The Synthesis of a Sterically Hindered Metallocene Catalyst
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Metallocene catalysts consist of two cyclopentadiene structures coordinated to a metal. The metallocenes of interest are enantioselective, tethered by an ethane bond, and coordinated to a lanthanide or group 4 metal such as zirconium. Metallocenes can be meso or racemic. Meso metallocenes contain a mirror plane, whereas racemic metallocenes contain no mirror plane. The presence of the mirror plane allows for meso metallocenes to catalyze equal amounts of meso and racemic products. Enantiomers of the racemic metallocene can be isolated to preferentially catalyze the formation of a greater amount of one enantiomer.

One application of the synthesis of enantioselective metallocene catalysts is in pharmacy. One enantiomer of a drug is often responsible for the desired effects, while the other enantiomer is responsible for the negative effects. For example, Citalopram (Celexa) is a racemate drug which acts as an antidepressant, whereas Escitalopram (Lexapro) contains the isolated s-enantiomer and has shown to be more effective in treatment (Sanchez et al. 2004).

In my summer research, I investigated how to optimize reaction conditions so that steric bulk (isopropyl groups) causes formation of the meso catalyst to be unfavorable. To synthesize the catalyst, there are multiple reaction steps. The first of these involves a Friedel-Crafts Acylation in which 1,4-diisopropylbenzene reacts with the acylating agent 3-chloropropionyl chloride in the presence of a catalyst. In the summer of 2003, Evron Legall investigated the optimal catalyst to use in the first reaction step, finding it to be FeCl₃ (Evron Legall 2003). In my investigation, I found there to be rearrangement of the isopropyl groups on diisopropylbenzene with the addition of both FeCl₃ and AlCl₃ in the absence of the acylating agent. With FeCl₃, there was a 1 isomerized diisopropylbenzene to 30 1,4-diisopropylbenzene ratio, while with AlCl₃ there was a 3 isomerized diisopropylbenzene to 4 1,4-diisopropylbenzene ratio (with room temperature stirring). The conditions investigated in the first step were the solvent (CH₂Cl₂, CCl₄, CS₂), catalyst (AlCl₃, FeCl₃), reaction time, and temperature (ice bath, room temperature, reflux). After the Friedel-Crafts Acylation, the uncyclized alkene product and chloropropionyl-diisopropylbenzene were acidified by adding conc. H₂SO₄ under heated stirring, which yields the cyclized, desired product, 1,4-diisopropylindanone. Optimal conditions for the Friedel-Crafts Acylation and acidification are shown below.

While the yield of the first step was 65-70%, the percent yield of the second step was considerably lower. Through the use of column chromatography, the product 1,4-diisopropylindanone was successfully isolated as supported by GC-MS and H NMR analysis.

In the future, the scaling up of the first two steps must be investigated as well as increasing the yield of the second step. The subsequent reaction steps including the reduction of the ketone, the elimination of the alcohol, the tethering, and the coordination to a metal must be investigated as well.

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References: