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Asymmetric synthesis via the iron chiral auxiliary $[(\eta^5\text{–}C_5H_5)Fe(CO)(PPh_3)]$

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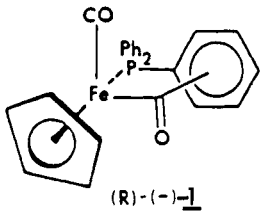
Abstract: The acetyl ligand attached to the iron chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ can be elaborated with a high degree of stereochemical control to yield, after decomplexation, (-)-captopril and β-lactams essentially optically pure. Methylation of the (R)-acetyl complex 1, via its enolate, gave the (R)-propanoyl complex 7. Treatment of 7 with butyllithium to generate the E-enolate and trapping with bromomethyl benzylthioether gave (RS)-8 as a single compound. Oxidative decomplexation of (RS)-8 in the presence of the benzyl ester of l-proline followed by deprotection gave (-)-captopril 6. Sequential O-methylation and base induced elimination of β-hydroxyacyl complexes derived by trapping the enolate from 1 with aldehydes generates stereoselectively E-α,β-unsaturated acyl complexes. These E-α,β-unsaturated acyl complexes undergo stereoselective tandem Michael addition reactions and alkylations to give single diastereoisomers of products indicating complete control over both new chiral centres. This methodology has been applied to the asymmetric synthesis of (2R,3R)-(-)-N-benzyl-2,3-dimethylheptanamide 20, (3R,4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 22 and (4S)-(-)-4-methyl-N-benzyl-β-lactam 25 via the (S)-E-crotonyl complex 23 derived from the (S)-acetyl complex 1.

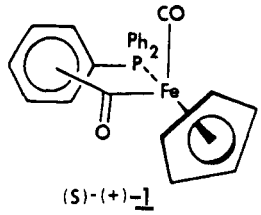
INTRODUCTION

The iron chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ has been extensively developed over the past few years by ourselves[1–15] and others[16] for the asymmetric synthesis of organic molecules generally via carbon-carbon bond forming reactions. The iron chiral auxiliary exerts powerful stereochemical control in a wide variety of reactions of attached acyl ligands including alkylations,[1–5] aldol reactions,[6–10] tandem Michael additions and alkylations[11–14] and Diels Alder reactions.[15] The potential of the parent iron acetyl complex 1, which is now commercially available,[17] for asymmetric synthesis is illustrated below by the asymmetric synthesis of the anti-hypertensive drug (-)-captopril and of a variety of β-lactams.

The iron acetyl complex 1 is a chiral[18] pseudo-octahedral[19–15] complex with the structure shown in Figure 1. It is orange air-stable crystalline material which when enantiomerically pure is configurationally stable. The conformation adopted by the acetyl ligand of 1 in the solid state is such that the acyl oxygen lies approximately anti-periplanar to the carbon monoxide ligand.[19,23] In order to minimise the steric interactions between the phenyl rings and the acetyl ligand the triphenylphosphine orientates itself so as to place one phenyl group under and approximately parallel to the acetyl ligand. There is a great deal of theoretical



(R)-(-)-1



(S)-(+)-1

and experimental evidence to suggest that this is the favoured conformation for any acyl attached to the iron chiral auxiliary.[19,23,26] There is a further degree of stereochemical complexity present in these complexes, namely the sense of the screw of the triphenylphosphine rotor. To date all acyl complexes of this type so far studied exhibit the same screw as shown in Figure 1 again to minimise steric interactions with the other ligands.

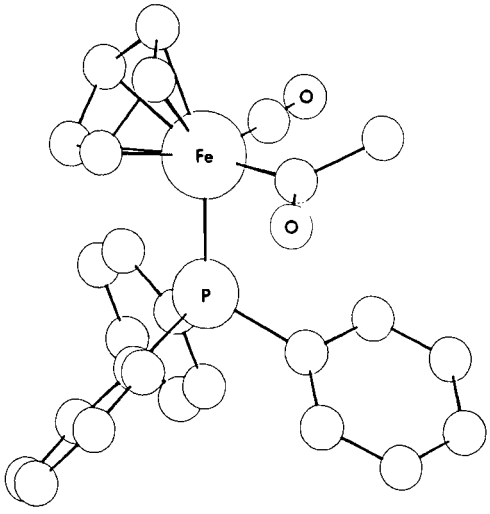


Figure 1: X-Ray crystal structure of $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3]$ 1

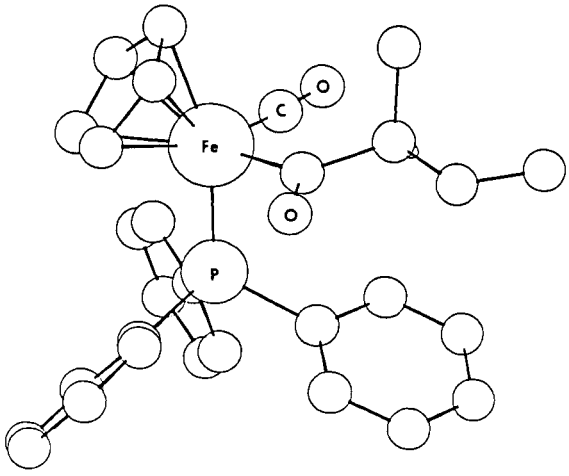
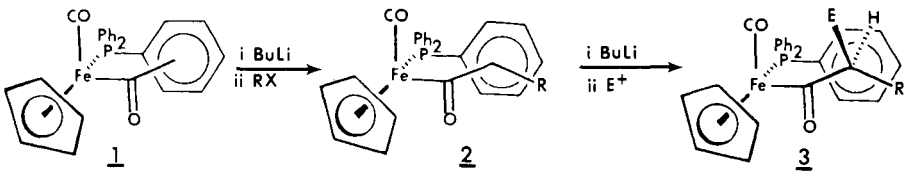


Figure 2: X-Ray crystal structure of complex 5

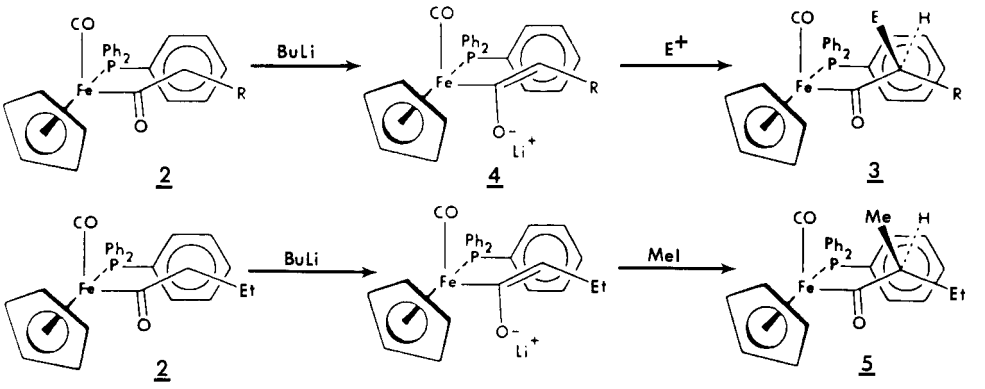
ALKYLATIONS (refs. 1–5)

Deprotonation of the acetyl complex 1 occurs cleanly with n-butyllithium in THF at -78°C to generate the corresponding enolate. Trapping of this enolate with primary alkyl halides or sulphonate esters cleanly gives the elaborated acyl complexes 2 (90-98%). Deprotonation of complexes 2 and alkylation of the derived lithium enolates gives complexes 3 essentially as single diastereoisomers as evidenced by 300 MHz ^1H n.m.r. spectroscopy using the ^{13}C satellites of the major diastereoisomer as internal standard.



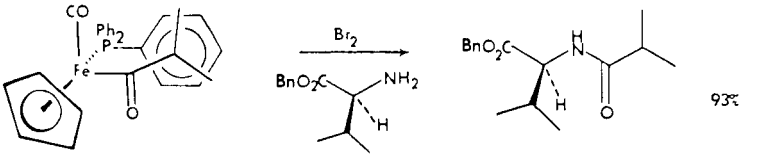
1 2 3

The high stereoselectivity observed in these alkylations is consistent with the following mechanism: Deprotonation of 2 gives only the E-enolate 4 which is alkylated from the unhindered face in the conformation with the enolate oxygen anti to the CO ligand.[5,19,23] The relative stereochemistry between the original iron centre and the new carbon centre was determined by X-ray analysis for the complex formed from 1 by sequential ethylation and methylation. This structure is shown in Figure 2.



DECOMPLEXATIONS (refs. 1–16)

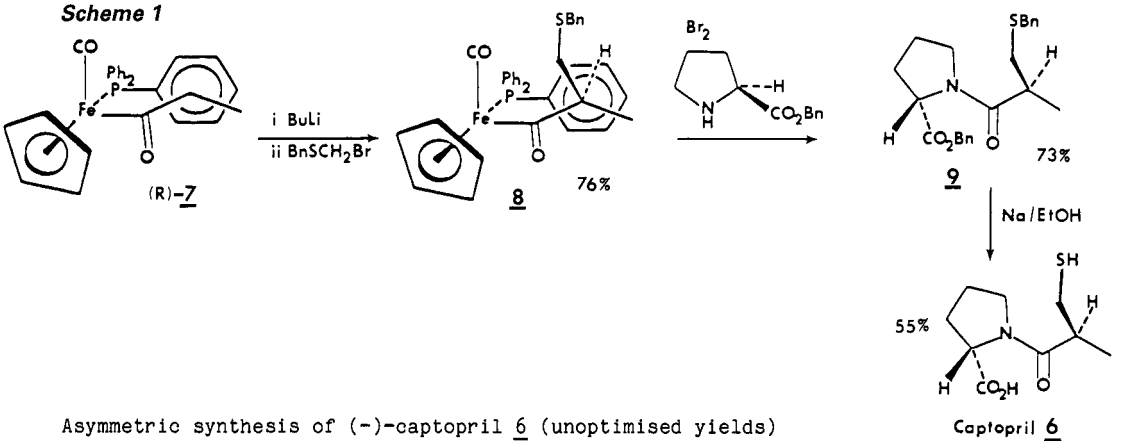
The iron acyl complexes such as 1, 3 or 5 are inert to most reagents except one electron oxidants. Oxidation of these acyl complexes (Br_2, I_2, Cl_2, Fe(III), Ce(IV), Cu(II) etc) in the presence of water, alcohols or amines generates the corresponding acids, esters and amides respectively. The α-centre of the acyl is configurationally stable during these decomplexations.



ASYMMETRIC SYNTHESIS OF CAPTOPRIL (ref. 27)

The application of the above alkylation methodology to asymmetric synthesis is illustrated below for the synthesis of the anti-hypertensive drug (-)-captopril 6 (Scheme 1). Methylation of commerically available[17] iron acetyl complex R-(-)-1 gave the (R)-propanoyl complex 7. Treatment of 7 with butyllithium to generate the E-enolate and trapping with bromomethyl benzyl thioether gave 8 as a single diastereoisomer with the expected (RS) absolute stereochemistry as evidenced by the characteristic chemical shift of the α-methyl group. Oxidative decomplexation of 8 in the presence of the benzyl ester of l-proline gave dibenzylcaptopril 9. Since 9 was diastereoisomerically pure this provided confirmation of the optical purity of 8 and demonstrates that decomplexation does not racemise the newly formed chiral centre. Finally deprotection of 9 gave (-)-captopril 6.

Scheme 1

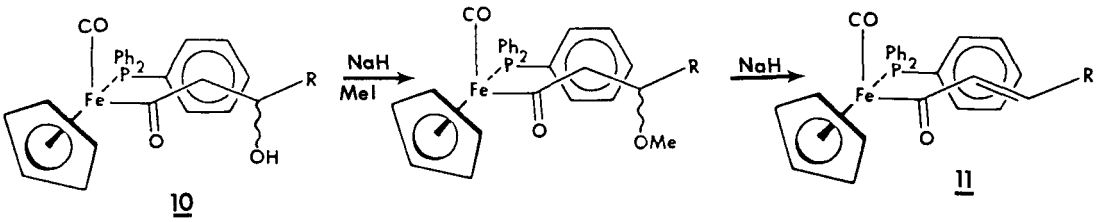


Asymmetric synthesis of (-)-captopril 6 (unoptimised yields)

Captopril 6

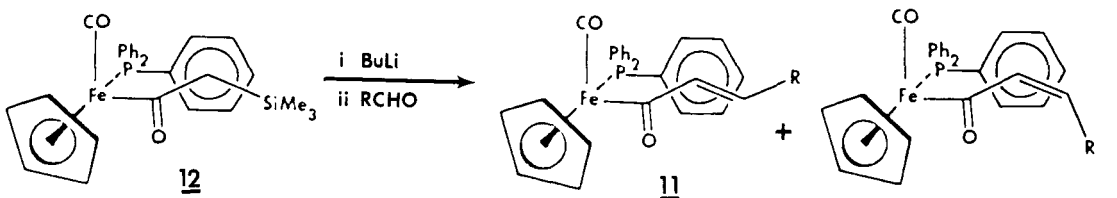
SYNTHESIS OF α, β-UNSATURATED IRON ACYL COMPLEXES (refs. 28, 29)

Trapping the lithium enolate derived from the parent acetyl complex 1 with aldehydes generates the β-hydroxy acyls 10, essentially non-stereoselectively. Sequential O-methylation and base induced elimination of these mixtures 10 generates the E-α,β-unsaturated acyl complexes 11 in high yield.



10 11

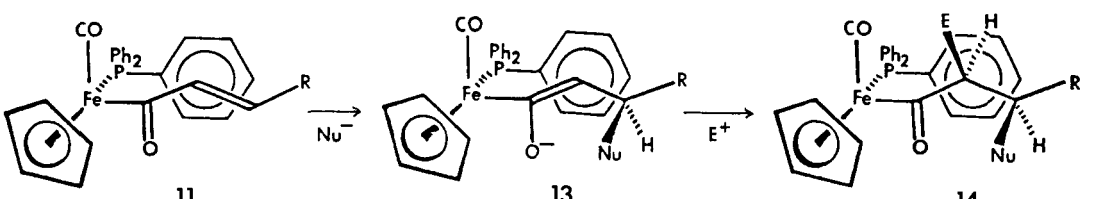
The α-trimethylsilyl iron acyl complex 12 can be prepared in large quantities by trapping the lithium enolate derived from 1 with trimethylsilyl chloride. Complex 12 can be employed in the Peterson olefination reaction to generate separable mixtures of E and Z-α,β-unsaturated acyl complexes. This method is the most convenient for the preparation of the Z-isomers.



12 11

TANDEM MICHAEL ADDITION–ALKYLATION REACTIONS (refs. 11–14)

The E-α,β-unsaturated acyl complexes 11 undergo stereoselective Michael addition reactions with alkyl lithiums to generate the corresponding E-enolates 13 which may be trapped stereoselectively by electrophiles. Generally only a single diastereoisomer of the product 14 is detectable indicating complete stereocontrol over both centres.



11 13 14

The stereoselectivities may be rationalised in terms of initial coordination of the alkyl lithium to the acyl oxygen followed by delivery of the alkyl group to the β-carbon of the α,β-unsaturated acyl ligand in the cisoid conformation thus generating the E-enolate 13. Alkylation of 13 for the unhindered face, as above, would then give 14. Overall the procedure represents the stereoselective 1,2-cis addition of two alkyl groups to only one of the faces of the original α,β-unsaturated acyl ligand.

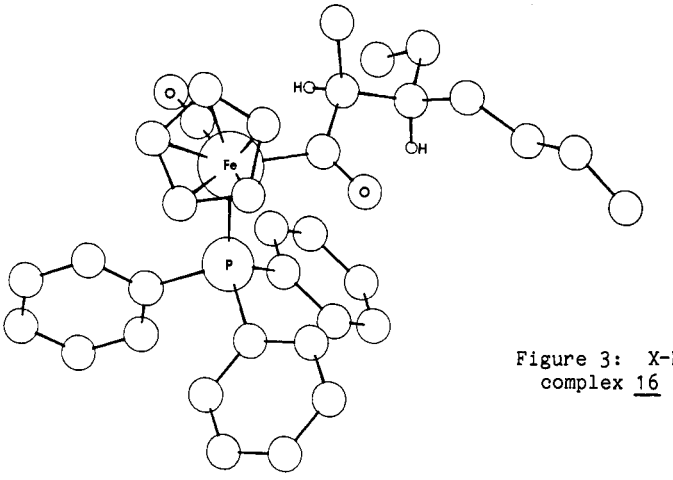
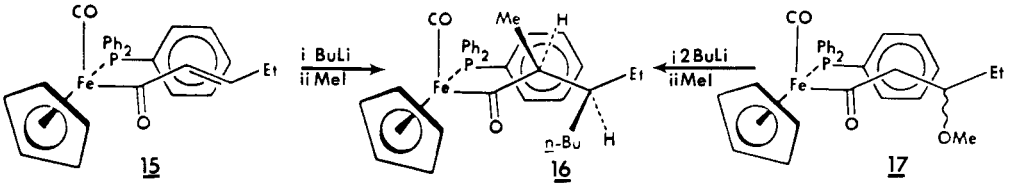
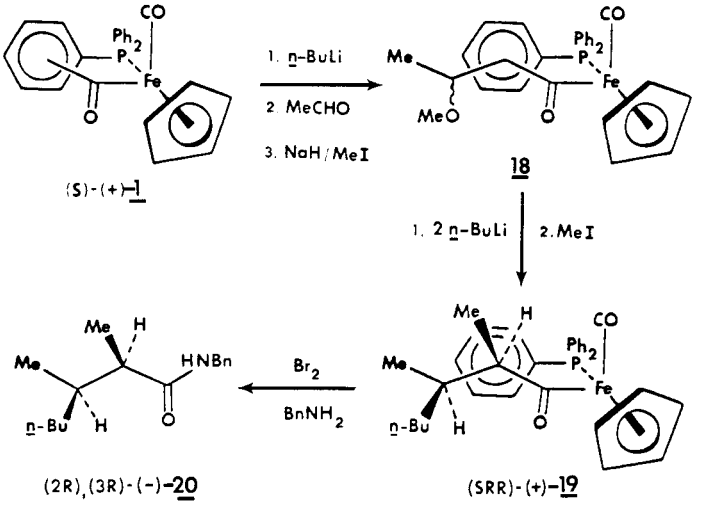


Figure 3: X-Ray crystal structure of complex 16

For example, sequential treatment of complex 15 with n-butyllithium and methyl iodide generated complex 16 as a single diastereoisomer. The relative stereochemistry of the three chiral centres in 16 was established by X-ray analysis (Figure 3). Complex 16 could also be obtained diastereoisomerically pure by seqential treatment of 17 with two equivalents of butyllithium followed by methyl iodide; the first butyl lithium presumably promoting elimination of 17 to give 15 which then undergoes *in situ* Michael addition with the second butyllithium as before.

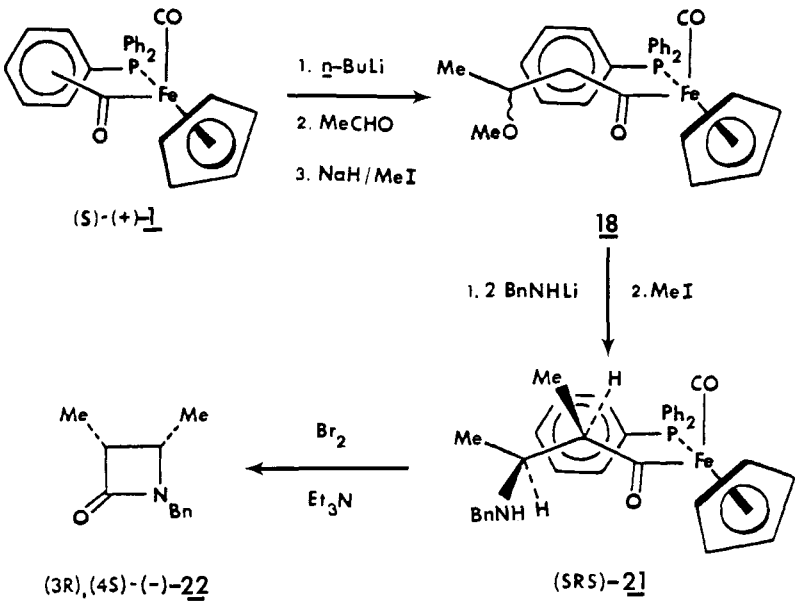


Treatment of the lithium enolate derived from S-(+)-1 with acetaldehyde gave a 1:1 mixture of β-hydroxy complexes which were O-methylated to give 18. Treatment of 18 with two equivalents of butyllithium followed by methyl iodide gave (S,2R,3R)-(+)-19 as essentially a single enantiomer. Oxidative decomplexation of 19 in the presence of benzylamine gave (2R,3R)-(-)-N-benzyl-2,3-dimethylheptanamide 20.

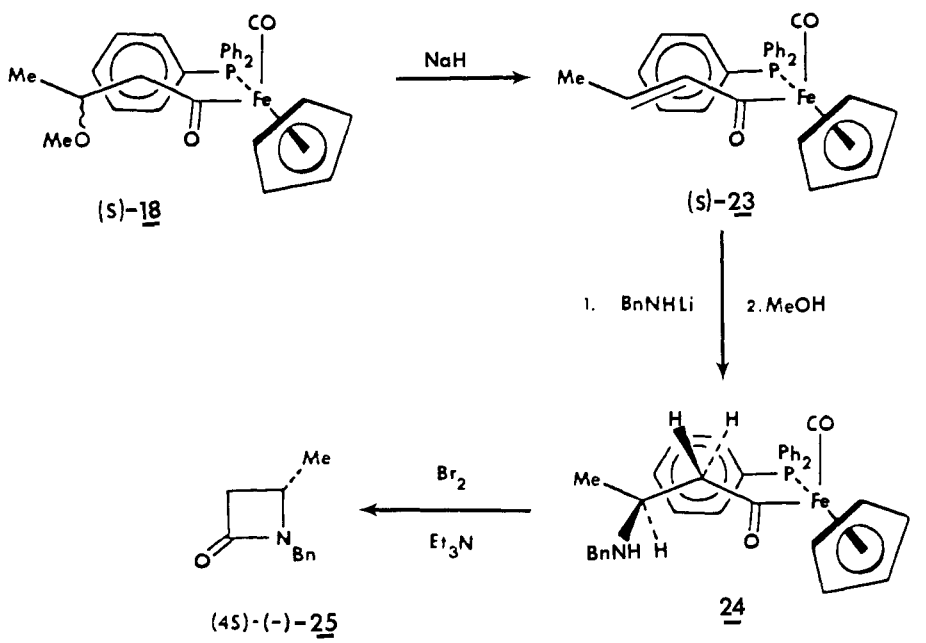


ASYMMETRIC SYNTHESIS OF β-LACTAMS (refs. 13, 14)

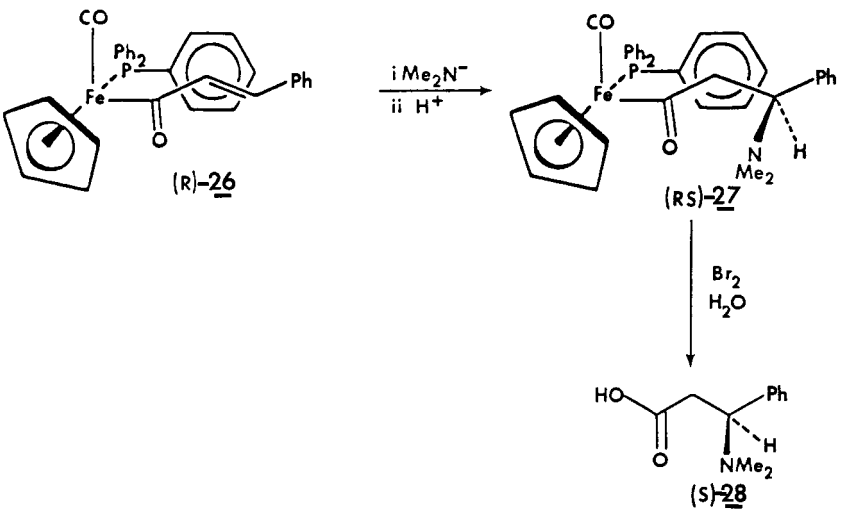
The above stereoselective tandem Michael addition-alkylation methodology may be extended to the formation of β-amino acyl complexes, precursors of β-amino acids[30] and β-lactams.[13,14,16] Thus addition of two equivalents of lithium benzylamide and then methyl iodide to (S)-18 gave the (S)-β-amino-α,β-dimethyl complex 21 as a single diastereoisomer. Decomplexation of 21 with bromine gave (3R,4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 22 essentially optically pure.



On subjection to sodium hydride (S)-18 generated the (S)-E-crotonyl complex 23, which was treated with lithium benzylamide followed by methanol to generate (S,2S)(+)-24 as a single compound. Oxidative decomplexation of 24 gave (4S)-(-)-4-methyl-N-benzyl-β-lactam 25 essentially optically pure.



Addition of lithium dimethylamide to the (R)-E-cinnamoyl complex 26 followed by protonation of the resulting enolate with methanol generated stereoselectively (RS)-27 as the only detectable product. Oxidative decomplexation of (RS)-27 yielded (S)-3-(dimethylamino)-3-phenylpropanoic acid 28.



CONCLUSION

The iron chiral auxiliary is able to exert essentially complete stereochemical control in a variety of carbon-carbon bond forming reactions of attached acyl ligands. The asymmetric syntheses, of (-)-captopril 6, (2R,3R)-(-)-N-benzyl-2,3-dimethylheptanamide 20, (3R,4S)-(-)-cis-3,4-dimethyl-N-benzyl-β-lactam 22, (4S)-(-)-4-methyl-N-benzyl-β-lactam 25, and (S)-3-(dimethylamino)-3-phenylpropanoic acid 28, all from the commercially available parent acetyl complex 1, are described above to illustrate the potential of this methodology. The stereocontrol observed for acyl ligands attached to the iron chiral auxiliary also manifests itself in the reactions of other ligands such as alkoxycarbenes, vinyls etc.[31]

Acknowledgement

The students and post doctoral collaborators responsible for developing this chemistry are named in the references and their efforts are gratefully acknowledged.

REFERENCES

1. S.G. Davies, N. Aktogu, and H. Felkin, Chem.Comm., 1982, 1303.
2. G.J. Baird and S.G. Davies, J.Organometal.Chem., 1983, 248, C1.
3. G.J. Baird, J.A. Bandy, S.G. Davies and K. Prout, Chem.Comm., 1983, 1202.
4. N. Aktogu, H. Felkin, G.J. Baird, S.G. Davies, and O. Watts, J.Organometal.Chem., 1984, 262, 49.
5. S.L. Brown, S.G. Davies, D.F. Foster, J.I. Seeman and P. Warner, Tetrahedron Letters, 1986, 27, 623.
6. S.G. Davies, I.M. Dordor, J.C. Walker and P. Warner, Tetrahedron Letters, 1984, 2709.
7. S.G. Davies, I.M. Dordor and P. Warner, Chem.Comm., 1984, 956.

8. S.G. Davies, I.M. Dordor-Hedgecock and P. Warner, Tetrahedron Letters, 1985, 2125.
9. P.W. Ambler and S.G. Davies, Tetrahedron Letters, 1985, 2129.
10. S.G. Davies, I.M. Dordor-Hedgecock, P. Warner, R.H. Jones and K. Prout, J.Organometal.Chem., 1985, 285, 213.
11. S.G. Davies and J.C. Walker, Chem.Comm., 1985, 209.
12. S.G. Davies and J.C. Walker, Chem.Comm., 1986, 495.
13. S.G. Davies, I.M. Dordor-Hedgecock, K.H. Sutton and J.C. Walker, Tetrahedron Letters, 1986, 27, 3787.
14. S.G. Davies, I.M. Dordor-Hedgecock, K.H. Sutton, J.C. Walker, R.H. Jones and K. Prout, Tetrahedron, 1986, 42, 5123.
15. S.G. Davies and J.C. Walker, Chem.Comm., 1986, 609.
16. L.S. Liebeskind, M.E. Welker and R.W. Fengl, J.Amer.Chem.Soc., 1986, 108, 6328.
17. Chiral Iron Acetyls are available from New Specialities Business, B.P. Chemicals Ltd., Belgrave House, 76, Buckingham Palace Road, London, SW1W OSU U.K.
18. S.G. Davies, I.M. Dordor-Hedgecock, K.H. Sutton, J.C. Walker, C. Bourne, R.H. Jones and K. Prout, Chem.Comm., 1986, 602.
19. S.G. Davies and J.I. Seeman, Tetrahedron Letters, 1984, 1845.
20. J.I. Seeman and S.G. Davies, Chem.Comm., 1984, 1019.
21. S.G. Davies and J.I. Seeman, J.Amer.Chem.Soc., 1985, 107, 6522.
22. J.I. Seeman and S.G. Davies, J.C.S. Dalton, 1985, 2691.
23. S.G. Davies, J.I. Seeman and I.H. Williams, Tetrahedron Letters, 1986, 27, 619.
24. S.G. Davies, I.M. Dordor-Hedgecock, K.H. Sutton, and M. Whittaker, J.Organometal.Chem., 1987, 320, C19.
25. S.G. Davies, I.M. Dordor-Hedgecock, K.H. Sutton and M. Whittaker, Chem and Ind., 1987, 338.
26. B.K. Blackburn, S.G. Davies and M. Whittaker, to be published.
27. G. Bashiardes and S.G. Davies, to be published.
28. S.G. Davies, R.J.C. Easton, J.C. Walker, and P. Warner, J.Organometal.Chem., 1985, 296, C40.
29. S.G. Davies, R.J.C. Easton, J.C. Walker and P. Warner, Tetrahedron, 1986, 42, 175.
30. S.G. Davies and R.J.C. Easton, to be published.
31. G.J. Baird, S.G. Davies, R.H. Jones, K. Prout and P. Warner, Chem.Comm., 1984, 745.
32. P.J. Curtis and S.G. Davies, Chem.Comm., 1984, 747.
33. G.J. Baird, S.G. Davies and T.R. Maberley, Organometallics, 1984, 1764.
34. A.P. Ayscough and S.G. Davies, Chem.Comm., 1986, 1648.