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A Tandem Aza-Claisen Rearrangement and Ring Closing Metathesis Reaction for the Synthesis of Cyclic Allylic Trichloroacetamides

Michael D. Swift and Andrew Sutherland*

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

andrews@chem.gla.ac.uk

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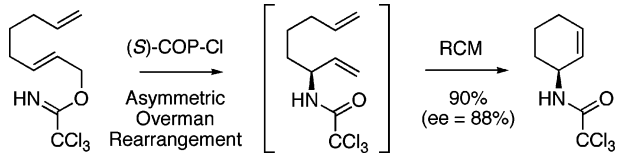
ABSTRACT



A one-pot tandem palladium(II)-catalyzed aza-Claisen rearrangement and ring closing metathesis process has been developed for the efficient synthesis of cyclic allylic trichloroacetamides. The use of chiral Pd(II) catalysts such as (*S*)-COP−Cl during the rearrangement stage results in the preparation of these compounds in excellent yields and in high enantiomeric excess.

Interest in the development and application of tandem, domino, and cascade processes continues to grow for obvious reasons. These processes allow several transformations in one synthetic operation, negating the need of handling and isolating intermediates.[1] Furthermore, the substantial reduction in waste generation using these processes has significant benefits for the environment. One class of reaction that has come to prominence in these processes is the ring closing metathesis (RCM) reaction. For example, RCM has been used in combination with dehydrogenation−hydrogenation reactions,[2] isomerizations,[3] aza-Michael reactions,[4] Claisen rearrangements,[5] Diels−Alder reactions,[6] Kharasch additions,[7] dihydroxylations,[8] as well as ring opening metathesis (ROM).[9] The successful application of RCM to so many tandem processes is mainly due to the continued development of stable ruthenium alkylidene complexes used to catalyze the transformation.

We recently reported the development of a diastereoselective Pd(II)-catalyzed ether-directed aza-Claisen (Overman) rearrangement of allylic trichloroacetimidates,[10] which has been used for the synthesis of β- and γ-hydroxy-α-amino acids.[11] The products of these reactions were also easily converted to dienes and used in RCM reactions for the preparation of piperidines and pyrrolidines.[12] During the

(1) For general reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619−1665. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143−2173. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134−7186.

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(4) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700−6701.

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(7) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329−16332.

(8) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900−1903.

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(10) Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: Hoboken, NJ, 2005; Vol. 66, pp 1−107 and references therein.

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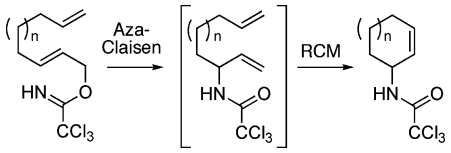
development of this directed rearrangement process and in an effort to optimize the diastereoselectivity of the reaction, a series of metal complexes were screened as catalysts.[13] Interestingly, it was found that ruthenium complexes do not catalyze the Overman rearrangement. This led to our proposal of a one-pot tandem process for the synthesis of cyclic allylic trichloroacetamides involving a palladium-catalyzed Overman rearrangement followed by a ruthenium-catalyzed RCM reaction of the resulting diene (Scheme 1). One of the reasons

Scheme 1. One-Pot Tandem Aza-Claisen Rearrangement and RCM Reaction

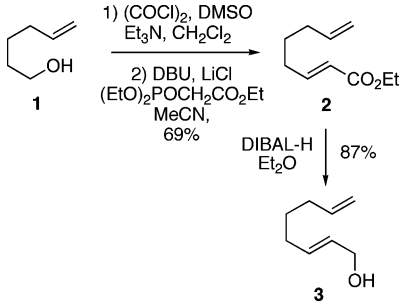


for our interest in developing such a process for the synthesis of these compounds is that cyclic allylic trichloroacetamides have been widely used as substrates for a range of reactions including dihydroxylations,[14] epoxidations,[15] Kharasch,[7,16] and other types of cyclization reactions.[17]

In this paper, we now report a one-pot tandem rearrangement and RCM reaction for the highly efficient synthesis of cyclic allylic trichloroacetamides as well as the use of chiral Pd(II) catalysts for the development of an asymmetric version of this process.

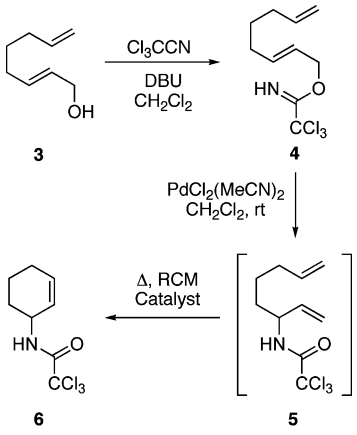
Initial investigations began with developing this one-pot process for the synthesis of a six-membered cyclic allylic trichloroacetamide. Accordingly, the corresponding allylic alcohol **3** was prepared in two steps from 5-hexen-1-ol **1** as outlined in Scheme 2. Thus, the use of a one-pot Swern oxidation and Horner−Wadsworth−Emmons (HWE) reaction[18,19] gave (*E*)-α,*β*-unsaturated ester **2** in 69% yield. Subsequent reduction of ester **2** using DIBAL-H gave allylic alcohol **3** in 87% yield.

Scheme 2. Synthesis of *E*-Allylic Alcohol **3**



Allylic alcohol **3** was then converted to allylic trichloroacetimidate **4** using trichloroacetonitrile and a catalytic amount of DBU (Scheme 3).[20] An initial attempt at preparing

Scheme 3. Development of the One-Pot Reaction



RCM catalyst	yield (%) of **6** from **3**
Grubbs I	89%
Grubbs II	95%
Hoveyda/ Grubbs II	95%

cyclic allylic trichloroacetamide **6** in a one-pot process by adding both the rearrangement and RCM catalysts (10 mol % of both) at the start of the reaction and heating the reaction mixture under reflux returned only rearrangement product **5**. As the Overman rearrangement takes place at room temperature, a second attempt involved the addition of both catalysts and allowed the rearrangement to take place at room temperature (∼3 h), before heating the reaction under reflux to effect the RCM reaction. However, this also gave only rearrangement product **5**. These results suggested that the RCM catalysts used in these attempts, Grubbs first-generation, Grubbs second-generation,[21] and Hoveyda−Grubbs

(11) (a) Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2005**, *3*, 735−736. (b) Jamieson, A. G.; Sutherland, A. *Tetrahedron* **2007**, *63*, 2123−2131. (c) Fanning, K. N.; Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2005**, *3*, 3749−3756. (d) Swift, M. D.; Sutherland, A. *Org. Biomol. Chem.* **2006**, *4*, 3889−3891.

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(13) Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2006**, *4*, 2932−2937.

(14) (a) Donohoe, T. J.; Blades, K.; Helliwell, M.; Moore, P. R.; Winter, J. J. G. *J. Org. Chem.* **1999**, *64*, 2980−2981. (b) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946−7956.

(15) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* **2003**, *5*, 4955−4957.

(16) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682−1689.

(17) (a) Cardillo, G.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1489−1490. (b) Cassayre, J.; Dauge, D.; Zard, S. Z. *Synlett* **2000**, 471−474.

(18) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198−2200.

(19) For high yielding preparation of (*E*)-alkenes from the one-pot Swern oxidation and HWE reaction, we use Masamune−Roush conditions for the HWE step. For reference, see: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masumune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(20) Anderson, C. E.; Overman, L. E.; Watson, M. P. *Org. Synth.* **2005**, *82*, 134−139.

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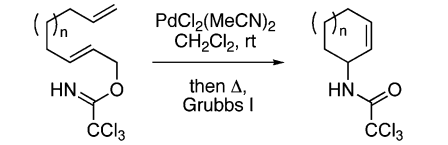
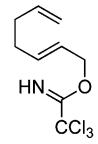
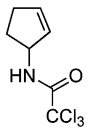
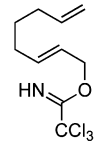
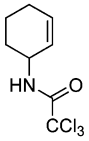
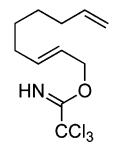
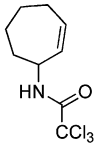
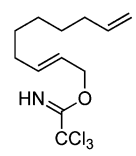
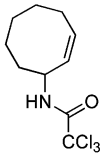
second-generation catalysts,[22] were all decomposing, probably due to a side reaction with the Pd(II) catalyst, before completion of the rearrangement step. To overcome this, a one-pot reaction was attempted involving stepwise addition of the catalysts. Thus, addition of bis(acetonitrile)palladium(II) chloride to allylic trichloroacetimidate **4** and stirring the reaction mixture at room temperature for 3 h followed by the addition of Grubbs first-generation catalyst and heating under reflux allowed the one-pot tandem synthesis of **6** in an excellent 89% yield over the three steps from allylic alcohol **3** (Scheme 3 and Table 1).[23] Similar results were obtained using Grubbs second-generation and Hoveyda−Grubbs second-generation catalysts.[24]

Table 1. Synthesis of Different Ring Sizes



entry	allylic imidate	cyclic allylic amide	yield (%) from allylic alcohol
1	 **7**	 **8**	84%
2	 **4**	 **6**	89%
3	 **9**	 **10**	93%
4[a]	 **11**	 **12**	62%

[a] RCM step was done using Grubbs second-generation catalyst.

Having successfully determined the reaction conditions for a one-pot synthesis of cyclic allylic trichloroacetamide **6**, we sought to expand the scope of this process for the preparation of other ring sizes. A series of allylic trichloroacetimidates, **7**, **9**, and **11** (Table 1) were prepared as described for compound **4**. Reaction of allylic trichloroacetimidate **7** using the one-pot tandem procedure under the same conditions as for **4** (substrate concentration of 0.08 M and 10 mol % of both catalysts) produced cyclopentene analogue **8** in 84% yield from the corresponding allylic alcohol. Attempted synthesis of the cycloheptene analogue **10** using these standard conditions gave a mixture of the desired and dimeric products. However, repeating the reaction under more dilute conditions (0.005 M)[25] allowed the isolation of **10** in an excellent 93% yield over the three steps.

Surprisingly, use of these optimized conditions for the synthesis of the cyclooctene analogue **12** gave only the rearrangement product, suggesting that Grubbs first-generation catalyst was unable to form the eight-membered ring.[26] Careful experimentation with other catalysts using higher catalyst loadings and more dilute reaction mixtures did yield **12**. For example, the use of 20 mol % of Grubbs second-generation catalyst and a substrate concentration of 0.0013 M gave cyclooctene **12** in 62% yield.

Our aim in developing a simple, one-pot tandem process for the highly efficient synthesis of cyclic allylic trichloroacetamides was for application in natural product synthesis. To realize this goal, the development of an asymmetric process for the enantioselective synthesis of these compounds was necessary. In 2003, Overman and co-workers reported a new chiral palladium catalyst, (*S*)-COP−Cl (**13**) (Scheme 4), which could catalyze the asymmetric rearrangement of allylic trichloroacetimidates in high yields and with excellent enantioselectivity.[20,27] Using this catalyst or the *R*-enantiomer (both of which are commercially available) during the first stage of our one-pot tandem rearrangement and RCM process allowed the asymmetric synthesis of cyclohexenes **14** and **15** (Scheme 4). For example, treatment of allylic trichloroacetimidate **4** with (*S*)-COP−Cl (**13**) at room temperature followed by the addition of Grubbs first-generation catalyst and heating the reaction mixture under reflux gave the *S*-enantiomer **14** in an excellent 90% yield from allylic alcohol **3** and in 88% ee.[28] Similar results were obtained for the synthesis of the *R*-enantiomer **15** using (*R*)-COP−Cl. In this study, these

(22) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(23) Allylic trichloroacetimidates are relatively unstable and, therefore, are not subjected to extensive purification. Hence, yields quoted for the preparation of the cyclic allylic trichloroacetamides are from the corresponding allylic alcohols.

(24) As highlighted in Scheme 3, use of Grubbs second-generation and Hoveyda−Grubbs second-generation catalysts gave cyclic allylic trichloroacetamide **6** in slightly higher yield than with the Grubbs first-generation catalyst. Nevertheless, in developing the subsequent reactions, we have used mainly Grubbs first-generation catalyst due to its relatively low cost and availability compared to the other catalysts.

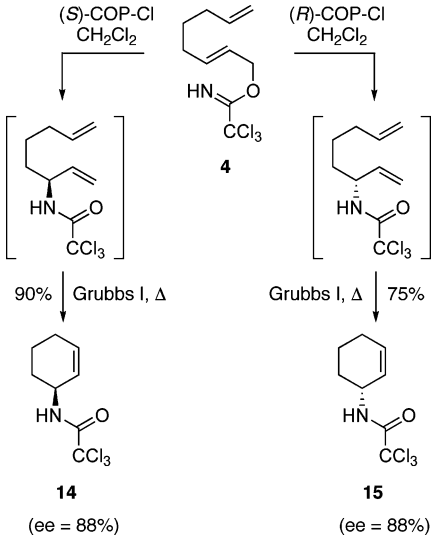
(25) Hodgson, D. M.; Robinson, L. A.; Jones, M. L. *Tetrahedron Lett.* **1999**, *40*, 8637−8640.

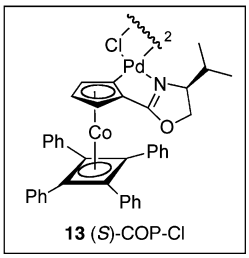
(26) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.

(27) (a) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809−1812. (b) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (c) Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031−5044.

(28) The enantiomeric excess of compounds **14** and **15** was determined by chiral HPLC. See Supporting Information for full details.

Scheme 4. Development of the Asymmetric Tandem Reaction





chiral catalysts were only used for the asymmetric synthesis of the cyclohexene analogues. However, we believe the use of these catalysts during the one-pot rearrangement and RCM reaction of allylic trichloroacetimidates **7**, **9**, and **11** should lead to the asymmetric synthesis of the five-, seven- and eight-membered analogues with similar enantioselectivity.

In summary, we have developed a facile one-pot tandem process for the highly efficient synthesis of cyclic allylic trichloroacetamides that utilizes a palladium-catalyzed Overman rearrangement at room temperature followed by a ruthenium-catalyzed RCM reaction under reflux. This process is flexible enough for the preparation of various ring sizes, and using commercially available chiral palladium catalysts during the first stage allows the asymmetric synthesis of these compounds in high enantiomeric excess. Further work is currently underway to expand this two-step tandem process to include additional reactions and to examine the synthetic application of cyclic allylic trichloroacetamides in natural product synthesis.

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Supporting Information Available: Full experimental procedures, spectroscopic data, and NMR spectra for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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