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Long-Range Asymmetric Induction by Conjugate Addition to Alkenylcyclohexadienyliron Complexes

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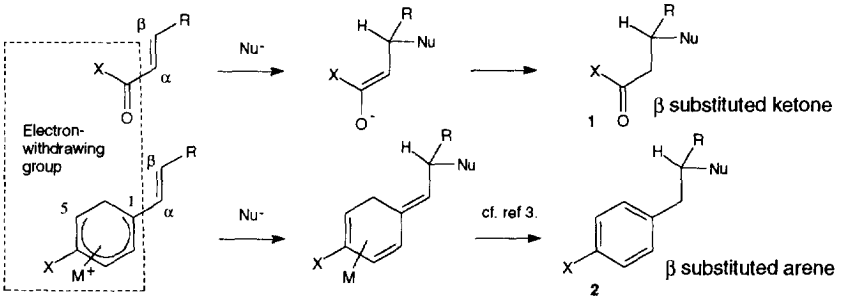
Abstract: A general method for the preparation of a series of vinyl-substituted tricarbonyl(cyclohexadienyl)iron(1+) salts is described. A novel regiocontrol switch from direct to conjugate addition is observed when stabilised enolates with differing metal counterions react with these complexes. Organocuprates show regio- and stereocontrol. Long range asymmetric induction by the metal control centre is improved from 2 : 1 to 8 : 1 by inclusion of a phosphine in place of CO. Copyright © 1996 Elsevier Science Ltd

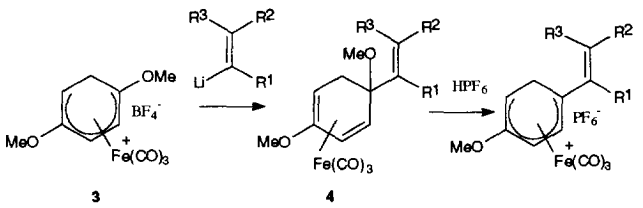
Alkenes are not themselves electrophilic, but when activated by an electron withdrawing π-system (e.g. the carbonyl group of an α,β-unsaturated ester or ketone; Scheme 1), they react well with suitable nucleophiles to afford products such as **1**. Enolates can be used, but organocuprate reagents are especially suited to conjugate addition reactions of this type.[1] We have examined[2] an analogous process in which the π-system is activated by conjugation with a cationic transition metal dienyl complex, giving access to arene derivatives **2**,[3] a process that is complementary in scope to the normal conjugate addition route to β-substituted ketones and esters. With cyclohexadienyliron-based electrophiles, *conjugate addition* proceeds in competition with *direct addition* to a metal-bound carbon atom, but we have shown[2] that a suitable regiodirecting group on the η^5-ligand can promote efficient conjugate addition with a variety of nucleophiles. Since the cyclohexadienyl complexes used for this purpose are chiral, a possibility exists for remote asymmetric induction, if control effects reach out from the organoiron complex to the β-carbon. We report here the development of a novel asymmetric conjugate addition process of this type.



Scheme 1. (M = $Fe(CO)_3$ or $Fe(CO)_2PPh_3$, R = H, Me)

Our first objective was to develop a general route to cyclohexadienyl complexes carrying substituted alkenes at C-1. In order to assess the extent to which steric hindrance by substituents would influence the conjugate addition process, we have prepared a series of methylalkenyl-substituted salts **6-8**. Following our preparation of the first alkenylcyclohexadienyl tricarbonyliron complex **5**,[2] we have developed[4,5] a convenient general method for the preparation of aryl-substituted cyclohexadienyl complexes by aryllithium addition to the 1,4-

dimethoxy-substituted compound **3**. Applying this procedure with alkenyllithium reagents, followed by the removal of the allylic OMe group, afforded the required alkenyl-substituted salts in good yield on a multigram scale (Scheme 2). The β-methyl regioisomer **7** is of particular importance since it contains a prochiral centre at the β carbon atom, and is less hindered than **8**. The *E* isomer **7** was obtained from (*Z*)-1-bromopropene, or, in a stereoconvergent fashion as a single stereoisomer in 56% yield from the less expensive stereo-undefined *E/Z* mixture of bromopropenes. This convenient stereoconvergent equilibration of *E/Z* alkenes, which takes place during the demethoxylation step, makes **7** readily available in exclusively the *E* form on a substantial scale.[6]



5 : $R^1 = R^2 = R^3 = H$; 69%
6 : R^1 = Me, $R^2 = R^3 = H$; 68%
7 : $R^1 = R^3 = H$, R^2 =Me; 59%
8 : $R^1 = R^2$ = Me, $R^3 = H$; 62%
(or $R^1 = R^3$ = Me, $R^2 = H$)

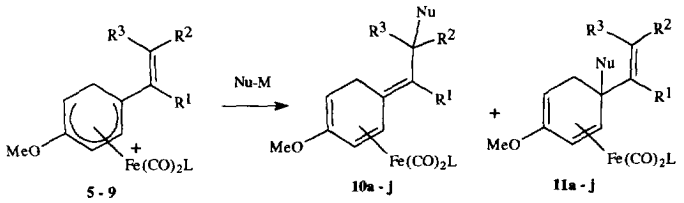
Scheme 2.

The results of nucleophile addition (Scheme 3) are presented in Table 1. When stabilised enolates are employed as the nucleophile, the regiochemistry of the addition process was found to depend on nature of the counterion, with lithium enolates promoting conjugate addition (entries 2,4,6) to a greater extent than sodium enolates (entries 3,5,7). Unlike the ethenyl-substituted parent compound **5**, none of the methylethenyl substituted salts gave exclusive conjugate addition, despite the presence of the OMe directing group on the cyclohexadienyl ligand. With **6** (entry 2), considerable conjugate addition was observed, but when the methyl group was placed at the β carbon (entries 4,6), conjugate addition was disfavoured and became the minor pathway.

Table 1: Regio- and Stereoselectivity of Nucleophile Addition Reactions shown in Scheme 3.

Entry	Salt	R^1	R^2	R^3	L	Nu-M	Prod.	Ratio **10** : **11**	yield (%)	dr[a]
1[b]	**5**	H	H	H	CO	$NaCH(CO_2Me)_2$	a	>99 : <1	73	-
2	**6**	Me	H	H	CO	$LiCH(CO_2Me)_2$	b	70 : 30	30	-
3	**6**	Me	H	H	CO	$NaCH(CO_2Me)_2$	b	<1 : >99	30	-
4	**7**	H	Me	H	CO	$LiCH(CO_2Me)_2$	c	25 : 75	40	1:1
5	**7**	H	Me	H	CO	$NaCH(CO_2Me)_2$	c	<1 : >99	45	-
6	**8**	Me	Me[c]	H[c]	CO	$LiCH(CO_2Me)_2$	d	20 : 80	40	8:5
7	**8**	Me	Me[c]	H[c]	CO	$NaCH(CO_2Me)_2$	d	<1 : >99	40	-
8	**6**	Me	H	H	CO	$Bu_2CuLi.SMe_2$	e	>99 : <1	70	-
9	**6**	Me	H	H	CO	$Ph_2CuLi.SMe_2$	f	>99 : <1	67	-
10	**7**	H	Me	H	CO	$Bu_2CuLi.SMe_2$	g	>99 : <1	20	2:1
11	**7**	H	Me	H	CO	$Ph_2CuLi.SMe_2$	h	>99 : <1	22	2:1
12	**9**	H	Me	H	PPh_3	$Ph_2CuLi.SMe_2$	i	>99 : <1	65	8:1
13	**9**	H	Me	H	PPh_3	$LiCH(CO_2Me)_2$	j	>99 : <1	30	3:1

[a] ratio of diastereoisomers at the β position of regioisomer **10**.
[b] Ref. 2.
[c] *E* / *Z* stereochemistry could not be unambiguously assigned. R^2 = H, R^3 = Me cannot be ruled out.

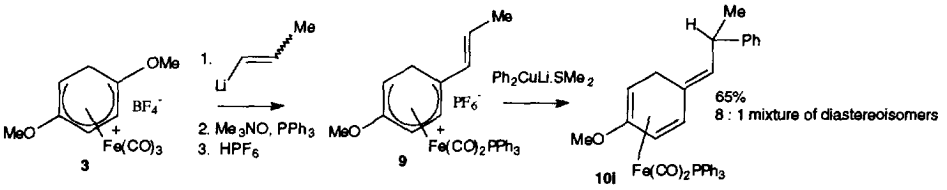


Scheme 3

Of the nucleophiles examined in our original study,[2] organocuprates had shown the greatest tendency for conjugate addition, perhaps because of the mechanism[7] of addition via π-association with the alkene. As a consequence, we turned our attention to organocuprate nucleophiles (entries 8-12), and were rewarded by the formation of single products in good yield.[8] Even with organocuprates, however, there remained a significant problem in the β-methyl case, giving yields of only 20-22% (entries 10,11) although the adduct was now formed as a single regioisomer. None of the products of direct addition were detectable in the reaction mixtures.

Two stereochemical features must be considered in these reactions, the orientation of the alkene during nucleophile addition and face-selectivity of the approach of the nucleophile. An unsymmetrically substituted exocyclic alkene is formed by the conjugate addition route. In each case, only a single alkene stereochemistry was observed, assigned as the *E* configuration (Scheme 3) on the basis of n.O.e. experiments on structures **10d-f**. Equilibration of the alkene stereochemistry after the nucleophile addition step seems unlikely since the presence of an α-methyl substituent in **6** and **8** should reduce the likelihood of totally selective interconversion of alkene products, but stereocontrol is retained. We favour an explanation based on kinetic control during the approach of the nucleophile, indicating that the reacting conformation of the alkenyl-substituted salts is as drawn in Scheme 3.[2,9] The second issue is face-selectivity of attack of the nucleophile to prochiral alkenyl substituents. The products **10g** and **10h** were examined by high field NMR and were shown to be a 2:1 mixture of diastereoisomers; control at the β-carbon arising from steric or electronic effects promoted by the tricarbonyliron group was clearly far from complete. Entries 4 and 6 also produced new chiral centres at the β-carbon in the minor products, and diastereoisomer ratios were estimated by NMR (Table 1). In all cases examined, diastereoselectivity was in the range 1:1 to 2:1.

A simple strategy was available to improve diastereoselectivity (Scheme 3; L=PPh_3). Increasing steric effects on the face of the ligand carrying the iron carbonyl moiety (the *endo* face) should improve selectivity for reaction by *exo* addition. Ligand exchange[10] (CO to PPh_3) was performed on the product from 1-lithioprop-1-ene addition to **3** and the resulting phosphine complex was converted into the salt **9** as before. Again this reaction was stereoconvergent, affording only the *E* stereoisomer. X-ray crystallography[11] revealed that like **7**, the salt **9** adopted in the solid state the conformation that is expected also to be preferred in the conjugate addition pathway. Diphenylcuprate was employed as the nucleophile to test diastereoselectivity (Scheme 4).



Scheme 4

The reaction proved more efficient (65%) and, as before, produced only the *E* stereoisomer of the exocyclic alkene, but now showed considerable stereoselectivity at the β-carbon. The product **10i** was

formed as an 8:1 mixture of diastereoisomers (table 1, entry 12). In contrast, addition of the lithiomalonate nucleophile (entry 13), whilst affording only the conjugate addition product **10j**, proceeded in lower (30%) yield and was less diastereoselective (3:1).

In conclusion, we have shown that it is possible to perform diastereoselective conjugate addition to a substituted prochiral alkenyl group activated by π-overlap with a cationic cyclohexadienyliron complex,[12] and that the most suitable procedure is the use of an organocuprate nucleophile with a dicarbonyl(triphenylphosphine)iron complex. The relative stereochemistry of the major products in all cases is unknown but nevertheless these examples demonstrate that significant d.e. values may be achieved during addition to the site remote from the iron. Our work on organoiron intermediates in organic synthesis has concentrated on the development of procedures[5,13,14] for the multiple use of the organoiron group to promote electrophilicity and stereocontrol in a series of key bond-formation steps. This is essential for efficient utilisation of a stoichiometric control group.[15] By inducing asymmetry in conjugate addition under control of the iron phosphine complex, we have demonstrated the practicality of an important strategy for application in synthesis, since the metal can reach out beyond its point of attachment to the working ligand, to impart activation and control at more remote sites. Protonation of the resulting exocyclic alkene in the η^4-triene ligand should reform a cyclohexadienyl complex,[16] so the conjugate addition process can be combined with well precedented nucleophilic elaboration of the metal-bound ring[17] in a multistep iron-mediated reaction sequence.

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9. In the case of **7**, this conformation was shown by X-ray crystallography to be also preferred in the solid state (Ref. 11). The alkenyl substituent lies nearly coplanar with the η^5 portion of the ligand, but is aligned opposite (*s-trans*) to the horseshoe of the dienyl system and tilted slightly up towards the cyclohexadienyl C-6 methylene group.
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