Notes

Asymmetric Tricarbonyliron Complexation of Cyclohexadiene Directed by Chiral Ester and Amide Auxiliaries

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Summary: Coupling of (+)-menthol, (+)-phenylethylamine and (−)-proline methyl ester with 4-methoxy-1-cyclohexa-2,4-dieneacetic acid gave the chiral ester ***1*** *and amides* ***2*** *and* ***3****, respectively, which were then isomerized into the 1,3-dienes. The diastereoselection induced by the chiral ester and amide auxiliaries during complexation with nonacarbonyliron was quite encouraging. The diastereomeric ratios of the ester- and amide−Fe(CO)*$_3$ *complexes formed were determined directly from the* ^{1}*H NMR integration of observable diastereotopic chemical shifts.*

The development of highly efficient methods for the construction of chiral tricarbonyliron complexes for organic synthesis has elicited considerable synthetic efforts.[1−5] Chiral tricarbonyliron complexes are powerful starting materials in enantioselective synthesis of natural products since the metal totally dominates stereocontrol in the subsequent bond constructions.

The use of chiral auxiliary-directed asymmetric tricarbonyliron complexation of acyclic dienes has been reported to proceed in good yield and high diastereoselectivity.[2] On the other hand, the level of diastereoisomeric enrichment during tricarbonyliron complexation using a chiral alkoxy auxiliary in the important class of cyclohexadiene ligands has been rather poor and remains a challenge.[3,4] New methods must be devised to increase the influence of the chiral auxiliary during tricarbonyliron complexation with the cyclohexadiene ligands. We here report the first attempt to effect facially selective complexation of the cyclohexadiene ligand *via* an intramolecular transfer of the tricarbonyliron group attached to chiral ester and amides auxiliaries. This type of approach has not previously been used in the case of cyclohexadiene ligands and Fe(CO)$_3$. The 4-methoxy-1-cyclohexa-1,3-dieneacetic acid derivative was chosen on the basis of the previous proposed coordination of the carbonyl group to Fe(CO)$_n$ during complexation.[6] Furthermore this complex has been shown to be an important building block for the iron-mediated diastereoselective synthesis of spirocycles.[7] The proposed intramolecular delivery of the Fe(CO)$_3$ moiety using chiral ester and amide auxiliaries might prove more successful for the asymmetric recognition of the two enantiofaces in cyclohexadiene. In this paper we describe the first stage of this endeavor and demonstrate the feasibility of using chiral ester and amides auxiliaries for the synthesis of enantiomerically enriched tricarbonyl−cyclohexadiene complexes.

4-Methoxy-1-cyclohexa-1,4-dieneacetic acid was prepared by the Birch reduction of commercially available (4-methoxyphenyl)acetic acid.[8] The Birch reduction product has been reported to be unstable and required immediate esterification. We have overcome this problem by washing the ethereal extract of the Birch product with a small amount of dilute sodium bicarbonate solution to remove residual formic acid present, thus preventing hydrolysis of the enol ether. The 4-methoxy-1-cyclohexa-1,4-dieneacetic acid, a white solid obtained in this way, was stable in the refrigerator for months. A number of chiral alcohols and amines were reacted with 4-methoxy-1-cyclohexa-2,4-dieneacetic acid by utilizing carbonyl diimidazole as a condensing agent to give the corresponding chiral ester and amide derivatives (Scheme 1). Thus (+)-menthol gave the chiral ester **1**; (+)-phenylethylamine and (−)-proline methyl ester gave the chiral amides **2** and **3**, respectively. The unconjugated cyclohexa-1,4-dienes were preconjugated into the respective 1,3-conjugated dienes **1a**, **2a**, and **3a** with Wilkinson's catalyst in good yields. Reactions of **1a**, **2a**, and **3a** with nonacarbonyldiiron in benzene at room temperature gave complexes **4**−**6**, respectively, in 40−50% yield. These yields were considered good for the complexation reaction. Our next task was to determine the degree of diastereoselectivity achieved during complexation for the various chiral ester and amide auxiliaries.

The diastereoselectivity (Table 1) may be determined directly from the complexes **4**−**6** if diastereotopic chemical shifts were observed in the ^{1}H NMR spectra. Another indirect method involved the conversion of the complexes **4**−**6** into the known tricarbonyl[methyl

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Scheme 1

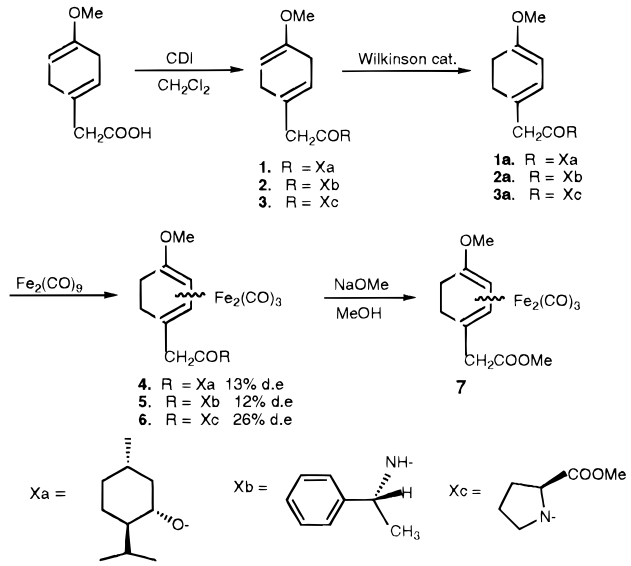

Table 1. Results of Complexation of 1a, 2a, and 3a with $Fe_2(CO)_9$ and the Observed Diastereoselectivity

compd	reacn conditions	yield	diastereo ratio	diastereo excess
4	$Fe_2(CO)_9/C_6H_6$/rt/72 h	40%	1.30:1.00	13%
5	$Fe_2(CO)_9/C_6H_6$/rt/72 h	45%	1.67:1.33	12%
6	$Fe_2(CO)_9/C_6H_6$/rt/72 h	40%	1.90:1.10	26%

4-methoxy-1-cyclohexa-1,3-dieneacetate]iron, **7**, which has been reported.[8] When tris[3-((heptafluoropropyl)-hydroxymethylene)-(+)-camphenato]europium chiral shift reagent was added to a racemic mixture of **7**, the carbomethoxy and methylene chemical shifts in the ^{1}H NMR spectrum were found to split into two sets of peaks with an integration ratio of 1:1, indicating an equimolar enantiomeric mixture. The conversion of **4**−**6** into **7** and the comparison of their diastereomeric ratios would allow us to ascertain the degree of diastereoselectivity achieved during complexation under the influence of the chiral ester and amides auxiliaries.

The ^{1}H NMR spectrum of the (+)-menthol ester complex **4** did not clearly indicate the presence of diastereoisomeric mixtures due to the complex menthyl peaks in the ^{1}H NMR spectrum. The only indication was from the two sets of very close doublets for the menthyl−methyl chemical shifts at δ 0.72, 0.76 and δ 0.73, 0.77 in the ^{1}H NMR having an estimated integration ratio of 1.3:1. In order to substantiate the accuracy using integration values of the diasteroisotopic peaks in the ^{1}H NMR, the complex **4** was converted into **7** with sodium methoxide/methanol in good yield, together with some tricarbonyl[(4-methoxy-1-cyclohexa-1,3-dieneacetic acid]iron due to hydrolysis. The acid complex obtained was re-esterified with diazomethane into the methyl ester. The combined yield of the methyl ester complex **7** was 90%. The ^{1}H NMR of the methyl ester in the presence of chiral shift reagent showed two sets of peaks for the carbomethoxy group at δ 4.11 and 4.09 having the same integration ratio of 1.3:1. Thus the (+)-menthyl ester derivative **1a** on complexation gave a 13% diastereoisomeric excess of complex **4**. In the case of the chiral amides **2a** and **3a**, the diastereomeric excesses of the complexes formed were determined directly from the integration of diastereomer peaks in the ^{1}H NMR spectra. Hydrolysis of the amide to the corresponding acid or methyl ester required drastic conditions, and this led to decomposition. Reaction of **2a** with $Fe_2(CO)_9$ was found to give a 12% diastereomeric excess of complex **5** as determined from the ^{1}H NMR integration of the diastereotopic methoxy peaks at δ 3.45 and 3.43 (1.67: 1.33) or methyl peaks at δ 1.50 and 1.48. The use of **3a** during complexation was found to give a much better diastereoisomeric excess of 26% as determined from the ^{1}H NMR integration of the diastereotopic carbomethoxy peaks at δ 3.73 and 3.71 (1.90:1.10). This result represents the best diastereoselectivity that has been achieved for complex **7** to this date. Recently Knolker[9] reported the synthesis of chiral complex **7** *via* asymmetric catalysis during complexation of the diene which gave both low yield (26%) and poor enantioselectivity (19%). Even though this does not compare well with the acyclic system studied,[2] our results are quite encouraging and clearly indicate the different behavior of the cyclohexadiene ligand which remains a challenge.

The degree of asymmetric induction exerted by the chiral auxiliary during the complexation reaction was thought to be highly dependent on the initial coordination of the carbonyl group to $Fe(CO)_n$, followed by an intramolecular transfer to the diene, whereby the chiral center was brought into close proximity of the reaction site. Competing direct complexation of the diene with $Fe_2(CO)_9$ might reduced the diastereoselectivity. In conclusion, we have demonstrated the feasibility of this type of approach for the asymmetric complexation for cyclohexadiene ligand. Preliminary results of diastereoselection reported here are encouraging, a significant step forward for this important class of cyclohexadiene ligand, and continual effort will be expended to seek the optimum chiral auxiliary.

Experimental Section

General Procedures. All manipulations were carried out under an atmosphere of nitrogen. NMR spectra were recorded on Varian Germini-200 instrument using $CDCl_3$ with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Biorad FTS-40 spectrophotometer. Melting points were measured on a Fisher John melting point apparatus. Elemental analyses were performed on Heraeus CHNO rapid analyzer. Mass spectra were measured on Biotech Qauttro GC mass spectrometer.

The starting compound, 4-methoxy-1-cyclohexa-1,4-dieneacetic acid was prepared as reported previously.[8]

Condensation of 4-Methoxy-1-cyclohexa-1,4-dieneacetic Acid with Chiral Alcohol and Amine. To an ether solution of 4-methoxy-1-cyclohexa-1,4-dieneacetic acid and the appropriate chiral alcohol ((+)-menthol) or amine ((+)-α-methylbenzylamine and (−)-2-carbomethoxypyrrolidine) at 0 °C was added 4-(dimethylamino)pyridine followed by dicyclohexylcarbodiimide. The resulting reaction mixture was stirred at room temperature for 72 h after which it was filtered and the solvent removed under reduced pressure. Elution on silica gel column with hexane/EtOAc (5:1) gave **1** (85%), hexane/EtOAc (1:1) gave **2** (83%), and hexane/EtOAc (1:7) gave **3** (80%).

Menthyl 4-Methoxy-1-cyclohexa-1,4-dieneacetate (1). IR ($CHCl_3$, cm^{-1}): ν = 1732. ^{1}H NMR ($CDCl_3$): δ 5.54 (bs, 1H), 4.67 (m, 1H), 4.61 (bs, 1H), 3.54 (s, 3H), 2.97 (s 2H), 2.77 (m, 4H), 2.01−1.75 (m, 7H), 1.70−0.80 (m, 8H), 0.75 (d, 3H). $[\alpha]_D^{22}$ = +48.6 (c = 1.9, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}O_3$:

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C, 74.48; H, 9.87. Found: C, 74.01; H, 9.79. MS (EI 70 eV): *m*/*z* 306 (M^+).

***N*-(α-Methylbenzyl)(4-methoxycyclohexa-1,4-dienyl)-acetamide (2).** Mp: 108−110 °C. IR ($CHCl_3$, cm^{-1}): ν = 1639, 1540. ^1H NMR ($CDCl_3$): δ 7.27 (m, 5H), 6.19 (m, 1H), 5.55 (bs, 1H), 5.10 (m, 1H), 4.59 (bs, 1H), 3.53 (s, 3H), 2,90 (s, 2H), 2.74 (s, 4H), 1.45 (d, 3H). $[\alpha]_D^{22} = +9.9$ (c = 1, $CHCl_3$). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.11; H, 7.72; N, 5.22. MS (EI 70 eV): *m*/*z* 271 (M^+).

1-(((2-(Carbomethoxy)pyrrolidino)carbonyl)methyl)-4-methoxycyclohexa-1,4-diene (3). IR ($CHCl_3$, cm^{-1}): ν = 1736, 1651. ^1H NMR ($CDCl_3$): δ 5.54 (bs, 1H), 4.62 (bs, 1H), 4.48 (m, 1H), 3.72 (s, 3H), 3.53 (s, 3H), 3.63 (m, 2H), 3.05 (s, 2H), 2.78 (s, 4H), 2.30−1.90 (m, 4H). $[\alpha]_D^{22} = -45.1$ (c = 3.8, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.34; H, 7.49; N, 5.13. MS (EI 70 eV): *m*/*z* 279 (M^+).

Conjugation of Cyclohexa-1,4-dienes into Cyclohexa-1,3-dienes. To a solution of the cyclohexa-1,4-diene obtained above in dichloromethane was added a catalytic amount of Wilkinson's catalyst ($RhCl(Ph_3P)_3$, 2% by weight) and refluxed for 72 h before workup. The cyclohexa-1,3-dienes **1a**, **2a**, and **3a** obtained also contained some unconjugated diene, and this was used for complexation reaction without prior separation.

General Procedure for the Complexation of Cyclohexa-1,3-dienes with $Fe_2(CO)_9$. The cyclohexa-1,3-dienes **1a**, **2a**, and **3a** obtained above (containing 1,4-diene) (10 g) were dissolved in benzene (150 mL) under nitrogen, $Fe_2(CO)_9$ (2 equiv) was added, and the reaction mixture was stirred at room temperature for 72 h. The reaction mixture was filtered through alumina and the yellowish filtrate was evaporated to dryness to give crude **4**−**6** as products. Elution with hexane/benzene (4:1) gave pure **4** (40%). Complexes **5** (45%) and **6** (40%) were purified by removal of the uncomplexed compounds under high vacuum.

Tricarbonyl{menthyl (1−4η)-4-methoxy-1-cyclohexa-1,3-dieneacetate}iron (4). IR ($CHCl_3$, cm^{-1}): ν = 2049, 1962, 1739. ^1H NMR ($CDCl_3$): δ 5.23 (d, 1H), 5.10 (d, 1H), 4.69 (m, 1H), 3.23 (s, 3H), 2.67 (m, 2H), 2.40−0.80 (m,13 H), 0.91 (diastereomeric mixture, 6H), 0.73 (diastereomeric mixture, 3H). $[\alpha]_D^{22}$ (diastereomeric mixture) = +17.2 (c = 1.2, $CHCl_3$). HRMS (EI) (*m*/*z*): Calcd for $C_{22}H_{30}FeO_6$, 446.1406; found, 446.1398.

Tricarbonyl{*N*-(α-methylbenzyl)(1−4η)-4-methoxycyclohexa-1,3-dienyl]acetamide}iron (5). IR ($CHCl_3$, cm^{-1}): ν = 2041, 1965, 1667. ^1H NMR ($CDCl_3$): δ 7.31 (m, 5H), 6.16 (m, 1H), 5.22 (d, 1H), 5.16 (d, 1H), 5.08 (m, 1H), 3.45 (s, 1.33H, diastereomeric mixture), 3.43 (s, 1.67H, diastereomeric mixture), 2.57 (m, 2H), 2.40−1.60 (m, 4H), 1.50 (d, 1.33H, diastereomeric mixture), 1.48 (d, 1.67H, diastereomeric mixture). $[\alpha]_D^{22} = +27.5$ (c = 0.7, $CHCl_3$). Anal. Calcd for $C_{20}H_{21}FeNO_5$: C, 58.41; H, 5.15; N, 3.41. Found: C, 58.46; H, 5.27; N, 3.48. Mass (EI 70 eV): *m*/*z* 411 (M^+), 355 (−2CO), 327 (−3CO).

Tricarbonyl{1-(((2-(carbomethoxy)pyrrolidino)-carbonyl)methyl)-(1−4η)-4-methoxycyclohexa-1,3-dienyl}-iron (6). IR ($CHCl_3$, cm^{-1}): ν = 2038, 1949, 1747, 1640. ^1H NMR ($CDCl_3$): δ 5.22 (m, 2H), 4.48 (m, 1H), 3.73 (s, 1.1H, diastereomeric mixture), 3.71 (s, 1.9H, diastereomeric mixture), 3.71−3.45 (m, 2H), 3.45 (s, 3H), 3.01−2.44 (m, 2H), 1.60−0.60 (m, 8H). $[\alpha]_D^{22} = -48.8$ (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{21}FeNO_7$: C, 51.57; H, 5.05; N, 3.34. Found: C, 51.44; H, 5.23; N, 3.32. Mass (EI 70 eV): *m*/*z* 419 (M^+), 363 (−2CO), 335 (−3CO).

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