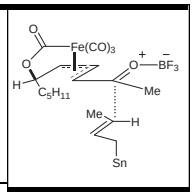
Tricarbonyliron complexes: an approach to acyclic stereocontrol



CHEMICAL SOCIETY REVIEWS

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π-Allyltricarbonyliron lactone complexes, η⁴-dienetricarbonyliron complexes and their relatives offer an interesting approach to the problem of acyclic stereocontrol. Functional groups appended to the organic ligand frequently adopt a preferred conformation. This, combined with the steric bulk of the $Fe(CO)_3$ moiety provides a means for controlling the addition of reagents to such pendant functionality in a defined manner. Thus addition of nucleophiles to aldehydes and ketones affords a route to diastereoisomerically pure secondary and tertiary alcohols while olefinic functionality in the side-chain can be utilised in stereoselective dihydroxylations, Diels–Alder and Michael addition reactions. Just as the formation of arene $Cr(CO)_3$ complexes modifies reactivity at the α-position of arene substituents, the $Fe(CO)_3$ group of η⁴-diene and trimethylenemethane tricarbonyliron complexes can be used to stabilise an adjacent positive charge. Trapping of the carbocation resulting from ionisation of an α-carbinol occurs with high diastereoselectivity, providing an unusual and useful stereoselective S_N1-type reaction. Such highly stereoselective reactions have been put to good use in the preparation of a number of biologically interesting natural products.

1 General introduction

The last few decades have seen an explosion of new methodology for organic synthesis. This has been fuelled by the need to perform reactions with increasingly high levels of chemo-, regio- and stereo-control. As synthetic targets have become more complex, this demand for high specificity and control has resulted in chemists reaching to all regions of the periodic table to develop reagents, not only for modifying and improving existing transformations, but also for making new processes possible.

The development of organometallic reagents derived from transition metals has been particularly successful and has had a profound effect on synthetic planning and design. Iron is clearly an important and synthetically useful transition metal. Its high natural abundance and ready accessibility have resulted in the development of a wide and varied organometallic chemistry. Most low valent organoiron complexes derive from inexpensive ironpentacarbonyl [$Fe(CO)_5$] or from one of its higher order congeners, diironnonacarbonyl [$Fe_2(CO)_9$] and triirondodecacarbonyl [$Fe_3(CO)_{12}$]. Such iron carbonyl complexes are relatively easy to prepare and can generally be handled without the need for specialised techniques or apparatus. Complexes can be formed with a wide range of organic substrates. These are usually sufficiently stable to survive a variety of functional group manipulations on side-chain appendages, yet can be easily decomplexed when required.[1,2]

A number of different types of organometallic complexes bearing the tricarbonyliron [$Fe(CO)_3$] moiety have been reported. Treatment of vinyl epoxides or vinyl cyclic sulfites with $Fe(CO)_5$ or $Fe_2(CO)_9$ affords π-allyltricarbonyliron lactone complexes **1**,[3] while dienes capable of adopting an s-*cis* conformation react to form η⁴-dienetricarbonyliron complexes **2**.[1,4] Suitably functionalised η⁴-diene complexes in turn can be used to generate η⁵-pentadienyltricarbonyliron cationic (+1) complexes **3**. 1,3-Dibromo- or dihydroxy-alk-2-enes have also been found to react with iron pentacarbonyl, affording trimethylenemethane (TMM) tricarbonyliron complexes **4** (Fig. 1).

This review is concerned with the use of the tricarbonyliron moiety as a temporary structural feature to control the

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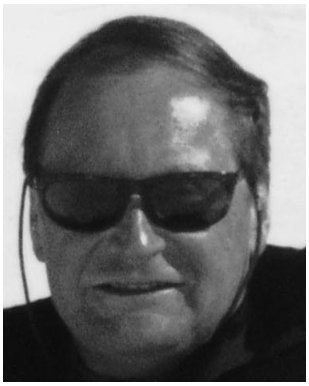

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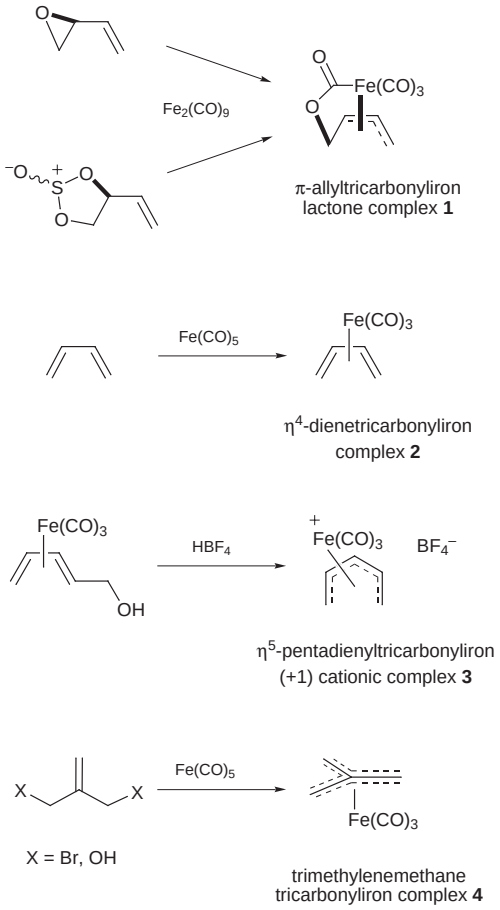


Fig. 1 A variety of tricarbonyliron complexes are readily prepared

stereochemical outcome of reactions carried out on functional groups appended to the organic ligand. Such a strategy can be used to effect stereocontrolled reactions on acyclic systems, a challenging problem which remains at the forefront of organic synthesis. While this is not intended to be an exhaustive review of the chemistry of tricarbonyliron complexes,[1–5] the areas chosen for discussion are representative of what can be achieved using this methodology. Thus by highlighting the concepts behind this approach to acyclic stereocontrol, in addition to its scope and limitations, it is hoped to provide a platform from which further imaginative and novel uses of these complexes in modern synthetic design may be conceived.

2 Tricarbonyliron complexes exhibit planar chirality

Dienes have been the most intensively studied organic substrates for complexation with the tricarbonyliron group. Reaction with any unsymmetrically substituted diene affords a racemic product by virtue of the iron moiety being able to complex to either of the prochiral faces of the diene substrate; the resulting complex possesses planar chirality (Fig. 2).

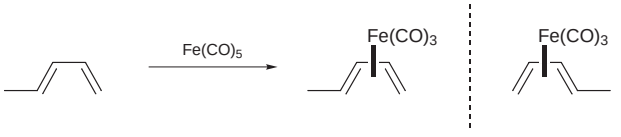


Fig. 2 Prochiral diene substrates afford a racemic complex

Efficient procedures have been developed which permit access to enantiomerically enriched complexes, frequently by applying classical resolution techniques on the racemate.[1] Enantiomerically enriched η^4-diene complexes can alternatively be prepared by decarboxylation of enantiomerically enriched π-allyltricarbonyliron lactone complexes (*vide infra*).[3,6] Trimethylenemethane tricarbonyliron complexes and η^5-pentadienyltricarbonyliron (+1) cationic complexes also possess planar chirality and may be prepared in enantiomerically enriched form by similar methods.

The vinyl epoxide or cyclic sulfite precursors for π-allytricarbonyliron lactone complexes are themselves chiral molecules, which are readily prepared in enantiomerically enriched form using Sharpless Asymmetric Epoxidation and Dihydroxylation protocols.[7,8] The mechanism of complex formation ensures that the enantiomeric excess in the organic precursor is preserved in the product complex. π-Allyltricarbonyliron lactone complexes are therefore also readily obtained in enantiomerically enriched form.[3]

3 A model for the use of tricarbonyliron complexes as stereocontrolling agents

Since the majority of methods for complex formation are mild, a wide range of functionality can be incorporated into side-chains of the organic ligand. It was postulated that the inherent chirality of these complexes could be utilised to perform asymmetric transformations of functional groups attached at the periphery of the organic ligand. Specifically, the steric encumbrance provided by the $Fe(CO)_3$ moiety could enforce a degree of facial selectivity on reactions carried out on planar functional groups (*e.g.* carbonyl groups and double bonds) held in close proximity to the ligand, by blocking one of their diastereotopic faces. This would also rely on the functional groups themselves occupying a preferred conformation in which the two faces are in different steric environments (Fig. 3).

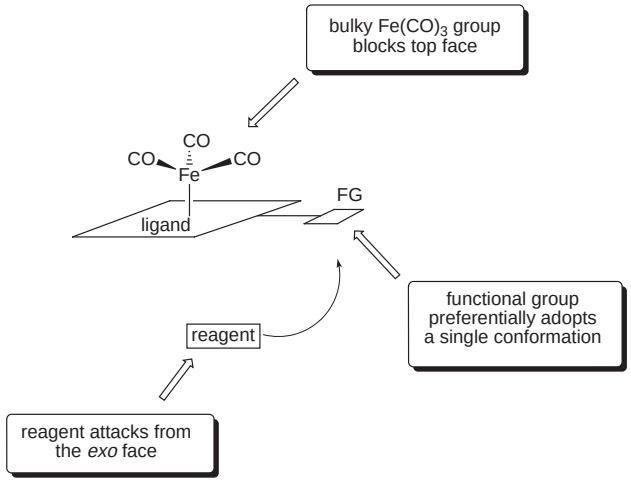


Fig. 3 Model for asymmetric synthesis using tricarbonyliron complexes

Examples in which tricarbonyliron complexes have realised their potential for use in the construction of new stereogenic centres will be discussed in the following sections.

4 Nucleophilic addition to carbonyl groups in the side-chain of the organic ligand.

The addition of nucleophiles into carbonyl groups is a reaction of fundamental importance and remains one of the most widely used transformations in synthesis. Under normal circumstances, the nucleophilic reagent adds indiscriminately to either face of the prochiral carbonyl group affording a racemic mixture of products. Differentiation of the two enantiotopic faces can be achieved by steric blocking, allowing the preparation of enantiomerically enriched products by ensuring the two different addition pathways are different in energy. If the reaction is under kinetic control then the larger the difference in activation energies, the greater the enantiomeric excess of the addition product.

Two criteria must be satisfied if the addition of a nucleophile into carbonyl functionality appended to the organic ligand of a tricarbonyliron complex is to proceed with high diastereocontrol. First, the carbonyl group must adopt a single reactive conformation. Second, its two diastereotopic faces should be sterically differentiated by the tricarbonyliron moiety such that addition proceeds, ideally, to exclusively the less hindered face.

Non-complexed dienones normally exhibit multiple bands in the carbonyl stretching region of their IR spectra owing to the presence of s-*cis* and s-*trans* conformations, both of which are significantly populated at ambient temperatures. Upon complexation to $Fe(CO)_3$, however, a single C=O stretching frequency is observed suggesting that only one conformer is significantly populated.[9] The preference of ketone-functionalised dienetricarbonyliron complexes to adopt a single conformation is widely accepted and both NOE and X-ray data support the exclusive adoption of an s-*cis* conformation. Similarly, π-allyltricarbonyliron lactone complexes bearing ketone functionality in the side-chain of the allyl ligand adopt exclusively an s-*cis* conformation in both the solid state (as determined by X-ray structure analysis) (Fig. 4) and importantly also in solution (as determined by NOE NMR studies) (Fig. 5).[10]

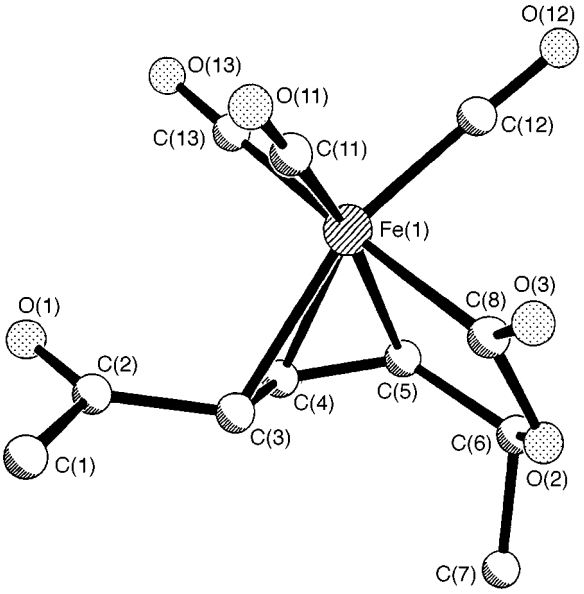


Fig. 4 X-Ray structure of complex **5** reveals that ketone functionality in the side-chain adopts an s-*cis* conformation

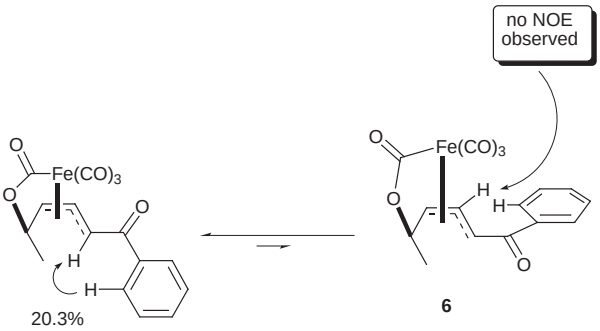


Fig. 5 NOE data showing that ketone functionality in the side-chain of lactone complex **6** adopts an s-*cis* conformation in solution

Residual conjugation to the organic ligand would be expected to favour the adoption of s-*cis* and s-*trans* conformations (as opposed to non-coplanar conformations). Furthermore, analysis of steric interactions between the alkyl substituent on the ketone and the ligand reveal the s-*trans* conformation to be disfavoured (Fig. 6). The adoption of the s-*cis* conformation by a ketone group is presumably a result of minimisation of these steric interactions, but may also be owing, at least in part, to electrostatic effects, *i.e.* the minimisation of unfavourable dipole–dipole interactions.

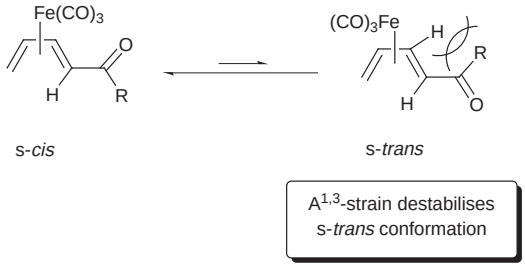


Fig. 6 The s-*cis* conformation is preferentially adopted by ketone functionality in side-chain appendages of tricarbonyliron complexes

The first criterion for diastereofacial selection appears to be satisfied; ketone groups adopt exclusively an s-*cis* conformation. Furthermore the X-ray crystal structures of ketone complexes such as **5** suggest that the blocking capability of the tricarbonyliron unit is high, with one of the carbonyl groups being positioned directly over, and therefore preventing direct access to, one of the stereofaces of the ketone group (Fig. 4).

On the basis of structural analysis of both η^4-diene complexes and π-allyltricarbonyliron lactone complexes, a model predicting the stereochemical outcome of the addition of a nucleophile into a ketone group appended to the organic ligand can be proposed (Fig. 7): the approaching nucleophile should attack *anti* to the tricarbonyliron moiety producing an alcohol stereogenic centre of predictable configuration.

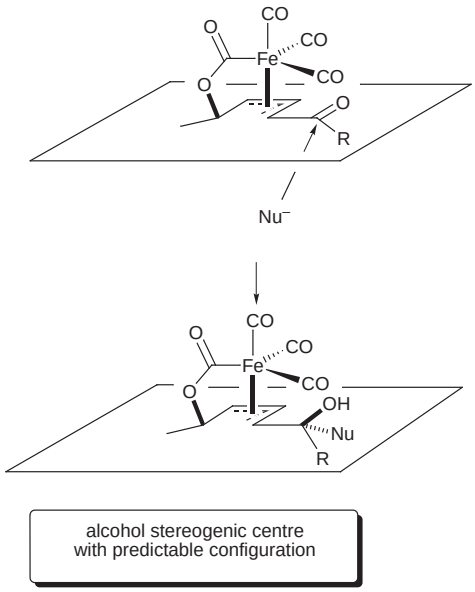


Fig. 7 Model used to predict the stereochemical outcome of addition of nucleophiles to ketone groups in the side-chain of tricarbonyliron complexes

Aldehydes might be expected to be less conformationally restricted owing to diminished steric interactions between the aldehydic hydrogen and the organic ligand. This would allow relatively free rotation about the C–C=O bond and significant population of both s-*cis* and s-*trans* conformations. NOE studies corroborate this hypothesis.[11] Irradiation of both the α- and β-hydrogens of the allyl ligand of lactone complex **7** reveal NOEs to the aldehydic proton resonance suggesting that in chloroform solution, both s-*cis* and s-*trans* conformations are populated (Fig. 8).

Thus from conformational analysis of carbonyl-functionalised $Fe(CO)_3$ complexes, one would anticipate that nucleo-

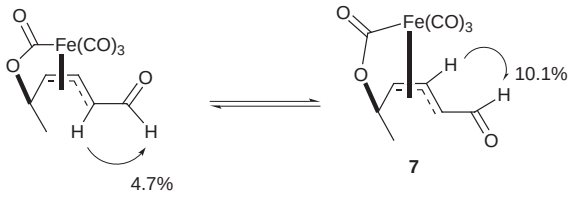


Fig. 8 NOE studies show that aldehyde functionality in the side-chain of lactone complex **7** adopts both s-*cis* and s-*trans* conformations

philic addition to ketone groups would be highly diastereoselective, with a predictable stereochemical outcome. The diastereoselectivity in additions to aldehydes would be expected to be lower and the stereochemical outcome less easy to predict. This has, for the most part, turned out to be the case.

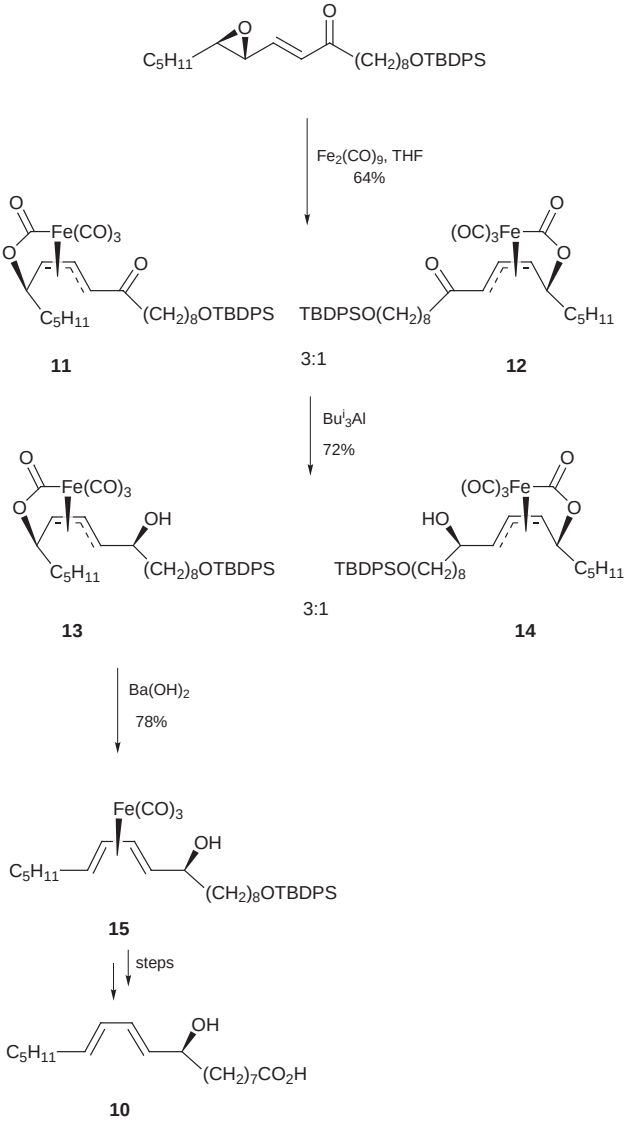
4.1 Nucleophilic addition to ketone functionality in the side-chain of tricarbonyliron complexes

The reduction of dienone tricarbonyliron complexes by $NaBH_4$ has long since been shown to be highly diastereoselective.[9] Franck-Neumann *et al*. have further shown that 1-keto η^4-diene complexes **8** react with complete stereocontrol with organolithium reagents affording a single diastereoisomeric product **9**. The stereoselectivity is readily accounted for by the proposed model with addition of the nucleophile proceeding onto the s-*cis*-conformation of the ketone *anti* to the bulky $Fe(CO)_3$ group (Scheme 1).[12]

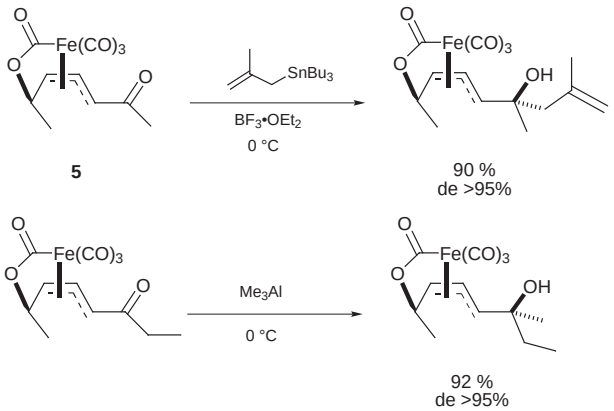
Scheme 1 Organolithium nucleophiles add in a highly stereoselective fashion to ketone functionality in the side-chain of η^4-diene complexes

Reduction of ketone groups appended to the allyl ligand of π-allyltricarbonyliron lactone complexes is best achieved using organoaluminium reagents bearing sterically bulky alkyl groups.[10] In these cases β-hydride transfer is a more facile process than whole group transfer and the resulting secondary alcohol product is obtained exclusively as a single diastereoisomer in complete accord with the proposed model. Such a stereoselective reduction of ketone functionality in the side-chain of a lactone complex was a key step in the synthesis of β-dimorphecolic acid **10** (Scheme 2).[13] Treatment of functionalised lactone complexes **11** and **12** with Bu^i_3Al afforded the secondary alcohols **13** and **14** as single diastereoisomers in 72% combined yield. After chromatographic separation, the next key step involved a stereoselective base induced decarboxylation of **13** to the corresponding (*E*,*E*)-η^4-diene complex **15**.[6] Subsequent manipulations led to the first total synthesis of β-dimorphecolic acid **10**.

Unlike their diene complex relatives, π-allyltricarbonyliron lactone complexes are unstable to strongly Lewis basic nucleophiles such as Grignard and organolithium reagents. However more Lewis acidic nucleophiles such as organoaluminium reagents and allylstannanes (in the presence of a Lewis acid) react chemoselectively with carbonyl functionality in the side-chain of the organic ligand leaving the complex itself intact. These nucleophiles react with ketone groups in the side-chain of the allyl ligand to afford the corresponding tertiary alcohol products with excellent levels of stereocontrol (Scheme 3).[10,14] In all cases only one diastereoisomer could be observed by either NMR spectroscopic or HPLC analysis. The excellent levels of stereocontrol and the relative configuration of the newly generated stereogenic centre are entirely consistent with



Scheme 2



Scheme 3 Allylstannanes and organoaluminium reagents react in a highly diastereoselective fashion with ketone functionality in the side-chain of lactone complexes

the proposed model (Fig. 7): the nucleophile approaches *anti* to the bulky tricarbonyliron moiety and reacts with the s-*cis*-conformation of the ketone.

Reaction of ketone complex **16** with crotyltributylstannane generates only two products, **17** and **18**, out of the four possible diastereoisomers.[14] Thus while the $Fe(CO)_3$ unit exerts absolute

control over the formation of the tertiary alcohol centre, it fails to control the stereochemical outcome of the adjacent centre. This is consistent with the reaction of ketones with crotyl metal reagents: the difference in effective size of the groups either side of the carbonyl group is small, allowing the reaction to proceed equally well through two possible open transition states (Fig. 9).

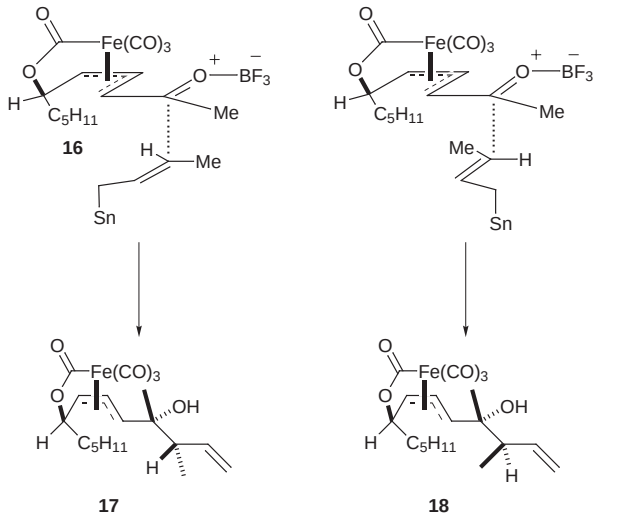


Fig. 9 Reaction of ketone complex **16** with crotyltributylstannane affords two diastereoisomeric complexes

4.1.1 Conclusions

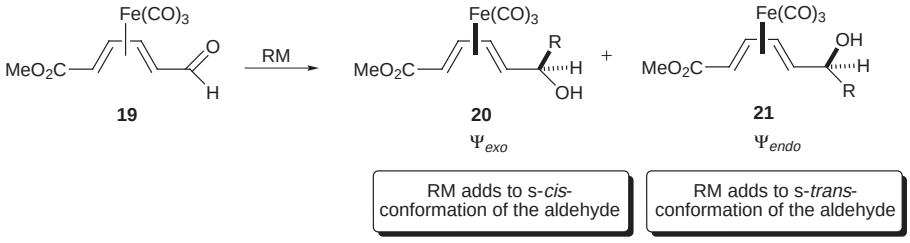
Addition of nucleophiles into ketone-functionalised tricarbonyliron complexes occurs with complete stereocontrol. The reaction provides a method for generating tertiary alcohol products of known configuration. This is a particularly valuable process as other methods for generating this type of stereogenic centre are rare. The excellent levels of stereocontrol can be attributed to the ketone adopting exclusively the s-*cis* conformation and addition proceeding *anti* to the bulky $Fe(CO)_3$ group. In the case of π-allyltricarbonyliron lactone complexes the reaction may be considered as a novel example of remote induction of chirality since there is a 1,5 relationship between the lactone tether and the newly formed tertiary alcohol stereogenic centre.

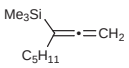
4.2 Nucleophilic addition to aldehyde functionality in the side-chain of tricarbonyliron complexes

4.2.1 Nucleophilic addition to aldehyde functionality in the side-chain of η⁴-dienetricarbonyliron complexes

Owing to their ease of preparation, the addition of nucleophiles to aldehydes attached to η⁴-dienetricarbonyliron complexes has received the most attention. Synthesis of η⁴-diene complexes bearing aldehyde functionality in the side-chain was first reported by Stone and co-workers in 1961.[15] A number of different nucleophiles have since been reacted with aldehyde **19** and some of the results are summarised in Scheme 4. *By convention* addition to the s-*cis*-conformation of the aldehyde leads to the Ψ_{exo} derivative **20** while addition to the s-*trans* conformer gives the Ψ_{endo} product **21**.[9] Strongly Lewis basic nucleophiles such as organolithium and organomagnesium reagents react preferentially with the s-*cis*-conformation of the aldehyde adding *anti* to the $Fe(CO)_3$ group and generating the Ψ_{exo} isomer as the major product.[5] Organolithiums are normally more diastereoselective than Grignard reagents but overall levels of diastereoselectivity remain only moderate. Lewis acid-mediated nucleophilic additions generally give the Ψ_{endo} product as the major isomer,[5,16] sometimes exclusively (see entry 3 of table, Scheme 4).[17] No other general patterns are apparent: the diastereoselectivity of the reactions is highly dependent on a number of features including temperature, nature of active nucleophile and the presence, or absence, of a Lewis acid. All these variables will potentially affect the relative populations of s-*cis* and s-*trans* aldehyde conformers and hence the diastereoselectivity, assuming that addition proceeds exclusively to the face *anti* to the bulky $Fe(CO)_3$ group.

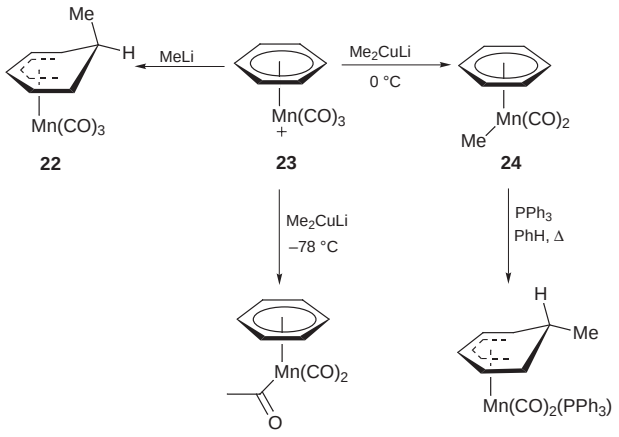
An alternative mechanism which could account for the change in stereoselectivity with different nucleophiles is for the reagent initially to attack the Fe centre or one of the CO ligands and then be transferred intramolecularly to the aldehyde which adopts an s-*cis* conformation. Owing to the opposite direction of attack, this would then give rise to the Ψ_{endo} product. Although less likely than a simple conformational change for the aldehyde, this overall *endo* delivery cannot be entirely ruled out. *Endo* attack of a nucleophile on cyclohexadienyltricarbonyliron (+1) cationic complexes has been suggested when the addition of the nucleophile is a reversible process or when the reaction centre is substituted.[18] Furthermore Brookhart *et al*. have reported quite different results concerning the addition of MeLi and Me_2CuLi to (arene)tricarbonylmanganese (+1) cationic complexes.[19] Whereas MeLi yields solely the *exo* addition product **22**, reaction of Me_2CuLi with arene complex **23** affords



	nucleophile (RM)	combined yield (%)	Ψ_{exo}:Ψ_{endo}
1	MeLi	85	80:20
2	MeMgI	80	67:33
3	 / $TiCl_4$	65	0:100

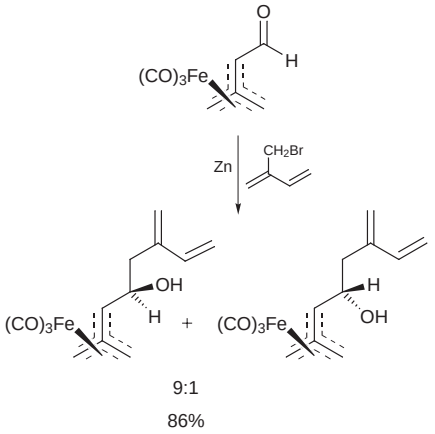
Scheme 4 Diastereoselective addition of nucleophiles into aldehyde functionality appended to η⁴-diene complex **19**

products resulting from apparent attack either at the metal centre or at one of the CO ligands (Scheme 5). Methyl transfer to the ring can be accomplished by heating the η^1-methyl Mn complex **24** in the presence of PPh_3.



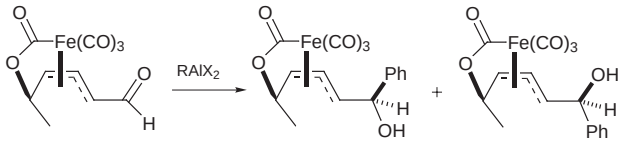
Scheme 5 MeLi and Me_2CuLi react quite differently with (arene)$Mn(CO)_3$ (+1) complex **23**

4.2.2 Nucleophilic addition to aldehyde functionality in the side-chain of trimethylenemethane tricarbonyliron complexes
Trimethylenemethane (TMM) complexes bearing aldehyde functionality have also been prepared and the few reported examples of their reaction with nucleophiles suggest similar patterns of reactivity and stereoselectivity to η^4-diene complexes. The readily separable diastereoisomers are formed in high yield and the nature of the nucleophile again affects the stereochemical outcome of the addition (Scheme 6).[20]



Scheme 6 Diastereoselective addition of an organozinc reagent into aldehyde functionality in the side-chain of a (TMM)$Fe(CO)_3$ complex

4.2.3 Nucleophilic addition to aldehyde functionality in the side-chain of π-allyltricarbonyliron lactone complexes
The stereochemical outcome of the reaction of π-allyltricarbonyliron lactone complexes with organoaluminium nucleophiles strongly depends on the nature of the nucleophile (Scheme 7).[11] Thus in the case of the addition of a phenyl group into the aldehyde functionality of complex **7**, using $PhAlMe_2$ as the nucleophile the addition product **25** was isolated in 26% yield (along with 36% of the product resulting from methyl group transfer) as a single diastereoisomer formed by addition of the nucleophile to the s-*cis*-conformation of the aldehyde *anti* to the tricarbonyliron moiety. This is in accord with the model proposed for the addition of nucleophiles into ketone functionality (Fig. 7). Conversely, when Ph_3Al was used as the nucleophile, while the yield was much improved, the diastereoselectivity of the reaction was almost completely



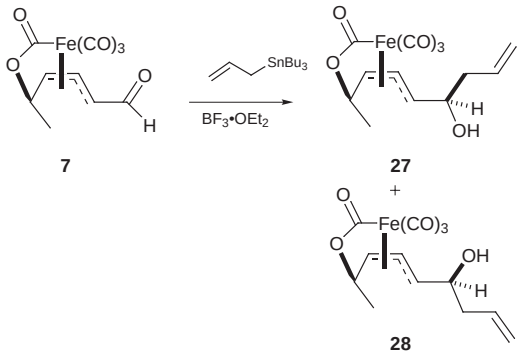
7 **25** **26**

nucleophile	**25:26**	combined yield (%)
$PhAlMe_2$	100:0	26
Ph_3Al	20:80	71

Scheme 7 The nature of the aluminium reagent affects the diastereoselectivity of the addition reaction to aldehyde functionality in the side-chain of lactone complexes

reversed with the major product **26** being that which would result from addition of the nucleophile to the s-*trans*-conformation of the aldehyde. While a simple explanation for this observation is not readily forthcoming, it provides a clear illustration that the nature of the nucleophile can have a profound effect on the relative stereochemical outcome of the addition event. A variety of other organoaluminium reagents were also investigated and while the stereoselectivity of the addition reaction was not always high, the major product remained that deriving from addition of the nucleophile *anti* to the $Fe(CO)_3$ moiety onto the s-*cis*-conformation of the aldehyde.

When allylstannanes were reacted with the same aldehyde complex **7** under Lewis acid activation, the diastereoselectivity of the reaction was found to be strongly temperature dependent.[11] Thus at −78 °C, the levels of stereocontrol were negligible and a 1 : 1 mixture of homoallylic alcohol products **27** and **28** was obtained albeit in excellent combined yield. At increased temperature, increased diastereoselection was observed with a maximum being obtained in the region −20 to −40 °C. The major diastereoisomer was that which would result from *anti* addition to the s-*trans*-conformation of the aldehyde. Upon raising the reaction temperature further, diastereoselectivity dropped off slightly once again (Scheme 8). This example serves to highlight that careful manipulation of reaction conditions can lead to good levels of diastereocontrol.



7 **27** **28**

temperature (°C)	**27:28**	combined yield (%)
25	14:86	100
–40	11:89	100
–78	50:50	100

Scheme 8 Temperature has a profound effect on the diastereoselectivity of the $BF{\cdot}OEt_2$-mediated addition of allyltributylstannane to aldehyde functionality in the side-chain of lactone complex **7**

4.2.4 Conclusions

Aldehyde groups are readily incorporated into the side-chains of the organic ligands of tricarbonyliron complexes and they react with a variety of nucleophilic reagents. Levels of diastereoselectivity are highly dependent on the exact reaction conditions employed and on the nature of the nucleophile, since both these factors appear to affect the equilibrium between the s-*cis* and s-*trans* conformations of the substrate which in turn affects the stereochemical outcome of the reaction (assuming reaction always proceeds *anti* to the tricarbonyliron moiety). Nevertheless one important property which holds true in a remarkable number of cases is that the diastereoisomeric addition products can be readily separated from one another (*vide infra*) enabling facile access to diastereoisomerically pure complexes.

5 Secondary alcohol addition products adopt semi rigid conformations

The Ψ_{endo} and Ψ_{exo} secondary alcohol addition products of tricarbonyliron complexes are usually readily separable by standard chromatographic techniques. This deserves a special mention as the Ψ_{exo} product is invariably the more polar product regardless of the actual complex involved and of the nucleophile used. So reliable is this polarity difference between diastereoisomers that frequently stereochemical assignments can be made by analysis of R_f data alone. In a pioneering paper, Clinton and Lillya proposed a model which accounted for the observed differences in polarity.[9] They proposed that the α-sp^3 centre of the diene ligand will adopt a staggered conformation in which the three sites are exposed to varying levels of steric crowding (Fig. 10). Position c is severely crowded by one of the

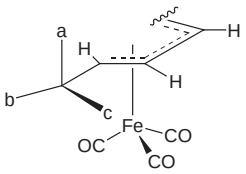


Fig. 10 The side-chains of η^4-diene complexes adopt a preferential conformation

CO ligands and the diene residue while position b suffers less steric crowding from two of the CO ligands. The preferred conformations of diastereoisomeric dienol complexes will therefore be those in which the hydrogen substituent adopts position c and the two larger groups (OH and alkyl) adopt positions a and b (Fig.11). These conformations (which are also relevant to analogous π-allyltricarbonyliron complexes) appear to be semi-rigid and can be used to account for the chromatographic behaviour of the two diastereoisomers. In the case of the Ψ_{exo} products, the exposed alcohol functionality allows extensive interactions with the stationary phase whereas the Ψ_{endo} alcohol, being more shielded, interacts less strongly. As a result the Ψ_{exo} complexes are invariably more polar than their Ψ_{endo} counterparts.

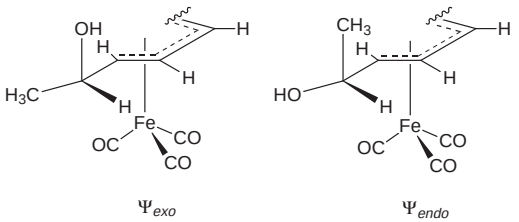
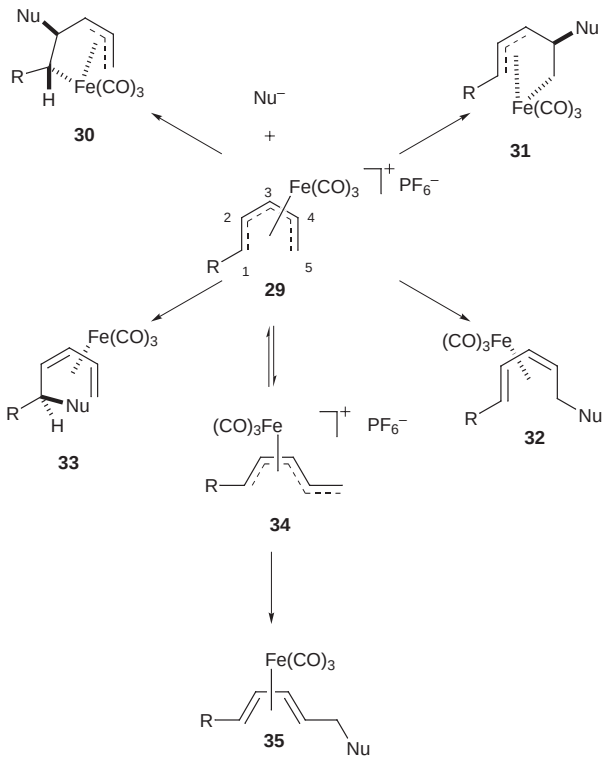


Fig. 11 Ψ_{exo} and Ψ_{endo} complexes adopt preferential conformations

6 Addition of nucleophiles into η^5-pentadienyltricarbonyliron (+1) cationic complexes

Upon complexation of an organic ligand to a metal, the normal patterns of reactivity for the free ligand are either repressed or, more frequently, reversed. This altering of the electronic properties of a substrate by metal complexation manifests itself in the opportunity not only to perform reactions which would normally be impossible on the non-complexed molecule, but also to practice completely novel chemistry.

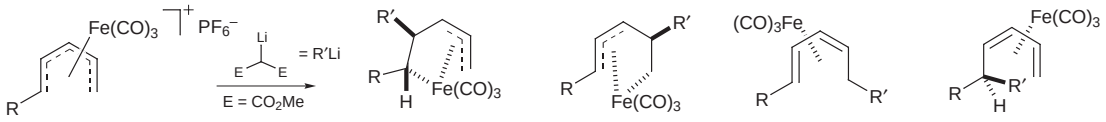
In the case of η^5-pentadienyltricarbonyliron (+1) cationic complex **29**, the organic ligand is electrophilic in character. This is primarily a result of the negative charge stabilising properties of the tricarbonyliron group. In theory nucleophilic attack can occur at any of the five carbon atoms. In practice however, only the outer carbon atoms are observed to react: reaction at C2 or at C4 is relatively unusual and affords σ,η^3-allyl tricarbonyliron complexes **30** and **31** respectively.[21] On steric grounds, attack at the dienyl termini might be expected to be more favourable especially if this position is unsubstituted. This is indeed the case and results in the formation of η^4-diene complexes **32** and **33** (Scheme 9). The transoid cationic complex **34**, although not isolable, is believed to be in equilibrium in solution with its more stable cisoid isomer **29**, thus nucleophilic attack can proceed on either or both isomers affording (*E*,*E*)- and (*E*,*Z*)-isomeric η^4-diene complexes **32** and **35** respectively (in the case of nucleophilic attack at C5) (Scheme 9).



Scheme 9 Reaction of nucleophiles with η^5-pentadienyltricarbonyliron (+1) cationic complexes affords a variety of products

The regioselectivity of nucleophilic attack is often difficult to predict and the observed products are formed owing to a subtle interplay between electronic and steric effects imposed by substituents on the dienyl ligand. One example will serve to illustrate the problems of regioselectivity frequently encountered with these complexes.

Donaldson *et al*. have investigated the reaction of malonate nucleophiles on C1-substituted η^5-pentadienyltricarbonyliron (+1) cationic complexes (Scheme 10).[22] In the case of methyl substituted complex **36**, the reaction is non-regioselective with the malonate nucleophile attacking at either terminus of the dienyl ligand affording after chromatography η^4-diene com-



36 - **39**

	R	ratio **a** : **b** : **c** : **d**			
36	Me	0	0	33	67
37	CO_2Me	>92	0	<8	0
38	Ph	0	7	10	83
39	*p*-$MeOC_6H_4$	0	0	0	100

Scheme 10 Reaction of lithium dimethyl malonate with C1-substituted η^5-pentadienyltricarbonyliron (+1) cationic complexes

plexes **36c** and **36d** (**36c**:**36d** 1 : 2). With ester substituted complex **37**, however, malonate addition occurs with almost complete regioselectivity at the C2 position to afford **37a** (a small quantity of a product resulting from attack at C5 is also observed). When R is a phenyl group (**38**), products arising from addition at C1, C4 and C5 are observed in the ratio 25 : 2 : 3. In contrast, when this is replaced by the more electron donating *para*-methoxyphenyl substituent (**39**), addition occurs with complete regiocontrol with attack at C1 exclusively. In the cases where a new stereogenic centre is produced, the relative stereochemistry can be predicted by assuming *exo* attack of the nucleophile on the dienyl ligand.

Pearson *et al*. have attempted to rationalise the regioselectivity of nucleophilic addition to unsymmetrically substituted pentadienyl complexes by proposing the addition to be under frontier orbital control, although they also suggest that more subtle effects involving the steric demand of the substituent and incoming ligand, in addition to Coulombic effects induced by the substituent, can clearly have a marked influence on the regioselectivity of the reaction.[23]

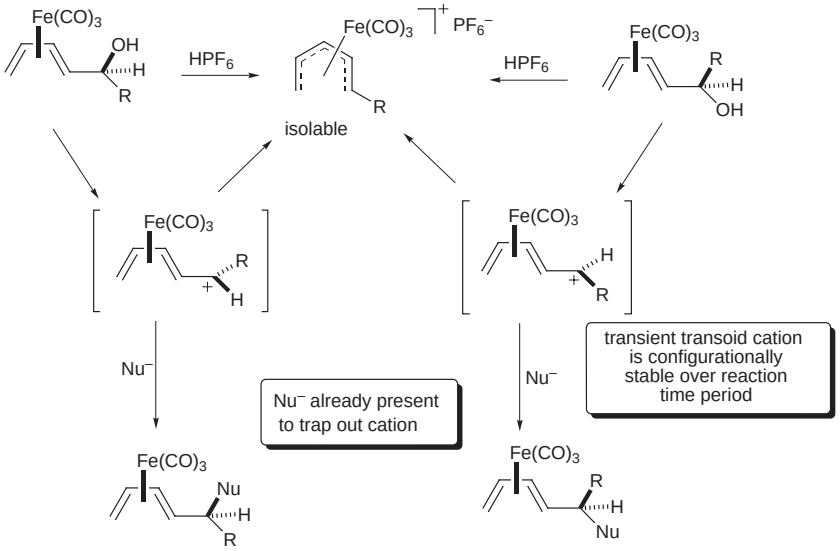
Donaldson has also provided a rationalisation of the regioselectivity of the addition reactions of malonate nucleophiles to C1-substituted dienyl cationic complexes.[22] Attack at the C2 position, observed in the case of ester functionality at C1, is very unusual. Addition at this position (effectively a Michael addition) is probably a result of the strongly electron withdrawing nature of the ester group decreasing the energy of the LUMO of the dienyl ligand. This allows an improved energy match with the metal d atomic orbitals and therefore increased back donation of electron density on to the ligand. The overall result is that C2 becomes the most electrophilic centre. In contrast the electron donating capacity of the *para*-methoxyphenyl group at C1 raises the energy of the LUMO of the dienyl ligand. Nucleophilic addition of the 'soft' malonate anion is now under frontier orbital control and occurs at C1. For the cases of methyl and phenyl substituents on C1 (neither of which are strongly electron donating or withdrawing), nucleophilic attack is less regioselective affording a mixture of products.

6.1 Conclusions

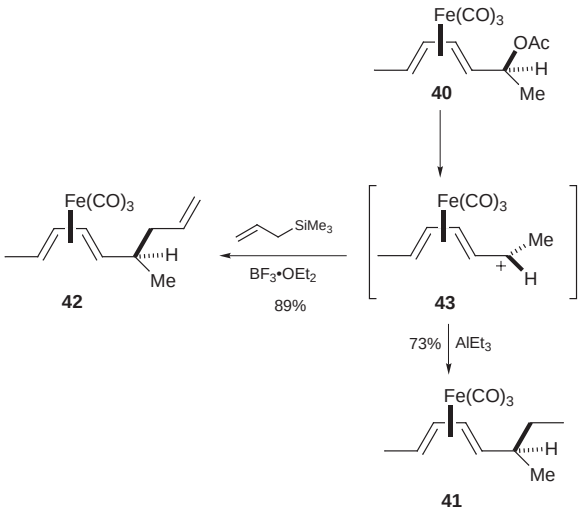
The reactions of nucleophiles with η^5-pentadienyltricarbonyliron complexes are illustrative of the influence metal complexation can have on the reactivity of organic ligands. Although the resulting products are potentially useful, regiocontrol is often poor unless strongly electron donating or withdrawing substituents are present on the ligand and this continues to limit their use in organic synthesis.

7 A solution to the problems of regioselectivity—stereoselective C–C bond formation with η^4-dienol tricarbonyliron complexes

Metal complexation not only affects the reactivity of the organic ligand itself but may also have powerful effects on the chemistry of functional groups in the immediate vicinity of the ligand. Uemura *et al*. were first to realise that *in situ* trapping of the cationic complex generated from an η^4-dienol complex might overcome the problems of regioselectivity described above (Scheme 11).[24] Treatment of acetate complex **40** with $AlEt_3$ or with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ resulted in the clean conversion to products **41** and **42** respectively (Scheme 12). The reactions were completely regioselective and significantly completely stereoselective. A mechanism can be proposed in which ionisation of the acetate



Scheme 11 *In situ* trapping of cationic complexes by nucleophiles



Scheme 12 Formation of the transoid η^5-pentadienyl cationic complex from **40** and subsequent reactions with nucleophiles

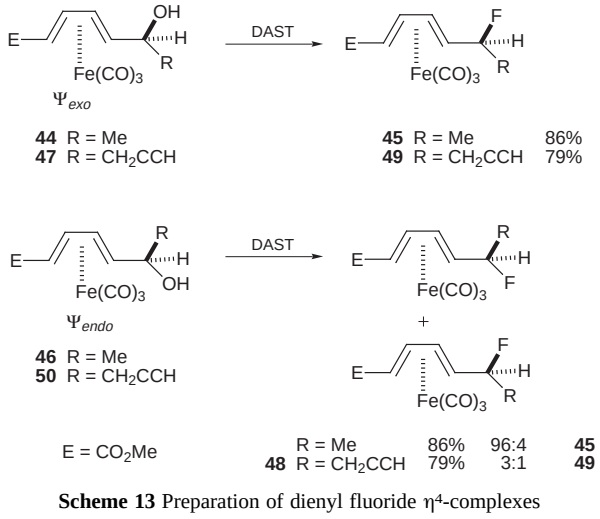
through neighbouring group participation of the $Fe(CO)_3$ moiety generates the transoid η^5-pentadienyl cationic complex **43** which is trapped by the nucleophile attacking *anti* to the $Fe(CO)_3$ group. The overall result is an S_N1-type substitution which proceeds with complete retention of configuration.

Roush and Wada have investigated the reaction in more detail.[25] They have shown that ionisation of a free alcohol with $BF_3{\cdot}OEt_2$ in the presence of $TMSN_3$ or allyltributylstannane generates the substitution products in excellent yield without the need for conversion to the acetate. With less Lewis acidic nucleophiles such as $AlMe_3$, substitution of the free alcohol is quite sluggish. However conversion to the acetate circumvents this problem and the reaction then occurs in excellent yield. Ester substituents on the diene ligand serve to deactivate the system, presumably by interfering with carbocation formation. However, conversion of the alcohol to the more labile chloroacetate again solves this problem and substitution typically occurs in excellent yield. In all cases, elimination products are very minor if observed at all.

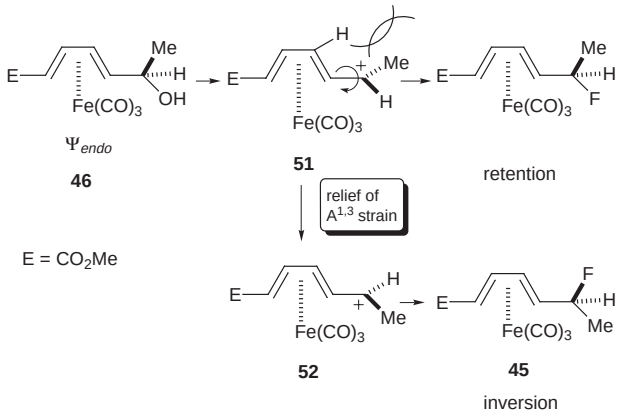
Grée *et al.* have used this reaction to synthesise diastereoisomerically pure dienyl fluorides.[26] Treatment of dienol Ψ_{exo} complex **44** with diethylaminosulfur trifluoride (DAST) at −50 °C afforded fluoride **45** in 86% yield and with complete retention of configuration. Interestingly the corresponding Ψ_{endo} complex **46** reacted in similarly high yield but was slightly less stereoselective with a small proportion of the apparent inversion product **45** being produced. The same result was observed with propargylic alcohol complexes: the Ψ_{exo} complex **47** reacted with complete retention of configuration whereas a 3 : 1 mixture of retention:inversion products **48** and **49** respectively, was observed with the Ψ_{endo} complex **50** (Scheme 13).

There appears to be a difference in reactivity between Ψ_{exo} and Ψ_{endo} complexes with the former complexes exhibiting higher levels of stereocontrol. Consideration of the preferred conformations adopted by the side-chain carbinol centres provides some insight into this difference. One may postulate that the Ψ_{endo} complex **46** initially forms cationic complex **51** which suffers from appreciable $A^{1,3}$-allylic strain. If isomerisation to the more stable complex **52** (as formed by ionisation of the Ψ_{exo} complex) occurs before the cation is trapped, product **45**, resulting from overall inversion of configuration, would be observed (Scheme 14).

The above rationale is based on the assumption that the $Fe(CO)_3$ is an active neighbouring group in aiding ionisation of the α-centre. Another possibility which would also account for the small degree of stereochemical leakage in the Ψ_{endo} series is that the α-centre also undergoes unassisted ionisation in its

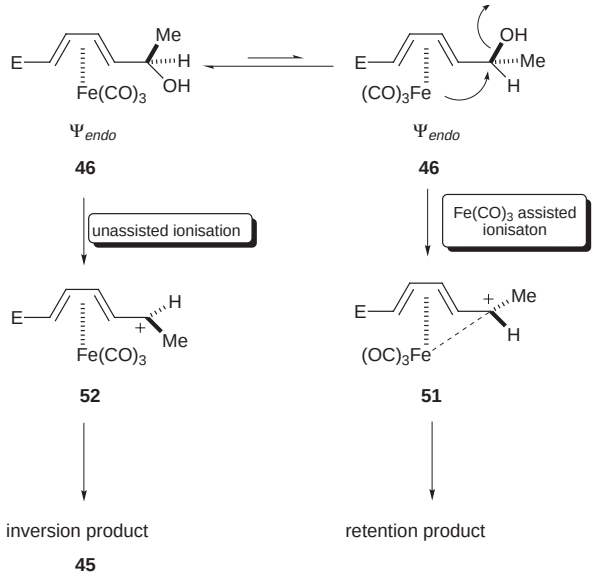


Scheme 13 Preparation of dienyl fluoride η^4-complexes



Scheme 14 A possible mechanism for the formation of the inversion product **45**

preferred conformation (*vide supra*).[27] In this case cationic complex **52** is formed directly and leads to the inversion product by nucleophilic trapping from the *exo* face (Scheme 15).

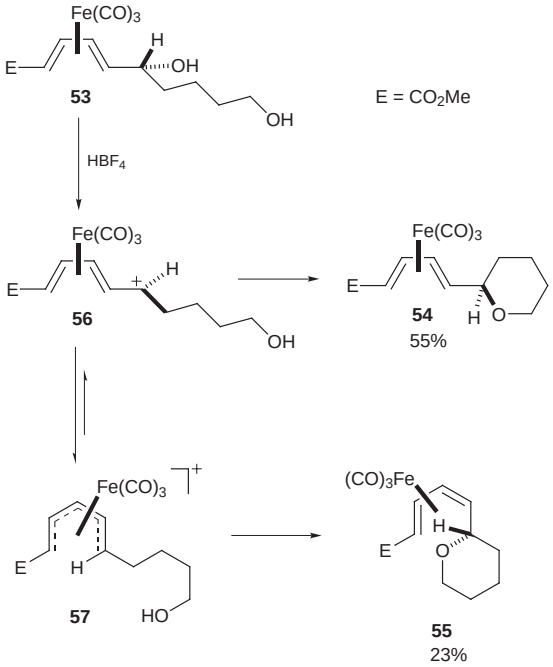


Scheme 15 An alternative mechanism for the formation of inversion product **45**

7.1 Synthesis of heterocycles

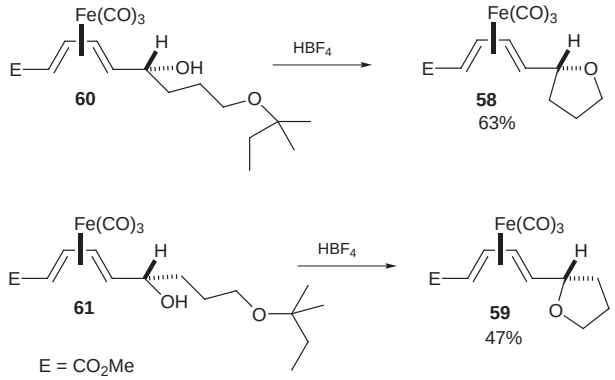
As an alternative to trapping the generated transoid cationic complex with an external nucleophile, intramolecular nucleo-

philic trapping provides an interesting route to cyclic products. Treatment of diol complex **53** with HBF_4 at 20 °C afforded a mixture of (*E,E*)- and (*E,Z*)-η^4-diene complexes **54** and **55** possessing tetrahydropyran substituents. Complex **54** results from *exo* attack of the primary alcohol on the generated pentadienyl cation **56** (Scheme 16).[28] Presumably isomerisation to the more stable cisoid geometry **57** is sufficiently rapid under the reaction conditions to compete with trapping of the cation hence the formation of the two (readily separable) products. Note that under the strongly acidic reaction conditions, the possibility that product formation is a reversible process and the reaction is under thermodynamic control cannot be discounted.



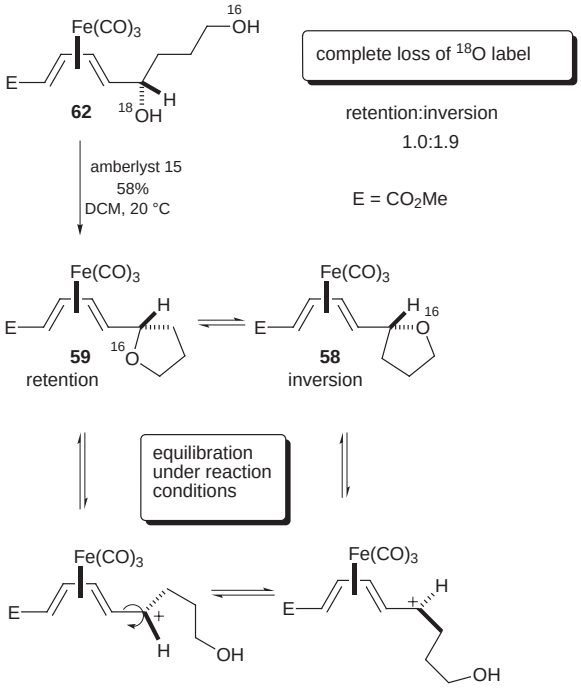
Scheme 16 Stereoselective synthesis of tetrahydropyrans

In a related system the tetrahydrofuran analogues **58** and **59** have been prepared by treating alcohol complexes **60** and **61** with HBF_4 respectively. No products arising from isomerisation to a cisoid geometry were observed in this case which may be due to the kinetic favourability of five-membered ring formation resulting in a much more rapid trapping of the cation such that isomerisation is no longer a competing process (Scheme 17).[28] This may also suggest that product formation is not reversible (but see below).



Scheme 17 Stereoselective synthesis of tetrahydrofurans

Grée and Paquette have probed the cyclisation mechanism for tetrahydrofuran formation using ^{18}O labelling studies.[29] Treatment of diol complex **62** with Amberlyst 15 results in the complete loss of any label in the formation of the tetrahydrofuran products **58** and **59** (Scheme 18). Under the reaction conditions employed, two products are isolated, with the major diastereoisomer **58** resulting from an apparent inversion of configuration. However the lack of a label in the product adds credence to an S_N1-type substitution pathway being followed and suggests that the occurrence of two products is owing to equilibration under the reaction conditions. The authors suggest that the extended reaction time required for complete conversion allows the reverse reaction to proceed and with it the potential for σ-bond rotation leading to a loss of stereoselectivity in spite of the nucleophile attacking exclusively *anti* to the $Fe(CO)_3$ group.



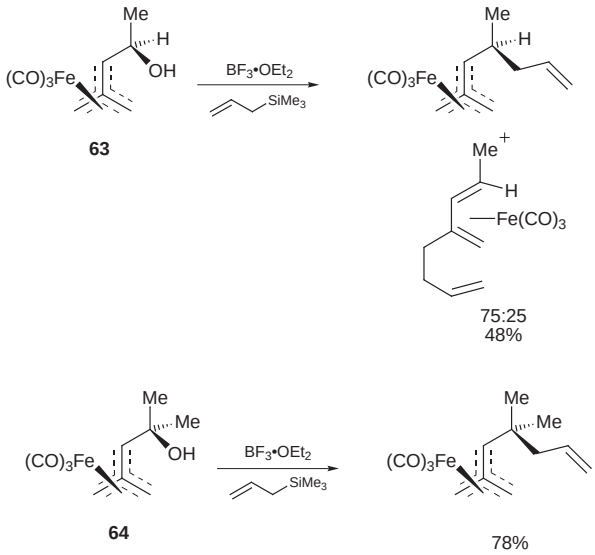
Scheme 18 Stereoselective synthesis of tetrahydrofurans

7.2 (Trimethylenemethane)tricarbonyliron complexes as a source of cross-conjugated pentadienyl cations

Generation of a cation α to TMM complex **63** by standard treatment of an α-hydroxy group with $BF_3{\cdot}OEt_2$ affords the corresponding cross-conjugated pentadienyl cation. *In situ*-trapping of this cation with allyltrimethylsilane affords the *ipso* substitution products in high yield and with complete retention of configuration (Scheme 19).[30] Complete regiocontrol is not always observed and the isoprene-type η^4-diene complexes resulting from substitution at one of the unsubstituted termini of the cation are sometimes observed. However, these side-products are usually minor and readily separable from the TMM products. Again, even when tertiary carbocations are generated (*e.g.* from complex **64**), elimination products are not observed.

7.3 π-Allyltricarbonyliron lactone complexes in nucleophilic substitution reactions

Attempts to repeat this type of substitution reaction on π-allyltricarbonyliron lactone complexes have not met with success. Subjection of complexes bearing α-tertiary alcohol stereogenic centres to analogous reaction conditions results in dehydration and the resulting complexes bearing an olefinic side-chain are isolated in high yield. Clearly the presence of the lactone tether in this family of complexes has an effect on the ability of the tricarbonyliron moiety to stabilise positive charge α to the ligand and this is sufficient to favour a dehydration pathway. No reaction is observed in the case of secondary alcohol complexes.



Scheme 19 Allyltrimethylsilane reacts with cross-conjugated pentadienyl cations generated from trimethylenemethane complexes

7.4 Conclusions

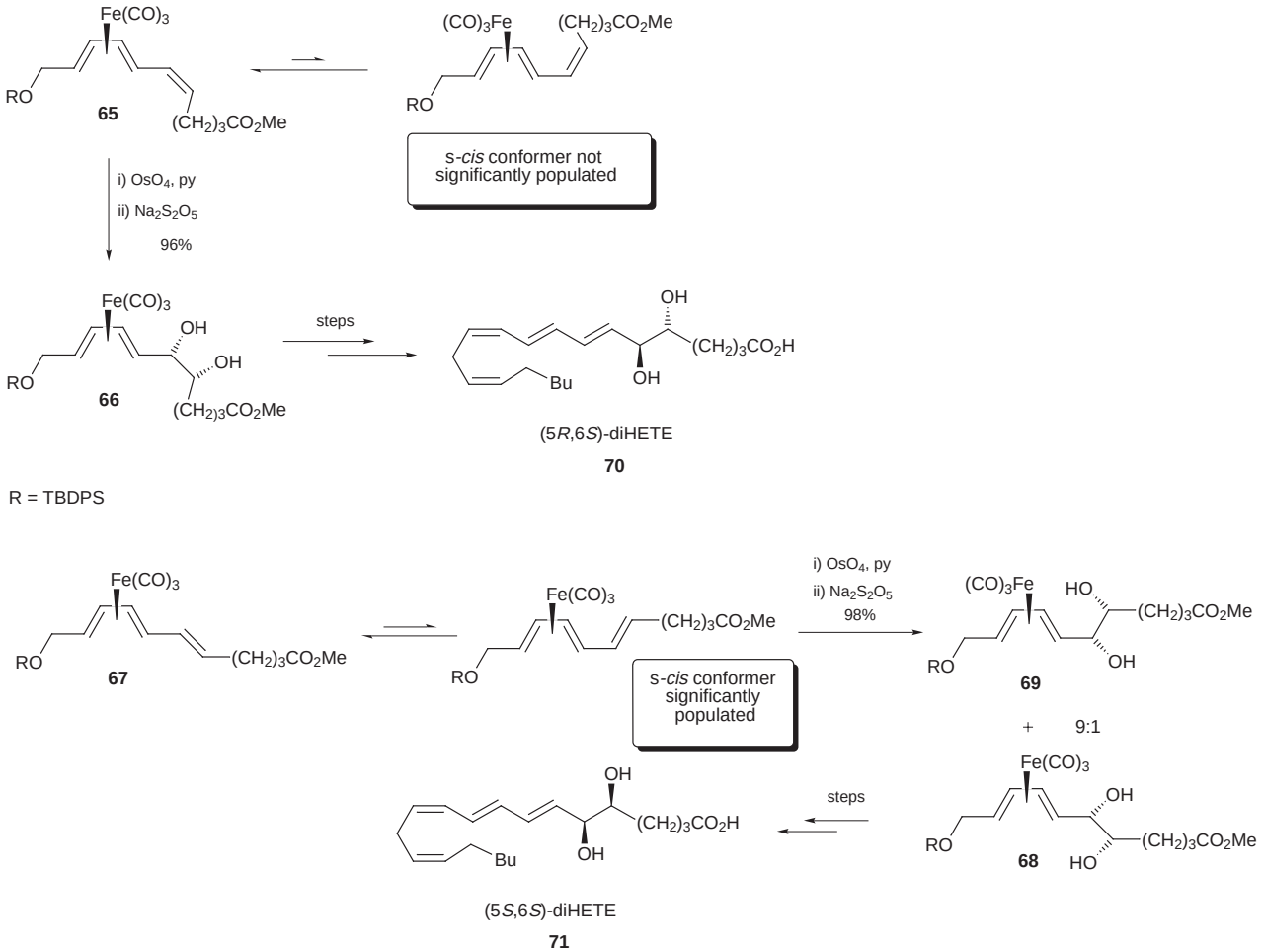
The unpredictable—and frequently low—regioselectivity in the reaction between nucleophiles and η^5-pentadienyltricarbonyliron cationic complexes has led to the development of a modification of the reaction: *in situ* nucleophilic trapping of the cation generated by ionisation of suitably functionalised η^4-diene complexes. This not only removes the need for isolation of the pentadienyl cationic complex intermediate, but in most cases occurs with complete regiocontrol. The reaction is also highly stereoselective with the incoming nucleophile attacking the *exo* face, *anti* to the sterically demanding $Fe(CO)_3$ unit. The reaction occurs under mild conditions and the products are usually formed in high yields. Intramolecular trapping of the cation has been investigated leading to the preparation of tetrahydropyrans, tetrahydrofurans and more recently tetrahydrothiopyrans and oxocenes.[31,32] The reaction works equally well with trimethylenemethane complexes although in some cases, complete regiocontrol is not observed. π-Allyltricarbonyliron lactone complexes do not undergo analogous reactions; only dehydration is observed in susceptible substrates.

8 Incorporation of olefin functionality in the side-chain of tricarbonyliron complexes

The tricarbonyliron moiety acts as a highly efficient protecting group for diene functionality. Thus while any olefin in the side-chain of these complexes observes normal patterns of reactivity, the protected diene remains intact. Again the steric bulk of the $Fe(CO)_3$ group, combined with the fact that side-chain appendages frequently adopt a preferential conformation, ensures ample opportunity for stereoselective synthesis.

8.1 Asymmetric dihydroxylation

Grée and co-workers have used a stoichiometric osmylation to effect glycolation of olefins directly attached to η^4-diene complexes.[33] (Note that although catalytic versions of the dihydroxylation reaction are compatible with the organometallic unit, diol products are usually contaminated with ketols

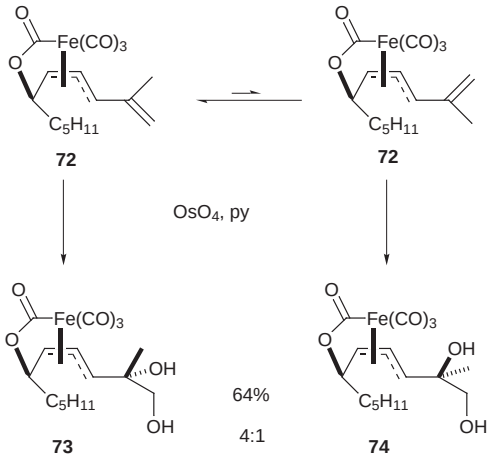


Scheme 20 Preparation of diHETE metabolites utilising a stereoselective glycolation of functionalised η^4-diene complexes **65** and **67**

resulting from over-oxidation). Since the $Fe(CO)_3$ moiety is acting as a protecting group for the diene, the overall outcome of the reaction is complete regiocontrol in the dihydroxylation of a triene.

Excellent stereocontrol is observed in the case of *cis* olefin complex **65** with only one diol product **66** being isolated. In the case of its *trans* isomer **67**, a separable 9:1 mixture of diols, **68** and **69**, is produced, again in excellent yield (Scheme 20). In both cases the major product derives from attack of the OsO_4 on the olefin *anti* to the $Fe(CO)_3$ unit. The olefin functionality preferentially adopts an s-*trans* conformation to minimise steric interactions between the side-chain and ligand. However, in the case of *trans* olefin complex **67**, even the s-*cis* conformation doesn't suffer from excessive steric repulsions. As a result, both conformations may be adopted, although the product deriving from attack on the more heavily populated s-*trans* conformer predominates. This high yielding, stereoselective glycolation has been successfully applied to the total syntheses of the arachidonic acid metabolites, (5*R*,6*S*) and (5*S*,6*S*)-diHETE, **70** and **71** respectively (Scheme 20).[33]

π-Allyltricarbonyliron lactone complexes have also been briefly investigated as a source of stereocontrol in an asymmetric dihydroxylation reaction. Treatment of olefin complex **72** with OsO_4 in pyridine afforded a 4 : 1 mixture of diastereoisomeric diols **73** and **74** with the major product resulting from *anti* attack of the OsO_4 reagent on the s-*trans*-conformation of the olefin in a completely analogous fashion to that reported for η^4-diene complexes (Scheme 21).



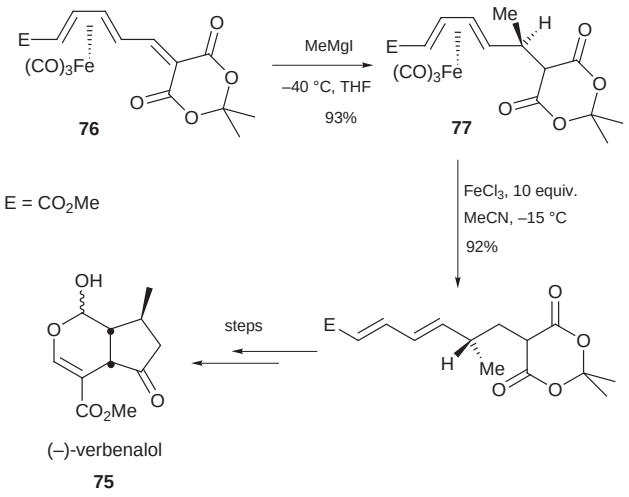
Scheme 21 Olefin functionality in the side-chain of π-allytricarbonyliron complex **72** undergoes stereoselective dihydroxylation

8.2 Enone functionality in the side-chain of η^4-diene complexes

η^4-Diene complexes bearing α,β-unsaturated carbonyl functionality in the side-chain have been prepared. They preferentially adopt the s-*trans* conformation thereby minimising steric interactions with the diene ligand. The powerful blocking capability of the $Fe(CO)_3$ unit has been utilised to perform a highly stereoselective 1,4-addition reaction in Grée's total synthesis of (−)-verbenalol **75** (Scheme 22).[34] Treatment of highly reactive enone **76** with MeMgI at −40 °C in THF produced the 1,4-addition product **77** in excellent yield and as a single diastereoisomer. Further manipulations led to (−)-verbenalol **75**.[34] Again partial complexation of the trienone by the $Fe(CO)_3$ unit ensures the exclusive formation of the 1,4-addition product **77**.

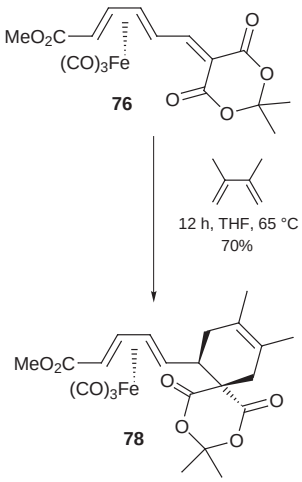
8.3 Incorporation of dienophiles in the side-chain of η^4-diene complexes

The same precursor **76** has also been used in a Diels–Alder reaction with 2,3-dimethylbutadiene.[35] Heating at reflux in THF for 12 h resulted in the isolation of the Diels–Alder adduct **78** in



Scheme 22 Use of a stereoselective Michael reaction in the synthesis of (−)-verbenalol

70% yield arising from *exo* addition of the diene to the s-*trans*-conformation of the dienophile (Scheme 23).



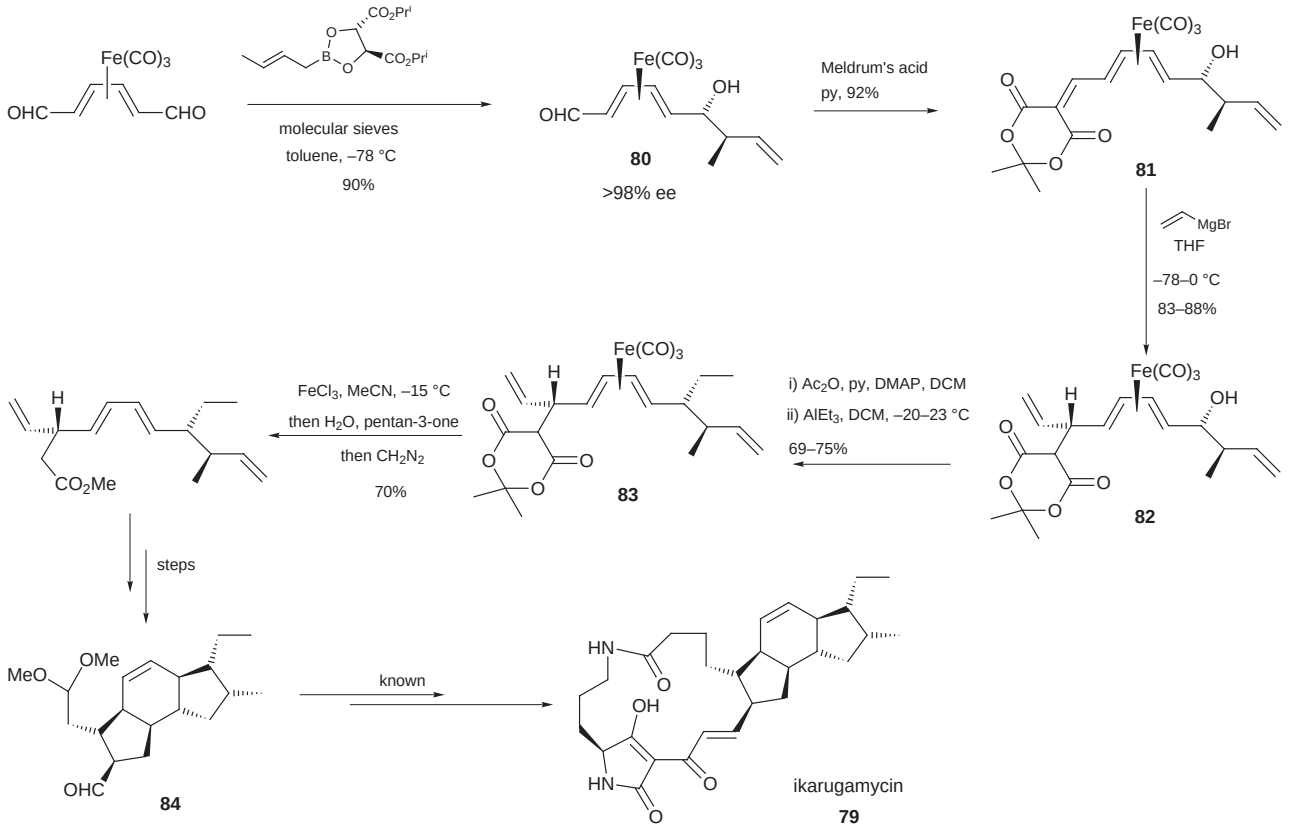
Scheme 23 Stereoselective Diels–Alder reaction

8.4 Conclusions

Incorporation of olefin functionality into the side-chain of η^4-diene complexes has been achieved. Again the minimisation of steric interactions between the ligand and the side-chain ensures the preferential adoption of one conformation by the appendage. This, in association with the steric blocking ability of the $Fe(CO)_3$ group provides an efficient means for stereocontrol in a number of typical reactions of olefins.

9 Tricarbonyliron complexes in asymmetric synthesis—a summary

Tricarbonyliron complexes bearing a wide variety of functional groups as side-chain appendages can be prepared in enantiomerically enriched form. The $Fe(CO)_3$ group acts as a sterically bulky unit directing the facial attack of reagents onto functional groups in the side-chain of the ligand. Steric interactions between the ligand and the side-chain appendage cause olefin and carbonyl functional groups preferentially to adopt one conformation. The degree of steric blocking by the $Fe(CO)_3$ moiety seems to be absolute with reagents approaching *anti* to the steric encumbrance. The nature of the functional group α to the ligand dictates the population of conformers with ketones and some olefinic substrates behaving as though only one reactive conformation is adopted and giving rise to excellent



Scheme 24 Roush's approach to ikarugamycin **79**

levels of stereocontrol. Aldehydes appear to be less conformationally biased although good to excellent levels of stereocontrol may still be obtained by careful choice of reagents and manipulation of reaction conditions.

The ability of the tricarbonyliron moiety to affect the reactivity of functionality in the side-chain is exemplified by the nucleophilic substitution reactions of η^4-diene and trimethylenemethane complexes in which products deriving exclusively from an S_N1-type substitution process are produced with the tricarbonyliron group participating in cation stabilisation in addition to acting as a blocking group to ensure excellent levels of stereocontrol. This balance is a fine one and in analogous reactions with π-allyltricarbonyliron complexes, the only products isolated are those resulting from dehydration.

A final example by Roush and Wada exemplifies how tricarbonyliron complexes can be elegantly incorporated into modern synthetic design.[36] In his formal synthesis of ikarugamycin **79**, Roush first utilises a face and group selective desymmetrisation using a tartrate-derived allylboronate reagent to obtain the enantiomerically enriched starting material **80**. Modification of a side-chain then affords a Michael acceptor **81** which is used in a highly stereoselective 1,4-addition reaction, affording **82**. Finally, generation of the transoid pentadienyl cationic complex with *in situ*-trapping with an organoaluminium reagent installs another stereocentre and forms **83.** Efficient decomplexation, another important characteristic of tricarbonyliron complex chemistry allows for the preparation of the indacene unit **84** of ikarugamycin **79** (Scheme 24).

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