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Novel ferrocenylphosphine-imines containing a pyridine unit as a new family of chiral ligands: the important influence of the position of the pyridine N-atom on the reactivity and enantioselectivity in palladium-catalyzed asymmetric allylic alkylations

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Abstract—A new class of ferrocene based phosphine-imine ligands with a pyridine moiety was used in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl ester **5** and cyclohexenyl acetate **8**, and it was found that the position of pyridine N-atom had an important influence on the catalytic activity and enantioselectivity of the Pd-complex. The Pd-complex derived from ligand (R,S_P)-**1c** with a 3-pyridine N-atom turned out to be an efficient catalyst, affording an allylic alkylation product with an ee of up to 99%, while the Pd-complex derived from ligand (R,S_P)-**1a** with a 2-pyridine N-atom surprisingly showed no activity. Using ligand (R,S_P)-**1b** with a 4-pyridine N-atom, an ee of 95% with 91% yield was obtained in the allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate, but no allylic alkylation product of cyclohexenyl acetate was obtained.

1. Introduction

Over the last decade, a large number of chiral ligands having hetero-donor with nitrogen and phosphorus functional moieties (P,N-ligands) have been prepared and successfully applied in a variety of asymmetric catalysis.[1] As an important class of P,N-ligands, chiral phosphine-Schiff based imines have received increasing attention recently due to their flexible coordination behavior associated with tunable steric and electronic properties, resulting in many fine-tuned phosphine-imines being found to be very effective in a variety of asymmetric catalytic reaction.[2] However, most of the chiral phosphine-imine ligands reported so far have only an sp^2 imine-N donor atom corresponding to a phosphorus donor atom in the structure, while a few phosphine-imine ligands with another sp^2 nitrogen, such as a pyridine N-donor, have been reported to exhibit good enantioselectivity in asymmetric catalytic reactions.[3] The presence of a pyridine N-donor could significantly affect the way a ligand complexes to the central metal, which in turn would lead to dramatic changes in the reactivity and enantioselectivity of the catalytic reaction. To confirm this, we herein report the synthesis of a new class of ferrocenylphosphine-imine ligands **1** bearing a pyridine sp^2 N-donor atom derived from chiral PPFNH$_2$–R **2** with a variety of pyridinecarboxaldehydes, and compare their efficiency in a Pd-catalyzed asymmetric allylic alkylation. As a result, a very interesting phenomenon was observed with ligand **1c** (derived from 3-pyridinecarboxaldehyde) exhibiting highly effective enantioselective induction in the Pd-catalyzed asymmetric allylic alkylation, while ligand **1a** derived from 2-pyridinecarboxaldehyde surprisingly showed no activity whatsoever, which is very meaningful for the design of novel efficient ligands for asymmetric catalysis.

2. Results and discussion

The synthesis of ferrocenylphosphine-imine ligands **1** was straightforward, and is outlined in Scheme 1. As we have previously reported, (R,S_P)-PPFNH$_2$–R **2** can be easily prepared from (R,S_P)-PPFA–R **3** through a two-step transformation.[4] The reaction of (R,S_P)-PPFNH$_2$–R **2** with a variety of different substituted pyridinecarboxaldehydes in refluxing ethanol in the presence of

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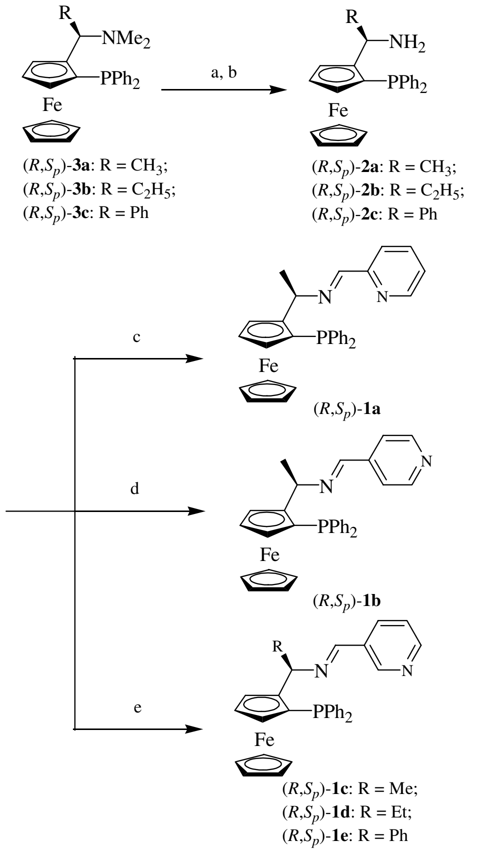
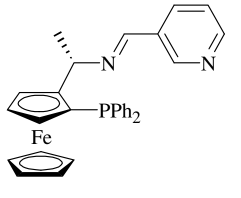
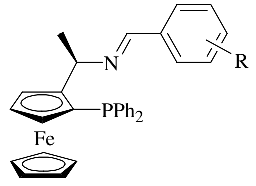


Scheme 1. Reagents and conditions: (a) Ac_2O, 100 °C; (b) NH_3/CH_3CN, 100 °C; (c) 2-pyridinecarboxaldehyde, $MgSO_4$, EtOH, reflux; (d) 4-pyridinecarboxaldehyde, $MgSO_4$, EtOH, reflux; (e) 3-pyridinecarboxaldehyde, $MgSO_4$, EtOH, reflux.

anhydrous $MgSO_4$ then gave the target ferrocenylphosphine-imine ligands **1** in nearly quantitative yields. In order to examine the effect of diastereomeric ligands in the catalytic reactions, the ligand with an (S,S_P)-configuration was also prepared according to the above-described method by the use of (S,S_P)-PPFNH$_2$.[5]



(S,S_p)-**1c**



(R,S_p)-**4a**: R = H;
(R,S_p)-**4b**: R = 4-NO_2;
(R,S_p)-**4c**: R = 3-NO_2;
(R,S_p)-**4d**: R = 3-OMe

The chiral ferrocenylphosphine-imine ligands **1** with a pyridine moiety were then applied in the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate **5a** and cyclohexenyl acetate **8** with dimethyl malonate **6a**.[6] This reaction was carried out in the presence of 2.0 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5.0 mol% of the chiral ligand, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate.

Table 1. Asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate **5a** with dimethyl malonate **6a** using ferrocenylphosphine-imine ligands **1** and **4**[a]

Entry	Ligand	Yield (%)[b]	Ee (%)[c] (configuration)[d]
1	(R,S_P)-**1a**	No reaction	—
2	(R,S_P)-**1b**	91	95 (*S*)
3	(R,S_P)-**1c**	95	98 (*S*)
4	(R,S_P)-**4a**	51	73 (*S*)
5	(R,S_P)-**4b**	91	87 (*S*)
6	(R,S_P)-**4c**	99	94 (*S*)
7	(R,S_P)-**4d**	97	91 (*S*)
8	(R,S_P)-**1d**	91	94 (*S*)
9	(R,S_P)-**1e**	73	69 (*S*)
10	(S,S_P)-**1c**	84	81 (*S*)

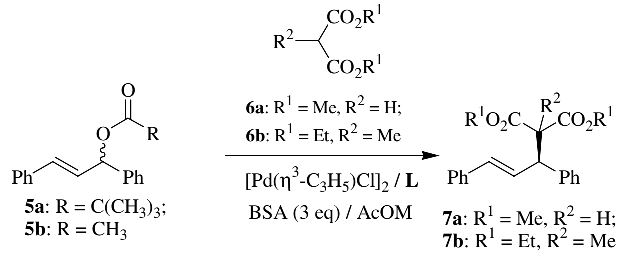
[a] The reactions were carried out in toluene in the presence of 2.0 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 5.0 mol% of chiral ligand, 3.0 equiv of dimethyl malonate, 3.0 equiv of BSA, and a catalytic amount of KOAc at rt.

[b] Isolated yields.

[c] Determined by HPLC analysis using a chiralpak AD column (eluent: hexane:2-propanol = 90:10, 1.0 mL/min).

[d] The (*S*)-configuration was confirmed by comparing the specific rotation with a literature value.[7]

Initially, the influence of ligands on the catalytic activity and enantioselectivity was investigated, with the results summarized in Table 1.



(1)

It was very surprising that extremely different results were obtained by the use of ligands **1a**, **1b**, and **1c**. No alkylation product was detected when ligand **1a** with a 2-position pyridine N-donor was used (entry 1). However, the Pd-complex derived from ligand **1b** with a 4-pyridine nitrogen atom turns out to be a reasonably active catalyst, affording the allylic alkylation product in 91% yield with an ee of 95% (entry 2). The use of ligand **1c** with a 3-pyridine nitrogen atom further increased the reactivity and enantioselectivity, with up to 98% ee with 95% yield being obtained (entry 3). We assumed that the presence of a 2-pyridine N-donor would strongly affect the way a phosphine-imine ligand **1a**, complexed to the central Pd-atom, resulting in a Pd/**1a** complex, which showed no activity for the test reaction. However, a pyridine N-donor at the 3- or 4-position had little effect on the complex of the ligand to the central metal, but strongly affected the electronic properties of the chiral ligands, which resulted in the dramatic changes in the catalytic activity and enantioselectivity of the Pd complex. In order to confirm our speculation, ferrocenylphosphine-imine ligands **4** without a pyridine moiety but with electron-withdrawing or donating group were used in the test reaction. As we have reported previously, the substituent on the phenyl ring strongly affected the activity of the catalyst, with ligands with 3-electron-withdrawing groups tending to give higher catalytic activities and enantioselectivities, which is consistent with our points (entries 4–7). This interesting result prompted us to synthesize a series of **1c** analogues to investigate the influence of the substituent at the ferrocenylmethyl position on the catalytic reaction. When the ethyl analogue **1d** was used, the enantioselectivity decreased slightly to 94% ee (entry 8). However, when a phenyl group was introduced onto the ferrocenylmethyl position, the reactivity and enantioselectivity decreased dramatically to 73% yield and 69% ee (entry 9). In addition, the impact of diastereomeric ferrocenyl ligands on the palladium-catalyzed asymmetric allylic alkylation was investigated. When compared to (R,S_P)-**1c**, (S,S_P)-**1c** showed lower enantioselectivity but gave the alkylation product **7a** with the same configuration (entry 3 vs entry 10). This result indicated that (R)-central chirality and (S_P)-planar chirality are matched in these ferrocenylphosphine-imine ligands for the palladium-catalyzed asymmetric allylic alkylation. The configuration of allylic alkylation product **7a** from these reactions proved to be S by comparing the specific rotation with the literature values.[7]

A similar phenomenon was also observed in the Pd-catalyzed asymmetric allylic alkylation of cyclohexenyl acetate **8** with dimethyl malonate **6a** by the use of ligands **1a** and **1c**. The results are summarized in Table 2. No alkylation product was obtained by the use of **1a** as ligand (entry 1), while the reaction catalyzed by **1c**/Pd complexes gave dimethyl (cyclohexen-2-yl)malonate **9** in moderate enantioselectivity and yield (entry 3). However, it was surprising that no alkylation product was obtained when using ligand **1b** (entry 2), which is contrary to the result obtained when using 1,3-diphenylprop-2-en-1-yl pivalate **5a** as substrate. As a comparison, ligand **4a** was also used, but exhibited lower enantioselectivity and reactivity (entry 4 vs entry 3). The above-results also indicate that pyridine N-atom has great influence on the way the ligand complexes to central metal. However, the reason why the complex of Pd/**1b** does not work in this reaction is unclear.

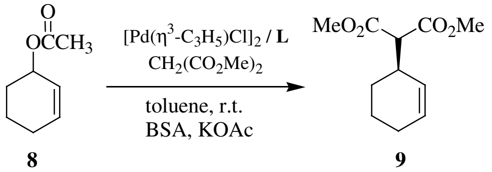
Table 2. Asymmetric allylic alkylation of cyclohexenyl acetate **8** with dimethyl malonate **6a** using ferrocenylphosphine-imine ligands **1** and **4a**[a]

Entry	Ligand	Yield (%)[b]	Ee (%)[c]
1	(R,S_P)-**1a**	No reaction	—
2	(R,S_P)-**1b**	No reaction	—
3	(R,S_P)-**1c**	69	73
4	(R,S_P)-**4a**	48	63

[a] The reactions were carried out in toluene in the presence of 2.0 mol% [Pd(η^3-C_3H_5)Cl]$_2$, 5.0 mol% of chiral ligand, 3.0 equiv of dimethyl malonate, 3.0 equiv of BSA, and a catalytic amount of KOAc at rt.

[b] Isolated yields.

[c] Determined by GC analysis using a β-390 stationary capillary column.



(2)

Optimization of the reaction conditions was then examined by the use of ligand **1c** with a 3-pyridine nitrogen atom with the results listed in Table 3. The effects of bases were first evaluated. Using BSA–LiOAc as base, afforded the allylic alkylation product in 96% yield with 93% ee (entry 1). Using NaOAc and KOAc instead of LiOAc, the enantiomeric excess increased to 97% and 98%, respectively (entries 2 and 3), while a slight decrease of ee to 96% was obtained by the use of CsOAc (entry 4). The investigation of the effect of solvents indicates that they have little effect on the catalytic reaction. All of the solvents gave the alkylation product with good enantioselectivity (entries 5–8). When the reaction temperature was lowered to 0 °C, an increase in enantioselectivity to 99% ee was obtained. However, longer reaction times were required (entry 9). Replacing pivalate **5a** with acetate **5b** as substrate, resulted in a slight decrease in enantioselectivity to 97% ee (entry 10).

Table 3. Asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate **5a** or acetate **5b** using ferrocenylphosphine-imine ligand (R,S_P)-**1c**[a]

Entry	Substrate	Nucleophile	Solvent	Base	Temperature (°C)	Yield (%)[b]	Ee (%)[c]
1	**5a**	**6a**	Toluene	BSA–LiOAc	20	96	93
2	**5a**	**6a**	Toluene	BSA–NaOAc	20	92	97
3	**5a**	**6a**	Toluene	BSA–KOAc	20	95	98
4	**5a**	**6a**	Toluene	BSA–CsOAc	20	91	96
5	**5a**	**6a**	CH_2Cl_2	BSA–KOAc	20	91	95
6	**5a**	**6a**	Et_2O	BSA–KOAc	20	90	97
7	**5a**	**6a**	THF	BSA–KOAc	20	99	96
8	**5a**	**6a**	Benzene	BSA–KOAc	20	93	98
9	**5a**	**6a**	Toluene	BSA–KOAc	0	73	99[d]
10	**5b**	**6a**	Toluene	BSA–KOAc	20	96	97
11	**5a**	**6b**	Toluene	BSA–KOAc	20	93	96[e]

[a] The reactions were carried out in toluene in the presence of 2.0 mol% [Pd(η^3-C_3H_5)Cl]$_2$, 5.0 mol% of chiral ligand, 3.0 equiv of dimethyl malonate or diethyl methylmalonate, 3.0 equiv of BSA, and a catalytic amount of metal acetate at rt.

[b] Isolated yields.

[c] Determined by HPLC analysis using a chiralpak AD column (eluent: hexane:2-propanol = 90:10, 1.0 mL/min).

[d] The reaction was carried out for 36 h.

[e] Determined by HPLC analysis using a chiralpak AD column (eluent: hexane:2-propanol = 97.5:2.5, 0.5 mL/min).

In order to show the validity of the developed ligands, the applications for other nucleophile such as diethyl methylmalonate were then investigated. When diethyl methylmalonate **6b** instead of dimethyl malonate **6a** was used as the nucleophile, ligand **1c** also exhibited high enantioselectivity with up to 96% ee and 93% yield of alkylation product **7b** being obtained (entry 11).

3. Conclusion

In conclusion, we have developed a new class of ferrocene based phosphine-imine ligands with a pyridine moiety for highly effective Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl ester **5** and cyclohexenyl acetate **8**, and found that the position of the pyridine N-atom had an important influence on the catalytic activity and enantioselectivity of the Pd-complex, which is very important for the design of novel chiral ligands. The Pd-complex derived from ligand **1c** with a 3-pyridine N-atom turned out to be an efficient catalyst, affording an allylic alkylation product with an ee-value of up to 99%, while the Pd-complex derived from ligand **1a** with a 2-pyridine N-atom surprisingly showed no activity. Using ligand (R,S_P)-**1b** with a 4-pyridine N-atom, an ee-value of 95% with 91% yield was obtained in the allylic alkylation of 1,3-diphenylprop-2-en-1-yl pivalate. However no allylic alkylation product of cyclohexenyl acetate was obtained. The investigation for the reason why the extremely different activities between **1a**, **1b**, and **1c** is still in progress.

Acknowledgements

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