Highly enantioselective Pd-catalyzed allylic alkylation using new chiral ferrocenylphosphinoimidazolidine ligands

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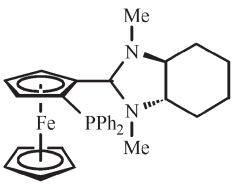
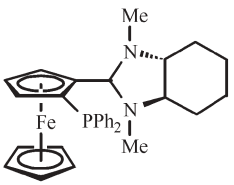
New ferrocenylphosphinoimidazolidines containing central chirality and planar chirality were found to act as highly effective chiral ligands in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

Pd-catalyzed asymmetric allylic alkylation is an attractive method for the enantioselective carbon–carbon bond formation in organic synthesis.[1] In particular, the search for more efficient chiral ligands is one of the most essential subjects in this area. Various types of chiral ligands were prepared in order to obtain high enantioselectivity in the allylic alkylation.[2] We have previously found chiral phosphinoimidazolidine to be an effective ligand for the reaction.[2f] Recently, chiral ligands based on ferrocene have become of interest in this transformation.[3] Our intriguing idea was construction of chiral ferrocenylphosphinoimidazolidine ligands **1** that contain both an imidazoline unit with central chirality and a ferrocenylphosphine unit with planar chirality. We wondered which chiral element would be the major contributor to the asymmetric induction in the catalytic process. In this paper we report our preliminary results on the performance of the new chiral ligands **1** in the catalytic asymmetric allylic alkylation.



1a

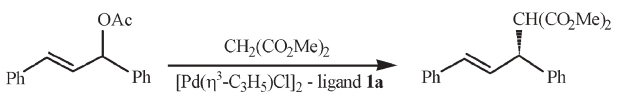


1b

Kagan has presented a general method for preparation of enantiomerically pure α-substituted ferrocene carboxaldehydes having only planar chirality.[4] According to the Kagan's method, the enantiomerically pure diphenylphosphinoferrocenecarboxaldehyde was obtained from ferrocenecarboxaldehyde. (*S*,*S*,S_p)-Ferrocenylphosphinoimidazolidine **1a** was easily prepared through condensation of the diphenylphosphinoferrocenecarboxaldehyde and (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine in refluxing benzene over 12 h in high yield.† (*R*,*R*,S_p)-Ferrocenylphosphinoimidazolidine **1b** was also obtained with (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine using the same method. In order to investigate the efficiency of the chiral ferrocenylphosphinoimidazolidines **1** in the asymmetric catalysis, the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (±)-**2** with dimethyl malonate was taken as a model reaction. As shown in Table 1, this reaction was carried out at room temperature in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 4.5 mol% of chiral ligand **1a**. *N*,*O*-Bis-(trimethylsilyl)acetamide (BSA) combined with a small amount of LiOAc, NaOAc or KOAc was used as a base. In the first experiment we used benzene as a nonpolar solvent and BSA–LiOAc as a base. The allylic alkylation proceeded perfectly both in terms of enantioselectivity and reactivity. The reaction was completed within a very short time (0.8 h) affording (*R*)-product **3** with 99.6% ee in nearly quantitative yield (entry 1). THF as a polar solvent also induced a similar result (entry 2). To our knowledge, the enantioselectivity achieved in this study is the highest value reported for the Pd-catalyzed asymmetric allylic alkylation. Unexpectedly, changing the solvent to CH_2Cl_2 or toluene caused only a slight drop in enantioselectivity (entries 3 and 4). The effect of bases on this reaction was surveyed. The use of sodium acetate, potassium acetate instead of lithium acetate as an additive gave enantioselectivity of 99% (entries 5–8). Both solvent and additive source seem to have only a little influence on the enantioselectivity. These results came as a surprise since significant effects of solvent and additive have so far been observed in most of the reactions.

We next investigated the role of planar and central chirality of ligands **1** on the stereochemical outcome. The results are summarized in Table 2. Compared to ligand (*S*,*S*,S_p)-**1a**, ligand (*R*,*R*,S_p)-**1b** showed lower enantioselectivity but the configuration

Table 1 Palladium-catalyzed asymmetric allylic alkylation of **2** with dimethyl malonate using ligand **1a**[a]



(±)-**2** (*R*)-**3**

Entry	Solvent	Additive	Time (h)	Yield (%)[b]	Ee (%)[c]
1	Benzene	LiOAc	0.8	99	99.6
2	THF	LiOAc	1	93	99.5
3	CH_2Cl_2	LiOAc	1	99	99.3
4	Toluene	LiOAc	3	90	99.3
5	Benzene	NaOAc	5	82	99
6	THF	NaOAc	1	92	99
7	Benzene	KOAc	5	80	99
8	Toluene	KOAc	5	81	99

[a] Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 equiv.), **1a** (0.045 equiv.), BSA (3.0 equiv.), dimethyl malonate (3.0 equiv.), and a catalytic amount of additive salts. [b] Isolated yield. [c] Determined by HPLC with a chiralcel OD-H column. Absolute configuration was assigned by comparing the specific rotation with a literature value: (*S*)-**3** $[\alpha]_D$ −18.4 (c 1.1, EtOH).[5]

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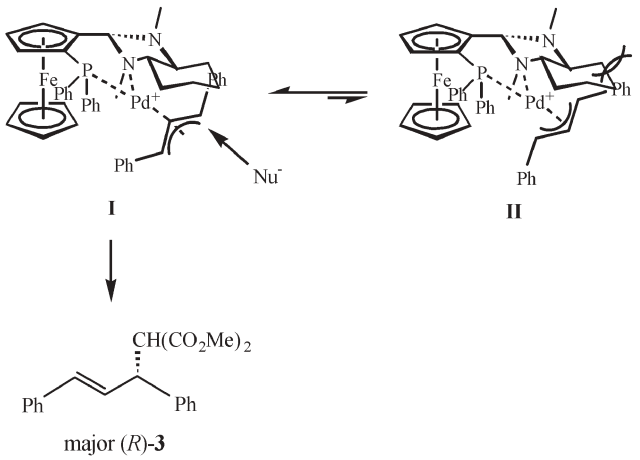
Table 2 The effect of central chirality in the ferrocenylphosphinoimidazolidine on enantioselectivity [a]

Ligand	Solvent	Additive	Time (h)	Yield (%)	Ee (%)
1a	Benzene	LiOAc	0.8	99	99.6
1b	Benzene	LiOAc	1	94	86
1b	THF	LiOAc	2	90	90
1b	CH_2Cl_2	LiOAc	1	92	68
1b	CH_2Cl_2	NaOAc	1	96	62
1b	THF	KOAc	1	95	70

[a] Experimental conditions as in Table 1.



Scheme 1

of the major product was the same. Combination of (*R*,*R*)-central chirality and (S_p)-planar chirality has a negative effect on the enantioselectivity. It should be noted that the influence of the planar chirality on the asymmetric induction is much higher than the central chirality. The central chirality of the imidazoline unit has a minor, but still significant effect. In the case of ligand **1b**, the enantioselectivity was dependent upon both solvent and additive source. The best result of 90% ee was obtained with LiOAc in THF.

The asymmetric induction by ligand **1a** can be briefly explained as follows. Molecular modelling suggests that the nucleophilic substitution proceeds through W-type π-allyl palladium complex **I** as a major intermediate (Scheme 1). In the case of M-type π-allyl complex **II**, severe repulsive interaction would be generated between imidazolidine ring and phenyl group in the substrate, no matter whether the central chirality is (*R*)- or (*S*)-configuration. The nucleophilic attack occurs preferentially at the allyl terminus *trans* to the phosphorus which is the better π-allyl acceptor. Therefore, the (*R*)-isomer is formed as the major product, in accordance with the experimental results.

In conclusion, we have synthesized new chiral ferrocenylphosphinoimidazolidines **1** having planar chirality as well as central chirality. In particular, ligand **1a** induced nearly perfect asymmetric catalysis in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The results show a considerable potential of such ligands in allylic substitution. Further study on exploring the scope of asymmetric catalysis with these promising ligands is in progress.

Notes and references

† Synthesis of **1a**: To a solution of diphenylphosphinoferrocenecarboxaldehyde (522 mg, 1 mmol) in degassed benzene (5 ml), (1*S*,2*S*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine (156 mg, 1.1 mmol) was added. The mixture was stirred at 75 °C for 12 h, then concentrated under reduced pressure. The crude product was purified by short flash chromatography on silica gel pretreated with triethylamine (5% EtOAc–hexane) to yield **1a** (590 mg) as a red-orange solid: yield 92%; $[\alpha]^{20}_D$ −259.3 (c 1.2, $CHCl_3$); ^{1}H-NMR δ ($CDCl_3$, 400 MHz) 7.60 (m, 2H), 7.43–7.16 (m, 8H), 4.63 (d, $^4J_{PH}$ 3.6 Hz, 1H), 4.45 (s, 1H), 4.36 (s, 1H), 3.98 (s, 1H), 3.93 (s, 5H), 2.72 (s, 3H), 2.11 (m, 3H), 1.97 (m, 1H), 1.73 (m 2H), 1.71 (s, 3H), 1.14 (m, 4H). Anal. Calcd for $C_{31}H_{35}FeN_2P$: C, 71.27; H, 6.75; N, 5.36. Found: C, 71.19; H, 6.79; N, 5.40%.

A representative procedure for allylic alkylation: In a Schlenk tube the ligand **1** (12.2 mg, 0.023 mmol) and allylpalladium chloride dimer (3.8 mg, 0.01 mmol) were dissolved in benzene (0.7 ml) and the mixture was stirred at room temperature for 20 min. To this solution were successively added 1,3-diphenyl-2-propenyl acetate (130 mg, 0.52 mmol) in benzene (1.6 ml), dimethyl malonate (206 mg, 1.56 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (317 mg, 1.56 mmol) and a catalytic amount of LiOAc. The mixture was stirred at a given temperature. After the reaction was complete, the reaction mixture was diluted with ether (15 ml), washed with cold saturated aqueous ammonium chloride solution (10 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15% EtOAc–hexane). The enantiomeric excess was determined by HPLC analysis (chiralcel OD-H column; flow rate, 0.5 mL min^{-1}; hexane : isopropanol = 99 : 1, t_r = 23.4 min, t_s = 25.0 min).

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