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Tandem aza-Claisen rearrangement and ring-closing metathesis reactions: the stereoselective synthesis of functionalised carbocyclic amides

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ABSTRACT

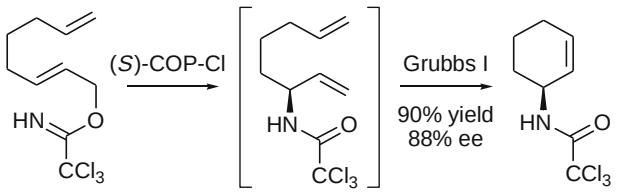
A one-pot, tandem process has been developed for the efficient synthesis of functionalised carbocyclic amides. A substituted cyclopentenyl trichloroacetamide was synthesised using a tandem thermal aza-Claisen rearrangement and RCM process, while an analogous cyclohexenyl trichloroacetamide was generated with high diastereoselectivity using a tandem MOM-ether directed metal-catalysed aza-Claisen rearrangement and RCM process.

Tandem and cascade reactions have emerged as powerful tools to perform several transformations in one synthetic operation rapidly increasing molecular complexity.[1] These processes avoid the excessive handling and isolation of synthetic intermediates, generating less waste and thus, contribute towards 'Green Chemistry'. Ring-closing metathesis (RCM) reactions have found widespread application for the efficient synthesis of cyclic compounds when utilised in a tandem process with other transformations such as dehydrogenation-hydrogenation reactions,[2] isomerisations,[3] aza-Michael reactions,[4] Claisen rearrangements,[5] Diels–Alder reactions,[6] Kharasch additions[7] and dihydroxylations.[8]

Our own research efforts have focused on developing a new tandem process involving the Overman rearrangement of allylic trichloroacetimidates to give allylic trichloroacetamides,[9] followed by a RCM reaction to produce the corresponding cyclic allylic trichloroacetamides.[10] This new flexible approach allowed the synthesis of 5-, 6-, 7- and 8-membered carbocyclic allylic amides and by using chiral palladium(II) catalysts such as the commercially available COP-Cl catalysts,[11] an asymmetric version of this one-pot tandem process was also achieved (Scheme 1).

Earlier studies from our group on the investigation of a diastereoselective Overman rearrangement led to the development of a MOM-ether directed rearrangement where both oxygen atoms of the MOM group coordinate to the palladium catalyst and direct it selectively to one face of the alkene, resulting in attack of the imidate nitrogen from the opposite face.[12] On optimisation, this process yielded *anti*-ether substituted allylic trichloroacetamides with excellent levels of selectivity.[12b,13] In an effort to synthesise functionalised carbocyclic amides stereoselectively using a tandem process, it was proposed that this could be achieved by combining the ether-directed Overman rearrangement with a RCM reaction (Scheme 2). This Letter describes the highly efficient synthesis of substrates **1** and **2** and the subsequent studies on the development of a tandem Overman rearrangement and RCM reaction for the one-pot synthesis of functionalised 5- and 6-membered carbocyclic amides.

The allylic alcohol substrates **11** and **12** required for this study were synthesised in seven steps as shown in Scheme 3. (*S*)-Glycidol **3** was protected under standard conditions as the *tert*-butyldimethylsilyl ether. Regioselective ring opening of the epoxide using a copper-catalysed Grignard reaction with either vinylmagnesium bromide or allylmagnesium bromide gave adducts **5** and **6**, respectively, both in high yields. Compounds **5** and **6** were converted to primary alcohols **7** and **8** by protection of the secondary alcohol with bromomethyl methyl ether followed by deprotection of the primary alcohol using TBAF. This allowed the one-pot Swern oxida-



Scheme 1. Tandem Overman rearrangement and RCM reaction.

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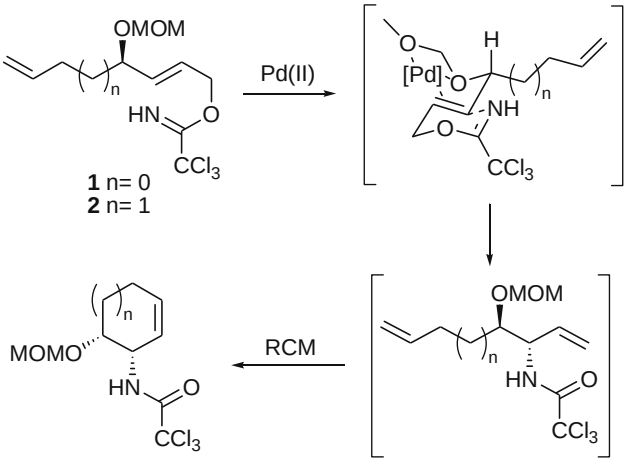
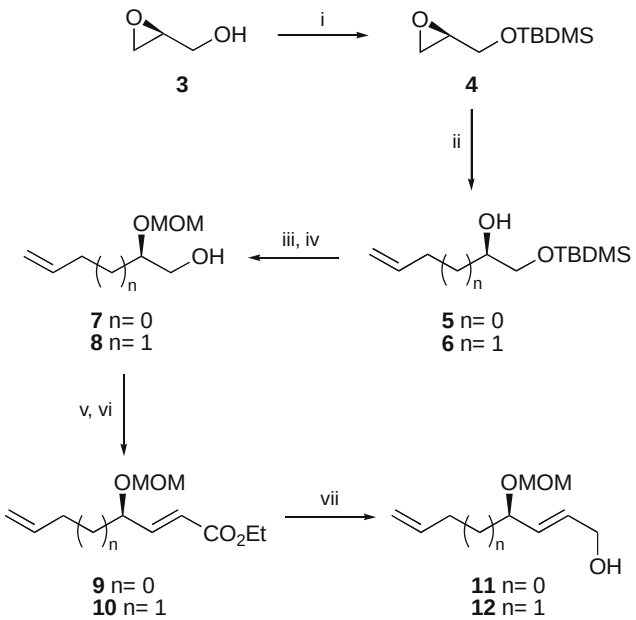


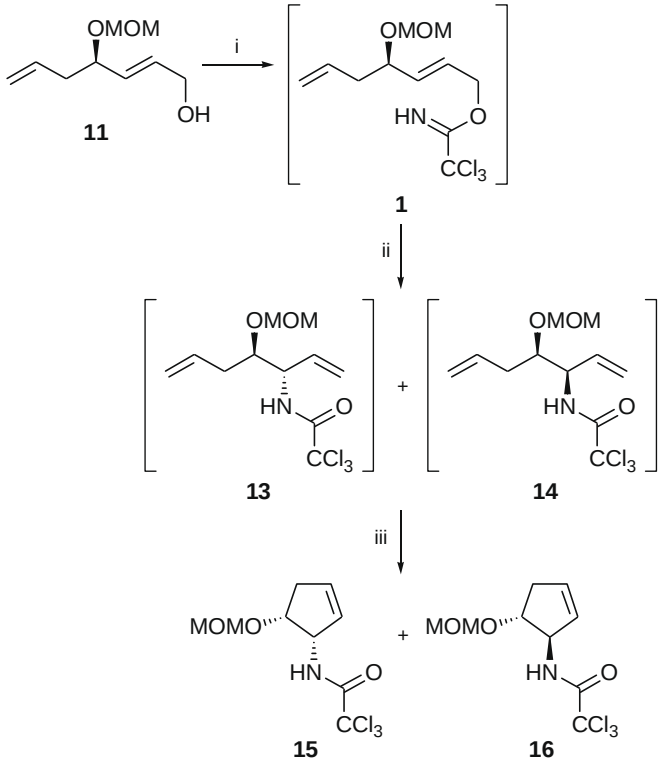
Scheme 2. Proposed tandem ether-directed Overman rearrangement and RCM reaction.

tion/Horner–Wadsworth–Emmons reaction of **7** and **8** to give α,β-unsaturated esters **9** and **10** in 99% and 94% yields, respectively.[14] Finally, DIBAL-H reduction of the esters completed the synthesis of allylic alcohols **11** and **12** in 68% and 78% overall yields, respectively.

Development of a tandem ether-directed Overman rearrangement and RCM reaction was initially attempted using allylic trichloroacetimidate **1** that was prepared from allylic alcohol **11** using trichloroacetonitrile and DBU (Scheme 4). Surprisingly, treatment of **1** with bis(acetonitrile)palladium(II) chloride under standard conditions returned only starting material. Several other palladium(II) catalysts were also investigated giving the same result.[12b] During the development of our original tandem process, the allylic acetimidate formed from (2*E*)-hepta-2,6-dien-1-ol



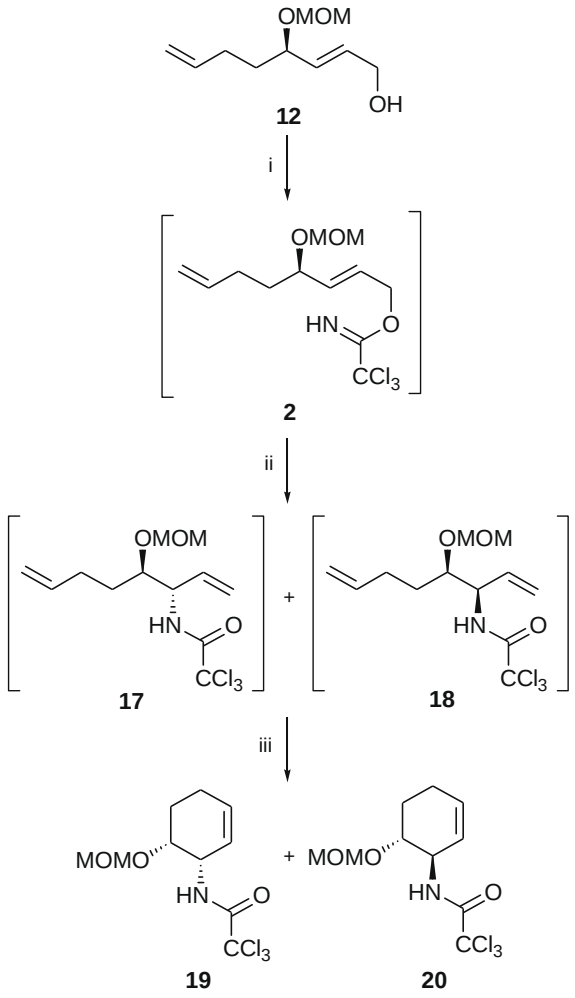
Scheme 3. Reagents and conditions: (i) TBDMSCl, imidazole, THF, 98%; (ii) CuBr·SMe$_2$, THF, −78 °C to 0 °C, 1.0 M CH_2=CHMgBr in THF (84%) or 1.0 M CH_2=$CHCH_2$MgBr in THF (90%); (iii) MOMBr, EtN(iPr)$_2$, CH_2Cl_2, Δ, n = 0 (92%), n = 1 (100%); (iv) TBAF, THF, 0 °C, n = 0 (98%), n = 1 (96%); (v) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (vi) triethyl phosphonoacetate, LiCl, DBU, MeCN, rt, n = 0 (99% over two steps), n = 1 (94% over two steps); (vii) DIBAL-H (2.2 equiv), Et_2O, −78 °C to rt, n = 0 (93%), n = 1 (98%).



Scheme 4. Reagents and conditions: (i) Cl_3CCN, DBU, CH_2Cl_2, 0 °C to rt; (ii) *p*-xylene, Δ; (iii) Grubbs I, 60 °C, 63% over three steps.

was shown to rearrange in the presence of bis(acetonitrile)palladium(II) chloride in under 3 h.[10] The only difference in structure between this substrate and allylic trichloroacetimidate **1** is the MOM-ether group. This suggests that the MOM-ether may be coordinating to the palladium catalyst and directing it to the terminal alkene rather than to the adjacent alkene of the trichloroacetimidate functional group. Such an intermediate would prevent the rearrangement from proceeding. A tandem rearrangement and RCM reaction of allylic trichloroacetimidate **1** was developed using a thermal rearrangement (Scheme 4). Allylic trichloroamides **13** and **14** were formed by heating **1** under reflux in *p*-xylene. On completion of the rearrangement, the reaction mixture was cooled to 60 °C and Grubbs' first-generation catalyst was added. This led to the formation of *N*-(cyclopentenyl)-trichloroacetamides **15** and **16** in 63% yield over the three steps and in a 2:1 ratio. As expected, the thermal rearrangement proceeds with low diastereoselectivity; however, the process produces **15** and **16** in good yield and these compounds are easily separated by column chromatography.

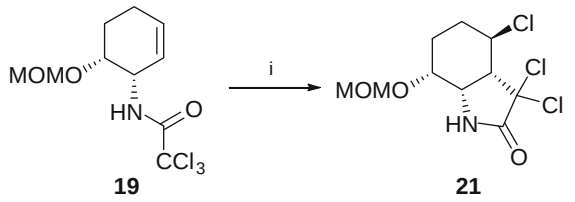
While allylic trichloroacetimidate **1** did not rearrange under metal-catalysed conditions, no such problems were encountered using allylic trichloroacetimidate **2** (Scheme 5). MOM-ether directed rearrangement of **2** with bis(acetonitrile)palladium(II) chloride in dichloromethane proceeded smoothly at room temperature. Subsequent addition of Grubbs' first-generation catalyst and heating the reaction mixture at 60 °C led to the isolation of *N*-(cyclohexenyl)-trichloroacetamides **19** and **20** in 45% yield over the three steps and in a 5:1 ratio. Previous work in our group had shown that the use of non-coordinating solvents such as toluene enhances the directing effect and allows for more efficient rearrangement reactions.[12b,13] Thus, the tandem process was repeated using toluene as a solvent as well as cooling the rearrangement step to 0 °C. This led to the isolation of **19** and **20** in 60% overall yield and in an excellent 10:1 ratio (Scheme



Scheme 5. Reagents and conditions: (i) Cl_3CCN, DBU, CH_2Cl_2, 0 °C to rt; (ii) $PdCl_2(MeCN)_2$, toluene, rt; (iii) Grubbs I, 60 °C, 60% over three steps.

5).[15] As above, the diastereomeric cyclic allylic trichloroacetamides generated from this tandem process are readily separated by column chromatography.

Cyclic allylic trichloroacetamides are excellent synthetic intermediates, and can undergo facile stereoselective dihydroxylation,[16] epoxidation[17] and ring-forming reactions.[18] Our interest in developing an efficient synthesis of carbocyclic amides such as **15** and **19** was for use in Ru(II)-catalysed Kharasch cyclisations[7,18a] and in the subsequent preparation of bicyclic natural products. Initial studies have already shown that these compounds readily undergo highly stereoselective Kharasch cyclisations. For example, reaction of **19** with dichlorotris(triphenylphosphine)ruthenium(II) under optimised conditions facilitates a Kharasch cyclisation generating bicyclic amide **21** as a single stereoisomer in 75% yield (Scheme 6).[19] Thus, the use of the tandem rearrangement and RCM process in combination with the Kharasch cyclisation allows the rapid stereo-defined assembly of highly functionalised bicyclic ring systems.



Scheme 6. Reagents and conditions: (i) $RuCl_2(PPh_3)_3$, 4 Å molecular sieves, *p*-xylene, 155 °C (sealed tube), 75%.

In summary, a new tandem MOM-ether directed Overman rearrangement and RCM reaction process has been developed for the efficient and highly selective synthesis of cyclohexenyl trichloroacetamide **19**. While the analogous hepta-2,6-dien-1-ol derived substrate was unable to undergo a metal-catalysed aza-Claisen rearrangement, a tandem process was developed for the synthesis of cyclopentenyl trichloroacetamide **15** using a thermal rearrangement. As shown by the efficient and highly selective Ru(II)-mediated Kharasch cyclisation of **19**, these functionalised carbocyclic amides are excellent synthetic intermediates, and work is currently underway to demonstrate their potential in natural product synthesis.

Acknowledgements

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Supplementary data

Experimental procedures and spectroscopic data for all compounds synthesised are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.032.

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through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give the allylic trichloroacetimidate, which was used without further purification. Allylic trichloroacetimidate (1 equiv) was dissolved in toluene (10 mL), and the reaction mixture was cooled to 0 °C under an argon atmosphere. Bis(acetonitrile)palladium(II) chloride (0.1 equiv, 10 mol %) was added to the solution, and the reaction mixture was slowly warmed to rt. After 24 h, Grubbs' catalyst (1st generation) (0.1 equiv, 10 mol %) was added and the reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature, and then filtered through a short pad of Celite® and washed with diethyl ether (100 mL). Concentration of the filtrate followed by flash column chromatography gave the cyclic allylic amides.

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