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Tetrahedron 60 (2004) 1849–1861
Tetrahedron

Copper(II)salen catalysed, asymmetric synthesis of α,α-disubstituted amino acids

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Received 10 October 2003; revised 24 November 2003; accepted 11 December 2003

Abstract—Cu(salen) complex **1** was found to be a versatile catalyst for the asymmetric alkylation of a range of enolates derived from α-amino acids, leading to α,α-disubstituted amino acids. The enantioselectivity of the process decreases as the size of the amino acid sidechain increases, but functionalized amino acids such as allylglycine and aspartic acid are substrates for the process. Benzylic bromides are found to be more enantioselective alkylating agents than propargylic bromides. As an example of the utility of this chemistry, an α-propargylic allylglycine derivative is prepared and subjected to ene–yne metathesis using Grubbs' catalyst to give a non-racemic cyclopentenyl amino acid.

1. Introduction

Phase transfer methodology offers many possibilities in allowing otherwise unfavourable reactions to be carried out.[1] In particular, liquid–liquid phase transfer catalysis allows reactions to be carried out involving reagents for which no convenient mutual solvent is available. Solid–liquid phase transfer catalysis is potentially even more general as a solvent only needs to be found for one component of a reaction.

Recently, there has been an upsurge of interest in asymmetric phase transfer catalysis in which a chiral, non-racemic phase transfer catalyst is used to induce the enantioselective conversion of a prochiral substrate into an enantiomerically enriched product. Most work in this area has focused upon the asymmetric synthesis of α-amino acids or α,α-disubstituted amino acids by the alkylation of achiral enolates of glycine or alanine derivatives, though other classes of reactions can also be catalysed. The first reports in this area were due to O'Donnell who demonstrated that quaternary ammonium salts derived from cinchona alkaloids could catalyse the asymmetric alkylation of a glycine enolate, leading to α-amino acids with moderate enantiomeric excesses.[2] This chemistry was subsequently developed simultaneously by Lygo[3] and Corey,[4] who both showed that the use of a 9-anthracenylmethyl group to quaternize the cinchona alkaloid resulted in a catalyst that exhibited enhanced enantioselectivity.[5] In addition to enolate alkylations,[6] this catalyst will also catalyse Michael additions,[7,8] aldol reactions,[9] and enone epoxidations.[10] It can also be used in conjunction with achiral palladium complexes to induce the asymmetric allylation of enolates.[11] However, only glycine derived imines give products with high enantiomeric excesses.[12] Recently, polymer supported[8,13] and oligomeric[14] versions of the cinchona derived phase transfer catalysts have been developed and used for asymmetric amino acid synthesis. The catalysts have also been used under micellar conditions.[15]

Maruoka has developed a class of binaphthyl derived quaternary ammonium salts and has shown that they act as asymmetric phase transfer catalysts for both the alkylation and dialkylation (with two different alkylating agents) of a glycine derived imine, leading to both α-amino acids and α,α-disubstituted amino acids with excellent enantiomeric excesses.[16] Aldol reactions,[17] Michael additions,[18] and the alkylation of β-keto esters[19] are also catalysed by this class of asymmetric phase transfer catalysts. Other groups have also investigated the use of synthetic ammonium[20] and guanidinium[21] salts and crown ethers[22] as asymmetric phase transfer catalysts.

In 1998, Belokon' and Kagan were the first to demonstrate that a metal complex could act as an asymmetric phase transfer catalyst. The sodium salt of TADDOL was found to catalyse the alkylation of alanine derivatives leading to

Keywords: Cu(salen) complex; Phase transfer methodology; Alkylation.
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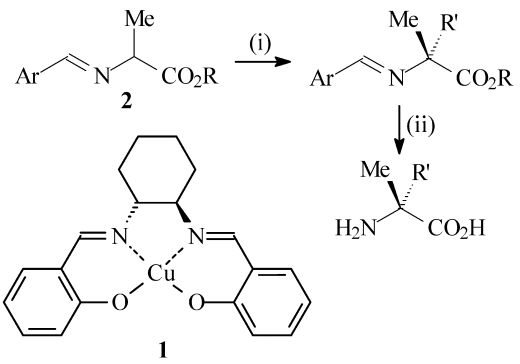
doi:10.1016/j.tet.2003.12.031

α-methyl-α-amino acids with up to 82% enantiomeric excess.[23] It was subsequently shown that the sodium salts of both NOBIN[24] and BINOLAM[25] could act as asymmetric phase transfer catalysts for the same reaction.

Although chiral transition metal complexes have been used to catalyse a wide range of asymmetric transformations, we were the first to show that they could be used to catalyse the asymmetric alkylation of amino acid enolates under phase transfer conditions. In particular, we have shown that copper(II)salen complex **1** will catalyse the asymmetric alkylation of the enolate of alanine derivative **2** leading to α-methyl, α-amino acids with up to 90% enantiomeric excess as shown in Scheme 1.[26] The key alkylation reaction is carried out under solid–liquid phase transfer conditions using solid sodium hydroxide as base, and toluene as the solvent. One of the advantages of this chemistry compared to the quaternary ammonium salt methodologies is the ability to use the readily available and inexpensive methyl ester of alanine as substrate, as the nature of the ester appears to make no significant difference to the level of asymmetric induction observed in the reactions. Although the methyl ester is hydrolysed under the reaction conditions, this appears to be slower than the enolate formation and alkylation and the product can readily be re-esterified as part of the work-up procedure.[27] In this manuscript, we report the extension of this chemistry to substrates derived from amino acids other than alanine.[28]

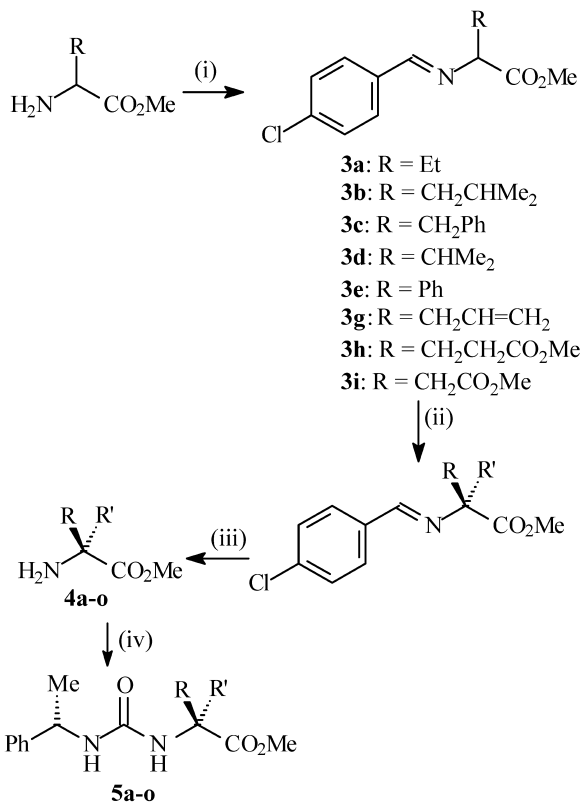


Scheme 1. (i) NaOH/R′X/**1** (2 mol%), toluene, R.T (ii) H_3O^+.

2. Results and discussion

The first substrate that we chose to investigate was aminobutyric acid derivative **3a** as this involved only a small change in the sidechain from methyl to ethyl. Imine **3a** was prepared from (*R*,*S*)-aminobutyric acid methyl ester and *para*-chlorobenzaldehyde (Scheme 2), and was then alkylated with allyl bromide under the standard conditions for the use of catalyst **1**, to give α-ethyl allylglycine methyl ester **4a** with 80% enantiomeric excess (Table 1 entry 1). By doubling the amount of allyl bromide used to 2.4 equiv., the yield of compound **4a** increased to >50%, though at the expense of a decrease in the enantiomeric excess (Table 1: entry 2).

The enantiomeric excess of all the α,α-disubstituted amino esters prepared in this work was determined by reaction of a sample of the amino ester with an excess of (*S*)-α-methyl



4/5a: R = Et, R' = $CH_2CH{=}CH_2$
4/5b: R = Et, R' = CH_2Ph
4/5c: R = Et, R' = 4-$O_2NC_6H_4CH_2$
4/5d: R = CH_2CHMe_2, R' = CH_2Ph
4/5e: R = CH_2CHMe_2, R' = 4-$O_2NC_6H_4CH_2$
4/5f: R = CH_2CHMe_2, R' = $CH_2CH{=}CH_2$
4/5g: R = CH_2Ph, R' = $CH_2CH{=}CH_2$
4/5h: R = CH_2Ph, R' = 4-$O_2NC_6H_4CH_2$
4/5i: R = Ph, R' = $CH_2CH{=}CH_2$
4/5j: R = Ph, R' = CH_2Ph
4/5k: R = $CH_2CH{=}CH_2$, R' = CH_2Ph
4/5l: R = $CH_2CH{=}CH_2$, R' = 4-$O_2NC_6H_4CH_2$
4/5m: R = $CH_2CH{=}CH_2$, R' = CH_2CCMe
4/5n: R = $CH_2CH{=}CH_2$, R' = CH_2CCH
4/5o: R = CH_2CO_2Me, R' = $CH_2CH{=}CH_2$
4/5p: R = CH_2CO_2Me, R' = CH_2Ph

Scheme 2. (i) 4-$ClC_6H_4CHO/MgSO_4$; (ii) NaOH/R′X/**1**, toluene, R.T., then MeOH/AcCl; (iii) SiO_2; (iv) excess (*S*)-PhCHMe-N=C=O, $CDCl_3$, RT.

benzylisocyanate followed by analysis of the resulting diastereomeric ureas **5** by ^1H NMR spectroscopy. When substrate **3a** was alkylated using benzyl bromide to give α-ethyl phenylalanine methyl ester **4b**, the standard conditions (Table 1: entry 3) gave a product with good enantiomeric excess but in very low yield. Simply extending the reaction time from 1 to 2 days increased the chemical yield to >90% whilst leaving the enantiomeric excess of the product essentially unchanged (Table 1: entry 4). The final alkylating agent studied in conjunction with substrate **3a** was 4-nitrobenzyl bromide. In this case, the standard conditions (Table 1: entry 5) again gave the product **4c** with ca. 80% enantiomeric excess but in low yield. Doubling either the reaction time (Table 1: entry 6) or the amount of

Table 1. Alkylation of amino acid derivatives **3a–i**

Entry	Substrate	Alkylating agent (equivalents) (product)	Catalyst (mol%)	Time (days)	Yield (%)	Enantiomeric excess (%)
1	**3a**	Allyl bromide (1.2) (**4a**)	2	1	46	80
2	**3a**	Allyl bromide (2.4) (**4a**)	2	1	54	70
3	**3a**	Benzyl bromide (1.2) (**4b**)	2	1	39	80
4	**3a**	Benzyl bromide (1.2) (**4b**)	2	2	91	82
5	**3a**	*Para*-nitro-benzyl bromide (1.2) (**4c**)	2	1	23	78
6	**3a**	*Para*-nitro-benzyl bromide (1.2) (**4c**)	2	2	83	79
7	**3a**	*Para*-nitro-benzyl bromide (2.4) (**4c**)	2	1	95	75
8	**3b**	Benzyl bromide (1.2) (**4d**)	2	1	0	
9	**3b**	Benzyl bromide (1.2) (**4d**)	10	1	41	27
10	**3b**	Benzyl bromide (1.2) (**4d**)	10	7	54	55
11	**3b**	*Para*-nitro-benzyl bromide (1.2) (**4e**)	10	1	46	40
12	**3b**	*Para*-nitro-benzyl bromide (1.2) (**4e**)	10	7	63	56
13	**3b**	*Para*-nitro-benzyl bromide (2.4) (**4e**)	10	1	64	47
14	**3b**	*Para*-nitro-benzyl bromide (2.4) (**4e**)	2	1	47	43
15	**3b**	Allyl bromide (1.2) (**4f**)	10	1	46	22
16	**3c**	Allyl bromide (1.2) (**4g**)	2	1	30	17
17	**3c**	Allyl bromide (1.2) (**4g**)	2	5	44	17
18	**3c**	Allyl bromide (2.4) (**4g**)	2	1	53	15
19	**3c**	Allyl bromide (4.8) (**4g**)	2	1	74	18
20	**3c**	Allyl bromide (4.8) (**4g**)	10	1	87	20
21	**3c**	Allyl bromide (1.2) (**4g**)	10	1	40	31
22	**3c**	Allyl bromide (1.2) (**4g**)	25	1	68	27
23	**3c**	Allyl bromide (1.2) (**4g**)	50	1	70	19
24	**3c**	*Para*-nitro-benzyl bromide (1.2) (**4h**)	10	1	67	34
25	**3d**	Allyl bromide (2.4)	2	7	0	
26	**3d**	Allyl bromide (2.4)	10	2	0	
27	**3d**	Benzyl bromide (2.4)	10	2	0	
28	**3e**	Allyl bromide (1.2) (**4i**)	2	1	31	48
29	**3e**	Benzyl bromide (1.2) (**4j**)	2	1	38	42
30	**3f**	Benzyl bromide (1.2) (**4k**)	2	1	66	57
31	**3f**	Benzyl bromide (2.4) (**4k**)	2	1	67	57
32	**3f**	Benzyl bromide (1.2) (**4k**)	10	1	38	43
33	**3f**	*Para*-nitro-benzyl bromide (1.2) (**4l**)	2	2	45	47
34	**3f**	1-Bromo-but-2-yne (**4m**)	2	2	46	25
35	**3f**	Propargyl bromide (**4n**)	2	2	49	20
36	**3g**	1-Bromo-but-2-yne (**4m**)	2	2	44	25
37	**3h**	Benzyl bromide (**7**)	2	2	52	
38	**3i**	Allyl bromide (1.2) (**4o**)	2	1	25	17
39	**3i**	Benzyl bromide (1.2) (**4p**)	2	1	75	10

4-nitrobenzyl bromide used (Table 1: entry 7) increased the chemical yield to >80% without significantly reducing the enantiomeric excess of the product. Thus, by choice of appropriate concentrations and/or reaction times it was possible to convert imine **3a** into α-ethyl amino acids in high yield and with ca. 80% enantiomeric excess in each case. Peptides incorporating α-ethyl amino acids have recently been shown to adopt unique conformations.[29] To further extend the scope of the chemistry, leucine derivative **3b** was used as substrate (Scheme 2, R=CH_2CHMe_2). The presence of a branch at the γ-carbon makes this a more hindered substrate than aminobutyric acid derivative **3a**, which was anticipated to affect the enantioselectivity of the alkylation reaction. Under the standard conditions (Table 1: entry 8) no reaction occurred when substrate **3b** was treated with benzyl bromide. Only by increasing the amount of catalyst to 10 mol% (Table 1: entry 9) could α-benzyl leucine methyl ester (**4d**) be isolated in moderate yield and with low enantiomeric purity. Interestingly, increasing the reaction time from 1 to 7 days (Table 1: entry 10) resulted in only a small increase in the isolated yield of compound **4d**, but doubled its enantiomeric purity to a respectable 55%.

para-Nitrobenzyl bromide also reacted with substrate **3b**, giving α,α-disubstituted amino ester **4e** with up to 56% enantiomeric excess (Table 1: entries 11–14). Employing 1.2 equiv. of the alkylating agent (Table 1: entries 11 and 12) gave results which are very similar to those obtained when benzyl bromide was used as the alkylating agent, with optimal yield and enantioselectivity being observed after a reaction time of 7 days. However, by increasing the amount of alkylating agent to 2.4 equiv., it was possible to reduce the reaction time to one day (Table 1: entry 13) with no reduction in the chemical yield, though the enantiomeric excess of the product was slightly reduced. Subsequent reduction of the amount of catalyst used back to 2 mol% (Table 1: entry 14) did give compound **4e**, all be it in reduced chemical yield and with a lower enantiomeric excess. Finally, allyl bromide reacted with substrate **3b** to give α-allyl leucine methyl ester **4f**, though again the reaction required 10 mol% of catalyst **1** and the enantiomeric excess of the product was very low (Table 1: entry 15).

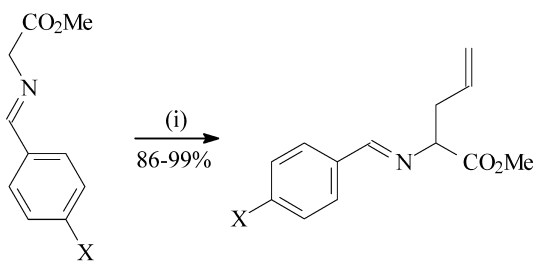
Phenylalanine derived substrate **3c** also branches at the γ-position. The initial studies using this substrate were carried out using allyl bromide as the alkylating agent (Table 1: entries 16–23). Despite numerous optimization attempts in which the catalyst concentration, alkylating agent concentration and reaction time were all varied, the

highest enantiomeric excess observed for product **4g** was 31%, and in a mediocre 40% yield. This enantiomeric excess was observed using 10 mol% of catalyst **1** (Table 1: entry 21), and use of a lower (Table 1: entry 16) or higher (Table 1: entries 22 and 23) concentration of catalyst **1** resulted in reduced enantioselectivity. The only other alkylating agent studied with substrate **3c** was *para*-nitrobenzyl bromide, and under the optimized conditions, this gave product **4h** with 34% enantiomeric excess (Table 1: entry 24) which is essentially identical to that observed using allyl bromide as the alkylating agent (Table 1: entry 21).

Valine derived substrate **3d** which is β-branched is amongst the most hindered possible substrates for this type of alkylation reaction. All attempts to react substrate **3d** with either allyl bromide (Table 1: entries 25 and 26) or benzyl bromide (Table 1: entry 27) were totally unsuccessful. It appears that substrate **3d** is too hindered to be a substrate for catalyst **1**.

The final unfunctionalized substrate that we have investigated is phenylglycine derivative **3e**. This substrate was of interest since although the sidechain branches at the β-position, the enolate of compound **3e** would be completely planar, unlike the enolates of compounds **3a**–**d**. Alkylation of substrate **3e** with allyl bromide (Table 1: entry 28) gave α-phenyl allylglycine with 48% enantiomeric excess. This enantioselectivity, whilst not comparable with that obtainable from aminobutyric acid derived substrate **31** (Table 1: entry 1), is significantly higher than that obtained from either leucine or phenylalanine derived substrates **3b** and **3c** (Table 1: entries 15 and 21). The alkylation of substrate **3e** by benzyl bromide was also investigated. In this case, the enantioselectivity was lower than that obtained for either substrate **3a** or **3b**, but the latter results are not strictly comparable due to the different amounts of catalyst used.

Substrates **3a**–**e** are all unfunctionalized but differ in their steric properties. It appears that the enantioselectivity of the alkylation of these substrates decreases as the substrate becomes more sterically hindered. We next decided to study more functionalized substrates to investigate the compatibility of the chemistry with functional groups. The first substrates chosen for this work were allylglycine derivatives **3f** and **3g**. Compounds **3f** and **3g** were prepared by the palladium catalysed allylation of glycine imines **6a** and **6b** as shown in Scheme 3.[30,31] This method has the advantage



6a: X = H
6b: X = Cl

3f: X = H
3g: X = Cl

Scheme 3. (i) $H_2C{=}CHCH_2OCO_2Me$/Pd(dppe) (5 mol%).

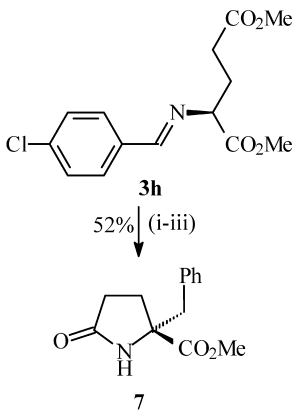
over a direct alkylation of the enolates of compounds **6a**,**b** in that no dialkylation occurs.

Imine **3f** was subsequently reacted with catalyst **1** and benzyl bromide according to Scheme 2 to give α-allyl-phenylalanine methyl ester **4k** in 66% yield and with 57% enantiomeric excess (Table 1: entry 30). Attempts to increase the enantioselectivity and/or chemical yield with this substrate by increasing the concentration of substrate or catalyst were unsuccessful (Table 1: entries 31 and 32). Optimal yields with all products derived from imines **3f** and **3g** were obtained by omitting the methanolic HCl treatment at the end of the alkylation reaction. Presumably, the products are sufficiently sterically hindered that ester hydrolysis does not occur on the reaction timescale and the methanolic HCl treatment reduces the isolated yield by inducing addition reactions to the alkene and/or alkyne units within products **4k**–**4n**. Product **4k** is constitutionally identical to product **4g** obtained by the allylation of phenylalanine derivative **3c**. However, analysis of the ^{1}H NMR spectra of the derived ureas **5g** and **5k** revealed that the major stereoisomer formed in each case was different. This implies that products **4g** and **4k** are enantiomeric, and this is consistent with the alkylation occurring enantioselectively on the *re*-face of the enolate. Further evidence for this hypothesis was obtained by hydrolysis of amino ester **4g** to give (+)-α-allyl-phenylalanine, which is known to correspond to the (*S*)-enantiomer of this amino acid.[32]

Use of *para*-nitrobenzyl bromide as the alkylating agent with substrate **3f** (Table 1: entry 33) gave α-*para*-nitrobenzyl-allylglycine **4l** with similar enantiomeric excess (47%) to that observed using benzyl bromide, though with a lower isolated yield. However, use of 1-bromo-2-butyne as the alkylating agent (Table 1: entry 34) gave α-but-2-ynyl-allylglycine **4m** with a much lower enantiomeric excess (25%) and with propargyl bromide as the alkylating agent, the enantioselectivity dropped still further (Table 1: entry 35). In this case, use of the *para*-chlorobenzylidene imine **3g** did not increase the enantioselectivity of the alkylation reaction (Table 1: entry 36). This result is consistent with our previous results on substrate **2** where propargyl bromide was found to give a product with lower enantiomeric excess than that observed using allylic or benzylic halides.[26,27]

Glutamic acid derivative **3h** was felt to be an interesting substrate for this chemistry since alkylated glutamic acid derivatives are known to be selective neurotransmitters.[33] In addition, since glutamic acid is branched only at the δ-carbon, it was expected to be a good substrate, and to lead to α-substituted derivatives with high enantiomeric excess. However, treatment of substrate **3h** with benzyl bromide in the presence of catalyst **1** (Table 1: entry 37) gave not the expected α-benzyl glutamic acid dimethyl ester, but α-benzyl-pyroglutamic acid methyl ester **7** as shown in Scheme 4. It appears that the alkylation chemistry works exactly as expected, but on work-up the α-substituted glutamic acid diester spontaneously cyclises to lactam **7**. Unfortunately, compound **7** failed to react with α-methyl benzylisocyanate, so we were unable to determine its enantiomeric excess.

To avoid the cyclisation problem encountered in the



Scheme 4. (i) **1** (2 mol%)/NaOH/BnBr; (ii) MeOH/AcCl; (iii) SiO_2.

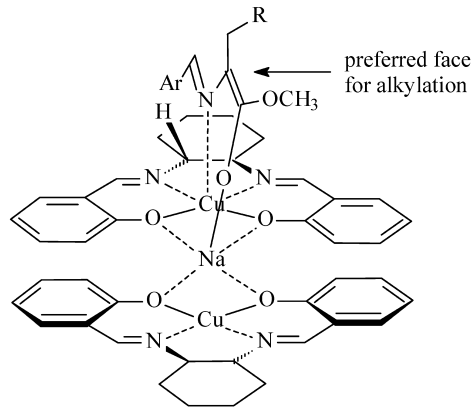
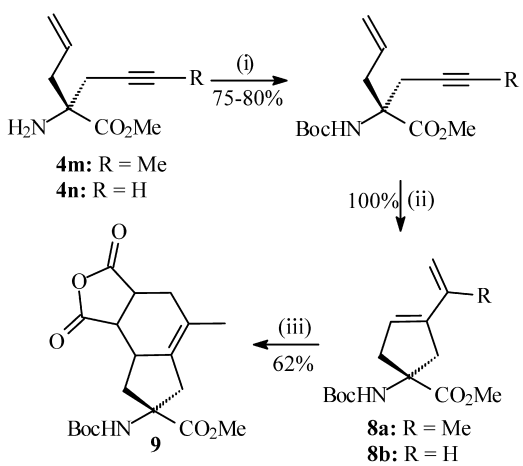


Figure 1.

synthesis of α-substituted glutamic acid derivatives, we turned to the lower homologue aspartic acid. Reaction of imine **3i** with allyl bromide gave α-allyl-aspartic acid dimethyl ester (**4o**) (Table 1: entry 38), and the corresponding reaction with benzyl bromide gave α-benzyl aspartic acid dimethyl ester (**4p**) (Table 1: entry 39). However, the enantiomeric excesses of products **4o/p** were disappointing (10–20%), possibly reflecting the fact that the sidechain of aspartic acid branches at the γ-carbon.

To demonstrate the utility of this methodology in the synthesis of complex amino acids, the further manipulation of adducts **4m** and **4n** was investigated. Thus, amino esters **4m** and **4n** were first protected with a Boc group, then treated with Grubbs' catalyst (5 mol%) under an ethene atmosphere to induce ring-closing ene–yne metathesis to give dienes **8a**,**b** as shown in Scheme 5. Subsequent Diels–Alder reaction of diene **8a** with maleic anhydride gave tricyclic amino acid derivative **9** as a 1:1 mixture of diastereomers.



Scheme 5. (i) Boc_2O; (ii) $(PCy_3)_2Ru(Cl)_2{=}CHPh$ (5 mol%) /$H_2C{=}CH_2$; (iii) maleic anhydride.

Our model for the alkylation of amino ester enolates catalysed by complex **1** is shown in Figure 1.[26,28] The enolate is coordinated to both the copper and sodium ions of a bimetallic complex and is held orthogonal to the plane of the salen ligand. Alkylation then occurs preferentially on the *re*-face of the enolate. This model works well for glycine and alanine substrates,[26] both of which are alkylated with high enantioselectivity. Other amino acid derived substrates are more complicated as an additional factor needs to be considered: rotation around the $C_\alpha-C_\beta$-bond of the enolate. Thus, the R-group shown in Figure 1 could be located over the *re*- (as shown) or *si*-face of the enolate. The former is more likely since the R-group will be repelled by the same features of the cyclohexane ring that direct alkylation to the *re*-face of the enolate. If the R-group is over the *re*-face of the enolate, then it will hinder the approach of the electrophile to the *re*-face and this will result in a lower enantioselectivity during the alkylation. The overall rate of reaction will also decrease as the size of the R-group increases. Thus, the model correctly predicts both the absolute configuration of the product, and the general relationship between the enantioselectivity of alkylation and the size of the amino acid sidechain.

Substrate **3e** derived from phenylglycine was included in this study specifically to probe the stereochemical model shown in Figure 1. Since the sidechain of this substrate consists of just a phenyl ring, the enolate of substrate **3e** should be completely planar and there should be no hindrance to alkylation on the preferred *re*-face of the enolate. Thus, substrate **3e** was expected to undergo highly enantioselective alkylation despite being a β-substituted amino acid. In the event, alkylation of enolate **3e** by allyl bromide (Table 1: entry 28) induced by catalyst **1** was not as highly enantioselective (48%) as the alkylation of the corresponding alanine[26,27] or aminobutyric acid derivatives (Table 1: entries 1 and 2) (70–80%). It was, however, considerably more enantioselective than the allylation of substrates **3b**,**c**,**i** (Table 1: entries 15, 21, 38) (17–30% ee). The reason for the lower than expected enantioselectivity observed with substrate **3e** is probably related to the highly acidic nature of the α-proton of this substrate. Control experiments have shown that substrates **3** undergo alkylation to give racemic products **4** under the reaction conditions, even in the absence of catalyst **1**. This uncatalysed process is expected to be particularly facile in the case of substrate **3e** which will lower the observed enantiomeric excess of the product, and account for the enantiomeric excess observed with this substrate being lower than would be predicted by the model shown in Figure 1.

3. Conclusions

Complex **1** has been shown to be a versatile catalyst for the asymmetric alkylation of enolates derived from a range of unhindered amino acids. Of the substrates studied, only the valine derivative failed to react, though for other substrates the enantioselectivity of the alkylation was found to diminish as the size of the sidechain increased.

Further work on the mechanism of the catalysis using complex **1** and the optimization of the catalyst for sterically hindered substrates is in progress and will be reported in due course.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 360 Spectrometer, (^{1}H 360 MHz and ^{13}C 90 MHz) The solvent for a particular spectrum is given in parentheses. Spectra were referenced to TMS and chemical-shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments. Infrared spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates or as KBr disks. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a 4.7T Bruker Apex III FTMS within the chemistry department at King's College. The sample was ionised by electron ionisation (EI), chemical ionisation (CI) or electrospray ionization (ES). The major fragment ions are reported and only the molecular ions are assigned.

Optical rotations were recorded on a Perkin–Elmer 343 polarimeter in a thermostated cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g/100 ml). Melting points are uncorrected.

Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin-layer chromatography was performed on polyester backed silica sheets, both supplied by Merck.

4.1.1. Methyl *N*-*para*-chlorobenzylidene-(*R*,*S*)-2-aminobutyrate 3a. To a stirred suspension of methyl (*R*,*S*)-2-aminobutyrate hydrochloride (18.1 g, 118.2 mmol) in dichloromethane (50 ml), triethylamine (8.5 ml, 59.1 mmol), *para*-chlorobenzaldehyde (8.3 g, 59.1 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The crude product was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give imine **3a** (8.47 g, 60%) as a yellow oil. ν_{max} (film) 2970 (m), 2878 (w), 1738 (s), 1643 (m), 1596 (w) and 1573 cm^{-1} (w); δ_H ($CDCl_3$) 0.79 (3H, t J=7.4 Hz, CH_3CH$_2$), 1.7–1.85 (1H, m, CH$_2$), 1.9–2.0 (1H, m, CH$_2$), 3.61 (3H, s, OCH$_3$), 3.78 (1H, t J=5.5 Hz, CHCH$_2$), 7.24 (2H, d J=8.4 Hz, ArCH), 7.59 (2H, d J=8.5 Hz, ArCH), 8.11 (1H, s, CH=N); δ_C ($CDCl_3$) 9.48 (*C*H$_3$CH$_2$), 25.69 (CH$_2$), 51.12 (OCH$_3$), 73.73 (*C*HCH$_2$), 126.91 (ArCH), 126.97 (ArCH), 127.16 (ArC), 128.77 (ArC), 161.00 (N=CH), 171.81 (CO_2); *m*/*z* (CI, NH_3) 240 (MH^+, 80), 180 (100); [found: (ES) 240.0794 (MH^+, $C_{12}H_{15}NO_2{}^{35}Cl$ requires 240.0791)].

4.1.2. α-Ethyl-allylglycine methyl ester 4a. Imine **3a** (0.24 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (7.7 mg, 0.02 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and allyl bromide (14.5 mg, 1.2 mmol) were added to the mixture. The resulting solution was stirred overnight under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4a** (72.2 mg, 46%) as a colourless oil. $[\alpha]_D^{20}$=+1.6 (c=1.85, $CHCl_3$); ν_{max} (film) 3372 (m), 3012 (w), 2978 (m), 2882 (m), 1732 (s), 1596 (s) and 1492 cm^{-1} (m); δ_H ($CDCl_3$) 0.79 (3H, t J=7.5 Hz, CH_3CH$_2$), 1.4–1.6 (1H, m, CH_2CH$_3$), 1.54 (2H, br s, NH$_2$), 1.7–1.8 (1H, m, CH_2CH$_3$), 2.15 (1H, dd J=13.5, 8.4 Hz, CH_2CH=), 2.45 (1H, dd J=13.5, 6.4 Hz, CH_2CH=), 3.65 (3H, s, OCH$_3$), 5.0–5.1 (2H, m, =CH$_2$), 5.6–5.7 (1H, m, =C*H*); δ_C ($CDCl_3$) 8.68 (*C*H$_3$CH$_2$), 33.22 (CH$_3$*C*H$_2$), 44.36 (*C*H$_2$CH=), 52.46 (OCH$_3$), 61.61 (N*C*CO$_2$), 119.75 (=CH$_2$), 133.23 (=CH), 177.64 (CO_2); *m*/*z* (CI, NH_3) 158 (MH^+, 100); [found: (ES) 158.1183 (MH^+, $C_8H_{16}NO_2$ requires 158.1181)].

4.1.3. α-Ethyl-phenylalanine methyl ester 4b. Imine **3a** (0.24 g, 1.00 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (7.7 mg, 0.02 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and benzyl bromide (205 mg, 1.2 mmol) were added to the mixture. The resulting solution was stirred for 2 days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4b** (188 mg, 91%) as a yellow oil. $[\alpha]_D^{20}$=+20 (c=1.75, $CHCl_3$); ν_{max} (film) 3373 (m), 2968 (m), 2880 (w), 1732 (s), 1603 (m), 1495 (w) and 1454 cm^{-1} (m); δ_H ($CDCl_3$) 0.82 (3H, t J=7.5 Hz, CH_3CH$_2$), 1.46 (2H, br s, NH$_2$), 1.5–1.6 (1H, m, CH_2CH$_3$), 1.8–2.0 (1H, m, CH_2CH$_3$), 2.68 (1H, d J=13.2 Hz, CH$_2$Ph), 3.11 (1H, d J=13.2 Hz, CH$_2$Ph), 3.63 (3H, s, OCH$_3$), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 7.41 (*C*H$_3$CH$_2$), 32.21 (*C*H$_2$CH$_3$), 44.83 (CH$_2$Ph), 50.92 (OCH$_3$), 61.62 (N*C*CO$_2$), 125.90 (ArCH), 127.36 (ArCH), 128.85 (ArCH), 135.44 (ArC), 175.99 (CO_2); *m*/*z* (CI, NH_3) 208 (MH^+, 100); [found: (CI, NH_3) 208.1338 (MH^+, $C_{12}H_{18}NO_2$ requires 208.1337)].

4.1.4. α-Ethyl-*para*-nitrophenylalanine methyl ester 4c. Imine **3a** (0.24 g, 1.00 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (7.7 mg, 0.02 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and *para*-nitrobenzyl bromide (0.259 g, 1.2 mmol) were added to the mixture. The resulting solution was stirred for two days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added in a dropwise manner to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4c** (209 mg, 83%) as a yellow oil. $[\alpha]_D^{20}=+21$ ($c=3.65$, $CHCl_3$); ν_{max} (film) 3370 (m), 1732 (s), 1604 (m), and 1518 cm^{-1} (s); δ_H ($CDCl_3$) 0.83 (3H, t $J=7.5$ Hz, CH_3CH_2), 1.41 (2H, br s, NH_2), 1.5–1.6 (1H, m, CH_2CH_3), 1.8–2.0 (1H, m, CH_2CH_3), 2.81 (1H, d $J=13.0$ Hz, CH_2Ar), 3.17 (1H, d $J=13.0$ Hz, CH_2Ar), 3.64 (3H, s, OCH_3), 7.27 (2H, d $J=8.6$ Hz, ArCH), 8.06 (2H, d $J=8.5$ Hz, ArCH); δ_C ($CDCl_3$) 8.69 (CH_3CH_2), 33.59 (CH_2CH_3), 45.91 (CH_2Ar), 52.57 (OCH_3), 62.99 ($NCCO_2$), 123.77 (ArCH), 131.25 (ArCH), 144.94 (ArC), 147.38 (ArC), 176.67 (CO_2); *m/z* (CI, NH_3) 253 (MH^+, 20), 223 (50), 116 (100); [found: (CI, NH_3) 253.1190 (MH^+, $C_{12}H_{17}N_2O_4$ requires 253.1188)].

4.1.5. *N*-*para*-Chlorobenzylidene (*R*,*S*)-leucine methyl ester 3b. To a stirred suspension of (*R*,*S*)-leucine methyl ester hydrochloride (9.43 g, 52.1 mmol) in dichloromethane (190 ml), triethylamine (5.26 g, 52.1 mmol), *para*-chlorobenzaldehyde (7.32 g, 52.1 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The crude product was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give compound **3b** (9.06 g, 65%) as a yellow oil. ν_{max} (film) 2956 (s), 2871 (m), 1742 (s), 1642 (m), 1596 (w) and 1572 cm^{-1} (w); δ_H ($CDCl_3$) 0.80 (3H, d $J=6.6$ Hz, CH_3CH), 0.85 (3H, d $J=6.6$ Hz, CH_3CH), 1.4–1.5 (1H, m, $CHMe_2$), 1.73–1.75 (1H, m, $CHCH_2CH$), 1.76–1.78 (1H, m, $CHCH_2CH$), 3.64 (3H, s, OCH_3), 4.22 (1H, dd $J=8.3$, 6.1 Hz, $NCHCO_2$), 7.28 (2H, d $J=8.5$ Hz, ArCH), 7.63 (2H, d $J=8.5$ Hz, ArCH), 8.16 (1H, s, N=CH); δ_C ($CDCl_3$) 21.85 (CH_3CH), 23.47 (CH_3CH), 24.79 ($CHMe_2$), 42.43 ($CHCH_2CH$), 52.51 (OCH_3), 71.83 ($NCHCO_2$), 129.22 (ArCH), 130.09 (ArCH), 134.50 (ArC), 137.45 (ArC), 162.12 (N=CH), 173.06 (CO_2); *m/z* (CI, NH_3) 268 (MH^+, 100); [found: (ES) 268.1100 (MH^+, $C_{14}H_{19}NO_2{}^{35}Cl$ requires 268.1104)].

4.1.6. α-Benzyl-leucine methyl ester 4d.[34,35] Imine **3b** (0.267 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (38.5 mg, 0.10 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and benzyl bromide (0.14 ml, 1.2 mmol) were added to the mixture. The resulting solution was stirred for 7 days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The crude residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4d** (127 mg, 54%) as a colourless oil. δ_H ($CDCl_3$) 0.76 (3H, d $J=6.6$ Hz, CH_3CH), 0.89 (3H, d $J=6.6$ Hz, CH_3CH), 1.46 (2H, br s, NH_2), 1.55 (1H, dd $J=13.7$, 4.6 Hz, CH_2CH), 1.6–1.75 (1H, m, $CHMe_2$), 1.82 (1H, dd $J=13.7$, 4.6 Hz, CH_2CH), 2.64 (1H, d $J=13.1$ Hz, CH_2Ph), 3.09 (1H, d $J=13.1$ Hz, CH_2Ph), 3.61 (3H, s, OCH_3), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 24.28 (CH_3CH), 26.06 (CH_3CH), 26.45 ($CHMe_2$), 49.24 (CH_2), 50.73 (CH_2), 53.51 (OCH_3), 63.40 ($NCCO_2$), 128.71 (ArCH), 130.11 (ArCH), 131.61 (ArCH), 137.87 (ArC), 179.31 (CO_2); *m/z* (CI, NH_3) 236 (MH^+, 100).

4.1.7. α-*para*-Nitrobenzyl-leucine methyl ester 4e. Imine **3b** (0.267 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (38.5 mg, 0.10 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and *para*-nitrobenzyl bromide (0.259 g, 1.2 mmol) were added to the mixture. The resulting solution was stirred for 7 days under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The crude residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4e** (176 mg, 63%) as a yellow oil. $[\alpha]_D^{20}=+2.7$ ($c=0.6$, $CHCl_3$); ν_{max} (film) 3390 (w), 2956 (s), 2872 (m), 1733 (s), 1605 (s) and 1521 cm^{-1} (s); δ_H ($CDCl_3$) 0.77 (3H, d $J=6.5$ Hz, CH_3CH), 0.90 (3H, d $J=6.5$ Hz, CH_3CH), 1.46 (2H, br s, NH_2), 1.60 (1H, dd $J=13.6$, 4.5 Hz, CH_2CH), 1.7–1.8 (1H, m, $CHMe_2$), 1.85 (1H, dd $J=13.6$, 8.0 Hz, CH_2CH), 2.82 (1H, d $J=13.0$ Hz, CH_2Ar), 3.17 (1H, d $J=13.0$ Hz, CH_2Ar), 3.63 (3H, s, OCH_3), 7.27 (2H, d $J=8.6$ Hz, ArCH), 8.07 (2H, d $J=8.6$ Hz, ArCH); δ_C ($CDCl_3$) 21.15 (CH_3CH), 22.88 (CH_3CH), 23.23 ($CHMe_2$), 45.83 (CH_2), 47.45 (CH_2), 50.66 (OCH_3), 60.32 ($NCCO_2$), 122.03 (ArCH), 130.20 (ArCH), 142.75 (ArC), 145.67 (ArC), 175.49 (CO_2); *m/z* (CI, NH_3) 281 (MH^+, 70), 251 (100); [found: (ES) 281.1501 (MH^+, $C_{14}H_{21}N_2O_4$ requires 281.1501)].

4.1.8. α-Allyl-leucine methyl ester 4f.[35] Imine **3b** (0.267 g, 1.0 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (38.5 mg, 0.10 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and allyl bromide (145 mg, 1.2 mmol) were added to the mixture. The resulting solution was stirred overnight under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4f** (85 mg, 46%) as a colourless oil. δ_H ($CDCl_3$) 0.75 (3H, d $J=6.2$ Hz, CH_3CH), 0.87 (3H, d $J=6.3$ Hz, CH_3CH), 1.4–1.5 (1H, m, CH_2CHMe_2), 1.6–1.7 (1H, m, CH_2CHMe_2), 2.14 (1H, dd $J=13.5$, 8.6 Hz, CH_2CH=), 2.39 (2H, br s, NH_2), 2.48 (1H, dd $J=13.4$, 6.5 Hz, CH_2CH=), 2.9–3.0 (1H, m, $CHMe_2$), 3.64 (3H, s, OCH_3), 5.0–5.1 (2H, m, =CH_2), 5.5–5.6 (1H, m, =CH); *m/z* (CI, NH_3) 186 (MH^+, 100).

4.1.9. *N*-*para*-Chlorobenzylidene (*R*,*S*)-phenylalanine methyl ester 3c.[36] To a stirred suspension of (*R*,*S*)-phenylalanine methyl ester hydrochloride (3.00 g,

13.95 mmol) in dichloromethane (40 ml), triethylamine (1.28 g, 12.68 mmol), *para*-chlorobenzaldehyde (1.78 g, 12.68 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The residue was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give compound **3c** (3.82 g, 90%) as yellow solid. Mp 63–65 °C; δ_H ($CDCl_3$) 3.06 (1H, dd J=13.5, 9.0 Hz, CH_2Ph), 3.28 (1H, dd J=13.5, 4.9 Hz, CH_2Ph), 3.67 (3H, s, OCH_3), 4.08 (1H, dd J=9.0, 4.9 Hz, $NCHCO_2$), 7.0–7.2 (5H, m, ArCH), 7.27 (2H, d J=8.5 Hz, ArCH), 7.53 (2H, d J=8.5 Hz, ArCH), 7.76 (1H, s, CH=N); δ_C ($CDCl_3$) 40.74 (CH_2Ph), 53.34 (OCH_3), 75.93 ($NCHCO_2$), 127.66 (ArCH), 129.36 (ArCH), 129.86 (ArCH), 130.66 (ArCH), 130.76 (ArCH), 134.96 (ArC), 138.12 (ArC), 138.24 (ArC), 163.42 (N=CH), 172.98 (CO_2).

4.1.10. α-Allyl-phenylalanine methyl ester 4g.[37] Imine **3c** (0.301 g, 1.00 mmol) was dissolved in dry toluene (2.5 ml) and copper(salen) complex **1** (96.25 mg, 0.25 mmol) was added. Powdered sodium hydroxide (0.14 g, 3.5 mmol) and allyl bromide (0.145 g, 1.2 mmol) were added to the mixture. The resulting solution was stirred overnight under an argon atmosphere at room temperature. Then, methanol (2 ml) followed by acetyl chloride (0.5 ml) were added dropwise to the mixture. The mixture was stirred for four more hours and the solvents were removed in vacuo. The crude residue was purified by column chromatography using first ethyl acetate and then a mixture of ethyl acetate and ethanol (4:1) as eluent to give compound **4g** (149 mg, 68%) as a colourless oil. ν_{max} (KBr) 3378 (w), 3030 (w), 2955 (w), 1738 (s), 1634 (m) and 1604 cm^{-1} (m); δ_H ($CDCl_3$) 1.48 (2H, br s, NH_2), 2.25 (1H, dd J=13.5, 8.5 Hz, CH_2CH=), 2.64 (1H, dd J=13.4, 6.4 Hz, CH_2CH=), 2.71 (1H, d J=13.2 Hz, CH_2Ph), 3.11 (1H, d J=13.2 Hz, CH_2Ph), 3.63 (3H, s, OCH_3), 5.08–5.09 (2H, m, CH_2=), 5.6–5.7 (1H, m, =CH), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 42.32 (CH_2), 43.79 (CH_2), 53.04 (OCH_3), 64.36 (NCCO_2), 121.98 (=CH_2), 128.07 (ArCH), 129.23 (ArCH), 130.55 (ArCH), 131.07 (=CH), 134.47 (ArC), 173.00 (CO_2); m/z (CI, NH_3) 220 (MH^+, 100); [found: (CI, NH_3) 220.1337 (MH^+, $C_{13}H_{17}NO_2$ requires 220.1337)].

4.1.11. Hydrolysis of 4g to α-Allyl-phenylalanine.[38,39] A sample of compound **4g** was refluxed overnight in 2 M hydrochloric acid. The solvent was evaporated as an azeotrope with toluene to leave α-allyl-phenylalanine as a white solid which was analysed without further purification. $[\alpha]_D^{25}$=+4.6 (c=1, 1 M HCl) $[\alpha]_D$=+16 (c=1, aqueous HCl) for (*S*)-enantiomer.[39] δ_H (CD_3OD) 2.66 (1H, dd J=14.5, 7.6 Hz, CH_2CH=), 2.86 (1H, dd J=14.5, 7.1 Hz, CH_2CH=), 3.16 (1H, d J=14.3 Hz, CH_2Ph), 3.35 (1H, d J=14.3 Hz, CH_2Ph), 5.3–5.4 (2H, m, =CH_2), 5.7–5.9 (1H, m, =CH), 7.2–7.4 (5H, m, ArCH).

4.1.12. α-(4-Nitrophenylmethyl)-phenylalanine methyl ester 4h. Imine **3c** (0.301 g, 1.00 mmol) was dissolved in dry toluene, then copper(salen) complex **1** (38.4 mg, 0.1 mmol), powdered NaOH (140 mg, 3.5 mmol) and 4-nitrobenzyl bromide (259.2 mg, 1.2 mmol) were added. The mixture was stirred overnight under an argon atmosphere at room temperature. Methanol and acetyl chloride were added and the mixture was stirred for 4 h. The solvents were then removed in vacuo. The residue was purified by column chromatography using ethyl acetate and ethanol (4:1) as eluent to give compound **4h** (210 mg, 67%) as light yellow oil. $[\alpha]_D^{20}$=+1.6 (c=0.6, $CHCl_3$); ν_{max} (KBr) 3028 (m), 2953 (m), 1951 (w), 1739 (s), 1603 (s) and 1520 cm^{-1} (s); δ_H ($CDCl_3$) 1.63 (2H, br s, NH_2), 2.79 (1H, d J=13.3 Hz, CH_2Ph), 2.88 (1H, d J=12.9 Hz, CH_2Ph), 3.29 (1H, d J=13.0 Hz, CH_2ArNO_2), 3.35 (1H, d J=13.0 Hz, CH_2ArNO_2), 3.59 (3H, s, OCH_3), 7.0–7.1 (2H, m, ArCH), 7.1–7.3 (3H, m, ArCH), 7.29 (2H, d J=8.6 Hz, ArCH), 8.07 (2H, d J=8.7 Hz, ArCH); δ_C ($CDCl_3$) 39.85 (CH_2), 41.03 (CH_2), 52.20 (OCH_3), 64.45 (NCCO_2), 123.07 (ArCH), 127.38 (ArCH), 128.17 (ArCH), 129.41 (ArCH), 130.1 (ArCH), 131.09 (ArC), 139.19 (ArC), 146.71 (ArC), 168.35 (CO_2); m/z (CI, NH_3) 315 (MH^+, 58), 285 (100); [found: (ES) 337.1141 (M+Na^+, $C_{17}H_{18}N_2O_4Na$ requires 337.1159)].

4.1.13. *N*-*para*-Chlorobenzylidene (*R*,*S*)-phenylglycine methyl ester 3e.[40] To a stirred suspension of (*R*,*S*)-phenylglycine methyl ester chloride (2.00 g, 9.92 mmol) in dichloromethane (28 ml), triethylamine (0.84 g, 8.27 mmol), *para*-chlorobenzaldehyde (1.16 g, 8.27 mmol) and a small amount of magnesium sulphate were added. The reaction mixture was stirred overnight, and was subsequently filtered and evaporated in vacuo. The crude product was then taken up in diethyl ether and washed with water (5×30 ml), dried with magnesium sulphate and evaporated to dryness to give compound **3e** (1.09 g, 46%) as a yellow oil. δ_H ($CDCl_3$) 3.67 (3H, s, OCH_3), 5.13 (1H, s, NCH), 7.1–7.5 (7H, m, ArCH), 7.69 (2H, d J=8.5 Hz, ArCH), 8.22 (1H, s, CH=N).

4.1.14. α-Phenyl-allylglycine methyl ester 4i.[41] Imine **3e** (0.200 g, 0.70 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (5 mg, 0.014 mmol) was added. Finely ground sodium hydroxide (0.097 g, 2.4 mmol) was then added, followed by allyl bromide (101 mg, 0.83 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.3 ml) and acetyl chloride (0.3 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4i** (43 mg, 31%) as a colourless oil. ν_{max} (KBr) 3389 (w), 3320 (w), 3070 (w), 3025 (w), 2952 (m), 1732 (s), 1640 (m) and 1600 cm^{-1} (m); δ_H ($CDCl_3$) 1.97 (2H, br s, NH_2), 2.59 (1H, dd J=13.6, 7.8 Hz, CH_2CH=), 2.91 (1H, dd J=13.6, 6.7 Hz, CH_2CH=), 3.64 (3H, s, OCH_3), 5.0–5.1 (2H, m, =CH_2), 5.5–5.7 (1H, m, =CH), 7.2–7.5 (5H, m, ArCH); δ_C ($CDCl_3$) 45.05 (CH_2), 52.92 (OCH_3), 63.54 (NCCO_2), 120.38 (=CH_2), 125.79 (ArCH), 127.92 (ArCH), 128.83 (ArCH), 133.34 (=CH), 143.14 (ArC), 176.05 (CO_2); m/z (CI, NH_3) 206 (MH^+, 20), 164 (97), 145 (81), 104 (100); [found: (ES) 206.1168 (MH^+, $C_{12}H_{16}NO_2$ requires 206.1176)].

4.1.15. α-Phenyl-phenylalanine methyl ester 4j.[42] Imine **3e** (0.200 g, 0.70 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (5 mg, 0.014 mmol) was added. Finely

ground sodium hydroxide (0.097 g, 2.4 mmol) was then added, followed by benzyl bromide (143 mg, 0.83 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.3 ml) and acetyl chloride (0.3 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4j** (67 mg, 38%) as a colourless oil. δ_H ($CDCl_3$) 1.61 (2H, br s, NH_2), 3.08 (1H, d J=13.3 Hz, CH_2Ph), 3.57 (1H, d J=13.3 Hz, CH_2Ph), 3.66 (3H, s, OCH_3), 7.0–7.5 (10H, m, ArCH); δ_C ($CDCl_3$) 46.40 (CH_2), 52.84 (OCH_3), 64.88 ($NCCO_2$), 125.94 (ArCH), 127.39 (ArCH), 128.01 (ArCH), 128.68 (ArCH), 128.81 (ArCH), 130.83 (ArCH), 136.53 (ArC), 175.72 (CO_2); *m/z* (CI, NH_3) 256 (MH^+, 20), 196 (90), 165 (100), 104 (100); [found: (ES) 256.1323 (MH^+, $C_{16}H_{18}NO_2$ requires 256.1338)].

4.1.16. α-Allyl-phenylalanine methyl ester 4k.[37] Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added followed by benzyl bromide (0.26 ml, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4k** (249 mg, 69%). $[\alpha]_D^{20}=-47.0$ (c=0.3, $CHCl_3$); other data as reported for compound **4g**.

4.1.17. α-(4-Nitrophenylmethyl)-allylglycine methyl ester 4l.[43] Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added, followed by *para*-nitrobenzyl bromide (0.477 g, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4l** (365 mg, 75%). $[\alpha]_D^{20}=-62.6$ (c=0.3, $CHCl_3$); ν_{max} (KBr) 3367 (w), 3010 (w), 2957 (w), 1733 (s), 1604 (m) and 1519 cm^{-1} (s); δ_H ($CDCl_3$) 1.64 (2H, br s, NH_2), 2.26 (1H, dd J=13.0, 8.4 Hz, CH_2CH=), 2.6–2.7 (1H, m, CH_2CH=), 2.84 (1H, d J=12.9 Hz, CH_2Ar), 3.18 (1H, d J=12.8 Hz, CH_2Ar), 3.65 (3H, s, OCH_3), 5.1–5.2 (2H, m, CH=CH_2), 5.5–5.7 (1H, m CH=CH_2), 7.28 (2H, d J=8.2 Hz, ArCH), 8.07 (2H, d J=8.0 Hz, ArCH); δ_C ($CDCl_3$) 44.9 (CH_2CH=), 46.0 (CH_2Ar), 52.7 (CH_3), 64.4 ($NCCO_2$), 120.8 (CH_2=CH), 123.9 (ArCH), 131.6 (ArCH), 132.2 (CH=CH_2), 132.9 (ArC), 144.5 (ArC), 173.0 (CO_2); *m/z* (CI, NH_3) 265 (MH^+, 60), 235 (100); [found: (CI, NH_3) 265.1188 (MH^+, $C_{13}H_{17}N_2O_4$ requires 265.1185)].

4.1.18. α-But-2-ynyl-allylglycine methyl ester 4m from imine 3f. Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added, followed by 1-bromo-2-butyne (294 mg, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4m** (154 mg, 46%). ν_{max} (KBr) 3395 (w), 3063 (w), 2951 (w), 1733 (s), 1642 (s), 1601 (m) and 1581 cm^{-1} (m); δ_H ($CDCl_3$) 1.71 (3H, t J=2.5 Hz, C≡CCH_3), 1.85 (2H, br s, NH_2), 2.24 (1H, dd J=13.4, 8.1 Hz, CH_2–CH), 2.34 (1H, dq J=16.3, 2.5 Hz, CH_2–C≡CMe), 2.45 (1H, dd J=13.4, 6.7 Hz, CH_2–CH), 2.55 (1H, dq J=16.3, 2.5 Hz, CH_2–C≡CMe), 3.67 (3H, s, OCH_3), 5.0–5.1 (2H, m, CH=CH_2), 5.5–5.7 (1H, m, CH=CH_2); δ_C ($CDCl_3$) 2.5 (CH_3C≡C), 29.0 (CH_2C≡CMe), 42.6 (CH_2CH), 51.3 (OCH_3), 59.7 ($NCCO_2$), 72.9 (C≡CCH_3), 78.1 (C≡CCH_2), 118.5 (CH_2=CH), 131.4 (CH=CH_2), 174.9 (CO_2); *m/z* (CI, NH_3) 182 (MH^+, 100); [found: (CI, NH_3) 182.1181 (MH^+, $C_{10}H_{16}NO_2$ requires 182.1180)].

4.1.19. α-But-2-ynyl-allylglycine methyl ester 4m from imine 3g. Imine **3g** (0.4 g, 1.59 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (12 mg, 0.03 mmol) was added. Finely ground sodium hydroxide (0.222 g, 5.57 mmol) was then added, followed by 1-bromo-2-butyne (254 mg, 1.91 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4m** (124 mg, 44%). $[\alpha]_D^{20}=-27.3$ (c=0.3, $CHCl_3$); other data as reported for the same compound prepared from imine **3f**.

4.1.20. α-Propargyl-allylglycine methyl ester 4n. Imine **3f** (0.4 g, 1.84 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (14 mg, 0.04 mmol) was added. Finely ground sodium hydroxide (0.258 g, 6.46 mmol) was then added, followed by propargyl bromide (263 mg, 2.21 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue which was added to a silica gel column and eluted first with EtOAc and then with EtOAc/EtOH (4:1) to give product **4n** (150 mg, 49%). $[\alpha]_D^{20}=-22.7$ (c=0.3, $CHCl_3$); ν_{max} (KBr) 3301 (w), 2952 (w), 1736 (s), and 1641 cm^{-1} (m); δ_H ($CDCl_3$) 1.8–2.0 (2H, br, NH_2), 2.00 (1H, t J=2.8 Hz, H–C≡), 2.28 (1H, dd J=13.5, 8.2 Hz, CH_2–CH=), 2.41 (1H, dd J=16.5, 2.6 Hz, CH_2–C≡), 2.48 (1H, dd J=13.5, 6.7 Hz, CH_2–CH=), 2.62 (1H, dd J=16.5, 2.6 Hz, CH_2–C≡), 3.69 (3H, s, OCH_3), 5.0–5.2 (2H, m, CH=CH_2), 5.5–5.7 (1H, m, CH=CH_2); δ_C ($CDCl_3$) 29.9 (CH_2C≡), 43.8 (CH_2CH=), 52.9 (OCH_3), 60.8 ($NCCO_2$), 72.0 (C≡CH), 79.8 (C≡CCH_2), 120.3 (CH_2=CH), 132.4 (CH=CH_2), 174.8 (CO_2); *m/z* (CI, NH_3) 168 (MH^+, 100); [found: (CI, NH_3) 168.1019 (MH^+, $C_9H_{14}NO_2$ requires 168.1019)].

4.1.21. Dimethyl *N*-*para*-chlorobenzylidene (*R*,*S*)-glutamate 3h. To a suspension of dimethyl glutamate hydrochloride (10.0 g, 47.5 mmol) in dichloromethane (110 ml), was added triethylamine (4.7 ml, 33.8 mmol), *para*-chlorobenzaldehyde (5.53 g, 39.6 mmol) and magnesium sulphate (4.0 g). The reaction was stirred overnight, filtered, and

evaporated in vacuo. The residue was redissolved in dichloromethane (50 ml) and washed with water (3×50 ml). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to leave imine **3h** (6.5 g, 69%) as a white solid. Mp 62–63 °C; ν_{max} (KBr) 3004 (s), 2954 (m), 1743 (s), 1642 (s) and 1593 cm^{-1} (m); δ_H ($CDCl_3$) 2.1–2.5 (4H, m, CH_2CH_2), 3.67 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.09 (1H, dd J=7.5, 4.9 Hz, N*C*HCO$_2$), 7.41 (2H, d J=8.7 Hz, ArCH), 7.73 (2H, d J=8.5 Hz, ArCH), 8.27 (1H, s, HC=N); δ_C ($CDCl_3$) 28.67 (CH_2), 30.53 (CH_2), 52.08 (OCH_3), 52.74 (OCH_3), 72.04 (NCHCO$_2$), 129.32 (ArCH), 130.18 (ArCH), 138.12 (ArC), 138.21 (ArC), 163.36 (HC=N), 172.36 (CO_2), 174.58 (CO_2); *m/z* (EI) 299 (M^+(^{37}Cl), 23), 297 (M^+(^{35}Cl), 42), 266 (40), 238 (100), 224 (65), 178 (91); [found: (ES) 320.0636 (M(^{35}Cl)+Na^+, $C_{14}H_{16}NO_4{}^{35}ClNa$ requires 320.0662)].

4.1.22. α-Benzyl-pyroglutamic acid methyl ester 7.[44] Imine **3h** (0.635 g, 2.13 mmol) was dissolved in dry toluene (5 ml) and catalyst **1** (16 mg, 0.043 mmol) was added. Finely ground sodium hydroxide (0.298 g, 7.46 mmol) was then added, followed by benzyl bromide (437 mg, 2.56 mmol). The mixture was allowed to stir for 48 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (4 ml) and acetyl chloride (1 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **7** (256 mg, 52%) as a colourless oil. ν_{max} (KBr) 3221 (br), 3025 (w), 2930 (m), 2859 (w), 1736 (s) and 1698 cm^{-1} (s); δ_H ($CDCl_3$) 2.0–2.5 (4H, m, CH_2CH_2), 2.85 (1H, d J=13.4 Hz, CH_2Ph), 3.18 (1H, d J=13.4 Hz, CH_2Ph), 3.64 (3H, s, OCH_3), 6.33 (1H, br s, NH), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 28.73 (CH_2), 29.53 (CH_2), 43.92 (CH_2), 51.64 (OCH_3), 65.42 (N*C*CO$_2$), 126.48 (ArCH), 127.68 (ArCH), 128.78 (ArCH), 133.75 (ArC), 172.63 (CO_2), 175.82 (NCO).

4.1.23. Dimethyl *N*-*para*-chlorobenzylidene (*R*,*S*)-aspartate 3i.[45] To a suspension of dimethyl aspartate hydrochloride (2.5 g, 12.8 mmol) in dichloromethane (35 ml), was added triethylamine (2.5 ml, 17.9 mmol), *para*-chlorobenzaldehyde (1.19 g, 8.4 mmol) and magnesium sulphate (2.0 g). The reaction was stirred overnight, filtered, and evaporated in vacuo. The residue was redissolved in dichloromethane (50 ml) and washed with water (3×50 ml). The organic layer was dried ($MgSO_4$) and evaporated in vacuo to leave imine **3i** (2.0 g, 84%) as a yellow oil. δ_H ($CDCl_3$) 2.89 (1H, dd J=16.8, 7.8 Hz, CH_2CO_2Me), 3.17 (1H, dd J=16.8, 5.8 Hz, CH_2CO_2Me), 3.68 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.49 (1H, dd J=7.8, 5.8 Hz, NCHCO$_2$Me), 7.40 (2H, d J=8.5 Hz, ArCH), 7.72 (2H, d J=8.5 Hz, ArCH), 8.36 (1H, s, HC=N); *m/z* (EI) 285 (M^+(^{37}Cl), 10), 283 (M^+(^{35}Cl), 30), 226 (35), 224 (100); [found: (ES) 306.0488 (M(^{35}Cl)+Na^+, $C_{13}H_{14}NO_4{}^{35}ClNa$ requires 306.0505)].

4.1.24. α-Allyl-aspartic acid dimethyl ester 4o. Imine **3i** (0.200 g, 0.71 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (5.4 mg, 0.043 mmol) was added. Finely ground sodium hydroxide (0.298 g, 7.5 mmol) was then added, followed by allyl bromide (102 mg, 0.85 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.3 ml) and acetyl chloride (0.3 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4o** (35 mg, 25%) as a colourless oil. $[\alpha]_D^{20}$=+0.9 (c=0.8, $CHCl_3$); ν_{max} (KBr) 3384 (w), 3002 (w), 2954 (m) and 1736 cm^{-1} (s); δ_H ($CDCl_3$) 1.89 (2H, br s, NH_2), 2.23 (1H, dd J=13.2, 8.3 Hz, C*H*$_2$CH=), 2.3–2.4 (1H, m, C*H*$_2$CH=), 2.48 (1H, d J=16.7 Hz, CH_2CO_2Me), 2.91 (1H, d J=16.6 Hz, CH_2CO_2Me), 3.61 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 5.0–5.2 (2H, m, =CH_2), 5.5–5.7 (1H, m, =CH); δ_C ($CDCl_3$) 43.57 (CH_2), 44.87 (CH_2), 52.17 (OCH_3), 52.82 (OCH_3), 59.20 (N*C*CO$_2$), 120.52 (=CH_2), 131.88 (=CH), 172.23 (CO_2); *m/z* (EI) 202 (MH^+, 8), 160 (100), 142 (90), 128 (30); [found: (ES) 224.0891 (M+Na^+, $C_9H_{15}NO_4Na$ requires 224.0893)].

4.1.25. α-Benzyl-aspartic acid dimethyl ester 4p. Imine **3i** (0.222 g, 0.78 mmol) was dissolved in dry toluene (2 ml) and catalyst **1** (6 mg, 0.043 mmol) was added. Finely ground sodium hydroxide (0.298 g, 7.5 mmol) was then added, followed by benzyl bromide (161 mg, 0.94 mmol). The mixture was allowed to stir for 24 h at room temperature under an argon atmosphere. The solution was then filtered and the solvent evaporated in vacuo to leave a residue to which a mixture of methanol (1.5 ml) and acetyl chloride (0.4 ml) was added. The resulting mixture was stirred at room temperature for 4 h, then evaporated in vacuo. The residue was added to a silica gel column and eluted with EtOAc/EtOH (4:1) to give product **4p** (146 mg, 75%) as a colourless oil. $[\alpha]_D^{20}$=+0.7 (c=0.7, $CHCl_3$); ν_{max} (KBr) 3386 (w), 3056 (w), 2925 (m), 2852 (m) and 1736 cm^{-1} (s); δ_H ($CDCl_3$) 1.98 (2H, br s, NH_2), 2.51 (1H, d J=16.7 Hz, CH_2CO_2Me), 2.77 (1H, d J=13.2 Hz, CH_2Ph), 2.95 (1H, d J=13.2 Hz, CH_2Ph), 2.99 (1H, d J=16.7 Hz, CH_2CO_2Me), 3.60 (6H, s, 2× CO_2Me), 7.0–7.3 (5H, m, ArCH); δ_C ($CDCl_3$) 43.73 (CH_2), 46.55 (CH_2), 52.15 (OCH_3), 52.62 (OCH_3), 60.47 (N*C*CO$_2$), 127.67 (ArCH), 128.81 (ArCH), 130.10 (ArCH), 135.48 (ArC), 172.16 (CO_2); *m/z* (EI) 252 (MH^+, 49), 192 (60), 160 (80), 100 (100); [found: (ES) 252.1222 (MH^+, $C_{13}H_{18}NO_4$ requires 252.1230)].

4.1.26. *N*-Boc-α-but-2-ynyl-allylglycine methyl ester. A solution of $(BOC)_2O$ (12 mg, 0.056 mmol) in *tert*-butanol (0.2 ml) was added dropwise at room temperature to a vigorously stirred solution of amine **4m** (10 mg, 0.055 mmol) in *tert*-butanol (0.5 ml). After the addition was complete, the reaction mixture was stirred at 30 °C for 3 h. The solvent was then evaporated in vacuo to leave a yellow oil which was purified by column chromatography on silica gel using EtOAc/hexane (4:1) as eluent to give *N*-Boc-α-but-2-ynyl-allylglycine methyl ester (12 mg, 80%) as a yellow oil. $[\alpha]_D^{20}$=+7 (c=0.6, $CHCl_3$); ν_{max} (KBr) 3565 (s), 3287 (s), 2902 (s) and 1704 cm^{-1} (m); δ_H ($CDCl_3$) 1.37 (9H, s, (CH_3)$_3$C), 1.70 (3H, t J=5.0 Hz, $CH_3C{\equiv}C$), 2.47 (1H, dd J=13.7, 6.9 Hz, CH_2–CH), 2.6–2.7 (1H, m, CH_2–C≡), 2.8–2.9 (1H, m, CH_2–CH), 2.9–3.0 (1H, m, CH_2–C≡), 3.69 (3H, s, OCH_3), 5.0–5.1 (2H,

m, CH═CH_2), 5.33 (1H, br s, NH), 5.5–5.7 (1H, m CH═CH_2); δ_C ($CDCl_3$) 2.6 (CH_3), 27.3 ((CH_3)$_3$C), 28.7 (CH_2C), 38.4 (CH_2CH), 51.7 (OCH_3), 61.4 ((CH_3)$_3$C), 72.6 (C≡CCH$_3$), 84.2 (C≡CCH$_2$), 118.4 (CH_2═CH), 130.1 (CH═CH_2), 153.2 (CONH), 171.7 (CO_2); *m/z* (CI, NH_3) 282 (MH^+, 54), 225 (100); [found: (CI, NH_3) 282.1698 (MH^+, $C_{15}H_{24}NO_4$ requires 282.1700)].

4.1.27. *N*-Boc-α-Propargyl-allylglycine methyl ester. A solution of $(BOC)_2O$ (40 mg, 0.181 mmol) in *tert*-butanol (0.5 ml) was added dropwise at room temperature to a vigorously stirred solution of amine **4n** (30 mg, 0.179 mmol) in *tert*-butanol (2 ml). After the addition was complete, the reaction mixture was stirred overnight at 30 °C. The solvent was then evaporated in vacuo to leave a yellow oil which was purified by column chromatography on silica gel using EtOAc/hexane (4:1) as eluent to give *N*-Boc-α-propargyl-allylglycine methyl ester (36 mg, 75%) as a yellow oil. $[\alpha]_D^{20}$=+4 (c=0.6, $CHCl_3$); ν_{max} (KBr) 3430 (s), 3305 (s), 2981 (s), 2123 (w), 1809 (s) and 1712 cm^{-1} (s); δ_H ($CDCl_3$) 1.37 (9H, s, (CH_3)$_3$C), 1.93 (1H, t J=2.5 Hz, H–C≡), 2.47 (1H, dd J=13.7, 7.3 Hz, CH_2–CH═), 2.7–2.8 (1H, m, CH_2–C≡), 2.8–2.9 (1H, m, CH_2–CH═), 3.0–3.1 (1H, m, CH_2–C≡), 3.71 (3H, s, OCH_3), 5.0–5.1 (2H, m, CH═CH_2), 5.35 (1H, br s, NH), 5.5–5.7 (1H, m, CH═CH_2); δ_C ($CDCl_3$) 25.9 (CH_2C≡), 27.8 ((CH_3)$_3$C), 40.0 (CH_2CH═), 53.2 (OCH_3), 62.4 ((CH_3)$_3$$C$), 71.4 (C≡$C$H), 85.6 (C≡$CCH_2$), 120.2 ($CH_2$═CH), 131.9 ($CH$═$CH_2$), 147.2 (OCONH), 172.8 (CO_2Me); *m/z* (CI, NH_3) 268 (MH^+, 93), 229 (100); [found: (CI, NH_3) 268.1539 (MH^+, $C_{14}H_{22}NO_4$ requires 268.1543)].

4.1.28. Diene 8a. *N*-Boc-α-but-2-ynyl-allylglycine methyl ester (7 mg, 0.025 mmol) was dissolved in dry dichloromethane (2.5 ml) and Grubbs' catalyst (1.0 mg, 5 mol%) was added to the solution. The reaction mixture was stirred overnight at room temperature under an ethene atmosphere. The solvent was removed in vacuo, the residue redissolved in dichloromethane and filtered through silica to remove the catalyst. The eluent was evaporated in vacuo to leave diene **8a** (10 mg, 100%) as a yellow oil. ν_{max} (KBr) 3364 (m), 2925 (s), 2854 (s), and 1715 cm^{-1} (s); δ_H ($CDCl_3$) 1.36 (9H, s, (CH_3)$_3$C), 1.85 (3H, s, CH_3C═), 2.6–2.7 (2H, m, CH_2), 3.1–3.2 (2H, m, CH_2), 3.69 (3H, s, OCH_3), 4.78 (1H, s, ═CH_2), 4.87 (1H, s, ═CH_2), 5.02 (1H, br s, NH), 5.57 (1H, s, CH═); δ_C ($CDCl_3$) 19.3 (CH_3), 27.3 ((CH_3)$_3$C), 34.6 (CH_2CH), 43.9 (CH_2C), 51.6 (OCH_3), 63.4 (NCCO_2), 84.2 ((CH_3)$_3$$C$), 112.4 ($CH_2$═CH), 122.5 (═$C$H), 138.0 ($C$═CH), 140.3 ($CH$═$CH_2$), 153.9 (CONH), 173.6 ($CO_2$); *m/z* (EI) 281 ($M^+$, 18), 207 (100); [found: (EI) 281.1622 (M^+, $C_{14}H_{22}NO_4$ requires 281.1628)].

4.1.29. Diene 8b. *N*-Boc-α-propargyl-allylglycine methyl ester (14 mg, 0.052 mmol) was dissolved in dry dichloromethane (5 ml) and Grubbs catalyst (2.1 mg, 5 mol%) was added to the solution. The reaction mixture was stirred overnight at room temperature under an ethene atmosphere. The solvent was removed in vacuo, the residue redissolved in dichloromethane and filtered through silica to remove the catalyst. The eluent was evaporated in vacuo to leave diene **8b** (14 mg, 100%) as a yellow oil. ν_{max} (KBr) 3372 (m), 2933 (s), and 1715 cm^{-1} (s); δ_H ($CDCl_3$) 1.37 (9H, s, (CH_3)$_3$C), 2.6–2.7 (2H, m, CH_2), 3.0–3.1 (2H, m, CH_2), 3.69 (3H, s, OCH_3), 4.9–5.1 (3H, m, ═CH_2 + ═HCCH_2), 5.55 (1H, br s, NH), 6.44 (1H, dd J=17.4, 10.8 Hz, H_2C═CH); δ_C ($CDCl_3$) 27.3 ((CH_3)$_3$C), 34.6 (CH_2CH═), 43.8 (CH_2C═), 51.6 (OCH_3), 63.2 (NCCO_2), 84.2 ((CH_3)$_3$$C$), 114.1 (═$CH_2$), 125.6 (═CH), 131.6 ($C$═CH), 145.7 (CH═), 154.2 (OCONH), 173.5 (CO_2Me); *m/z* (CI, NH_3) 268 (MH^+, 54), 229 (100); [found: (CI, NH_3) 268.1547 (MH^+, $C_{14}H_{22}NO_4$ requires 268.1543)].

4.1.30. Diels–Alder adduct 9. To a solution of diene **8a** (10 mg, 0.036 mmol) in ethyl acetate (2 ml) at room temperature was added maleic anhydride (8 mg, 0.078 mmol). The mixture was stirred at room temperature overnight. The solvent was then removed in vacuo and the residue was dissolved in dichloromethane and filtered twice through a pad of Celite, leaving product **9** (8 mg, 62%) as a 1:1 mixture of diastereomers. ν_{max} (KBr) 2929 (m), 2855 (w), 2254 (w), 1850 (w) and 1779 cm^{-1} (s); δ_H ($CDCl_3$) 1.37 (18H, s, 2× (CH_3)$_3$C), 1.6–1.7 (6H, m, 2× CH_3), 1.8–2.0 (4H, m, 2× CH_2), 2.2–2.3 (2H, m, 2× CH), 2.4–2.6 (4H, m, 2× CH_2), 2.6–2.7 (4H, m, 2× CH_2), 3.3–3.4 (4H, m, 4× CH), 3.68 and 3.65 (3H, 2× s, OCH_3), 4.7–4.8 and 5.0–5.1 (2H, 2× br s, NH); δ_C ($CDCl_3$) 16.9 (CH_3), 27.3 (C(CH_3)$_3$), 28.8 (COCH), 31.2 (COCH), 36.0 (CH_2), 38.2 (CH–C═), 42.4 (CH_2), 43.8 (CH_2), 51.6 (OCH_3), 63.2 (NCCO_2), 84.2 ($OCMe_3$), 133.6 (═CH), 142.2 (═C), 154.2 (OCONH), 167.7 (CO_2), 173.6 (CO_2); *m/z* (CI, NH_3) 397 (M+NH_4^+, 100), 380 (MH^+, 70); [found: (CI, NH_3) 397.1971 (M+NH_4^+, $C_{19}H_{29}N_2O_7$ requires 397.1969)].

4.2. Determination of enantiomeric excess

(*S*)-α-Methylbenzyl isocyanate (one or two drops) was added to an NMR sample of α,α-disubstituted amino acid methyl ester and left overnight to react completely with the amino ester. The diastereomeric excess and therefore enantiomeric excess was determined from the integration of the methylene or methyl ester region of the ^{1}H NMR spectrum of the resulting diastereomers.

Acknowledgements

The authors thank the EU for funding a Socrates exchange visit (V.T.) and for funding this project through the Descartes prize research grant. Mass spectra were recorded by the EPSRC national service at the University of Wales, Swansea.

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