Stereoselective chromium- and molybdenum-mediated transformations of arenes*

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Abstract: Tricarbonylchromium-mediated dearomatization provides a rapid access to substituted cyclohexadienes. Efficient asymmetric routes to planar chiral arene complexes and to substituted cyclohexadienes have been developed. The article sums up the main features of this chemistry. Highly enantiomerically enriched *ortho*-substituted benzaldehyde complexes are accessible via asymmetric lithiation followed by trapping with electrophiles. In different solvents, the trimethylsilyl complex exhibits [α] values ranging from –174 to +108 for the same enantiomer. Details of two asymmetric syntheses of natural products are given: the alkaloid lasubine I starting from a highly enantiomerically enriched planar chiral arene complex and the marine furanosesquiterpene acetoxytubipofuran. The latter is assembled via asymmetric dearomatization of a benzaldehyde imine complex. Other key steps include an Eschenmoser–Claisen rearrangement and a regio- and diastereoselective Pd-catalyzed allylic substitution. The final section deals with labile arene metal complexes. For the first time, dearomatization reactions mediated by the $Mo(CO)_3$ group have been realized. The reactions show strong analogies to the $Cr(CO)_3$-mediated reactions, but exhibit also marked differences: the arene–Mo bond is stronger, but more labile, and the sequential double additions show different selectivities compared to the chromium analogs.

The search for ever more efficient chemo-, regio-, and stereoselective routes to complex molecules from simple starting materials is an important task in organic synthesis. Progress in this area continues to advance at a fast pace. Arenes, the subject of this article, are widely available, highly stable, and readily derivatized through reactions such as electrophilic and nucleophilic aromatic substitution [1], *ortho*-lithiation followed by reaction with electrophiles [2], or metal-catalyzed substitution and coupling reactions [3–4]. Routes to differentially substituted aromatic products are thus well established. Benzene and its derivatives are attractive starting materials because they have the potential to provide a rapid entry into complex alicyclic synthetic building blocks containing unmasked functionality, new carbon–carbon bonds, and new stereogenic centers [5]. However, this route to functionalized nonaromatic six-membered carbocycles is not common because substitutive dearomatization reactions require disruption of the aromatic π-system and this severely limits the scope of viable methodologies.

This notwithstanding, the synthesis of complex organic molecules via elegant dearomatization chemistry has undergone intensive investigation. Examples involve the Birch reduction, which achieves

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dearomatization via single electron transfer [6,7], photocycloaddition of arenes to alkenes [8], and methods which rely on nucleophilic addition to electron-deficient arenes [9–13].

Arene dearomatization reactions can also be induced by temporary complexation of its π-system to a transition metal with the fragments $Cr(CO)_3$, $Mn(CO)_3^+$, and $Os(NH_3)_5^{2+}$ being most prominent [14]. Recently, this has been extended to the $CpRu^+$- [15,16] and $Mo(CO)_3$- fragments [17].

Tricarbonylchromium-mediated dearomatization provides an efficient direct access to substituted cyclohexadienes [14]. Up to three C-substituents can be added in a regioselective and stereoselective manner across an arene double bond in a one-pot sequence (Scheme 1). Complexation is a high-yield, efficient process with $[Cr(CO)_6]$, $[Cr(CO)_3(CH_3CN)_3]$, $[Cr(CO)_3(NH_3)_3]/BF_3 \cdot OEt_2$, and [(naphthalene) $Cr(CO)_3$] being suitable, and selective "$Cr(CO)_3$" transfer reagents [18]. The scope of reactive nucleophiles for the addition reaction ranges from sulfur-stabilized carbanions to alkyl, vinyl, and aryl lithium reagents. In situ treatment of the resulting anionic cyclohexadienyl complex with a reactive electrophile results in protonation, alkylation, allylation, or propargylation at the Cr center. This is followed by reductive elimination (*endo* migration) with or without prior migratory CO insertion. Alkyl groups always undergo carbonylation, propargyl groups always migrate directly, and with allyl and benzyl moieties, it is the nature of the arene substituents that determine the outcome. Decomplexation of the *trans*-1,2-disubstituted cyclohexadiene product occurs readily because of the high lability of the Cr(0)-diene bond. Extension of this methodology to the synthesis of enantioenriched products has been successful [14].
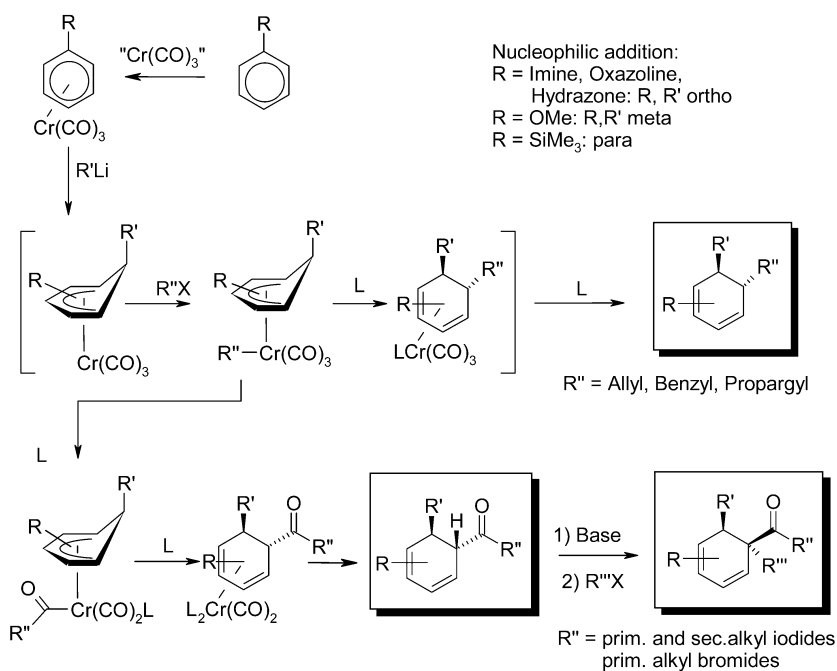

Scheme 1 $Cr(CO)_3$-mediated substitutive dearomatization.

Scheme 2 shows the successful extension of this methodology to the synthesis of enantioenriched products, and new examples of both, the chiral auxiliary approach and the use of a chiral nucleophile, will be presented later in this article. We have also pursued the development of new routes of access to planar chiral complexes. Most applications in either synthesis or chiral ligand preparations of planar chiral arene complexes involve *o*-substituted benzaldehyde complexes. Earlier, we developed a nucleophile addition/hydride abstraction route [19,20] and, more recently, have found a lithiation/electrophile trapping/imine hydrolysis route as shown in Scheme 3 [21]. The value and sign of the optical rotation
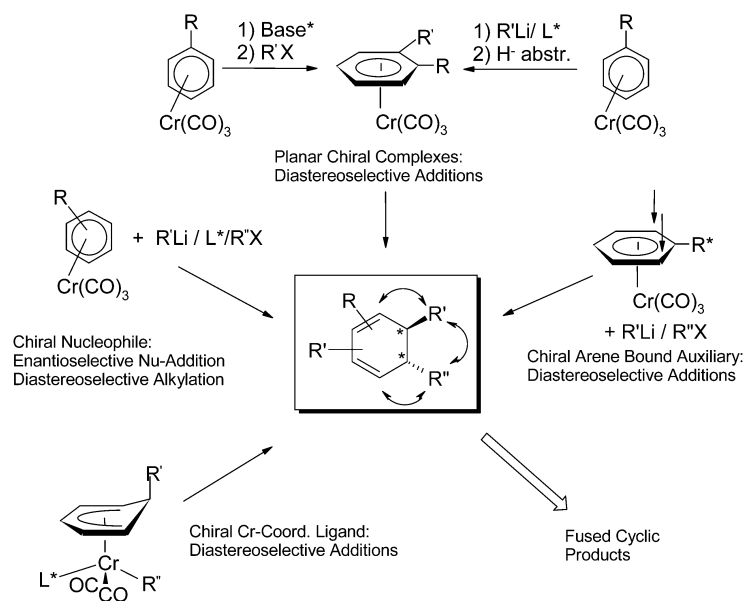
Scheme 2 Routes of access to enantiomerically enriched substituted cyclohexadienes.
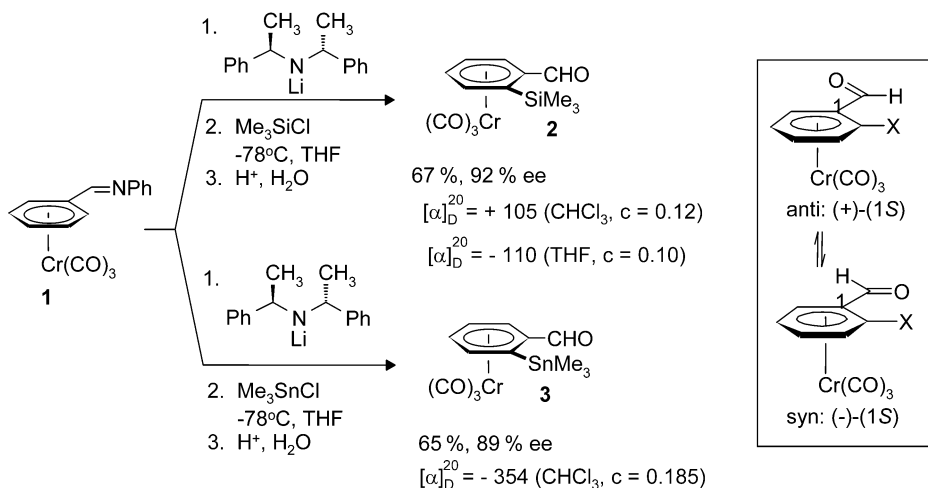
Scheme 3 Enantioselective lithiation/electrophile trapping with a benzaldehyde imine complex.

of complex (*1S*)-**2** in different solvents shows a very large variation and values of [α] range from –174 (EtOH) to +108 (CHCl$_3$). This is interpreted as arising from different preferential conformations adopted by the aldehyde function in the complex. NMR nuclear Overhauser effect (NOE) measurements are in agreement with this proposal [22]. Complex (*1S*)-**3** adopts a preferential *syn* aldehyde conformation because of the Lewis acid properties of the *ortho*-SnMe$_3$ group.

The highly enantiomerically enriched complex **4** has been used in a synthesis of (–)-lasubine I (**5**) with the key steps being a diastereoselective aza-Diels–Alder reaction and an equally highly diastereoselective radical cyclization (Scheme 4) [23]. At present, the same route is being followed for the synthesis of (+)-vertine (**6**).
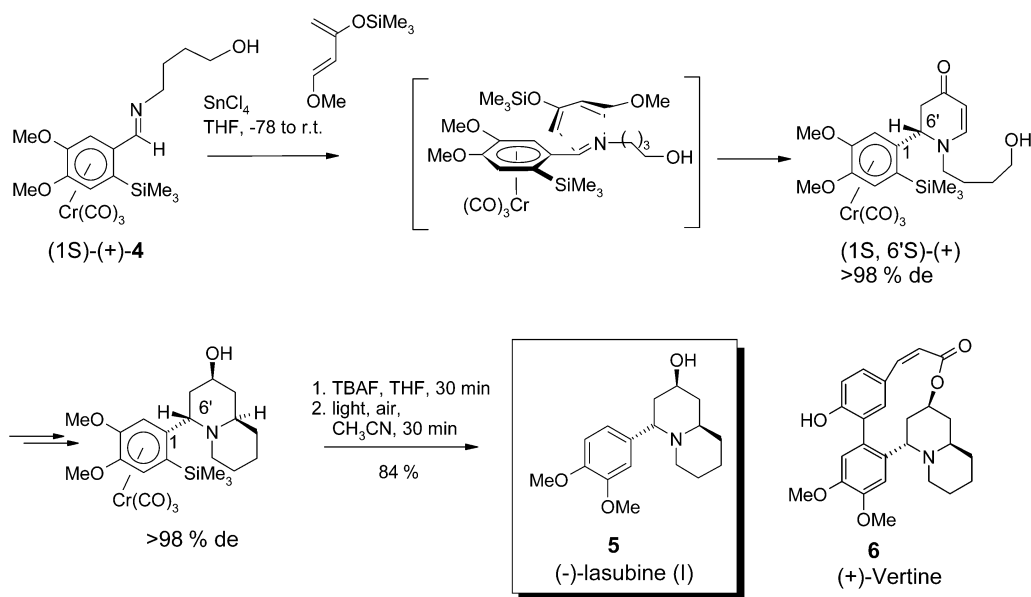
Scheme 4 Application of the planar chiral (arene)Cr(CO)$_3$ complex **4** to the synthesis of lasubine I (**5**).

Asymmetric synthesis of natural products via (arene)Cr(CO)$_3$ complexes has received attention from several groups [24–26]. We have recently accomplished the synthesis of both enantiomers of the marine furanosesquiterpene acetoxytubipofuran [27]. The key intermediate **11** was obtained using either an enantioselective or a diastereoselective nucleophilic addition. The enantiomeric acetoxytubipofurans were then obtained via the routes shown in Scheme 6. For the natural (+)-acetoxytubipofuran, the key step is a very efficient Eschenmoser–Claisen rearrangement while the (–)-ent-product was obtained via Pd-catalyzed allylic substitution.
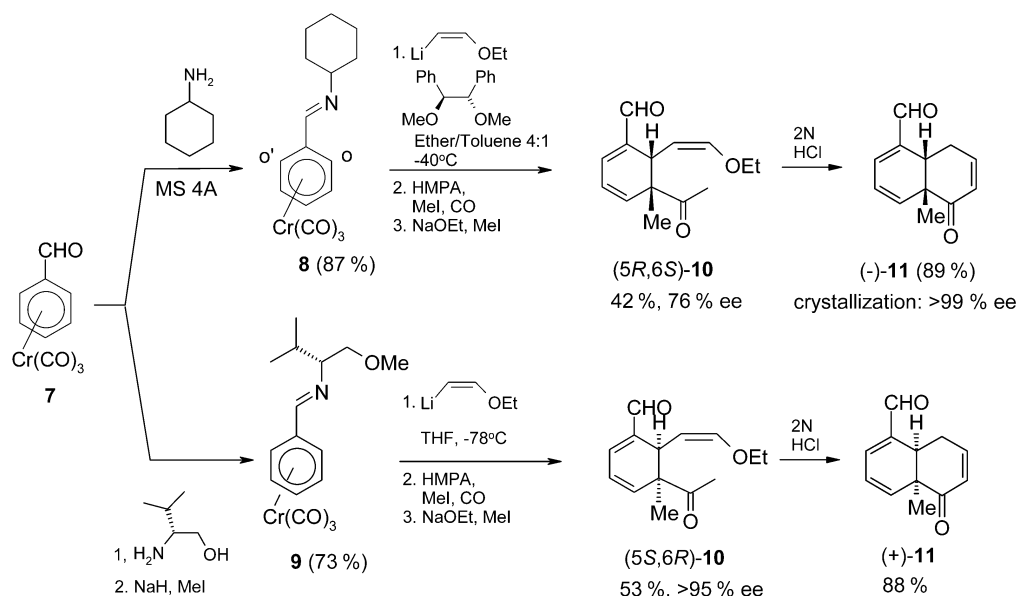

Scheme 5 Routes of access to both enantiomers of a key intermediate in the synthesis of (+)- and of (–)-acetoxytubipofuran.
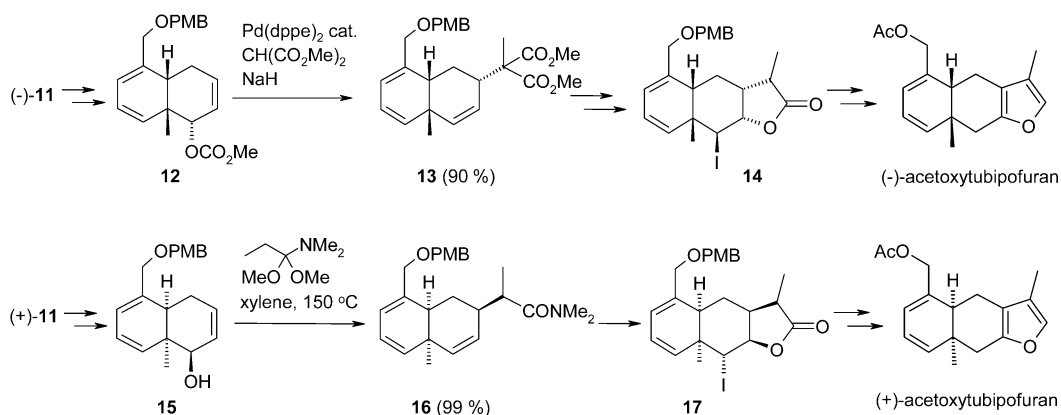
Scheme 6 Completion of the synthesis of both enantiomers of acetoxytubipofuran.

To this day, all $Cr(CO)_3$-mediated arene transformations are stoichiometric. While catalytic use of the Lewis acid activating group would be highly desirable, this fails primarily because of the robust arene metal bond in these complexes. For this reason, we and others have been searching for transition-metal fragments that form labile complexes with arenes, but that retain electrophilic activation. One approach makes use of $Cr(CO)_2L$ fragments in which the ligand L functions as arene-labilizing group. Examples include the methyl acrylate complex **18** [28] and the tris(pyrrol)phosphine complex **19** [29]. In both complexes, the proposed mode of action is a labilization of the arene via temporary complexation of the ester function to the transition metal. Thus, complex **18** exchanges the arene at ambient temperature and complex **19** at 70 °C. In [Cr(benzene)$(CO)_3$], no arene exchange occurs up to 150 °C. Catalytic arene functionalizations via this route have not yet been realized, but the acrylate complex has been used in hydrogenation catalysis [28] and as catalyst for higher-order cycloaddition reactions under mild conditions [30]. Another approach focuses on (arene)Mo$(CO)_3$ complexes. The notorious lability of the Mo–arene bond in these compounds has hitherto prevented their use in arene transformations. The results of a first study of a sequential nucleophile/electrophile addition sequence to an arene Mo$(CO)_3$ complex in a nucleophilic/allyl bromide double addition sequence is shown in Scheme 7 [17]. It demonstrates the viability of using π-arene molybdenum complexes in organic synthesis. The reactions, the isolation of intermediates, and the final products highlight analogies but also differences between the chromium and molybdenum complexes.
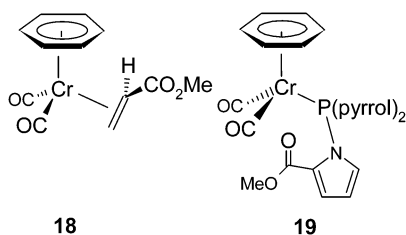
The results presented in this article and in the cited references make it clear that the activation of an arene by temporary complexation to an electrophilic transition-metal fragment offers a powerful tool to asymmetric organic synthesis and catalysis, and new reactions and applications are bound to emerge.
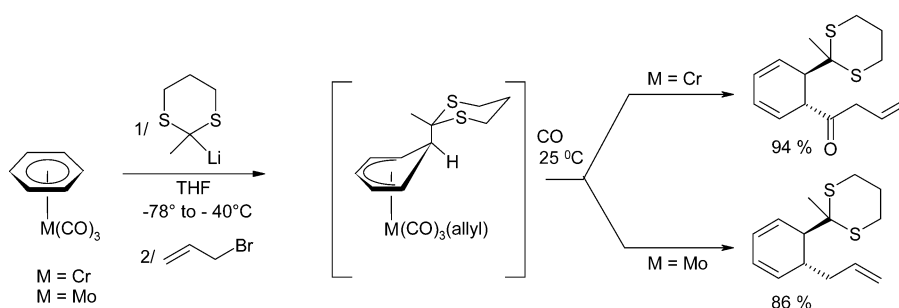
Scheme 7 Analogies and differences in the sequential Mo- and Cr-mediated *trans* addition of a C-nucleophile and a C-electrophile to arene complexes.

ACKNOWLEDGMENT

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