Scope and limitations of ether-directed, metal-catalysed aza-Claisen rearrangements; improved stereoselectivity using non-coordinating solvents

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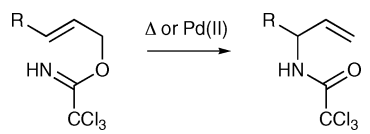
In an effort to understand and enhance the stereochemical outcome of the MOM-ether directed rearrangement of allylic trichloroacetimidates we have investigated various reaction conditions for this process. A range of Pd(II) and other metal catalysts have been shown to effectively catalyse the rearrangement providing the subsequent allylic amides in high selectivity (up to 11 : 1 ratio of diastereomers). The replacement of THF as a solvent in this reaction with non-coordinating solvents such as toluene has led to an enhancement of the directing effect resulting in a significant increase in the diastereoselective outcome (15 : 1 ratio). The reaction was also carried out for the first time, using a highly coordinating ionic solvent which disrupts binding of the Pd(II)-catalyst to the MOM-ether yielding the allylic amide in only moderate diastereoselectivity. These results provide further evidence for the ether directed aza-Claisen rearrangement of allylic trichloroacetimidates.

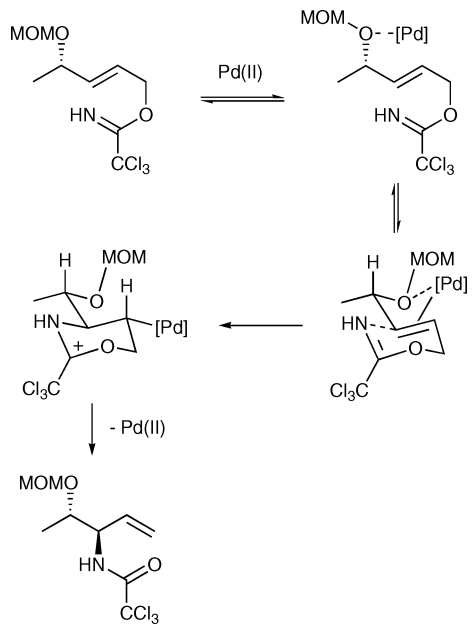
Introduction

The thermal and metal-catalysed rearrangement of allylic trichloroacetimidates (Scheme 1), first reported by Overman,[1] has found widespread application in the synthesis of nitrogen containing molecules including alkaloids, antibiotics and unnatural amino acids.[2] This synthetic transformation which involves clean 1,3-transposition of the alkene moiety proceeds *via* a highly ordered chair-like transition state allowing excellent transfer of chirality to the final product.[1b,3]



Scheme 1 Rearrangement of allylic trichloroacetimidates.

In recent years asymmetric variants of the metal-catalysed reaction have been developed including processes involving a number of chiral palladium(II)-catalysts which carry out this transformation in high yields with excellent enantioselectivity.[4] Our own research has utilised a substrate-directed approach, and we have shown that the MOM-ether group in particular, can effectively coordinate the Pd(II)-catalyst and direct this to one face of the alkene resulting in a highly diastereoselective synthesis of allylic trichloroacetimidates (10 : 1 ratio of diastereomers).[5,6] The outcome of this highly selective process was rationalised using the well characterised chair-like transition state which is controlled by both the directing effect of the MOM-group as well as 1,3-allylic strain (Scheme 2).[6a] Evidence for the involvement of the MOM-ether oxygens during the rearrangement reaction has been provided by the synthesis and subsequent rearrangement of a carbon analogue resulting in a relatively unselective reaction (2 : 1).[6a] Having developed this MOM-ether directed approach for the asymmetric synthesis of allylic 1,2-amino alcohols we have been seeking to understand how this process operates and whether the stereoselective outcome can be enhanced.



Scheme 2 MOM-ether directed rearrangement *via* the cyclisation-induced pathway.

In this paper, we report the effect of differing reaction conditions on the stereoselectivity of this directed rearrangement, including the use of Pd(II) and other metal catalysts. We also demonstrate how non-coordinating solvents such as toluene can significantly enhance the stereoselectivity of this process, while highly coordinating solvents such as ionic liquids severely disrupt the coordination of the Pd(II)-catalyst with the MOM-ether, producing the allylic amide in moderate diastereoselectivity and thus, providing further evidence for the directing effect.

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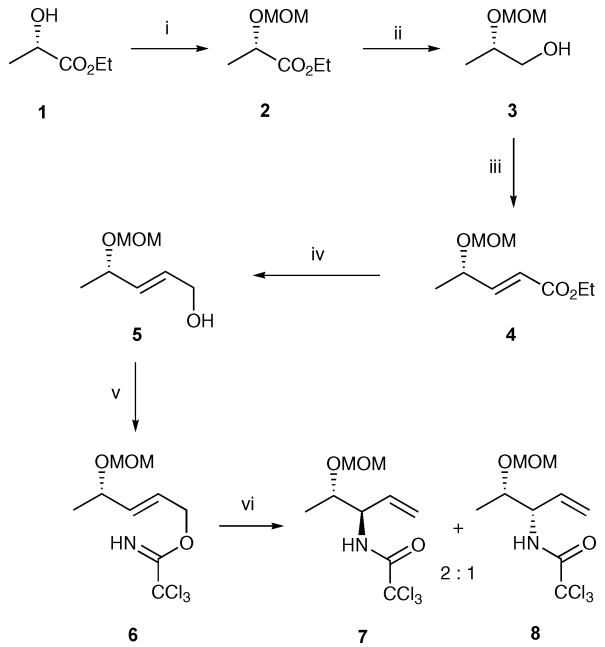
Results and discussion

The allylic alcohol substrate used in this study, (2*E*,2*S*)-4-methoxymethoxypent-2-en-1-ol **5** was prepared using an approach previously reported by our group (Scheme 3).[6] The MOM-ether **2** was formed in excellent yield by reaction of ethyl (*S*)-lactate **1** with sodium hydride and MOM-Cl.[7] Reduction of the ester functional group using DIBAL-H gave the corresponding alcohol **3**. This was converted cleanly to the (*E*)-α,β-unsaturated ester **4** using a one-pot, Swern oxidation/Horner–Wadsworth–Emmons (HWE) reaction.[8] Finally reduction of **4** with DIBAL-H gave the allylic alcohol **5** in 49% overall yield from ethyl (*S*)-lactate.



Scheme 3 *Reagents and conditions*: i. MOMCl, NaH, THF, 95%; ii. DIBAL-H (2.2 equiv.), Et_2O, −78 °C to RT, 82%; iii. DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C to RT, then triethyl phosphonoacetate, LiCl, DBU, MeCN, 65%; iv. DIBAL-H (2.2 equiv.), Et_2O, −78 °C to RT, 96%; v. DBU, Cl_3CCN, CH_2Cl_2; vi. Δ, *p*-xylene, K_2CO_3, 91% over two steps.

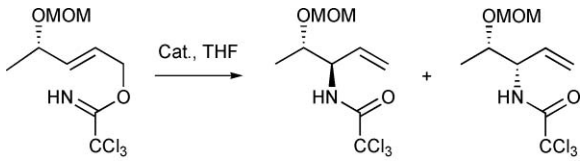
The allylic alcohol **5** was then reacted with trichloroacetonitrile and DBU to give the allylic trichloroacetimidate **6** (Scheme 3). Compounds such as **6** are known to be relatively unstable and thus, are not subjected to extensive purification.[6b,9] Hence, yields quoted for all rearrangements are calculated from the allylic alcohol **5** (over two steps). Allylic trichloroacetimidate **6** was initially subjected to a thermal rearrangement in refluxing *p*-xylene.[1] The ^{1}H NMR spectrum of the crude reaction mixture showed a 2 : 1 ratio of diastereomers **7** and **8** respectively.[10] Rearrangement from the least hindered front face of the alkene is preferred, giving allylic amide **7** as the major product. The low diastereoselectivity of this process arises from the small energy difference between the two possible reacting conformers at high temperatures. Purification of the reaction mixture by column chromatography gave the two diastereomers in very modest yield (20%) with a number of unidentifiable decomposition products. However, using a modified thermal rearrangement procedure developed by Isobe and co-workers,[11] which involves the addition of potassium carbonate to neutralise any acid formed during the reaction gave the rearrangement products in a much improved yield of 91%.

As previously reported, treatment of allylic trichloroacetimidate **6** with bis(acetonitrile)palladium(II) chloride in THF gave the aza-Claisen products, **7** and **8** in a 10 : 1 ratio and in 64% yield from the allylic alcohol (Table 1).[6a] The increase in diastereoselectivity relative to the thermal rearrangement was attributed to the pre-association of the Pd(II)-catalyst with the MOM-ether which then directs the catalyst to the back face of the alkene resulting in a highly diastereoselective rearrangement (Scheme 2). Having demonstrated the directing effect of the MOM-ether with bis(acetonitrile)palladium(II) chloride other Pd(II)-catalysts with larger ligands were sought to enhance the stereochemical outcome of the rearrangement. As expected, bis(benzonitrile)palladium(II) chloride gave similar yields and ratio of diastereomers when treated with allylic trichloroacetimidate **6**. On coordination of the catalyst with the MOM-ether and then the alkene both benzonitrile ligands are likely lost from the metal centre forming a similar intermediate as that for the acetonitrile catalyst. Palladium(II) bromide and palladium(II) acetate (Table 1) all gave high but similar ratios of diastereomers compared to that of palladium(II) chloride, while palladium(II) iodide showed no catalytic activity for this rearrangement. Moreover, these Pd(II) catalysts were only partially soluble in THF and thus, reaction times were considerably longer than for the reactions involving the nitrile catalysts. These prolonged reaction times led to partial decomposition of the allylic trichloroacetimidate **6** resulting in lower yields of the allylic amides, **7** and **8**.

A number of "soft" electrophilic metal catalysts have been utilised in the rearrangement of Claisen-type reactions.[2a,12] Several of these were screened for catalytic rearrangement of allylic trichloroacetimidate **6**, some of which are listed in Table 1.[13] However, Ni(II)- and Ru(II)-catalysts showed no catalytic activity for this rearrangement even after 5 days. Mercury(II)-triflate, a catalyst Overman and co-workers used to develop the rearrangement of allylic trichloroacetimidates, surprisingly also showed no activity for the rearrangement of **6**.[1b,2a] Recently Jaunzeme and Jirgensons reported novel platinum and gold catalysts for the Overman rearrangement.[14] Gratifyingly, treatment of **6** with either platinum(II) chloride or hydrogen tetrachloroaurate(III) hydrate gave the rearrangement products **7** and **8** in good yields over the two steps. Nevertheless, no improvement in diastereoselectivity was observed using these catalysts and thus, for optimal rate of reaction, ease of purification, high yields and high selectivity, bis(acetonitrile)palladium(II) chloride is the preferred catalyst for this directed rearrangement reaction.

All the rearrangements in this study have utilised THF as a solvent. It was proposed that THF may compete with the MOM-ether for the coordination of the Pd(II)-catalyst restricting the directing effect and that the use of other solvents, especially non-coordinating solvents, may lead to an enhancement of this directing effect. Thus, using bis(acetonitrile)palladium(II) chloride, the rearrangement of allylic trichloroacetimidate **6** was repeated using various solvents (Table 2). As highlighted above, this catalyst is readily soluble in organic solvents which meant these reactions were complete in around 24 hours giving the allylic amides, **7** and **8**, in typically good yields over the two steps. The use of diethyl ether and dichloromethane did lead to a slight increase in diastereoselectivity. However, the most dramatic

Table 1 Rearrangement of allylic trichloroacetimidate **6** using various catalysts

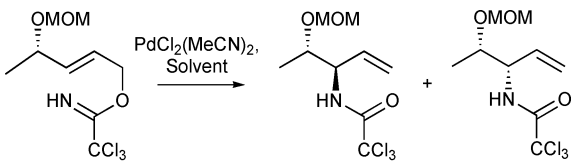


6 **7** **8**

Entry	Catalyst	Reaction time/h	Yield[a]	Ratio[b] (**7** : **8**)
1	$PdCl_2(MeCN)_2$	24	64%	10 : 1
2	$PdCl_2(PhCN)_2$	24	57%	9 : 1
3	$PdCl_2$	120	45%	11 : 1
4	$PdBr_2$	72	44%	9 : 1
5[c]	PdI_2	—	—	—
6	$Pd(OAc)_2$	96	18%	9 : 1
7[c]	$NiCl_2$	—	—	—
8[c]	$Cl_2Ru(PPh_3)_3$	—	—	—
9[c]	$Hg(OTf)_2$	—	—	—
10	$PtCl_2$	48	49%	10 : 1
11	$HAuCl_4{\cdot}2H_2O$	144	49%	6 : 1

[a] Isolated combined yields of **7** and **8** from *E*-allylic alcohol. [b] Ratio in crude reaction mixture. [c] No reaction after 120 hours.

Table 2 Rearrangement of allylic trichloroacetimidate **6** using various solvents



6 **7** **8**

Entry	Solvent	Reaction time/h	Yield[a]	Ratio[b] (**7** : **8**)
1	THF	24	64%	10 : 1
2	Et_2O	24	47%	12 : 1
3	MeCN	24	32%	9 : 1
4	CH_2Cl_2	24	49%	12 : 1
5	Toluene	24	56%	15 : 1
6	$(BMI)BF_4$	148	37%	5 : 1

[a] Isolated combined yields of **7** and **8** from *E*-allylic alcohol. [b] Ratio in crude reaction mixture.

increase was observed using toluene as a solvent which gave **7** and **8** in an excellent 15 : 1 ratio. In this reaction we believe the use of a non-coordinating solvent allows for the more efficient coordination of the MOM-ether to the Pd(II)-catalyst resulting in a more selective rearrangement. The reaction was also repeated using a highly coordinating solvent, the commercially available ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate. The increased viscosity of the ionic liquid compared with the other organic solvents led to a longer reaction time. However, allylic amides **7** and **8** were still isolated in a reasonable 37% yield over the two steps. More importantly, the rearranged products were isolated in a ratio of 5 : 1 effectively demonstrating that the use of a coordinating solvent can disrupt the binding of the catalyst to the MOM-ether leading to a less selective process. These results provide further evidence for the directing effect of the MOM-ether group during this Pd(II)-catalysed rearrangement.

Conclusions

In summary, we have demonstrated the scope of the metal-catalysed, directed rearrangement of allylic trichloroacetimidates using the MOM-ether as an effective directing group. While the thermal rearrangement is obviously unselective for allylic trichloroacetimidates such as **6**, the use of various "soft" metal catalysts such as Pd(II), Pt(II) and Au(III) can catalyse this directed rearrangement with high diastereoselectivity. More importantly, the use of non-coordinating solvents such as toluene minimises competition for coordination with the catalyst resulting in excellent diastereoselectivity, providing further evidence for this directing effect. Further work investigating the specific role of the MOM-ether oxygens during this rearrangement and the application of this process for the synthesis of piperidine alkaloids is currently underway.

Experimental

All reactions were performed under a nitrogen atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received. THF and diethyl ether were distilled from sodium and benzophenone. Lithium chloride was oven dried (100 °C) for at least 12 h before use. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher Matrex silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to residual chloroform (δ_H 7.28 and δ_C 77.2) as a standard. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using a AA

series Automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Ethyl (2*S*)-2-methoxymethoxypropanoate (2)

Sodium hydride (60% in mineral oil) (0.37 g, 9.3 mmol) was washed with petroleum ether (3 × 3 mL). The grey powder was then suspended in THF (20 mL) and cooled to 0 °C. Ethyl (*S*)-lactate (1.0 g, 8.5 mmol) was then added, dropwise, and the solution was allowed to stir for 0.5 h. Chloromethyl methyl ether (0.96 g, 11.8 mmol) was added and, after 0.75 h, the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was concentrated, acidified with 2 M hydrochloric acid (20 mL) and extracted with ethyl acetate (2 × 40 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo.* Purification was carried out by flash column chromatography using 40% ethyl acetate–petroleum ether to give the title compound (1.30 g, 95%) as a colourless oil. $[\alpha]_D^{20}$ −92.3 (*c* 1.0, $CHCl_3$); lit.[15] $[\alpha]_D^{22}$ −88.1 (*c* 2.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.43 (3H, d, *J* 7.0 Hz, 3-H_3), 3.39 (3H, s, OMe), 4.21 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.24 (1H, q, *J* 7.0 Hz, 2-H), 4.69 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.72 (1H, d, *J* 7.0 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.9 (CH_3), 18.5 (CH_3), 55.9 (CH_3), 60.9 (CH_2), 71.5 (CH), 95.9 (CH_2), 173.1 (C); *m*/*z* (CI) 163.0969 (MH^+. $C_7H_{15}O_4$ requires 163.0970), 131 (100%) and 119 (5).

(2*S*)-2-Methoxymethoxypropan-1-ol (3)

Ethyl (2*S*)-2-methoxymethoxypropanoate (1.0 g, 6.2 mmol) was dissolved in diethyl ether (30 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (13.6 mL, 13.5 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 1 h then overnight at room temperature. The reaction mixture was cooled to 0 °C before being quenched by the addition of a saturated solution of ammonium chloride (20 mL) and warmed to room temperature producing a white precipitate. The reaction mixture was filtered through a pad of Celite® and washed with diethyl ether (3 × 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography using 90% diethyl ether–petroleum ether gave the title compound (0.61 g, 82%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3409 (OH), 2930 (CH), 1454, 1377, 1141, 1101, 1025; $[\alpha]_D^{25}$ −80.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.4 Hz, 3-H_3), 2.60 (1H, br s, OH), 3.43 (3H, s, OMe), 3.46 (1H, dd, *J* 11.8, 7.3 Hz, 1-*H*H), 3.57 (1H, dd, *J* 11.8, 2.8 Hz, 1-H*H*), 3.70 (1H, m, 2-H), 4.71 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 17.4 (CH_3), 55.9 (CH_3), 67.4 (CH_2), 77.3 (CH), 96.5 (CH_2); *m*/*z* (CI) 121.0866 (MH^+. $C_5H_{13}O_3$ requires 121.0865), 119 (8%), 89 (100) and 87 (19).

Ethyl (2*E*,4*S*)-4-methoxymethoxypentan-2-enoate (4)

Methyl sulfoxide (3.7 mL, 51.6 mmol) was added to a stirred solution of oxalyl chloride (2.3 mL, 25.8 mmol) in dichloromethane (50 mL) at −78 °C. This mixture was stirred for 0.25 h before (2*S*)-2-methoxymethoxypropan-1-ol (2.58 g, 21.5 mmol) in dichloromethane (30 mL) was added. The mixture was stirred for a further 0.25 h before triethylamine (15 mL, 107.5 mmol) was added. This reaction mixture was then warmed to room temperature over 2 h. In a second flask, a solution of lithium chloride (1.37 g, 32.3 mmol), triethyl phosphonoacetate (6.4 mL, 32.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.8 mL, 32.3 mmol) in acetonitrile (30 mL) was prepared and stirred for 0.5 h. The contents of the second flask were then added to the Swern solution and the reaction mixture was allowed to stir at room temperature overnight. The reaction was quenched with brine (50 mL) and then concentrated *in vacuo*. This residue was extracted with diethyl ether (5 × 50 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange liquid. Purification was carried out by flash column chromatography using 40% diethyl ether–petroleum ether to give the desired compound (2.64 g, 65%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2981 (CH), 1720 (CO), 1660 (C=C), 1271, 1032; $[\alpha]_D^{21}$ −80.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (6H, m, OCH_2CH_3 and 5-H_3), 3.37 (3H, s, OMe), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.35 (1H, quin of d, *J* 6.5, 1.3 Hz, 4-H), 4.62 (2H, s, OCH_2O), 5.99 (1H, dd, *J* 15.7, 2.1 Hz, 2-H), 6.87 (1H, dd, *J* 15.7, 6.5 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 20.9 (CH_3), 55.8 (CH_3), 60.8 (CH_2), 71.4 (CH), 94.8 (CH_2), 121.4 (CH), 149.1 (CH), 166.7 (C); *m*/*z* (CI) 189.1125 (MH^+. $C_9H_{17}O_4$ requires 189.1127), 159 (39%), 143 (46), 127 (58) and 101 (12).

(2*E*,4*S*)-4-Methoxymethoxypentan-2-en-1-ol (5)

Ethyl (2*E*,4*S*)-4-methoxymethoxypentan-2-enoate (2.56 g, 13.6 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (30 mL, 30.0 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 2 h then overnight at room temperature. The reaction was cooled to 0 °C, quenched by the addition of a saturated solution of ammonium chloride (20 mL) and warmed to room temperature. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 × 100 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using 75% diethyl ether–petroleum ether to give the desired compound (1.90 g, 96%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3404 (OH), 2931 (CH), 1446, 1373, 1217, 1026; $[\alpha]_D^{23}$ −117.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4 Hz, 5-H_3), 2.21 (1H, br s, OH), 3.37 (3H, s, OMe), 4.14 (2H, dd, *J* 5.1, 1.6 Hz, 1-H_2), 4.16 (1H, quin, *J* 6.8 Hz, 4-H), 4.57 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.63 (1H, ddt, *J* 15.0, 6.8, 1.6 Hz, 3-H), 5.81 (1H, dt, *J* 15.0, 5.1 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 55.3 (CH_3), 63.0 (CH_2), 72.0 (CH), 93.8 (CH_2), 130.9 (CH), 132.8 (CH); *m*/*z* (CI) 129.0910 ($MH^+ - H_2O$. $C_7H_{13}O_2$ requires 129.0916), 117 (63) and 85 (100%).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-penta-1-ene (7) and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (8) from Overman thermal rearrangement

(2*E*,4*S*)-4-Methoxymethoxypent-2-en-1-ol (0.10 g, 0.69 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.10 g, 0.69 mmol) and trichloroacetonitrile (0.1 mL, 1.03 mmol) were then added and the mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was filtered through a dry

silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate and potassium carbonate (0.20 g) were dissolved in *p*-xylene (10 mL) and heated under reflux for 3 days. The mixture was then concentrated to give a brown liquid. Purification was carried out by flash column chromatography (20% diethyl ether–petroleum ether) to give (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (0.18 g, 91% over two steps) as a brown oil, in a 2 : 1 (3*R* : 3*S*) ratio. ν_{max}/cm^{-1} (neat) 3302 (NH), 2935 (CH), 1712 (CO), 1643 (C=C), 1511, 1148, 1028, 819; (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (major compound): δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.4 Hz, 5-H_3), 3.43 (3H, s, OMe), 3.88 (1H, qd, *J* 6.4 and 3.0 Hz, 4-H), 4.35 (1H, m, 3-H), 4.69 (1H, d, *J* 6.8, OC*H*HO), 4.71 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.36 (2H, m, 1-H_2), 5.89 (1H, m, 2-H), 7.89 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_3), 56.2 (CH), 58.1 (CH_3), 77.7 (CH), 92.1 (C), 97.0 (CH_2), 119.6 (CH_2), 131.8 (CH), 161.7 (C); (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (minor compound): δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.4 Hz, 5-H_3), 3.39 (3H, s, OMe), 3.93 (1H, qd, *J* 6.4 and 3.0 Hz, 4-H), 4.43 (1H, m, 3-H), 4.63 (1H, d, *J* 6.8, OC*H*HO), 4.79 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.27 (2H, m, 1-H_2), 5.89 (1H, m, 2-H), 7.10 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 17.8 (CH_3), 56.1 (CH), 58.2 (CH_3), 74.1 (CH), 94.3 (C), 95.3 (CH_2), 117.3 (CH_2), 135.3 (CH), 161.7 (C); *m/z* (CI) 290.0127 (MH^+. $C_9H_{14}O_3N^{35}Cl_3$ requires 290.0118) 258 (76%), 246 (21), 214 (28), 196 (62) and 162 (29).

General procedure 1: allylic trichloroacetimidate synthesis and subsequent metal catalysed rearrangement

Allylic alcohol (2 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.2 equiv.) and trichloroacetonitrile (1.5 equiv.) were then added and the mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Catalyst (10 mol%) was then added and the reaction mixture was stirred and monitored to completion by ^{1}H NMR spectroscopy. Concentration *in vacuo* followed by purification by flash column chromatography eluting with 20% diethyl ether–petroleum ether gave the target compounds.

Using bis(acetonitrile)palladium(II) chloride. The reaction was carried out according to general procedure 1 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (94 mg, 0.64 mmol) and bis(acetonitrile)palladium(II) chloride (14 mg, 10 mol%) to give allylic amides **7** and **8** (104 mg, 64% over two steps) as a brown oil, in a 10 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using bis(benzonitrile)palladium(II) chloride. The reaction was carried out according to general procedure 1 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (61 mg, 0.42 mmol) and bis(benzonitrile)palladium(II) chloride (22 mg, 10 mol%) to give the allylic amides **7** and **8** (102 mg, 57% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using palladium(II) chloride. The reaction was carried out according to general procedure 1 for 120 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (100 mg, 0.69 mmol) and palladium(II) chloride (12 mg, 10 mol%) to give allylic amides **7** and **8** (90 mg, 45% over two steps) as a brown oil, in a 11 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using palladium(II) bromide. The reaction was carried out according to general procedure 1 for 72 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (100 mg, 0.69 mmol) and palladium(II) bromide (18 mg, 10 mol%) to give allylic amides **7** and **8** (87 mg, 44% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using palladium(II) acetate. The reaction was carried out according to general procedure 1 for 96 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (72 mg, 0.49 mmol) and palladium(II) acetate (18 mg, 10 mol%) to give allylic amides **7** and **8** (25 mg, 18% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using platinum(II) chloride. The reaction was carried out according to general procedure 1 for 48 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (50 mg, 0.34 mmol) and platinum(II) chloride (9 mg, 10 mol%) to give allylic amides **7** and **8** (49 mg, 49% over two steps) as a brown oil, in a 10 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using hydrogen tetrachloroaurate(III) hydrate. The reaction was carried out according to general procedure 1 for 144 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (100 mg, 0.69 mmol) and hydrogen tetrachloroaurate(III) hydrate (24 mg, 10 mol%) to give the allylic amides **7** and **8** (98 mg, 49% over two steps) as a brown oil, in a 6 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

General procedure 2: allylic trichloroacetimidate synthesis and subsequent metal catalysed rearrangement in various solvents.

Allylic alcohol (2 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.2 equiv.) and trichloroacetonitrile (1.5 equiv.) were then added and the mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was then filtered through a dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. The product was used without further purification. The allylic trichloroacetimidate was dissolved in solvent (10 mL). Bis(acetonitrile)palladium(II) chloride (10 mol%) was then added and the reaction mixture was stirred and monitored to completion by ^{1}H NMR spectroscopy. Concentration *in vacuo* followed by purification by flash column chromatography eluting with 20% diethyl ether–petroleum ether gave the target compounds.

Using diethyl ether as solvent. The reaction was carried out according to general procedure 2 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in diethyl ether (10 mL) to give allylic amides **7** and **8** (47 mg, 47% over two

steps) as a brown oil, in a 12 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using acetonitrile as solvent. The reaction was carried out according to general procedure 2 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in acetonitrile (10 mL) to give allylic amides **7** and **8** (37 mg, 32% over two steps) as a brown oil, in a 9 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using dichloromethane as solvent. The reaction was carried out according to general procedure 2 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in dichloromethane (10 mL) to give allylic amides **7** and **8** (47 mg, 49% over two steps) as a brown oil, in a 12 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using toluene as solvent. The reaction was carried out according to general procedure 2 for 24 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (50 mg, 0.34 mmol) then bis(acetonitrile)palladium(II) chloride (8 mg, 10 mol%) in toluene (10 mL) to give allylic amides **7** and **8** (56 mg, 56% over two steps) as a brown oil, in a 15 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

Using 1-butyl-3-methylimidazolium tetrafluoroborate as solvent. The reaction was carried out according to general procedure 2 for 148 h using (2*E*,4*S*)-4-methoxymethoxypent-2-en-1-ol (100 mg, 0.69 mmol) then bis(acetonitrile)palladium(II) chloride (18 mg, 10 mol%) in 1-butyl-3-methylimidazolium tetrafluoroborate (3 mL) to give allylic amides **7** and **8** (74 mg, 37% over two steps) as a brown oil, in a 5 : 1 (3*R* : 3*S*) ratio. Spectroscopic data as described above.

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