Mukaiyama aldol reactions of π-allyltricarbonyliron lactone and lactam complexes bearing trimethylsilyl enol ether side-chains. Not just formal, but genuine 1,7 induction of chirality

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A comparison of diastereoselectivities in the Mukaiyama aldol reactions of three types of trimethylsilyl enol ether substituted iron carbonyl complexes has provided evidence for the stereodirecting effect of remote substituents in π-allyltricarbonyliron lactone and lactam complexes.

The complexation of an organic ligand to a metal can influence the stereoselectivity of its reactions in a variety of ways. We have previously demonstrated the use of the π-allyltricarbonyliron lactone framework[1] as a chiral template to provide diastereocontrol in the manipulation of a ketone functionality appended to the allyl unit.[2,3] The reactions of such ketones with nucleophiles proceed with predictable stereochemistry, the ketone adopting an s-*cis* conformation and the nucleophile approaching *anti* to the bulky $Fe(CO)_3$ moiety. This parallels the reactivity pattern of the related η⁴ dienone tricarbonyliron complexes (Fig. 1).[4]

More recently, we have shown that trimethylsilyl enol ethers derived from *endo* substituted π-allyltricarbonyliron lactone complexes can undergo highly diastereoselective Mukaiyama aldol reactions with a variety of aldehydes under $BF_3{\cdot}OEt_2$ activation.[5] The selectivity in these reactions is more difficult to explain, as it is dependent only on the ability of the enol ether side-chain to distinguish between the prochiral faces of the Lewis acid–aldehyde complex. Interestingly, the trimethylsilyl enol ethers of η⁴ dienone tricarbonyliron complexes have been reported to show poor diastereoselectivity in their reactions with aldehydes under $BF_3{\cdot}OEt_2$ activation.[6] This apparent difference in the influence of the structurally similar enol ether substrates implies that the lactone portion of the π-allyl complexes might be involved in controlling the delivery of the aldehyde. More specifically, the *endo* substituent at the lactone tether, *seven* carbon atoms distant from the developing stereocentre, could interact directly with the incoming Lewis acid–aldehyde complex (Fig. 2).

This communication reports an investigation of diastereocontrol in the Mukaiyama aldol reactions of π-allyltricarbonyliron lactone and lactam complexes by variation of the substitution pattern at the tether and a direct comparison with a representative η⁴ diene tricarbonyliron complex.

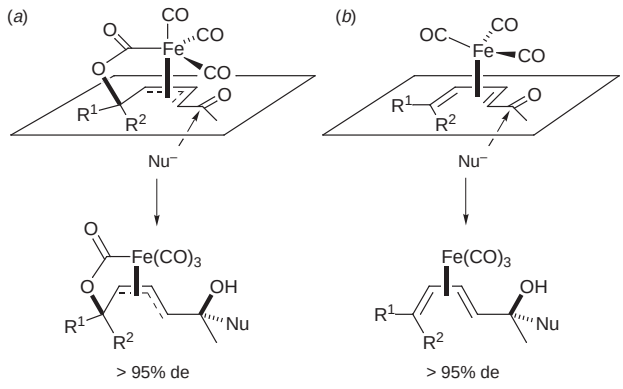


Fig. 1 Tricarbonyliron-mediated diastereocontrol: reaction of (*a*) ketone functionalised π-allyltricarbonyliron lactones and (*b*) η⁴-dienone complexes with nucleophiles

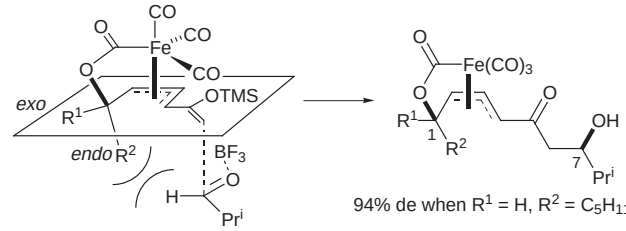
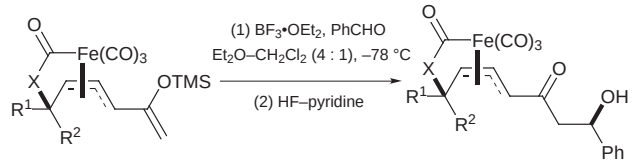


Fig. 2 Possible involvement of the *endo* substituent in directing Mukaiyama aldol reactions of π-allyltricarbonyliron lactone complexes

Trimethylsilyl enol ethers were prepared in excellent yields from the corresponding methyl ketone complexes by reaction with TMSOTf and Et_3N in CH_2Cl_2 at 0 °C. Treatment with premixed benzaldehyde and $BF_3{\cdot}OEt_2$ in Et_2O–CH_2Cl_2 at −78 °C afforded mixtures of TMS protected and unprotected aldol products which were desilylated using HF–pyridine during the work-up. A comparison of the yields and diastereoselectivities obtained using π-allyltricarbonyliron lactone and lactam complexes is shown in Table 1.

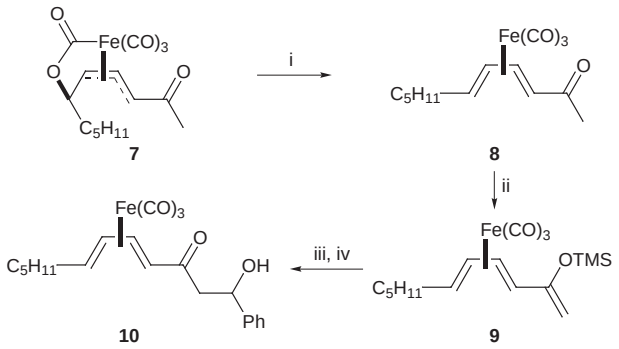
The *endo* substituted complexes **1**, **2**, **3** and **5** showed good to excellent levels of asymmetric induction in their reactions with benzaldehyde. The slightly lower diastereomeric excess obtained with the *endo* phenyl complex **3** may reflect the contribution of a favourable interaction between the aromatic rings of the complex and aldehyde. The diastereomeric excesses obtained when the complex was *exo* substituted (complexes **4** and **6**) were significantly reduced, showing that an important

Table 1 Mukaiyama aldol reaction of silyl enol ethers derived from π-allyltricarbonyliron lactone and lactam complexes with benzaldehyde



Complex	R^1	R^2	X	Yield (%)	De (%)[a]
1	H	C_5H_{11}	O	81	86
2	H	Me	O	81[b]	87
3	H	Ph	O	72	67
4	C_5H_{11}	H	O	53	55
5	H	Me	NBn	66[b]	90
6	Me	H	NBn	62[b]	57

[a] Diastereomeric excess determined by comparison of integrals in the ^1H NMR spectrum of the crude reaction mixture. [b] Reaction carried out in neat CH_2Cl_2 due to low Et_2O solubility of the substrate; this led to improved yields but did not affect the de.



Scheme 1 *Reagents and conditions*: i, $Ba(OH)_2$ MeOH, room temp., 15 min, 92%; ii, Et_3N, TMSOTf, CH_2Cl_2, 0 °C, 90 min, 92%; iii, $BF_3{\cdot}OEt_2$, PhCHO, Et_2O–CH_2Cl_2 (4 : 1), − 78 °C, 1 h; iv, HF–Py, THF, 30 min, 64% yield over 2 steps, 25% de

element of the stereocontrol is indeed lost when the *endo* substituent R^2 is replaced by hydrogen. No significant difference in selectivity was observed between π-allyltricarbonyliron lactone and lactam complexes.

The (*E*,*E*) η^4-diene complex **8** was easily prepared from lactone complex **7** by treatment with barium hydroxide solution.[2b,7] Formation of the trimethylsilyl enol ether **9** in the usual way and reaction with benzaldehyde under standard conditions resulted in the formation of aldol product **10** with only 25% diastereomeric excess (Scheme 1). The selectivity is therefore significantly lower than even that achieved with *exo* substituted lactone and lactam complexes. The relative stereochemistry of the major diastereoisomer was determined for the reactions of complexes **1**, **6** and **9** by stereospecific reduction of the β-hydroxy ketone products to 1,3-diols followed by acetonide formation[5] and was found to be the same in each case as shown.

In summary, the Mukaiyama aldol reactions of a range of *endo* substituted π-allyltricarbonyliron lactone and lactam complexes proceed with high yields and diastereoselectivities. The lack of an *endo* substituent results in a significant decrease in the observed selectivity. A further decrease in selectivity occurs when the mode of attachment of the iron tricarbonyl unit is altered by conversion of the π-allyl complex into an η^4 diene complex. It therefore appears that the tricarbonyliron lactone or lactam unit provides control on a number of different levels during the reaction. The silyl enol ether functionality is maintained in a specific orientation and shielded from one face by the tricarbonyliron group, while on the opposite face a remote substituent is projected to create a chiral environment, restricting the possible orientations of the incoming boron trifluoride–aldehyde complex.

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Notes and References

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