On the role of planar chirality: a tunable enantioselectivity in palladium-catalyzed allylic alkylation with planar chiral 1,1′-P,N-ferrocene ligands

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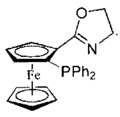
A series of planar chiral 1,1′-P,N-2′-substituted ferrocene ligands 9–12 and 16, prepared with diastereopurity >99 : 1, have been used to examine the role of planar chirality, and significant effects on enantioselectivity as well as the control of absolute configuration in palladium-catalyzed allylic alkylation as a model reaction were observed.

Catalytic enantioselective reactions have attracted great interest among synthetic chemists in recent years, and many efforts in preparing efficient ligands have been made.[1,2] Most of the chiral ligands currently used consist of central chirality and/or axial chirality. Chiral ferrocene ligands with planar chirality began to be used in industrial processes only two or three years ago.[3] Ferrocene ligands have thus received more intensive attention.[4–7] Although these ferrocene ligands usually have planar chirality, the role of this chirality element is not clear. Some examples showed that the planar chirality had a significant effect on the enantioselectivity,[5] while in other examples the effect was not so apparent.[6] To date, there have been only a few attempts to ascertain the effect of planar chirality on stereochemical outcome in asymmetric synthesis.[5b,6a] Moreover, most works dealt with 1,2-disubstituted ferrocene ligands having two donor groups on the same Cp ring, such as compounds **1**,[7] **2**[5a] and **3**.[5b] Quite recently, Ikeda,[8a,b] Ahn[8c] and Knochel[9] reported new 1,1′-disubstituted ferrocenyl ligands **4–6**, and good enantioselectivities have been obtained with these ligands. As a part of our program[5c,6] aimed at the design and application of chiral ligands to asymmetric synthesis, we studied the role of planar chirality in asymmetric induction. We envisage that, if planar chirality is introduced into this kind of 1,1′-disubstituted ferrocene ligand, it may provide a good model to investigate the role of planar chirality. Moreover, it is worthwhile to note that, after the planar chirality is introduced into such ligands, there are three elements of chirality—central, planar and axial chirality—upon their coordination with metal palladium. Herein we report the synthesis of planar chiral 1,1′-P,N-2′-disubstituted ferrocene ligands and the observation of significant effects on enantioselectivity as well as the control of absolute configuration in palladium-catalyzed allylic alkylation upon introducing a new element of chirality—planar chirality—into the 1,1′-P,N-ferrocene ligands.



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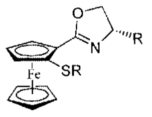

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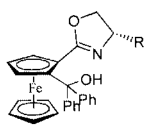

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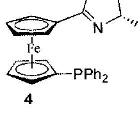

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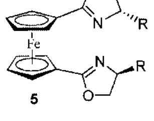

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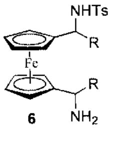

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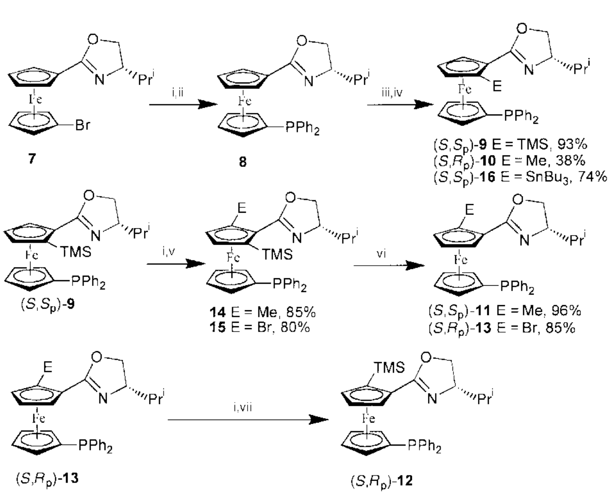
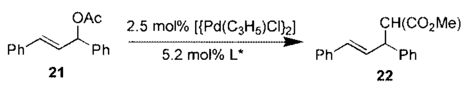
As shown in Scheme 1, ferrocenyloxazoline derivative **7**, which was synthesized according to Bryce's method,[9] was treated with BuLi followed by trapping with Ph_2PCl to afford 1-diphenylphosphino-1′-oxazolinylferrocene **8** in 78% yield. Directed diastereoselective *ortho*-lithiation of **8** according to Richards' procedure[8e] and subsequent treatment with electrophiles gave 2′-substituted compounds **9**, **10** and **16**. Compound **9** was again lithiated followed by trapping with electrophiles to afford ferrocene derivatives **14** and **15**. Conversion of **14** and **15** to **11** and **13** respectively was accomplished by removing the TMS group with TBAF in THF at reflux. Then, a bromo–lithium exchange of **13** followed by quenching the resulting anion with TMSCl furnished **12**. The diastereopurities of all compounds containing planar chirality, determined by 300 MHz ^1H NMR, were >99 : 1.

Chiral P,N-ligands have proved to be effective in several kinds of metal-catalyzed asymmetric reactions,[11] especially palladium-catalyzed allylic substitutions,[11a,b,12] and ligand **8** has also proved effective in palladium-catalyzed allylic substitutions with 91% ee.[8b–d] In our previous work, we studied the role of the planar chirality of 1,2-N,S-ferrocene ligands in palladium-catalyzed allylic alkylations.[6a] Therefore, in order to investigate the role of the planar chirality of this new kind of 1,1′-P,N-2′-disubstituted ferrocene ligand in metal-catalyzed asymmetric reaction, we also used allylic alkylation as the model reaction. The results are summarized in Table 1. Our attention was first focused on the role of planar chirality in this reaction. A dramatic change in the enantioselectivity of the reaction was observed with (S,S_p)-**9**; the enantioselectivity of the reaction product **22** changed from 91% with *S* configuration using ligand **8** to 69.7% with *R* configuration using ligand **9** (entries 1 and 3). In considering the change of absolute configuration, the effect of the newly introduced group is significant. This exciting result encouraged us to probe the effect of the newly introduced group with opposite planar



Scheme 1 *Reagents and conditions*: i, BuLi, THF, −78 °C; ii, Ph_2PCl, 78%; iii, BuLi, Et_2O, TMEDA, −78 °C; iv, E^+ (MeI, TMSCl or Bu_3SnCl); v, E^+ (MeI or $BrCF_2CF_2Br$); vi, TBAF, THF, reflux; vii, TMSCl, 73%.

Table 1 The effect of different ligands on enantioselectivity and configuration of product in palladium-catalyzed allylic alkylation[a]

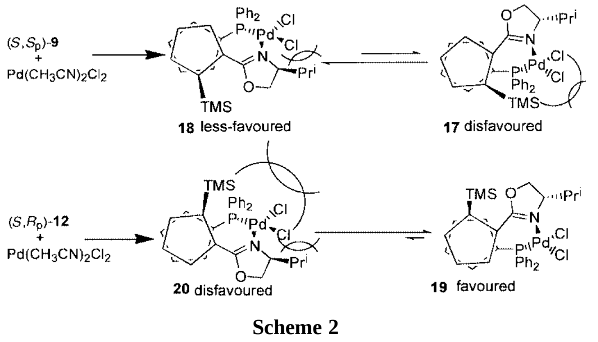


Entry	Ligand	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	**8**	99	91.0	*S*
2	**8**	98	92.8[e]	*S*
3	**9**	98	69.7	*R*
4	**9**	99	64.0[e]	*R*
5	**10**	98	34.2	*R*
6	**11**	99	98.5[e]	*S*
7	**11**	99	98.2	*S*
8	**11**	99	87.8[f]	*S*
9	**12**	99	98.6[e]	*S*
10	**12**	99	97.8	*S*
11	**16**	98	83.3	*R*
12	**16**	98	77.7[e]	*R*

[a] Molecular ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$: ligand : **21** : dimethyl malonate : BSA : KOAc = 2.5 : 5.2 : 100 : 300 : 300 : 5. [b] Isolated yield. [c] The ee value for **22** was determined by HPLC analysis using a Chiralcel OD column. [d] Configurations were assigned by comparison of the sign of optical rotation. [e] No KOAc was used. [f] 10 equiv. KOAc was used *vs.* ligand.

chirality, which may increase the ee value in comparison with that of ligand **8**. Therefore, (S,S_p)-**11** was synthesized and subjected to the same reaction. Just as expected, a remarkable improvement in the ee value (98.5%, *S* configuration) was revealed. This result indicates that the effect of planar chirality on the stereochemical outcome is significant in this model reaction. In order to study the steric effect of the 2′-substituted group, (S,R_p)-**10** and (S,R_p)-**12** were synthesized and also used for this reaction. A reasonable result was obtained, that is, the steric bulkiness of the group was found to directly correlate with the enantioselectivity; the larger the group, the higher the ee value (compare ligand **9** *vs.* **10** and **11** *vs.* **12**). From this result, we envisaged that further increasing the steric bulkiness of the 2′-substituent of ligand **9** should also increase the enantioselectivity of the reaction. As expected, a higher ee value (83.3% ee, entry 11) was obtained when ligand **16** was used for this reaction. It was reported in the literature[12] that the addition of KOAc may sometimes increase the ee value. However, non-uniform results were obtained in our case (Table 1).

In order to explain the significant role of the planar chirality of this kind of ligand in this model reaction, the complexation behavior of **8**, **9** and **12** with $Pd(CH_3CN)_2Cl_2$ in CD_3CN was examined by ^{31}P NMR. The results showed that the ^{31}P NMR of the complex of **8** with $Pd(CH_3CN)_2Cl_2$ gave two peaks in a ratio of 7 : 3, which was consistent with the literature.[8b] However, for **9** the ratio dropped to 2 : 3, which might be assigned as diastereomers **17** and **18**, and for **12** the ratio became 22 : 1, which might be assigned as diastereomers **19** and **20** (Scheme 2). The ^{31}P NMR data showed that the addition of a third group in a proper disposition may favor the formation of one rotamer over the other, consistent with the ee values of the products. On the other hand, from Scheme 2, if the TMS group of compound **17** is replaced by the larger Bu_3Sn group, the balance should move towards the left. As a result, the entioselectivity of the reaction should also be increased by using ligand **16** in comparison with ligand **9**. In fact, the experimental results did agree with the above reasoning (entries 3 *vs.* 11).



Scheme 2

In summary, we have synthesized a new kind of 1,1′-P,N-2′-disubstituted ferrocene ligand in which planar chirality was introduced. Comparison of the results for ligands **8**, **9** and **12** showed that the planar chirality is decisive in exerting control over both absolute configuration and enantiomeric excess. In addition, this kind of ligand is unique due to its multi-chirality (central, planar and axial chirality) upon coordination with Pd, and provides a new approach to the design of novel ligands. Further studies on the detailed transition-state structures, and the mechanism, and the exploration of the scope of asymmetric reactions with these promising ligands are in progress.

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