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New enantioselective chiral imidazolidine ligands for Pd-catalyzed asymmetric allylic alkylation

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Abstract—Chiral imidazolidine ligands have been synthesized from *N*,*N*′-dialkylated cyclohexanediamine derivatives and they were found to act as effective ligands in the palladium-catalyzed asymmetric allylic substitution. The excellent levels of enantiomeric excess up to 98% were obtained in high yield.

During the last decade, various enantioselective catalysts have been developed for palladium-catalyzed allylic substitution reactions.[1] In particular, chiral phosphino–oxazoline ligands are one of the effective ligands in this reaction.[2] The design of efficient chiral ligands is essential for asymmetric allylic alkylation (AAA) and has become one of the most intense areas of investigation. A series of C_2-symmetric diphosphines such as chiraphos, DIOP and BINAP, which gave high enantioselectivities in asymmetric hydrogenation, have been used in early study.

High levels of asymmetric induction have been achieved in AAA using the palladium complexes of chiral oxazolines tethered to aryl sulfides,[3] phosphine–oxazoline hybrid ligands,[4] amidine[5] and ferrocene-based C_2-symmetric phosphine–oxazoline ligands.[6] Tetradentate ligands such as bisphosphinobioxazolines are also known to afford a high enantioselectivity.[7] However, in contrast with five-membered oxazolines, the chiral imidazolines[8] or imidazolidines has not been extensively studied as ligands to date.

Because the combination of an imidazolidine group with an auxiliary donor atom provides the different electronic and steric environment around the metal, we have prepared new ligands containing both the imidazolidine moiety and an auxiliary S or P donor in order to examine such influences.

This communication describes the preparation of the new imidazolidines possessing a five membered backbone and their application to the palladium-catalyzed AAA.

Scheme 1 shows the method to synthesize the phosphinoimidazolidines and thioimidazolidines. Enantiomerically pure (*R*,*R*)-1,2-diaminocyclohexane was converted into its *N*,*N*′-dialkyl analogs of type (**1**–**3**) in the same manner as the procedure reported by Bennani and Hanessian.[9]

Chiral phosphinoimidazolidine ligands (**4**–**6**) can be readily synthesized by condensation of *N*,*N*′-dialkylated diamine derivatives (**1**–**3**)[10–12] and 2-(diphenylphosphino)benzaldehyde in the boiling benzene.[13–15]

Treatment of *o*-bromobenzaldehyde with chiral dialkyl cyclohexane-1,2-diamine derivatives yielded the bromoimidazolidines, and these imidazolidines were treated with *tert*-butyllithium at −78°C in THF under argon and allowed to react with diphenyl disulfide furnishing the chiral thioimidazolidine (**7**) and (**8**).[16,17]

To examine the catalytic activity of imidazolidine (**4**–**8**) as chiral ligands in palladium-catalyzed AAA, the reaction between *rac*-1,3-diphenyl-2-propenyl acetate and dimethyl malonate has been investigated under standard conditions in the presence of *N*,*O*-bis(trimethylsilyl)acetamide and KOAc. The AAA of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate was carried out with LiOAc instead of KOAc, when the Pd complexes of chiral thioimidazolidines were used as catalysts.

As shown in Table 1, the enantioselectivity and the reactivity are strongly dependant on the structure of

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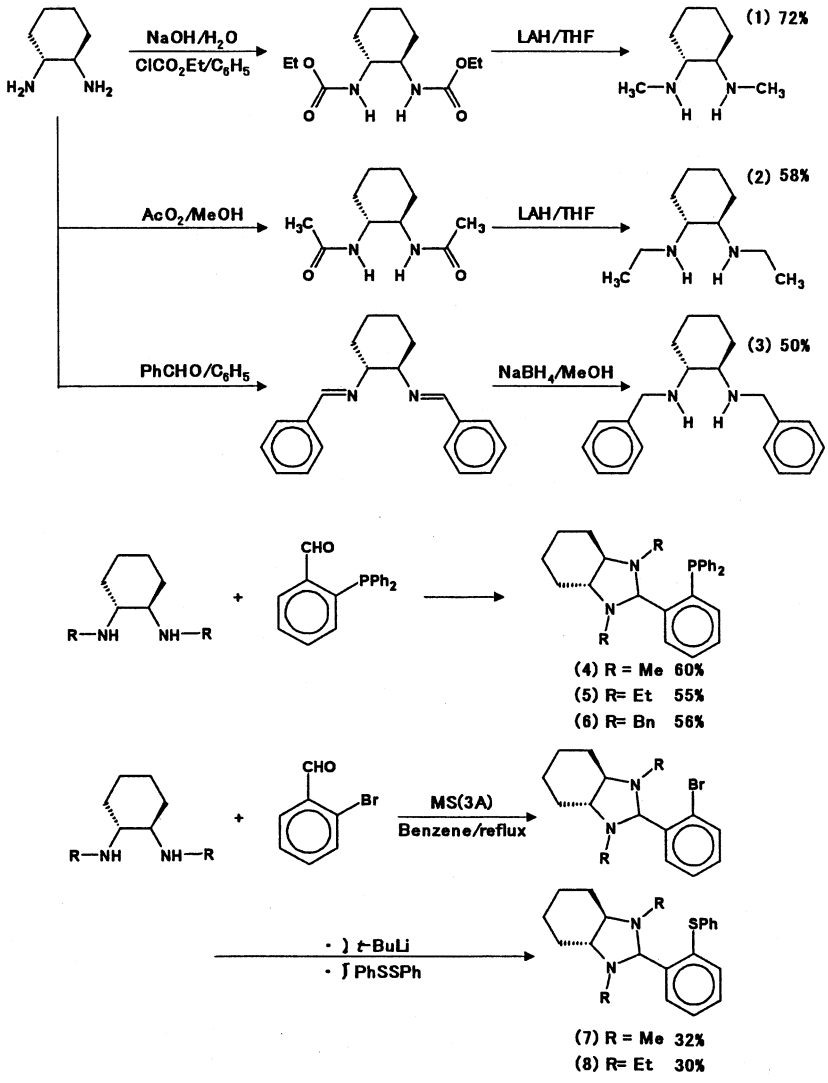


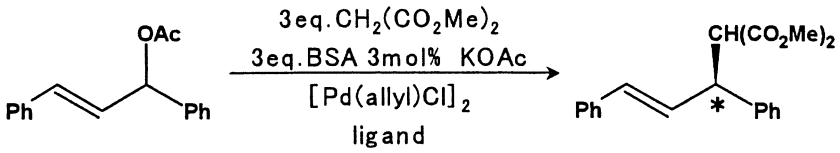
Scheme 1.

imidazolidines. The new phosphinoimidazolidine ligands (**4**), (**5**) and (**6**) are proved to be very efficient in terms of both reactivity and enantioselectivity in AAA. The carbon adjacent to the nitrogen bears the chirality. It appears that the phosphinoimidazolidines of *N*,*N*′-dimethylated diamine derivatives that are sterically less hindered at the nitrogen gave slightly better results in enantioselectivity than those of *N*,*N*′-dibenzylated diamine derivatives. The phosphino imidazolidine (**4**) synthesized from *N*,*N*′-dimethyl-1,2-diaminocyclohexane (**1**) affords the substitution product with 98% ee (entry 6), whereas the chiral ligand (**6**) obtained from *N*,*N*′-dibenzyldiamine (**3**) affords 91% ee (entry 16). The excellent asymmetric inductions have been achieved with the phosphinoimidazolidine ligands synthesized from *N*,*N*′-dialkylated cyclohexane diamines (**1**–**3**). The reactions have proceeded in high enantioselectivity even with 1 mol% of palladium catalyst. The product was isolated in a high yield with high ee.

However, the reactivity and enantioselectivity are almost independent on the reaction temperature at 0–25°C and significant solvent effect on the enantioselectivity was not observed. The reaction in THF afforded a slightly higher enantioselectivity (entry 6, 98% ee) than in methylene chloride (entry 8, 95% ee) at 0°C with the same conversion. In addition, variations in the ratio of ligand to palladium increased the enantioselectivities of the product, suggesting that the ligands do not bind strongly to the palladium allyl complexes. The effects of acetate source on the selectivity were investigated and the results are also shown in Table 1. The reaction rates and enantioselectivities were almost independent on the kinds of acetate. The enantiomeric excess obtained using thioimidazolidine (**7**) is lower than that for the phosphinoimidazolidine ligand (**4**), which has the same backbone structure. The AAA reaction using thioimidazolidines proceeded very slowly.

In conclusion, the asymmetric Pd-catalyzed allylic alkylation using chiral phosphinoimidazolidines could be applied with success and the high enantioselectivities were attainable in this asymmetric reaction. Further investigations are currently in progress to apply these new chiral ligands to other asymmetric catalysis.

Table 1. Asymmetric Pd-catalyzed allylic substitution of 1,3-diphenyl-2-propenyl acetate in the presence of imidazolidine ligands **4–8**



Entry	Ligand	S/L/Pd (mol ratio)	Solvent	Additive	Temp. (°C)	Time (h)	Conv.[a] (%)	% ee[b]
1	**4**	40/4/1	THF	KOAc	22	4	>99	97
2	**4**	40/4/1	THF	LiOAc	22	4	>99	97
3	**4**	100/2.5/1	THF	KOAc	22	4	>99	95
4	**4**	100/1/1	THF	KOAc	22	4	>99	93
5	**4**	100/2.5/2.5	THF	KOAc	22	4	>99	94
6	**4**	40/4/1	THF	KOAc	0	4	>99	98
7	**4**	40/4/1	CH_2Cl_2	KOAc	22	4	>99	95
8	**4**	40/4/1	CH_2Cl_2	KOAc	0	4	>99	95
9	**4**	100/2.5/1	CH_2Cl_2	KOAc	0	4	>99	95
10	**5**	40/4/1	THF	KOAc	22	4	99	94
11	**5**	40/4/1	THF	LiOAc	22	4	>99	95
12	**5**	100/2.5/1	THF	KOAc	22	4	99	93
13	**5**	100/1/1	THF	KOAc	22	4	>99	78
14	**5**	100/2.5/2.5	THF	KOAc	22	4	>99	82
15	**5**	40/4/1	CH_2Cl_2	KOAc	22	4	99	92
16	**6**	40/4/1	THF	KOAc	22	4	99	91
17	**6**	40/4/1	THF	LiOAc	22	4	>99	92
18	**6**	100/2.5/1	THF	KOAc	22	4	99	84
19	**6**	100/1/1	THF	KOAc	22	4	99	74
20	**6**	100/2.5/2.5	THF	KOAc	22	4	99	79
21	**7**	40/4/1	THF	LiOAc	22	24	29	45
22	**8**	40/4/1	THF	LiOAc	22	24	24	35

[a] The conversion was determined by GC analysis.
[b] The enantiomeric excess was determined by HPLC with a chiral column, Daicel chiralcel OD column (1% 2-propanol in hexane).

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10. For **1**; IR ν_{max} 3300, 2582, 1503, 1441, 1143, 1100, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (m, 2H, ring), 1.38 (m, 2H, ring), 1.79 (m, 2H, ring), 1.95 (m, 2H, ring), 2.30 (s, 6H, 2×CH_3).
11. For **2**; ^1H NMR ($CDCl_3$) δ 0.92 (m, 2H, ring), 1.20 (m, 2H, ring), 1.63 (m, 2H, ring), 2.09 (m, 2H, ring), 2.60 (q, 4H, 2×CH_2), 1.08 (t, 6H, 2×CH_3).

12. For **3**; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 2H, ring), 1.75 (m, 2H, ring), 2.20 (m, 2H, ring), 2.52 (m, 2H, ring), 3.76 (d, 2H, CH_2Ph), 4.02 (d, 2H, CH_2Ph), 7.24–7.39 (2m, 10H, ArH).
13. To a solution of (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane (**1**) (21 mmol) in benzene (5 mL) was added 2-(diphenylphosphino)benzaldehyde (20 mmol) at room temperature. The resulting mixture was refluxed for 48 h in the presence of 3 Å molecular sieve and the solvent was evaporated. The residue was purified by silica gel column chromatography (5% triethylamine/5% ethylacetate/90% hexane) to give phosphinoimidazolidine (**4**) of *N*,*N*′-dimethyl analog in 60% yield. IR ν_{max} 3050, 2930, 2855, 1550, 1450, 1260, 1210, 1090, 1070, 1010, 980, 840 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ 1.20–1.94 (m, 10H, ring), 1.83 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 5.13 (d, 1H, NCH), 6.93–7.64 (m, 14H, ArH): ^{13}C ($CDCl_3$) δ 24.38, 28.95, 36.17, 68.66, 86.17, 128.43, 129.97, 133.72, 134.14, 137.38, 144.60: Anal. calcd. for $C_{27}H_{31}N_2P$; C, 78.23, H, 7.54, N, 6.76; found C, 78.12, H, 7.51, N, 6.68%.
14. Phosphinoimidazolidine (**5**) was prepared in the same manner as described above by the reaction of (*R*,*R*)-*N*,*N*′-diethyl-1,2-diaminocyclohexane (**2**) (21 mmol) and 2-(diphenylphosphino)benzaldehyde (20 mmol) in boiling benzene. IR ν_{max} 3050, 2920, 2850, 1550, 1440, 1260, 1215, 1100, 1010, 980, 840 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ 1.20–2.05 (m, 10H, ring), 2.68 (q, 4H, 2×CH_2), 0.83 (t, 6H, 2×CH_3), 5.61 (d, 1H, NCH), 7.10–7.70 (m, 14H, ArH): ^{13}C ($CDCl_3$) δ 15.87, 24.41, 43.33, 65.86, 81.40, 128.34, 133.63, 136.38, 137.49, 148.14: Anal. calcd. for $C_{29}H_{35}N_2P$; C, 78.70, H, 7.97, N, 6.33; found C, 78.58, H, 7.91, N, 6.30%.
15. Phosphinoimidazolidine (**6**); IR ν_{max} 3050, 2930, 2850, 1545, 1455, 1430, 1260, 1215, 1095, 1070, 1010, 980, 840 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ 1.02–2.90 (m, 10H, ring), 3.39 (q, 4H, 2×CH_2), 5.64 (d, 1H, NCH), 7.03–7.42 (m, 24H, ArH): ^{13}C ($CDCl_3$) δ 24.51, 55.27, 69.43, 84.04, 126.47, 127.88, 133.78, 137.79, 145.45: Anal. calcd. for $C_{39}H_{39}N_2P$; C, 82.65, H, 6.94, N, 4.94; found C, 82.71, H, 6.88, N, 4.91%.
16. Thioimidazolidine (**7**); ^{1}H NMR ($CDCl_3$) δ 1.20–2.83 (m, 10H, ring), 2.02 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 7.22–7.45 (m, 9H, ArH): ^{13}C ($CDCl_3$) δ 24.31, 28.86, 34.43, 37.86, 67.05, 69.19, 83.78, 126.50, 127.68, 129.75, 130.59, 133.93, 140.27: Anal. calcd. for $C_{21}H_{26}N_2S$; C, 74.51, H, 7.74, N, 8.28; found C, 74.45, H, 7.71, N, 8.22%.
17. Thioimidazolidine (**8**); ^{1}H NMR ($CDCl_3$) δ 1.22–2.15 (m, 10H, ring), 2.70 (q, 4H, 2×CH_2), 0.86 (t, 6H, 2×CH_3), 5.09 (d, 1H, NCH), 7.10–7.55 (m, 9H, ArH).