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Palladium-catalyzed asymmetric tandem allylic substitution using chiral 2-(phosphinophenyl)pyridine ligand

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Abstract—Palladium-catalyzed asymmetric tandem allylic substitution of (*Z*)-1,4-diacyloxy- and (*Z*)-1,4-bis(alkoxycarbonyloxy)-2-butene (**2a–c**) using 2-(phosphinophenyl)pyridine **1** as chiral ligand provided optically active six-membered 2-vinyl-1,4-diheterocyclic compounds with good to high enantioselectivity. For example, the reactions with catechol, 2-(benzylamino)phenol, or 1,2-bis(benzylamino)ethane as a nucleophile gave 2-vinyl-1,4-benzodioxane (71% ee), 4-benzyl-2-vinyl-1,4-benzoxazine (86% ee), and 1,4-dibenzyl-2-vinylpiperazine (86% ee), respectively.

Palladium-catalyzed asymmetric allylic substitution is a major topic in catalytic asymmetric synthesis and various chiral ligands for this reaction have been developed to date.[1] In 1993, 2-(phosphinophenyl)oxazolines (P,N ligands) were reported to be excellent chiral ligands for asymmetric allylic alkylation.[2] The ensuing introduction of various types of P,N ligands has expanded the scope of asymmetric allylic alkylation.[3] We have demonstrated that 2-(phosphinophenyl)pyridine **1** bearing an isopropyl group at C7 is an efficient chiral auxiliary for palladium-catalyzed allylic alkylation of both acyclic and cyclic alkenyl substrates (Scheme 1).[4a,b] Furthermore, we have found that a palladium–**1** complex serves as a good catalyst for asymmetric intramolecular allylic amination.[4c]

On the other hand, most heterocyclic compounds possessing heteroatoms at C1 and C4 show unique therapeutical and biological activities. Palladium-catalyzed tandem allylic substitution (PTAS) of 1,4-diacyloxy-2-butene or 1,4-bis(alkoxycarbonyloxy)-2-butene using a 1,2-heterofunctionalized compound as nucleophile is a useful method for the synthesis of these types of heterocyclic compounds.[5] Thus, much effort has been directed toward asymmetrization of the tandem allylic substitutions. Although many chiral ligands have been applied to these tandem reactions (Scheme 2),[6] Nakano et al. have recently demonstrated that the xylofuranose-based chiral P,N ligand induces good to high asymmetry in the synthesis of 2-vinylmorpholine and 2-vinylpiperazine derivatives, indicating that the chiral P,N ligand is a promising chiral ligand for catalytic asymmetric tandem allylic substitution.[6h]

In PTAS, the first substitution reaction gives a ω-hetero substituted allyl ester derivative that undergoes intramolecular allylic substitution. Since compound **1** is a potent chiral ligand for palladium-mediated intramolecular allylic amination (Scheme 1),[4c] we expected that asymmetric PTAS would be effected by using **1** as the chiral ligand.

We first examined the reaction of (*Z*)-1,4-diacetoxy-2-butene (**2a**) with catechol in the presence of the Pd–**1** complex as catalyst and K_2CO_3 as a base (Table 1). The reaction was completed after 7 days and was moderately enantioselective (entry 1). Replacement of the

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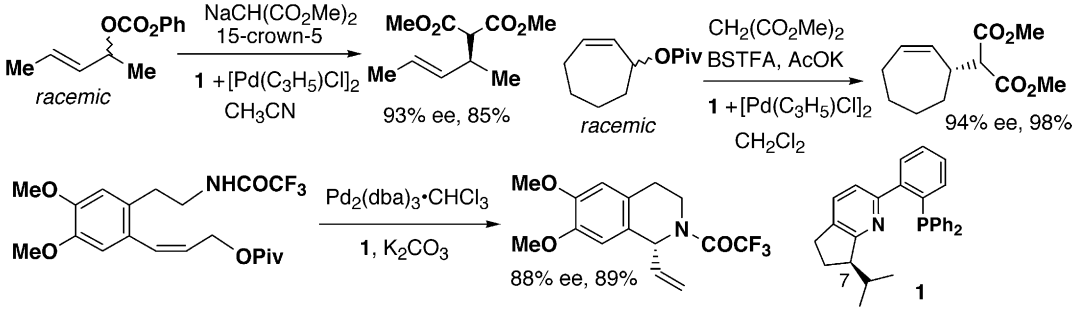
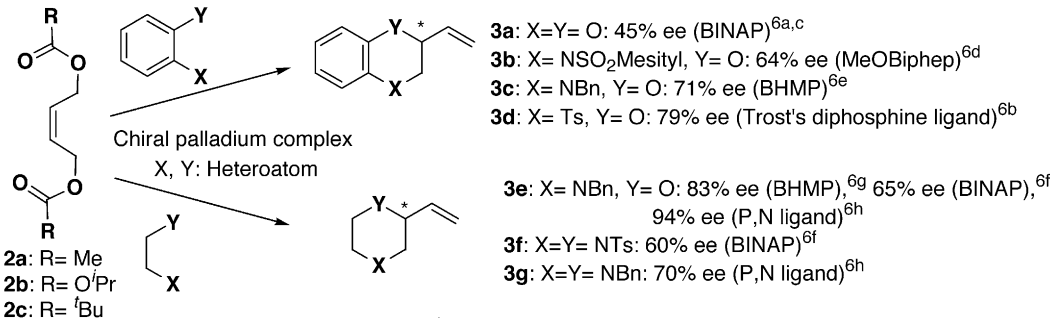


Scheme 1.



Scheme 2.

Table 1. Asymmetric PTAS of **2a–c** with catechol, giving **3a** as the product[a]

Entry	Substrate	Base	Time (d)	Yield (%)	%ee[b]	Confign[c]
1	**2a**	K_2CO_3	7	97	62	*R*
2	**2b**	K_2CO_3	19	65[d]	64	*R*
3	**2c**	K_2CO_3	8	74[d]	65	*R*
4	**2a**	Cs_2CO_3	1	91	24	*R*
5	**2a**	Na_2CO_3	—	—	—	—
6	**2a**	CsF	1	77	56	*R*
7	**2a**	KF	9	87	71	*R*
8[e]	**2a**	KF	14	17[d]	66	*R*
9	**2c**	KF	14	85	71	*R*

[a] All reactions were carried out in CH_2Cl_2 at room temperature with a **2**/catechol/base/$[Pd(C_3H_5)Cl]_2$/**1** molar ratio = 1:3:3:0.025:0.05, unless otherwise mentioned.
[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OJ-H; hexane–*i*-PrOH = 99.5:0.5).
[c] Absolute configuration was determined by chiroptical comparison with the published value (Ref. 6c).
[d] Reaction was not completed.
[e] Reaction was performed at 0 °C.

acetyl group in **2a** with an *i*-propoxycarbonyl (**2b**) or a pivaloyl group (**2c**) slowed the reaction, though the enantioselectivities were slightly improved (entries 2 and 3). Thus, the reaction conditions were optimized by using **2a** as the substrate. It is well known that the base affects the reaction rate and/or the enantioselectivity in allylic substitution. Thus, the effect of the base was next examined. Use of Cs_2CO_3 accelerated the reaction but adversely affected enantioselectivity (entry 4). On the other hand, use of Na_2CO_3 badly decelerated the reaction (entry 5). Use of CsF also accelerated the reaction but somewhat diminished enantioselectivity (entry 6). Use of an amine base such as triethylamine or Proton sponge® reduced the reaction rate seriously. Finally, the highest enantioselectivity of 71% ee was observed when KF was used as the base (entry 7).[7]

Lowering the reaction temperature to 0 °C diminished the enantioselectivity and the reaction rate (entry 8). We examined the reactions of **2b** and **2c** under the optimized conditions: the reaction of **2c** proceeded somewhat slowly with the same enantioselectivity as that of **2a** (entry 9), but that of **2b** was much slower.

The reaction using 2-(benzylamino)phenol was next examined with KF as the base (Table 2). The reaction of **2a** was fast but moderately enantioselective (entry 1). Fortunately, the reaction of **2b** proceeded smoothly

Table 2. Asymmetric PTAS of **2a–c** with other nucleophiles, giving **3c,e,g** as the products[a]

Entry	Substrate	Nucleophile	Product	Base	Time (h)	Yield (%)	%ee[b]	Confign
1	**2a**	2-(Benzylamino)phenol	**3c**	KF	24	98	66	*R*[c]
2	**2b**		**3c**	KF	24	89	72	*R*[c]
3[d]	**2b**		**3c**	KF	72	96	86	*R*[c]
4	**2c**		**3c**	KF	24	92	67	*R*[c]
5	**2b**		**3c**	K_2CO_3	144	72[e]	69	*R*[c]
6	**2a**	2-(Benzylamino)ethanol	**3e**	KF	24	67	69	*R*[f]
7	**2b**		**3e**	KF	48	51[e]	75	*R*[f]
8	**2c**		**3e**	KF	24	91	75	*R*[f]
9[d]	**2c**		**3e**	KF	72	74	81	*R*[f]
10	**2a**	1,2-Bis(benzylamino)ethane	**3g**	K_2CO_3	24	99	64	*R*[f]
11	**2a**		**3g**	KF	24	85	54	*R*[f]
12	**2b**		**3g**	K_2CO_3	24	88	80	*R*[f]
13[d]	**2b**		**3g**	K_2CO_3	72	88	86	*R*[f]
14	**2b**		**3g**	KF	24	81	76	*R*[f]
15	**2c**		**3g**	K_2CO_3	120	83	73	*R*[f]

[a] All reactions were carried out in CH_2Cl_2 at room temperature with a **2**/nucleophile/base/$[Pd(C_3H_5)Cl]_2$/**1** molar ratio = 1:3:3:0.025:0.05, unless otherwise mentioned.
[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH = 99:1).
[c] Absolute configuration was determined by chiroptical comparison with the published value (Ref. 6c).
[d] Reaction was performed at 0 °C.
[e] Reaction was not completed.
[f] Absolute configuration was determined by chiroptical comparison with the published value (Ref. 6f).

with improved enantioselectivity (entry 2). Lowering the reaction temperature to 0 °C further improved the enantioselectivity to 86% ee (entry 3). The reaction of **2c** also proceeded smoothly but the enantioselectivity was diminished (entry 4). The reaction of **2b** with K_2CO_3 was slow.

We also examined the reaction with 2-(benzylamino)ethanol (entries 6–9). Of **2a–c**, **2c** was the best substrate in terms of enantioselectivity and chemical yield. The reaction at 0 °C showed 81% ee.

The reactions of 1,2-bis(benzylamino)ethane were, however, the best effected with K_2CO_3 as the base and enantioselectivity of 80% ee was achieved when **2b** was used as the substrate (entry 12). Lowering the reaction temperature to 0 °C improved the enantioselectivity up to 86% ee (entry 13).

As discussed above, the best enantioselectivities ever have been achieved in three of the reactions of four different nucleophiles with **1** as the chiral ligand, except for the reaction of 2-(benzylamino)ethanol.[6h] We have designed **1** with the expectation that the 7-isopropyl group would direct inward to regulate the coordination sphere around the palladium ion efficiently and induce high asymmetry.[4] To clarify the structure of the Pd–**1** complex, we performed its X-ray analysis (Fig. 1).[8] Although the crystal of the $PdCl_2$–**1** complex possessed two molecules in a crystal lattice, their structural features are almost identical and the discussion is limited to one of them. The six-membered chelate ring adopts an envelope-like form and the palladium atom is out of the plane. One of the phenyl groups on the phosphorus atom, which is *cis* to the isopropyl group, occupies a pseudoaxial position, and the other occupies a pseudoequatorial one. The Pd–Cl bond *trans* to the P atom is longer than that *trans* to the N atom, reflecting the *trans* effects of the phosphorus and nitrogen atoms. These structural features are common to other P,N-ligand–Pd complexes.[9] However, the $PdCl_2$–**1** complex has the following unique features. The geometry around the palladium ion is a distorted square planar configuration, in which the Cl1 atom is located below the N–Pd–P plane. This distortion is probably caused by the repulsion between the Cl1 and the C7 atoms. One methyl group in

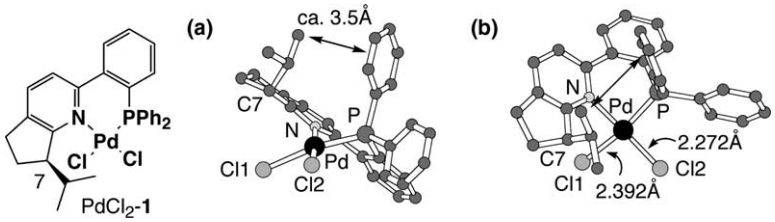
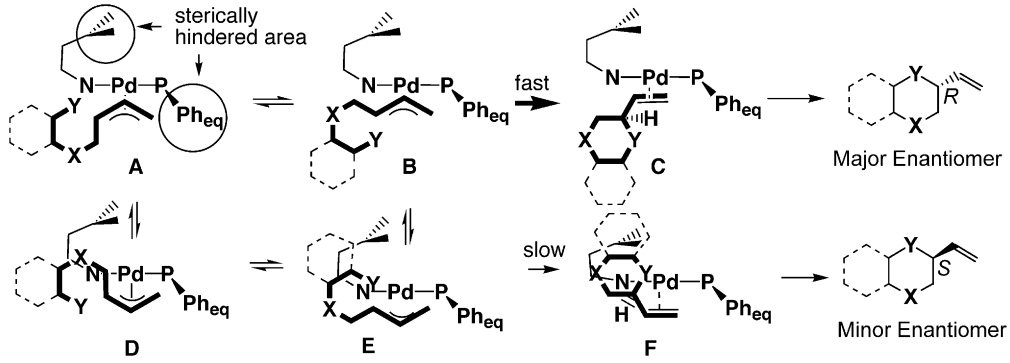


Figure 1. Structure of $PdCl_2$–**1** complex (hydrogen atoms are omitted for clarity). (a) Front view from chloro ligand; (b) top view from isopropyl group.



Scheme 3.

the isopropyl group is close to the pseudoaxial phenyl group at ca. 3.5 Å, probably due to an attractive CH–π interaction.[10] This directs the other methyl group over the Cl1 atom, constituting an asymmetric coordination sphere, as we expected (see also Scheme 3). This also explains why the isopropyl group is superior to other groups as the C7 substituent of **1**.[4]

PTAS is a four-step reaction:[5,6d,f] (i) oxidative addition; (ii) intermolecular allylic substitution at the terminal carbon; (iii) the second π-allyl palladium formation; and (iv) intramolecular ring formation giving a diheterocyclic compound. The final ring formation should be the step determining the stereochemistry. In the step, the possible diastereomeric π-allyl palladium complexes (**A**, **B**, **D**, and **E**) have been reported to be in a rapid equilibrium (Scheme 3).[1] A nucleophile has been reported to preferentially attack the carbon *trans* to the P-atom, reflecting the strong *trans*-effect of phosphorus.[1b] Furthermore, it has been proposed that the allyl system rotates in the direction causing less steric repulsion, when the nucleophile attacks the π-allyl complex to give a Pd(0)–olefin complex. Taking into account the above proposals[1b] together with the X-ray structure, the reaction is considered to give the *R*-isomer as the major product via **C**.

In conclusion, we have demonstrated that 2-(phosphinophenyl)pyridine **1** was an efficient chiral ligand for PTAS and discussed asymmetric induction by **1** based on the X-ray structure of $PdCl_2$–**1** complex.

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7. Typical experimental procedure was exemplified by asymmetric PTAS of **2a** and catechol: Allylpalladium(II) chloride dimer (1.3 mg, 3.6 μmol) and **1** (3.1 mg, 7.3 μmol) were dissolved in dichloromethane (1.5 mL) under nitrogen and stirred for 1 h at room temperature. Compound **2a** (25.0 mg, 0.145 mmol), catechol (16.0 mg, 0.145 mmol), and potassium fluoride (25.3 mg, 0.435 mmol) were successively added to the solution and stirred for 9 days at the temperature. The mixture was quenched with water and extracted with dichloromethane. The extract was dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (pentane–diethyl ether = 30:1) gave 2-vinyl-1,4-benzodioxane (20.4 mg, 87%) as an oil. Its ee was determined as described in the footnote to Table 1.
8. Crystallographic data for $PdCl_2$–**1**: Recrystallized from dichloromethane–ethyl acetate, $C_{29}H_{28}NPCl_2Pd$, M = 598.83, monoclinic, space group $P2_1$, a = 10.0767 Å, b = 18.5150 Å, c = 14.8170 Å, β = 102.3170°, V = 2700.7800 Å^3, Z = 4, Dc = 1.473 g cm^{-3}, μ(Mo-K$_\alpha$) = 7.107 cm^{-1}, *R1* = 0.0385, *wR2* = 0.1119 for 9006 reflections and 614 variables, GOF = 0.890. Data were collected

on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K_α at 20 °C. Structural analysis was performed using the teXsan crystallographic software package. The structure was solved by direct methods (SIR92) and expanded using Fourier techniques (DIRDIF94). Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were refined using the riding model. The Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 244644.

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