Chiral-at-Metal Complexes and the Diels-Alder Reaction

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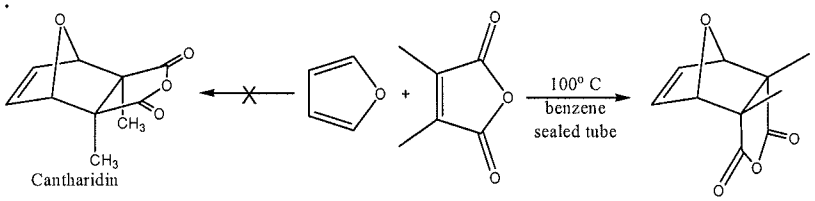
Chiral-at-metal complexes are molecules in which the metal center itself is either a stereogenic center or part of an axis of symmetry. The first 6- coordinate, non-racemic organometallic chiral-at-metal complex was synthesized by Brunner in 1970.[i] While many chiral-at-metal complexes now exist, few promote or catalyze organic reactions. This is in part due to epimerization about the metal center under reaction conditions, which renders the catalyst racemic.[ii] Recently, Diels-Alder reactions using chiral-at-metal complexes demonstrate that these complexes have utility in organic syntheses.

The need to access chiral, non-racemic compounds synthetically is well recognized. There are two major routes toward the synthesis of chiral, non-racemic compounds. The first is the physical separation of a racemic mixture via chiral resolution. This process is inherently inefficient, as ~50% of the mixture (the undesired enantiomer) is not used. The second route relies on synthesizing stereopure compounds using existing chirality to set new stereocenters. Stereoselective synthesis, the synthesis of one optical isomer of a compound over another, is one of the main challenges in synthetic chemistry. The use of chiral auxiliaries, chiral moieties attached to reagents that dictate the stereochemical outcome of a reaction, is one type of stereoselective synthesis. Chiral catalysis in stereochemical synthesis is well documented. Many of these catalysts rely on C_2-symmetrical, organic ligands to impart stereochemical information on the reagents involved in the reaction.[iii]

The Diels-Alder reaction is the key step in many stereoselective total syntheses of natural products. The reaction is innately diastereoselective. The attempted synthesis of the achiral molecule cantharidin by Diels and Alder in 1929 shows the synthetic power of the Diels-Alder reaction (*Scheme 1*). Although cantharidin was not synthesized, only one compound was. The reaction yields a substituted cyclohexene, setting four stereocenters simultaneously.[iv]



Scheme1: Diastereselective synthesis of Cantharidin

Pseudo-tetrahedral chiral-at-metal organometallic complexes, where the metal is a stereogenic center, are well documented in the literature.[v] In 1982 Stephen Davies designed the chiral-at-iron complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(COCH_3)(PPh_3)]$. Davies and coworkers were able to use this complex as a chiral auxiliary for asymmetric reactions including alkylations, aldol reactions, and Michael additions, utilizing the stability of the enolate anion of the acetyl moiety. In 1986 they carried out an asymmetric Diels-Alder reaction using one enantiomer of a derivative of the iron complex as a stoichiometric

chiral auxiliary. The reaction between $[(\eta^5\text{-}C_5H_5)Fe(CO)(COCHCH_2)(PPh_3)]$ and acrolein in the presence of $ZnCl_2$, followed by oxidation/hydolysis of the pendant auxiliary, yields the bridged cyclohexene in 88% yield, with a diastereomeric ratio of 21:3:1. The major diastereomer was synthesized in 95% ee. Although this method yields the desired product in moderate yield with good enantioselectivity, the synthesis is wasteful because it requires a chiral auxiliary itself, the chiral iron complex is not recoverable, and a stoichiometric lewis acid.[5]

Many Diels-Alder reactions require a Lewis acid to activate the dienophile so that the reaction can be carried out at a practical temperature. Many chiral at ligand Lewis acid catalysts, including those synthesized by Corey[vi] and Evans,[vii] are effective in the asymmetric Diels-Alder reaction, but few chiral-at-metal Lewis acid catalysts exist. The reason for this is the instability of many enantiomerically pure Lewis acids, which is well documented in the literature.[2] Kundig et al. studied the racemization of chiral-at-metal Lewis acids extensively with their chiral-at-ligand precatalyst [CpRu-((*R*)-BINOP-F)(I)]. Theoretical and NMR studies indicate that once the iodine is removed and replaced by solvent, a dissociative mechanism of the solvent ligand results in the pendular motion of the BINOP-F ligand. While the catalyst is not stereogenic at the metal, these findings help explain the instability of chiral-at-metal Lewis acids in solution.[viii]

One solution to the Lewis acid stability problem is to employ diastereomerically enhanced catalyst mixtures. Carmona and coworkers developed chiral-at-metal catalysts that are not enantiomerically pure. Rather both $[\eta^5\text{–}C_5Me_5)IrCl(N\text{-}(2\text{-pyridylmethylene-}(R)\text{-}1\text{-naphthylethylamine})][SbF_6]$ and $(R_{Ir})\text{-}[\eta^5\text{–}C_5Me_5)Ir(solvent)(PN\text{-}^{I}Pr)][SbF_6]_2$ utilize chiral ligands as well as stereogenic metal centers. In both cases the bidentate ligands have immutable stereogenic carbons in their backbone and an epimerizable stereogenic metal center. Upon reaching equilibrium in solution, one diastereomer forms in excess, resulting in good endo:exo ratios for the product but poor to moderate enantioselectivities. Use of the C_1 symmetrical phosphinooxazoline ligand increases the ee substantially, however the reaction between methacrolein and cyclopentadiene produces the cycloadduct in only 60% ee.[ix]

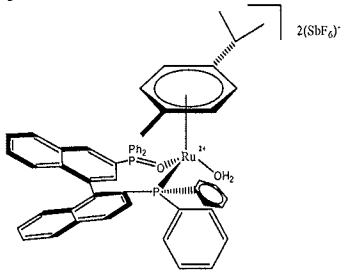


Figure 1: $(R_{Ru})\text{-}[CyRu(OH_2)\text{-}BINPO][SbF_6]_2$

Faller and coworkers developed a chiral-at-metal catalyst that is configurationally stable at the metal center. The bulky (2-diphenylphosphino,-2'-diphenylphosphineoxide)binaphthyl (BINPO) ligand does not allow for epimerization through an $\eta^2\text{–}\eta^1\text{–}\eta^2$ dissociation like many bidentate ligands. Preparation of the complex $(R_{Ru})\text{-}[CyRu(OH_2)\text{-}BINPO][SbF_6]$ *(Fig. 1)* takes place in good yield with a diastereomeric ratio >99:1. With this complex, the Diels-Alder reaction between α-alkyl and α-bromo acrolein and cyclopentadiene occurs with excellent yield, and in the case of

methacrolein excellent ee's (>99%). Although Faller suggests that stereoselectivity is derived from electronic asymmetry, the steric bulk of the BINPO ligand likely affects the stereochemical outcome of the products.[x]

Although recent research has lead to a few succesful chiral-at-metal catalysts, much work still needs to be done. The mechanism of epimerization has yet to be elucidated, and the lack of stabililty of stereogenic metal centers hinders future progress. A better understanding of the racemization process must be gained before chiral-at-metal catalysis becomes a viable alternative to C_2 symetrical, chiral-at-ligand catalysis.

References