoxy and δ-TBDMSO substituted allylic trichloroacetimidates were chosen as test substrates since diastereoselectivity in the rearrangement of such substrates requires substantial improvement. The use of the TBDMS ether as a directing group is of notable synthetic importance since *O*-TBDMS-protected 1,2-aminoalcohol derivatives obtained as rearrangement products have high potential for further derivatisation.

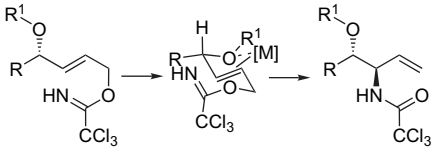

Figure 1. Proposed stereoinduction model.[4d]

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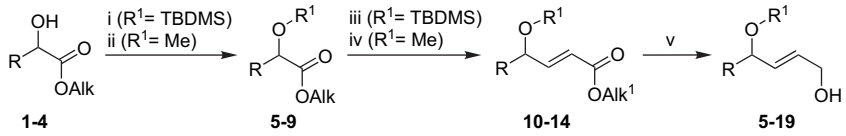
doi:10.1016/j.tet.2008.03.099



Scheme 1. Reagents and conditions: (i) TBDMSCl (1.1 equiv), imidazole (1.2 equiv), CH_2Cl_2; (ii) NaH (1.2 equiv), MeI (1.2 equiv), THF, 0 °C; (iii) (a) DIBAL-H (1.1 equiv), Et_2O, −78 °C, (b) $(EtO)_2P(O)CH_2CO_2Et$ (1.1 equiv), NaH (1.2 equiv), Et_2O or Ph_3PCHCO_2Me (1.1 equiv), toluene, reflux; (iv) (a) $LiAlH_4$ (1.0 equiv), Et_2O, 0 °C, (b) DMSO (2.4 equiv), $(COCl)_2$ (1.2 equiv), NEt_3 (5.0 equiv), CH_2Cl_2, (c) $(EtO)_2P(O)CH_2CO_2Et$ (4.2 equiv), NaH (4.2 equiv), Et_2O; (v) DIBAL-H (2.2 equiv), Et_2O, −78 °C to rt.

2. Results and discussion

The key intermediates for the synthesis of *O*-allyltrichloroacetimidates—allylic alcohols **15**–**19**, were prepared according to a slightly modified known synthetic route (Scheme 1).[4a] Commercially available α-hydroxy-carboxylic acid esters **1**–**4** were O-derivatised with MeI or TBDMSCl. The resulting methyl ether **5** was transformed to α,β-unsaturated ester **10** using a three-step procedure that involves reduction of the ester to the primary alcohol, Swern oxidation and Horner–Wadsworth–Emons olefination.[4a] Unfortunately, we were not able to achieve the yield of the ester **10** reported in the literature probably due to high volatility of intermediates. Final reduction of α,β-unsaturated ester **10** using standard procedure with DIBAL-H resulted in allylic alcohol **15** in low overall yield. TBDMS-protected esters **6**–**9** were reduced to aldehydes and these were used without further purification in the olefination reaction to yield α,β-unsaturated esters **11**–**14**. After separation of the undesired *Z*-isomer in the case of olefins **12**–**14**, all esters **11**–**14** were reduced using DIBAL-H to allylic alcohols **16**–**19** in good overall yields (Table 1).

Trichloroacetimidates **20** and **21** were freshly prepared from allylic alcohols **15** and **16** by a standard procedure and subjected to catalysis using $PtCl_2$, $PtCl_4$, AuCl, $AuCl_3$ as well as $PdCl_2$ as the reference catalyst in CH_2Cl_2 (Scheme 2). The reaction was run for 18 h—this was a sufficient time to achieve complete conversion of trichloroacetimidates **20** and **21** (according to TLC or GC). After removal of the catalyst by filtration trough a pad of Florisil®, reaction mixture was studied by GC analysis and ^1H NMR spectroscopy.

According to ^1H NMR spectroscopic data of the crude reaction mixture obtained from the rearrangement of δ-methoxy substituted trichloroacetimidate **20**, the expected Overman rearrangement products *anti*-**22** and *syn*-**22** were formed together with oxazoline **24** as the main side product. Isolation of oxazoline **24** proved to be difficult due to its volatility and low stability when exposed to moisture in the presence of the Lewis acidic catalyst. As a result, trichloroacetamide **25** (Fig. 2) was obtained when the product mixture was separated by flash chromatography. In several cases product **24** was isolated in trace amounts after flash chromatography.

Table 1
Substitution pattern, configuration and overall yield of allylic alcohols **15**–**19**

Compound	Configuration	Alk	Alk[1]	R	R[1]	Overall yield (%)
1, **5**, **10**, **15**	*S*	Me	Et	Me	Me	8
1, **6**, **11**, **16**	*S*	Me	Et	Me	TBDMS	52
2, **7**, **12**, **17**	*S*,*R*	Et	Me	Bu	TBDMS	52
3, **8**, **13**, **18**	*S*,*R*	Me	Me	Ph	TBDMS	52
4, **9**, **14**, **19**	*S*	Me	Me	*i*-Pr	TBDMS	59

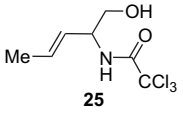


Figure 2. The product **25** of oxazoline **24** ring opening.

The best *anti*/*syn*-ratio of the amide **22** was achieved using $PtCl_2$ as catalyst (Table 2, entry 1), which was higher than using Pd(II) catalysts (entries 5 and 6). Moreover, compared to all other metal catalysts explored, $PtCl_2$ catalysed reaction was the least favourable for undesired oxazoline **24** formation and consequently amide **22** was obtained in improved yield. In the case of AuCl and $AuCl_3$, the lowest *anti*-**22**/*syn*-**22** ratio and the highest formation of oxazoline **24** was obtained (entries 3 and 4).

Similar results were observed with δ-TBDMSO substituted trichloroacetimidate **21** as the rearrangement substrate (Table 3). High yield of rearrangement product **23** and substantially improved

Table 2
Rearrangement of δ-methoxytrichloroacetimidate **20**

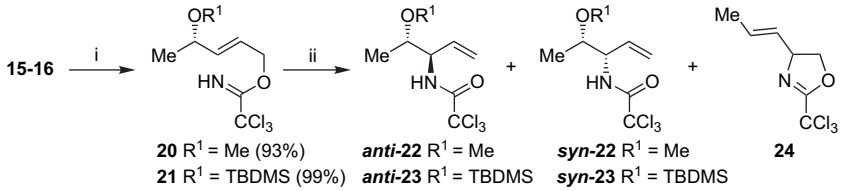
Entry	Catalyst	Yield of **22** (%)	Ratio[b] (*anti*/*syn*)	Ratio[c] of **22**:**24**	Yield of **25** (%)
1.	$PtCl_2$	65	11:1	3:1	16
2.	$PtCl_4$	35	10:1	2:1	12
3.	AuCl	48	5:1	1:1	—
4	$AuCl_3$	41	5:1	1:1	—
5.	$PdCl_2$	50	8:1	2:1	21
6.	$PdCl_2(MeCN)_2$[a]	49[a]	7:1[a]	—	—

[a] Data from Ref. 4a.
[b] According to GC analysis of crude reaction mixture.
[c] According to ^1H NMR spectroscopic data of crude reaction mixture.

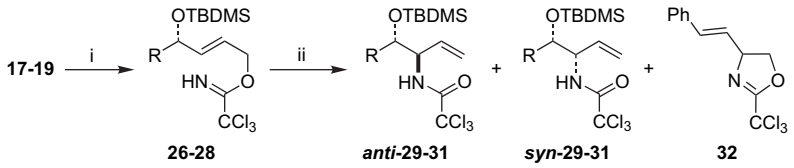
Table 3
Rearrangement of δ-TBDMSO-trichloroacetimidate **21**

Entry	Catalyst	Yield of **23** (%)	Ratio[b] (*anti*/*syn*)	Ratio[c] **23**: **24**	Yield of **25** (%)
1.	$PtCl_2$	85	6:1	8:1	8
2.	$PtCl_4$	50	6:1	10:1	—
3.	AuCl	70	2:1	5:1	—
4.	$AuCl_3$	40	2:1	5:1	—
5.	$PdCl_2$	62	2:1	n.d.	—
6.	$PdCl_2(MeCN)_2$[a]	68[a]	2:1[a]	—	—

[a] Data from Ref. 4a.
[b] According to GC analysis of crude reaction mixture.
[c] According to ^1H NMR spectroscopic data of crude reaction mixture.



Scheme 2. Reagents and conditions: (i) CCl_3CN (1.1 equiv), NaH (10 mol %), Et_2O, 0 °C to rt; (ii) catalyst, CH_2Cl_2, rt.



Scheme 3. Reagents and conditions: (i) CCl_3CN (1.1 equiv), NaH (10 mol%), Et_2O, 0 °C to rt; (ii) catalyst, CH_2Cl_2, rt.

anti-**23**/*syn*-**23** ratio was obtained with $PtCl_2$ as the catalyst (entry 1). Again AuCl and $AuCl_3$ gave the lowest *anti*-**23**/*syn*-**23** ratio and highest formation of oxazoline **24** (entries 3 and 4). Noteworthy, in all cases oxazoline **24** formation was less favourable from δ-TBDMSO substituted trichloroacetimidate **21** compared to δ-methoxy substituted trichloroacetimidate **20**.

Structurally different δ-TBDMSO substituted *O*-allylic trichloroacetimidates **26**–**28** were used as substrates for the $PtCl_2$ and $PdCl_2$ catalysed Overman rearrangement (Scheme 3). Good yields with both catalysts were observed only in the case of *n*-Bu substituted trichloroacetimidate **26** (Table 4, entries 1 and 2). $PtCl_2$ again provided considerably better *anti*/*syn*-ratio compared to $PdCl_2$ catalyst. Trichloroacetimidate **27** bearing phenyl substituent gave low chemical yield and *anti*/*syn*-selectivity of amides *anti*,*syn*-**30** (Table 3, entries 3 and 4) and notable amount of oxazoline **32**. Oxazoline **32** was stable to be isolated by flash chromatography in 52% for $PtCl_2$ and 44% yield for $PdCl_2$ catalysed reactions. In the case of trichloroacetimidate **28** bearing an *iso*-propyl substituent, decomposition was observed with only trace of amide **31** formation (Table 3, entries 5 and 6) leading to the mixture of unidentified products. In this case, formation of oxazoline was not observed in contrast to other rearrangement substrates **20**, **21** and **26**, **27**.

The formation of oxazolines **24** and **32** in the rearrangement of trichloroacetimidates **20**, **21** and **27** deserves attention as a dominant side reaction in the rearrangement of δ-oxy substituted allylic trichloroacetimidates.

Although such a product formation has not been reported previously in ether-directed diastereoselective Overman rearrangement, vinyloxazoline has been isolated as the major product in the metal catalysed rearrangement of trichloroacetimidate derived from *Z*-(3-benzyloxy)crotyl alcohol or bis-trichloroacetimidate from *Z*-but-2-ene-1,4-diol.[5,6] In analogy to the CIR mechanism of the Overman rearrangement, we hypothesise that oxazoline **24** results from the metal ion induced 5-*exo*-*trig* cyclisation to aminometallation intermediate **34** and a subsequent de-oxymetalation step in which methanol elimination regenerates the catalyst in the original oxidation state (Fig. 3). It is puzzling why the 5-*exo*-*trig* cyclisation product is observed with δ-oxy substituted trichloroacetimidates while it has never been observed as a dominant side reaction for δ-unsubstituted allylic trichloroacetimidates that should give β-hydride elimination product with Pd(0) formation. One of the explanations would be that the imidate nitrogen attack at C-2 is driven by the electronic effect of the δ-oxygen assuming intermolecular aminometallation as the first irreversible step for

Table 4
Rearrangement of trichloroacetimidates **26**–**28**

Entry	Imidate	Catalyst	Yield of **29**–**31** (%)	Ratio[a] (*anti*/*syn*)
1.	**26**, R=*n*-Bu	$PtCl_2$	71	6:1
2.		$PdCl_2$	65	3:1
3.	**27**, R=Ph	$PtCl_2$	22	3:1
4.		$PdCl_2$	18	2:1
5.	**28**, R=*i*-Pr	$PtCl_2$	<5	2:1
6.		$PdCl_2$	—	—

[a] According to GC analysis of crude reaction mixture.

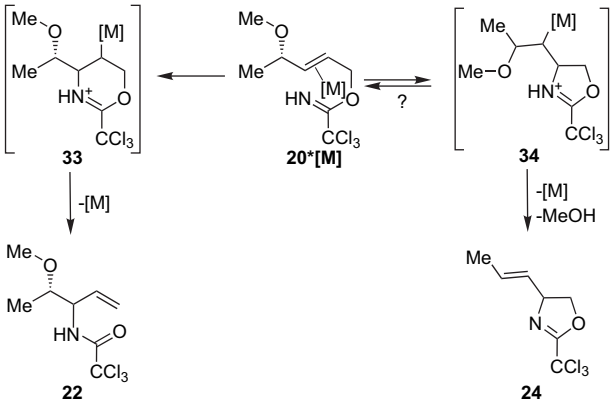


Figure 3. Mechanistic explanation of oxazoline **24** formation.

both 5-*exo*-*trig* and 6-*endo*-*trig* cyclisations. An evidence has been recently provided that C–N bond formation is rate limiting (first irreversible step) in the rearrangement of allylic trichloroacetimidates to amides, e.g., **22**.[7] It cannot be excluded, however, that for oxazoline **24** formation de-oxymetallation is the first irreversible step due to lower ability of methanol to serve as a leaving group in intermediate **34** compared to protonated imidate in **33**. In this case, not only 5-*exo*-*trig* and 6-*endo*-*trig* cyclisations but also de-aminometallation and de-oxymetallation rates of intermediate **34** may determine the products **22** and **24** ratio.

3. Conclusions

In summary, we have shown that for both δ-methoxy and δ-TBDMSO substituted trichloroacetimidates the use of $PtCl_2$ catalyst gives notably improved *anti*/*syn*-ratio of 1,2-aminoalcohol derivatives compared to all metal catalysts known to promote Overman rearrangement. The formation of 2-trichloromethyloxazoline was observed as a dominant side reaction reducing the yield of Overman rearrangement product. This side reaction was suppressed by using a δ-TBDMS-ether as a directing group. For the $PtCl_2$ catalysed rearrangement of such substrates, both the yield and improved *anti*/*syn*-ratio of the resulting protected 1,2-aminoalcohols are satisfactory to be used as a synthetic method. Further investigation to understand factors determining formation of Overman rearrangement product versus 2-trichloromethyloxazoline formation is underway.

4. Experimental section

4.1. General

Reagents and starting materials were obtained from commercial sources and used as-received. The solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used. All reactions were performed under an argon atmosphere. Flash chromatography was carried out using Merck Kieselgel (230–400 mesh). Thin layer chromatography was performed on silica gel and was visualised by staining with $KMnO_4$. NMR spectra were recorded on Varian Mercury spectrometer (400

and 200 MHz) with chemical shifts values (δ) in parts per million (ppm) relative to TMS using residual chloroform signal as internal standard. Gas chromatographic analysis was performed using HP 6890 gas chromatographic system with HP 5972 MSD detector. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. IR spectra were measured on a Shimadzu FTIR IR Prestige-21 spectrometer.

*4.1.1. (S)-2-Methoxypropionic acid methyl ester (**5**)*

Sodium hydride (60% in mineral oil) (1.2 g, 0.03 mol) was washed with hexane (2×5 mL). The powder was suspended in THF (22 mL) and cooled to 0 °C, and the solution of methyl (*S*)-lactate **1** (2.6 g, 0.025 mol) in THF (10 mL) was added dropwise. After stirring for 0.5 h, methyl iodide (4.26 g, 0.03 mol) was added and the reaction mixture was warmed to room temperature and stirred for 4 h. To the reaction mixture, NH_4Cl solution (50 mL) was added and the resulting mixture extracted with diethyl ether (2×50 mL). The organic layers were combined and washed with brine (20 mL), dried (Mg_2SO_4) and concentrated in vacuo to yield 1.49 g (50%) of the title compound as colourless oil.

Spectroscopic data is identical to that reported in the literature.[8]

4.2. General procedure for the preparation of TBDMS ethers 6–9

To the solution of α-hydroxy ester (18.7 mmol) in CH_2Cl_2 (23 mL), imidazole (19.6 mmol) and *tert*-butyldimethylsilyl chloride (19.6 mmol) were added. The reaction mixture was stirred at room temperature for 24 h and then water (40 mL) was added. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×25 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated in vacuo. Purification of the product was performed by means of flash chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (15:1).

*4.2.1. (S)-2-(tert-Butyldimethylsilanyloxy)propionic acid methyl ester (**6**)*

Yield: 4.04 g (99%); colourless oil; $[\alpha]_D^{20}$ −27.7 (*c* 2.0, CCl_4) {lit.[8] $[\alpha]_D$ −26.9 (*c* 1.9, CCl_4)}. Spectroscopic data is identical to that reported in the literature.[9]

*4.2.2. 2-(tert-Butyldimethylsilanyloxy)hexanoic acid ethyl ester (**7**)*

Yield: 4.05 g (79%); colourless oil; ν_{max} (neat): 2953, 2927, 2856, 1753, 1733, 1471, 1251, 1143; δ_H (400 MHz, $CDCl_3$): 4.10–4.25 (3H, m, Et CH_2 and O*CH*), 1.65–1.75 (2H, m) and 1.25–1.45 (4H, m, *n*-Bu $(CH_2)_3$), 1.27 (3H, t, *J* 7.2 Hz, Et CH_3), 0.85–0.95 (12H, m, *n*-Bu CH_3 and Si$C(CH_3)_3$), 0.08 (3H, s, SiCH_3) and 0.05 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 174.0, 72.3, 60.6, 34.9, 27.3, 25.7, 22.4, 18.3, 14.2, 13.9, −4.9 and −5.3; *m*/*z* (EI): 259 (M^+-CH_3, 1%), 217 (53), 201 (30), 189 (72), 161 (10), 145 (25), 115 (19), 103 (36), 75 (100), 59 (30) and 45 (15).

*4.2.3. (tert-Butyldimethylsilanyloxy)phenylacetic acid methyl ester (**8**)*

Yield: 5.14 g (98%); colourless oil. Spectroscopic data is identical to that reported in the literature.[10]

*4.2.4. (S)-2-(tert-Butyldimethylsilanyloxy)-3-methylbutyric acid methyl ester (**9**)*

Yield: (96%); colourless oil; $[\alpha]_D^{20}$ −31.3 (*c* 2.0, CCl_4); ν_{max} (neat): 2953, 1755, 1471, 1387, 1250, 1188, 1145, 1070, 1005; δ_H (200 MHz, $CDCl_3$): 3.97 (1H, d, *J* 5.2 Hz, O*CH*), 3.71 (3H, s, CO_2CH_3), 2.02 (1H, m, *i*-Pr *CH*), 0.85–0.95 (15H, m, *i*-Pr $(CH_3)_2$ Si$C(CH_3)_3$), 0.05 (3H, s, SiCH_3) and 0.04 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 174.0, 77.1, 51.5, 32.8, 25.7, 19.0, 17.0, −5.1 and −5.4; *m*/*z* (EI): 231 (M^+-CH_3, 1%), 189 (48), 161 (24), 131 (10), 89 (100), 73 (47), 59 (36) and 41 (15).

*4.2.5. (E)-(S)-4-Methoxypent-2-enoic acid ethyl ester (**10**)*

$LiAlH_4$ (1.82 g, 0.048 mol) was suspended in Et_2O (100 mL) and the mixture cooled to 0 °C. The solution of methyl (*S*)-2-methoxypropanoate (**5**) (5.6 g, 0.048 mol) in Et_2O (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. Water was added to the reaction mixture until white precipitate has formed. The precipitate was filtered through a pad of Celite®, which was washed with Et_2O. The filtrate was dried (Na_2SO_4) and concentrated in vacuo. The (*S*)-2-methoxypropanol obtained was used without further purification.

Dimethyl sulfoxide (3.26 mL, 0.046 mol) was added to a solution of oxalyl chloride (1.97 mL, 0.022 mol) in CH_2Cl_2 (100 mL) at −78 °C. The resulting solution was stirred for 15 min and then (*S*)-2-methoxypropanol solution in CH_2Cl_2 (120 mL) was added. This solution was allowed to stir for additional 15 min. Triethylamine (13.44 mL) was then added and the reaction mixture brought to room temperature over 2 h. Aldehyde obtained from (*S*)-2-methoxypropanol was used for the next transformation without isolation from reaction mixture.

In a separate flask, sodium hydride (60% in mineral oil) (3.12 g, 0.078 mol) was washed with hexane (2×15 mL) and suspended in THF (50 mL). Triethyl phosphonoacetate (16 mL, 0.08 mol) was added and the mixture was allowed to stir for 40 min. The deprotonated phosphonoacetate solution was slowly added to the aldehyde solution at 0 °C and the reaction mixture was allowed to stir for 2 h at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and quenched with brine. The organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. Purification was performed by flash chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (4:1) to give the title compound (1.9 g, 25% over three steps).

Spectroscopic data is identical to that reported in the literature.[4a]

*4.2.6. (E)-(S)-4-(tert-Butyldimethylsilanyloxy)pent-2-enoic acid ethyl ester (**11**)*

To the solution of methyl ester **6** (3.0 g, 0.0137 mol) in Et_2O (60 mL) at −78 °C, 1 M DIBAL-H solution in hexane (14 mL) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 2 h. The reaction was quenched with MeOH (4 mL) and allowed to warm to room temperature. This mixture was treated with brine (70 mL) and the aqueous phase was separated and extracted with Et_2O (3×50 mL). The combined organic phase was washed with brine (50 mL) and dried (Na_2SO_4). The crude aldehyde was obtained after filtration and concentration in vacuo and was used further without purification.

Solution of triethyl phosphonoacetate (3.07 g, 0.0137 mol) in Et_2O (20 mL) was added dropwise to a suspension of sodium hydride (60%, 0.55 g, 0.0137 mol) in Et_2O (30 mL). To this mixture was added the solution of crude aldehyde in Et_2O (20 mL) and the mixture stirred at room temperature overnight. After addition of water (70 mL), the product was extracted with Et_2O, dried over Na_2SO_4 and purified by flash chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (20:1) to give the title compound in 67% (2.3 g) yield as a colourless oil; $[\alpha]_D^{20}$ +4.2 (*c* 3.0, $CHCl_3$) {lit.[4a] $[\alpha]_D^{21}$ +4.4 (*c* 1.0, $CHCl_3$)}. Spectroscopic data is identical to that reported in the literature.[4a]

4.3. General procedure for the preparation of α,β-unsaturated methyl esters 12–14

The reductions of esters 7–**9** to aldehydes were performed as in the case of TBDMS-protected ester **6** using 1 M DIBAL-H solution. The crude aldehyde (~1 mmol) was taken up in toluene (3 mL) and methyl (triphenylphosphoranylidene)acetate (1 mmol) was added. The reaction mixture was refluxed for 30 min, cooled to room

temperature and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (20:1).

*4.3.1. (E)-4-(tert-Butyldimethylsilanyloxy)oct-2-enoic acid methyl ester (**12**)*

Yield: 72%; colourless oil; ν_{max} (neat) 2956, 2931, 2859, 1730, 1661, 1463, 1274, 1259, 1165, 1092 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 6.94 (1H, dd, *J* 15.5, 4.5 Hz, =*CH*), 5.98 (1H, dd, *J* 15.4, 1.7 Hz, =*CH*), 4.25–4.35 (1H, m, O*CH*), 3.74 (3H, s, CO_2CH_3), 1.50–1.60 (2H, m) and 1.25–1.35 (4H, m, *n*-Bu (CH_2)$_3$), 0.80–1.00 (12H, m, *n*-Bu CH_3 and Si(C(CH_3)$_3$)), 0.03 (3H, s, SiCH_3) and 0.05 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 167.2, 151.5, 119.2, 71.5, 51.5, 37.0, 26.9, 25.8, 22.7, 18.2, 14.0, −4.6 and −4.9; *m*/*z* (EI): 286 (M^+, 1%), 229 (71), 197 (40), 129 (10), 89 (100), 81 (23), 73 (78), 59 (32) and 41 (33).

*4.3.2. (E)-4-(tert-Butyldimethylsilanyloxy)-4-phenylbut-2-enoic acid methyl ester (**13**)*

Yield: 60%; colourless oil; ν_{max} (neat) 2952, 2930, 2858, 1726, 1659, 1436, 1298, 1279, 1259, 1193, 1165, 1125 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.05–7.35 (5H, m, *Ph*), 6.98 (1H, dd, *J* 15.5, 4.5 Hz, =*CH*), 6.12 (1H, dd, *J* 15.5, 2.0 Hz, =*CH*), 5.31 (1H, dd, *J* 4.2, 1.8 Hz, O*CH*), 3.72 (3H, s, CO_2CH_3), 0.91 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3) and −0.06 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 167.1, 150.6, 141.6, 128.5, 127.7, 126.2, 118.4, 74.1, 51.5, 25.7, 18.3, −4.9 and −4.9; *m*/*z* (EI): 291 (M^+-CH_3, 1%), 249 (45), 173 (7), 115 (100), 89 (59), 75 (23), 59 (15) and 41 (10).

*4.3.3. (E)-(S)-4-(tert-Butyldimethylsilanyloxy)-5-methylhex-2-enoic acid methyl ester (**14**)*

Yield: 62%; colourless oil; $[\alpha]_D^{20}$ +2.0 (*c* 2.0, CCl_4) {lit.[9] $[\alpha]_D$ +1.0 (*c* 1.0, $CHCl_3$)}. Spectroscopic data is identical to that reported in the literature.[9]

4.4. General procedure for the preparation of allylic alcohols 15–19

The solution of unsaturated ester (1 mmol) in Et_2O (20 mL) was cooled to −78 °C and 1 M DIBAL-H solution in hexane (2.2 equiv) was added dropwise. The reaction mixture was allowed to stir at −78 °C for 2 h and then warmed to room temperature. A solution of Rochelle salt (30 mL) was added and stirred until the phases have separated. The aqueous phase was separated and extracted with Et_2O (2×20 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 and purified by flash chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (20:1).

*4.4.1. (E)-(S)-4-Methoxypent-2-en-1-ol (**15**)*

Yield: 0.07 g (61%); colourless oil. Spectroscopic data is identical to that reported in the literature.[4a]

*4.4.2. (E)-(S)-4-(tert-Butyldimethylsilanyloxy)pent-2-en-1-ol (**16**)*

Yield: 0.17 g (79%); colourless oil; $[\alpha]_D^{20}$ +3.6 (*c* 3.0, $CHCl_3$) {lit.[4a] $[\alpha]_D^{19}$ +3.7 (*c* 3.0, $CHCl_3$)}. Spectroscopic data is identical to that reported in the literature.[4a]

*4.4.3. (E)-4-(tert-Butyldimethylsilanyloxy)oct-2-en-1-ol (**17**)*

Yield: 0.24 g (92%); colourless oil; ν_{max} (neat) 3600–3100 (br), 2957, 2930, 2859, 1473, 1463, 1361, 1256, 1083, 1006 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 5.60–5.80 (2H, m, *HC*=*CH*), 4.10–4.15 (2H, m, OCH_2), 1.40–1.55 (2H, m) and 1.25–1.35 (4H, m, *n*-Bu (CH_2)$_3$), 0.85–0.95 (12H, m, *n*-Bu CH_3 and Si(C(CH_3)$_3$)), 0.05 (3H, s, SiCH_3) and 0.03 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 135.5, 128.2, 72.7, 63.3, 37.9, 27.4, 25.9, 22.7, 18.2, 14.1, −4.3 and −4.8; *m*/*z* (EI): 243 (M^+-CH_3, 1%), 201 (23), 75 (100), 67 (24) and 41 (23).

*4.4.4. (E)-4-(tert-Butyldimethylsilanyloxy)-4-phenylbut-2-en-1-ol (**18**)*

Yield: 0.25 (89%); colourless oil; ν_{max} (neat): 3327, 2950, 2924, 2852, 1741, 1600, 1469, 1360, 1251, 1093, 1057, 1002; δ_H (400 MHz, $CDCl_3$): 7.20–7.35 (5H, m, *Ph*), 5.75–5.90 (2H, m, *HC*=*CH*), 5.19 (1H, d, *J* 5.3 Hz, O*CH*), 4.14 (2H, m, OCH_2), 1.26 (1H, m, *OH*), 0.90 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3), −0.02 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 143.7, 135.3, 128.2, 128.0, 127.1, 125.9, 74.8, 63.1, 25.8, 18.3, −4.6 and −4.8; *m*/*z* (EI): 221 (M^+-t-Bu, 3%), 129 (50), 115 (7), 91 (13), 75 (100), 57 (8) and 41 (13).

*4.4.5. (E)-(S)-4-(tert-Butyldimethylsilanyloxy)-5-methylhex-2-en-1-ol (**19**)*

Yield: 0.24 g (99%); colourless oil; $[\alpha]_D^{20}$ +2.8 (*c* 3.0, $CHCl_3$). Spectroscopic data is identical to that reported in the literature.[9]

4.5. General procedure for the preparation of trichloroacetimidates 20, 21, and 26–28

Sodium hydride (60% in mineral oil) (10 mol %) was added to a solution of allylic alcohol **15**–**19** (10 mmol) in Et_2O (15 mL). The reaction mixture was cooled to −10 °C and a solution of trichloroacetonitrile (11 mmol) in diethyl ether (10 mL) was added dropwise. The solution was allowed to warm to room temperature and the solvent was evaporated. Light petroleum ether (20 mL) containing methanol (0.1 mL) was added to the residue. The solution was filtered through a pad of Celite®, evaporated and used without further purification.

*4.5.1. 2,2,2-Trichloroacetimidic acid (E)-(S)-4-methoxypent-2-enyl ester (**20**)*

Yield: 2.42 g (93%); colourless oil; δ_H (200 MHz, $CDCl_3$): 8.32 (1H, br s, *NH*), 5.70–5.95 (2H, m, *HC*=*CH*), 4.14 (2H, d, *J* 4.5 Hz, OCH_2), 3.78 (1H, m, O*CH*), 3.29 (3H, s, OCH_3), 1.26 (3H, d, *J* 6.5 Hz, CH_3).

*4.5.2. 2,2,2-Trichloroacetimidic acid (E)-(S)-4-(tert-butyldimethylsilanyloxy)pent-2-enyl ester (**21**)*

Yield: 3.71 g (99%); colourless oil; δ_H (200 MHz, $CDCl_3$): 8.29 (1H, br s, *NH*), 5.75–5.95 (2H, m, *CH*=*CH*), 4.79 (2H, d, *J* 4.5 Hz, OCH_2), 4.25–4.40 (1H, m, O*CH*), 1.23 (3H, d, *J* 6.5 Hz, CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s, SiCH_3) and 0.05 (3H, s, SiCH_3).

*4.5.3. 2,2,2-Trichloroacetimidic acid (E)-4-(tert-butyldimethylsilanyloxy)oct-2-enyl ester (**26**)*

Yield: 4.12 g (99%); colourless oil; δ_H (200 MHz, $CDCl_3$): 8.28 (1H, br s, *NH*), 5.70–5.95 (2H, m, *CH*=*CH*), 4.79 (2H, d, *J* 5.0 Hz, OCH_2), 4.05–4.20 (1H, m, O*CH*), 1.20–1.55 (6H, m, *n*-Bu (CH_2)$_3$), 0.80–0.95 (3H, m, *n*-Bu CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 69.1, 72.6, 91.5, 122.2, 139.2, 162.5, 37.7, 27.3, 25.9, 22.6, 18.2, 14.1, −4.3 and −4.8.

*4.5.4. 2,2,2-Trichloroacetimidic acid (E)-4-(tert-butyldimethylsilanyloxy)-4-phenylbut-2-enyl ester (**27**)*

Yield: 3.89 g (89%); colourless oil; δ_H (200 MHz, $CDCl_3$): 8.29 (1H, br s, *NH*), 7.20–7.35 (5H, m, Ph), 5.90–6.00 (2H, m, *CH*=*CH*), 5.20–5.25 (1H, m, O*CH*), 4.75–4.85 (2H, m, OCH_2), 0.91 (9H, s, SiC(CH_3)$_3$), 0.07 (3H, s, SiCH_3) and −0.01 (3H, s, SiCH_3).

*4.5.5. 2,2,2-Trichloroacetimidic acid (E)-(S)-4-(tert-butyldimethylsilanyloxy)-5-methylhex-2-enyl ester (**28**)*

Yield: 3.22 g (80%); colourless oil; δ_H (200 MHz, $CDCl_3$): 8.28 (1H, br s, *NH*), 5.70–5.90 (2H, m, *CH*=*CH*), 3.87 (2H, m, OCH_2), 1.60–1.70 (1H, m, *CH*(CH_3)$_2$), 0.80–0.90 (15H, s, CH(CH_3)$_2$ and SiC(CH_3)$_3$), 0.03 (3H, s, SiCH_3) and −0.01 (3H, s, SiCH_3).

4.6. General procedure for the Overman rearrangement

To the solution of trichloroacetimidate **20**, **21**, and **26**–**28** (1 mmol) in CH_2Cl_2 (or THF in the case of $PtCl_4$) (0.5 M) under argon atmosphere, metal catalyst (10 mol %) was added and stirred for 18 h at room temperature. The reaction mixture was filtered through a pad of Florisil® and the isomers were separated by flash chromatography on silica gel eluting with a mixture of petroleum ether and ethyl acetate (10:1).

*4.6.1. 2,2,2-Trichloro-N-[(R)-1-((S)-1-methoxyethyl)-allyl]acetamide (anti-**22**)*

Yields are shown in Table 2; pale yellow oil; $[\alpha]_D^{19}$ +17.5 (*c* 3.0, $CHCl_3$). Spectroscopic data is identical to that reported in the literature.[4a]

*4.6.2. N-{(R)-1-[(S)-1-(tert-Butyldimethylsilanyloxy)-ethyl]-allyl}-2,2,2-trichloroacetamide (anti-**23**) and N-{(S)-1-[(S)-1-(tert-butyldimethylsilanyloxy)-ethyl]-allyl}-2,2,2-trichloroacetamide (syn-**23**)*

Yields are shown in Table 3; pale yellow oil. Spectroscopic data is identical to that reported in the literature.[4a]

*4.6.3. 4-((E)-Propenyl)-2-trichloromethyl-4,5-dihydrooxazole (**24**)*

Yellow oil; ν_{max} (neat): 3421, 2968, 1718, 1654, 1449, 1226 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 5.78 (1H, dq, *J* 15.1, 6.4 Hz, =*CH*), 5.48 (1H, ddq, *J* 15.1, 7.6, 1.8 Hz, =*CH*), 4.75–4.85 (1H, m, *CH*O), 4.72 (1H, dd, *J* 9.6, 8.2 Hz), 4.29 (1H, t, *J* 8.2 Hz, CH_2N), and 1.73 (3H, dd, *J* 6.6, 1.8 Hz, CH_3); δ_C (100 MHz, $CDCl_3$): 162.8, 130.1, 128.6, 76.2, 68.6 and 17.8.

*4.6.4. 2,2,2-Trichloro-N-((E)-1-hydroxymethylbut-2-enyl)-acetamide (**25**)*

Yields are shown in Tables 2 and 3; white solid, mp 67–69 °C; [Found: C, 34.3; H, 3.9; N, 5.5. $C_7H_{10}Cl_3NO_2$ requires C, 34.11; H, 4.09; N, 5.68%] ν_{max} (liquid film): 3302, 2938, 1710, 1688, 1530, 1454, 1259, 1032 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 7.26 (1H, br s, *NH*), 5.70–5.85 (1H, m, =*CH*), 5.45–5.55 (1H, m, =*CH*), 4.40–4.50 (1H, m, N*CH*), 2.13 (1H, br s, *OH*), 3.70–3.85 (2H, m, CH_2O) and 1.70–1.75 (3H, m, CH_3); δ_C (100 MHz, $CDCl_3$): 161.6, 129.7, 126.1, 92.6, 64.3, 54.6 and 17.9.

*4.6.5. N-[2-(tert-Butyldimethylsilanyloxy)-1-vinylhexyl]-2,2,2-trichloroacetamide (anti-**29**) and N-[2-(tert-butyldimethylsilanyloxy)-1-vinylhexyl]-2,2,2-trichloro-acetamide (syn-**29**)*

Yields are shown in Table 4, entries 1 and 2.

anti-**29**: colourless oil; ν_{max} (neat): 3405 (br), 2958, 2873, 1699, 1511, 1329 and 1055 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 7.00–7.10 (1H, br s, *NH*), 5.80 (1H, ddd, *J* 16.8, 10.2 and 7.3 Hz, =*CH*), 5.25–5.40 (2H, m, =CH_2), 4.35–4.45 (1H, m, N*CH*), 3.75–3.85 (1H, O*CH*), 1.20–1.55 (6H, m, *n*-Bu (CH_2)$_3$), 0.85–1.00 (3H, m, *n*-Bu CH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.09 (3H, s, SiCH_3) and 0.10 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 161.6, 135.5, 116.6, 92.9, 69.7, 58.6, 25.7, 21.4, 17.9, −4.3 and −4.8; *m*/*z* (EI): 346 (M^+−*t*-Bu, 13%), 260 (15), 218 (38), 201 (82), 183 (12), 145 (13), 115 (19), 93 (18), 73 (100), 59 (14) and 41 (10).

syn-**29**: δ_H (200 MHz, $CDCl_3$): 7.20–7.30 (1H, br s, *NH*), 5.70–5.85 (1H, m, =*CH*), 5.15–5.30 (2H, m, =CH_2), 4.35–4.45 (1H, m, N*CH*), 3.75–3.85 (1H, O*CH*), 1.20–1.55 (6H, m, *n*-Bu (CH_2)$_3$), 0.85–1.00 (3H, m, *n*-Bu CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.08 (3H, s, SiCH_3) and 0.05 (3H, s, SiCH_3)—extracted from the spectra of isomeric mixture; *m*/*z* (EI): 346 (M^+−*t*-Bu, 15%), 220 (39), 201 (78), 183 (15), 145 (15), 115 (18), 93 (20), 73 (100), 59 (14) and 41 (10).

*4.6.6. N-{1-[(tert-Butyldimethylsilanyloxy)-phenylmethyl]-allyl}-2,2,2-trichloroacetamide (anti-**30**) and N-{1-[(tert-butyldimethylsilanyloxy)-phenylmethyl]-allyl}-2,2,2-trichloroacetamide (syn-**30**)*

Yields are shown in Table 4, entries 3 and 4.

anti-**30**: white solid, mp 74–76 °C; [Found: C, 51.3; H, 6.0; N, 3.2. $C_{18}H_{26}Cl_3NO_2Si$ requires C, 51.13; H, 6.20; N, 3.31%] ν_{max} (Nujol): 3374 (br), 1699, 1514 and 1044 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 7.25–7.40 (5H, m, Ph), 6.98 (1H, m, *NH*), 5.78 (1H, ddd, *J* 16.8, 11.0 and 6.6 Hz, =*CH*), 5.00–5.20 (2H, m, =CH_2), 4.94 (1H, d, *J* 3.6 Hz, O*CH*), 4.57 (1H, m, N*CH*), 0.94 (9H, s, SiC(CH_3)$_3$), 0.09 (3H, s, SiCH_3) and −0.17 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$): 161.0, 139.8, 131.6, 128.1, 127.9, 126.5, 118.3, 75.8, 59.8, 25.8, 18.1, −4.5 and −5.2; *m*/*z* (EI): 366 (M^+−*t*-Bu, 13%), 221 (100), 203 (14), 163 (12), 149 (15), 129 (10) and 73 (53).

syn-**30**: colourless oil; δ_H (200 MHz, $CDCl_3$): 7.25–7.40 (5H, m, Ph), 7.21 (1H, m, *NH*), 6.02 (1H, ddd, *J* 17.6, 9.8 and 4.8 Hz, =*CH*), 5.20–5.35 (2H, m, =CH_2), 4.87 (1H, d, *J* 3.0 Hz, O*CH*), 4.48 (1H, m, N*CH*), 0.93 (9H, s, SiC(CH_3)$_3$), 0.07 (3H, s, SiCH_3) and −0.14 (3H, s, SiCH_3).

*4.6.7. 4-((E)-Styryl)-2-trichloromethyl-4,5-dihydrooxazole (**32**)*

Yield: 52%—$PtCl_2$, and 44%—$PdCl_2$. Yellow oil; δ_H (200 MHz, $CDCl_3$): 7.25–7.45 (5H, m, Ph), 6.66 (1H, d, *J* 16.1 Hz, =*CH*), 6.19 (1H, dd, *J* 16.1 and 8.0 Hz, =*CH*), 4.95–5.15 (1H, m, N*CH*), 4.84 (1H, t, *J* 9.0 Hz) and 4.43 (1H, t, *J* 8.0 Hz, OCH_2); δ_C (100 MHz, $CDCl_3$): 163.3, 136.0, 133.3, 128.6, 128.2, 126.6, 126.6, 76.1 and 68.6; *m*/*z* (EI): 291 (M^+, 4%), 254 (27), 224 (15), 189 (13), 182 (53), 154 (11), 142 (16), 128 (46), 115 (100), 102 (16), 91 (29), 77 (24), 63 (24), 51 (24), 51 (22) and 39 (17).

Acknowledgements

The work was supported by a grant from Latvian Council of Science and European Social Fund within the National Programme 'Support for the carrying out doctoral study programm's and post-doctoral researches'. The authors thank Dr. Juris Fotins for valuable suggestions during the preparation of the manuscript.

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