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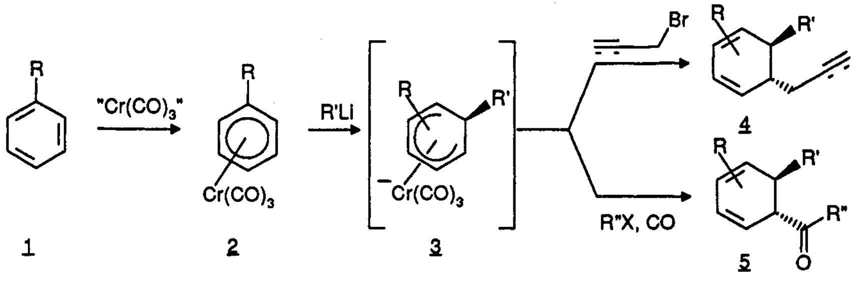
Chiral auxiliaries, ligands and arene chromium complexes

E. P. Kündig*, D. Amurrio, G. Anderson, D. Beruben, K. Khan, A. Ripa, and
L. Ronggang,

Département de Chimie Organique, Université de Genève, 30 quai Ernest Ansermet,
CH-1211 Geneva 4, Switzerland

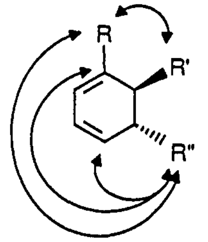
Abstract: Sequential addition of organolithium compounds and allyl- or propargyl bromide to (phenyloxazoline)$Cr(CO)_3$ gave 1-oxazolyl-5,6-*trans*-disubstituted cyclohexadienes. Regioselective radical ($SnBu_3$) addition to the alkyne and cyclization of the vinylic radical to the diene moiety afforded fused bicyclic ring systems. Depending on whether the reaction was carried out with a terminal or internal alkyne, the reaction gave either *cis*-fused tetrahydroindanes or bicyclo[3.2.1]octenes selectively. Asymmetric methodologies for the synthesis of diastereo- or enantioenriched cyclohexadienes *via* temporary complexation of the arene to the electrophilic $Cr(CO)_3$ include chiral auxiliaries on the arene (oxazolines, SAMP-hydrazone), chiral ligands at Cr, chiral nucleophiles (organolithium reagents modified by chiral ligands) and planar chiral complexes synthesized *via* enantioselective lithiation. The article contains new developments and examples of the first and third approach of this asymmetric dearomatization methodology.

Arenes are convenient starting materials for the regio- and stereoselective synthesis of functionalized six-membered ring compounds. The transformation shown in Scheme 1 involves complexation of an arene (1) to the electrophilic $Cr(CO)_3$ group to give complex 2 , followed by the sequential addition of an organolithium compound and a C-electrophile across an arene double bond yielding either 4 or 5 (1).



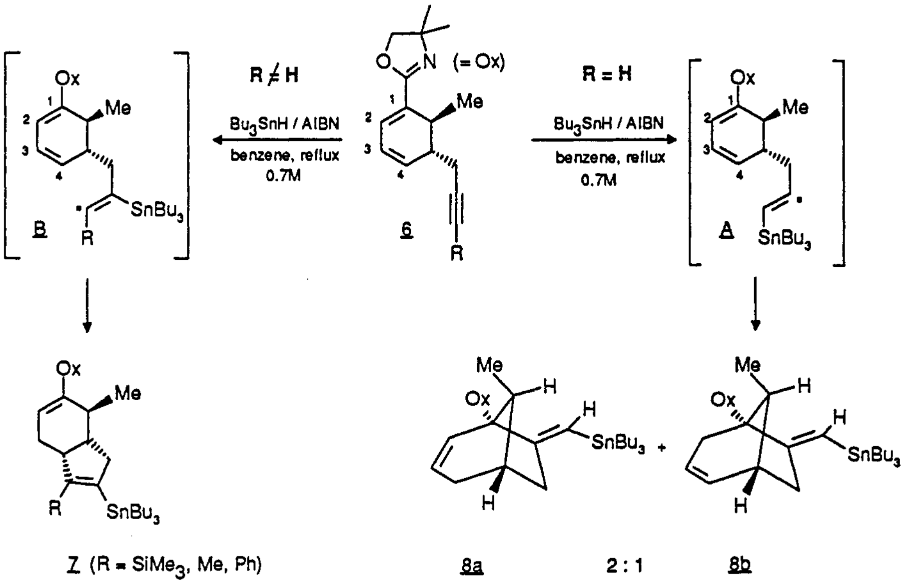
The course of the reaction depends on the nature of the C-electrophile and the arene. Alkyl halides react by Cr-alkylation, migratory CO-insertion, and reductive elimination to give 5. Propargyl bromides, and in some cases, allyl bromides, having a lower migratory aptitude towards carbonylation, react to give products without CO-insertion (4).

Regioselectivity of nucleophilic addition can be high. At low temperature, orbital and charge control are dominant but at higher temp. and/or longer reaction time, changes in regioselectivity are frequent (2). They are associated with the relative stability of equilibrating regioisomeric intermediates 3. Generally, aldimine, oxazoline or hydrazones direct *ortho* (3), methoxy directs meta and $SiMe_3$ directs para (2).



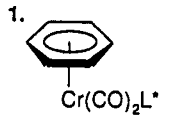
Both dihydroarenes 4 and 5 offer a number of possibilities for polar, radical (4) or transition metal mediated (5)(6) intramolecular diastereoselective cyclization reactions. For 5 (R = oxazoline, aldehyde, hydrazone; R' = alkyl, aryl, vinyl; R" = allyl, propargyl), these are schematically shown.

As example, let us consider the transformation of the alkynyl moiety in 6 to a vinylic radical and the regioselectivity of the ensuing cyclization to the diene system. Both of the possible regioisomeric vinylic radical intermediates can undergo 5-exo-trig cyclizations to one of the termini of the diene moiety. Reaction with $SnBu_3$ selectively transformed propargyl diene 6a (R=H) into the bicyclo[3.2.1]octenes 11a and 11b (ca. 2:1). The tin radical thus added to the terminal alkyne position to give intermediate A (7), followed by cyclization (8) to C(1) of the cyclohexadiene and Bu_3SnH reduction. A different pathway is followed in analogous reactions with 6b-d where R ≠ H. The single products obtained are the *cis*-tetrahydroindenes 12-14, formed *via* intermediate B which then undergoes cyclization followed by reduction (Scheme 2).

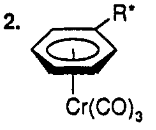


Preliminary mechanistic investigations provide evidence that only vinylic radical A is formed from the terminal alkyne. Equilibration to radical B is not only slower than ring closure but also slower than than reduction by the tin hydride if the structure is modified in such a way that ring closure from A is no longer possible (9). Synthetically, the cyclohexadienes 6 provide a convenient access to the diastereomerically pure tetrahydroindenes 7 and the bicyclo[3.2.1]octenes 8.

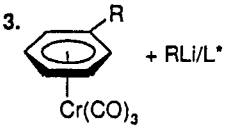
In view of the highly diastereoselective alkylation and cyclyzation procedures, asymmetric methodology for the synthesis of 4 and 5 would be very attractive. Four different approaches can be envisaged and have been realized in this group (10).



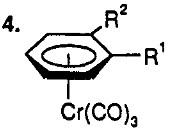
Chiral ligands
ee=15-70%



Chiral Auxiliary
de=60-98%



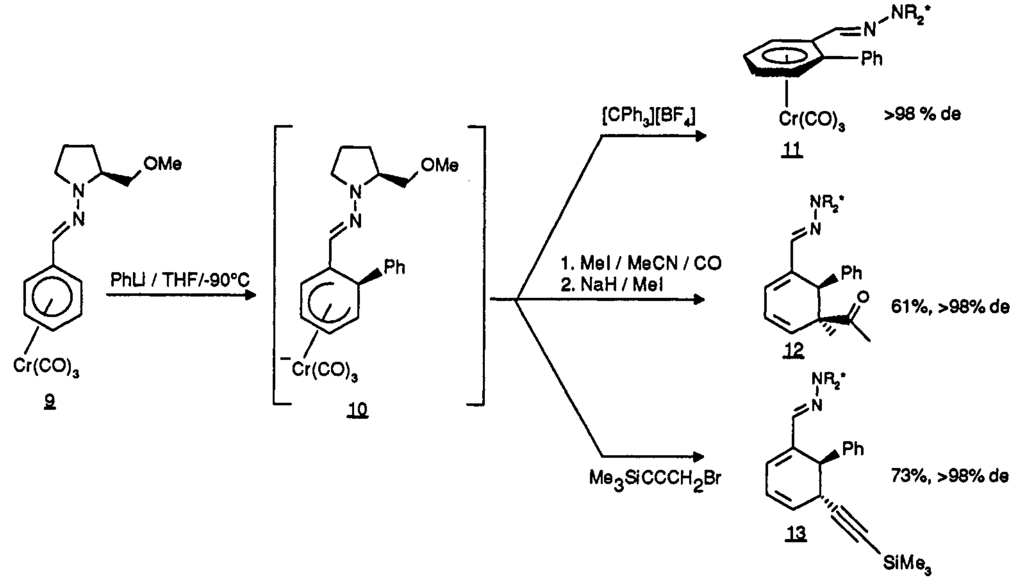
Chiral Nucleophile
ee=65-93%



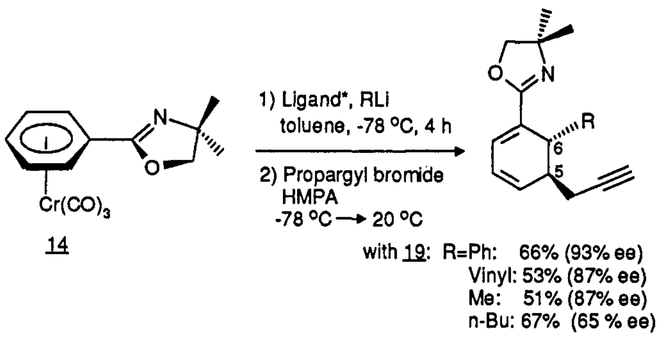
Planar Chiral Complex

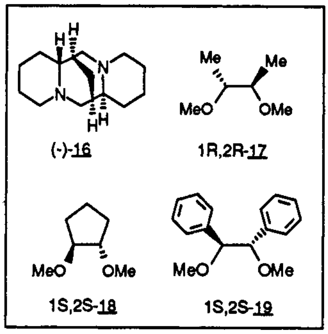
As shown, three of the chiral modifications of the sequential addition of C-nucleophiles and C-electrophiles involve chiral arene complexes while the fourth involves chiral nucleophiles. In approaches 2.-4., asymmetric induction takes place in the nucleophilic addition step whereas in 1. induction occurs later on in the sequence, either during migratory CO insertion or reductive elimination (10a).

Chiral auxiliaries: SAMP-hydrazone (11). The enantiopure benzaldehyde SAMP-hydrazone complex 9 reacts with high diastereoselectivity in nucleophile addition/hydride abstraction reactions to give diastereomerically pure 11.(12) The intermediate cyclohexadienyl complex 10 can be successfully trapped by a C-electrophile to give dienes 12 or 13. Diastereoselectivities match or exceed those obtained with chiral oxazolines (10b).

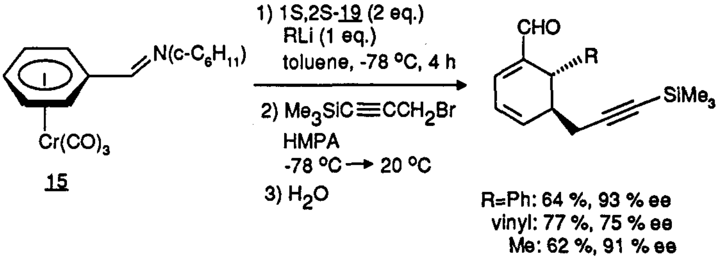


Chiral nucleophile: external chiral ligands: The external ligand-controlled enantioselective addition of organometallic reagents to prochiral molecules is a powerful tool in asymmetric methodology (13) with considerable potential when used in nucleophilic additions to organic ligands π-bound to transition metals.





Our first results with the phenyl oxazoline complex 14 and the phenylmethanimine complex 15 bear this out. Of the four chiral ligands (16-19) tested, the diether 19 performed best, giving enantiomeric enrichements of up to 93 % ee (10c). In the examples described with the phenyloxazoline complex, the methodology presented here is complementary to that developed with chiral oxazolines (10b). The reactions with the imine complex 7 are unique in that there are as yet no chiral imines which give both high 1,4-regio- and diastereocontrol in arene addition reactions (14). The advantage of this methodology over that using chiral auxiliaries σ-bound to the arene is its potential for catalysis. Research on this project is directed towards this goal.



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