Study on the Design, Synthesis and Application of Ferrocene-derived Chiral Ligands Containing Dioxazoline

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Abstract: in the asymmetric synthesis of metal catalysis, chiral dioxazoline ligands have been widely used in various asymmetric catalytic processes, such as the formation of carbon-carbon bonds, due to their easy raw materials, easy synthesis and easy structure modification. Nitrogen heterocyclic propane reaction, oxidation reaction and hydrosilanization reaction all showed excellent chiral inductive properties. On the other hand, ferrocene is used as skeleton ligand, especially chiral ferrocene phosphine ligand, in addition to carbon-carbon double bond, hydrosilylation and reduction of dibasic compounds, Aldol reaction of aldehydes, Heck reaction. Cross coupling reactions and many other reactions also show High enantioselectivity. It is predicted that the chiral dioxazoline ligands with ferrocene as the skeleton will have better asymmetric inductive properties. In this paper, four chiral dioxazoline ferrocene ligands (Lip,Lph,Lbn,Lme,) have been synthesized to study their chiral induction properties in Cu (I) catalyzed asymmetric cyclopropane reaction and Mg (11) -catalyzed Diels Alder reaction.

1. Introduction

Ferrocene is a kind of organometallic compound. In 1951, Kealy and Pauson used Grignard reagent CSHSMgBr as raw material and Fecl3 as catalyst for the synthesis of fulvene (fulvalene) without success, but ferrocene [1] was accidentally obtained in 1952. Wilkinson and woodward confirmed that ferrocene is a sandwich metal dione complex [2]. By means of x-ray diffraction, Fische: et al found that ferrocene has a pentagonal antiprism structure [3]. Fsseher and wilkinson for this purpose Received the 1973 Nobex Prize in Chemistry. The discovery and structure determination of ferrocene have greatly promoted the development of organometallic compounds and structure theory, and made organometallic chemistry enter a new era. Ferrocene and its derivatives are widely used in industry, agriculture, medicine, aerospace, energy conservation, environmental protection and other industries. With the development of catalytic asymmetric synthesis chemistry, chiral ferrocene derivatives have attracted wide attention of chemists because of their unique properties[4,5].

In this paper, ferrocene was used as starting material to synthesize 1'-1'-ferrocene dicarboxylic acid phthalate by Fourier's phthalylation reaction, haloform reaction and chlorination reaction. The synthesis routes and reaction conditions were compared and optimized. In this paper, the natural photoactive L-a- amino acid was reduced to photoactive (S)-β -amino alcohol as chiral source in the system of sodium borohydride and iodine reduction. β -hydroxyamides were synthesized by the reaction of acyl chloride with chiral amino alcohol. Dioxazoline ferrocene ligand was synthesized by cyclization under the action of alkali.

The chiral inductive properties of ligands in asymmetric cyclopropanation of styrene with diazoacetic acid ethyl acetate catalyzed by copper (I) were studied. A new method for the analysis of enantioselectivity and enantioselectivity of the reaction was established. The process of the reaction and the enantioselectivity of the reaction were detected by gas chromatographic column SE-30. The enantioselectivity of trans-bodies was determined by differential isomerization of cyclopropane products. The enantioselectivity of cis products was determined by chiral capillary

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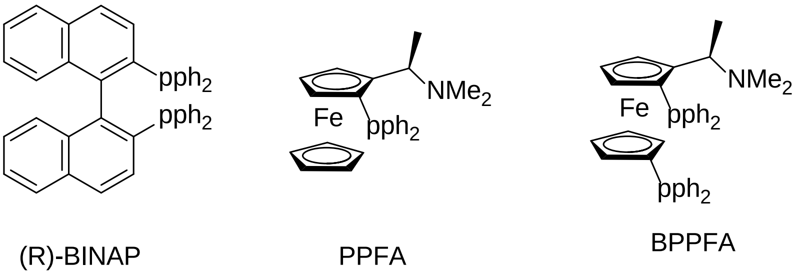
gas chromatography with β -cyclodextrin prepared by laboratory. The experimental results show that all ligands exhibit certain chiral inducement. The highest enantioselectivity is 24. The factors affecting the reaction, such as the amount of catalyst and the reaction temperature, were studied in detail, and the reasons for the low enantioselectivity of the reaction were analyzed theoretically.

2. Related work

Many catalysts contain chiral phosphine ligands in catalytic reactions, so how to design and prepare chiral phosphine ligands is very important for obtaining high enantioselectivity and catalytic activity [6]. Many chiral phosphorous ligands are prominent in the hydrogenation of dehydrogenated amino acids and their analogues catalyzed by Rh-, and their enantioselectivity is higher than 90. But a very small number of ligands also exhibit high enantioselectivity in many types of asymmetric reactions at the same time. But there are two kinds of ligands: one is BINAP, and the other is ferrocene phosphine ligand.



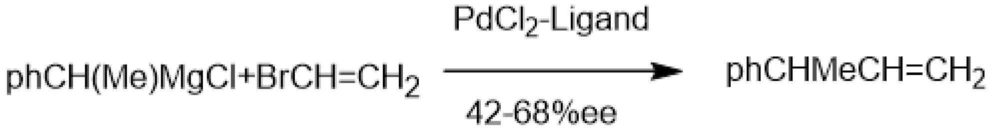
(R)-BINAP PPFA BPPFA

Fig.1

BINAP was developed by Noyori in 1980. It is used in the hydrogenation of olefins catalyzed by Rh and Heck reaction catalyzed by Pd.High enantioselectivity was obtained in many asymmetric reactions such as isomerization of enylamine catalyzed by Rh, hydrogenation of alkene and ketone catalyzed by Rh and Ru [7]. In 1974, the chiral ferrocene phosphine ligands PPFA and BPPFA [6-8] were first prepared by Hayashi and Kumada. This kind of ligands have the following characteristics: 1. The side chain functional group NMe_2.2. which is easy to modify, has planar chiral property, no isomerization. 3. single phosphine, bisphosphine can be prepared by a chiral source. Characteristic orange, easy to define in column chromatography. Such ligands and The complexes of their derivatives with transition metals have been successfully used in the following asymmetric reactions:

2.1 Cross-coupling reaction for organometallic reagents and halogen compounds

In 1976, Hayasi [8] reported the catalysis of Pdcl: complexes with chiral ferrocene phosphine ligands BPPFA and PPFx.The following response (1):



$$phCH(Me)MgCl+BrCH{=}CH_2 \xrightarrow[42\text{-}68\%ee]{PdCl_2\text{-}Ligand} phCHMeCH{=}CH_2 \tag{1}$$

2.2 For allylation reactions

The substitution reaction of the nucleophilic reagent to the allyl group is carried out under the catalysis of the Pd chiral polar ligand. The catalytic mechanism is also very mature; it is an important intermediate[8] to form a chain-complex with allyl. The results show that the chiral ferrocene diphosphorus ligand BPPFx with the amino alcohol side chain is the most effective[9], and the interaction between the side chain hydroxyl group and the nucleophilic reagent in the ligand is the cause of high enantioselectivity. The more hydroxyl, the higher the ee value (upto96% ee)[10].

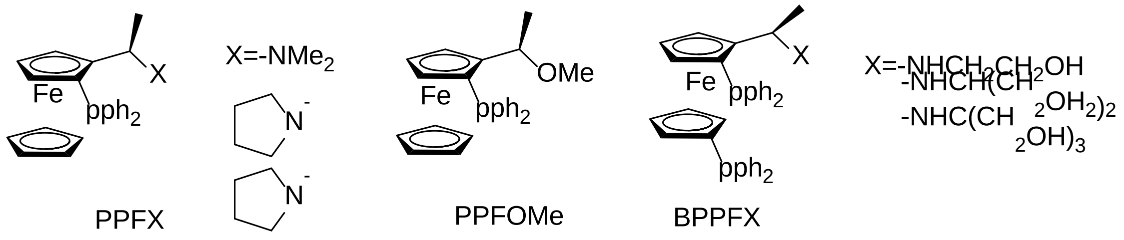
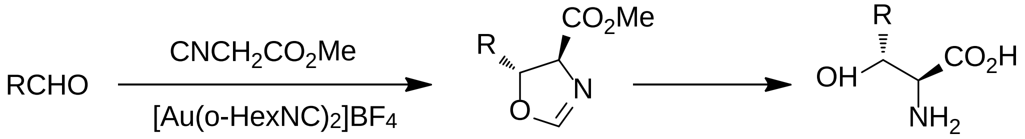


Fig.2

2.3 For Aklol reaction

The addition reaction of aldehydes catalyzed by Au (I) with α -isonitrile hydroxyl carboxyl esters (or amides, phosphonates) is an effective method for the preparation of β -hydroxy-a- amino acids, and the chiral ferrocene bisphosphine BppFx with ethylenediamine groups in the side chain is the most effective ligand. The following response (2):



(2)

3. Synthetic Route Design of Ferrocene-derived Chiral Ligands Containing Dioxazoline.

β-hydroxyamides were synthesized by the reaction of acyl chloride with chiral amino alcohol. Then the ligand Ll~L4. was synthesized by cyclization of dioxazoline ferrocene ligands under the action of alkali by hydroxyl activation. Diacetylferrocene was synthesized from ferrocene by Friedel-ketoacylation reaction [10-11], and then 1 1 '-ferrocene dicarboxylic acid was synthesized by haloform reaction [11]. 1'- ferrocene dicarboxylic acid acyl chloride was synthesized by the reaction of dicarboxylic acid with oxaloyl chloride [12]. Chiral amino alcohols were synthesized by the reduction of L-amino acids by NaBH4/I2.

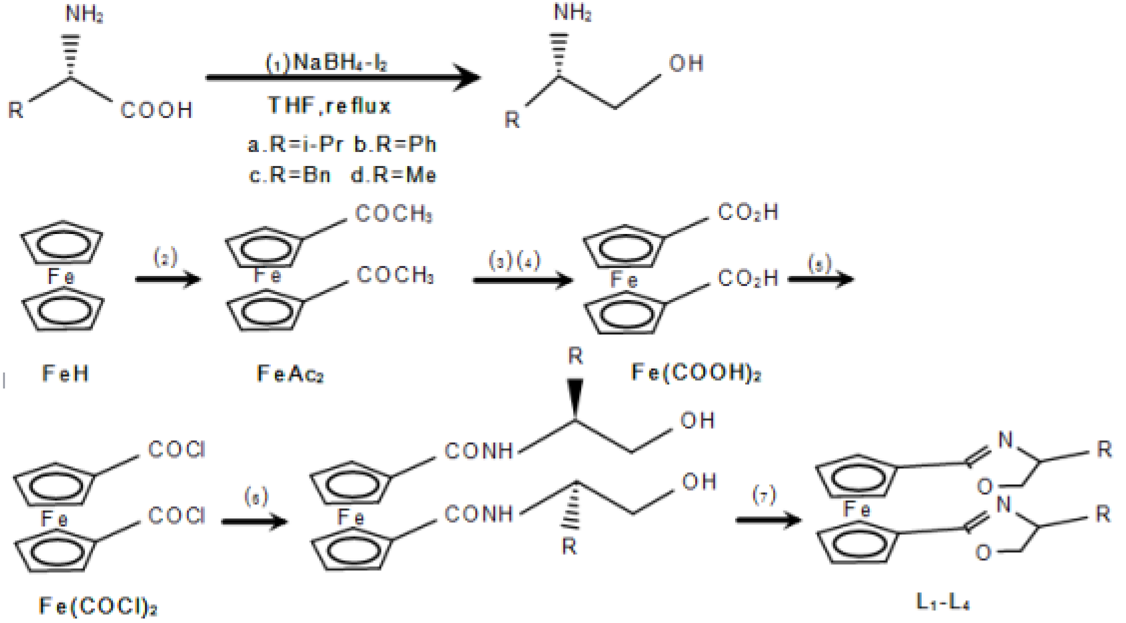


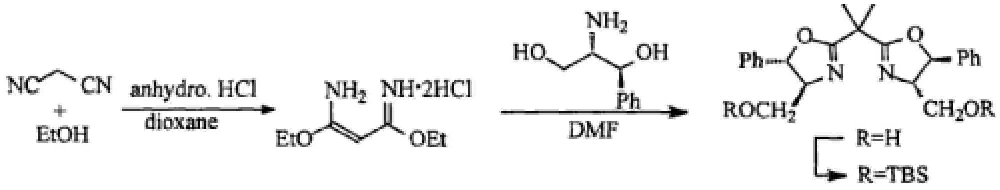
Fig.3

4. Synthesis of Shiral Dioxazoline Ligands.

As early as 1974, witte and Seellger synthesized a series of 5-methyl substituted non-chiral dioxazoline derivatives (3) from aryldisonitrile, cyclohexanil and amino alcohol catalyzed by metal salts.

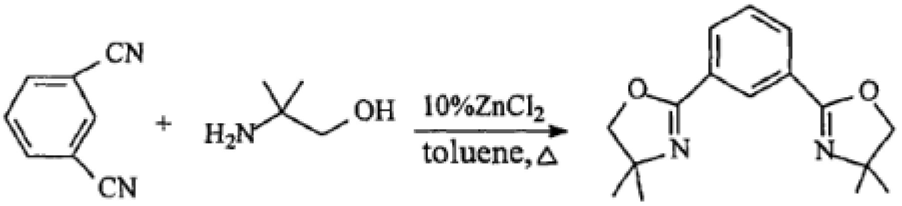
(3)

The metal salts used are ZnX2 (Xcl-Br-so _ 4), M (oAc) _ 2), which are effective catalysts for the reaction. [10].Lehn et al.] reacted with ethanol in the presence of anhydrous HCI to form corresponding imide salts. Chiral bisoxazoline (4) [11] was obtained by condensation with photoactive amino alcohols.



(4)

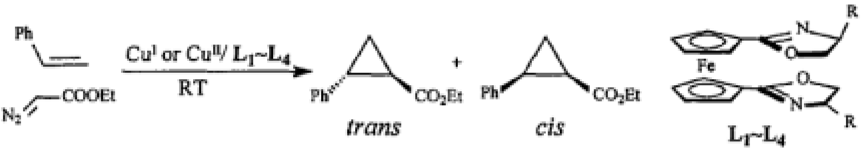
Dioxazoline (5) [12] was synthesized from dioxazoline (5) in one step process by ssage with ZnCl2 catalyzed by dinitrile and amino alcohol.



(5)

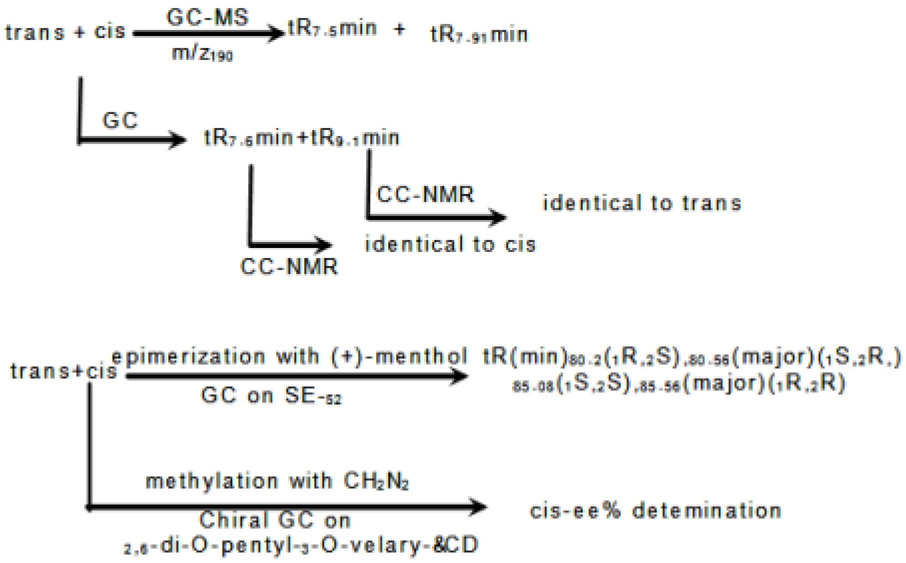
5. Application Research

In the study of asymmetric cyclopropanation, the most commonly used mode reaction is the reaction of styrene with diazoacetate. In addition, the cyclopropanation of polysubstituted olefin and the intramolecular cyclopropanation are also studied. Using styrene and ethyl diazoacetate as substrates and cu (1) as catalyst, the asymmetric induced properties of ligand Ll~L; such as reaction (6) were studied.



(6)

Beta- cyclodextrin chiral gas chromatographic column was used to determine the ee value of the product after hydrolysis of methyl ester, and (+)-menthol was used for differential isomerization of the product. The ee value of the trans-body was determined by conventional gas chromatographic column SE-30, such as reaction (7).



(7)

6. Comparison of Enantioselectivity of Four Ligands (Lip,Lph,Lbn,Lme) with Cu (1) Complexes.

The optimum conditions for the use of ligand Lip were as follows: 1, 2-dichloroethane was used as solvent, fresh CuoTf.0.SC6H6 was used as catalyst, and the amount of catalyst was 5 mol / L. The mixture of ligand and catalyst (1:1 molar ratio) was heated and stirred at 40 ~ 50 ℃ for 2 hours, then cooled to room temperature, then slowly dripped with EDA, and then continued to react at room temperature. The chiral induction properties of the other three ligands (Lph,Lbn,Lme) were compared. The results showed that among the four ligands, the chiral induction performance of LIP was the strongest, and that of Lph was the weakest. Lbn. The catalytic activity of / Cu (D complex is very poor, and 64hr is required for the reaction at room temperature (Table 1).

Table1.ComParisionofasymmetrieinduetionsoftheligandsLIP,LPh,LbnandLme wheneomplexedwitheuoTr.o.se6H6“

ligand	Reaetion condition	Trans/cis	yield	Ee%(configuration)	
				cis	trans
Lip	rt,34h	59:41	61%	24(1R,2S)	13(1R,2R)
Lph	rt,18h	68:32	78%	3(1S,2R)	5(1R,2R)
Lbn	rt,64h	64:36	89%	9(1R,2S)	5(1R,2R)
Lme	rt,38h	63：37	78%	8(1R,2S)	6(1R,2R)

7. Conclusion

The four ligands were used for the cyclopropanation of styrene and ethyl diazoacetate catalyzed by copper (I). The chiral induction performance of ligand Lip was the best, and the enantioselectivity of IR,ZS was 24%. When cu (0Tf) 2 was used as the precursor of the catalyst, the chiral induction performance of Lph was very weak, but the asymmetric induction performance of Lph was contrary to that of the other three ligands. This phenomenon needs further explanation.

It is concluded that the low enantioselectivity is due to the fact that the two oxazoline rings in the ligand are parallel to the ferrocene ring (the angle of the two sides is 5. 5). Two oxazoline rings need to be distorted to a large extent if ligand and metal center are to be effectively complexed. Because of the fluidity of the two cyclopentadienes in the molecule, the complexation of copper atoms with them becomes difficult, or copper atoms cannot fully complex with them, resulting in a decrease in enantioselectivity. On the other hand, because of the sandwich structure of ferrocene, the substrate olefins can not approach the catalytic center effectively, which is the reason for the low catalytic activity. According to the structure and reaction mechanism of the complex The diastereoselectivity and enantioselectivity of the reaction were explained. The main products of the reaction were trans-body products with a configuration of (1R ~ (2R), while the dominant conformation of the cis-products was (lR,2S).

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