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IMPROVED STEREOCHEMICAL CONTROL AND MECHANISTIC ASPECTS OF THE ALKYLATION OF ENOLATES DERIVED FROM $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2R]$

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Summary: An analysis of the factors controlling the stereoselective alkylation reations of enolates derived from $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2R]$ results in an amelioration in the observed stereoselectivities to >200:1.

Enolates derived from acyl ligands attached to the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ undergo highly stereoselective alkylation reactions.[1,2] The stereochemical control observed in these reactions is consistent with preferential formation of E-enolates and their subsequent alkylation in the anti conformation (O^- to CO) from the unhindered face; the other face being completely shielded by the triphenylphosphine ligand[2,3] (Figure 1). We describe here a detailed analysis of the origins of this selectivity which allows significant improvements in the stereocontrol to be achieved.

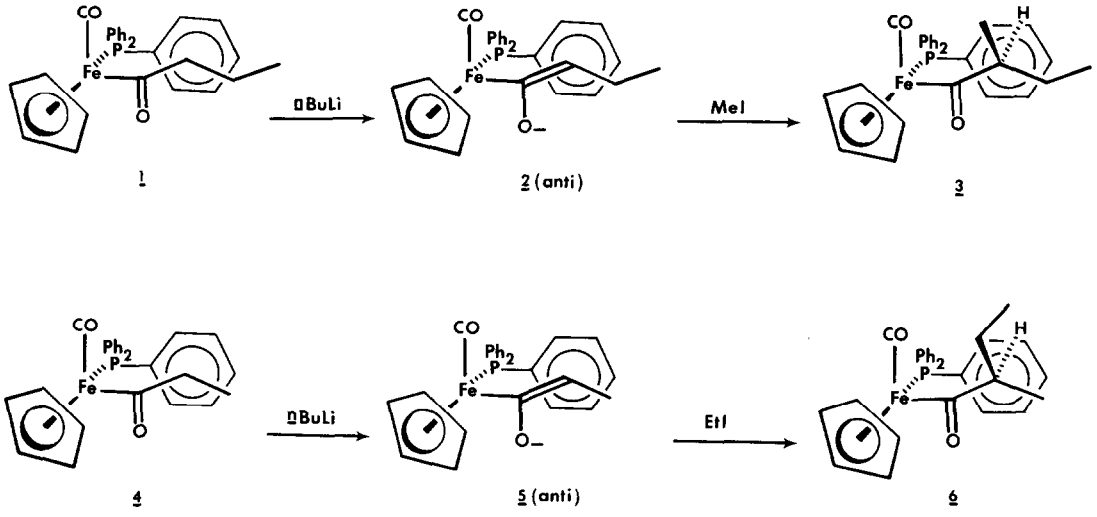

Figure 1 Stereoselective alkylations of iron acyl enolates.

In the preceding paper[4] we demonstrated for the parent acetyl complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_3]$ 1 that it is the steric interaction between the acetyl ligand and one of the phenyl groups of PPh_3 that is responsible for the acetyl group preferring to lie in the plane containing Fe, CO and the acetyl-carbonyl-carbon. However it is the destabilising steric interaction between the methyl group and a second phenyl group in the syn conformation that is responsible for the anti, acyl-oxygen to CO, conformation being preferred. This latter steric interaction and hence anti-preference would be expected to be very much reduced in the enolates 2 and 5 (sp^2 hydridisation vs sp^3) and even if the anti conformation were still the more favourable the syn conformation would be readily accessible and could be the more reactive (Curtin-Hammett principle[5]). In order to remove the anti-directing effect of this second phenyl group, complexes analogous to 1 and 4 with the triphenylphosphine replaced by 9-phenyl-9-phosphafluorene[6] were prepared. Alkylation of these complexes via their corresponding enolates proved as stereoselective as for complexes 1 and 4 (ca. 30:1) consistent with the stereoselectivities being dependent on factors other than those arising from interactions with the PPh_3 ligand.

Inspection of the molecular structures of iron acyl complexes such as 3[2,4] strongly suggested the involvement of the cyclopentadienyl ligand in these reactions. Figure 2 illustrates Newman projections for the anti and syn enolates together with the approach paths of the incoming electrophile. For the anti enolate conformation the approach of the electrophile is completely unimpeded. In contrast, for the syn enolate, the incoming electrophile must pass close too if not through the space occupied by the cyclopentadienyl ligand.

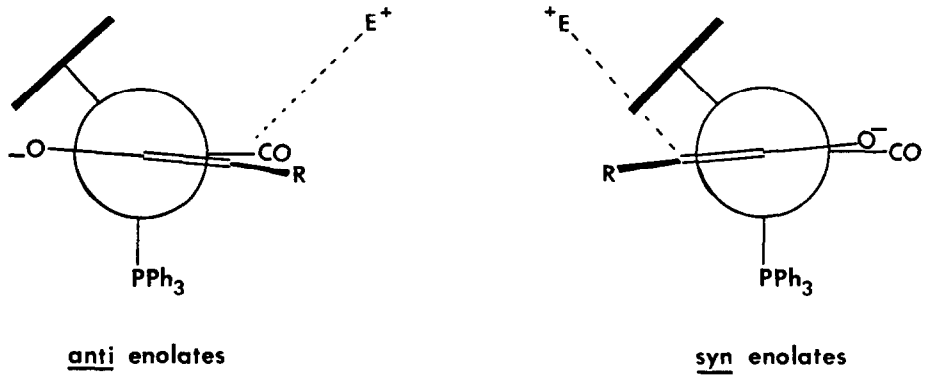

Figure 2: Electrophilic additions to anti and syn E-iron enolates.

In order to probe the effect of the cyclopentadienyl ligand, extended Huckel (EH) calculations were performed, as described previously,[4,7] on the model complexes $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPhH_2)COR]$ R=CH_2CH_3, 7 and R=$CH(CH_3)_2$, 8. (The $PPhH_2$ rather than the PPh_2H model was chosen specifically to probe the effect of the cyclopentadienyl ligand on the anti-syn populations since the $PPhH_2$ ligand imparts essentially no anti or syn preference itself). The calculations on the ethyl acyl complex 7 showed that for both the anti and syn acyl oxygen to CO orientations, only conformations of the ethyl fragment where its methyl group is cis to the acyl oxygen, i.e. trans to the large iron moiety, are populated. This is

consistent with complexes 1 and 4 both giving exclusively the E-enolates 2 and 5 respectively since the enolate geometry should be independent of whichever acyl conformer, acyl oxygen to CO anti or syn, is deprotonated, although the anti conformation is expected to be deprotonated faster due to unhindered access by the base. Of particular importance is that the calculated minimum energies of the anti and syn conformers of 7 are essentially the same, in accord with our preceding conformational analysis of $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPhH_2)COCH_3]$.[4] Calculations on the isopropyl acyl complex 8 revealed that for both the anti and syn acyl-oxygen to CO orientations, the isopropyl group is restricted to essentially a single conformation in each case, as illustrated in Figure 3. Of crucial importance is that the EH calculated minimum energies for 8-anti and 8-syn differ by ca. 12 kcal. mol^{-1} with the syn conformation being destabilised by steric interactions between the methyl groups and the cyclopentadienyl ligand (Figure 3). This bias, due to interactions with the cyclopentadienyl ligand, in favour of the anti-conformation reinforces that caused by the PPh_3 ligand.[4]

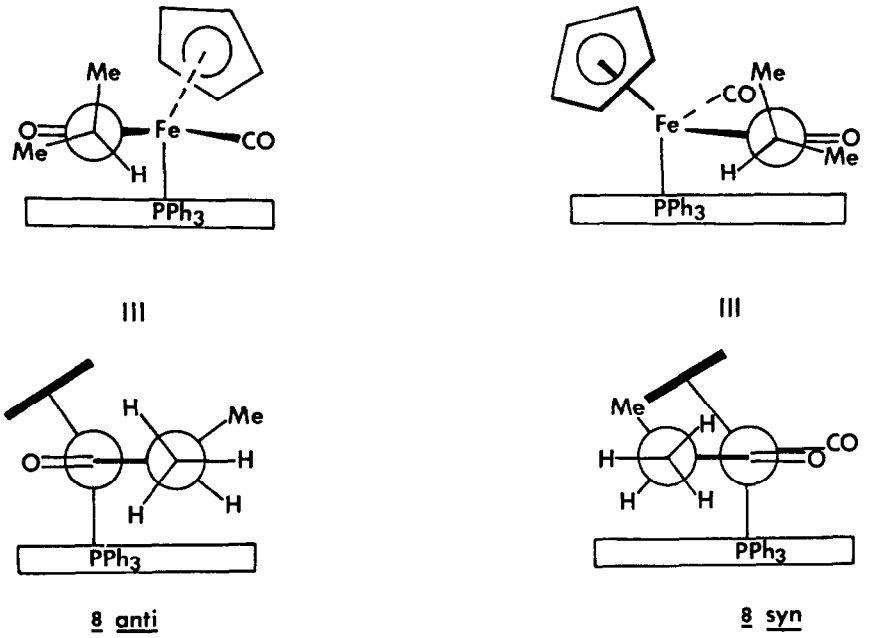

Figure 3: Calculated preferred conformations for 8-anti and 8-syn

Irrespective of whether the transition state is early (approach control, Figure 2) or late (product development control, Figure 3), our conformational anaylsis predicts that alkylation reactions of enolates 2 and 5 occur via their anti enolate-oxygen to CO conformations. Furthermore increased size of the electrophile should enhance the observed stereoselectivity. This is fully borne out in practice as shown in the Table. Changing the alkylating agent from the alkyl iodide to the large tosylate or by adding Et_2AlCl to increase the bulk of the electrophile by coordination results in a significant amelioration in the stereoselectivities observed such that the minor diastereoisomer ceases to be detectable by 300 MH ^1H n.m.r. spectroscopy (>200:1).

Table: Stereoselective alkylations of enolates 2 and 5

enolate	RX	Diastereoisomer ratios 3:6
2	MeBr	~ 30 : 1
2	MeI	~ 30 : 1
2	MeOTs	>200 : 1*
2	MeI/Et_2AlCl†	>200 : 1*
5	EtI	~ 1 : 45
5	EtI/Et_2AlCl†	< 1 : 200*

† Et_2AlCl added to enolate immediately followed by RI.

* estimated using the ^{13}C satellites of the major diastereoisomer as an internal standard corresponding to 180:1.

In summary, under the optimum conditions described above, acyl ligands bound to the chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] undergo deprotonation by n-butyllithium to give exclusively (>200:1) the corresponding E-enolates. These E-enolates undergo alkylation reactions exclusively (>200:1) in the anti acyl-oxygen to CO conformation from the unhindered face opposite the PPh_3. The resulting overall elaboration of a new chiral centre via carbon-carbon bond formation occurs with extremely high stereoselectivity (>200:1). The above analysis is also applicable to alkoxyvinyl complexes attached to this iron[8] or the analogous rhenium[9] chiral auxiliaries which also undergo highly stereoselective alkylation reaction preferentially in the anti alkoxy-oxygen to CO or NO conformations respectively from the unhindered face opposite PPh_3.

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