Chiral auxiliaries, ligands and arene chromium complexes

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Abstract: Sequential addition of organolithium compounds and allyl- or propargyl bromide to (phenyloxazoline)Cr(CO)3 gave 1-oxazolyl-5,6-disubstituted cyclohexadienes. Regioselective radical (SnBu3) 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 deariomatization 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).
are associated with the relative stability of equilibrating regioisomeric intermediates 3. Generally, aldimine, oxazoline or hydrazones direct \textit{ortho} (3), methoxy directs meta and SiMe\textsubscript{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\textsubscript{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\textsubscript{3}SnH reduction. A different pathway is followed in analogous reactions with 6b-d where R \neq 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 cyclization 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).
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 2 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 enrichments 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 oxazolines is that the reactions are compleMenTARY to those 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 $\sigma$-bound to the arene is its potential for catalysis. Research on this project is directed towards this goal.

$\text{Cr(CO)}_3\rightarrow$N($\sigma$-C$_6$$H_5$)$_2$

1) $1S,2S$-$12$ (2 eq.)

R Li (1 eq.)

toluene, $-78$ °C, 4 h

2) Me$_3$SiC=CCH$_2$Br

HMPA $-78$ °C $\rightarrow$ 20 °C

3) H$_2$O

R=Ph: 64 %, 93 % ee

vinyl: 77 %, 75 % ee

Me: 62 %, 91 % ee

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REFERENCES


14. Compared to imines, hydrazones are far more resistant to non-oxidative hydrolysis (11).