# ENANTIOSELECTIVE ALLYLIC ALKYLATION AND AMINATION CATALYZED BY A CHIRAL P/N LIGAND-PALLADIUM COMPLEX#

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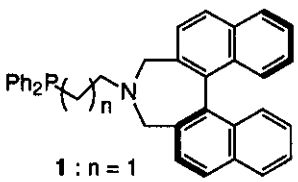
**Abstract** - The phosphorus-containing $C_2$-symmetric chiral amine ligand (**3**) has been found to be highly effective for enantioselective allylic substitution catalyzed by palladium complex. A high level of enantioselectivity has been achieved in the reaction of racemic 1,3-diphenyl-2-propenyl acetate with various C-nucleophiles (>95% e.e.) and N-nucleophiles (84-92% e.e.).

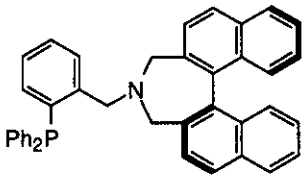
In recent years, chiral P/N ligands have received a great deal of attention and have been employed to control the enantioselectivity of such metal catalyzed processes as Grignard cross coupling,[1] allylic substitution,[2] and hydroboration.[3]

In the preceding paper, we have shown that palladium complexes with phosphorus-containing $C_2$-symmetric chiral amine ligands are very effective for enantioselective allylic alkylation.[4] In the reaction of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, chiral P/N ligands (**1** and **2**) which contain the chiral amine (*R*)-4,5-dihydro-3*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine, attain a high level of enantioselectivity (93% e.e. using **1**, 96% e.e. using **2**) when the relative ratio of chiral ligand to palladium is less than one.

In this paper, we wish to report enantioselective allylic alkylation and amination catalyzed by the palladium complex with **3**.[5, 6]




1 : n = 1
2 : n = 2




3

Enantioselective palladium catalyzed allylic alkylation employing **3** was investigated. Thus, allyl palladium complex generated in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (5 mol% as Pd) and **3** was treated successively with racemic 1,3-diphenyl-2-propenyl acetate and dimethyl malonate (3 equiv.) in the presence of N,O-bis(trimethylsilyl)acetamide (BSA) (3 equiv.) and a catalytic amount of potassium acetate, to afford the alkylated product with the same level of enantioselectivity as that using **1** or **2** (Table 1). Interestingly, the enantiomeric excess is independent on the ratio of ligand to palladium in the case of using **3**. This suggests that **3** should chelate to palladium more strongly than **1** and **2**, and that excess ligand does not prevent the formation of the bidentate ligand-palladium complex.

The palladium complex with **3** also showed excellent asymmetric induction with other C-nucleophiles. Bis(phenylsulfonyl)methane was inert under the reaction conditions using BSA. However, the reaction was carried out successfully by using the sodium salt of bis(phenylsulfonyl)methane in THF.

Next, we investigated enantioselective allylic amination catalyzed by palladium complex[7] with **1~3**. Since amines as well as soft carbon nucleophiles attack the $\eta^3$-allyl carbon from the side opposite to the palladium,[8] good enantioselectivity was expected.

The enantioselective allylic amination of racemic 1,3-diphenyl-2-propenyl acetate with benzylamine as a N-nucleophile was slower than the alkylation with dimethyl malonate. However, the reaction proceeded smoothly in THF at 50°C to afford an allylamine derivative. The chiral ligand (**3**) shows the highest reactivity and best enantioselectivity among **1~3** (Table 2).[9]

Ligand (**3**) also showed a high level of enantioselectivity with other N-nucleophiles. The reaction with the sodium salt of di-*tert*-butyl iminodicarboxylate resulted in the highest enantiomeric excess (92% e.e.). The palladium complex with **1** or **2** instead of **3** required a much longer reaction time and gave a lower enantiomeric excess.

In summary, we have demonstrated that the palladium complex with chiral P/N ligand (**3**) is an efficient catalyst for both enantioselective alkylation and amination and is superior to that with **1** or **2**.

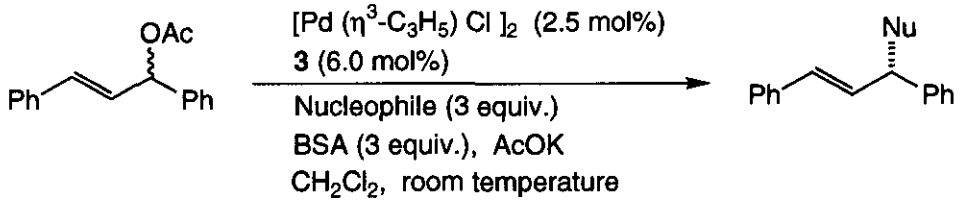



**Table 1.** Enantioselective allylic alkylation

| Nucleophile | 3/Pd | Time (min) | Yield (%) | % e.e. (Abs. confign.) |
|---|---|---|---|---|
| $CH_2(COOMe)_2$ | 0.5 | 60 | 95 | 96[a] (R) |
| $CH_2(COOMe)_2$ | 1.2 | 30 | 99 | 96[a,b] (R) |
| $AcNHCH(COOEt)_2$ | 1.2 | 30 | 98 | 97[a,c] (R) |
| $NaCH(SO_2Ph)_2$[d] | 1.2 | 90 | 98 | >95[e] (R) |

a: The e.e. values were determined by hplc with chiral column (Daicel CHIRALPAK AD).
b: $[\alpha]_D^{25}$ +19.8° (c 1.14, EtOH).
c: $[\alpha]_D^{25}$ - 52.2° (c 1.0, EtOH).
d: $NaHCH(SO_2Ph)_2$ (2 equiv.), *THF*, 50°C.
e: $[\alpha]_D^{25}$ +5.6° (c 1.01, $CHCl_3$). The minor enantiomer was not detected by $^1$H-nmr using $Eu(hfc)_3$.

**Table 2.** Enantioselective allylic amination

| Nucleophile | Ligand | Time(h) | Yield (%) | % e.e.[c] |
|---|---|---|---|---|
| $PhCH_2NH_2$ | **1**[a] | 24 | 95 | 70 |
| $PhCH_2NH_2$ | **2**[a] | 120 | 35 | 29 |
| $PhCH_2NH_2$ | **3**[b] | 2 | 94 | 84[d] |
| TsNHNa | **3**[b] | 3 | 92 | 84[e] |
| $(Boc)_2NNa$ | **1**[a] | 24 | 8 | 85 |
| $(Boc)_2NNa$ | **3**[b] | 1 | 92 | 92[f] |

a: 2.5 mol% of ligand was used.
b: 6.0 mol% of ligand was used.
c: The e.e. values were determined by hplc using chiral columns (Daicel CHIRALPAK AD or CHIRALCEL OD-H)
d: $[\alpha]_D^{25}$ +20.9° (c 1.01, $CHCl_3$).
e: $[\alpha]_D^{25}$ +29.4° (c 1.01, $CHCl_3$).
f: $[\alpha]_D^{25}$ - 47.2° (c 1.04, $CHCl_3$).

## REFERENCES AND NOTES


# This paper is dedicated to the late Professor Yoshio Ban.

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4. H. Kubota and K. Koga, *Tetrahedron Lett.*, 1994, **35**, 6689; H. Kubota, M. Nakajima, and K. Koga, *Tetrahedron Lett.*, 1993, **34**, 8135.

5. During the preparation of this manuscript, a paper was published which describes the synthesis of **3** and its use in asymmetric catalysis including allylic alkylation of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate: P. Wimmer and M. Widhalm, *Tetrahedron: Asymmetry*, 1995, **6**, 657.

6. $[\alpha]_D^{25}$ -218° (c, 1.0, $CH_2Cl_2$); $^1$H-nmr (270 MHz, $CDCl_3$) δ: 2.85 (d, 2H, *J*=12.2 Hz), 3.45 (d, 2H, *J*=12.2 Hz), 3.74 (d, 1H, *J*=13.3 Hz), 3.87 (d, 1H, *J*=13.3 Hz), 6.95-7.55 (m, 22H), 7.86 (d, 2H, *J*=8.3 Hz), 7.93 (d, 2H, *J*=8.3 Hz); $^{13}$C-nmr (67.8 MHz, $CDCl_3$) δ: 54.05, 58.23 (d, *J*=15.9 Hz), 125-145 (ArC).

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9. The representative procedure is as follows: To a solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (9.1 mg, 0.025 mmol) in degassed THF (2.0 ml) was added chiral ligand (**3**) (34.2 mg, 0.06 mmol) under Ar atmosphere at room temperature. The pale yellow solution was degassed by freeze and thaw cycle and stirred for 30 min. The whole was treated successively with 1,3-diphenyl-2-propenyl acetate (252 mg, 1.0 mmol) in THF (3.0 ml) and benzylamine (214 mg, 2 mmol). The mixture was degassed and then stirred at 50°C for 2 h. After evaporation of the solvent, purification by silica gel chromatography (hexane-ether (6~4:1)) afforded amination product as a colorless oil.

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