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Lipase-Mediated Resolution and Higher-Order Cycloaddition of Substituted Tricarbonyl (η^6-cycloheptatriene)chromium(0) Complexes.

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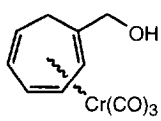
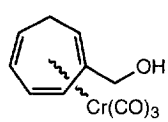
Summary: A series of substituted cycloheptatriene-$Cr(CO)_3$ complexes were resolved enzymatically, and the resultant chiral, non-racemic complexes underwent higher-order photocycloaddition to afford enantiomerically-enriched cycloadducts in high chemical yield. Copyright © 1996 Elsevier Science Ltd

Chromium(0) complexes of cyclic trienes are useful intermediates for the construction of structurally elaborate and stereochemically-rich polycyclic ring systems through higher-order cycloaddition.[1] To date, strategies for producing enantiomerically-enriched cycloadducts in these reactions have focused primarily on auxiliary-control methods.[1a,2] We now report successful biocatalytic resolution of substituted cycloheptatriene-Cr(0) complexes and their subsequent [6π+4π] photocycloaddition to afford chiral, non-racemic bicyclo[4.4.1]undecadiene adducts.

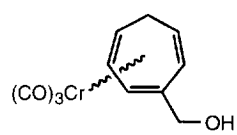
Enzymatic resolution of organic substrates has enjoyed tremendous success in recent years,[3] and a number of organometallic species have also been accessed in enantiomerically-enriched form in this fashion.[4-6] Although to the best of our knowledge no cycloheptatriene chromium(0) complexes have been resolved enzymatically,[7] this tactic appeared to be ideally suited for preparing certain types of higher-order cycloaddition substrates in optically active form. To obtain an accurate picture of the capabilities of enzyme resolution in the cycloheptatriene series, three racemic complexes with appropriate substituents located at the 1, 2 and 3 positions of the triene ligand were examined.



(±)-**1**



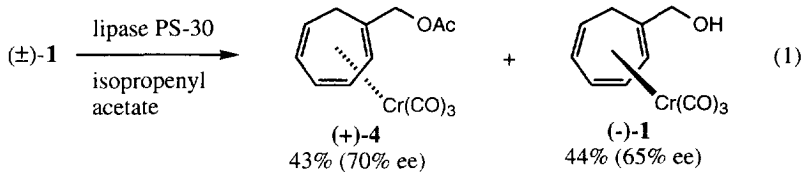
(±)-**2**



(±)-**3**

The three isomeric hydroxymethylcycloheptatriene complexes **1**-**3**[8] selected for study were prepared in racemic form by known methods[9] and each was exposed to Amano PS-30 lipase[10] in isopropenyl acetate to give a mixture of enantiomerically enriched products. Equations (1) - (3) illustrate the results of these resolution experiments. In each case the enzyme, substrate and isopropenyl acetate were stirred at room temperature in the dark for 24-48 h, and the reactions were terminated at approximately 50% completion.[11] The enantiomeric excess of the unreacted alcohol in each example was

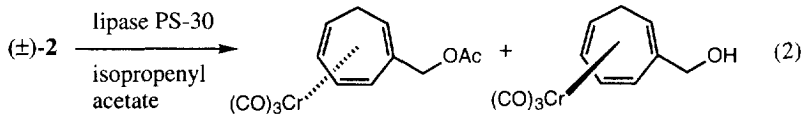
determined by conversion into the corresponding Mosher ester, while the acylated species (+)-**4**,[8] (+)-**5**[8] and (+)-**6**[8] were saponified (K_2CO_3/MeOH) prior to derivatization as the Mosher ester.



(+)-**4**
43% (70% ee)

(-)-**1**
44% (65% ee)

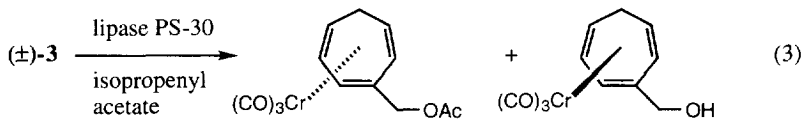
(1)



(+)-**5**
42% (60% ee)

(-)-**2**
48% (65% ee)

(2)

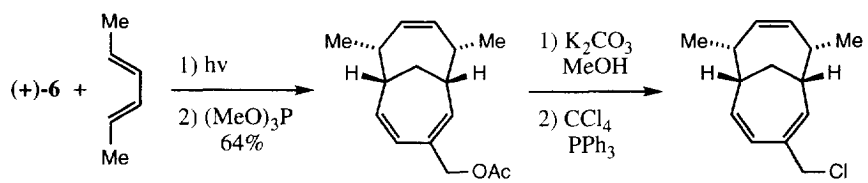


(+)-**6**
34% (75% ee)

(-)-**3**
30% (80% ee)

(3)

The absolute stereogenicity of complex (+)-**6** was established by conversion into a compound of known configuration. Thus photocycloaddition of (+)-**6** with 2,4-hexadiene[12] followed by saponification and exposure of the resultant alcohol to PPh_3/CCl_4[13] yielded (-)-**8**[8] (eq. (4)). This material was shown to have the same absolute configuration as a compound of known stereogenicity prepared previously in our laboratory.[14] The absolute stereochemistries of the other complexes were determined by facile interconversions from (+)-**6** by way of metal-mediated, thermal 1,5-hydrogen sigmatropy[16] under conditions that have been shown not to compromise the planar chirality of the complexes.



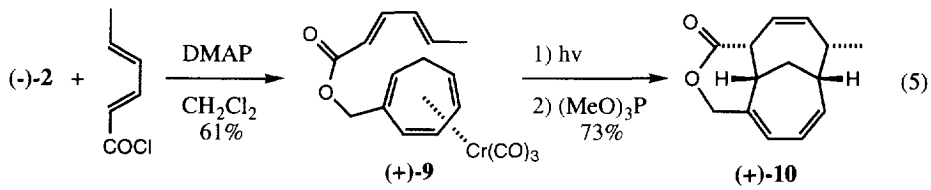
(-)-**7**

(-)-**8** ($[\alpha]_D^{25}$= -30)

(4)

The hydroxymethyl substituents in resolved complexes (-)-**1**, (-)-**2** and (-)-**3** could be useful for attaching 4π reaction partners to the triene complexes for subsequent intramolecular [6π+4π]

cycloadditions[17] that would provide enantiomerically-enriched cycloadducts. In a typical example of this transformation, **(-)-2**[8] can be esterified with sorboyl chloride to afford **(+)-9**,[8] which when photolyzed (Pyrex) provided the enantiomerically-enriched adduct **(+)-10**[8] in good yield and with complete retention of the enantiomeric purity of the starting complex.



(+)-9 **(+)-10** (5)

In summary, substituted cycloheptatriene-$Cr(CO)_3$ complexes can be resolved enzymatically and the resultant enantiomerically-enriched complexes are useful for both inter- and intramolecular higher-order cycloaddition chemistry.

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10. Obtained from Amano International Enzyme Co., Troy, VA.
11. Typical resolution procedure: A mixture of (±)-**1** (80 mg, 3.1 mmol) and lipase PS-30 (213 mg) in isopropenyl acetate (2.1 mL) was stirred under N_2 in the dark for 48 h at which time the reaction was judged to be at 50% completion. The mixture was filtered and the residue washed with methylene chloride. The solvent was removed *in vacuo* and the crude residue chromatographed (silica gel, hexanes/diethyl ether, 10:1) to afford (+)-**4** (40 mg, 43%) and (-)-**1** (35 mg, 44%).
12. It has been established that metal-promoted higher-order photocycloaddition proceeds without loss of planar chirality in the triene complex.[2]
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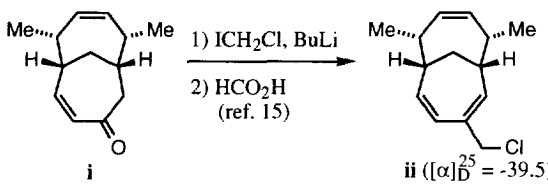
14. Chloride (-)-**8** (from (+)-**6**) was shown to be identical with the corresponding chloride **ii** derived from enantiomerically pure enone **i** of known absolute configuration.[2]



i **ii** ($[\alpha]_D^{25}$ = -39.5)

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