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Published on Web 04/14/2006

Nucleophilic Addition to (3-Methylpentadienyl)iron(1+) Cations: Counterion Control of Regioselectivity; Application to the Enantioselective Synthesis of 4,5-Disubstituted Cyclohexenones

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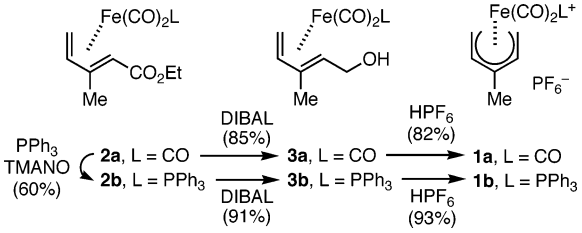
Nucleophilic attack on coordinated polyenes is one of the paradigms of π-organometallic chemistry.[1] We and others have examined the reactivity of (pentadienyl)iron(1+) cations, in particular for applications to organic synthesis.[2] These studies indicate that the regioselectivity of nucleophilic attack depends on the nucleophile, substituents present on the pentadienyl ligand, and "spectator" ligands on iron. As part of our interest in the synthesis of diterpenes containing a 3-methyl-1,3*Z*-pentadienyl side chain[3] we have recently prepared the symmetrical iron(1+) cations **1a** and **b** (Scheme 1). As part of these studies, we now report a counterion-controlled regioselectivity of nucleophilic attack.[4]

Scheme 1



Reduction of the known[5] dienoate complex **2a** gave the alcohol **3a**, which upon acid-mediated dehydration gave the (tricarbonyl)-iron ligated cation **1a** (Scheme 1). In a similar fashion, ligand substitution of **2a** with triphenylphosphine, followed by reduction and acid-mediated dehydration, gave the $PPh_3(CO)_2$ ligated cation **1b**.

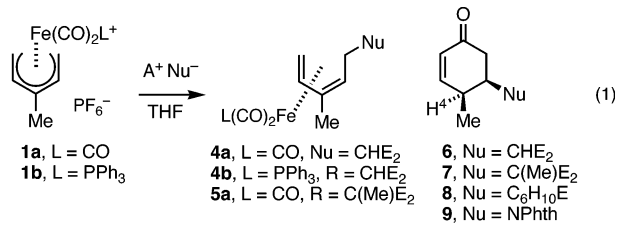
The reaction of **1a** with lithium dimethyl malonate gave the 1,3*Z*-diene complex *rac*-**4a** in good yield (Table 1, entry 1). In contrast,

Table 1. Nucleophilic Addition to (3-Methylpentadienyl)Fe(1+)

entry	cation	counterion/nucleophile	4a/4b/5a	6/7/8/9
1	**1a**	$LiCH(CO_2Me)_2$	**4a** (80%)	
2	**1a**	$NaCH(CO_2Me_2$[a]		**6** (91%)
3	**1a**	$LiCH(CO_2Me)_2$/12-crown-4[a]		**6** (84%)
4	**1a**	$NaCH(CO_2Me)_2/ZnCl_2$	**4a** (60%)	
5	**1a**	$LiC(Me)(CO_2Me)_2$	**5a** (45%)	
6	**1a**	$NaC(Me)(CO_2Me)_2$[a]	**5a** (34%)	**7** (55%)
7	**1b**	$NaCH(CO_2Me)_2$	**4b** (93%)	
8	**1a**	LDA/methyl cyclohexanecarboxylate		**8** (80%)[b]
9	**1a**	KPhth[c]		**9** (34%)[d]

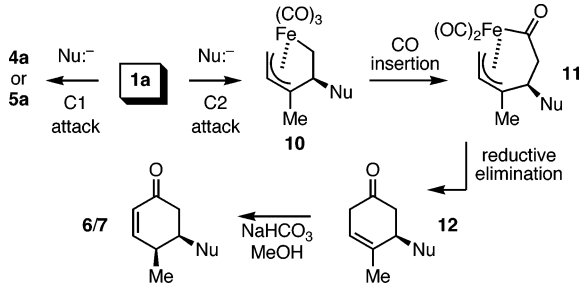
[a] After 2 h, the reaction mixture was diluted with CH_2Cl_2, and methanolic $NaHCO_3$ was added. The mixture was stirred for an additional 18 h. [b] The product is a 6:1 mixture of 2- and 3-cyclohexenones. [c] Reaction solvent is acetone, and the crude reaction mixture was treated with CAN/CH_3CN to effect complete decomposition of the iron acyl intermediate. [d] The product is a 2.5:1 mixture of 2- and 3-cyclohexenones.

the reaction of **1a** with *sodium* dimethyl malonate exhibited copious decomposition upon standing. Treatment of the reaction mixture with methanolic $NaHCO_3$ lead to isolation of the 4,5-disubstituted cyclohexenone *rac*-**6** (entry 2).[6] Furthermore, the reaction of **1a** with lithium dimethyl malonate in the presence of 12-crown-4 gave only the cyclohexenone product **6**, while reaction of **1a** with sodium dimethyl malonate/$ZnCl_2$ gave only the diene complex **4a**. In a similar fashion, reaction of **1a** with lithium methyl dimethylmalonate anion afforded the diene complex **5a** (entry 5), while reaction of the sodium salt of methyl dimethylmalonate gave a separable mixture of **5a** and cyclohexenone **7**.[6] In contrast, reaction of the $(CO)_2PPh_3$ ligated cation **1b** with sodium dimethyl malonate gave the diene complex **4b**. Formation of cyclohexenone products is not limited to malonate anions; reaction of **1a** with the anion from methyl cyclohexanecarboxylate or with phthalimide gave **8** or **9**.



The (diene)iron complexes **4a**/**4b**/**5a** arise via nucleophilic attack at C1, while the cyclohexenone products **6**−**9** are formed via nucleophilic attack at the C2 internal carbon to generate a (pentenediyl)iron complex **10** (Scheme 2).[7] Carbonyl insertion[8] into

Scheme 2



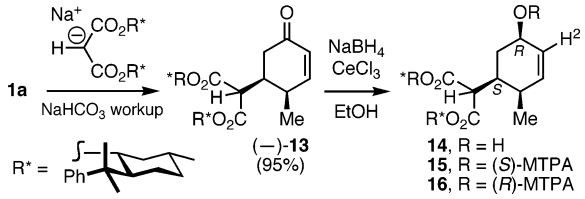
10 affords the acyl complex **11** which upon reductive elimination gives the 3-cyclohexenone **12**. Workup with methanolic $NaHCO_3$ effects conjugation to give the product **6**/**7**. It has been previously noted that the site of nucleophilic attack is dependent on the nucleophile and on "spectator" ligands present on the metal.[9] The above results indicate that the regioselectivity for attack on **1a** is also dependent on the counterion of the nucleophile. On the basis of ^{13}C NMR spectroscopy[10] and DFT calculations[11c] the C2/C4 carbons of the pentadienyl ligand are believed to bear greater partial positive charge than the C1/C3/C5 positions, while molecular orbital calculations indicate that the LUMO of the (dienyl)iron cations has greater orbital contribution from C1/C5 than from C2/C4.[10a,12] Thus,

10.1021/ja055668y CCC: $33.50

nucleophilic attack at C2/C4 is believed to be due to charge control, while attack at C1/C5 is attributed to frontier orbital control.[9] In the present case, for the sodium salts (and Li^+/12-crown-4), the malonate anion is expected to be completely dissociated, and thus nucleophilic attack is anticipated to occur under charge control. In comparison, for the lithium salts (and $Na^+/ZnCl_2$), there should be greater association between the malonate anion and the counterion; this decreased polarization in electron density would lead to frontier orbital controlled nucleophilic attack. It should be noted that the steric bulk of the nucleophile may play an additional role on the regioselectivity of nucleophilic attack (entry 6). In the case of lithium methyl cyclohexanecarboxylate (entry 8), attack at C2 may be due to the greater strength of this nucleophile, compared to malonate (i.e., charge control).

Previous efforts at the desymmetrization of achiral (cyclohexadienyl)- and (cycloheptadienyl)iron(1+) cations with chiral sulfoximinyl acetates[13a] or chiral *N*-acetyl- or *N*-propionyl oxazolidinones[13b] resulted in enantioselectivities ranging from 11 to 60% ee. With these precedents in mind, we therefore sought the desymmetrization of achiral cation **1a**. To this end, reaction **1a** with sodium bis[(−)-8-phenylmenthyl]malonate[14] gave the cyclohexenone (−)-**13** as a *single diastereomer* in excellent yield (Scheme 3). Luche

Scheme 3



reduction of (−)-**13** gave the equatorial cyclohexenol **14**.[15] Assignment of the absolute stereochemistry at the carbinol carbon was based on the ^{1}H NMR chemical shifts of the alkenyl proton (H^2) of the derived (*S*)- and (*R*)- Mosher's esters **15** and **16** (δ 5.41 and 5.33 ppm, respectively). These relative chemical shifts are consistent with an (*R*)-stereochemical assignment at C1, and therefore C5 is assigned as (*S*).

The diastereoselectivity for addition of the chiral malonate to **1a** is rationalized in the following fashion. Nucleophilic attack occurs on the face of the pentadienyl ligand opposite to the Fe metal, and the malonate is oriented such that the π-system of the nucleophile is synclinal with respect to the electrophilic π-system (i.e., the C1−C2 bond) (Figure 1). Steric interaction between the phenyl substitutent and the pentadienyl ligand present in **TS2** (see arrow) is expected to raise the energy of this transition state compared to **TS1**.

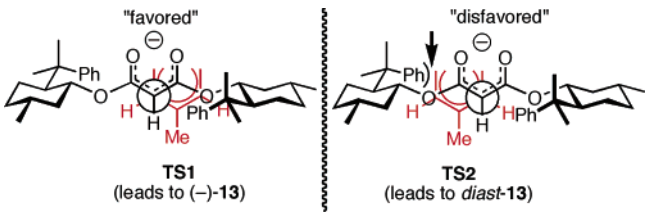


Figure 1. Diastereomeric transition states for attack on **1a**. [$Fe(CO)_3$], which points away from view, is not shown for clarity.

In conclusion, the malonate−cation association controls the regioselectivity for nucleophilic attack on **1a**. Use of strongly associated salts of malonate gave C1 nucleophilic attack, while reaction of the dissociated malonate−counterion pairs proceed at the C2 internal carbon of the pentadienyl ligand. Reaction of **1a** with the sodium salt of bis(8-phenylmenthyl)malonate proceeds with excellent diastereocontrol to afford a single diastereomeric cyclohexenone.

Acknowledgment. This material is based upon work supported by the National Science Foundation (CHE-0415771). Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954).

Supporting Information Available: Details of experimental procedures, characterization, and analytical data for the products (18 pages, PDF). This material is available fee of charge via the Internet at http://pubs.acs.org.

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JA055668Y