

Nucleophilic Addition to Vinylketenimine Complexes. The Asymmetric Synthesis of Carbon Quaternary Centres

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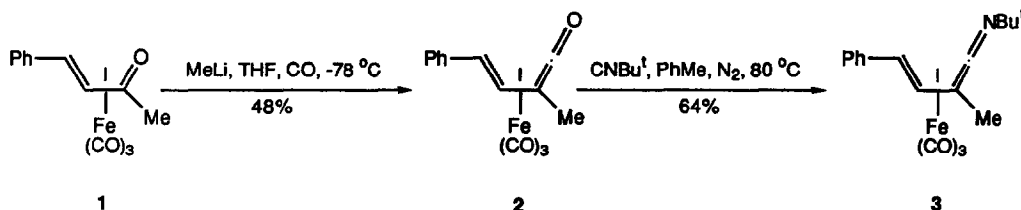
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(Received 28 November 1991)

Abstract: Addition of alkyl-lithium reagents to (vinylketenimine)tricarbonyliron(0) complexes generates compounds containing carbon quaternary centres. The major products from these reactions are either amides or aldehydes depending upon the conditions employed. Diastereomerically pure vinylketenimine complexes **7** and **8** of known absolute configuration were synthesised from (*S*)- α -methylbenzylisocyanide **6** (96% e.e.) and the (vinylketene)tricarbonyliron(0) complex **2**. The addition of alkyl-lithium reagents to **7** and **8** occurred exclusively *exo* to the Fe(CO)₃ group and the resulting compounds, which contained chiral quaternary centres, were found to be of high optical purity.

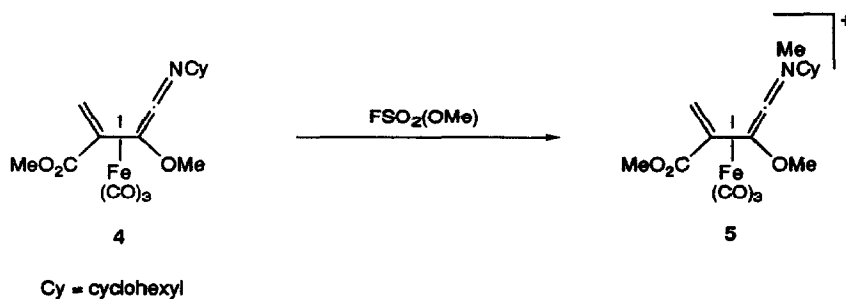
Introduction

As a result of our investigations into the reactivity of tricarbonyliron(0) complexes of vinylketones (*e.g.* **1**), we recently discovered that they may be transformed into (vinylketene)tricarbonyliron(0) complexes (*e.g.* **2**) upon reaction with methyl-lithium under an atmosphere of carbon monoxide.^{1,2} Furthermore we found that complexes of type **2** may be cleanly converted through to (vinylketenimine)tricarbonyliron(0) complexes (*e.g.* **3**) simply by heating with an isocyanide.^{2,3}



This viable route through to complexes of type **3** has subsequently allowed us to investigate the chemistry of the coordinated vinylketenimine ligand, the results of which are presented herein. Prior to this work the only reported reaction of (vinylketenimine)tricarbonyliron(0) complexes was with FSO₂(OMe); this led to methylation of the nitrogen atom and the generation of cationic complexes (*e.g.* complex **4** gave cation **5**).⁴

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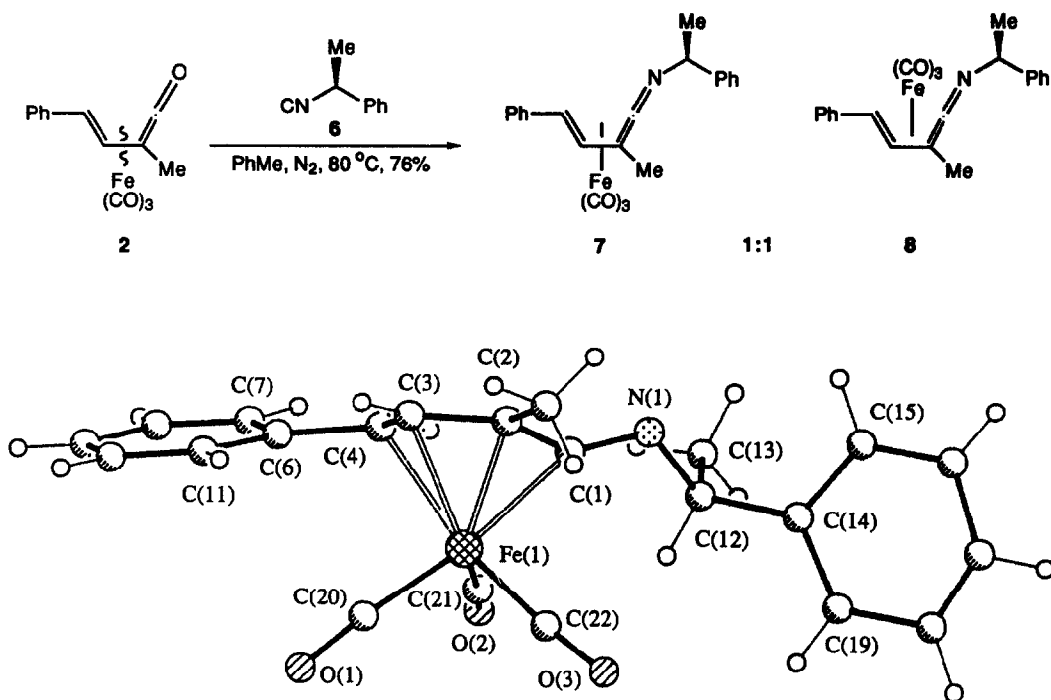
For clarity this paper is separated into three sections: (a) the synthesis of diastereomerically pure, optically active (vinylketenimine)tricarbonyliron(0) complexes, (b) an investigation into the addition of alkyl-lithium reagents to (vinylketenimine)tricarbonyliron(0) complexes, and (c) the asymmetric synthesis of organic molecules containing chiral quaternary centres obtained from a combination of the chemistry described in the first two sections. Part of this work has been the subject of two preliminary communications.^{5,6}

Results and Discussion

A) Synthesis of Optically Active Vinylketenimine Complexes

The (vinylketenimine)tricarbonyliron(0) complex 3 contains a similar element of planar chirality to substituted (η^4 -diene)tricarbonyliron(0) complexes, many examples of which have been obtained in optically pure form.⁷ Thus we reasoned that replacement of the *tert*-butyl nitrogen substituent of 3 with a homochiral substituent, and separation of the resulting diastereoisomers would effect a resolution of the metal based chiral centre.

Commercial (*S*)-(-)- α -methylbenzylamine of 96% e.e.⁸ was converted into (*S*)-(-)- α -methylbenzylisonitrile 6 by a known literature procedure.⁹ As it had been previously established that formation of the isonitrile 6 proceeds without any racemisation occurring, this compound was assumed to have an e.e. of 96%. Heating the vinylketene complex 2 with one equivalent of 6 resulted in a 1:1 mixture of the two diastereomeric vinylketenimine complexes 7 and 8. These were separated by chromatography on SiO_2 (EtOAc:40-60 petroleum ether, 1:9) which gave the two complexes as stable viscous yellow oils. After several days in solution at room temperature no epimerisation of 7 and 8 could be detected by ^1H n.m.r. spectroscopy. It eventually proved possible to crystallise from *n*-pentane the complex that was the slower moving diastereoisomer on the silica column, the faster moving diastereoisomer resisting all attempts at crystallisation. Subsequent X-ray crystallographic analysis⁶ (Figure 1, Tables 1, 2 and 3) established that the crystalline sample had the absolute configuration shown below for 7.

Figure 1. Molecular structure of **7**

The crystal structure of **7** reveals that the nitrogen substituent is essentially *syn* to the metal. It is of note that the N-C(1)-C(2) angle is only 140° thus implying that there is also a contribution to the bonding from structure A in addition to the vinylketenimine description B. No single representation alone adequately accounts for the metal-ligand linkage in these complexes.



The orientation of the nitrogen substituent of **7** is the same as that previously reported for complex **4**, the only other (vinylketenimine)tricarbonyliron(0) complex for which an X-ray crystal structure analysis has been obtained.⁴ It is noteworthy that in the synthesis of complexes **7** and **8** only one of the two possible isomers with respect to the orientation of the nitrogen substituent was observed, and that all previous (vinylketenimine)-tricarbonyliron(0) complexes synthesised from (vinylketene)tricarbonyliron(0) complexes and isocyanides were formed as one isomer with respect to the orientation of the nitrogen substituent.

Table 1: Fractional atomic coordinates ($\times 10^4$) for 7 with estimated standard deviations in parentheses.

Atom	x	y	z
Fe(1)	11052.1(20)	10000.0	8241.8(9)
O(1)	11658(14)	7961(14)	9677(6)
O(2)	11232(20)	7245(16)	7113(9)
O(3)	14590(12)	11356(13)	8492(7)
N(1)	10775(15)	12490(17)	6848(7)
C(1)	10512(16)	11903(15)	7472(9)
C(2)	9802(16)	12405(16)	8134(7)
C(3)	8748(15)	11234(16)	8432(8)
C(4)	8247(16)	9739(16)	8012(7)
C(5)	10377(17)	14123(14)	8539(8)
C(6)	7321(16)	8317(17)	8341(8)
C(7)	6449(18)	7064(19)	7856(9)
C(8)	5547(20)	5759(19)	8117(11)
C(9)	5480(19)	5613(18)	8893(12)
C(10)	6322(20)	6832(21)	9380(9)
C(11)	7194(16)	8157(16)	9113(8)
C(12)	11902(19)	11627(20)	6370(8)
C(13)	10860(23)	10905(23)	5656(9)
C(14)	13256(20)	12815(21)	6188(7)
C(15)	12850(20)	14479(23)	5889(9)
C(16)	14091(29)	15628(29)	5736(10)
C(17)	15738(35)	15047(61)	5857(17)
C(18)	16324(41)	13666(57)	6147(19)
C(19)	15046(24)	12507(27)	6322(10)
C(20)	11351(14)	8818(25)	9121(7)
C(21)	11241(20)	8332(24)	7535(10)
C(22)	13206(19)	10757(17)	8418(8)

Table 2: Selected bond lengths (Å).

Fe(1)-C(1)	1.995(14)
Fe(1)-C(2)	2.088(12)
Fe(1)-C(3)	2.090(12)
Fe(1)-C(4)	2.157(12)
N(1)-C(1)	1.225(20)
C(1)-C(2)	1.406(21)
C(2)-C(3)	1.370(18)
C(3)-C(4)	1.392(17)
C(2)-C(5)	1.538(17)

Table 3: Selected bond angles (deg).

N(1)-C(1)-C(2)	140.0(13)
C(1)-C(2)-C(5)	119.7(11)
C(1)-C(2)-C(3)	117.2(11)
C(5)-C(2)-C(3)	122.8(12)
C(2)-C(3)-C(4)	118.8(12)

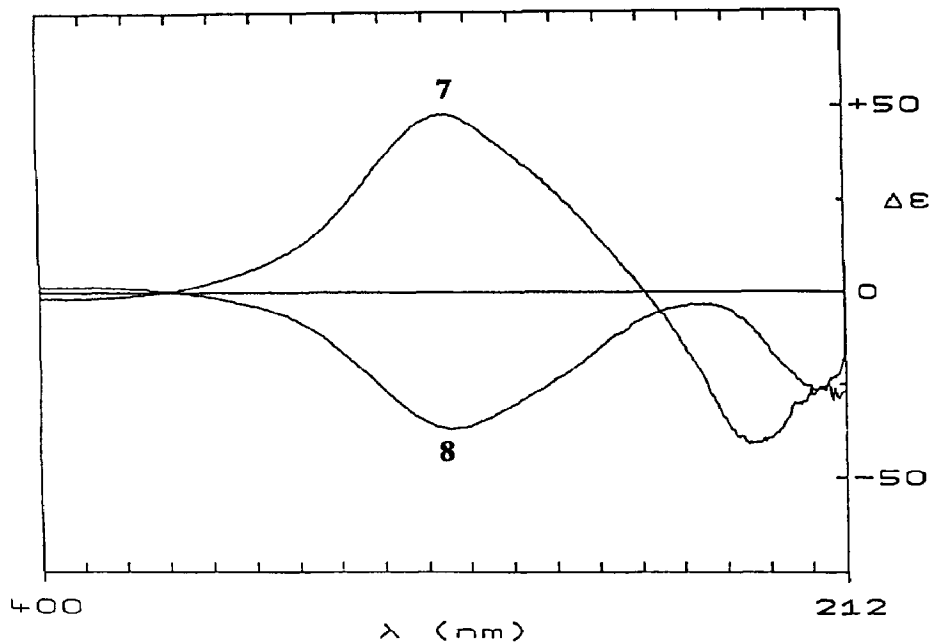


Figure 2. CD spectra of 7 and 8 between 212 and 400 nm

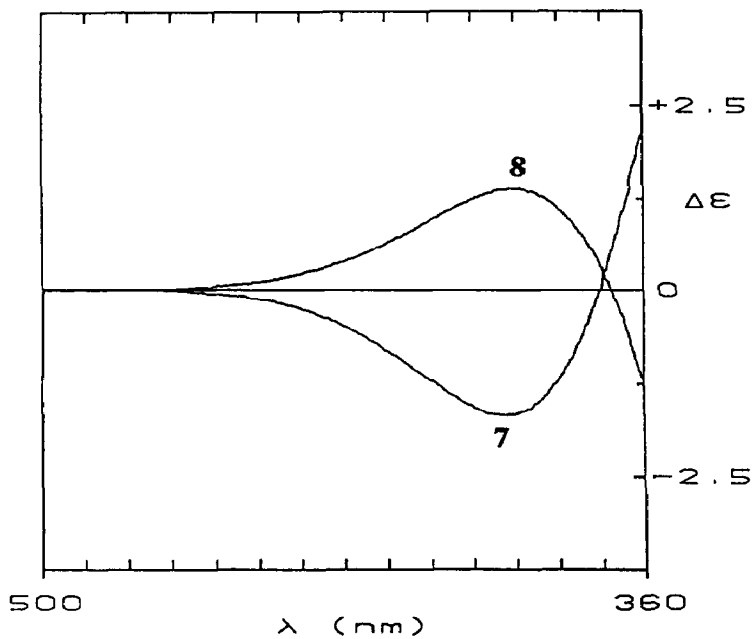
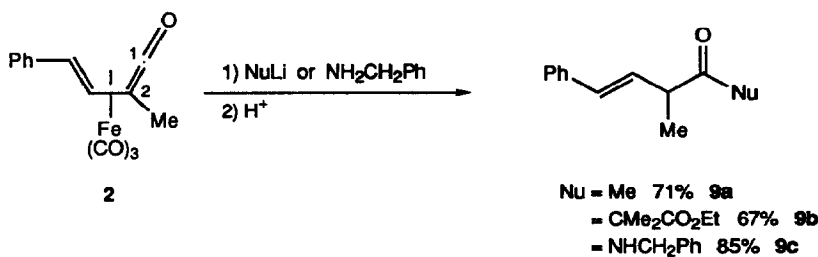


Figure 3. CD spectra of 7 and 8 between 360 and 500 nm

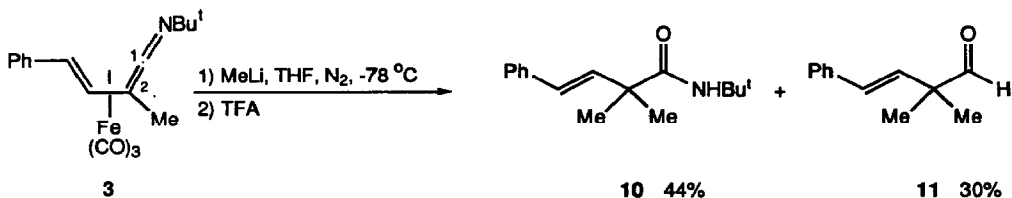
For optically active (η^4 -diene)tricarbonyliron(0) complexes there exists a strong relationship between the absolute configuration of the complexes and the signs of the maxima arising in their circular dichroism (CD) spectra in the region between 300 and 400 nm.¹⁰ In order to examine whether vinylketenimine complexes are similar in this respect to diene complexes, the CD spectra of **7** and **8** were recorded and are shown in Figures 2 and 3. Both complexes have maxima at approximately 390 nm and 305 nm, and in this region of the spectrum the curves arising from the two complexes are almost mirror images, indicating that the circular dichroism results from the metal π -ligand chiral element. The third maxima at approximately 225 nm has the same sign in both spectra, suggesting that this arises from the chirality of the (*S*)- α -methylbenzyl centre. Previous observations on pairs of diastereomeric complexes have also found the CD spectra dominated by the chiral metal element with little contribution made from auxiliary ligands.¹¹ The solid state and solution spectra of complex **7** were essentially identical, a result which confirms the conformational stability of these complexes in solution.

B) Addition of Alkyl-Lithium Reagents to Vinylketenimine Complexes

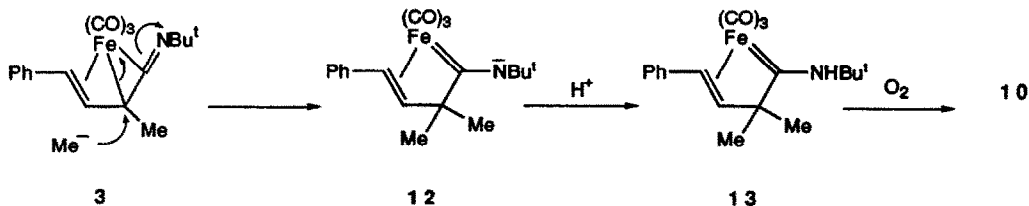
The (vinylketene)tricarbonyliron(0) complex **2** has previously been shown to react with a range of nucleophiles at C(1), resulting in unsaturated carbonyl compounds **9a-9c** after protonation at C(2) and decomplexation.⁵



Thus in order to examine whether the vinylketenimine complexes reacted similarly, methyl-lithium was added to a yellow solution of complex **3** in THF at -78 °C. The resultant orange solution was quenched with trifluoroacetic acid (TFA) to give, after warming to room temperature and removal of the solvent *in vacuo*, an air sensitive yellow residue. As a result of the instability of this material it was not possible to record its ¹H n.m.r. spectrum and so decomposition was completed by stirring a CHCl₃ solution exposed to the atmosphere at room temperature overnight. Subsequent workup resulted in the isolation of the amide **10** and the aldehyde **11**, both of which clearly arise from attack of the nucleophile at C(2) of the vinylketenimine ligand.

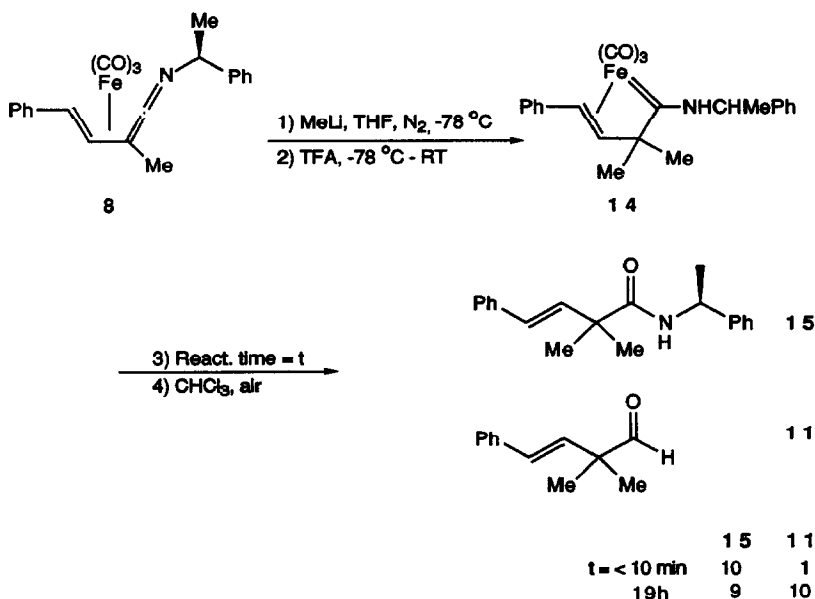


It was postulated that the amide **10** resulted from the oxidation of a carbene precursor as similar transformations have been previously reported.¹² Such an intermediate could result from the protonation of the anionic complex **12** at nitrogen to give the allyl carbene **13**.

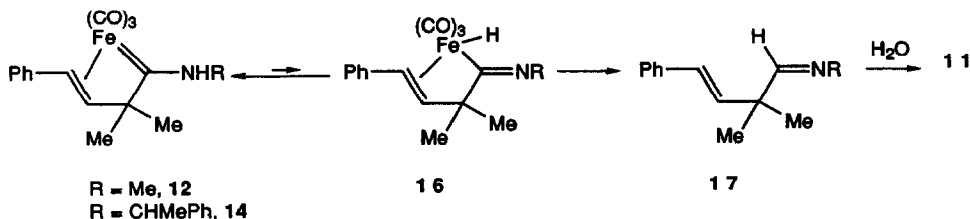


As the synthesis of **10** and **11** required the decomposition of an intermediate yellow organometallic material, it was postulated that this was a mixture of the carbene complex **13** and possibly an organometallic precursor to the aldehyde. In an attempt to gain further information about this material, the reaction of **3** with methyl-lithium was repeated and the major organometallic species present was isolated after careful chromatography under nitrogen. The i.r. spectrum of this complex contained three metal carbonyl bands at 2 018, 1 955 and 1 922 cm^{-1} indicative of the $\text{Fe}(\text{CO})_3$ moiety. An NH stretch was also observed at 3 299 cm^{-1} giving further support for this material being the carbene complex **13**. Unfortunately the instability of this complex precluded further spectroscopic examination, it being readily oxidised to amide **10**. The labile nature of iron carbene complexes has been remarked upon and most work in this area has been carried out on the more stable cationic complexes.¹³

Preliminary experiments on the reactivity of the optically active vinylketenimine complexes **7** and **8** suggested that the product ratio of amide to aldehyde was dependent upon the length of time the reaction mixtures were allowed to stir at room temperature under nitrogen prior to the oxidation step. To investigate this further, methyl-lithium was added to **8** and the mixture quenched with TFA to give the corresponding allylcarbene complex **14**. This unstable complex was characterised by its i.r. spectrum which contained three metal carbonyl bands at 2 006, 1 941 and 1 908 cm^{-1} , although the NH stretch was not clearly defined. In addition the complex was immediately oxidised in CHCl_3 and the crude product mixture was shown by ^1H n.m.r. spectroscopy to contain primarily the corresponding amide **15** (amide **15** : aldehyde **11** = 10:1). If however, the carbene complex was allowed to remain in solution in the presence of excess TFA, the slow disappearance of this material could be monitored by i.r. spectroscopy. After 17 h the intensity of the three metal carbonyl bands of **14** had decreased by *ca.* 50%. Subsequent oxidation resulted in a significantly increased percentage of the aldehyde **11** compared to the amide **15** (amide **15** : aldehyde **11** = 9:10 by ^1H n.m.r. spectroscopy).

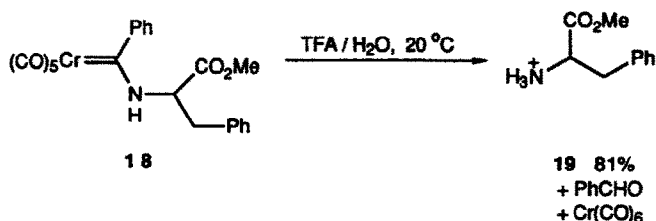


These results suggest that both the amide and the aldehyde are derived from a common allylcarbene complex, this being formed as the major product when the reaction mixture is quenched with TFA. The subsequent rearrangement of the allylcarbene complex leading ultimately to an aldehyde, is postulated to proceed *via* the metal-hydride tautomer **16**. Reductive elimination and decomplexation of the η^2 -styryl moiety in **16** would then lead to the imine **17**, hydrolysis of which results in the formation of the aldehyde **11**.



During the examination of this process by i.r. spectroscopy the formation of other organometallic complexes was not observed. Thus it is postulated that the equilibrium between **12**(**14**) and **16** favours **12**(**14**) and that the irreversible reductive elimination and decomplexation process to give **17** is rate-determining.

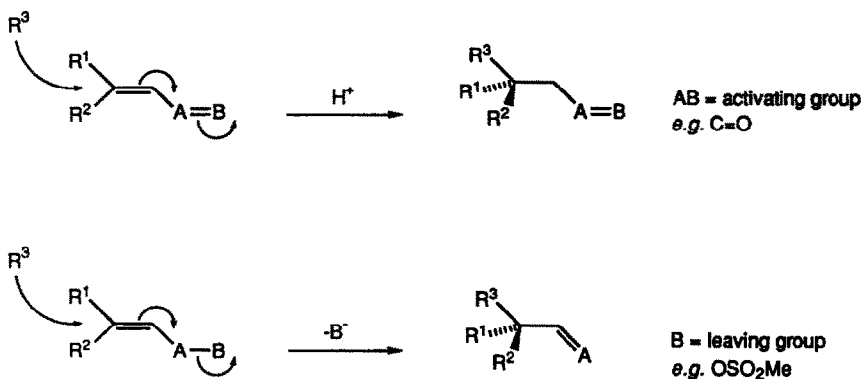
A similar reaction has been reported for the chromium carbene complex **18**. Treatment of this with TFA and water resulted in the isolation of **19** and the formation of benzaldehyde and Cr(CO)₆.¹⁴ This result gives further support to the hypothesis that the aldehyde **11** is formed from an allylcarbene complex.



The difference in the position of nucleophilic attack on the vinylketene and vinylketenimine ligands is quite striking. In none of the reactions described above were any products observed from attack at C(1) of the vinylketenimine ligand. It is of note that protic nucleophiles have been shown to react with coordinated ketenimine ligands at C(2),¹⁵ whilst attack upon uncoordinated ketenimine ligands occurs at C(1).¹⁶

C) Asymmetric Synthesis of Quaternary Centres

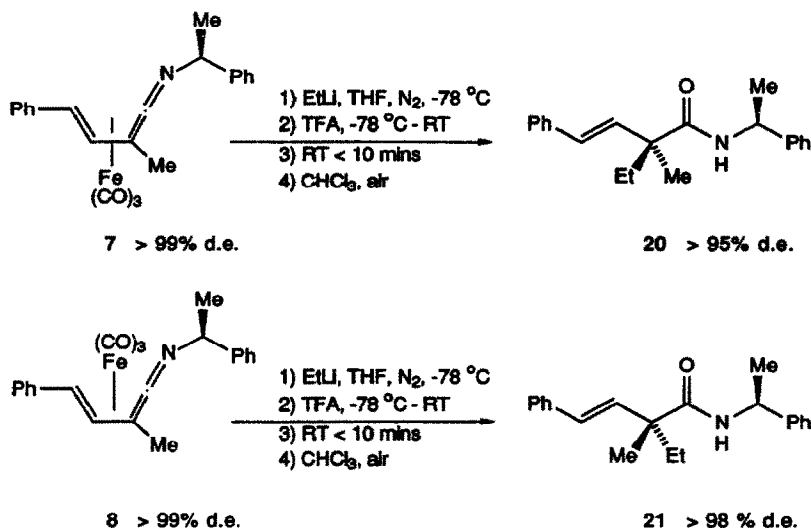
Despite there now being many methods available for the construction of homochiral quaternary centres,¹⁷ comparatively few methods involve the addition of a nucleophile to a trisubstituted electrophilic centre as outlined below.¹⁸



Thus as alkyl-lithium addition to the vinylketenimine complexes generates a quaternary centre by such means, we were interested to see whether the optically active complexes **7** and **8** could be utilized for the synthesis of molecules containing homochiral quaternary centres. It was anticipated that the Fe(CO)₃ moiety would direct the nucleophile stereospecifically to the opposite face of the vinylketenimine ligand.

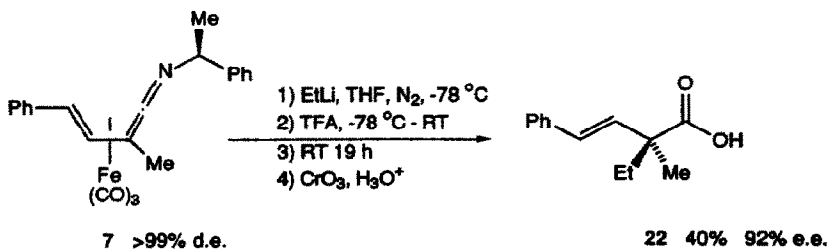
Initially the diastereoselectivity of alkyl-lithium addition was examined. Ethyl-lithium was reacted with **7** and **8**, and in order to ensure that an amide was formed as the major product, the reaction mixtures were exposed to the atmosphere as CHCl₃ solutions almost immediately after the addition of TFA. Following complete decomplexation the crude reaction mixtures were filtered through alumina and examined by ¹H n.m.r. spectroscopy. This revealed that for both reactions only a single diastereoisomer of the corresponding amides **20** and **21** could be detected. The figures obtained for the diastereomeric purity of the amides reflect the quality of the spectra and the presence of other minor impurity peaks. Subsequently an X-ray crystal structure analysis was carried out on a sample of **21** recrystallised from hexane and this confirmed that nucleophilic addition had

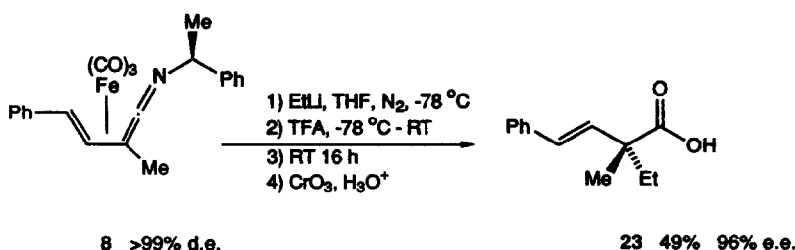
occurred at the *exo* face.¹⁹ The high diastereoselectivities obtained with both complexes reveal that addition is completely controlled by the metal centre, with no secondary influence from the α -methylbenzyl auxiliary.



As it had not proven possible to measure the e.e. of the vinylketenimine complexes 7 and 8 directly (to establish whether any racemisation of the α -methylbenzyl centre had occurred during their formation), and as addition to these complexes occurred with high diastereoselectivity, it was reasoned that a measurement of the e.e. of the generated quaternary centres would give a measure of the optical purity of the starting complexes. Thus an attempt was made to hydrolyse the amides 20 and 21 with the aim of recoupling the resultant carboxylic acids with a new sample of α -methylbenzylamine under mild non-racemising conditions. However the two amides proved very resistant to hydrolysis and so the synthesis of the carboxylic acids was attempted directly from the vinylketenimine complexes.

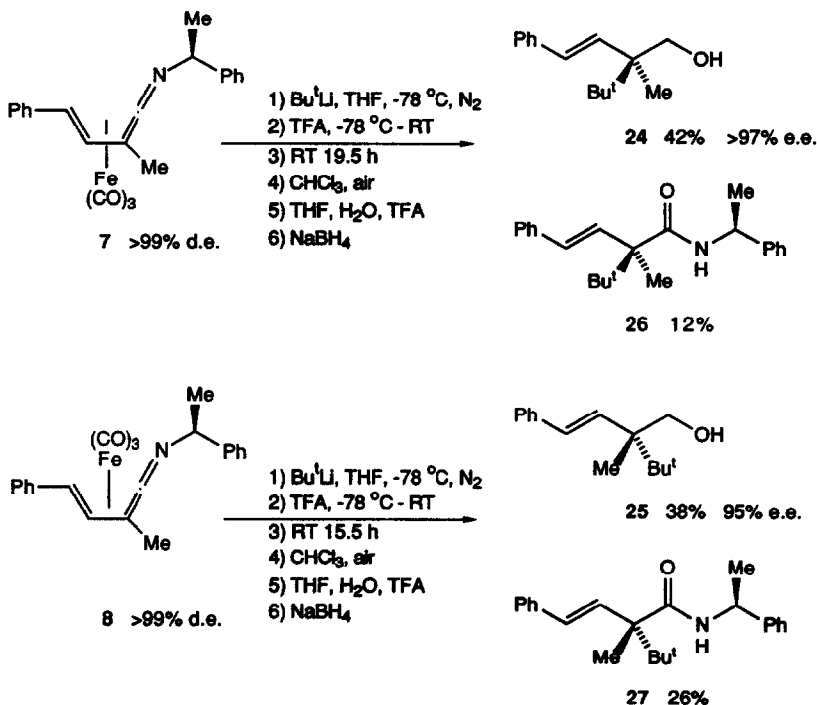
Addition of ethyl-lithium and TFA was carried out as before except that after stirring at room temperature, a solution of CrO₃ in H₂SO₄ was added directly to the reaction mixtures.²⁰ These conditions permitted initial iron complex oxidation, imine hydrolysis and aldehyde oxidation to be carried out in one flask resulting in moderate yields of the desired acids.





After coupling of **22** and **23** with α -methylbenzylamine (96% e.e.) in the presence of dicyclohexylcarbodiimide,²¹ the two acids were calculated to be of 92% and 96% e.e. respectively when account was made for the optical impurity of the amine. Within the limits of experimental error, these results suggest that no racemisation of the α -methylbenzyl centre occurs during the synthesis of **7** and **8** and that the optical purity of the complexes is only limited by the optical purity of the starting amine.

An interesting feature of the vinylketenimine complexes is that they react with *tert*-butyl-lithium forming two contiguous quaternary centres.⁵ Therefore it was anticipated that complexes **7** and **8** would enable the asymmetric synthesis of molecules containing a quaternary centre adjacent to a chiral quaternary centre to be carried out. The addition of Bu^tLi and TFA to complexes **7** and **8** was performed as before generating the aldehydes *in situ*. The crude reaction mixtures were treated with NaBH_4 resulting in the formation of the alcohols **24** and **25** together with smaller amounts of the amides **26** and **27**, formed as single diastereoisomers. The stereochemistry of the products was assigned on the basis of *exo* addition as before.



After their purification by column chromatography, the enantiomeric purities of **24** and **25** were determined as >97% and 95% e.e. respectively by examination of the ^1H n.m.r. spectra of their corresponding Mosher's esters.²² These figures again show that the optical purity of complexes **7** and **8** is only limited by the purity of α -methylbenzylamine used initially,²³ and the e.e. observed for **24** may indicate that recrystallisation of **7** results in material of >97% enantiomeric excess.

Conclusion

Nucleophilic attack of alkyl-lithium reagents on (vinylketenimine)tricarbonyliron(0) complexes is completely controlled by the metal. Reaction only occurs at (C)2 and is exclusively *exo* to the $\text{Fe}(\text{CO})_3$ moiety. Protonation of the resulting mixture generates an allylcarbene complex which may be oxidised immediately to an amide, or allowed to rearrange resulting ultimately in the formation of an aldehyde. As the vinylketenimine complexes were found to be configurationally stable at room temperature, they were employed for the highly enantioselective synthesis of molecules containing carbon quaternary centres. A particular feature of this chemistry is the ease with which two contiguous quaternary centres may be generated, a process for which few methods exist especially in asymmetric synthesis.

Experimental

All reactions involving metal complexes were performed using standard vacuum line techniques under an atmosphere of nitrogen. Tetrahydrofuran was distilled from sodium benzophenone ketyl and dichloromethane from calcium hydride. Toluene was dried over sodium wire. Petroleum ether and hexane refer to the fractions boiling in the range 40-60 °C and 65.5-70 °C respectively. Methyl-lithium (1.4 M in Et_2O) and *tert*-butyllithium (1.7 M in pentane) were purchased from Aldrich and ethyl-lithium was prepared as a solution in Et_2O by a literature procedure.²⁴ The concentrations of all the alkyl-lithium reagents were determined by titration against diphenylacetic acid.²⁵ Unless otherwise stated chromatography was performed on SiO_2 (Merck 9385, 40-60 μm) and Al_2O_3 used for filtrations was deactivated with H_2O ($\text{Al}_2\text{O}_3/\text{H}_2\text{O} = 10:1$ w/w). M.p.s were determined on a Gallenkamp digital m.p. apparatus and are not corrected. Elemental analyses were performed by Butterworth Laboratories Ltd. I.r spectra were obtained on Perkin-Elmer 580B and 1720X instruments. N.m.r. spectra were recorded on Perkin-Elmer R34 (220 MHz ^1H) and Bruker (400 MHz ^1H and 100.6 MHz ^{13}C) spectrometers. Mass spectra were recorded on a MS 80 instrument using FAB (matrix - *m*-nitrobenzyl alcohol²⁶), CI (reactant gas - NH_3), and EI techniques. Optical rotations were measured on an Optical Activity AA-1000 instrument using 2 dm cells.

Synthesis of (vinylketenimine)tricarbonyliron(0) complexes 7 and 8.

A stirred solution of **22** (1.633 g, 5.48 mmol) and (*S*)-CNCHPhMe **69** (0.721 g, 5.5 mmol) were heated together in toluene (55 ml) at 80 °C for 20 h. After cooling, the reaction mixture was filtered through Al_2O_3 and the solvent removed *in vacuo*. Preliminary chromatography on SiO_2 (10% EtOAc-petroleum ether) gave recovered **2** (0.168 g, 10%) and a 1:1 mixture of **7** and **8** as a viscous yellow oil (1.50 g, 76% - accounting for recovered **2**). The two diastereoisomers were separated by further column chromatography on SiO_2 (Merck 7747, 10% EtOAc-petroleum ether). Under these conditions **8** was eluted faster than **7**. Crystallisation of **7** from *n*-pentane gave a yellow crystalline solid, but **8** resisted all attempts at crystallisation and remained as a yellow viscous oil.

7: m.p. 84–85 °C (*n*-C₅H₁₂) (Found: C, 65.89; H, 4.84; N, 3.53. C₂₂H₁₉FeNO₃ requires C, 65.86; H, 4.77; N, 3.49%); [α]_D²³ +673 (*c* 0.2, MeOH); circular dichroism (MeOH) λ_{max} 392 (-1.7), 305 (+48), 220 (-40) nm (Δε); ν_{max} (C₆H₁₂) 2 050vs and 1 985vs (C=O), 1 738 cm⁻¹ (C=N); ν_{max} (nujol mull) 2 040vs, 1 987vs, and 1 969vs (C=O), 1 736 cm⁻¹ (C=N); δ_H (400 MHz, CDCl₃) 7.49–7.20 (10 H, m, 2 x Ph), 6.14 (1 H, d, *J* 9.1 Hz, -CH=CHPh), 4.41 (1 H, q, *J* 6.7 Hz, -NCHPhMe), 2.84 (1 H, d, *J* 9.1 Hz, -CH=CHPh), 2.01 (3 H, s, -(CH₃)CN-), 1.57 (3 H, d, *J* 6.7 Hz, -NCHPh(CH₃)); δ_C {¹H} (CDCl₃) 191.2 (-CMe=C=N-), 144.5 (NCH-Ph, *C-ipso*), 138.8 (4-Ph, *C-ipso*), 128.8, 128.4, 127.0, 126.9, 126.7, 126.2, 92.7 (-CH=CHPh), 70.3 (-NCHPhMe), 60.9 (-CMeCN-), 58.7 (-CH=CHPh), 24.8 (-NCHPh(CH₃)), 17.0 (-C(CH₃)CN-), (C=O not observed); *m/z* (FAB) 402 (MH⁺, 38%), 374 (MH-CO, 10), 346 (MH-(CO)₂, 10), 317 (M-(CO)₃, 100).

8: (Found: C, 65.87; H, 4.92; N, 3.44. C₂₂H₁₉FeNO₃ requires C, 65.86; H, 4.77; N, 3.49%); [α]_D²¹ -1127 (*c* 0.2, MeOH); circular dichroism (MeOH) λ_{max} 389 (+1.4), 304 (-37), 220 (-27) nm (Δε); ν_{max} (C₆H₁₂) 2 049vs, 1 988vs, and 1 981vs (C=O), 1 737 cm⁻¹ (C=N); δ_H (400 MHz, CDCl₃) 7.44–7.17 (10 H, m, 2 x Ph), 6.14 (1 H, d, *J* 9.2 Hz, -CH=CHPh), 4.44 (1 H, q, *J* 6.7 Hz, -NCHPhMe), 2.70 (1 H, d, *J* 9.2 Hz, -CH=CHPh), 2.11 (3 H, s, -C(CH₃)CN-), 1.66 (3 H, d, *J* 6.7 Hz, -NCHPh(CH₃)); δ_C {¹H} (CDCl₃) *ca.* 209 (br, 3 x C=O), 189.9 (-CMe=C=N-), 144.9 (NCH-Ph, *C-ipso*), 138.6 (4-Ph, *C-ipso*), 128.8, 128.4, 126.9, 126.8, 126.25, 126.20, 92.8 (-CH=CHPh), 70.6 (-NCHPhMe), 60.6 (-CMeCN-), 59.1 (-CH=CHPh), 23.8 (-NCHPh(CH₃)), 17.1 (-C(CH₃)CN-); *m/z* (FAB) 402 (MH⁺, 88%), 374 (MH-CO, 24), 346 (MH-(CO)₂, 9), 318 (MH-(CO)₃, 100).

Reaction of ((E)-PhCH=CHCMe=C=NBu^t)Fe(CO)₃ 3² with methyl-lithium.

To a stirred yellow solution of 3 (0.185 g, 0.52 mmol) in THF (5 ml) at -78 °C was added methyl-lithium (0.36 ml, 0.54 mmol) resulting in the reaction mixture immediately turning orange. After stirring at -78 °C for 1 h TFA (0.06 ml, 0.8 mmol) was added which caused the reaction mixture to change immediately to dark yellow. The solution was removed from the cooling bath and stirred at room temperature for 1 h, after which the solvent was removed *in vacuo*, and the residue taken up in CDCl₃ (10 ml) and stirred open to the atmosphere at room temperature overnight. The resulting mixture was filtered through Al₂O₃, the solvent removed *in vacuo*, and the residue column chromatographed (SiO₂, 2–10% EtOAc-petroleum ether) to give 10 (0.056 g, 44%) and 11 (0.027 g, 30%).

10: m.p. 98.5–99.5 °C (hexane) (Found: C, 78.01; H, 9.60; N, 5.79. C₁₆H₂₃NO requires C, 78.32; H, 9.45; N, 5.71%); ν_{max} (C₆H₁₂) 3 423w (NH), 1 687s cm⁻¹ (C=O); ν_{max} (nujol mull) 3 414m (NH), 1 671s cm⁻¹ (C=O); δ_H (CDCl₃) 7.47–7.26 (5 H, m, Ph), 6.56 (1 H, d, *J* 16 Hz, -CH=CHPh), 6.37 (1 H, d, *J* 16 Hz, -CH=CHPh), 5.54 (1 H, brs, NH), 1.36 (6 H, s, 2 x Me), 1.31 (9 H, s, Bu^t); δ_C {¹H} (CDCl₃) 175.3 (-CONH-), 136.8 (Ph, *C-ipso*), 135.2 (-CH=CHPh), 129.0 (-CH=CHPh), 128.6, 127.5 (Ph, *C-para*), 126.2, 50.8 and 45.4 (-CMe₂CO- and NHCMe₃), 28.6 (-C(CH₃)₃), 25.2 (-C(CH₃)₂-); *m/z* (EI) 245 (M⁺, 10%), 145 (M-CONHBu^t, 100).

11: ν_{max} (CDCl₃) 1 725s cm⁻¹ (C=O); δ_H (CDCl₃) 9.53 (1 H, s, -CHO), 7.49–7.22 (5 H, m, Ph), 6.51 (1 H, d, *J* 16 Hz, -CH=CHPh), 6.21 (1 H, d, *J* 16 Hz, -CH=CHPh), 1.32 (6 H, s, 2 x Me).

Isolation of ((E)-PhCH=CHCMe₂C(NHBu^t)=)Fe(CO)₃ 13.

To a stirred solution of 3 (0.079 g, 0.22 mmol) in THF (2 ml) at -78 °C was added methyl-lithium (0.26 ml, 0.34 mmol), and the solution stirred at -78 °C for 1 h. Addition of TFA (0.04 ml, 0.5 mmol) was followed by the reaction mixture being immediately removed from the cooling bath and stirred at room temperature for 10 minutes before the solvent was removed *in vacuo*. The resultant dark yellow residue was column chromatographed (SiO₂, 6% EtOAc-petroleum ether) under a positive pressure of nitrogen with degassed solvents. An intense yellow band was collected and the solvent removed *in vacuo* to give 13 as a viscous yellow oil.

13: ν_{\max} (C₆H₁₂) 3 299w (NH), 2 018vs, 1 955vs, and 1 922vs cm⁻¹ (C≡O).

Synthesis and decomposition of (E)-PhCH=CHCMe₂C(NHCHPhMe)=)Fe(CO)₃ 14.

To a stirred yellow solution of 8 (0.047 g, 0.12 mmol) in THF (3 ml) at -78 °C was added methyl-lithium (0.14 ml, 0.18 mmol), the colour of the reaction mixture changing to a darker yellow. After stirring at -78 °C for 0.75 h, TFA (0.03 ml, 0.4 mmol) was added and the reaction mixture was then immediately removed from the cooling bath and allowed to warm to room temperature. A portion of the resulting solution was removed and the solvent evaporated *in vacuo* within 10 minutes of the addition of TFA. After decomposition (CHCl₃/air), filtration through Al₂O₃ and removal of the solvent *in vacuo*, the residue was shown by ¹H n.m.r. spectroscopy to contain the amide 15 and the aldehyde 11 in a ratio of 10:1. The remaining reaction mixture was stirred at room temperature for 19 h. Periodic monitoring of the THF solution revealed a decrease in the intensity of the three (C=O) bands corresponding to the carbene complex 14. After 18.5 h the intensity had decreased to *ca.* 50% of that found after 1.5 h. Removal of the solvent *in vacuo* was followed by decomposition (CHCl₃/air) and filtration through Al₂O₃. Subsequent examination of the residue by ¹H n.m.r. spectroscopy revealed a 9:10 ratio of 15 and 11.

14: ν_{\max} (THF) 2 006vs, 1 941vs, and 1 908vs cm⁻¹ (C≡O).

15: δ_{H} (400 MHz, CDCl₃) 7.4-7.2 (10 H, m, 2 x Ph), 6.52 (1 H, d, *J* 16.3 Hz, -CH=CHPh), 6.35 (1 H, d, *J* 16.3 Hz, -CH=CHPh), 5.91 (1 H, brd, *J* 7 Hz, NH), 5.08 (1 H, quintet, *J* 7 Hz, -CHPhMe), 1.43 (3 H, d, *J* 7 Hz, -CHPhCH₃), 1.40 (3 H, s, Me), 1.37 (3 H, s, Me).

Synthesis of 1'(S), 2(S)-20 and 1'(S), 2(R)-21 (E)-PhCH=CHCtMeCONHCHPhMe.

To a stirred yellow solution of complex 7 (0.063 g, 0.16 mmol) in THF (2 ml) at -78 °C was added ethyl-lithium (0.42 ml, 0.24 mmol) which immediately resulted in a darker yellow/orange reaction mixture. After stirring at -78 °C for 1 h TFA (0.03 ml, 0.4 mmol) was added and the resultant yellow solution was removed from the cooling bath and allowed to warm to room temperature. The solvent was removed *in vacuo* 10 minutes after the solution had been removed from the cooling bath to give a viscous yellow oil. This was taken up in CHCl₃ (5ml) and stirred at room temperature open to the atmosphere for 23.5 h. The resultant dark solution which contained a 'rusty' precipitate was filtered through Al₂O₃ and the solvent removed *in vacuo* to give an opaque oil. This was examined by ¹H n.m.r. spectroscopy in order to determine the diastereoselectivity of addition. Subsequent column chromatography (SiO₂, 10% EtOAc-petroleum ether) gave 20 as a colourless crystalline solid (0.034 g, 70%), d.e. >95%.

20: m.p. 91-91.5 °C (*n*-C₅H₁₂) (Found: C, 81.7; H, 8.3; N, 4.3. C₂₁H₂₅NO requires C, 82.04; H, 8.20; N, 4.56%); ν_{\max} (C₆H₁₂) 3 426 (NH), 1 682s cm⁻¹ (C=O); ν_{\max} (nujol mull) 3 390s (NH), 1 651s and 1 639s cm⁻¹ (C=O); δ_{H} (400 MHz, CDCl₃) 7.39-7.21 (10 H, m, 2 x Ph), 6.52 (1 H, d, *J* 16.4 Hz, -CH=CHPh), 6.34 (1 H, d, *J* 16.4 Hz, -CH=CHPh), 5.91 (1 H, brd, *J* 8 Hz, NH), 5.11 (1 H, quintet, *J* 7 Hz, -NHCHPhMe), 1.83-1.74 (2 H, m, -CH₂CH₃), 1.43 (3 H, d, *J* 7 Hz, -NHCHPhCH₃), 1.37 (3 H, s, -CEtCH₃CO-), 0.85 (3 H, t, *J* 7.5 Hz, -CH₂CH₃); δ_{C} {¹H} (CDCl₃) 174.6 (-CONH-), 143.4 (NCH-Ph, *C*-*ipso*), 136.8 (4-Ph, *C*-*ipso*), 133.4 (-CH=CHPh), 130.3 (-CH=CHPh), 128.6, 128.5, 127.6, 127.1, 126.2, 125.9, 48.6 (NHCHPhMe), 31.6 (-CH₂CH₃), 21.8 and 21.7 (-CEtCH₃- and -NHCHPhCH₃), 8.7 (-CH₂CH₃), (-CEtMeCO- not observed); *m/z* (EI) 307 (M⁺, 4%), 159 (M-CONHCHPhMe, 100).

Similarly prepared from 8 (0.060 g, 0.15 mmol) was 21 (0.030g, 65%), d.e. >98% (from crude product mixture).

21: m.p. 60-60.5 °C (*n*-C₅H₁₂); ν_{\max} (C₆H₁₂) 3 429w (NH), 1 682s cm⁻¹ (C=O); δ_{H} (400 MHz, CDCl₃) 7.39-7.21 (10 H, m, 2 x Ph), 6.50 (1 H, d, *J* 16.4 Hz, -CH=CHPh), 6.35 (1 H, d, *J* 16.4 Hz, -CH=CHPh), 5.92 (1 H, brd, *J* 8 Hz, NH), 5.11 (1 H, quintet, *J* 7 Hz, -NHCHPhMe), 1.81 (2 H, q, *J* 7.5 Hz, -CH₂CH₃), 1.44 (3 H, d, *J* 7 Hz, -NHCHPhCH₃), 1.33 (3 H, s, -CEtCH₃CO-), 0.91 (3 H, t, *J* 7.5 Hz, -CH₂CH₃); δ_{C} {¹H} (CDCl₃) 174.6 (-CONH-), 143.4 (NCH-Ph, *C*-*ipso*), 136.8 (4-Ph, *C*-*ipso*), 133.4 (-CH=CHPh), 130.3 (-CH=CHPh), 128.6, 128.5, 127.6, 127.1, 126.2, 125.8, 48.64 (-CEtMeCO-), 48.57 (-NHCHPhMe), 31.6 (-CH₂CH₃) 2 x 21.8 (-CEtCH₃- and -NHCHPhCH₃), 8.8 (-CH₂CH₃); *m/z* (EI) 307 (M⁺, 4%), 159 (M-CONHCHPhMe, 100) (Found: M⁺, *m/z* (EI) 307.1941. C₂₁H₂₅NO requires 307.1936).

Synthesis of (R)-(E)-PhCH=CHCEtMeCO₂H 23 and (S)-(E)-PhCH=CHCEtMeCO₂H 22.

To a stirred solution of 8 (0.036g, 0.09 mmol) in THF (2ml) at -78 °C was added EtLi (0.30 ml, 0.14 mmol) and the solution was stirred at -78 °C for 1h. After addition of TFA (0.03 ml, 0.4 mmol) the reaction mixture was removed from the cooling bath and stirred at room temperature for 16 h. Removal of the solvent *in vacuo* gave a viscous yellow residue that was dissolved in acetone (4 ml) and cooled in an ice bath with the solution open to the atmosphere. To this was added 0.21 ml of a solution of CrO₃ (0.10 g, 1 mmol) in concentrated H₂SO₄ (0.08 ml) and H₂O (volume of solution made up to 0.44 ml) over a period of 5 hours during which time the solution was also allowed to warm to room temperature. The resultant solution was partitioned between CH₂Cl₂ (10 ml) and H₂O (10 ml), and the aqueous phase extracted further with CH₂Cl₂ (10 ml). The combined organic layers were washed with brine (10 ml) and H₂O (10 ml) and dried (MgSO₄). Removal of the solvent *in vacuo* and column chromatography of the residue (SiO₂, 30-50% EtOAc-petroleum ether) gave 23 as a colourless crystalline solid (0.009 g, 49%).

23: m.p. 83-83.5 °C (hexane) (lit.,²⁷ 82.2-83 °C (hexane)); $[\alpha]_{546}^{22} +10$ (*c* 0.1, CHCl₃) (lit.,²⁷ $[\alpha]_{546}^{25} +8.8$ (*c* 1.7, CHCl₃)); ν_{\max} (CCl₄) 1 703s cm⁻¹ (C=O); δ_{H} (400 MHz, CCl₄) 7.30 (2 H, d, *J* 7 Hz, Ph, *H*-*ortho*), 7.21 (2 H, t, *J* 7 Hz, Ph, *H*-*meta*), 7.13 (1 H, t, *J* 7 Hz, Ph, *H*-*para*), 6.40 (1 H, d, *J* 16 Hz, -CH=CHPh), 6.33 (1 H, d, *J* 16 Hz, -CH=CHPh), 1.91-1.82 (1 H, m, -CHHCH₃), 1.79-1.68 (1 H, m, -CHHCH₃), 1.38 (3 H, s, -EtCH₃-), 0.94 (3 H, t, *J* 7.2 Hz, -CH₂CH₃), (-CO₂H, not observed); *m/z* (EI) 204 (M⁺, 26%), 159 (M-CO₂H, 100).

Similarly prepared from 7 (0.039 g, 0.10 mmol) was (S)-(E) 22 (0.008 g, 40%).

The i.r. and ^1H n.m.r. spectra of this compound were essentially identical to those reported above for 23. $[\alpha]_{546}^{23} -9$ (c 0.15, CHCl_3) (lit.,²⁷ $[\alpha]_{546}^{25} -8$ (c 1.3, CHCl_3).

Determination of the optical purity of 22 and 23.

A solution of 22 (0.0023 g, 0.01 mmol) and (*S*)- α -methylbenzylamine (96% e.e., 0.0020 g, 0.02 mmol) in CH_2Cl_2 (1 ml) under a nitrogen atmosphere was cooled in an ice bath. To this was added a solution of dicyclohexylcarbodiimide (0.0035 g, 0.02 mmol) in CH_2Cl_2 (0.3 ml) and the solution was slowly allowed to warm to room temperature and then stirred for 2 days. The solvent and excess amine were removed *in vacuo* and the white crystalline residue was examined by ^1H n.m.r. spectroscopy. This indicated that the resultant amide 20 was formed with a diastereoselectivity of 95:5.

Similarly 23 yielded amide 21 with a diastereoselectivity of 97:3.

Synthesis of (R)-(E)-PhCH=CHC^tBu^tMeCH₂OH 24 and (S)-(E)-PhCH=CHC^tBu^tMeCH₂OH 25.

To a stirred solution of 7 (0.057 g, 0.14 mmol) in THF (3 ml) at -78°C was added Bu^tLi (0.13 ml, 0.22 mmol) which immediately resulted in a darker yellow/orange reaction mixture. After stirring at -78°C for 1 h, TFA (0.05 ml, 0.6 mmol) was added and the resultant yellow solution was removed from the cooling bath and allowed to warm to room temperature. Stirring was continued at room temperature for 19.5 h and then the solvent was removed *in vacuo* to give a viscous orange oil. This was taken up in wet CHCl_3 (5 ml) and stirred open to the atmosphere for 1 h. The resultant brown solution was filtered through a cotton wool plug and the solvent removed *in vacuo* to give a dark brown oil. This was dissolved in THF (5 ml), H_2O (1 ml), and TFA (0.02 ml) and stirred open to the atmosphere for 1.5 h (to ensure complete imine hydrolysis). Subsequent removal of the solvent *in vacuo* again gave a brown oil. This was taken up in MeOH (3 ml) and NaBH_4 (0.019 g, 0.5 mmol) was added over a period of 2.5 h at room temperature. After stirring for a further 1 h the solvent was removed to give a brown residue that was partitioned between CH_2Cl_2 (5 ml) and H_2O (5 ml). The aqueous layer was further extracted with CH_2Cl_2 (2 x 5 ml) and the combined organic layers were dried (MgSO_4) and evaporated. Column chromatography of the resultant light brown oil (SiO_2 , 5-10% EtOAc-petroleum ether) gave 24 as a colourless crystalline solid (0.013 g, 42%) and 1'(S), 2(R)-(E)-PhCH=CHC^tBu^tMeCONHCHPhMe 26 as a colourless oil (0.0055 g, 12%).

24: m.p. $74-76^\circ\text{C}$ (hexane); $[\alpha]_{589}^{22} +37$ (c 0.1, MeOH); ν_{max} (CDCl_3) 3 584m (OH), 1 600m cm^{-1} (C=C); δ_{H} (400 MHz, CDCl_3) 7.40-7.30 (5 H, m, Ph), 6.43 (1 H, d, *J* 16.4 Hz, $-\text{CH}=\text{CHPh}$), 6.30 (1 H, d, *J* 16.4 Hz, $-\text{CH}=\text{CHPh}$), 3.79 (1 H, d, *J* 10.6 Hz, $-\text{CH}/\text{OH}$), 3.54 (1 H, d, *J* 10.6 Hz, $-\text{CH}/\text{OH}$), 1.57 (1 H, brs, OH), 1.16 (3 H, s, Me), 0.94 (9 H, s, Bu^t); δ_{C} (^1H) (CDCl_3) 137.4, (Ph, C-*ipso*), 133.9 ($-\text{CH}=\text{CHPh}$), 130.8 ($-\text{CH}=\text{CHPh}$), 128.5, 127.2 (Ph, C-*para*), 126.1, 66.5 ($-\text{CH}_2\text{OH}$), 46.9 ($-\text{CBu}^t\text{Me}$), 35.5 ($-\text{C}(\text{CH}_3)_3$), 26.1 ($-\text{C}(\text{CH}_3)_3$), 15.7 ($-\text{CH}_3$); *m/z* (EI) 218 (M^+ , 2%), 187 (M- CH_2OH , 6), 91 (C_7H_7 , 100) (Found: M^+ , *m/z* (EI) 218.1674. $\text{C}_{15}\text{H}_{22}\text{O}$ requires 218.1671).

26: ν_{max} (C_6H_{12}) 3 432w (NH), 1 674 cm^{-1} (C=O); δ_{H} (400 MHz, CDCl_3) 7.40-7.21 (10 H, m, 2 x Ph), 6.67 (1 H, d, *J* 16.4 Hz, $-\text{CH}=\text{CHPh}$), 6.49 (1 H, d, *J* 16.4 Hz, $-\text{CH}=\text{CHPh}$), 5.89 (1 H, brd, *J* 8 Hz, NH), 5.10 (1 H, quintet, *J* 7 Hz, NHCHPhMe), 1.42 (3 H, d, *J* 7 Hz, $-\text{NHCHPhCH}_3$), 1.40 (3 H, s, $-\text{CBu}^t\text{CH}_3$), 1.02

(9 H, s, Bu^t); *m/z* (CI) 336 (MH⁺, 14%), 279 (M-Me₂C=CH₂, 83), 187 (M-CONHCHPhMe, 62), 105 (C₈H₉, 100) (Found: MH⁺, *m/z* (CI) 336.2337. C₂₃H₃₀NO requires 336.2327).

Similarly prepared from 8 (0.092 g, 0.23 mmol) were 25 (0.019 g, 38%) and 27 (0.018 g, 26%) isolated as a colourless crystalline solid and a colourless oil respectively.

25: The IR, ¹H NMR, ¹³C NMR spectra, and mass spectrum of this compound were essentially identical to those reported above for 24. [α]_D²² -36 (c 0.1, MeOH).

27: ν_{max} (C₆H₁₂) 3 431w (NH), 1 675s cm⁻¹ (C=O); δ_H (400 MHz, CDCl₃) 7.39-7.20 (10 H, m, 2 x Ph), 6.68 (1 H, d, *J* 16.4 Hz, -CH=CHPh), 6.47 (1 H, d, *J* 16.4 Hz, -CH=CHPh), 5.93 (1 H, brd, *J* 8 Hz, NH), 5.11 (1 H, quintet, *J* 7 Hz, NHCHPhMe), 1.44 (3 H, d, *J* 7 Hz, NHCHPhCH₃), 1.37 (3 H, s, -CBu^tCH₃-), 1.05 (9 H, s, Bu^t); *m/z* (CI) 336 (MH⁺, 20%), 279 (M-Me₂C=CH₂, 72), 187 (M-CONHCHPhMe, 47), 105 (C₈H₉, 100) (Found: MH⁺, *m/z* (CI) 336.2333. C₂₃H₃₀NO requires 336.2327).

Determination of the optical purity of 24 and 25.

Both compounds were converted to their corresponding Mosher's esters by reaction with (S)-(+)-MTPACl.²² Examination of the crude reaction mixtures revealed that the ester derived from 24 had a doublet at 4.66 ppm (1 H, *J* 10.7 Hz, -CHHO-). The corresponding signal for the ester of 25 was found at 4.68 ppm (*J* 10.8 Hz). Using these signals the optical purity of 24 and 25 was estimated as >97% e.e. and 95% e.e. respectively.

Acknowledgements

We thank Dr N. W. Alcock and Mr G. A. Pike for the crystal structure determinations; Dr O. W. Howarth, Dr J. Lall and Mr J. Hastings for the high field n.m.r. spectra; and Dr A. F. Drake and Mr J. Hoadly of the SERC National Chiroptical Spectroscopy Service for the CD spectra. Additionally C.J.R. would like to thank the S.E.R.C. for support.

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