PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Asymmetric Synthesis via Chiral Transition Metal Auxiliaries [and Discussion]

S. G. Davies, G. Bashiardes, R. P. Beckett, S. J. Coote, Isabelle M. Dordor-Hedgecock, C. L. Goodfellow, G. L. Gravatt, J. P. McNally, M. Whittaker and M. T. Reetz

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Asymmetric synthesis via chiral transition metal auxiliaries

By S. G. Davies, G. Bashiardes, R. P. Beckett, S. J. Coote, Isabelle M. Dordor-Hedgecock, C. L. Goodfellow, G. L. Gravatt, J. P. McNally and M. Whittaker

Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

Stoichiometric reagents for the control of the absolute stereochemistry of new chiral centres produced during reactions involving carbon–carbon bond formation are described.

Chiral iron acyl reagents act as chiral equivalents of a variety of carbonyl functionalities and their potential for asymmetric synthesis can be illustrated for pseudopeptides, amino acids, β-lactams, γ-lactams and lactones.

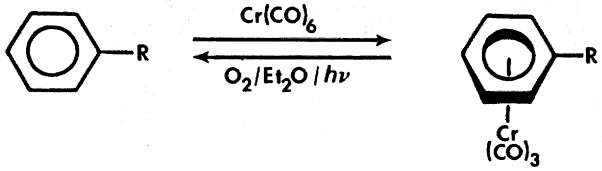
A simple methodology based on arene chromium tricarbonyl chemistry allows the elaboration of benzylic chiral centres with complete control over the absolute stereochemistry. This may be illustrated, for example, by the conversion of amphetamine derivatives into pseudoephedrines.

1. Introduction

The two enantiomers of a chiral organic molecule often exhibit different pharmacological effects. This is one of the major reasons why the search of novel general methods for the synthesis of enantiomerically pure organic molecules is at the cutting-edge of modern chemical research. Organo-transition metal chemistry offers unique opportunities for the control of stereochemistry in synthesis. Two approaches will be demonstrated. Arene chromium tricarbonyl mediated amplification of chirality may be employed to increase the number of chiral centres in readily available natural products containing only a single chiral centre. The chiral iron auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$ can be used to control the relative and absolute stereochemistry of all the chiral centres required in the target molecules.

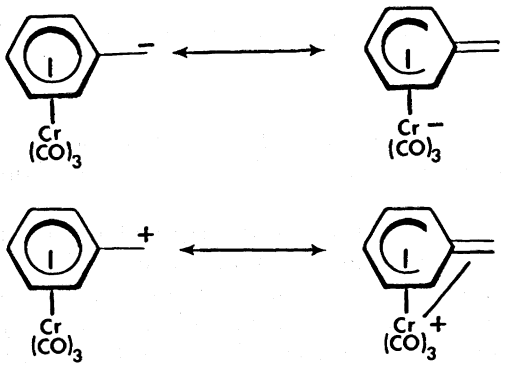
2. Arene chromium tricarbonyl complexes

Arene chromium tricarbonyl complexes are generally easy to prepare by thermolysis of chromium hexacarbonyl, a white air-stable solid, with the arene in di-*n*-butyl ether containing 10% tetrahydrofuran (scheme 1). Complexation of arenes to chromium tricarbonyl markedly alters their chemical properties. Of relevance to the following discussion is the fact that the



Scheme 1

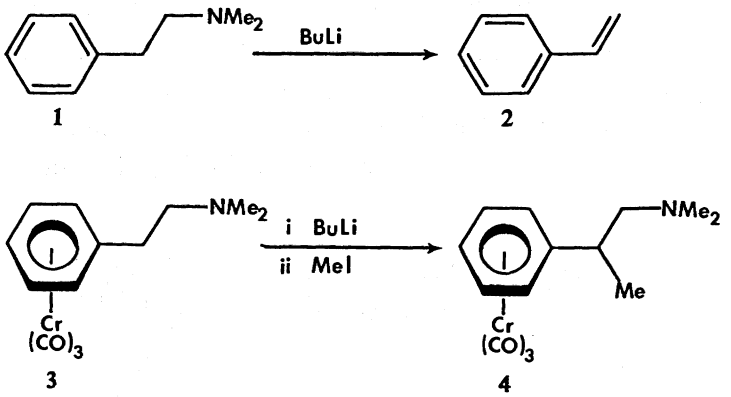
chromium tricarbonyl moiety is capable of stabilizing both benzylic carbanions and benzylic carbonium ions by resonance effects. The reactivity of such charged intermediates and the stereochemistry of their reactions is best understood in terms of the resonance structures that possess an *exocyclic* methylene (scheme 2). Finally decomplexation of arene chromium tricarbonyl complexes is readily achieved by exposure of diethyl ether solutions to air and sunlight (scheme 1).



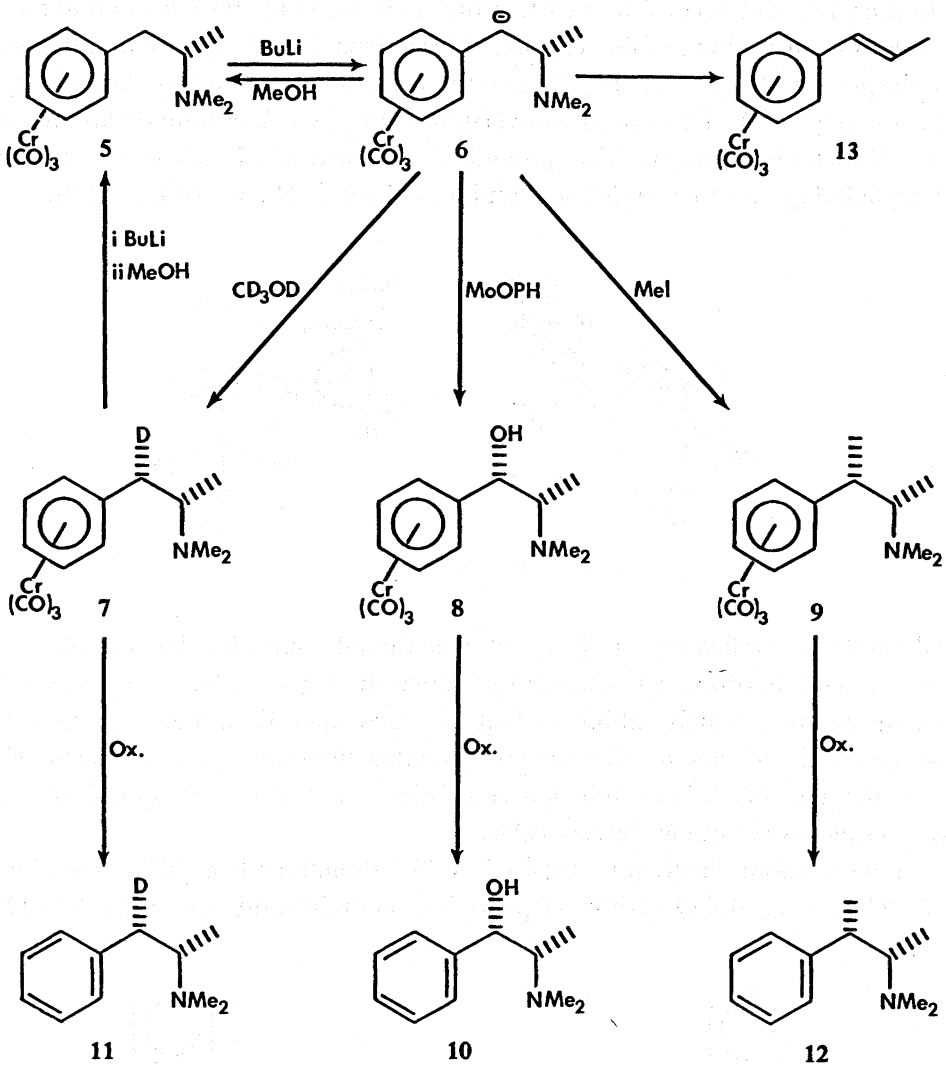
SCHEME 2

The stabilization of benzylic carbanions derived from arenes complexed to chromium tricarbonyl may be demonstrated by consideration of the reaction of β-phenylethylamines with strong base. Addition of butyllithium to *N*,*N*-dimethyl-β-phenylethylamine **1** at −78 °C results in the rapid formation of styrene **2** presumably via initial formation of a benzylic carbanion followed by elimination of the β-amino group. In contrast, addition of butyllithium to the complex **3** results in exclusive formation of the benzylic carbanion, which is now stable over long periods to elimination, and which may be trapped by appropriate electrophiles such as methyl iodide to give **4** (scheme 3).

Thermolysis of chromium hexacarbonyl with (*S*)-(+)-*N*,*N*-dimethylamphetamine gave complex **5** as a relatively air-stable fluorescent yellow crystalline solid (scheme 4). On addition of butyllithium, solutions of **5** became incarnidine, a colour characteristic of benzylic carbanion formation. The carbanion **6** was stable below −40 °C and could be trapped by a variety of electrophiles including H^+(MeOH; to regenerate **5**), $D^+(CD_3OD)$, OH^+(MoOPH) or methyl



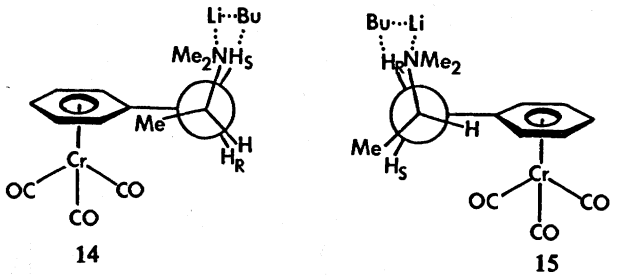
SCHEME 3



SCHEME 4

iodide. Thus complexes **7**, **8** and **9** were formed in this manner. The reactions were completely stereoselective **7**, **8** and **9** each being produced as single diastereoisomers. The relative and absolute stereochemistry of complex **8** was assigned by decomplexation to the free arene **10**, which proved identical in every respect, including optical rotation, to an authentic sample of *N*-methylpseudoephedrine and clearly different from an authentic sample of the epimer *N*-methylephedrine. The assignment was double checked by establishing that **8** was identical to the complex derived directly from authentic *N*-methylpseudoephedrine and non-identical to that derived directly from authentic *N*-methylephedrine. The relative and absolute configurations of **7**, **9**, **11** and **12** were assigned by analogy with **8** and **10**. Above −40 °C, **6** undergoes elimination to the β-methylstyrene complex **13**. Treatment of complex **7** with butyllithium followed by a methanol quench regenerated the starting complex **5** containing no deuterium. Thus both steps, the deprotonation and the addition of electrophiles, are completely stereoselective. These results demonstrate the completely stereoselective substitution of the *pro-R*-hydrogen in complex **5** with retention of configuration. The selective removal of

the *pro-R*-hydrogen from **5** is consistent with initial chelation of the butyllithium to the nitrogen lone pair resulting in unfavourable eclipsing interactions for all transition states leading to removal of the *pro-S*-hydrogen, e.g. **14**, whereas those leading to removal of the *pro-R*-hydrogen, e.g. **15**, do not (figure 1). The overall conversion of (*S*)-(+)-*N*,*N*-dimethylamphetamine to (1*S*,2*S*)-(+)-*N*-methylpseudoephedrine provides a chemical mimic of the enzymic hydroxylation of 2-arylethylamines to 1-arylethanolamines (Blagg & Davies 1985, 1987).

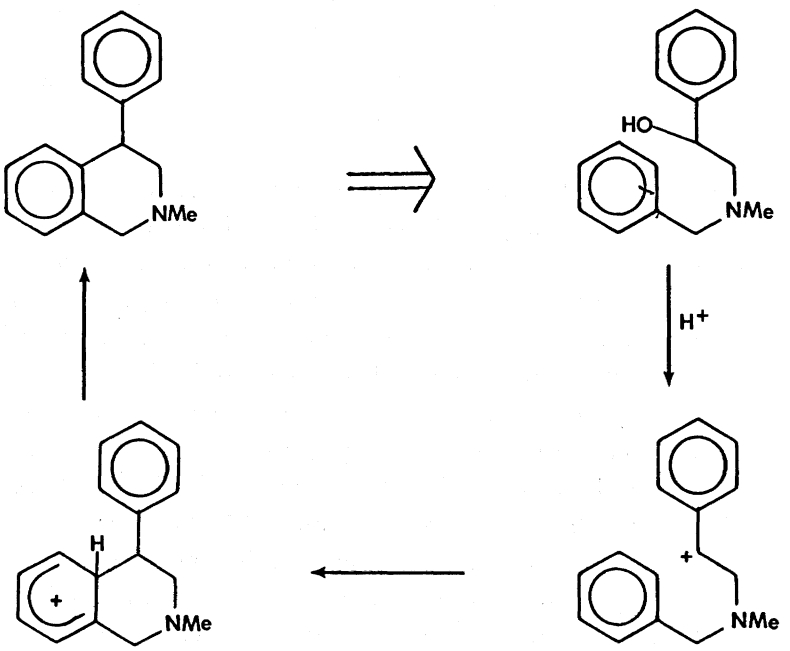


14 15

FIGURE 1

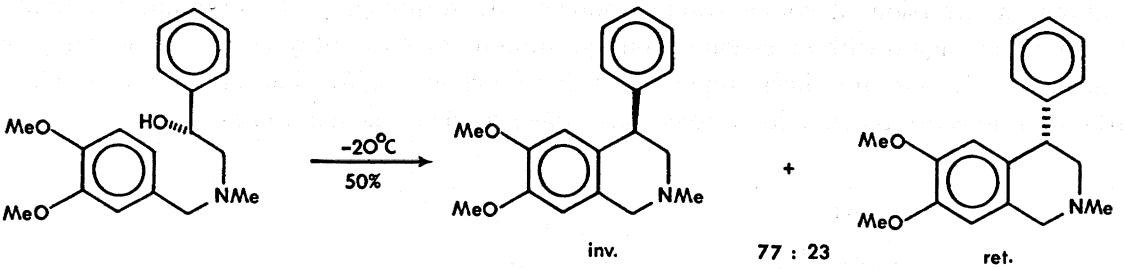
The acid-catalysed cyclization of *N*-benzylphenethanolamines has been implicated in the biosynthesis of 4-aryltetrahydroisoquinolines (Fuganti 1975). Most syntheses of 4-aryltetrahydroisoquinolines, which exhibit potent pharmacological properties, are based on a biomimetic approach (scheme 5). We have investigated the stereochemical course of the acid catalysed cyclization of *N*-benzylphenethanolamines and the corresponding chromium tricarbonyl complexes (Coote & Davies 1988).

Treatment of enantiomerically pure (*S*)-(−)-*N*-(3,4-dimethoxybenzyl)halostachine **16** with acid at −20 °C gave (*R*)-6,7-dimethoxy-4-phenyl-*N*-methyltetrahydroisoquinoline **17** in 54 %



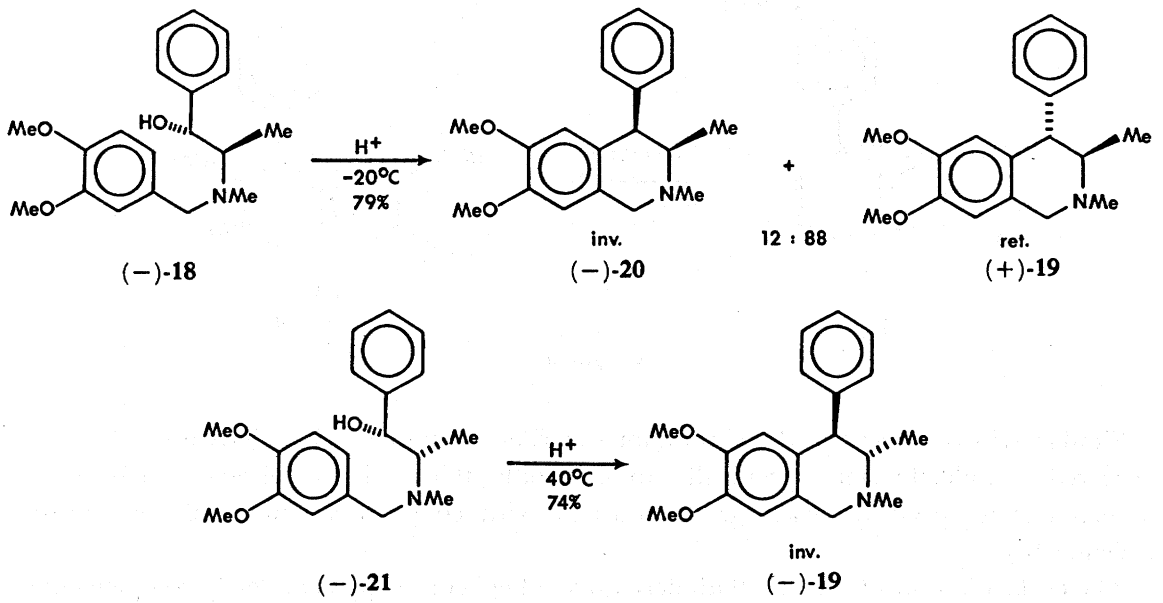
SCHEME 5

e.e. (scheme 6). This was consistent with the reactions proceeding with 77% inversion of configuration. If a free benzylic carbonium ion were an intermediate in this process complete racemization would be expected. The observed preponderance for inversion of configuration is consistent with neighbouring group participation by the *N*-benzyl group in the ionization of the benzyl hydroxyl group competing with the spontaneous ionization route.



SCHEME 6

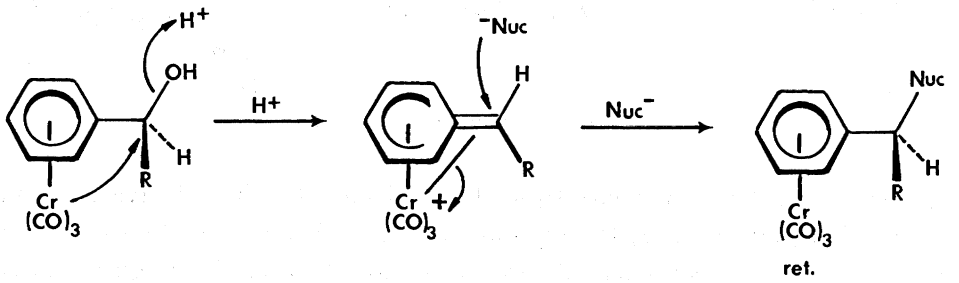
Heating (−)-*N*-(3,4-dimethoxybenzyl)pseudoephedrine **18** with acid gave a 7:1 mixture of the *trans*- and *cis*-4-phenyltetrahydroisoquinolines (+)-**19** and (−)-**20** (scheme 7). Preferential formation of diastereoisomer **19** corresponds to retention of configuration. Although the β-chiral centre in **18** will remain intact during the reaction thereby acting as an internal monitor of the α-stereochemistry it will not remain passive. Thus neighbouring group participation in the ring closure reaction of **18** will be disfavoured by eclipsing interactions involving the β-methyl group whereas the same interactions will favour intramolecular trapping of a free benzylic carbonium ion from the face leading to the thermodynamically more stable *trans*-isomer **19**. Similar acid treatment of (−)-*N*-(3,4-dimethoxybenzyl)ephedrine **21** gave only a single diastereoisomer *trans*-(−)-**19** corresponding to complete inversion of configuration



SCHEME 7

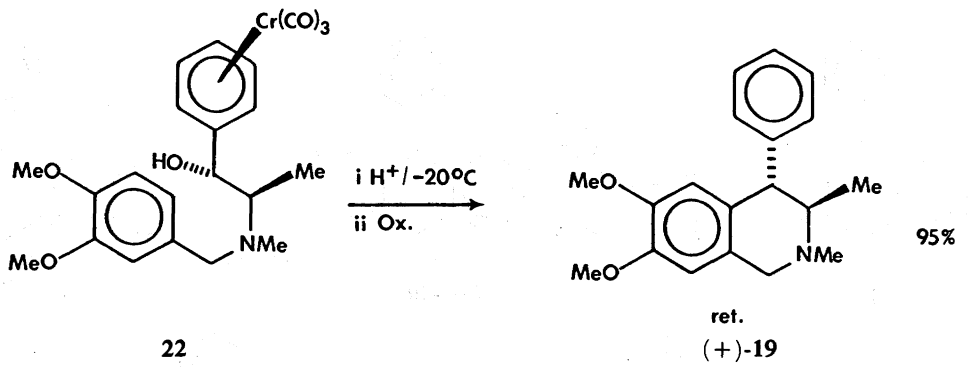
(scheme 7). In this case the conformational restriction imposed by the β-methyl group reinforces the neighbouring group participation in the ring closure (Coote & Davies 1988).

Acid-promoted benzylic substitution reactions of (benzyl alcohol)chromium tricarbonyl complexes proceed with retention of configuration in cases where the benzylic hydroxyl group can adopt a conformation close to antiperiplanar to the arene chromium tricarbonyl axis (Top & Jaouen 1981). This is consistent with participation by the chromium in the initial ionization resulting in inversion of configuration, followed by trapping of the chromium-stabilized carbonium ion again with inversion of configuration to give overall retention of configuration (scheme 8). It has also been reported (Uemura *et al.* 1986) that chromium-stabilized carbonium ions are reactive intermolecularly towards electron-rich arenes.



Scheme 8

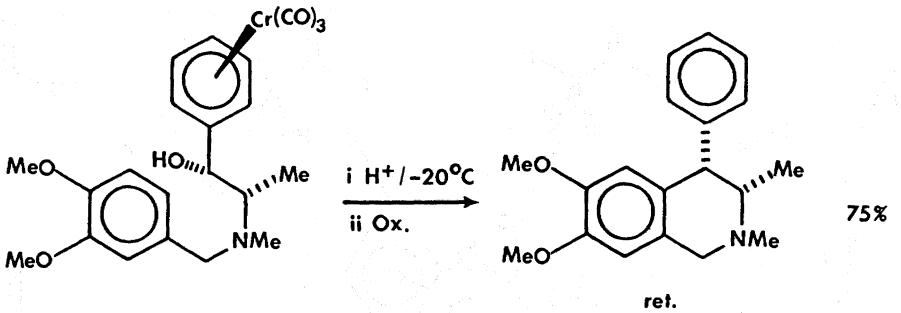
Treatment of the chromium tricarbonyl complex **22**, a derivative of **18**, with acid gave, after decomplexation, only the *trans*-diastereoisomer (+)-**19**. The stereospecificity of this reaction corresponded as expected to complete retention of configuration, i.e. double inversion at the benzylic centre (scheme 9).



Scheme 9

Similar acid treatment of the chromium tricarbonyl complex **23**, a derivative of **21**, also occurred completely stereospecifically to give only the *cis*-diastereoisomer (+)-**20**. The observed stereospecificity was again consistent with complete retention of configuration (scheme 10).

The cyclizations of **21** and **23**, both derivatives of ephedrine are completely complementary producing from (−)-ephedrine the *trans*- and *cis*-2,3-dimethyl-4-phenyl-6,7-dimethoxytetra-

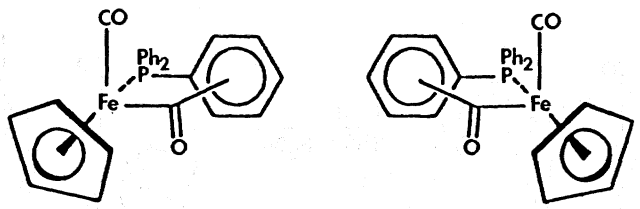


SCHEME 10

hydroisoquinolines (−)-**19** and (+)-**20** respectively. The cyclizations of **21** and **22** are also complementary, producing (−)- and (+)-*trans*-2,3-dimethyl-4-phenyl-6,7-dimethoxytetrahydroisoquinoline **19** from (−)-ephedrine and (−)-pseudoephedrine respectively.

3. THE IRON CHIRAL AUXILIARY $[(C_5H_5)Fe(CO)(PPh_3)]$

The iron chiral auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$ exerts powerful stereochemical control during the reactions of attached ligands by effectively ordering the proximate three-dimensional space. The parent acetyl complex **24**, from which all the others can be derived, is now commercially available (BP Chemicals Ltd) as either pure enantiomer or as the racemate. The acetyl complex **24** is chiral (figure 2) and configurationally stable. Furthermore, the acetyl complex **24** and its derivatives are air stable in the solid state allowing easy handling and storage.

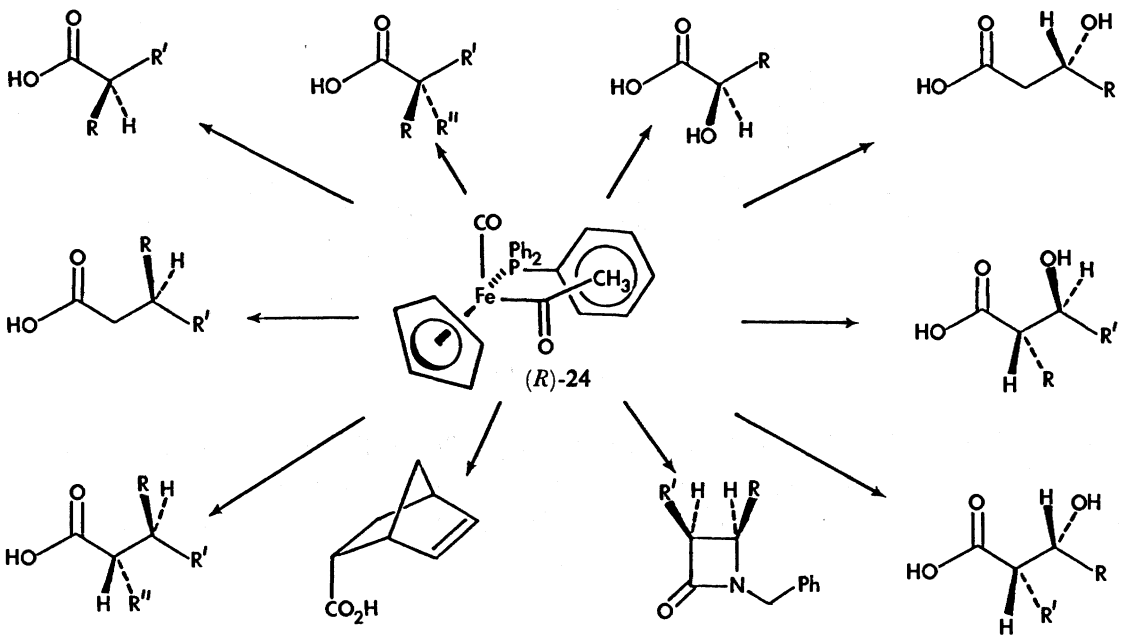


(*R*)-(−)-**24** (*S*)-(+)-**24**

FIGURE 2

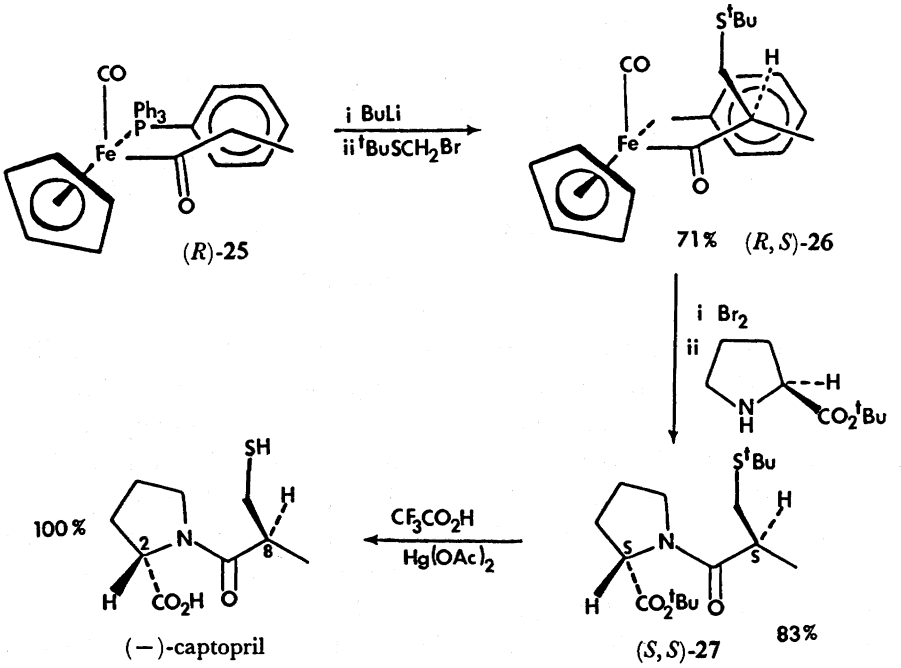
Acyl ligands attached to the iron chiral auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$ undergo most reactions associated with the carbonyl group such as enolate alkylations, aldol reactions, Michael addition reactions and Diels–Alder reactions highly stereoselectively. Efficient removal of the chiral auxiliary at the end of a synthetic sequence is readily achieved by treatment with a one-electron oxidant, e.g. Br_2, I_2, Ce^{IV}, Fe^{III}, in the presence of water, alcohols or amines to generate carboxylic acids, esters or amides respectively. Scheme 11 illustrates some of the general classes of compound available as single enantiomers via chiral iron acyl methodology (Davies *et al.* 1987; Davies 1988).

We have recently applied the stereoselective alkylation reactions of enolates derived from **24** (Brown *et al.* 1986) to the asymmetric synthesis of the angiotensin-converting enzyme inhibitor



Scheme 11

(−)-captopril (Bashiardes & Davies 1987). Treatment of the (*R*)-acetyl complex **24** with butyllithium followed by methyl iodide gave the propanoyl complex (*R*)-**25** in 99% yield. Subsequent alkylation of (*R*)-**25** by deprotonation with butyllithium and addition of bromomethyl *t*-butyl sulphide gave stereoselectively (*R*,*S*)-**26** as a single diastereoisomer (scheme 12). Decomplexation of (*R*,*S*)-**26** by bromine with the *t*-butyl ester of L-proline gave (*S*,*S*)-**27**. The diastereoisomeric purity of (*S*,*S*)-**27** confirmed the stereoselectivity of the

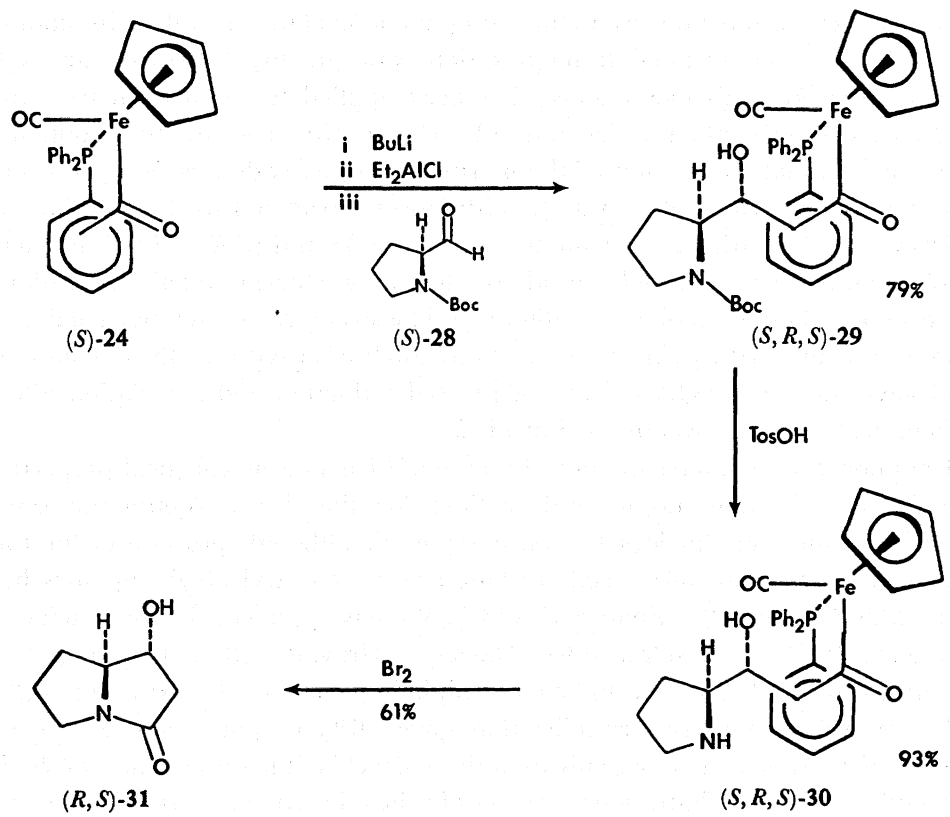


Scheme 12

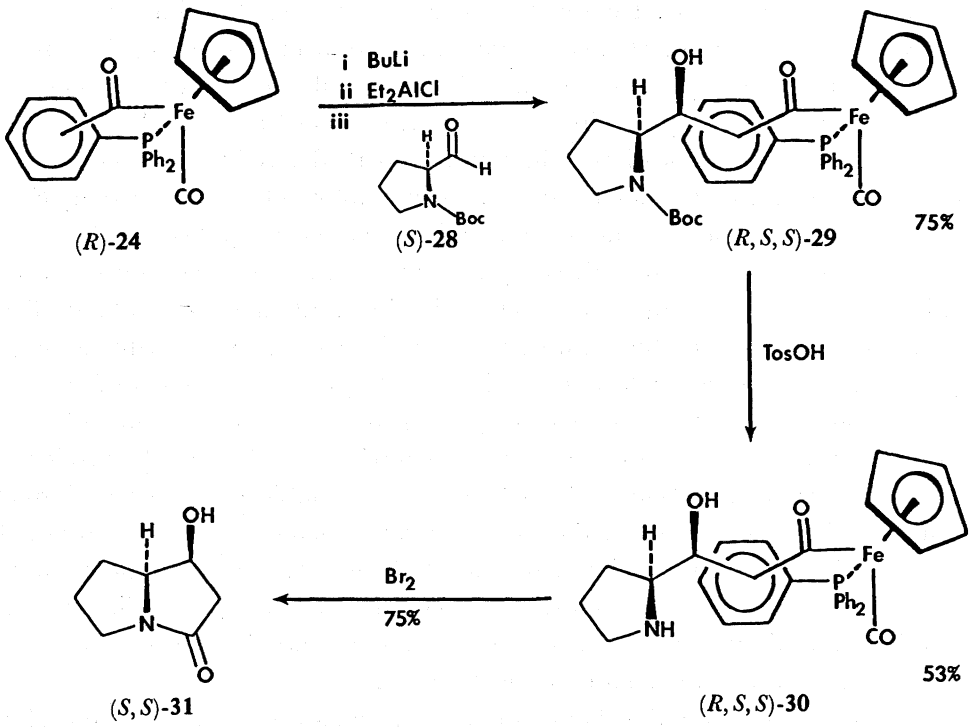
previous alkylation process. Deprotection then gave (−)-(*S*,*S*)-captopril in an overall yield of 59%. The synthetic (−)-captopril was identical in all respects, including ^{1}H NMR, melting point, mixed melting point, optical rotation, and enzyme inhibition activity, to an authentic sample; 8-*epi*-captopril was prepared in an analogous manner from (*S*)-**24**.

We have demonstrated that the diethylaluminium enolate derived from the chiral iron acetyl **24** functions as a chiral acetate enolate equivalent in aldol reactions with aldehydes (Davies *et al.* 1985*a*). This stereoselective aldol methodology has been applied to the asymmetric synthesis of (1*R*,8*S*)- and (1*S*,8*S*)-1-hydroxypyrrolizidin-3-ones from Boc-L-prolinal where the iron chirality overpowers the latent stereoselectivity inherent in Boc-L-prolinal (Beckett & Davies 1988). Reaction of the aluminium enolate derived from (*S*)-**24** with Boc-L-prolinal, (*S*)-**28**, gave (*S*,*R*,*S*)-**29** as a single diastereoisomer. Deprotection gave (*S*,*R*,*S*)-**30**, which on decomplexation yielded (1*R*,8*S*)-1-hydroxypyrrolizidin-3-one **31** (scheme 13). A similar reaction of the aluminium enolate derived from (*R*)-**24** with (*S*)-**28** gave (*R*,*S*,*S*)-**29** and hence (1*S*,8*S*)-1-hydroxypyrrolizidin-3-one **31** (scheme 14). Double asymmetric induction is operating in the above reactions. In the first reaction (scheme 13) the two original chiral centres are acting in concert. In the latter reaction (scheme 14) they are opposed and a small amount (less than 3%) of the other diastereoisomer is formed: the minor diastereoisomer is, however, easily removed by a single crystallization of the product. Hence both (1*R*,8*S*)-**31** and (1*S*,8*S*)-**31** are readily accessible enantiomerically pure.

We have demonstrated that the diethylaluminium enolate derived from the chiral iron



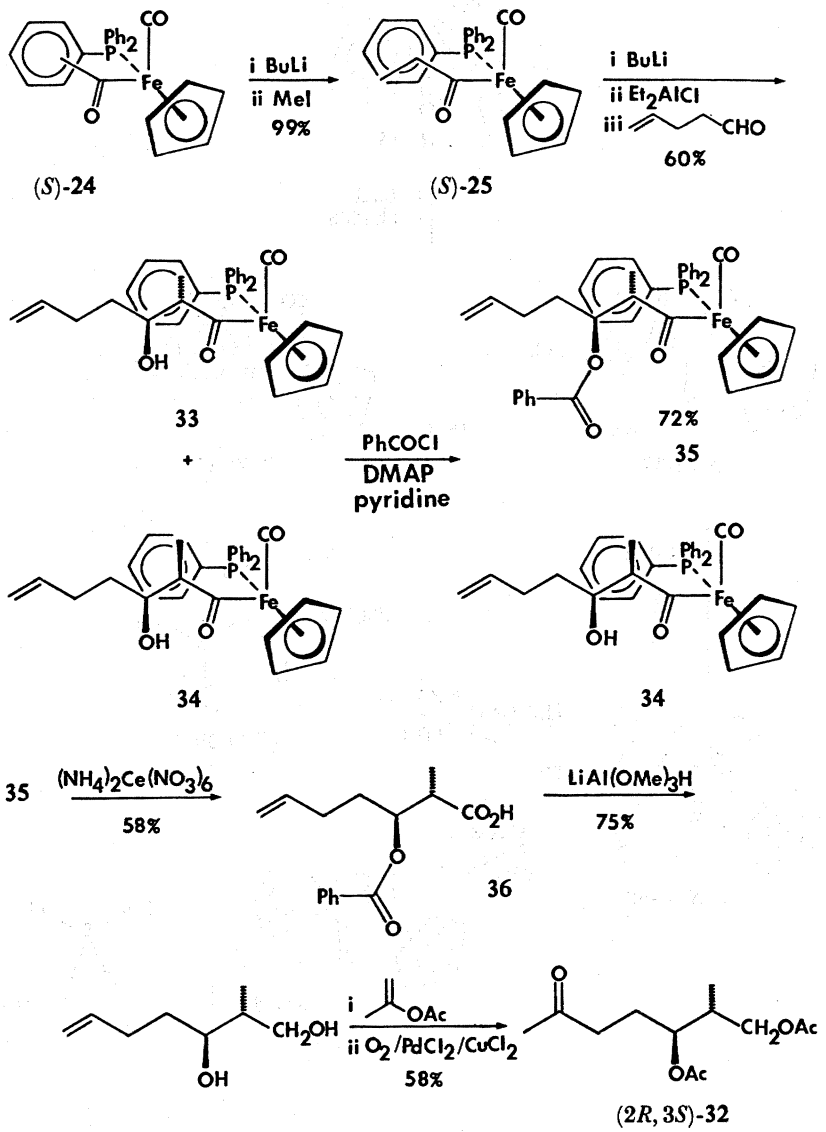
SCHEME 13



SCHEME 14

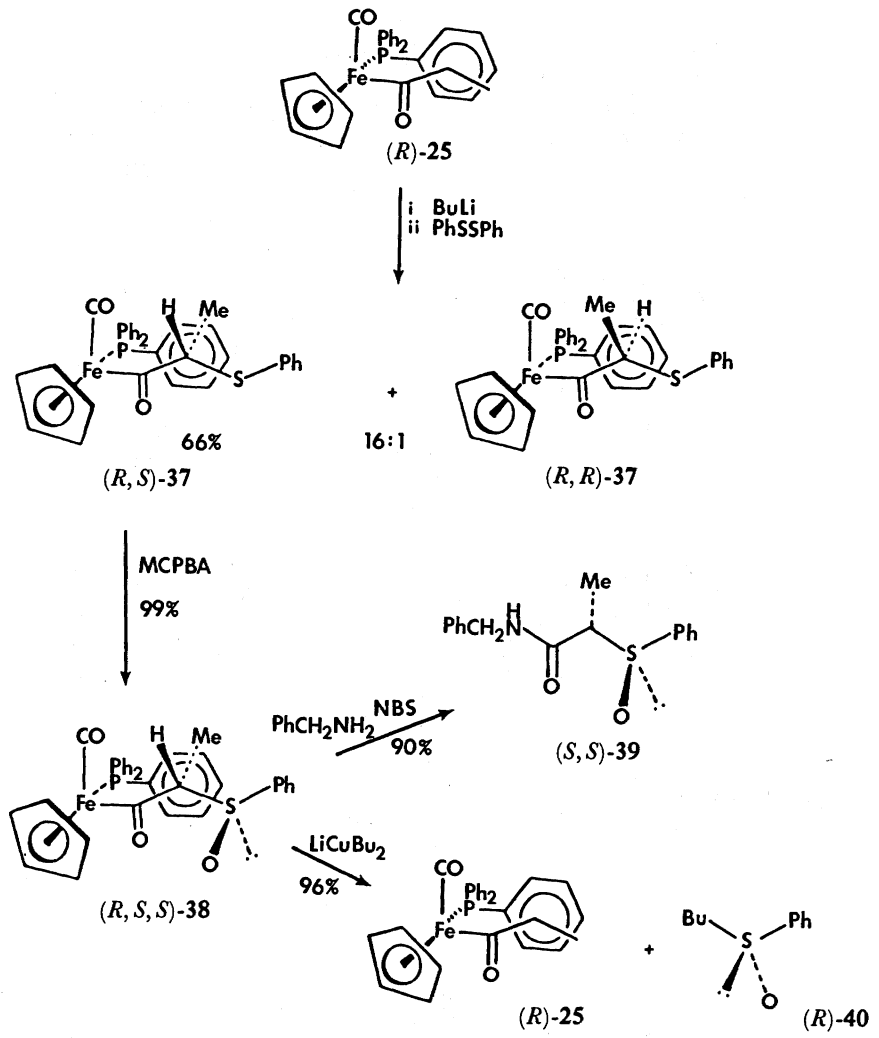
propanoyl complex **25** functions as a chiral propionate enolate equivalent in aldol reactions with aldehydes to generate after decomplexation *threo*-α-methyl-β-hydroxycarboxylic acids (Davies *et al.* 1985*b*). This methodology has been applied to the asymmetric synthesis of (2*R*,3*S*)-2-methyl-6-oxohepta-1,3-diacetate **32** (scheme 15). The absolute configuration of (2*R*,3*S*)-**32**, a degradation product of the marine cyclic peroxide *enantio*-sigmosceptrellin-A, was thus established (Capon *et al.* 1988). Addition of 4-pentenal to the aluminium enolate derived from (*S*)-**25** afforded a 15:1 mixture of (*S*,*S*,*S*)-**33** and (*S*,*R*,*S*)-**34**. Treatment of this mixture of **33** and **34** with benzoyl chloride resulted in an efficient kinetic separation to yield the desired (*S*,*S*,*S*)-**35** diastereoisomerically pure. The structure and relative configurations of (*S*,*S*,*S*)-**35** were confirmed by single crystal X-ray analysis of racemic **35**. Decomplexation of (*S*,*S*,*S*)-**35** gave the acid (2*S*,3*S*)-**36** and sequential reduction and acetylation afforded the (2*R*,3*S*)-keto-acid **32** in an overall yield of 11%.

Chiral sulphoxides are interesting both because of their pharmacological properties and as chiral auxiliaries. To date no general method for the direct asymmetric synthesis of enantiomerically pure sulphoxides has been reported, although procedures for the highly diastereoselective (less than 96% e.e.) oxidation of certain aryl alkyl sulphides have been developed (Madesclaire 1986; Zhao *et al.* 1987). We have applied iron acyl methodology to the asymmetric synthesis of sulphoxides (Davies & Gravatt 1988). Trapping the lithium enolate derived from (*R*)-**25** with diphenyl disulphide gave a 16:1 mixture of (*R*,*S*)-**37** and (*R*,*R*)-**37** from which a single crystallization gave 66% of pure (*R*,*S*)-**37** (scheme 16). Oxidation of (*R*,*S*)-**37** gave an essentially quantitative yield of the sulphoxide (*R*,*S*,*S*)-**38** whose structure and relative configurations were established by single crystal X-ray analysis of racemic **38**. Oxidative decomplexation of (*R*,*S*,*S*)-**38** in the presence of benzylamine gave the



SCHEME 15

β-sulphinyl amide (*S*,*S*)-**39** whose enantiomeric purity was confirmed by ^{1}H NMR analysis in the presence of the chiral shift reagent 2,2,2-trifluoro-1-(9-anthryl)ethanol. Treatment of (*R*,*S*,*S*)-**38** with lithium dibutylcuprate gave a 1:1 mixture of the initial starting propanoyl complex (*R*)-**25** and (*R*)-(+)-phenyl butyl sulphoxide (*R*)-**40**. Some recovered (*R*,*S*,*S*)-**38** was also obtained, because of a competing enolization reaction but this could be recycled. The corrected yields of (*R*)-**25** and (*R*)-**40** were 96%. Both (*R*)-**25** and (*R*)-**40** were optically pure to the limits of the standard analytical techniques. Because the (*R*)-(+)-sulphoxide **40** is obtained from (*R*,*S*,*S*)-**38** the displacement reaction at sulphur proceeded, as expected, with clean inversion of configuration. Ethyl phenyl sulphoxide and *t*-butyl phenyl sulphoxide have been prepared in an analogous manner and we are in the process of extending this chemistry to dialkyl and diaryl sulphoxides. Of particular significance is the fact that the procedure involves the non-destructive mediation of the chiral iron complex **25**.



Scheme 16

4. Conclusions

The amplification of existing chirality demonstrated by the chromium chemistry and the chirality generation using the iron chiral auxiliary illustrates the power and potential of organometallic complexes for the synthesis of optically pure organic compounds.

The enormous contribution provided by the members, past and present, of my research group is acknowledged. Generous financial support by the BP Venture Research Unit (iron chemistry) and Glaxo Group Research, Ware (chromium chemistry), and a contribution from the SERC are gratefully acknowledged.

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Discussion

M. T. Reetz (*Universität Marburg, F.R.G.*). What is the structure of the benzylic chromium lithium reagents? Where is the lithium located? (This could be determined by NMR C–Li coupling.)

S. G. Davies. To date we have no direct evidence concerning the structure of the benzylic anions or the lithium counter ions. The high stereoselectivities observed would be consistent with the counter ion being proximate to the benzylic carbon or to the chromium atom.

M. T. Reetz. Does (benzyl allyl ether)chromium tricarbonyl undergo a Wittig rearrangement?

S. G. Davies. (Benzyl allyl ether)chromium tricarbonyl is α-methylated on sequential treatment with butyllithium and methyl iodide, i.e. the intermediate anion does not undergo the Wittig rearrangement.

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