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Novel bis-*N*-[2-(diphenylphosphino)ferrocenylcarbonyl]diaminocyclohexane ligands: application in asymmetric allylic alkylation of imino esters with simple allyl carbonate

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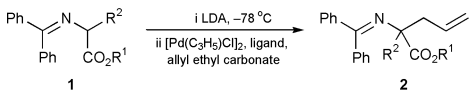
Several derivatives of ferrocene ligands with planar chirality were investigated in palladium-catalysed asymmetric allylic alkylation of iminoesters, in which bis-ferrocene ligand 7 containing a chiral pocket showed good enantiocontrol in this reaction; the products having a quaternary chiral center were obtained with up to 75.3% ee.

Chiral α,α-dialkyl-α-amino acids are an important class of non-coded amino acids and have attracted an ever growing interest in biological and pharmacological problems.[1] The quaternary chiral center leads to many of the desirable properties associated with this class of amino acid, but offers a significant challenge with respect to asymmetric synthesis.[2] Many methods reported to date involve either the use of chiral auxiliaries or strategies that utilize self-regeneration of stereocenters.[3] The catalytic asymmetric hydrogenation of dehydroamino acids is not applicable to synthesis of quaternary amino acids.[4] Thus, the procedure of their catalytic asymmetric synthesis remains to be established. Imino esters as nucleophiles in Pd-catalyzed asymmetric allylic alkylation reactions give chiral α-mono-alkylated amino acids,[5,6] however, the ee was not high when simple allyl acetate was used. Though a significant improvement of the asymmetric alkylation of a glycine Schiff's base under PTC conditions has been reported, an amino acid with a quaternary chiral centre could not be easily constructed in general.[7] Recently, Trost and Ariza reported the asymmetric synthesis of α-alkylated amino acids by using their chiral pocket strategy in catalytic asymmetric allylic alkylation and good to excellent results were obtained when substituted allyl acetates were used—for the simplest member of this family, the allyl acetate, only 40% ee value was provided.[8]

In the course of studying the synthesis and applications of ferrocenyl derivatives with planar chirality in metal-catalysed asymmetric reactions,[9] we investigated the role of planar chirality and found that the enantioselectivity could be affected by planar chirality, and that high enantioselectivity would be reached when the ligand contained a pair of matched chiralities. Combining these results and Trost's chiral pocket concept[10] we designed new planar chiral ligands **7** and **8** and used them in a synthesis of α-alkylated amino ester derivatives with a quaternary chiral carbon center through catalytic asymmetric allylic alkylation. Herein we would like to report our preliminary results.

The reaction of imino esters **1** with allyl ethyl carbonate in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and ligands **3**–**8** was carried out [eqn. (1)]† and results were summarized in Table 1.



1 **2** (1)

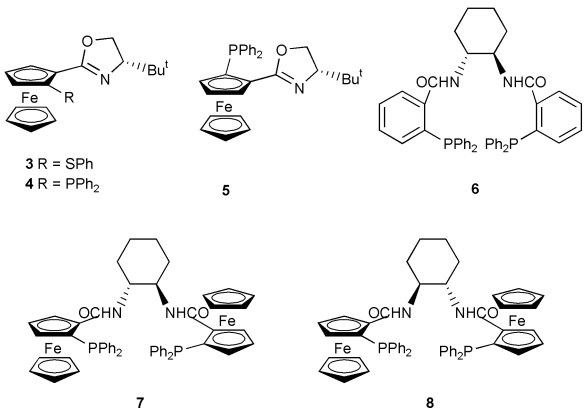
a, R^1 = Me, R^2 = Bn; **b**, R^1 = Me, R^2 = Me; **c**, R^1 = Bu^t, R^2 = Me; **d**, R^1 = Bu^t, R^2 = H; **e**, R^1 = Et, R^2 = H; **f**, R^1 = Me, R^2 = H.

From Table 1, we found that planar chirality showed great influence on the enantioselectivity of the product. By using (*S*, *R*$_p$)-ligand **5** the product with 34.5% ee was given but only 2% ee for (*S*, *S*$_p$)-ligand **4** (entries 3 and 4), apparently central and planar chirality in ligand **5** is matched in this reaction. With BINAP as the ligand, the product was isolated in high yield but low ee. Ligand **6**, developed by Trost's group, showed high enantioselectivity in many kinds of asymmetric alkylation reactions due to its 'chiral pocket effect'.[10] Only 40% ee was given when it was used in this reaction. This value is the same as in the reaction of allyl acetate and azalactone reported by Trost.[8] Above all, we deduced that both planar chirality and the chiral pocket could improve the enantioselectivity of the product. Therefore, ligands **7** or **8**, the ferrocene modification of the chiral pocket, were synthesized in high yields from **4** [eqn.

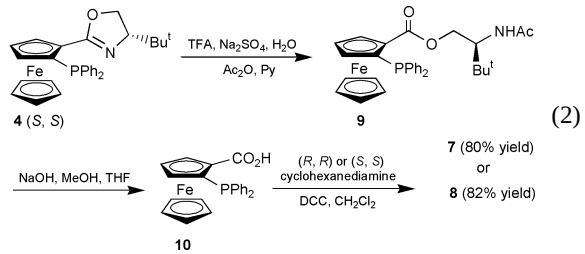
Table 1 Palladium-catalysed asymmetric allylation of **1a** with different ligands†

Entry	Ligand	Base	Yield (%)[a]	Ee (%)[b]	Optical rotation[c]
1	**(S)-BINAP**	LDA	95	18.2	–
2	**3**	LDA	—	—	–
3	**4**	LDA	91	2.0	–
4	**5**	LDA	89	34.5	–
5	**5**	KHMDS	77	9.3	–
6	**6**	LDA	93	40.0	+
7	**7**	LDA	87	57.4	+
8	**8**	LDA	93	3.8	+
9[d]	**7**	LDA	91	22.2	+
10[e]	**7**	LDA	81	50.0	+

[a] Isolated yield based on imino esters. [b] Determined by HPLC (chiralcel OJ column). [c] Detected in trichloromethane. [d] 2 mmol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 4 mmol% ligand were used as catalyst. [e] After completion of addition, the reaction mixture was allowed to stir at 0 °C.



(2)].[12] As expected, when ligand **7** was injected into the above



reaction, the enantioselectivity of the product was raised to 57.4% ee. On the other hand, the product with 3.8% ee was produced when ligand **8**, derived from (*S*,*S*)-cyclohexanediamine, was used. Obviously, ligand **7** possesses the matched chiralities. In addition, changing reaction temperature or the ratio between ligand and palladium did not improve the enantioselectivity (entries 9 and 10). The enantioselectivity of the product decreased greatly when the base was changed to KHMDS with ligand **5** (entry 5).

Several imino esters were examined with ligand **7** under the optimized conditions. The results are summarized in Table 2. It can be seen that different R^1 of the esters has a great influence on the enantioselectivities of the products. It was improved by increased steric demand of R^1 substitution. The ee values of the products were 56.9% (entry 5, R^1 = Bu^t), 52.6% (entry 6, R^1 = Et), 24.6% (entry 7, R^1 = Me), respectively, This effect was also operated in the α-methyl substituted imino esters which are important in the synthesis of quaternary carbon centers. When **1b** and **1c** were injected into this reaction, ee values of products were 53.6% (entry 2, R^1 = Me) and 75.3% (entry 4, R^1 = Bu^t), respectively. It was very strange that the product from **1b** achieved 71.6% ee when equimolar amounts of palladium and ligand were used as catalyst. The changing of the ratio of palladium to ligand has no effect in the case of **1c**.

Ligand **7** was viewed more clearly by its crystal structure (Fig. 1).‡ It was easy to deduce that the two Cp rings could become a part of a better pocket if the two phosphorus atoms were coordinated with palladium, which might be responsible for the better enantiocontrol.

Table 2 Palladium-catalysed asymmetric allylation of different amino esters with ligand **7**†

Entry	Substrate	Yield (%)[a]	Ee (%)[b]
1	**1a**	87	57.4
2	**1b**	93	53.6
3[c]	**1b**	92	71.6
4	**1c**	95	75.3
5[d]	**1d**	94	56.9
6[d]	**1e**	93	52.6
7[d]	**1f**	92	24.6

[a] Isolated yield based on imino esters. [b] Determined by HPLC. [c] 2 mmol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 4 mmol% ligand were used as catalyst. [d] 110 mmol% LDA and 110 mmol% allyl ethyl carbonate were used.

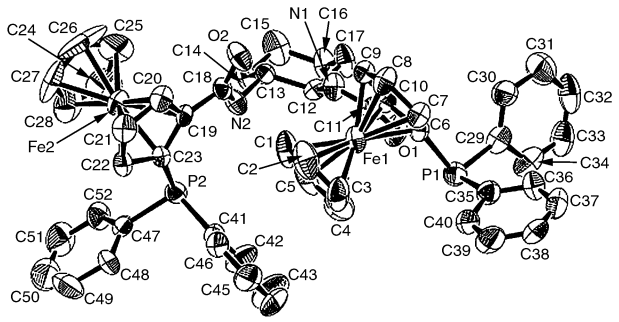


Fig. 1 ORTEP view of **7**·$2H_2O$ (hydrogen atom and water molecule omitted for clarity).

In conclusion, the catalytic asymmetric allylic alkylation between imino esters and chiral palladium allylic intermediates can be used to construct a chiral quaternary carbon center. Combination of planar chirality and a chiral pocket effect in the same ligand may provide product with a higher enantioselectivity. Up to 75% ee was realized by using ligand **7**. To the best of our knowledge, this is the highest ee value for a simple allyl system in this type of reaction. This concept for designing new ligands is worth further study. We are now exploring the application of ligand **7** and its analogues in other asymmetric reactions.

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Notes and references

† To a solution of 1 mL of THF and 103 mg (0.3 mmol) of ester **1a** was added 0.23 mL (0.45 mmol, 2 M heptane–THF–ethylbenzene) of LDA at −78 °C. The solution was stirred for 1 h, then charged with a solution containing 2.2 mg (0.006 mmol) of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 16.3 mg (0.018 mmol) of chiral ligand **7** in 0.5 mL of THF, and a solution of 59 mg (0.45 mmol) allyl ethyl carbonate in 0.25 mL THF. The reaction was allowed to proceed at rt to completion. Work up as usual and purification by column chromatography [EtOAc–petroleum ether (1/20), the silica gel was eluted with Et_3N in advance] afforded 100 mg of **2a** in 87% yield, 57.4% ee, determined by HPLC [Chiralcel OJ Column, hexane–isopropyl alcohol (96/4)].

‡ *Crystal data* for **7**·$2H_2O$: $C_{52}H_{52}N_2O_4Fe_2P_2$, M = 942.64, monoclinic, space group $P2_1$(no. 4), a = 11.195(2), b = 14.972(2), c = 14.316(3) Å, β = 96.43(2)°, V = 2384.6(7) Å^3, Z = 2, D_c = 1.313 g cm^{-3}, T = 293 K, Mo-Kα radiation (λ = 0.7107 Å, μ = 7.21 cm^{-1}, 4610 measured reflections, 4377 observed reflections, R_{int} = 0.052, S = 0.02, Δ_{max}, Δ_{min} = 0.94, −0.35 Å^{-3}.

CCDC 182/1751. See http://www.rsc.org/suppdata/cc/b0/b008304k/ for crystallographic files in .cif format.

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