Tetrahedron Letters,Vol.29,No.52,pp 6979-6982,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE ASYMMETRIC SYNTHESIS OF *CIS*-SUBSTITUTED CYCLOPROPANECARBOXYLIC ACID DERIVATIVES

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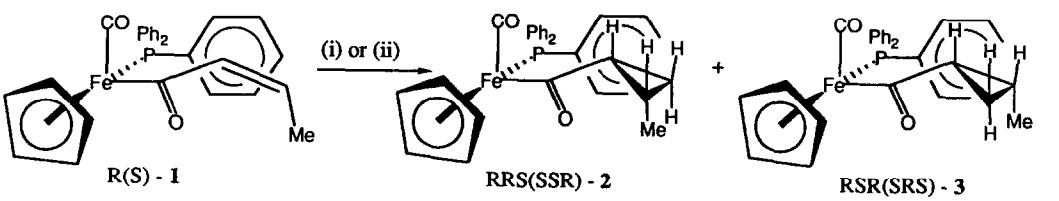
Summary: The asymmetric synthesis of *cis*-substituted cyclopropanecarboxylic acid derivatives is achieved *via* stereoselective electrophilic methylene transfer to Z-α,β-unsaturated acyl ligands bound to the iron chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)].

It is frequently observed that the biological activity of a molecule containing a substituted cyclopropane ring is dependent upon the relative and absolute stereochemistry of the ring.[1] Stereospecific electrophilic methylene additions to olefins (*e.g.* Simmons-Smith reactions) have proved useful in the synthesis of diastereoisomerically pure cyclopropanes. However, these methods are not usually applicable to the direct synthesis of cyclopropanecarboxylic acid derivatives since α,β-unsaturated carbonyl compounds are generally unreactive.[2] Furthermore, relatively few examples of asymmetric variants of this type of reaction have been reported.[3] We describe here the asymmetric synthesis of *cis*-substituted cyclopropanecarboxylic acid derivatives *via* electrophilic methylene addition to α,β-unsaturated acyl ligands attached to the chiral auxiliary [(η^5-C_5H_5)-Fe(CO)(PPh_3)].[4]

Sequential addition of zinc dichloride, diethylzinc and methylene iodide to a solution of racemic (η^5-C_5H_5)Fe(CO)(PPh_3)($COCH{=}CHCH_3$) **1**[5] in toluene at 20°C resulted in a rapid cyclopropanation reaction.[6] The ^{1}H n.m.r. spectrum of the crude product mixture showed the presence of the *cis*-substituted cyclopropyl derivatives **2** and **3** in a ratio of 9:1 and allowed the stereochemistries of **2** and **3** to be assigned as RRS(SSR) and RSR(SRS) respectively. Confirmation of these assignments was provided by correlation to a related compound for which an X-ray crystal structure was available.[7] Similarly, addition of triethylaluminium to a solution of **1** and methylene iodide in toluene at -40°C, and allowing the reaction to warm to 20°C over two hours, also gave only complexes **2** and **3** in an improved ratio of 16:1.[8]

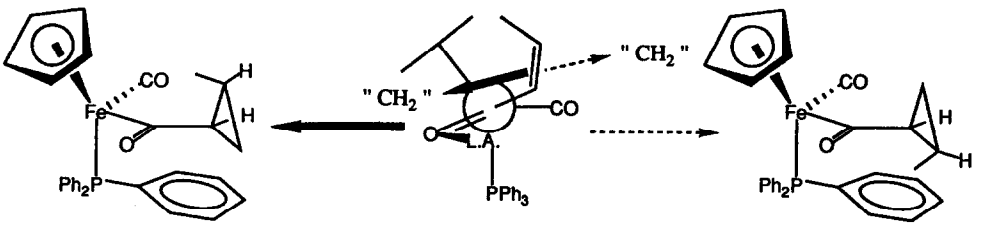


R(S) - **1** RRS(SSR) - **2** RSR(SRS) - **3**

(i) $4ZnCl_2$ / $1.5Et_2Zn$ / $4CH_2I_2$ (91%) 9 : 1

(ii) $4CH_2I_2$ / $4Et_3Al$ (74%) 16 : 1

The observed stereoselectivity is consistent with Lewis acid coordination to the acyl oxygen introducing interactions with the *cis*-β-substituent which force the olefinic bond to adopt a conformation approximately orthogonal to the acyl group. The olefinic bond is thus rendered more nucleophilic, accounting for the rapid reaction, and the electrophile approaches preferentially the face of the olefinic bond not shielded by the iron auxiliary, resulting in the stereoselective synthesis of **2** (Figure).

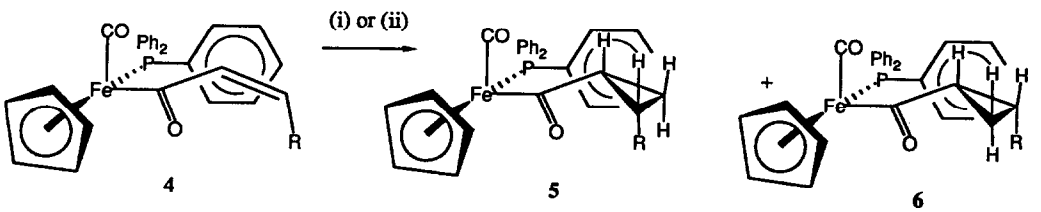


RRS(SSR) - 2 RSR(SRS) - 3

Figure: The stereoselective synthesis of RRS(SSR)-2.

Increasing the size of the β-substituent on the Z-α,β-unsaturated iron acyl complexes led to increased stereoselectivities (Table).

Table: Stereoselectivities (ratio 5:6) observed in methylene addition reactions of Z-α,β-unsaturated iron acyl complexes.

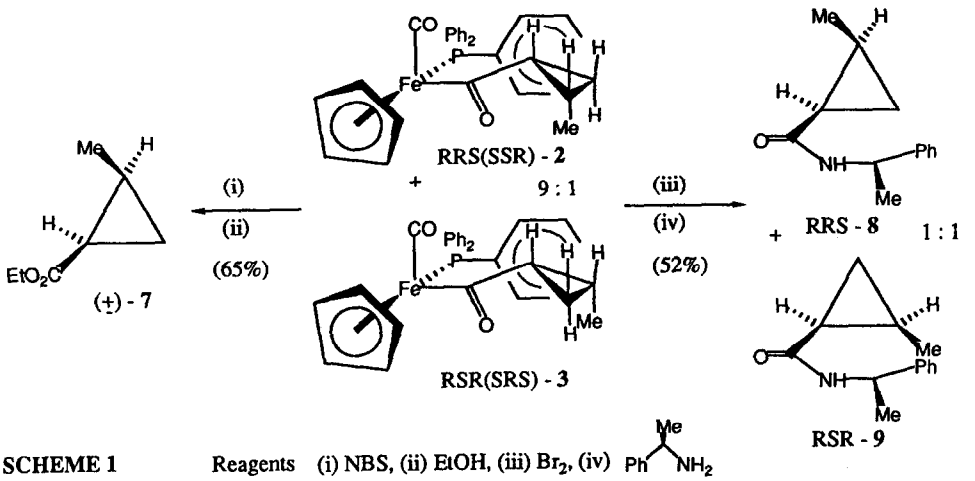


4	(i) $4ZnCl_2$ / $1.5Et_2Zn$ / $4CH_2I_2$		(ii) $4CH_2I_2$ / $4Et_3Al$	
R	Ratio 5:6	Yield / %	Ratio 5:6	Yield / %
Me	9:1	91	16:1	74
nPr	14:1	91	18:1	86
nBu	16:1	95	19:1	62
iPr	24:1	93	24:1	49

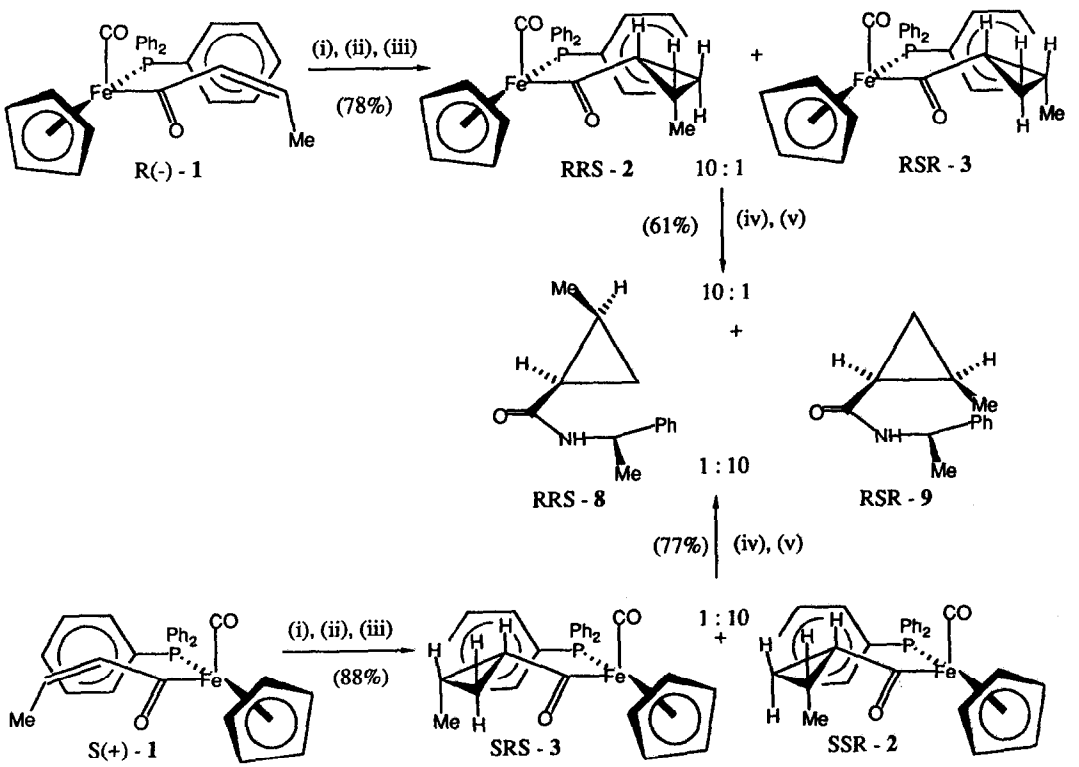
Decomplexation of the mixture of *cis*-methyl substituted complexes **2** and **3** with N-bromosuccinimide in ethanol gave exclusively the corresponding racemic *cis*-substituted cyclopropanecarboxylic ester **7** (Scheme 1). The diastereospecific synthesis of **7** contrasts with previous routes to this, and related, compounds in which *cis/trans* mixtures of the esters are synthesised and subsequently separated.[9] Decomplexation of **2** and **3** (2:3= 9:1) with bromine in the presence of R(+)-1-phenylethylamine gave the *cis*-substituted diastereoisomeric amides **8** and **9** as a 1:1 mixture (Scheme 1). The isolation of a 1:1 diastereoisomeric mixture of **8** and **9** demonstrates an equal rate of formation under the reaction conditions and that no diastereoisomeric separation occurs on work up .

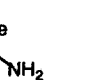
The use of homochiral R(-)-**1** allowed the stereoselective synthesis of the amide **8**. Hence treatment of R(-)-**1** with zinc dichloride, diethylzinc and methylene iodide, as before, gave a 10:1 mxture of RRS-**2**:RSR-**3** (Scheme 2). Decomplexation in the presence of R(+)-1-phenylethylamine gave a 10:1 mixture of RRS-**8**:RSR-**9**. Similar treatment of S(+)-**1** resulted in the synthesis of a 10:1 mixture of RSR-**9**:RRS-**8**. The results show that by the use of homochiral starting materials the enantioselective syntheses of cyclopropanecarboxylic acid derivatives can be achieved in which the enantiomeric ratios will equal the diastereoisomeric ratios (Table) of the intermediate iron acyl complexes.

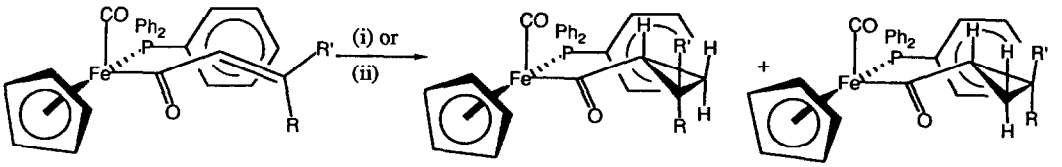
The cyclopropanation reactions described previously were repeated with the complexes E-(η^5-C_5H_5)-Fe(CO)(PPh3)(COCH=CHCH3) **10** and (η^5-C_5H_5)Fe(CO)(PPh_3)(COCH=C(CH_3)$_2$) **11** and the results are shown in scheme 3.



SCHEME 1 Reagents (i) NBS, (ii) EtOH, (iii) Br_2, (iv)



SCHEME 2 Reagents (i) $4ZnCl_2$, (ii) $1.5Et_2Zn$, (iii) $4CH_2I_2$, (iv) Br_2, (v) 



R = H, R' = Me, **10**	(i)	(63%)	1.3 : 1
	(ii)	(11%)	1 : 1
R = Me, R' = Me, **11**	(i)	(89%)	11 : 1
	(ii)	(80%)	30 : 1

SCHEME 3 Reagents : (i) $4ZnCl_2$ / $1.5Et_2Zn$ / $4CH_2I_2$ (ii) $4CH_2I_2$ / $4Et_3Al$

The results demonstrate that a *cis*-β-substituent is essential for the diastereoselective cyclopropanation reaction to occur, an observation consistent with the previous analysis.

The stereospecific synthesis of *cis*-substituted cyclopropanecarboxylic acid derivatives *via* the use of Z-α,β-unsaturated iron acyl complexes has been demonstrated. The use of homochiral starting materials allows asymmetric syntheses of these compounds to be achieved. The asymmetric synthesis of the corresponding *trans*-isomers could not be achieved by this methodology and alternative routes to these compounds are described in the following paper.

References

1. For examples see: **a)** D.W. Graham, W.T. Ashton, L. Barash, J.E. Brown, R.D Brown, L.F. Canning, A. Chen, J.P. Springer and E.F. Rogers, *J. Med. Chem.*, 1987, *30*, 1074. **b)** R. Pellicciari, B. Natalini, S. Cecchetti, B. Porter, A. Roda, B. Grigolo and R. Balducci, *J. Med. Chem.*, 1988, *31*, 730. **c)** P.E. Burt, M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, *Pesticide Sci.*, 1974, *5*, 791.

2. H.E. Simmons, T.L. Cairns, S.A. Vladuchick and C.M. Hoiness, *Org. React.*, 1973, *20*, 1.

3. a) A. Nakamura, A. Konishi, Y. Tatsuno and S. Otsuka, *J. Am. Chem. Soc.*, 1978, *100*, 3443. **b)** T. Aratani, *Pure Appl. Chem.*, 1985, *57*, 1845. **c)** H. Fritschi, U. Leutenegger and A. Pfalz, *Angew. Chem. Int. Ed. Engl.*, 1986, *25*, 1005. **d)** M.D. Cooke and E.O. Fischer, *J. Organomet. Chem.*, 1973, *56*, 279. **e)** A. Davison, W.C. Krusell and R.C. Michaelson, *J. Organomet. Chem.*, 1974, *72*, C7. **f)** T.C Flood, F.J. DiSanti and D.L. Miles, *Inorg. Chem.*, 1976, *15*, 1910. **g)** M. Brookhart, D. Timmers, J.R. Tucker, G.D. Williams, G.R. Husk, H. Brunner and B. Hammer, *J. Am. Chem. Soc.*, 1983, *105*, 6721. **h)** S. Sawada, J. Oda and Y. Inouye, *J. Org. Chem.*, 1968, *33*, 2141. **i)** S. Sawada, K. Takehana and Y. Inouye, *J. Org. Chem.*, 1968, *33*, 1767. **j)** C.R. Johnson and M.R. Barbachyn, *J. Am. Chem. Soc.*, 1982, *104*, 4290. **k)** E.A. Mash, K.A. Nelson and P.C. Heidt, *Tetrahedron* , 1987,*28*,1865. **l)** I. Arai, A.Mori and H. Yamamoto, *Tetrahedron*, 1986, *42*, 6447.

4. S.G. Davies, I.M. Dordor-Hedgecock, R.J.C. Easton, S.C. Preston, K.H. Sutton and J.C. Walker, *Bull. Soc. Chim. Fr.*, 1987, 608.

5. S.G. Davies, R.J.C. Easton, J.C. Walker and P. Warner, *Tetrahedron*, 1986, *42*, 175.

6. J. Furakawa. N. Kawabata and J. Nishimura, *Tetrahedron*, 1968, *24*, 53.

7. P.W. Ambler, S.G. Davies and K.H. Sutton, unpublished results.

8. K.Maruoka, Y. Fukutani and H. Yamamoto, *J. Org. Chem.*, 1985, *50*, 4412.

9. For examples see: **a)** M.P. Doyle, R.L. Dorow, W.E. Buhro, J.H. Griffin, W.H. Tamblyn and M.L. Trudell, *Organometallics*, 1984, *3*, 44. **b)** H.J. Callot, F. Metz and C. Piechocki, *Tetrahedron*, 1982, *38*, 2365. **c)** M. Julia and C. Descoins, *Bull. Soc. Chim. Fr.*, 1970, 1805. **d)** Y. Kusuyama, *Bull. Chem. Soc. Jpn.*, 1979, *52*, 1944.

(Received in UK 29 September 1988)