Cross metathesis of the amino acid homoallylglycine

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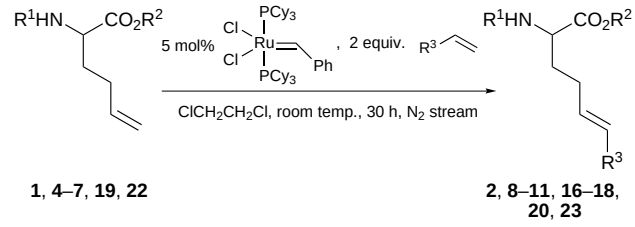
Reaction of various protected forms of the amino acid homoallylglycine with aryl- and alkyl-substituted alkenes in the presence of 5 mol% $Cl_2(PCy_3)_2Ru$=CHPh gives cross metathesis products in acceptable synthetic yield (43–66%).

The development of olefin metathesis, until recently a reaction applied mainly in bulk chemical production and polymer synthesis, into a reaction of general use in fine organic chemical synthesis continues to gain momentum. Seminal studies earlier this decade[1] led to the ring closing metathesis reaction (RCM) being used in several successful pioneering organic syntheses,[2] and the number of applications of this reaction in the past year suggests that it is now accepted as a useful synthetic tool.[3] The entropically more challenging but equally promising cross metathesis reaction has received much less attention from synthetic chemists and has been the subject of a mere handful of reports to date: early studies involved styrenes[4] and acrylonitrile[5] and very recently successful reactions using allylsilanes,[6] polymer-bound amino alcohols[7] and allyl stannanes[8] have been reported. Styrene cross metathesis has been applied recently to the elaboration of allylboration products[9] and β-lactams.[10]

In view of their biological role and myriad applications, it is not surprising that amino acids and their protected derivatives are attracting considerable attention as metathesis substrates. Initially they were ROMPed into polymers[11] and there now appears to be phrenetic interest in the use of amino acid derived substrates in RCM reactions.[12] In view of the level of activity in this area and the increasing interest in cross metathesis, we report here the first examples of cross metathesis reactions involving (protected) amino acids.

Homoallylglycine (Hag) was prepared by alkylation of diethyl acetamidomalonate with 4-bromobut-1-ene, ester loss and hydrolysis,[13] and subsequent amide hydrolysis. Standard protection procedures were then employed to generate the various protected forms of Hag discussed below.

Initially BocHagOMe **1**[14] was reacted with 2 equiv. of styrene in the presence of the ruthenium metathesis catalyst $Cl_2(PCy_3)_2Ru$=CHPh[15] using a variety of solvents, temperatures, reaction times, catalyst loadings and BocHagOMe concentrations. The yields of the cross metathesis product **2** were also measured from a reaction performed in a glove box under nitrogen, and from reactions carried out using Schlenk line techniques under both a static pressure and a steady stream of both nitrogen and argon. Interestingly there was no advantage to working in the glove box or under argon and, more significantly, changing the nitrogen atmosphere from a static pressure (*ca*. 1 atm) to a steady stream across the reaction mixture led to a 30% yield enhancement. The optimum conditions for the cross metathesis reaction between **1** and styrene were found to involve stirring a 0.25 M solution of BocHagOMe **1** in dichloroethane with 2 equiv. of styrene and 5 mol% of $Cl_2(PCy_3)_2Ru$=CHPh at room temperature with a steady stream of nitrogen blowing across the top of the reaction mixture for 30 h. These conditions gave a 52% isolated yield of the novel amino acid **2**† (based on BocHagOMe **1**) and a 40% yield of the BocHagOMe self metathesis product **3** (also based on **1**) (Table 1, entry 1).



In order to assess the merits of various protecting groups in the cross metathesis reaction, PhthHagOMe **4**, AcHagOMe **5**, BocHagOBn **6**[14] and BocHagOBu^t **7**[16] were synthesised and reacted with styrene under the conditions described above. The

Table 1 Cross metathesis of homoallylglycine derivatives with styrene, hex-1-ene and oct-1-ene[a]

Entry	Substrate	Alkene R1	Alkene R2	Alkene R3	Cross metathesis product[b]	Isolated yield (%)[c]	Self metathesis product[d]	Isolated yield (%)[e]
1	**1**	Boc	Me	Ph	**2**	52	**3**	40
2	**4**	Phth	Me	Ph	**8**	55	**12**	35
3	**5**	Ac	Me	Ph	**9**	43	**13**	48
4	**6**	Boc	Bn	Ph	**10**	53	**14**	44
5	**7**	Boc	Bu^t	Ph	**11**	55	**15**	45
6	**1**	Boc	Me	Bu	**16**	55	**3**	43
7	**1**	Boc	Me	Hex	**17**	66	**3**	28
8	**7**	Boc	Bu^t	Hex	**18**	63	**15**	28
9	**19**	Fmoc	Me	Hex	**20**	58	**21**	25
10	**22**	Fmoc	H	Hex	**23**	58[d]	**24**	18

[a] The experimental procedure for the conversion of **1** to **17** (entry 7) is typical: A nitrogen-saturated solution of **1** (0.121 g, 0.50 mmol) and oct-1-ene (0.156 cm^3, 1.00 mmol) in dichloroethane (2 cm^3) was added *via* a cannula to solid $Cl_2(PCy_3)_2Ru$=CHPh (0.021 g, 0.0235 mmol). The resulting purple solution was stirred under a steady stream of nitrogen for 30 h at room temperature. The dichloroethane was subsequently replaced with diethyl ether (*ca*. 50 cm^3) and the mixture stirred for 16 h under air to effect decomposition of the catalyst. Removal of the diethyl ether *in vacuo* and flash chromatography [SiO_2; light petroleum (40–60 °C)–diethyl ether, 1 : 0–5 : 1–1 : 2 gradient elution] gave the cross metathesis product **17** (0.108 g, 66%) and the self metathesis product **3** (0.032 g, 28%) as microanalytically pure colourless oils. [b] R^3 = Ph, *trans* : *cis* ≥ 10 : 1; R^3 = alkyl, *trans* : *cis ca.* 4 : 1. [c] Based on amino acid substrate. [d] Amino acid self metathesis product; alkene self metathesis products were also observed. [e] Product contaminated with 6% starting material.

yields of the cross metathesis products **2**, **8**–**11** and the self metathesis products **3**, **12**–**15** indicated that, with the exception of AcHagOMe **5**, the course of the reaction is independent of the nature of the protecting groups (Table 1, entries 1–5).

In order to determine whether the cross metathesis of Hag may be used to introduce alkyl groups into the amino acid side chain, BocHagOMe **1** and BocHagOBu^t **7** were reacted with hex-1-ene and oct-1-ene (Table 1, entries 6–8). Comparison of the yields of the cross metathesis products **16**–**18** with entries 1 and 5 reveals that whilst the yields obtained for styrene and the relatively volatile hex-1-ene are essentially equivalent, use of the less volatile oct-1-ene gives significantly higher yields of cross metathesis product than styrene. Reaction of FmocHagOMe **19** with oct-1-ene also gave an acceptable yield of the cross metathesis product **20** together with some self metathesis product **21** (Table 1, entry 9) indicating that the commonly used Fmoc protecting group is compatible with these cross metathesis conditions.

Finally, in view of the importance of FmocXaaOH components in solid phase peptide synthesis, a cross metathesis reaction between FmocHagOH **22** and oct-1-ene was examined. This gave the cross metathesis product **23** (and the self-metathesis product **24**) in good yield (Table 1, entry 10) thus demonstrating that an unprotected carboxylic acid may be used in cross metathesis reactions.

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Footnotes

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† The novel substrates **4**, **5**, **19**, **22** and the novel cross metathesis products **2**, **8**–**11**, **16**–**18**, **20**, **23** all gave satisfactory microanalytical and spectroscopic (IR, ^{1}H and ^{13}C NMR, MS) data.

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