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A stereoselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid using an ether directed aza-Claisen rearrangement

Michael D. Swift and Andrew Sutherland*

WestChem, Department of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK

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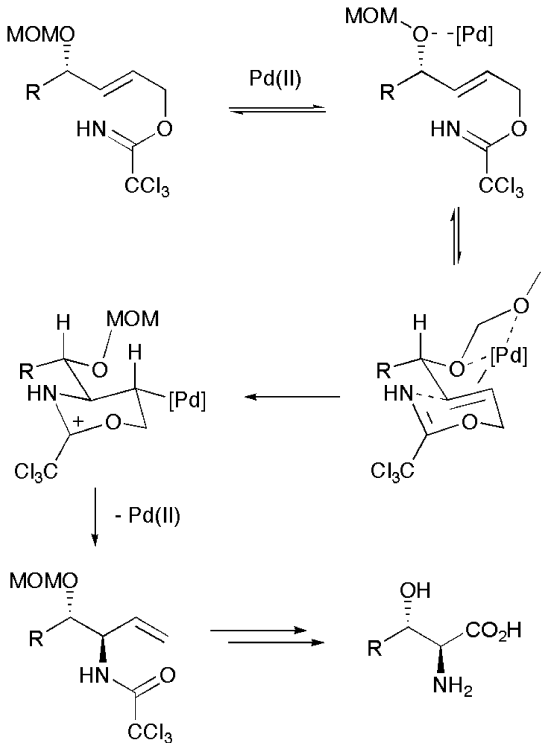
Abstract—A new approach for the stereoselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid, an α-amino acid from *Lyophyllum ulmarium*, has been accomplished using an ether directed aza-Claisen rearrangement. On investigation of optimal conditions for this key step it was shown for the first time that Au(I) can be used to catalyse this transformation.

β-Hydroxy-α-amino acids are widely prevalent in Nature occurring as structural components in many biologically active peptides and natural products.[1] Due to their importance, many different approaches have been developed for their stereoselective synthesis[2] including asymmetric aldol additions of benzophenone glycinates,[3] Sharpless epoxidation of allylic alcohols,[4] Strecker synthesis of protected glyceraldehydes[5] and threonine aldolase mediated reactions with glycine.[6]

We have recently developed an ether directed, palladium(II)-catalysed, aza-Claisen rearrangement of allylic trichloroacetimidates[7] which, when carried out in non-coordinating solvents such as toluene, produces the corresponding allylic amides in good yields and in high diastereoselectivity (up to 15:1).[8] Oxidation of the allylic amides followed by deprotection then gave direct access to a range of *erythro*-β-hydroxy-α-amino acids with simple alkyl side chains (Scheme 1).[9] Having established an efficient synthesis of these compounds we sought to expand the scope of this ether directed rearrangement for the stereoselective preparation of more complex β-hydroxy-α-amino acids and other natural products. Our initial target was (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1**, a dihydroxylated α-amino acid which has been isolated from the edible mushroom, *Lyophyllum ulmarium*.[10] In this Letter, we now report the ether directed rearrangement of a novel 4,5-disubstituted allylic acetimidate which has been used to complete a stereoselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1**. We also show for the first



Scheme 1. Synthesis of β-hydroxy-α-amino acids via an ether directed aza-Claisen rearrangement.

Keywords: β-Hydroxy-α-amino acid; Natural product; Rearrangement; Stereoselective synthesis; Palladium catalysis.
* Corresponding author. Tel.: +44 141 330 5936; fax: +44 141 330 4888; e-mail: andrews@chem.gla.ac.uk

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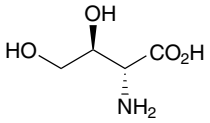
time that an Au(I)-catalyst can be used to effect ether directed rearrangements.



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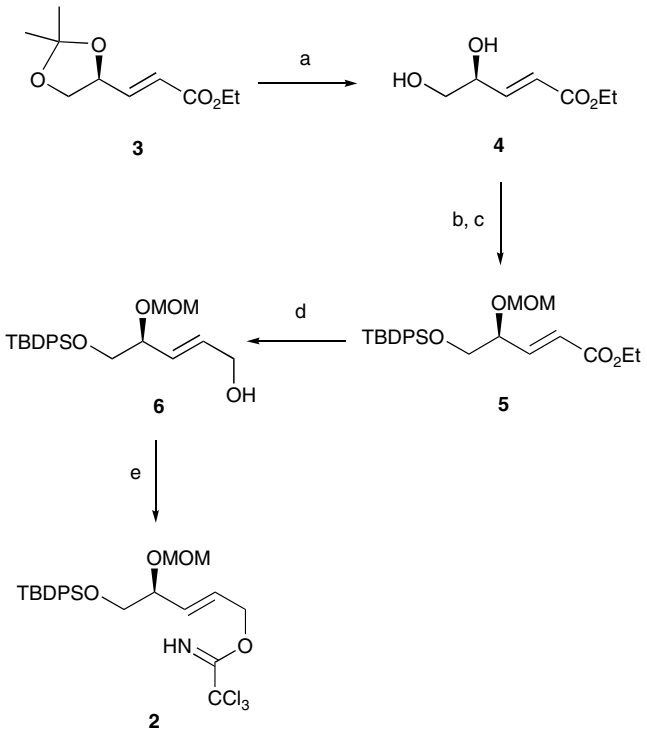
The initial stage of this project involved the efficient preparation of the rearrangement substrate **2**, which was achieved in five steps from commercially available α,β-unsaturated ester **3** (Scheme 2). We have shown that ether directed rearrangements are most effective when the MOM-ether group is used to direct the metal catalyst.[8] Thus, acid mediated hydrolysis of the acetonide protecting group of **3** gave the corresponding diol **4** in 94% yield. Subsequent protection of the primary alcohol as the *tert*-butyldiphenylsilyl ether and the secondary alcohol as the required MOM-ether both under standard conditions, gave **5** in excellent overall yield. Reduction of **5** using 2.2 equiv of DIBAL-H gave allylic alcohol **6** in 70% overall yield from the commercially available starting material **3**. Finally, reaction with DBU and trichloroacetonitrile gave the desired rearrangement substrate **2**.

With allylic trichloroacetimidate **2** in hand, a series of reactions were carried out to find the optimal conditions for the rearrangement (Table 1). Initially, **2** was subjected to a thermal rearrangement in refluxing *p*-xylene (entry 1).[11,12] While this gave the corresponding allylic amides **7a** and **7b** in good yield over the two steps from allylic alcohol **6**, the reaction time was excessively long (120 h) and more importantly, the transformation was not selective for the desired diastereomer, **7a**. Allylic trichloroacetimidate **2** was then subjected to Pd(II)-catalysis using both bis(acetonitrile)- and bis(benzonitrile)-palladium(II) chloride under standard conditions (entries 2 and 3).[13] These reactions were complete in only 12 h and although the yields were only 32% and 30%, respectively, from **6**, the reaction was now selective for diastereomer **7a**. In our studies on the ether directed rearrangement of allylic trichloroacetimidates, we have found that using non-coordinating solvents such as toluene not only results in a more selective rearrangement but that the reactions are cleaner giving the allylic trichloroamides in higher yields.[8b,14] It has also been shown that the rearrangement of allylic trichloroacetimidates can also be catalysed using platinum and gold complexes.[8b,15] Thus, allylic trichloroacetimidate **2** was treated with platinum(II)-, gold(III)- and gold(I)-catalysts in toluene. These were all able to catalyse this transformation (entries 4–6), and for the gold catalysts, in higher yield than previous metal catalysed conditions. Moreover, the use of gold(I) chloride represents the first example of an Au(I)-catalyst to effect an ether directed rearrangement. The reaction was also repeated using a Pd(II)-catalyst in toluene (entry 7) and this gave an excellent yield of the allylic amides (68% over the two steps) and with a 4:1 ratio of diastereomers. Our previous work[9] on MOM-ether directed rearrangements using less complex substrates has produced allylic trichloroamides with diastereoselective ratios of at least 9:1 and thus, the modest selectivities observed here are surprising. It is likely that the steric bulk of the *tert*-butyldiphenylsilyl ether while not completely preventing coordination of the catalyst to the MOM-ether does hinder the effectiveness of the directing effect.

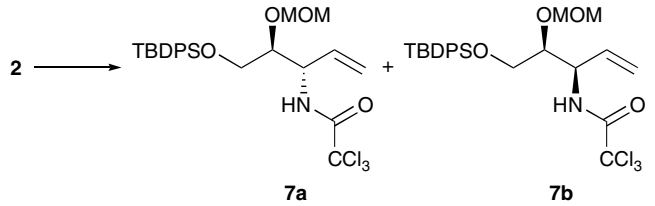


Scheme 2. Reagents and conditions: (a) 2 M HCl, 94%; (b) TBDPSCl, imidazole, THF, 100%; (c) MOMBr, EtN(*i*Pr)$_2$, CH_2Cl_2, 86%; (d) DIBAL-H (2.2 equiv), Et_2O, −78 °C to rt, 86%; (e) Cl_3CCN, DBU, CH_2Cl_2.

Nevertheless, using this approach does give allylic amides **7a** and **7b** in only six steps, and in 48% overall yield from commercially available starting material **3**. At this stage **7a** was easily separated from **7b** using flash column chromatography. Ruthenium(III) trichloride catalysed oxidation[16] of allylic amide **7a** gave the corresponding carboxylic acid **8** in 71% yield (Scheme 3). Removal of the silyl ether using TBAF and acid mediated deprotection of the other functional groups gave (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1** in 44% yield over the two steps.[17]

In conclusion, we have developed a direct, novel approach for the synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1** using an MOM-ether directed rearrangement of an allylic trichloroacetimidate to effect the key step. As well as using Pd(II), Pt(II) and Au(III) for this transformation, we have also shown for the first time that an Au(I)-catalyst can be used during an ether directed rearrangement. Further studies are currently underway to expand the scope of directed rearrangements of highly substituted allylic acetimidate for natural product synthesis.

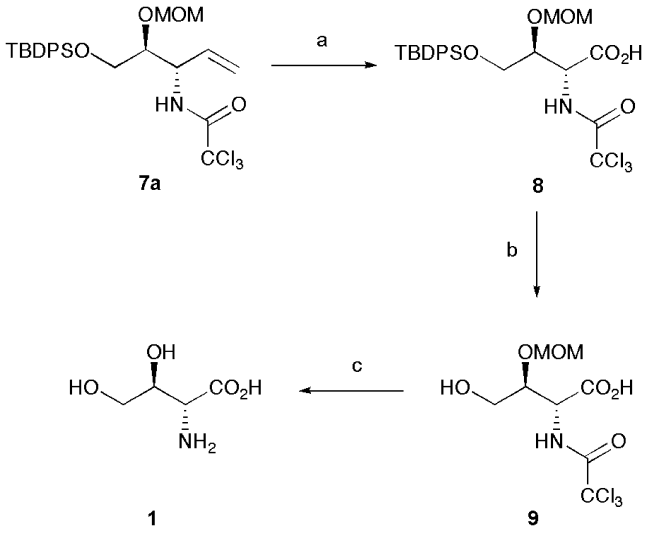
Table 1.



7a **7b**

Entry	Reaction conditions[a]	Reaction time (h)	Yield[b] (%)	Ratio[c] (**7a**/**7b**)
1	Δ, *p*-Xylene	120	61	1:1
2	$PdCl_2(MeCN)_2$, THF	12	32	4:1
3	$PdCl_2(PhCN)_2$, THF	12	30	4:1
4	$PtCl_2$, toluene	168	25	4:1
5	$HAuCl_4{\cdot}3H_2O$, toluene	48	49	2:1
6	AuCl, toluene	168	40	3:1
7	$PdCl_2(MeCN)_2$, toluene	12	68	4:1

[a] All reactions using a catalyst were carried out at room temperature.
[b] Isolated combined yields of **7a** and **7b** from *E*-allylic alcohol **6**.
[c] Ratio in crude reaction mixture.



Scheme 3. Reagents and conditions: (a) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, 71%; (b) TBAF, THF; (c) 6 M HCl, Δ, 44% over two steps.

Acknowledgements

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17. Optical rotation for **1**: $[\alpha]_D^{24}$ +10.6 (*c* 0.5, H_2O); lit.[5] +11.3 (*c* 7.0, H_2O). Spectroscopic data were entirely consistent with that published for (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1**.[5]