Diastereoselective Addition Reactions to Carbonyl Groups in the Side-chain of π-Allyltricarbonyliron Lactone Complexes

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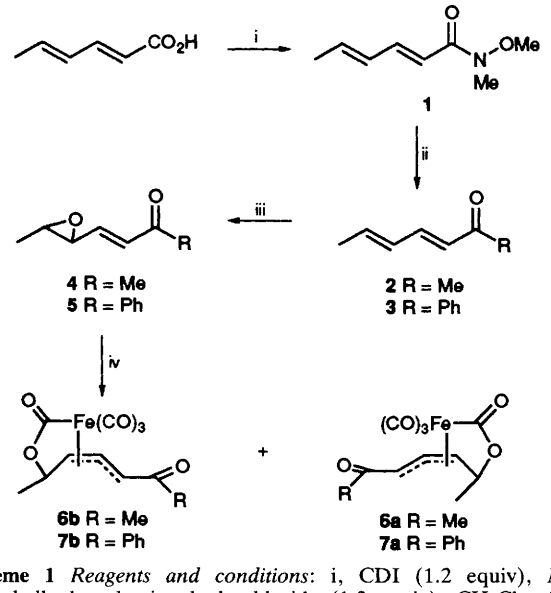
Organoaluminium reagents add in a highly diastereoselective fashion to carbonyl groups adjacent to the allyl system of π-allyltricarbonyliron lactone complexes.

Highly diastereoselective addition reactions to a carbonyl group in the side-chains of acyclic η^4-dienetricarbonyliron complexes are well documented[1] and have featured in many natural product syntheses.[1a,e] The preparation of these compounds in optically pure form, however, has caused many problems and often involves inefficient resolution methods.[1a,d,2] We wish to report here some diastereoselective addition reactions to carbonyl groups adjacent to the π-allyl system of π-allyltricarbonyliron lactone complexes and subsequent stereoselective manipulation to η^4-dienetricarbonyliron complexes. Furthermore, the reaction constitutes an example of 1,5-asymmetric induction of chirality[3] using an $Fe(CO)_3$ complexing lactone tether to promote the induction process.

In this study we have concentrated primarily on addition reactions to two *endo* complexes, **6a** and **7a** (Scheme 1). (*E,E*)-2,4-hexadienoic acid was transformed into the dienones **2** and **3** *via* the Weinreb amide[4] **1** followed by regioselective epoxidation with dimethyldioxirane[5] or *in situ* generated trifluoroperacetic acid.[6] Treatment of **4** or **5** with diironnonacarbonyl in THF at room temperature[7] afforded **6a** or **7a**, respectively, together with small amounts of the diastereoisomeric *exo* complexes **6b** or **7b**. Separation by flash column chromatography or preparative HPLC afforded the pure compounds.

A number of addition reactions to these complexes were examined using a variety of Lewis acidic alkyl, aryl, alkenyl, and alkynylorganoaluminium reagents[8] which gave good to excellent yields of product (Table 1). In all cases, with both *endo* or *exo* complexes only one diastereoisomeric product could be observed by 400 MHz ^1H NMR or HPLC analysis. Hence, >95% de is a conservative estimate of the selectivity of the addition reaction. With organoaluminium reagents containing β hydrogen atoms the reduction products of the side-chain carbonyl group were observed, however, the normal addition products predominated in all examples (Table 1). In the case of alkenylaluminium reagents formation of the reduction product could be prevented using alkenyldimethylaluminium compounds.

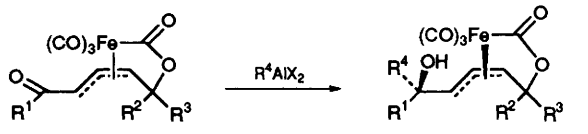


Scheme 1 *Reagents and conditions*: i, CDI (1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (1.3 equiv), CH_2Cl_2, 40 h, 90%; ii, RMgBr (1.1 equiv.), THF, 0 °C, 30 min, 96% (**2**), or 1 h, 84% (**3**); iii, dimethyldioxirane (1.1 equiv.), CH_2Cl_2, 0 °C, 3.5 h, 95% (**4**), or $(CF_3CO)_2O$ (10 equiv.), H_2NCONH_2 (40 equiv.), K_2HPO_4, CH_2Cl_2, 1 h, 94% (**5**); iv, $Fe_2(CO)_9$ (1.8 equiv.), THF, 3 h, 54% (**6a**), 14% (**6b**), or 1 h, 67% (**7a**), 9% (**7b**)

The relative stereochemical outcome of the addition has been established through extensive ^1H NMR studies and by X-ray crystallography. From these data it is apparent that nucleophilic addition occurs opposite to the tricarbonyliron unit *via* the *S-cis* conformer. X-ray crystallographic analysis of **6a** showed that this apparent reactive conformation was also adopted in the starting material in the solid state. Furthermore, NOE studies performed on **6a** and **7a** both showed large enhancements between the carbonyl substituent R^1 and only the α-H of the allyl unit, indicating that both adopt the same *S-cis* conformation in solution. This, in combination with the formation of complementary diastereomeric addition products **13** and **17**, indicates that a common stereochemical pathway is operating in the reactions of **6** and **7**.

Having demonstrated the high level of diastereoselectivity of these addition reactions we proceeded to investigate

Table 1 Diastereoselective additions of organoaluminium compounds to racemic π-allyltricarbonyliron lactone complexes



6a R^1=Me, R^2=Me, R^3=H
6b R^1=Me, R^2=H, R^3=Me
7a R^1=Ph, R^2=Me, R^3=H
7b R^1=Ph, R^2=H, R^3=Me

rac **8–24**

Complex	R^4AlX_2	Product	Yield[a] (%)	de[b] (%)
6a	$AlEt_3$	**8**	68 (7)	>95
6a	Bu^n—≡—$AlMe_2$	**9**	95	>98[c]
6a	Bu^t—≡—$AlMe_2$	**10**	95	>98[c]
6a	Bu^n—⁄⁄—$AlBu^i_2$	**11**	54 (9)	>95
6a	Bu^n—⁄⁄—$AlMe_2$	**12**	72	>95
6a	$AlPh_3$	**13**	67	>95
6b	$AlEt_3$	**14**	58 (6)	>95
6b	Bu^n—≡—$AlMe_2$	**15**	95	>95
6b	Bu^n—⁄⁄—$AlMe_2$	**16**	87	>95
7a	$AlMe_3$	**17**	88	>95
7a	$AlEt_3$	**18**	72 (24)	>95
7a	Bu^n—≡—$AlMe_2$	**19**	70	>98[c]
7a	Bu^t—≡—$AlMe_2$	**20**	58	>95
7a	Bu^n—⁄⁄—$AlBu^i_2$	**21**	93 (5)	>98[c]
7b	$AlMe_3$	**22**	95	>95
7b	Bu^n—≡—$AlMe_2$	**23**	64	>95
7b	Bu^n—⁄⁄—$AlBu^i_2$	**24**	52 (5)	97

[a] Figures in parentheses refer to the isolated yield of a second product in which the side-chain carbonyl group was reduced. [b] Determined by ^1H NMR unless otherwise indicated. [c] Determined by chiral HPLC analysis (Daicel®, OD column).

Table 2 Diastereoselective additions to enantiomerically enriched π-allyltricarbonyliron lactone complexes

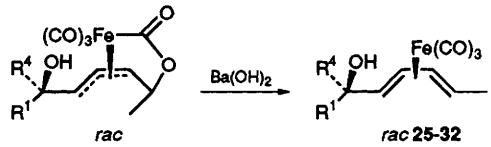
(S)-6a R¹ = Me
(S)-7a R¹ = Ph

(R,S)-9,10
(S,S)-22,23,24

Complex	R^4AlX_2	Product	Yield[a] (%)	de[b] (%)	ee[b] (%)
(S)-6a	Bu^n—≡—$AlMe_2$	(R,S)-9	78	>98	84
(S)-6a	Bu^t—≡—$AlMe_2$	(R,S)-10	72	>98	86
(S)-7a	$AlMe_3$	(S,S)-22	89	>95[c]	>85[d]
(S)-7a	Bu^n—≡—$AlMe_2$	(S,S)-23	65	>98	82
(S)-7a	Bu^n—//—$AlBu^i_2$	(S,S)-24	67 (9)	>98	83[e]

[a] Figure in parentheses refers to the isolated yield of the product arising from reduction of the side-chain carbonyl group. [b] Determined by HPLC analysis (Daicel®, OD Column) unless otherwise indicated. [c] Determined by ^1H NMR. [d] Determined on the decarboxylated product (see text). [e] Determined using the chiral shift reagent $Pr(hfc)_3$.

Table 3 Formation of η^4-dienetricarbonyliron complexes



rac *rac* **25-32**

Complex	R^1	R^4	Yield (%)	Product
8	Me	Et	87	**25**
13	Me	Ph	85	**26**
10	Me	Bu^t—≡—§	95	**27**
11	Me	Bu^n—//—§	95	**28**
17	Ph	Me	80	**29**
22	Ph	H	94	**30**
20	Ph	Bu^t—≡—§	80	**31**
25	Ph	Bu^n—//—§	81	**32**

reactions with enantiomerically enriched π-allyltricarbonyliron lactone complexes (S)-**6a** and (S)-**7a**, which were readily prepared from (E)-crotyl alcohol, *via* Sharpless asymmetric epoxidation.[9] Additions of organoaluminium reagents proceeded with good efficiency (Table 2) and with no significant loss of optical purity.

Finally, with a number of the addition complexes to hand we have examined their conversion to the corresponding η^4-dienetricarbonyliron complexes by treatment with barium hydroxide (Table 3) using the method developed by Aumann.[10] In these reactions decarboxylation occurs in a stereoselective manner to give geometrically defined (E,E)-complexes. The stereochemistry of the diene unit was established as being (E,E) in a series of NOE experiments in which large enhancements between the terminal vinylic protons were observed. The value of the coupling constant between the vinylic protons, typically 8.5 and 5.0 Hz, was consistent with the values found in similar literature known compounds.[1c] Comparison of the ^1H NMR of **25** and **30** with samples of known relative configuration[1c] supports the assignment of the relative stereochemistry. In one case an optically enriched addition product **17** was subjected to treatment with $Ba(OH)_2$ and the resulting η^4-dienetricarbonyliron complex had an ee of 85%, indicating that there was no racemisation of the tertiary stereocentre. The outcome of this reaction is in accord with the mechanism proposed by Aumann.[10]

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