Experimental and Theoretical Investigation of Asymmetric Induction in the Synthesis of Disubstituted Cyclohexadienes via Chiral Benzene Chromium Complexes

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Abstract. A series of [Cr(benzene)(CO)\(_3\)L] complexes with L = PPh\(_3\), P(OMe)\(_3\), PPh\(_2\)((-)-menthyl), P(O)\(_2\)(-)-menthyl), P(-)-menthyl) were subjected to a nucleophile addition/acylation sequence to give trans-5,6-disubstituted cyclohexadienes. Low-to-moderate asymmetric induction was observed with the chiralligands. Experimental and theoretical evidence for an alkylation at the metal center was obtained with moderate asymmetric induction.

Introduction

We have recently shown that trans-5,6-disubstituted cyclohexadienes B can be obtained via a one pot reaction sequence which involves the sequential addition of a nucleophile and an electrophile to the readily accessible [Cr(benzene)(CO)\(_3\)] complex A (Scheme 1) [1]. In this article, we show that at this stage chiral non-racemic cyclohexadienes can be obtained with moderate asymmetric induction via this methodology by substituting a CO ligand with a chiral P ligand.

As changes in the electron density at the metal center (i.e. by the replacement of a CO ligand by a phosphine or phosphite) can drastically alter the reactivity of a complex [2], our first objective was to prepare simple achiral derivatives of this class of compounds and to verify that they could also be converted to cyclohexadienes 3 (Scheme 2) by the same reaction sequence. In parallel, to rationalize reactivity, we have carried out a theoretical study of the reactivity of the modified aromatic complexes towards nucleophilic addition and of the cyclohexadienyl intermediates towards electrophilic addition.

Theoretical Model

Our model is based on a local reactivity index made of the interaction energy \(E_{int}(\gamma)\) between an organometallic substrate S and an incoming electrophile or nucleophile reactant R located in \(\gamma\), which is expressed as:

\[
E_{int}(\gamma) = E_{ex}(\gamma) + E_{es}(\gamma) + E_{exc}(\gamma) + E_{ect}(\gamma)
\]

where \(E_{ex}, E_{es}\) and \(E_{exc}\) are the electrostatic, charge-transfer, and exchange energy components, respectively. Whereas \(E_{ex}\) and \(E_{es}\) are evaluated in the framework of the extended Hückel quantum chemical method [3], using the electrostatic potential and the supermolecule approach, respectively, \(E_{exc}\) is calculated from a parametrized potential of Buckingham type [4][5]. The reactivity index is such that negative (or positive) values of \(E_{int}\) correspond to S-R attractive (repulsive) interactions. The regions where \(E_{int}\) is minimum are, therefore, the most reactive sites of S towards attack by R. To have \(E_{int}\) values that depend only on the position of R and not on its orientation, two spherically symmetric model reactants have been chosen: a proton with a virtual 1s orbital for the electrophile and an H\(^+\) ion with two 1s electrons for the nucleophile.

We have employed two different molecular graphics representations of \(E_{int}\): i) the molecular surface of S, color-coded according to the \(E_{int}\) value (red: most favorable sites of attack); ii) the isoenergy surfaces of \(E_{int}\) represented as three-dimensional solid models.

Results and Discussion

The structure and reactivity of [Cr(benzene)(CO)\(_3\)] (1a) have been the subject of intensive investigations in organometallic chemistry. It is generally accepted that metal-benzene bonding leads to a net intramolecular charge transfer from the ring to the carbonyls, with the result that this compound is easily attacked by a nucleophile on the exo-face of the ring. Fig. 1 represents the \(E_{int}\) reactivity index calculated for the nucleophilic attack of this compound, which shows that, indeed, the most reactive site is located on the exo-face of the ligand ring. For comparison, the same index is also displayed for an uncoordinated benzene molecule. It is immediately seen that, as expected, an important change in reactivity accompanies benzene complexation: whereas for the isolated aromatic ring one observes essentially slightly negative iso-

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**Scheme 1**

![Scheme 1](image-url)
**Scheme 2**

\[ \begin{align*}
1a & \quad \text{hv, COE} \\
& \quad 1. \text{hv, COE} \\
& \quad \text{LiMeS(CH}_2\text{)} \text{S} \\
& \quad \text{RX} \\
& \quad \text{R = SnPh, L} = \text{P(O} \text{Me})_3 : 3
\end{align*} \]

Table. Nucleophile Addition/Acylation Reaction with Complexes 1a–f

| Entry | Complex | RX | Decompl. \(a\) | \(T^0 [\text{°C}]\) | Product | Yield\(b\) \([\%]\) | ee\(c\) \([\%]\) | Absolute\(d\) configuration |
|-------|---------|----|-----------------|----------------|---------|----------------|----------------|------------------------|
| 1     | 1a \((L = \text{CO})\) | Mel | CO              | \(-196 \rightarrow 20\) | 4        | 89\(f\)         | –              | –                      |
| 2     | 1a      | EtI | CO              | \(-196 \rightarrow 20\) | 5        | 81\(g\)         | –              | –                      |
| 3     | 1b \((L = \text{PPh}_3)\) | Mel | CO              | \(-196 \rightarrow 20\) | 4        | 69\(h\)         | –              | –                      |
| 4     | 1e \((L = \text{P(O} \text{Me})_3)\) | Mel | CO              | \(-196 \rightarrow -50\) | 4        | 60\(i\)         | –              | –                      |
| 5     | 1d \((L = (--)-\text{menthyl})\text{PPh}_3)\) | Mel | CO              | \(-196 \rightarrow -50\) | 4        | 60\(j\)         | 8              | SS                     |
| 6     | 1d      | EtI | CO              | \(-196 \rightarrow -50\) | 5        | 44\(k\)         | 19             | SS                     |
| 7     | 1e \((L = (--)-\text{menthyl})\text{O})\text{P(O} \text{Ph})_3\) | Mel | CO              | \(-196 \rightarrow -50\) | 4        | 55\(l\)         | 14             | RR                     |
| 8     | 1e      | Mel | P(OPh)_3        | \(-78 \rightarrow -50\) | 4        | 91\(m\)         | 16             | RR                     |
| 9     | 1e      | EtI | CO              | \(-196 \rightarrow -50\) | 5        | 67\(n\)         | 28             | RR                     |
| 10    | 1f \((L = \text{P(O} (--)-\text{menthyl})_3)\) | Mel | CO              | \(-196 \rightarrow -50\) | 4        | 54\(o\)         | 40             | SS                     |
| 11    | 1f      | Mel | P(OPh)_3        | \(-78 \rightarrow -50\) | 4        | 70\(p\)         | 31             | SS                     |
| 12    | 1f      | EtI | P(OPh)_3        | \(-78 \rightarrow -50\) | 5        | 57\(q\)         | 21             | SS                     |

\(a\) Either 5 bar CO or 3 equiv. of P(OPh)_3.
\(b\) Temperature of addition of alkyl halide and ligand used in the decomplexation, reaction temperature.
\(c\) Isolated product after flash chromatography.
\(d\) The enantiomeric excess was determined by \(\text{IH NMR with the chiral shift reagent} \) tris(3-(heptafluoropropylhydroxymethylene)-4-camphorate)europium(II) \(\text{[Eu(hfc)\text{]}\text{].}}\)
\(e\) Absolute configuration of the major product. The absolute configuration indicated is derived from the X-ray structure of the Diels-Alder adduct of RR-4 with (R)-4-phenylethylmaleimide. This was obtained by fractional crystallization of the minor diastereoisomer obtained from the reaction of product 4 from **Entry 10**.
\(f\) Results taken from [1a] and included for comparison.
energy envelopes centered on the $C_6$ axis above and below the molecular plane (representative of a weak van der Waals interaction) the situation changes dramatically for the coordinated arene. In the latter case, several imbricated surfaces are found at much lower energies, revealing as expected an important activation of the benzene ring through coordination to the electrophilic Cr(CO)$_3$ group. As a consequence, our theoretical results show that the initial nucleophilic attack is likely to occur on the face opposite to the metal of complexed benzene, as has been found in experiment [6].

Preliminary reactions with [Cr(benzene)(CO)$_3$L] complexes were carried out with the triphenylphosphine (1b, $L = PPh_3$) [7] and trimethylphosphite (1c, $L = P(OCH_3)_3$) [8] derivatives. The former was prepared in 74% yield by direct irradiation of a solution of [Cr(benzene)(CO)$_3$] (1a) and PPh$_3$ at 15° with a 125 W high pressure Hg lamp using a Pyrex filter. As this procedure when applied to 1c gave a mixture of 1a, 1c, and the corresponding diphosphate complex, we used a two-step sequence via irradiation of 1a in the presence of a large excess of cyclooctene, followed by reaction of the intermediate olefin complex (1, $L =$ cyclooctene) by P(OCH$_3$)$_3$ [9]. This method allowed the preparation of 1c in 81% yield. These two procedures were applied in the preparation of the analogous chiral phosphine and phosphate complexes (see Table).

The complexes 1b and 1c were then subjected to the 'double addition' reaction conditions (Scheme 2). Throughout this study, the nucleophile used was 2-lithio-2-methyl-1,3-dithiane and the electrophile either Mel or EtI, or, for the isolation of intermediate 3, CISnPh$_3$. Typically, the complexes were added as solids to 1.1 equiv. of 2-lithio-2-methyl-1,3-dithiane in THF (10 ml/mmol) at $-78°$ followed by the addition of HMPA (3 ml/mmol). After stirring at 0° for 15–20 h, the reaction mixture was treated with an excess of alkyl halide (10 equiv.) and CO ($\approx$5 bar) at $-196°$ (or an excess of alkyl halide and 3 equiv. of P(OPh)$_3$ at $-78°$) [10], then allowed to warm slowly to the desired temperature. Workup yielded the trans-disubstituted cyclohexadiene 4. As the Table shows, the phosphine derivatives led to somewhat lower yields than the phosphate derivatives and the parent tricarbonyl complex. This can be attributed to the first step of the mechanism, i.e. the addition of the nucleophile to the complexed arene. As the phosphate (and to a lesser extent the phosphite) complexes are more electron-rich, they are less susceptible to nucleophilic attack. For the same reason, the resulting anions, 2b–f, are expected to be better nucleophiles than their tricarbonyl counterpart 2a. Experimentally, this latter assumption has been verified. Whereas 2a requires temperatures near 0° to react with primary alkyl iodides [1a], 2b–f can be alkylated at $-50°$.

Having demonstrated the successful conversion of 1b and 1c to 4, we then investigated the possibility of asymmetric induction. Given the proximity of a chiral ligand $L$ to the site of alkylation, one could anticipate diastereoselectivity upon alkylation of the intermediate 2. Provided that the carbonyl insertion and acyl migration steps are fast, this diastereoselectivity could be partially or entirely conserved in the
The Table shows first results of the nucleophile addition/acylation sequence with complexes containing P(OCMe)3 and PPh3 as well as three (-)-menthol-derived ligands, (methyl)(diphenyl)phosphite [12], (methyl)(diphenyl)phosphine [13], and trimethylphosphate [15]. It is interesting to note that the (methyl)(diphenyl)phosphite induces the opposite sense of chirality in the product than (methyl)(diphenyl)phosphine and the more efficient trimethylphosphate. Further studies with these and other chiral ligands are under way. In parallel, we are investigating the preparation and chemistry of chelating diphosphorous derivatives of (benzene)(tricarbonyl)chromium. A chelating chiral diphosphorous ligand can be expected to direct alkylation of the single CO ligand. This will eliminate the possible loss of asymmetric induction in the migratory insertion step and hopefully lead to higher diastereoselectivity in the product.

In conclusion, we have shown that the addition of two C-substituents across a benzene double bond is feasible with Cr complexes containing a phosphite ligand. The computational results correctly predict the site of electrophilic attack of the cyclohexadienyl intermediate. While asymmetric induction via chiral P ligands has not yet reached useful levels, the first results using this approach are encouraging.

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