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Palladium-catalyzed asymmetric allylic substitution using novel phosphino-ester (PHEST) ligands with 1,1′-binaphthyl skeleton

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Abstract

The asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **1** with dimethyl malonate **2a** proceeded smoothly in the presence of lithium acetate, BSA (*N*,*O*-bis(trimethylsilyl)acetamide), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and the chiral ligand (*R*)-*i*-Pr_2N-PHEST (*R*)-**5a** to give the allylic alkylation product (*R*)-**3a** in 89% yield with 99% ee. Furthermore, the asymmetric allylic amination of **1** with potassium phthalimide **2c** has been carried out using the same ligand to give the allylic amination product (*S*)-**3c** in 10% yield with 66% ee.

1. Introduction

The palladium-catalyzed asymmetric allylic substitution reactions,[1] alkylation and amination, have been attracting considerable attention due to their potential for the enantioselective formation of new covalent bonds such as carbon–carbon and carbon–nitrogen bonds. These reactions have been extensively studied[2] for the palladium-catalyzed substitution on racemic 1,3-diphenyl-2-propenyl acetate **1** with carbon or nitrogen nucleophiles and are excellent models for testing the design principles of asymmetric ligands.

The design and synthesis of ligands have mainly focused on chiral phosphorus-containing ligands as chiral phosphines are excellent ligands in asymmetric catalysis, and among them, the prime role is played by those possessing the binaphthyl scaffold.[3] Both C_2-symmetrical (e.g. BINAP[4]) and unsymmetrical (e.g. MOP,[5] MAP[6] and NOBIN[7]) representatives often give levels of asymmetric induction previously reserved to enzymes. Although many palladium complexes of bidentate ligands are excellent catalysts for allylic substitution reactions, the palladium complexes of conventional chiral monophosphines are normally not effective.[8] Therefore, we

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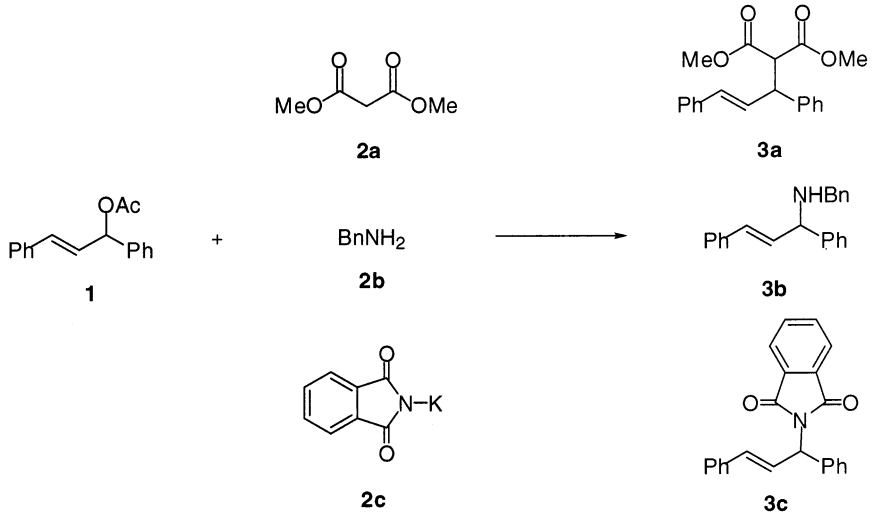
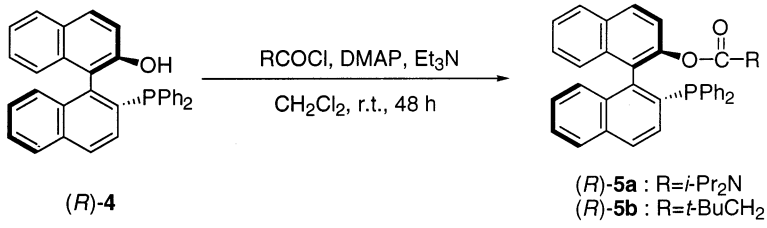
synthesized novel chiral phosphino-ester (PHEST) ligands with a 1,1′-binaphthyl skeleton and performed the palladium-catalyzed allylic substitution with carbon or nitrogen nucleophiles.



2. Results and discussion

Novel phosphino-ester (PHEST) ligands, (*R*)-**5a** and (*R*)-**5b**, were obtained from (*R*)-2-diphenylphosphino-2′-hydroxy-1,1′-binaphthyl (*R*)-**4**[9] and the corresponding acid chlorides in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) in 92 and 95% yields, respectively (Scheme 1). These PHEST ligands were characterized using infrared, ^{1}H and ^{31}P NMR spectra, and elemental analysis.

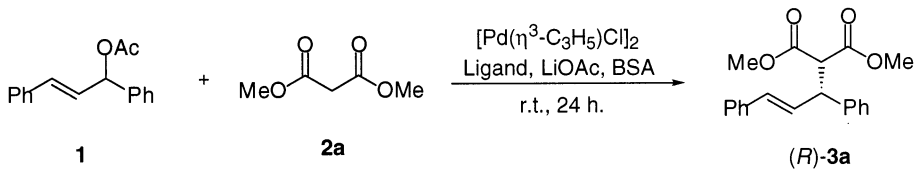


Scheme 1.

The asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **1** was performed at room temperature in the presence of the Pd–PHEST complex generated in situ from 2 mol% of bis[(π-allyl)palladium chloride] and 6 mol% of (*R*)-**5a** or (*R*)-**5b**. The nucleophile was generated from dimethyl malonate in the presence of BSA (*N*,*O*-bis(trimethylsilyl)acetamide) and a catalytic amount of lithium acetate.

As shown in Table 1, the allylic alkylation catalyzed by 6 mol% (*R*)-**5a** and 2 mol% bis[(π-allyl)palladium chloride] in dichloromethane as the solvent at room temperature for 24 h smoothly proceeded to afford the product (*R*)-**3a** in 89% yield with 99% ee (Table 1, entry 1). The effect of solvent on this reaction was examined using (*R*)-**5a** as the ligand (Table 1, entries

Table 1
Palladium-catalyzed asymmetric allylic alkylation[a]



1 2a (*R*)-**3a**

Entry	Ligand	Solvent	Yield (%)[b]	Ee (%)[c]
1	(*R*)-**5a**	CH_2Cl_2	89	99[d]
2	(*R*)-**5a**	THF	55	90
3	(*R*)-**5a**	$PhCH_3$	21	95
4	(*R*)-**5a**	Et_2O	44	88
5	(*R*)-**5a**	CH_3CN	80	85
6[e]	(*R*)-**5a**	CH_2Cl_2	71	94
7	(*R*)-**5b**	CH_2Cl_2	86	96
8	(*R*)-**5b**	THF	38	96
9	(*R*)-MeO-MOP	CH_2Cl_2	59	85

[a] Reaction conditions: The catalyst $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol) and PHEST ligand ((*R*)-**5a**,**b**) (0.03 mmol) were stirred in solvent (1.0 mL) for 0.5 h, and **1** (0.50 mmol) in solvent (2 mL), dimethyl malonate (**2**) (1.5 mmol), lithium acetate (0.01 mmol) and BSA (1.5 mmol) were added to the catalyst solution, and then the mixture was stirred for 24 h at room temperature.

[b] Isolated yield.

[c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column.

[d] $[\alpha]_D^{23} = +18.0$ (*c* 1.1, EtOH) (lit.[10] $[\alpha]_D^{23} = +18.4$ (*c* 1.1, EtOH)).

[e] The catalyst, 0.67 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and 2.0 mol% PHEST ligand were used.

2–5). The reaction proceeded faster in dichloromethane and acetonitrile as the solvent (Table 1, entries 1 and 5), and slower in tetrahydrofuran, toluene and diethyl ether (Table 1, entries 2–4). Moreover, the effect of the amount of catalyst was also examined. The allylic alkylation catalyzed by 2 mol% (*R*)-**5a** and 0.67 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ at room temperature smoothly proceeded to give (*R*)-**3a** in 71% yield with 94% ee (Table 1, entry 6). The effect of the ligand was next examined. There were few differences in the yields and enantiomeric excesses of the product between the reaction using (*R*)-**5a** and (*R*)-**5b** as the ligand (Table 1, entries 7 and 8). However, using the (*R*)-MeO-MOP ligand led to a lower enantiomeric excess of (*R*)-**3a** (Table 1, entry 9). Interestingly, in this reaction, the absolute configuration of allylic product was changed in comparison with the results of bidentate ligands, such as BINAP[11] or MAP.[6]

Next, the effect of base on the reaction with (*R*)-**5a** and (*R*)-**5b** was evaluated (Table 2). The allylic alkylation catalyzed by (*R*)-**5a** using sodium acetate or potassium acetate, instead of lithium acetate, proceeded to give (*R*)-**3a** in 85 and 72% yields with 65 and 64% ee, respectively (Table 2, entries 2 and 3). Using (*R*)-**5b** as the ligand also led to low enantiomeric excesses of (*R*)-**3a** (Table 2, entries 5 and 6).

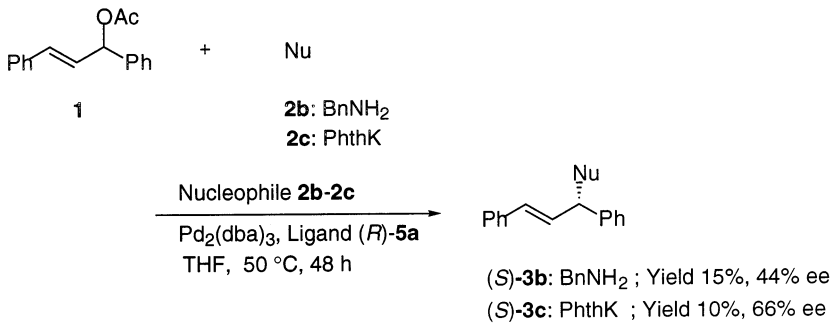
Table 2
Effect of base on palladium-catalyzed asymmetric allylic alkylation[a]

Entry	Ligand	Base	Yield (%)[b]	Ee (%)[c]
1	(*R*)-**5a**	LiOAc + BSA	89	99
2	(*R*)-**5a**	NaOAc + BSA	85	65
3	(*R*)-**5a**	KOAc + BSA	72	64
4	(*R*)-**5b**	LiOAc + BSA	86	96
5	(*R*)-**5b**	NaOAc + BSA	94	50
6	(*R*)-**5b**	KOAc + BSA	62	47

[a] See Table 1. CH_2Cl_2 was used as the solvent.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column.

Clearly, these results demonstrated the superiority of lithium acetate and BSA as the base in dichloromethane as the solvent (Table 2). If lithium acetate is taken into account, we can envisage the chelation of the lithium cation by the carbonyl moiety including the PHEST ligand and oxygen atom of the dimethyl malonate anion, thus this chelation stabilizes the transition state even further.

Moreover, the asymmetric allylic amination of *rac*-1,3-diphenyl-2-propenyl acetate **1** was performed at 50°C in the presence of the Pd(0)–ligand complex generated in situ from 2.5 mol% of $Pd_2(dba)_3$ and 5 mol% of (*R*)-**5a**. Benzylamine **2b** and potassium phthalimide **2c** as the nucleophile were used. The reaction using benzylamine proceeded to give (*S*)-**3b** in 15% yield with 44% ee. Using potassium phthalimide as the nucleophile instead of benzylamine led to a 66% ee.



3. Conclusion

In conclusion, the palladium-catalyzed asymmetric allylic alkylation of *rac*-1,3-diphenyl-2-propenyl acetate **1** with dimethyl malonate **2a** smoothly proceeded in the presence of lithium acetate, BSA (*N*,*O*-bis(trimethylsilyl)acetamide), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, and the chiral ligand (*R*)-*i*-Pr_2N-PHEST (*R*)-**5a** to give the allylic alkylation product (*R*)-**3a** in 89% yield with 99% ee. We found that the choice of the metal acetate was very important in this reaction.

4. Experimental

All experiments were carried out under an argon atmosphere. Commercial reagents were used as received without further purification. All solvents were dried using standard procedures. The ^{1}H NMR (400 MHz) spectra were recorded on a Jeol JNM A-400 spectrometer with TMS as the internal standard. The ^{31}P NMR (161 MHz) spectra were recorded using a Jeol JNM A-400 spectrometer with 85% phosphoric acid as the external standard. Optical rotations were recorded using a Horiba SEPA-200 polarimeter. Enantiomeric excesses (% ees) were determined by HPLC analyses. The preparation of (*R*)-2-diphenylphosphino-2′-hydroxy-1,1′-binaphthyl (*R*)-**4** was carried out according to the reported method.[9]

4.1. Preparation of phosphino-ester (PHEST) ligands

(*R*)-2-(*N*,*N*-Diisopropylcarbamoyloxy)-2′-diphenylphosphino-1,1′-binaphthyl (*R*)-**5a**: To a solution of (*R*)-2-diphenylphospino-2′-hydroxy-1,1′-binaphthyl (*R*)-**4** (0.52 g, 1.14 mmol) in dichloromethane (15 mL) were added *N*,*N*-diisopropylcarbamoyl chloride (0.22 g, 1.32 mmol), triethylamine (0.19 g, 1.39 mmol), and 4-dimethylaminopyridine (0.036 g, 0.29 mmol). The reaction mixture was stirred for 48 h at room temperature. The resulting mixture was quenched with water, and then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness, and the residue was chromatographed on silica gel (dichloromethane) to give (*R*)-2-(*N*,*N*-diisopropylcarbamoyloxy)-2′-diphenylphosphino-1,1′-binaphthyl (*R*)-**5a** as a white solid (0.61g, 92%); mp 158–161°C; MS *m*/*z* 582 (M^+); $[\alpha]_D^{25}$ +50.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.18 (d, J=5.6 Hz, 3H), 0.66 (d, J=6.0 Hz, 3H), 0.74 (d, J=5.2 Hz, 3H), 1.07 (d, J=6.0 Hz, 3H), 3.34 (m, 2H), 6.96–7.50 (m, 17H), 7.55 (d, J=8.8 Hz, 1H), 7.83 (t, J=8.0 Hz, 2H), 7.88 (d, J=8.4 Hz, 1H), 8.00 (d, J=9.2 Hz, 1H); ^{31}P NMR ($CDCl_3$): δ −14.79; IR (KBr): 3050, 2900, 1715, 1425, 1310, 1220, 1150, 1045, 1005 cm^{-1}. Found: C, 80.53; H, 6.24; N, 2.41. Calcd for $C_{39}H_{36}NO_2P$: C, 80.25; H, 6.17; N, 2.22.

In a similar method, compound (*R*)-**5b** was prepared from (*R*)-2-diphenylphospino-2′-hydroxy-1,1′-binaphthyl (*R*)-**4** and *tert*-butylacetyl chloride.

(*R*)-2-(*tert*-Butylacetyloxy)-2′-diphenylphosphino-1,1′-binaphthyl (*R*)-**5b**: Yield 95%; mp 136–138°C; MS *m*/*z* 553 (M^+); $[\alpha]_D^{25}$ +14.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.48 (s, 9H), 1.85 (s, 2H), 6.93–6.95 (m, 2H), 7.04–7.47 (m, 16H), 7.84 (t, J=8.8 Hz, 2H), 7.90 (d, J=8.0 Hz, 1H), 8.00 (d, J=8.8 Hz, 1H); ^{31}P NMR ($CDCl_3$): δ −14.02; IR (KBr): 3030, 2940, 1750, 1470, 1430, 1320, 1210, 1190, 1110, 970 cm^{-1}. Found: C, 82.40; H, 6.01. Calcd for $C_{38}H_{33}O_2P$: C, 82.59; H, 6.02.

4.2. A typical procedure for palladium-catalyzed asymmetric allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate **1** with dimethyl malonate **2a**

A solution of the PHEST ligand (0.03 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.004 g, 0.01 mmol) in dichloromethane (1 mL) was stirred at room temperature for 30 min. This solution was successively treated with a solution of *rac*-1,3-diphenyl-2-propenyl acetate (**1**) (0.13 g, 0.50 mmol) in dichloromethane (2 mL), dimethyl malonate (**2a**) (0.17 mL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.37 mL, 1.5 mmol) and metal acetate (0.01 mmol). The reaction mixture was then stirred for 24 h at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride, and then extracted with diethyl ether. The organic layer

was dried over anhydrous sodium sulfate and evaporated to dryness, and the residue was chromatographed on silica gel (ethyl acetate:hexane = 1:4) to give dimethyl (1,3-diphenyl-2-propenyl)malonate (*R*)-**3a**. The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralcel OD-H column (eluent, 1:99 2-propanol:hexane; flow rate 0.3 mL/min; detection, UV 254 nm; retention times, 27.9 (*R*):29.2 min (*S*)).

4.3. A typical procedure for palladium-catalyzed asymmetric allylic amination of rac-*1,3-diphenyl-2-propenyl acetate* ***1*** *with benzylamine* ***2b***

A solution of the PHEST ligand (0.025 mmol) and $Pd_2(dba)_3$ (0.017 g, 0.013 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature for 30 min. This solution was then successively treated with a solution of *rac*-1,3-diphenyl-2-propenyl acetate **1** (0.13 g, 0.50 mmol) in tetrahydrofuran (1 mL) and benzylamine **2b** (0.13 g, 1.2 mmol). The reaction mixture was stirred for 48 h at 50°C. The reaction mixture was quenched with saturated aqueous ammonium chloride, and then extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness, and the residue was chromatographed on silica gel (ethyl acetate:hexane = 1:4) to give *N*-((*E*)-1,3-diphenyl-2-propenyl)benzylamine (*S*)-**3b**. The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralcel OD-H column (eluent, 1:99 2-propanol:hexane; flow rate 0.5 mL/min; detection, UV 254 nm; retention times, 15.4 (*R*):16.2 min (*S*)). $[\alpha]_D^{23} = +12$ (*c* 1.76, $CHCl_3$) (lit.[12] $[\alpha]_D^{23} = +25$ (*c* 1.76, $CHCl_3$); 96% ee).

In a similar method, *N*-((*E*)-1,3-diphenyl-2-propenyl)phthalimide (*S*)-**3c** was prepared from *rac*-1,3-diphenyl-2-propenyl acetate **1** and potassium phthalimide **2c** as the nitrogen nucleophile. The work up and determination of the enantiomeric excesses and the absolute configurations were performed in the same way as described above. The enantiomeric excess was determined using a Daicel Chiralcel OD-H column (eluent, 1:99 2-propanol:hexane; flow rate 0.5 mL/min; detection, UV 254 nm; retention times, 22.3 min (*S*):30.8 min (*R*)). $[\alpha]_D^{23} = +11$ (*c* 1.70, $CHCl_3$) (lit.[12] $[\alpha]_D^{23} = -17$ (*c* 1.70, $CHCl_3$); 99% ee *R*).

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