# Stereocontrol of palladium(II)-catalysed aza-Claisen rearrangements using a combination of 1,3-allylic strain and a solvent mediated directing effect†

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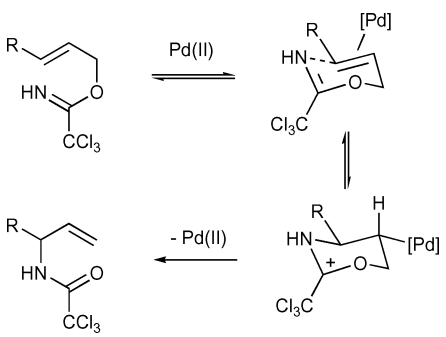
**The use of a non-coordinating solvent for the aza-Claisen rearrangement of δ,ε-disubstituted acetimidates switches on a substrate directing effect that gives excellent stereoselectivity.**

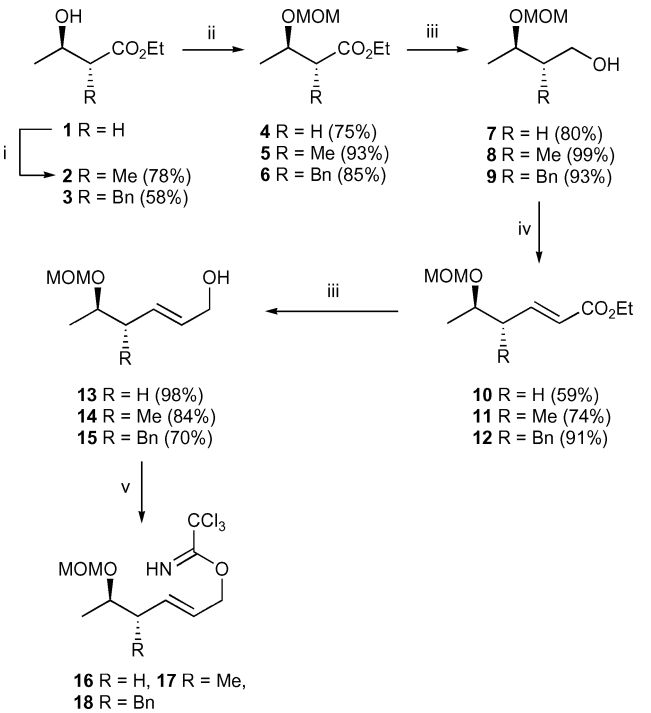
[3,3]-Sigmatropic rearrangements have found widespread application in synthesis for the preparation of organic molecules.[1] An important reaction from this class is the aza-Claisen rearrangement of allylic trichloroacetimidates (commonly known as the Overman rearrangement), which allows the allylic interchange of alcohol and amine functional groups.[2] Traditionally, these transformations have been carried out thermally[3] taking place *via* a concerted, suprafacial reaction pathway according to the Woodward–Hoffmann rules.[4] The discovery of the metal-catalysed reaction, which proceeds *via* a cyclisation-induced mechanism (Scheme 1) under mild conditions,[5] has led to its widespread use in the synthesis of biologically active compounds and natural products.[6] Lately, efforts have focused on developing an asymmetric version of the Pd(II)-catalysed process using either chiral substrates or chiral palladium catalysts.[2,6,7] For example, Overman and others have reported a number of chiral Pd(II) complexes which catalyse the rearrangement giving allylic amides in high yields and excellent enantioselectivities.[7]




**Scheme 1** Palladium(II) catalysed aza-Claisen rearrangement.

With the goal of utilizing this reaction for the asymmetric synthesis of complex amino acids, we became interested in developing an understanding of how the rearrangement of chiral substrates is influenced intramolecularly by stereogenic centres and functional groups. This led to the development of an ether directed, Pd(II)-catalysed process which has been used for the synthesis of β-hydroxy-α-amino acids.[6g,8] Our current studies have focused on the rearrangement of allylic trichloroacetimidates derived from δ,ε-disubstituted allylic alcohols. In this communication we demonstrate that, while the stereoselective rearrangement of these compounds in THF is controlled solely by 1,3-allylic strain, the use of a non-coordinating solvent (such as toluene) results in the switching on of a substrate directing effect which significantly enhances the diastereoselective outcome of the reaction allowing the efficient synthesis of the natural products, (2*S*,4*R*)-γ-hydroxynorvaline and (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine.

For investigating the effects of 1,3-allylic strain on the stereochemical outcome of this rearrangement, allylic trichloroacetimidates **16**–**18** were prepared as outlined in Scheme 2.




**Scheme 2** Reagents and conditions: (i) LDA (2.0 eq), THF, −78 °C, MeI or BnBr; (ii) MOMCl, $NEt(iPr)_2$, $CH_2Cl_2$; (iii) DIBAL-H (2.2 eq.), $Et_2O$, −78 °C; (iv) DMSO, $(COCl)_2$, $NEt_3$, $CH_2Cl_2$, −78 °C to RT, then LiCl, DBU, triethyl phosphonoacetate, MeCN; (v) DBU, $Cl_3CCN$, 0 °C, $CH_2Cl_2$.

The methyl and benzyl derivatives **2** and **3** were synthesised from ethyl (*R*)-3-hydroxybutanoate **1** using a LDA mediated stereoselective alkylation which gives excellent levels of the desired *erthyro* product.[9] The MOM-ethers were formed under standard conditions[6g] and this was followed by reduction of

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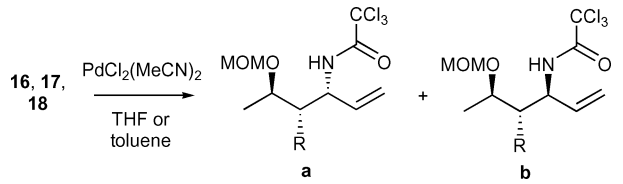
**Table 1** Palladium(II) catalysed rearrangement of acetimidates **16**, **17** and **18** in THF and toluene



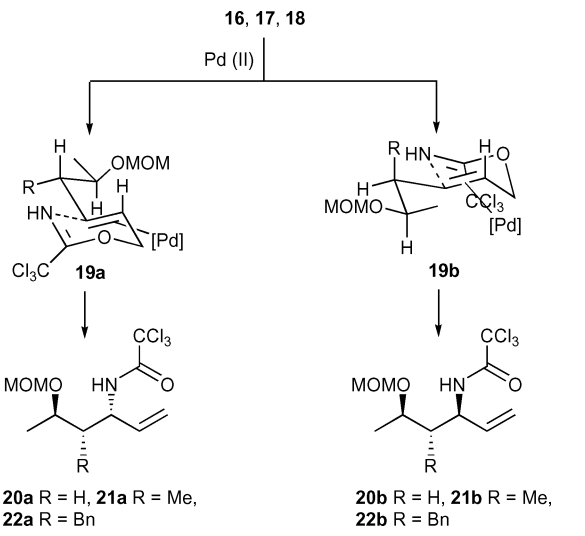

| Entry | R | Solvent | Yield[a] (%) | Ratio[b] (a : b) |
|---|---|---|---|---|
| 1 | H (**20**) | THF | 50% | 1 : 1 |
| 2 | Me (**21**) | THF | 49% | 3 : 1 |
| 3 | Bn (**22**) | THF | 72% | 6 : 1 |
| 4 | H (**20**) | Toluene | 71% | 3 : 1 |
| 5 | Me (**21**) | Toluene | 66% | 13 : 1 |
| 6 | Bn (**22**) | Toluene | 82% | 11 : 1 |

[a] Isolated combined yields of **a** and **b** from allylic alcohols **13**–**15**. [b] Ratio in crude reaction mixture.

the ester functional groups using DIBAL-H. A one-pot Swern oxidation/Horner–Wadsworth–Emmons reaction[10] then gave (*E*)-α,β-unsaturated esters **10**–**12** in good yields and these were converted to the corresponding allylic alcohols **13**–**15** again using DIBAL-H. Finally, treatment of the allylic alcohols with DBU and trichloroacetonitrile gave the desired substrates **16**–**18**.

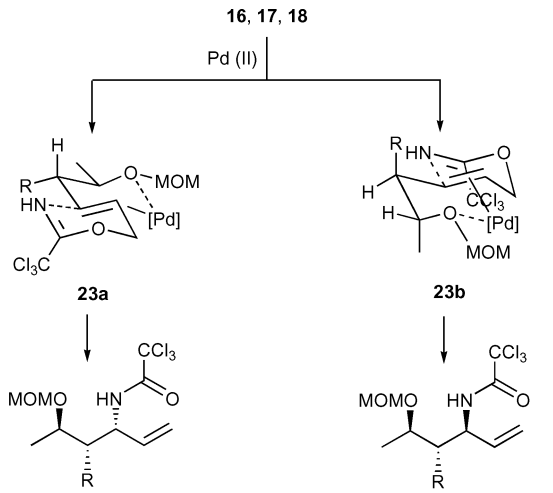
The aza-Claisen rearrangement of allylic trichloroacetimidates **16**–**18** was then carried out at room temperature in THF using bis(acetonitrile)palladium(II) chloride as the catalyst (Table 1). Unsurprisingly, rearrangement of the mono-substituted analogue, **16** gave only a 1 : 1 mixture of diastereomers in 50% yield. Rearrangement of **17** and **18** which have increasing steric bulk at the δ-position gave the corresponding alyllic amides in ratios of 3 : 1 and 6 : 1, respectively.

Analysis of the transition states for acetimidate **16** show that both reaction pathways are equally likely, leading to the observed 1 : 1 ratio of diastereomers **20a** and **20b** (Scheme 3). However, introduction of substituents at the δ-position as for acetimidates **17** and **18** results in the destabilisation of transition state **19b** due to 1,3-allylic strain between the 2-H and the R-group.[11] This leads to the preferred formation of diastereomer **a** in increasing amounts as the steric bulk of the R-group increases, thereby effectively demonstrating stereocontrol of the rearrangement by 1,3-allylic strain.




**Scheme 3**

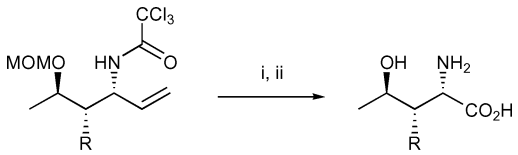
We have previously reported a highly diastereoselective, substrate directed aza-Claisen rearrangement in a non-coordinating solvent where the facial coordination of the Pd(II)-catalyst is controlled by an adjacent MOM-ether.[8b] Thus, in an effort to improve the diastereoselectivity of the aza-Claisen rearrangement of acetimidates, **16**–**18**, the reactions were repeated using toluene as a solvent. As can be seen from Table 1, the change in solvent leads to cleaner reactions producing the allylic amides in higher yields. More importantly, the diastereoselective outcome of each rearrangement is greatly enhanced. Without the competition of THF, the MOM-ether group can now coordinate to the catalyst and direct the stereoselective outcome of the rearrangement. The different ratios of diastereomers can again be rationalized by the transition states (Scheme 4). For acetimidate **16**, transition state **23b** is destabilised due to the action of the directing effect, causing the methyl group to adopt an axial position and leading to the preferred formation of **20a** in a 3 : 1 ratio of diastereomers. In the case of acetimidates **17** and **18**, where transition state **23b** is already destabilised by 1,3-allylic strain, the positioning of the axial methyl group adds to this destabilization leading to an enhancement of diastereoselectivity. Thus, the combination of both the 1,3-allylic strain and the MOM-ether directing effect led to an excellent 13 : 1 and 11 : 1 ratio for diastereomers **21** and **22**, respectively.




**Scheme 4**

To confirm our stereochemical assignment of the products of these aza-Claisen rearrangements, the major diasteromers **20a** and **21a** were converted to the corresponding amino acid using a ruthenium(III) trichloride catalysed oxidation[12] followed by an acid mediated deprotection step (Scheme 5). This gave the natural products, (2*S*,4*R*)-γ-hydroxynorvaline,[13] **24**, and (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine,[14] **25**, which showed optical activity and NMR spectra consistent with published values. In a similar fashion,




**20a** R = H
**21a** R = Me
**22a** R = Bn

**24** R = H
**25** R = Me
**26** R = Bn

**Scheme 5** Reagents and conditions: (i) $RuCl_3 \cdot xH_2O$, $NaIO_4$, $H_2O$, $CCl_4$, MeCN, R = H (65%), Me (62%), Bn (82%); (ii) 6 M HCl, Δ, R = H (74%), Me (55%), Bn (55%).

allylic amide **22a** was converted to the novel benzyl derived γ-hydroxy-α-amino acid **26** (Scheme 5).

In conclusion, we have demonstrated that while the aza-Claisen rearrangement of allylic acetimidates derived from δ,ε-disubstituted allylic alcohols in THF is controlled solely using 1,3-allylic strain the use of a non-coordinating solvent results in the switching on of a substrate directing effect which substantially enhances the stereochemical outcome. Studies are currently underway on the modelling of these reaction pathways and further applications of the allylic amides.

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