

The application of ligands with planar chirality in asymmetric synthesis*

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Abstract: A series of chiral ligands with planar chirality were synthesized, and have been shown to be highly efficient catalysts in some asymmetric reactions. The role of central and planar chirality in ligands with multi-chirality was also discussed.

INTRODUCTION

Since the structure of ferrocene was elucidated, the fascinating structural properties of ferrocene and its derivatives caused an unrivalled interest in all fields of organometallic chemistry [1]. In 1970, Ugi and co-workers found a diastereoselectively directed ortho-metalation on chiral *N,N*-dimethyl- α -ferrocenyl-ethylamine to induce planar chiralities [2]. Since then, Sammakia, Richards, Uemura, Kagan, Snieckus, and others have developed some alternative methods of asymmetric ortho-metallation [3]. Because of these convenient procedures of introducing planar chirality, a large structural variety of ferrocene derivatives with planar and/or central chirality is known today. Some of these ferrocene derivatives have played an essential role in the development of important catalytic systems, and among them, two have recently found practical applications in industrial processes [4].

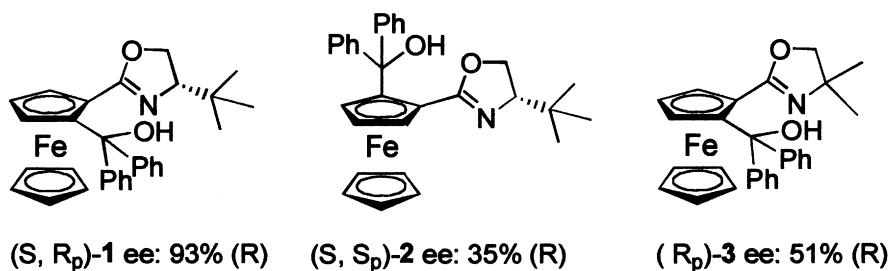
For most metal-catalyzed asymmetric reactions involving ferrocene ligands with both planar and central chirality, the effect of planar chirality on enantiomeric excess and absolute configuration varied from case to case. Kumada *et al.* reported their findings in comparing the impact of (*S*, *R_p*)-PPFA with that of its diastereomer (*R*, *R_p*)-PPFA and the analogue (*S_p*)-FcPN with only planar chirality in a Ni-catalyzed Grignard cross-coupling reaction [5]. They found that the planar chirality is a decisive factor for exerting control over enantiomer excess and absolute configuration. In 1997, Sammakia reported an asymmetric copper catalyzed conjugated addition of Grignard reagents to enones with chiral ferrocenyl phosphine oxazoline ligands [6]. A comparison of the ferrocene derived ligands with the corresponding benzene derived ligands reveals that the ferrocene template (planar chirality) plays an essential role in this reaction. Recently, Bolm reported the chiral ferrocene-based hydroxyoxazolines catalyzed asymmetric diethylzinc addition to benzaldehyde [7]. The ferrocene derivatives (*S*, *R_p*)-**1** and (*S*, *S_p*)-**2** are diastereomer with the identical central chirality but opposite in planar chirality, while (*R_p*)-**3** have only single planar chirality, the results of Scheme 1 indicated the differences in catalytic efficiency and enantioselectivity. The comparison made evident how central and planar chirality cooperate or match with each other. In this account, some experimental evidence from our group which show the role of planar chirality in ferrocene ligands are reported.

RESULT AND DISCUSSION

At first, the ferrocene derived chiral ligands **4** and **5**, which have the same central chirality but are opposite in planar chirality, were synthesized, and subjected to asymmetric hydrogen transfer

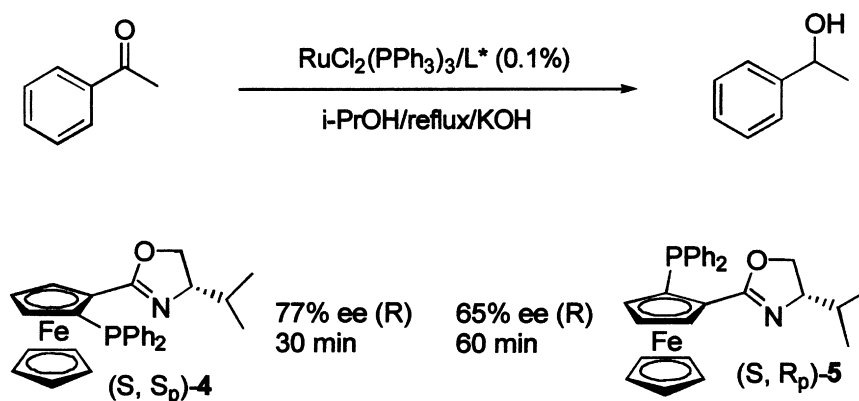
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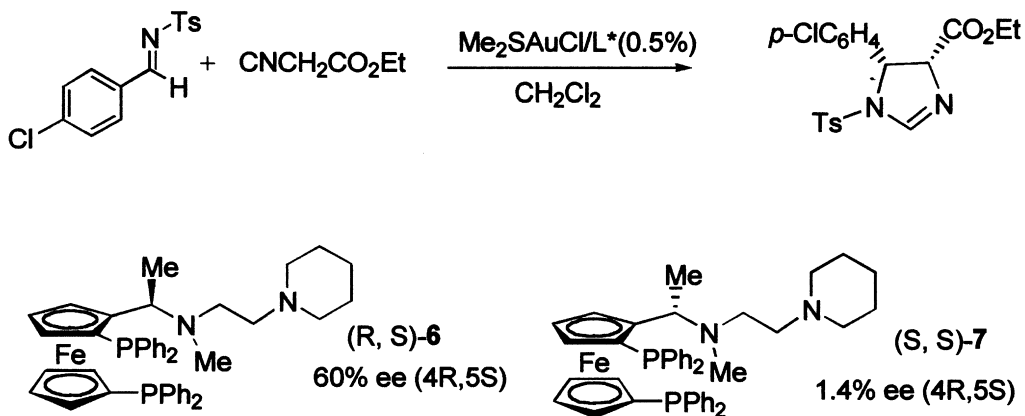
Scheme 1

hydrogenation (Scheme 2). Our results revealed that the absolute configuration of the reaction product is mainly governed by the central chirality in the oxazoline ring [8].



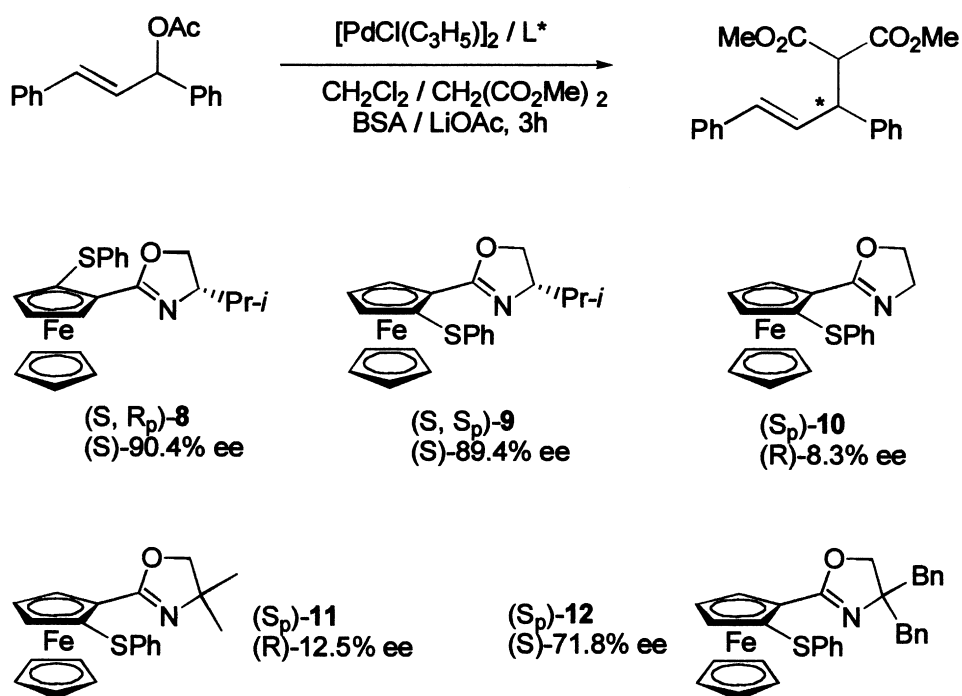
Scheme 2

In the asymmetric Aldol reaction of *N*-tosylimines and ethyl isocyanoacetate with chiral ferrocene-derived Au-complexes as catalyst, when ligand **6** was used as catalyst, moderate enantiomer excess was obtained, but using the similar ligand **7**, which has the same planar chirality as **6**, but is merely different in the configuration on the chiral carbon atom, only 1.4% enantiomer excess was obtained (Scheme 3). These results reveal either that central chirality is also an important factor in this asymmetric reaction, or that the matching of central and planar chirality is very important [9].



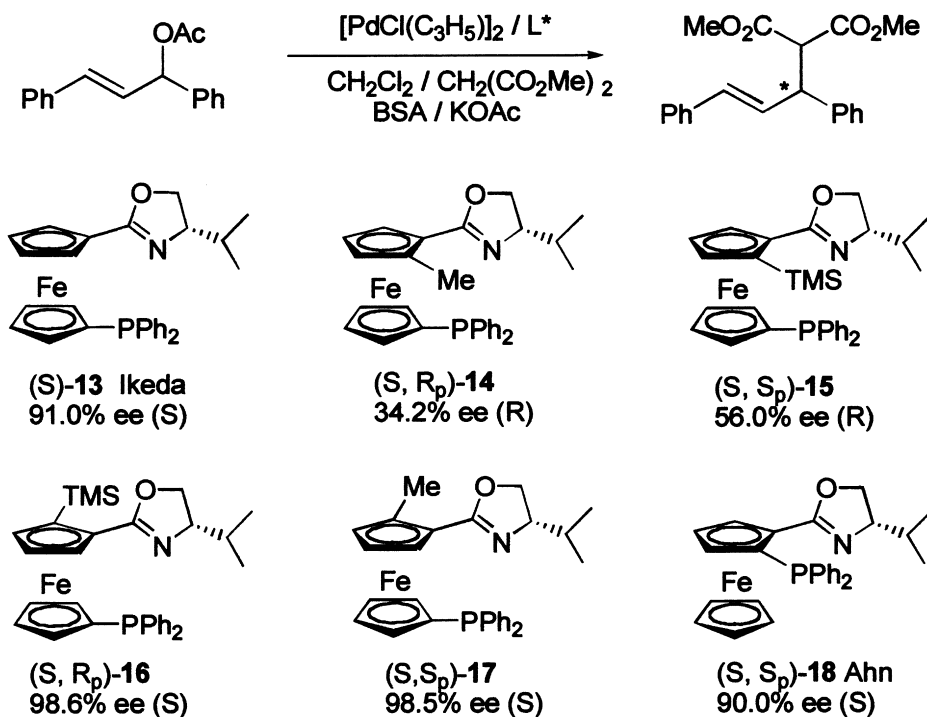
Scheme 3

Following the method of Ahn, a series of chiral thioether derivatives of ferrocenyloxazolines were synthesized; these are ligands which have been shown to be a highly efficient catalyst for a palladium catalyzed allylic substitution reaction (Scheme 4). When ligands **8** and **9** were used, a similar enantioselectivity and the same absolute configuration was obtained. It seems that the absolute configuration and enantiomer excess value are governed mainly by the central chirality of the oxazoline ring. In order to clarify the effect of planar chirality on the absolute configuration and enantioselectivity of this reaction, ligands **10**, **11** and **12**, which only have a planar chirality, were synthesized, and subjected to this reaction under identical conditions. For ligands **10** and **11**, only a low enantiomer excess (8.3% and 12.5%) was obtained but the absolute configuration of the product was changed to R; this could explain why the diastereomer **8** achieved only a slightly higher enantiomer excess than ligand **9** (90.4% enantiomer excess vs. 89.4% enantiomer excess). The planar chirality matched the central chirality in **8** for the oxazoline ring whereas they are mismatched in ligands **9**. Anyhow, in this comparison, the central chirality seems to play a more important role. However, the similar dibenzyl ligands **12** with only a planar chirality gave the opposite (S)-configuration product with rather high enantiomer excess values, which was an unexpected result, compared with **10** and **11** [10].



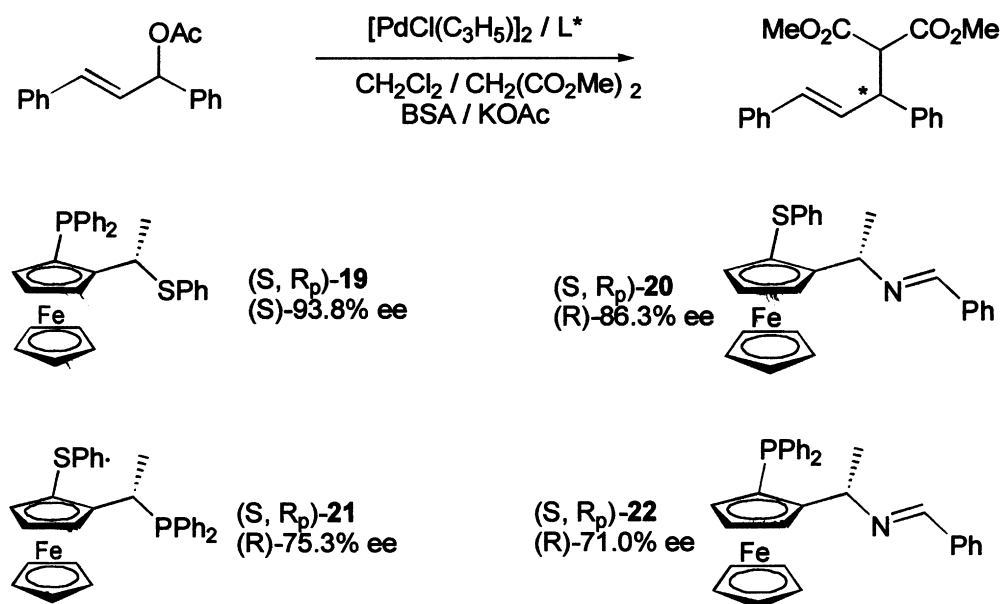
Scheme 4

In the above cases, the two coordinating groups are situated on the same Cp ring. We then examined the case, in which they are disposed on two different Cp rings. Chiral *P,N*-ligand **13**, which has two chiral elements—central and axial in coordination to palladium—has been proved to be effective in palladium catalyzed allylic substitution with a 91% enantiomer excess [11]. When we introduced the third chiral element—planar chirality into ligand **13**, two planar chiral ligands **14** and **15** were synthesized. We found that a dramatic change of enantio-induction occurred. From (*S*)-**13** to (*S*, *R_p*)-**14**, it changed from 91% enantiomer excess (*S*) to 34.2% enantiomer excess (*R*) and from (*S*)-**13** to (*S*, *S_p*)-**15**, we had a change of 91% enantiomer excess (*S*) to 56% enantiomer excess (*R*). It is now envisaged that the diastereoisomers holding the other planar chirality (*S*, *R_p*)-**16** and (*S*, *S_p*)-**17** may be the matched isomers for this reaction. Just as we expected, (*S*, *R_p*)-**16** showed 98.6% enantiomer excess (*S*); while that of (*S*, *R_p*)-**17** is 98.5% enantiomer excess (*S*). The steric hindrance of the introduced third group TMS and Me was found to correlate directly with the enantioselectivities (34.2% vs. 56%, 98.5% vs. 98.6%). In this case, either the planar chirality played a very important role or the matching of three chiral elements is very important (Scheme 5).



Scheme 5

In addition, we also studied the coordinating ability of the heteroatom in the *trans*-effect in the Pd-catalyzed asymmetric allylic substitution reaction with ligands of multichirality. The results are shown in Scheme 6. It was found that ligands with a different coordinated atom showed different enantioselectivity and absolute configuration. Ligands **19** and **21** have a different disposition of the coordinated atoms. For **19**, the PPh₂ group is placed directly on the Cp ring and thioether group on the chiral carbon atom. For **21**, the disposition of the two groups is simply reversed. When ligands **19** and **21** were used, an opposite asymmetric induction was obtained. For ligands **20**, **21** and **22**, all of them gave reaction products with an



Scheme 6

R configuration. By correlating the results, a sequence of *trans*-effect of the C=N, P, S coordinating groups in this reaction is obtained.

In summary, we have synthesized a series of chiral ligands with planar chirality, and investigated their role in some asymmetric reactions. It is found that planar chirality and central chirality have a significant impact on the stereochemical outcome, but they have different effects in different reactions. This may be used as a reference in the design and application of ligands with planar chirality and central chirality in catalytic asymmetric reactions.

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