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Selective Recognition of Diastereoisomeric Tricarbonyl(isobornoxycyclohexa-1,3-dienylium)iron Complexes with Achiral Nucleophiles

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The first example is reported for the selective reaction of a diastereoisomeric mixture of tricarbonyl(2-isobornoxy-5-methylcyclohexadienylium)iron hexafluorophosphate with achiral potassium–dimethyl malonate to give the highly enantiomerically enriched diene complex **6** (84% ee). The two diastereoisomeric complexes **3** and **4** showed considerable differences in their ^{1}H NMR chemical shifts.

The use of stoichiometric tricarbonyl(cyclohexadienylium)iron complexes in organic synthesis has been amply demonstrated by Birch[1] and Pearson.[2] The potential of these complexes for enantioselective synthesis has long been recognized, since the lateral coordination of the $Fe(CO)_3$ moiety to achiral substituted cyclohexadiene produces enantiomeric pairs. Even though numerous methods toward enantiomerically pure complexes such as chiral $Fe(CO)_3$ transfer reagents,[3] classical separation of diastereomeric pairs,[4] and, more recently, the use of chiral alkoxy asymmetic induction[5] exist, the levels of enantiomeric enrichment are rather poor and continue to be a challenging problem in this field.

Curent interest in our laboratory is aimed at the selective reaction of diastereoisomeric mixtures of cyclohexadienylium salts having a chiral alkoxy auxiliary with achiral nucleophiles in a one-pot reaction without the need of prior separation to obtain optically active diene complexes. Our approach is based on the use of cheap, commercially available bulky camphene as a chiral alkoxy auxiliary for the application of iron complexes in homochiral synthesis.

The O-alkylation of phenol with camphene under acid catalysis to give isobornyl ether has been reported by Kitchen.[6] Accordingly, a high yield of 4-isobornoxytoluene (**1**) as obtained from the reaction of (+)-camphene with 4-cresol under the catalysis of boron trifluoride etherate at 25 °C for 5 days. The use of more vigorous reaction conditions was found to give the rearranged C-alkylation product, 2-isobornyl-4-methylphenol. Birch reduction (Li/NH_3, 3 days) of **1** gave the unconjugated 1,4-diene, which was conjugated into its 1,3-diene **2** with Wilkinson's catalyst. The reaction of **2** with $Fe(CO)_5$ in refluxing dibutyl ether can gave rise to a mixture of diastereoisomeric complexes **3** and **4** which have the iron coordinated at opposite sides of the diene. The ^{1}H NMR of the diastereomeric mixture of complexes **3** and **4** showed three sets of doublets at δ 5.06, 4.97, and 4.78 in a 1:1:2 ratio for the 2-H and 3-H protons of the diene complexes to $Fe(CO)_3$ and also two sets of multiplets at δ 3.67 and 3.54 for the isobornoxy OCH. Decoupling experiments on the doublets at δ 5.06 and 4.97 caused the doublets at δ 4.78 to collapse into a singlet, indicating that the peaks at δ 5.06 and 4.97 belong to the individual diastereoisomeric complexes **3** and **4**. We have also proved this by obtaining a pure crystalline sample of one diastereoisomer after several recrystallizations which showed peaks at δ 5.06 and 4.78 for the 2-H and 3-H protons. The ratio of the two diastereoisomeric mixtures can thus be calculated from the accurate integrals of the peaks at δ 5.06 and 4.97, which gave a 8% enantiomeric excess of one diastereoisomer, very similar to that reported by Potter[5] for the menthoxy chiral auxiliary. The enantiomeric excess is doubly checked by converting the mixture of diastereoisomers **3** and **4** into tricarbonyl(2-methylcyclohexadienylium)iron complex whose absolute configuration has been unambiguously assigned by Birch,[7] and this again gave a value of 8% ee ($[\alpha]_D$ +2° (*c* 0.9, MeCN)).

In view of the harsh reaction conditions, we have examined milder complexation conditions such as $Fe_2(CO)_9$ in refluxing benzene and ether with the aim of obtaining better diastereoselectivity. These conditions only gave a marginal increase in diastereoselectivity, with an enantiomeric excess of 10%. This is in contrast to the chiral auxiliary directed asymmetric tricarbonyliron complexation of acyclic dienes reported by Pearson,[8] which showed good diastereoselectivilty under milder conditions.

Potter[5] has reported the separation of the diastereomeric menthyl ether complex prior to its application in homochiral synthesis. Rigorous purification is usually required before a pure diastereomer can be obtained, as we have encountered with the isobornoxy complexes **3** and **4**, and this has led us to examine more efficient methods for using diastereomeric mixtures of complexes

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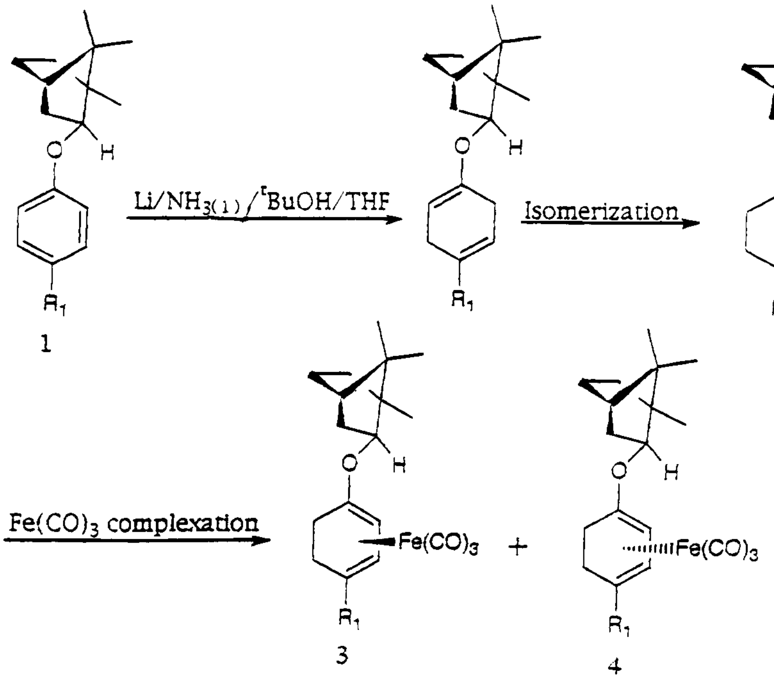
Scheme 1. Synthesis of Tricarbonyl[isobornoxyclohexa-1,3-dienyl]iron Complexes



directly in homochiral synthesis. We thus sought to achieve homochiral synthesis via a direct method from the diastereoisomeric mixture of **3** and **4** through a sequence of hydride abstraction followed by achiral nucleophilic addition, in the hope that either kinetic or thermodynamic diastereoselectivty will occur during these steps, thus amounting to direct multistep resolution during the reaction. The use of such a strategy has not been examined and is synthetically useful, since there currently exist no efficient methods for the direct preparation of optically pure cyclohexadienyl$-Fe(CO)_3$ complexes.

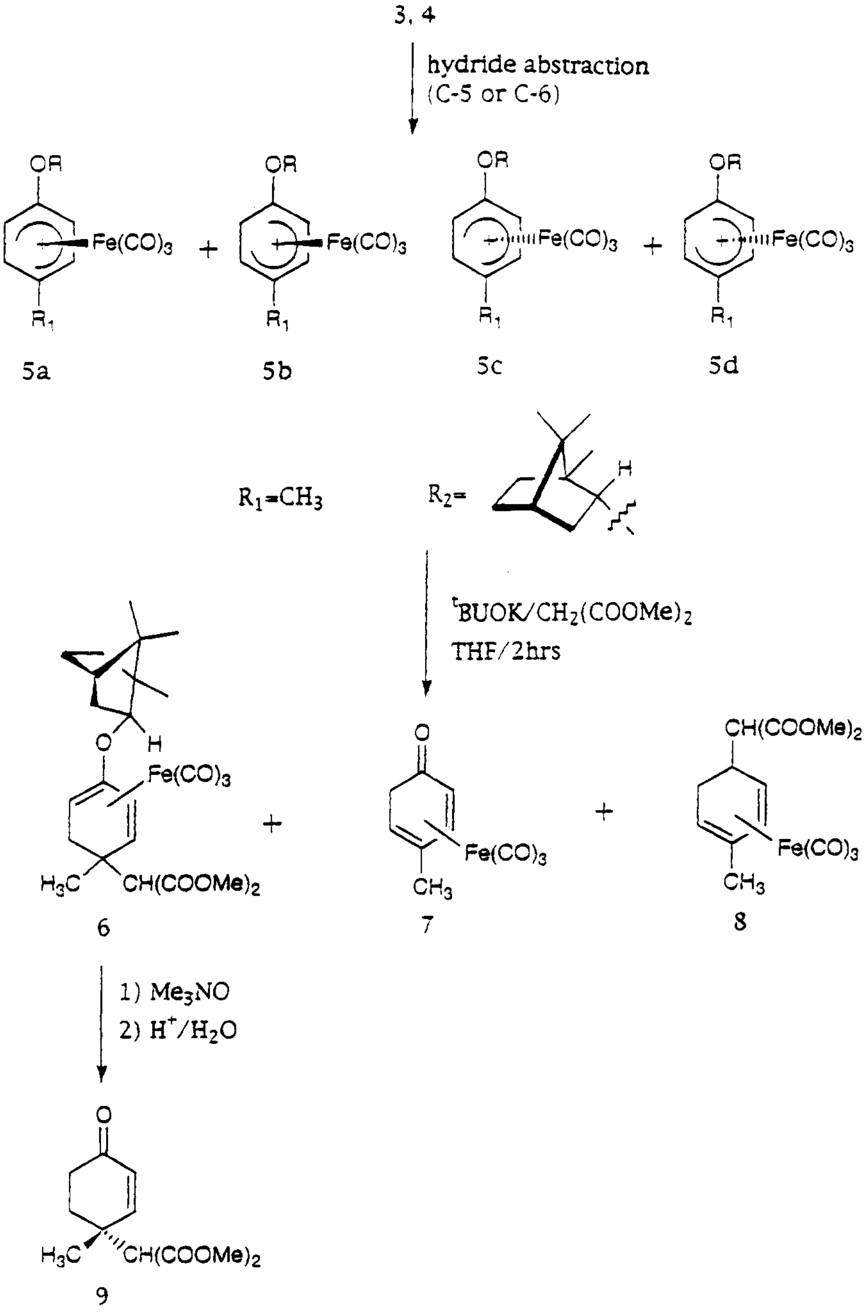
The hydride abstraction of the tricarbonyl(1-menthoxy-4-methylcyclohexadienyl)iron complex with trityl hexafluorophosphate has been reported[5] to take place at both the C-5 and C-6 positions. Thus, a mixture of diastereoisomeric complexes **3** and **4** having a bulky isobornoxy substituent can gave rise to four possible products: **5a** and **5c** for hydride abstraction at C-6 and **5b** and **5d** for hydride abstraction at C-5, which are diastereoisomeric pairs, respectively. The diastereoisomeric mixture of four salts, when reacted with potassium–dimethyl malonate, is expected to give rise to a mixture of compounds **6**–**8** and some decomplexation products. Hydride abstraction products at C-6 (**5a**,**c**), when undergoing nondiastereoselective, but regioselective, nucleophilic addition at C-1, should give racemic **6**. The salts resulting from hydride abstraction at C-5 (**5b**,**d**) will be hydrolyzed to the racemic cyclohexadienone complex **7** during workup, which can be separated by chromatography. Thus, there is no need for its tedious removal by hydrolysis at the earlier stage of hydride abstraction.

In order to determine whether resolution during the sequences of hydride abstraction and nucleophilic addition have indeed taken place, the absolute configuration of the synthetically useful regioselective addition product **6** must be determiend next. It was treated with trimethylamine *N*-oxide to remove the $Fe(CO)_3$ followed by hydrolysis of the enol ether to give dimethyl (1-methyl-4-oxocyclohex-2-enyl)malonate (**9**) of known absolute configuration. The product **9** obtained in 20% overall yield (40% based on chemical yield for one optically pure complex) after three consecutive steps had $[\alpha]_D$ -25° (*c* 0.2, $CHCl_3$),[5] corresponding to 84% enantiomeric excess. The yield was controlled by the competing hydride abstraction at C-5 for stereically demanding alkoxy substituents.[5] This result rigorously established that the complex **6** obtained from a mixture of diastereoisomeric complexes **3** and **4** after the sequences of hydride abstraction followed by nucleophilic addition itself was enantiomerically enriched. Resolution has indeed occurred during the reaction without the need of prior separation of diastereoisomers.

The product **7** obtained from the hydrolysis of the C-5 hydride abstraction product was of low optical activity ($[\alpha]_D$ -9.3°, *c* 0.8 ($CHCl_3$); 2% ee). This indicates that the hydride abstraction at C-5 must not be diastereoselective for **3** and **4**. This might be expected, since the C-5 hydrogen is placed further away from the chiral auxiliary, which feels a lesser influence.

We next needed to determien the step at which selective reaction of the mixture of diastereoisomeric complexes to afford optically pure product occurred. The sequence to be considered includes (i) kinetic resolution during hydride abstraction to give the enantiomerically enriched cyclohexadienylium salt, followed by nucleophilic addition, or (ii) nonselective hydride abstraction to give the diastereoisomeric cyclohexadienylium salt followed by diastereoselective addition with nucleophiles, which gave rise to enatiomeric enrichment. If kinetic resolution did occur during hydride abstraction, we would expect the mother liquor after salt formation to be highly enriched by one of the diastereoisomeric complexes **3** and **4**. From the ^1H NMR spectrum, the composition of **3** and **4** in the mother liquor was found to be very similar to the initial ratio; no enrichment of either complex was found. On the basis of this evidence,

Scheme 2. Salt Formation and Nucleophilic Addition



we tentatively propose that enantiomeric enrichment has occurred by the diastereoselective recognition of the nucleophile on the cyclohexadienylium salts.

Tricarbonyl(2-methylcyclohexadienylium)iron hexafluorophosphate was also formed in the reaction due to minute amounts of HPF_6 present, and this reacted with the nucleophile to give isolable amounts of **8**.

Clearly, there is considerable potential for asymmetric synthesis using the techniques of direct diastereoresolution during reactions as reported herein. This represents an alternative approach for asymmetric synthesis using organoiron complexes. The general approaches toward the direct synthesis of homochiral cyclohexadienyl$-Fe(CO)_3$ complexes has so far been disappointing. Unlike the case for its acyclic counterpart,[8] the optical yield was not improved using milder reaction conditions. The cyclohexadienyl$-Fe(CO)_3$ complexes are the most versatile organoiron complexes, which are synthetic equivalents of cyclohexenone γ-cations, and this has led to many natural product syntheses employing that particular synthon.[2] Future work will examine the generality of the procedure as well as its optimization in both enantiomeric excess and yield.

Experimental Section

General Procedures. Infrared spectra were recorded with a Bio-Rad FTS-40, mass spectra with a VG Quattro 5022, ^1H NMR with a Varian Gemini 200 ($CDCl_3$), and elemental analyses with Heraeus CHNO instruments. The optical rotations were recorded on a Jasco DIP-181 polarimeter at room temperature. All reactions and chromatographic separations were performed under nitrogen.

4-Isobornoxytoluene (1). The report by Kitchen[6] did not give the procedure in detail. To a stirred solution of (+)-camphene (50 g) and 4-cresol (40 g) in ether (200 mL) at 0 °C was added slowly via a dropping funnel a solution of boron trifluoride-etherate (1% by weight) in ether (20 mL). The reaction mixture was then stirred at room temperature (25 °C) for 5 days. The reaction mixture was washed repeatedly with dilute 5% NaOH solution to remove unreacted 4-cresol. Evaporation of the crude extract afforded the crude product contaminated with unreacted camphene. Purification by distillation afforded pure **2** (47 g, 52%). IR ($CHCl_3$): ν_{max} 1651, 1560, 1508, 1454 cm^{-1}. ^1H NMR: δ 7.00 (2H, d, Ar), 6.71 (2H, d, Ar), 3.96 (1H, q, CHO), 2.25 (3H, s, CH_3), 1.81−1.56 (5H, m), 1.19−1.08 (2H, m), 1.06−0.86 (9H, 3 × s, CH_3). $[\alpha]_D$ -4.8° (*c* 4.2, $CHCl_3$). Mass (*m/z*): 244, 137, 108. Anal. Calcd for $C_{17}H_{24}O$: C, 83.61; H, 9.84. Found: C, 83.67; H, 9.89.

4-Isobornoxy-1-methylcyclohexa-1,3-diene (2). 4-Isobornoxytoluene (25 g) was subjected to Birch reduction in liquid ammonia (1 L) containing tetrahydrofuran (100 mL) and *tert*-butyl alcohol (15 mL), using lithium metal (5 equiv) for 3 days. The usual workup afforded crude 4-isobornoxy-1-methylcyclohexa-2,5-diene (23 g), which was conjugated to 4-isobornoxy-1-methylcyclohexa-1,3-diene using Wilkinson catalyst in refluxing toluene. The cooled product was washed with aqueous sodium bicarbonate and filtered through a short column of silica gel to affored a 4:1 mixtlure of conjugated and unconjugated diene. IR ($CHCl_3$): ν_{max} 1650, 1601, 1454 cm^{-1}. ^1H NMR: δ 5.53 (1H, d, 3-H), 4.75 (1H, d, 2-H), 3.74 (1H, q, OCH), 2.23 (4H, br, CH_2 × 2), 1.68 (3H, s, Me), 1.83−1.54 (5H, m), 1.15−1.03 (2H, m), 0.94−0.84 (9H, 3 × s, 3 × Me). $[\alpha]_D$ -4.6° (*c* 3.6, $CHCl_3$). Mass (*m/z*): 246, 137, 110. Anal. Calcd for $C_{17}H_{26}O$: C, 82.93; H, 10.57. Found: C, 82.74; H, 10.50.

Tricarbonyl(4-isobornoxy-1-methylcyclohexa-1,3-diene)iron (3, 4). The mixture of dienes above (20 g) was treated with pentacarbonyliron (27 g, 2.5 equiv.) in di-*n*-butyl ether (100 mL) at 140 °C under nitrogen for 48 h. The cooled mixture was filtered through basic alumina, and the solvent and excess pentacarbonyliron were removed at aspirator pressure, followed by high vacuum, to afford a diastereomeric mixture of products **3** and **4** in a 56:46 ratio (yield 70%). One of the diastereomers could be obtained pure after several tedious recrystallizations from methanol to give a yellowish solid. Data for the pure solid complex are as follows. Mp: 105−106 °C. IR ($CHCl_3$): ν_{max} 2025, 1956, 1650, 1600 cm^{-1}. ^1H NMR: δ 5.07 (1H, d, J = 4.4 Hz, 3-H), 4.79 (1H, J = 4.4 Hz, 2-H), 3.54 (1H, q, OCH), 2.35−2.21 (1H, m), 2.01−1.60 (8H, m), 1.54 (3H, s, Me), 1.11−1.06 (2H, m), 0.95−0.81 (9H, 3 × s, 3 × Me). $[\alpha]_D$ -8.3° (c 1.0, $CHCl_3$). Mass (*m/z*) 386, 358, 330, 302. Anal. Calcd for $C_{20}H_{26}FeO_4$: C, 62.18; H, 6.74. Found: C, 62.02; H, 6.66.

Data for the other diastereomer, which cannot be obtained pure, but is enriched, are as follows. ^1H NMR: δ 4.97 (1H, d, J = 4.2 Hz, 3-H), 4.76 (1H, d, J = 4.2 Hz, 2-H), 3.69 (1H, q, OCH), 2.35−2.21 (1H, m), 1.92−1.60 (8H, m), 1.53 (3H, s, Me), 1.09−1.00 (2H, m), 0.93−0.80 (9H, 3 × s, 3 × Me).

Hydride Abstraction and Reaction with Potassium−Dimethyl Malonate. Treatment of the diastereoisomeric mixture of complexes **3** and **4** (3.00 g) with triphenylmethyl hexafluorophosphate (2.86 g, 0.95 equiv) in dry dichloromethane (20 mL) at room temperature for 3 h, followed by removal of some dichloromethane and precipitation with moist ether, afforded the yellowish salt **5** (1.92 g, 49%).

To a stirred solution of potassium *tert*-butoxide (395 mg) in dry THF (10 mL) under nitrogen was added dropwise dimethyl malonate (340 μL). The mixture was stirred at room temperature for 1 h; the reaction flask was opened briefly and the yellowish salt obtained above (1.60 g) was added in one portion. Stirring was continued for 2 h. The mixture was evaporated to remove some of the THF and then extracted with ether in the usual way to afford the crude product (560 mg, 72% yield). Separation of the mixture (4:1 hexane/petroleum ether) afforded **6** (20%), **7** (25%), and **8** (11%), together with the decomplexed aromatic starting material (40%).

Tricarbonyl[dimethyl (4-isobornoxy-1-methylcyclohexa-2,4-dienyl)malonate]iron (6). IR ($CHCl_3$): ν_{max} 2045, 1972, 1732, 1701, 1430 cm^{-1}. ^1H NMR: δ 4.83 (1H, dd, J = 6.5, 2.3 Hz, 3-H), 3.75 (3H, s, COOMe), 3.71 (3H, s, COOMe), 3.65 (1H, m, OCH), 3.31 (1H, m, 5-H), 3.10 (1H, s, CH), 2.48 (1H, d, J = 6.4, 2-H), 2.31 (1H, dd, J = 15.3, 2.3 Hz, 6-endo-H), 2.05−1.55 (7H, m), 1.20−1.11 (4H, s and dd, 6-exo-H, Me), 1.02−0.97 (9H, 3 × s, 3 ×Me). Mass (*m/z*): 516, 488, 460, 432. Anal. Calcd for $C_{25}H_{32}FeO_8$: C, 58.14; H, 6.20. Found: C, 58.13; H, 6.28.

Tricarbonyl(4-methylycyclohexa-2,4-dien-1-one)iron (7). IR ($CHCl_3$): ν_{max} 2063, 2000, 1659 cm^{-1}. ^1H NMR: δ 5.79 (1H, dd, J = 6.1, 2.3 Hz, 3-H), 3.30 (1H, m, 2-H), 3.06 (1H, d, J = 6.1 Hz, 5-H), 2.45 (1H, dd, 6 endo-H), 2.29−2.20 (4H, dd and s, 6-exo-H and Me). $[\alpha]_D$ -9.3° (*c* 0.8 ($CHCl_3$); 2% ee. Mass (*m/z*): 248, 220, 192, 164. Anal. Calcd for $C_{10}H_8FeO_4$: C, 48.39; H, 3.23. Found: C, 48.09; H, 3.21.

Tricarbonyl[dimethyl (4-methylcyclohexa-2,4-dienyl)malonate]iron (8). IR ($CHCl_3$): ν_{max} 2045, 1976, 1725 cm^{-1}. ^1H NMR: δ 5.18 (1H, dd, J = 6.0, 2.2 Hz, 3-H), 3.74, 3.69 (6H, s each, 2 × COOMe), 3.06−3.01 (2H, s and m, 2-H, CH), 2.85−2.69 (2H, m, 5-H, 6-endo-H), 2.07 (3H, s, Me), 1.58 (1H, dd, 6-exo-H), 1.49−1.39 (1H, m, 1-H). Mass (*m/z*): 364, 336, 308, 220. Anal. Calcd for $C_{15}H_{16}FeO_7$: C, 49.45; H, 4.40. Found: C, 49.41; H, 4.42.

Dimethyl (1-Methyl-4-oxocyclohexa-2-enyl)malonate (9). The complex **7** (50 mg) was stirred in benzene (10 mL) at 50 °C with anhydrous trimethylamine *N*-oxide (300 mg) for 2 h. The mixture was cooled and filtered through Celite and the cake washed with ether. The crude extract was than dissolved in methanol, and oxalic acid was added (40 mg) to hydrolyze the enol ether. Removal of the solvent followed by the usual workup procedure gave **9** in near-quantitative yield. IR ($CHCl_3$): ν_{max} 1742, 1682 cm^{-1}. ^1H NMR: δ 7.10 (1H, dd, J = 11, 2.8 Hz, 2-H), 5.94 (1H, d, J = 11 Hz, 3-H), 3.78, 3.77 (6H, s each, 2 × COOMe), 3.56 (1H, s, CH), 2.55−1.90 (4H, m, 2 × CH_2). $[\alpha]_D$ -25° (*c* 0.4, $CHCl_3$); 84% ee.

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