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Vicinal Stereocontrol during Nucleophilic Addition to Arene Chromium Tricarbonyl Complexes: Formal Synthesis of (±)-*erythro* Juvabione

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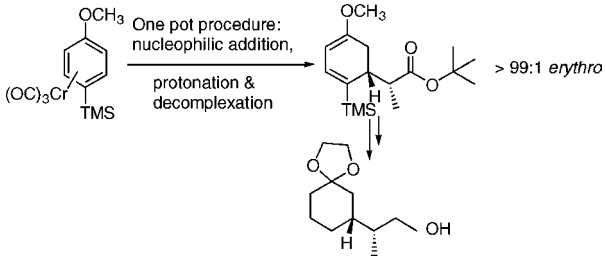
ABSTRACT



Vicinal stereocontrol during nucleophilic addition of *tert*-butyl lithiopropionate to η^6-anisole chromium tricarbonyl complexes with differing *para* substituents has been studied. Excellent vicinal double stereoinduction (>99:1) was observed when the *para* substituent was $Si(CH_3)_3$, and this has been applied to a stereoselective formal synthesis of (±)-*erythro* Juvabione. Asymmetric synthesis by chiral auxiliary directed nucleophilic addition is also discussed.

Dearomatization of arenes to nonaromatic six-membered functionalized carbocycles mediated by transition metals, especially η^6-arene tricarbonyl chromium complexes, is a widely studied area.[1] This chemistry has the potential to solve some interesting problems in organic synthesis owing to its capability for mild and rapid entry into functionalized carbocycles, selectivity in reactions, and creation of new stereogenic centers. This has been illustrated by the synthesis of numerous natural products[2] starting from these complexes. One interesting problem in organic synthesis is the control of vicinal stereochemistry of two adjacent stereocenters, one at a ring position and the other at the carbon proximal to this juncture.[3] We herein present our results addressing this problem through our study on vicinal stereocontrol during nucleophilic addition to certain η^6-arene chromium tricarbonyl complexes.[4]

The one-pot dearomatization procedure of nucleophilic addition, electrophilic addition, and decomplexation of η^6-anisole tricarbonylchromium leads selectively to 5-substituted

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(1) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev. (Washington, D. C.)* **2000**, *100*, 2917−2940.

(2) For recent applications in organic synthesis, see: (a) Kündig, E. P.; Cannas, R.; Laxmisha, M.; Ronggang, L.; Tchertchian, S. *J. Am. Chem. Soc.* **2003**, *125*, 5642−5643. (b) Schmalz, H.-G.; Kiehl, O.; Korell, U.; Lex, J. *Synthesis* **2003**, 1851−1855. (c) Kündig, E. P.; Bellido, A.; Kaliappan, K.; Pape, A.; Radix, S. *Synlett* **2003**, 2407.

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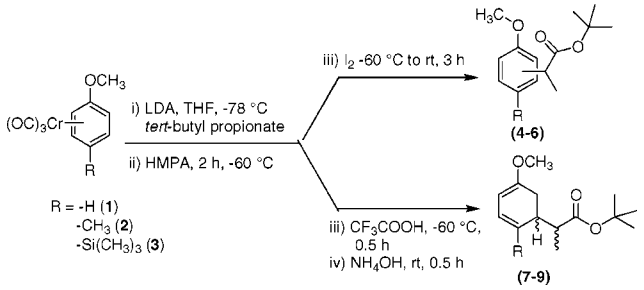
methoxycyclohexadienes and thereby to synthetically useful 5-substituted cyclohexenones.[5] The use of prochiral nucleophiles in the dearomatization procedure leads to formation of two new adjacent stereocenters. Though prochiral nucleophiles such as *tert*-butyl lithiopropionate are known to attack selectively the *meta* position of η^6-anisole tricarbonylchromium,[6] no systematic study has been reported on the degree of vicinal stereocontrol during this reaction.

4-Substituted η^6-anisole tricarbonyl chromium complexes **1** (R = H), **2** (R = CH_3), and **3** (R = $Si(CH_3)_3$) with varying steric bulk at the 4-position of the anisole were chosen for the study. The presence of a substituent at the position *para* to the methoxy group was expected to influence the vicinal selectivity of the reaction, considering addition would be selectively *meta* to the methoxy substituent. The complexes were prepared by the standard procedure of refluxing the corresponding arenes with chromium hexacarbonyl in a dibutyl ether and THF mixture.[7] The one-pot dearomatization procedure was carried out with *tert*-butyl lithiopropionate at −60 °C (Scheme 1) with HMPA as additive to enhance the reactivity of the ester enolate.

Scheme 1. Nucleophilic Addition and Protonation−Decomplexation/Oxidation Sequence



The regioselectivity in the nucleophilic addition step was determined by GC−MS analysis and integration of ^{1}H NMR spectra of the crude aromatized products (**4**−**6**) obtained from oxidation with iodine. The ratios of regio- and stereoisomers of cyclohexadienol ethers (**7**−**9**) obtained for the three complexes on reaction with the enolate of *tert*-butyl propionate were determined by integrating suitably separated ^{1}H NMR signals (Table 1). The regioselectivity results obtained from capillary GC and ^{1}H NMR spectra were comparable (<3% error).

The regioselectivity of nucleophilic addition has often been explained in terms of charge and/or orbital control.[8] More recently regioselectivity of nucleophilic addition to anisole chromium tricarbonyl complexes was correlated with stability of the η^5-cyclohexadienyl anionic intermediate.[9]

Table 1. Ratio of Regio- and Stereoisomeric Cyclohexadienol Ether Products from Addition of *tert*-Butyl Lithiopropionate to Anisole Chromium Tricarbonyl Complexes **1**−**3**

R	*meta*:*ortho* ratio[a]	*meta* isomers	*ortho* isomers	combined yield %
H (**1**)	96:4	*d*	*d*	74
CH_3 (**2**)	75:25	2:1[b]	2:3[b]	55
$Si(CH_3)_3$ (**3**)	96:4	>99:1[c]		92

[a] Ratios from ^{1}H NMR analysis of aromatized products from oxidation reaction. [b] Major stereoisomer not assigned. [c] >99:1 means only one isomer was detected by ^{1}H NMR. [d] Ratios of stereoisomers could not be determined (see text).

In general the arene carbon atom eclipsed by a carbonyl ligand is attacked by the nucleophile. In the absence of steric effects, the conformation of the tricarbonyl is *syn*-eclipsed to the electron-donating groups (one of the carbonyl ligands eclipses the arene carbon bonded to electron-donating groups such as OCH_3 and CH_3) and *anti*-eclipsed to electron-withdrawing groups (one of the carbonyl ligands eclipses the arene carbon *para* to an electron-withdrawing group such as $Si(CH_3)_3$) on the arene.[10]

Substituents *para* to the methoxy group were initially chosen with regard to their anticipated steric effect on the reaction, thereby influencing vicinal stereocontrol during *meta* addition, but their electronic properties that determine the conformation of the tricarbonyl chromium also play a significant role, as reflected in the regioselectivity of the reactions. In the case of complex **3**, with electron-donating and electron-accepting substituent at the 1- and 4-positions, respectively, the tricarbonyl would adopt a conformation that is electronically favored with respect to both substituents. This is not the case with complex **2**, which has two electron-donating substituents, albeit with different capacities, and both the 2- and 3-positions on the arene might compete for the incoming nucleophile. This results in addition to both positions, but with a preponderance of *meta* addition due to the greater directing effect of the methoxy group versus the methyl group. The significant *ortho* addition can also be rationalized by the stability of the corresponding η^5-cyclohexadienyl anion with the carbonyl ligands eclipsing the methyl group and the carbon attacked by the nucleophile. The regioselectivity of addition to anisole chromium tricarbonyl complex **1** was as reported in the literature.[5] Interestingly, the complexes **1** and **3** gave similar regioselectivities.

Addition of tert-butyl lithiopropionate to 4-trimethylsilylanisole chromium tricarbonyl (***3***) *followed by protonation gave diene* ***9*** *not only in excellent regioselectivity but also vicinal stereocontrol* (*>99:1*)! In the case of complex **2**, the

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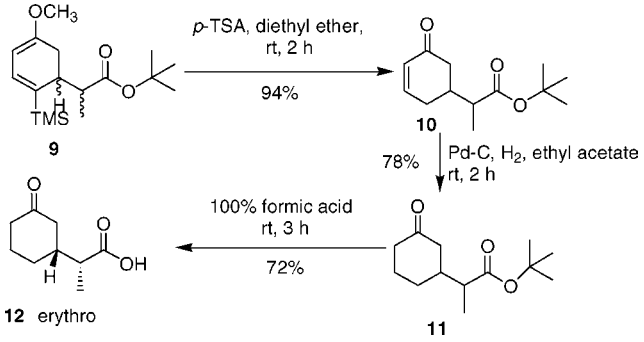
diastereoselectivity observed for each of the regioisomers was not appreciable. Complex **1** gave a mixture of several isomeric products. Although it is known to produce the 1,3-cyclohexadiene selectively, under the stated reaction conditions diene isomerization occurs, annihilating any stereochemistry induced at the ring carbon during the nucleophilic addition step.

The stereochemistry of the single stereoisomer **9** (*erythro* or *threo*) was determined by converting it to the known keto carboxylic acid **12** (Scheme 2). Thus, hydrolysis of cyclo-

Scheme 2. Determination of Major Stereoisomer from Complex **3**



hexadiene **9** afforded cyclohexenone **10**, which on catalytic hydrogenation yielded keto ester **11**.[11] The *tert*-butyl group was removed by treating **11** with formic acid, resulting in the known keto acid **12**.[12] Comparison of ^{1}H and ^{13}C NMR of **12** with literature data confirmed the isomer to be *erythro*.[13]

Stereoselective formation of the *erythro* isomer from complex **3** can be reasoned by considering two possible open transition states, **TS-1** and **TS-2** (Figure 1). The gauche

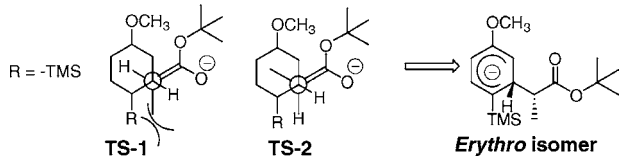


Figure 1. Possible open transition states of the intermediate (The π cloud and the complexed chromium tricarbonyl on the top face are omitted for clarity).

interaction of the trimethylsilyl group with the methyl group of enolate in **TS-1** appears to be responsible for favoring transition state **TS-2** and ensuring the formation of a single *erythro* isomer.

Molecular mechanics strain energy calculations performed using PC Spartan[14] for the corresponding three η^5-cyclohexadienyl complex conformations in both cases supports this proposition (Figure 2). The energy of the *erythro*

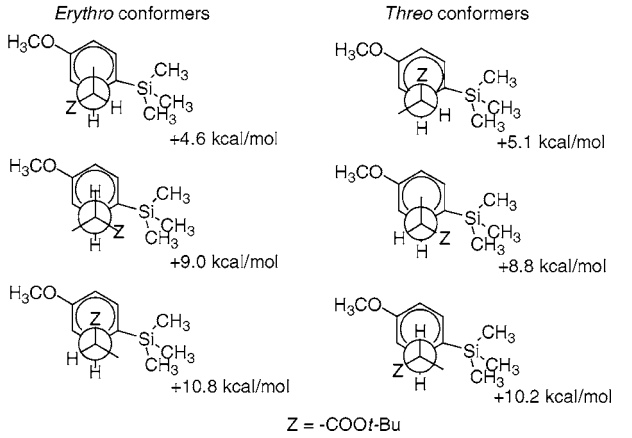


Figure 2. Calculated molecular mechanics strain energy of the possible *erythro* and *threo* η^5-cyclohexadienyl tricarbonyl chromium conformers. (The complexed chromium tricarbonyl on the bottom face is omitted for clarity.)

conformer with the least strain is 0.5 kcal/mol lower than the *threo* conformer with the least strain. Though this energy difference does not account for the very high selectivity observed, it leads us to favor **TS-2**. In both cases the conformation with the highest strain is the one with the methyl group of the enolate gauche to the TMS group. The trimethylsilyl group serves a number of roles in this stereoselective addition reaction. Its electron-accepting ability prevents the 1,3-diene from isomerizing, and its steric effect promotes selective formation of the *erythro* isomer.

Numerous steroid and terpenoid natural products possess a structural moiety with stereocenters at a ring position and at the proximal exocyclic carbon. The sesquiterpene Juvabione, an insect sex pheromone, is an illustrative example. Ketalization of keto ester **11** by ethylene glycol[15] to yield **13**, followed by reduction of the ester carbonyl by lithium aluminum hydride yielded ketal alcohol **14**, a known intermediate for the synthesis of (±)-*erythro* Juvabione **15** (Scheme 3).[16]

Miles et al. have reported addition of a chiral Evans enolate to arene manganese tricarbonyl complexes with modest 3.5:1

(11) The mixture of isomeric dienes **7** from complex **1** when converted to the corresponding keto ester revealed an equimolar mixture of *erythro* and *threo* stereoisomers.

(12) Chandrasekaran, S.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 3972−3974.

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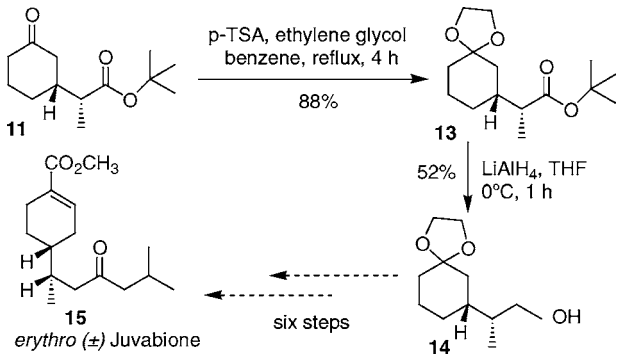
(14) *Spartan'02*; Wavefunction, Inc.: Irvine, CA.

(15) Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800−806.

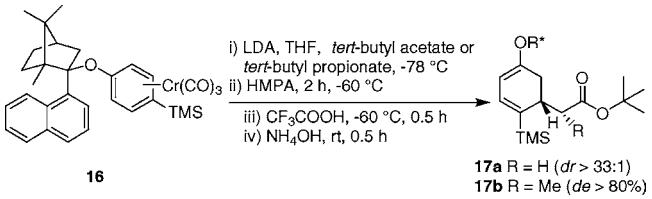
(16) For recent syntheses of Juvabione, see: (a) Soldermann, N.; Velker, J.; Vallat, O.; Stoeckli-Evans, H.; Neier, R. *Helv. Chim. Acta* **2000**, *83*, 2266−2276. (b) Kawamura, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2403−2404. (c) Watanabe, H.; Shimizu, H.; Mori, K. *Synthesis* **1994**, 1249−1254.

Scheme 3. Synthesis of Intermediate **14** in a Formal Synthesis of (±)-Juvabione



selectivity.[17] Asymmetric nucleophilic additions directed by suitable chiral auxiliaries substituted on the arene for related complexes have been reported, and the absolute stereochemistries of the cyclohexenones, which are obtained by enol ether hydrolysis, have been established.[18] More recently we have obtained diastereoselectivity of 33:1 from *tert*-butyl lithioacetate reaction with **16** to give **17a**, with *S* stereochemistry at the newly formed stereogenic center.[19] Addition of *tert*-butyl lithiopropionate to the complex **16** followed by protonation and decomplexation furnished cyclohexadienol ether **17b** in good diastereoselectivity (>80% de) (Scheme 4). The major diastereomer is assigned as *S*,*S* on the basis of our earlier work and the present study.

Scheme 4. Chiral Auxiliary Directed Nucleophilic Addition of *tert*-Butyl Lithiopropionate to Complex **16**



Of the four stereoisomers of Juvabione, the isomer with the most potent biological activity is the (4*R*,1′*R*) isomer.[20] Use of the presently available chiral auxiliaries in fact furnishes the opposite enantiomer. While it is certainly possible to obtain the *R* isomer by using chiral isoborneols derived from the unnatural L-(−)-camphor, we intend to design auxiliaries from D-(+)-camphor proceeding from an understanding of the hitherto unknown origins of 1,5-asymmetric induction.

This study on vicinal stereocontrol during nucleophilic addition to arene-$Cr(CO)_3$ complexes has provided a solution to the problem of vicinal *erythro* stereocontrol in the context of six-membered carbocycles. The results have been applied to a five-step synthesis of the formal Juvabione intermediate **14** from complex **3**. It is now established that by having substituents that prevent diene isomerization, the nucleophilic addition, protonation, and decomplexation sequence can be utilized to obtain diastereomeric addition products selectively as shown here. A complete study of chiral auxiliary directed nucleophilic addition will be reported in due course.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for important compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Unpublished results. The stereochemistry of the cyclohexenone was determined to be *S*, by measuring its optical rotation. See ref 18b.

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