Kinetic Resolution of the Chiral Iron Acetyl [Fe(η⁵-C_5H_5)(CO)(PPh_3)COMe]

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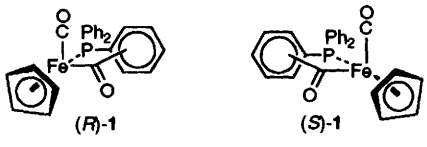
The chiral discrimination displayed between the enolate derived from (*RS*)-[Fe(η⁵-C_5H_5)(CO)(PPh_3)COMe] and (1*R*)-(+)-camphor furnishes a practical route to homochiral (*R*)-[Fe(η⁵-C_5H_5)(CO)(PPh_3)COMe] *via* a kinetic resolution protocol, while a retro-aldol reaction of the diastereoisomerically pure aldol addition product of this kinetic resolution sequence provides a complementary route to the opposite enantiomer (*S*)-[Fe(η⁵-C_5H_5)(CO)(PPh_3)COMe].

The iron chiral auxiliary [Fe(η⁵-C_5H_5)(CO)(PPh_3)] exerts powerful stereocontrol over a wide variety of reactions associated with attached acyl fragments.[1] In order to realise fully the potential of this chiral auxiliary in asymmetric synthesis, practical routes to the parent acetyl complex [Fe(η⁵-C_5H_5)(CO)(PPh_3)COMe] **1** in homochiral (enantiomerically pure) form are required. Since the original procedures[2] for the preparation of the homochiral complex **1** provide only very limited access to these materials, we have been investigating a series of alternative procedures.[3] The iron chiral auxiliary [Fe(η⁵-C_5H_5)(CO)(PPh_3)] has been reported to undergo reactions which involve remarkable degrees of chiral recognition.[4,5] For example,[5] treatment of the lithium enolate generated from (*S*)-**1**, with racemic propylene oxide in the presence of diethylaluminium chloride leads to a selective reaction whereby only the (*R*)-enantiomer of the epoxide reacts with the homochiral enolate, to form the corresponding (*S*,*R*)-4-hydroxypentanoyl complex. Herein, we describe the high enantiomeric discrimination that can be achieved in the aldol addition of the lithium enolate derived from **1** and camphor, which culminates in a simple and practical method for the kinetic resolution of the chiral iron acetyl complex [(*RS*)-Fe(η⁵-C_5H_5)(CO)(PPh_3)COMe] **1**.

Treatment of the lithium enolate derived from racemic iron acetyl complex (*RS*)-**1** and butyl lithium at −78 °C with racemic (1*RS*)-camphor gave only one diastereoisomer (>100 : 1; 500 MHz ^{1}H NMR) of the aldol addition product **2** (40% yield by ^{31}P NMR of the crude reaction mixture) together with recovered iron acetyl complex **1** (60% by ^{31}P NMR of the crude reaction mixture). The high diastereoselectivity observed in the aldol product in this all racemic case is indicative of efficient chiral discrimination (relative rates between matched and mismatched pairs > 100 : 1) while recovery of iron acetyl suggests deprotonation of camphor competes with the aldol addition under these reaction conditions.

The relative stereochemistries within the product **2** were assigned as ($S_{Fe}R_{Fe}$,1*RS*,2*SR*,4*RS*) on the assumption that only *endo* addition to camphor had occurred[6] since homochiral (*S*)-**1** reacted with homochiral (1*R*)-(+)-camphor† to give the same diastereoisomer (S_{Fe},1*R*,2*S*,4*R*)-**2** (48% isolated yield) while little reaction was observed, producing < 5% of (R_{Fe},1*R*,2*S*,4*R*)-**3**, with homochiral (*R*)-**1** under the same conditions. These assignments were later unambiguously confirmed‡ by X-ray crystal structure analyses of both homochiral (S_{Fe},1*R*,2*S*,4*R*)-**2** and (R_{Fe},1*R*,2*S*,4*R*)-**3**.

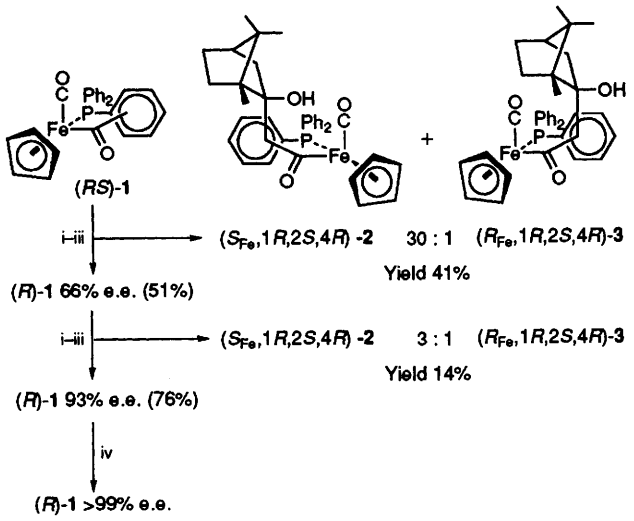
The very high chiral discrimination observed in the all racemic case described above suggests that it should be possible to kinetically resolve the racemic iron acetyl **1** with homochiral camphor. Thus, treatment of (1*R*)-(+)-camphor with the lithium enolate derived from (*RS*)-**1** afforded a 30 : 1§ mixture of the diastereoisomeric aldol products (S_{Fe},1*R*,2*S*,4*R*)-**2** and (R_{Fe},1*R*,2*S*,4*R*)-**3**, respectively (Scheme 1). Enantiomerically enriched (*R*)-**1** [66% enantiomene excess (e.e.)] could be recovered from the crude reaction mixture *via* chromatography on SiO_2 [EtOAc–light petroleum ether (40–60 °C), 1 : 15 → 1 : 3 v/v]. Further amplification of the e.e. of (*R*)-**1** was achieved by retreatment of the lithium enolate of this scalemic mixture with (1*R*)-(+)-camphor. (*R*)-**1** was recovered with an e.e. of 93%, and was rendered homochiral (>99% e.e.) after a single crystallisation (hexane–$CHCl_3$). The chiral shift reagent (*S*)-(+)-1-(9-



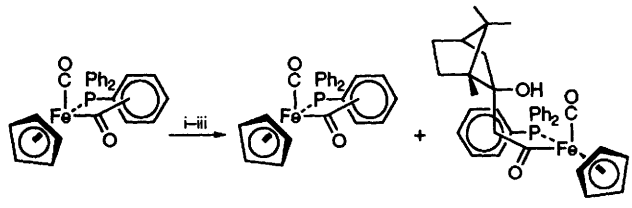
† (1*R*)-(+)-camphor is the trivial name given to (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one.

‡ Complexes **1**, **2** and **3** were fully characterised by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy, microanalysis and X-ray crystal structure analysis.

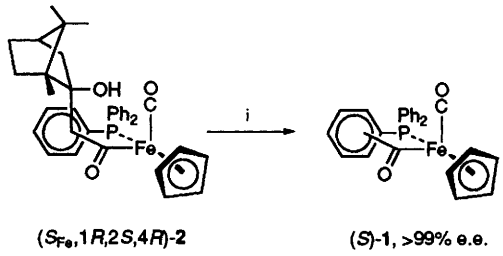
§ The change in diastereoselectivity from 100 : 1 in the all racemic case to 30 : 1 in the homochiral plus racemic case is consistent with mass action operating in the latter case but not in the former.



Scheme 1 The sequential kinetic resolution of (*RS*)-**1**. *Reagents*: i, BuLi, THF, −78 °C; ii, (1*R*)-(+)-camphor; iii, MeOH; iv, recrystallise.



Scheme 2 The kinetic resolution of (*RS*)-**1**. *Reagents*: i, BuLi, LiCl (1.5 equiv.), THF, −78 °C; ii, (1*R*)-(+)-camphor; iii, MeOH.



Scheme 3 The synthesis of (*S*)-**1** from (S_{Fe}, 1*R*,2*S*,4*R*)-**2**. *Reagents*: i, NaH, or NaOMe, 1.5 h, THF, heat.

anthryl)-2,2,2-trifluoroethanol, was used to establish that the recovered iron complex (*R*)-**1** was homochiral.¶ Overall, 19–36%‖ homochiral (*R*)-**1** {$[\alpha]^{25}_{546}$ − 288 (*c* 0.04, C_6H_6)}[7] was recovered from the starting racemate (*RS*)-**1**, using (1*R*)-(+)-camphor in a sequential kinetic resolution protocol.

The sequential kinetic resolution protocol is necessary despite the high enantiomeric discrimination, because of the competing protonation reaction of the enolate by the camphor. However the efficiency of the resolution methodology described here may be enhanced significantly by the addition of lithium chloride.[8] Thus, generation of the enolate from (*RS*)-**1** with butyl lithium in the presence of 1.5 equiv.** of lithium chloride, followed by treatment with (1*R*)-(+)-camphor, affords (*R*)-**1** with an e.e. of 91% (Scheme 2). A single crystallisation from hexane–$CHCl_3$ affords the homochiral (*R*)-**1** in one step, in an overall yield‖ of 20–35%. The aldol product (S_{Fe},1*R*,2*S*,4*R*)-**2**, is recovered from the reaction mixture in > 96% d.e. (diastereoisomeric excess).

A retro-aldol reaction was next developed to regenerate (*S*)-**1** from the aldol product. Pure diastereoisomer (S_{Fe},1*R*,2*S*,4*R*)-**2**, may be crystallised from a mixture of **2** and **3** (30 : 1) in dichloromethane, using hexane. Treatment of a refluxing tetrahydrofuran (THF) solution of (S_{Fe},1*R*,2*S*,4*R*)-**2** with base [NaH (3 equiv.) or NaOMe (1 equiv.)] afforded, after 1.5 h, the iron acetyl complex (*S*)-**1** (Scheme 3). Flash chromatography (SiO_2, hexane–EtOAc; 3 : 1 v/v) of the crude reaction mixture furnished (*S*)-**1** in 87% yield. The chiral shift reagent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol,¶ was used to establish that the recovered iron complex (*S*)-**1** was homochiral, thus indicating that racemisation does not occur under these reaction conditions.

In conclusion, a complementary and efficient route to both the enantiomers (*R*)-**1** and (*S*)-**1**, has been developed, starting from the racemate (*RS*)-**1**. Using (1*R*)-(+)-camphor in a kinetic resolution protocol, homochiral (*R*)-**1** may be obtained in 20–35% overall yield,‖ after recrystallisation, in a single step from (*RS*)-**1**. The retro-aldol reaction of the recovered diastereoisomer (S_{Fe},1*R*,2*S*,4*R*)-**2**, furnishes the complementary enantiomer, homochiral (*S*)-**1**.

We thank Roussel Laboratories Limited for a studentship (to S. C. C-G) and the SERC for support (to J. F. C).

Received, 21st July 1993; Com. 3/04324J

References

1 S. G. Davies, *Aldrichimica Acta*, 1990, **23**, 31.
2 H. Brunner and E. Schmidt, *J. Organomet. Chem.*, 1972, **36**, C18; H. Brunner and E. Schmidt, *J. Organomet. Chem.*, 1973, **50**, 219; H. Brunner and J. Strutz, *Z. Naturforsch., Teil B*, 1974, **29**, 446.
3 R. W. Baker and S. G. Davies, *Tetrahedron Asymmetry*, 1993, **4**, 1479.
4 S. P. Collingwood, S. G. Davies and S. C. Preston, *Tetrahedron Lett.*, 1990, **31**, 4067; S. L. Brown, S. G. Davies, P. Warner, R. H. Jones and K. Prout, *J. Chem. Soc., Chem. Commun.*, 1985, 1446; S. G. Davies, D. Middlemiss, A. Naylor and M. Wills, *Tetrahedron Lett.*, 1989, **30**, 587; S. G. Davies, R. Polywka and P. Warner, *Tetrahedron*, 1990, **46**, 4847.
5 S. G. Davies and P. Warner, *Tetrahedron Lett.*, 1985, **26**, 4815.
6 The ability of the *syn* C_7 methyl group of camphor to block the *exo* attack of nucleophiles is well documented. E.g., see E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, 1975, **75**, 521; J. R. Boone and E. C. Ashby, in *Topics in Stereochemistry*, ed. N. L. Allinger and E. L. Eliel, Interscience, New York, 1981, vol. 11, ch. 2.
7 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.
8 The discovery that the addition of LiCl can effect the selectivity of reactions associated with lithium enolates is not new. For an excellent review, see D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1624. For a recent example of the LiX effect, see B. J. Bunn and N. S. Simpkins, *J. Org. Chem.*, 1993, **58**, 533, and references cited therein.

¶ A threefold mass equivalent of the chiral shift reagent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol was added to a C_6D_6 solution of the iron acetyl complex (5–7 mg). Δδ for the resonance arising from the acetyl methyl group is approximately 0.1 ppm (300 MHz). Under these conditions, the singlet associated with the methyl group of (*S*)-**1** resonates downfield (δ 2.5) of the corresponding signal arising from (*R*)-**1**(δ 2.4).

‖ Based upon a maximum yield of 50% for a single enantiomer of the starting racemate. Overall yield depends upon the efficiency of the final crystallisation.

** Preliminary investigations suggest that the optimum e.e. of recovered (*R*)-**1** is achieved with 1.5 equiv. of LiCl. The following equivalents of LiCl afford (*R*)-**1** with the stated e.e.s: 0.5, 81%; 1.0, 63%; 1.5, 91%; 2.0, 74%; 10.0, 65%.