Diastereoselective additions to aldehyde groups in the side-chain of π-allyltricarbonyliron lactone complexes

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π-Allyltricarbonyliron lactone complexes containing aldehyde groups adjacent to the allyl system undergo addition reactions with a variety of organoaluminium reagents in moderate to excellent diastereoselectivity.

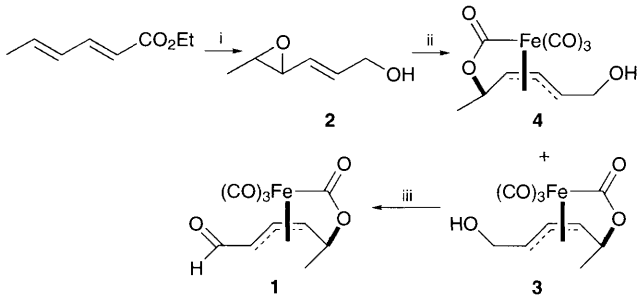
We recently reported that π-allyltricarbonyliron lactone complexes bearing ketone groups in the side-chain undergo efficient addition reactions with a variety of organoaluminium reagents with excellent diastereoselectivity.[1] The alcohol adducts obtained can be manipulated in a highly selective manner to afford stereodefined η^4-dienetricarbonyliron complexes. In addition, application of the Sharpless asymmetric epoxidation protocol[2] generates these π-allyltricarbonyliron lactone complexes in enantiomerically enriched form, and the addition reactions and subsequent manipulations can be carried out without significant loss of enantiopurity. Our recent enantioselective synthesis of (+)-β-dimorphecolic acid[3] exploited this chemistry in using the tricarbonyliron tether to control all the elements of stereochemistry in the natural product. Here we report that π-allyltricarbonyliron lactone complexes bearing aldehyde groups in the side-chain also exhibit similar 1,5-aymmetric induction in their reactions with organoaluminium reagents, which proceed with moderate to excellent diastereoselectivity. This behaviour contrasts sharply to similarly formyl-substituted η^4-dienetricarbonyliron complexes which exhibit poor stereoselectivity in their reactions with organometallic reagents,[4] and further demonstrates the superiority of π-allyltricarbonyliron lactone complexes in such reactions.

In this work we have concentrated on addition reactions to the racemic aldehyde complex **1**, whose preparation is outlined in Scheme 1. Regioselective epoxidation of (2*E*,4*E*) ethyl hexa-2,4-dienoate, mediated by *in situ* generated trifluoroperacetic acid,[5] followed by chemoselective reduction of the ester functionality occurred smoothly to provide the epoxy alcohol **2**. Treatment of this vinyl epoxide with diironnonacarbonyl in THF[6] furnished the separable diastereoisomeric complexes *endo* **3** and *exo* **4**, in 64% combined yield and a ratio of 2 : 1 respectively. Oxidation of the alcohol in **3** using pyridinium dichromate (PDC), prepared according to the procedure of Corey,†[7] afforded the desired aldehyde **1** in 79% yield. Preliminary investigations had revealed that π-allyltricarbonyliron complexes containing aldehyde groups are unstable to chromatographic purification on a variety of stationary phases. This route therefore allows the facile preparation of these complexes as the oxidation step merely requires filtration to provide pure material,‡ and has the added advantage of avoiding potentially volatile intermediates containing aldehyde functionality.

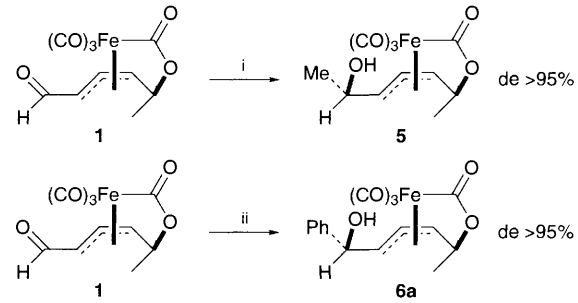
In our previous work we established that ketone substituted π-allyltricarbonyliron lactone complexes preferentially react in the *s-cis* conformation.[1] In addition, this apparent reactive conformation was also adopted in the ground state, as determined by ^{1}H NMR and X-ray studies. In this work, NOE studies performed on the aldehyde **1** indicated that both *s-cis* and *s-trans* conformations were populated in the ground state. Reaction with trimethylaluminium and dimethylphenylaluminium,§ however, demonstrated that the aldehyde still attains the same apparent *s-cis* reactive conformation as single diastereoisomeric products, **5** and **6a**, respectively, were obtained (Scheme 2).

The relative stereochemical outcome of these addition reactions was determined by comparison with their diastereoisomeric counterparts produced in our earlier work[1] by reduction of the respective ketones. We have clearly established that reduction of these ketones occurs *anti* to the bulky tricarbonyliron unit on the *s-cis* conformer. In this study, dramatic differences in the ^{1}H NMR spectra of **5** and **6a**, compared to the ketone reduction products, allow us to state with certainty their relative stereochemistry. Moreover, **5** and **6a** were significantly less polar than their diastereoisomeric partners, a phenomenon observed in related iron complexes,[8] and this aided us in our stereochemical assignments.

Addition reactions with a variety of organoaluminium reagents are listed in Table 1, from which it is apparent that the stereochemical course of the reaction is dependent on the nature of the aluminium reagent. Thus, as the steric demands of the dummy ligands attached to the aluminium change, there is an associated change in the stereoselectivity of the addition reaction, culminating in the reaction with triphenylaluminium in which the stereochemical outcome is reversed. An attempt to



Scheme 1 *Reagents and conditions*: i, $(CF_3CO)_2O$ (10 equiv.), $H_2NCONH_2.H_2O_2$ (40 equiv.), Na_2HPO_4 (20 equiv.), CH_2Cl_2, 0 °C, 45 min; DIBAL-H (1 mol dm^{-3} in hexanes), THF, −78 °C, 30 min, 62% over both steps; ii, $Fe_2(CO)_9$ (2.1 equiv.), THF, 1 h, 40% (**3**), 24% (**4**); iii, (PDC) (1.5 equiv.), 4 Å molecular sieves, CH_2Cl_2, 2 h, 79%



Scheme 2 *Reagents and conditions*: i, $AlMe_3$ (1 mol dm^{-3} solution in hexanes), benzene/toluene (4 : 1), 0 °C, 10 min, 76%; ii, PhLi, $AlMe_2Cl$ (1 mol dm^{-3} solution in hexanes), 0 °C, 45 min then **1**, 0 °C, 10 min, 26%

obtain a similar result with trimethylaluminium exploiting prechelation with Yamamoto's bulky Lewis acid MAD[9] further highlighted the sensitivity of the steric demands the aldehyde **1**; the stereochemical course was not affected and this was presumably due to the excessive bulk of MAD precluding efficient complexation. In spite of the decrease in stereoselectivity upon use of bulky organoaluminium reagents, the observed high stereoselectivity makes these addition reactions potentially valuable for organic synthesis. Moreover, they compare very favourably with the reactions of similarly formyl-substituted η^4-dienetricarbonyliron complexes with organometallic reagents, which typically proceed with diastereoisomeric excesses (de's) in the range 0–50%.[4]

All the addition products **5–8** were demonstrated, by ^{1}H NMR to attain the same conformation in solution as evidenced by the coupling constants between the carbinol proton and the terminal allyl proton being consistently between 3–4 Hz. This suggests, on the basis of work by Lillya on similar iron complexes,[8] that the relative polarities of **5–8** are related to their relative stereochemistry. Using this principle, comparison of the relative polarities of the adducts **6b–8b** with **5** and **6a** allowed us to tentatively assign their relative stereochemistry.

Finally, with the adducts in hand we have examined the oxidation of the alcohol function. Since these complexes are susceptible to oxidative decomplexation,[10] we were pleased to find that the activated alcohols **6b** and **7** as well as the unactivated alcohol **5** were readily transformed into the respective ketones upon treatment with barium manganate[11] or PDC, respectively (Table 2). Since we have established that such ketones undergo highly diastereoselective addition reactions, this approach will allow for a flexible synthesis of either diastereoisomeric tertiary alcohol. Simply by selecting the order of addition of the nucleophilic moieties added to the aldehyde and to the ketone produced after oxidation of the resultant secondary alcohol, the tertiary alcohol of choice will be obtained.

In conclusion, we have further demonstrated the utility of π-allyltricarbonyliron lactone complexes in stereoselective synthesis. Thus, the ability of the templating tricarbonyliron tether to influence remote stereoselection and to effect 1,5-asymmetric induction has been extended to include aldehyde-substituted complexes, which exhibit moderate to excellent stereoselectivity upon reaction with a variety of organoaluminium reagents. We envisage that these reactions can be performed equally as well on enantiomerically enriched complexes, and that the aldehyde complex **1** will prove to be a valuable source of compounds for further investigations in the area of stereoselective synthesis.

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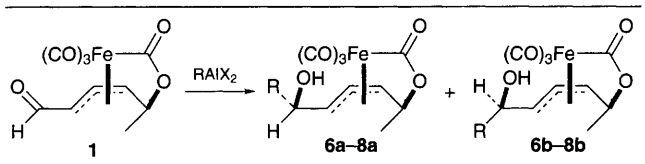
Table 1 Diastereoselective addition reactions to racemic π-allyltricarbonyliron lactone complex **1**

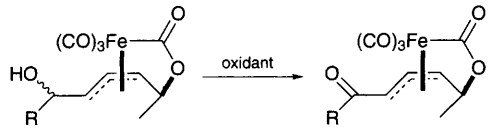


1 **6a–8a** **6b–8b**

Entry	$RAlX_2$	Product ratio[a]	Combined yield (%)
1	Bu—≡—$AlMe_2$	**7a**:**7b** 9:1	70
2	Bu—//—$AlBu^i_2$	**8a**:**8b** 5:1	65
3	Bu—≡—)$_3$Al	**7a**:**7b** 2:1	56
4	Ph_3Al	**6a**:**6b** 1:4[b]	71

[a] Determined by ^{1}H NMR of the mixture unless otherwise indicated. [b] Based on isolated material.

Table 2 Oxidation of alcohol functionality in addition products



Complex	R	Oxidant	Yield (%)
7	Bu—≡—ξ	$BaMnO_4$	80
5	Me	PDC	80
6b	Ph	$BaMnO_4$	94

Footnotes

† Commercially supplied PDC proved inferior, giving inconsistent results.

‡ *Selected spectroscopic data* for aldehyde **1**: mp 125–127 °C (dec.); ν_{max} ($CHCl_3$)/cm^{-1} 3019, 2975, 2925, 2810, 2810, 2010 (CO), 2030 (CO), 1674 (C=O), 1448, 1372, 1216 and 1047; ^{1}H NMR δ (200 MHz, $CDCl_3$) 1.39 (3 H, d, *J* 6.4 Hz, 6-H × 3), 4.01 (1 H, dd, *J* 11.4 Hz, 3.1, 2-H), 4.56 (1 H, qd, *J* 6.4 Hz, 5.6, 5-H), 5.09 (1 H, dd, *J* 8.6 Hz, 4.6, 4-H), 5.44 (1 H, dd, *J* 11.4 Hz, 8.6, 3-H) and 9.72 (1 H, d, *J* 3.1 Hz, 1-H); *m/z* (FAB) 281 (MH^+, 24%), 279 ([M − H]$^+$, 17%), 253 ([MH − CO]$^+$, 16%), 197 ([MH − 3CO]$^+$, 17%), 153 ([MH − 3CO − CO_2]$^+$, 100%)

§ The methyl adduct **5** was also produced as a single diastereoisomer in 36% yield.

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