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Axially chiral *N*-alkyl-*N*-cinnamoyl amide type P, olefin ligands for Pd-catalyzed reactions†

Takashi Mino, *[a,b,c] Kaho Takaya,‡[a] Kaito Koki,‡[a] Natsume Akimoto,‡[a] Yasushi Yoshida, [a,b,c] Yoshio Kasashima[d] and Masami Sakamoto [a,b]

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We synthesized *N*-alkyl-*N*-cinnamoyl amide type phosphine–olefin compounds **1** and found axial chirality in a C(aryl)–N(amide) bond in compounds **1** by HPLC analysis using a chiral stationary phase column. We successfully obtained enantiomeric isomers of **1** and demonstrated the use of (−)-**1** for chiral ligands in Pd-catalyzed asymmetric allylic substitution reactions of allylic esters with indoles (up to 97% ee).

Introduction

The development of chiral ligands is significant for transition metal catalyzed reactions because the enantioselectivity in asymmetric induction depends on chiral ligand selection. Recently, new chiral ligands with axial chirality for the Pd-catalyzed asymmetric allylic substitution reaction of allylic esters with indoles were reported by several groups.[1] For example, the Zhou group reported a P,olefin type chiral ligand **L1**[2] with C(aryl)–C(aryl) bond axial chirality for this reaction (Fig. 1). We also recently reported *N*-alkyl-*N*-cinnamyl type chiral ligands **L2**[3] and **L3**[4] with C(aryl)–N(amine) bond axial chirality and an *N*-cinnamoyl amide type chiral ligand **L4**[5] with central chirality and C(aryl)–N(amide) bond axial chirality.

Related to investigations of ligands **L2** and **L3**, we are interested in P,olefin chiral ligands with the cinnamoyl group instead of the cinnamyl group. Here, we describe the synthesis of *N*-alkyl-*N*-cinnamoyl amides **1** with only C(aryl)–N(amide) bond axial chirality without a chiral center (Fig. 2) and their applications to chiral ligands for the Pd-catalyzed asymmetric allylic substitution reaction of allylic esters with indoles.

Results and discussion

N-Alkyl-*N*-cinnamoyl amides **1** were prepared from phosphine oxide **2** *via* reduction using trichlorosilane with triethylamine and *N*-acylation with cinnamoyl chloride in two steps (Scheme 1).

We analyzed amide compounds **1** by HPLC analysis using a chiral stationary phase column with a CD detector. Although we previously failed to find the axial chirality in the cinnamyl

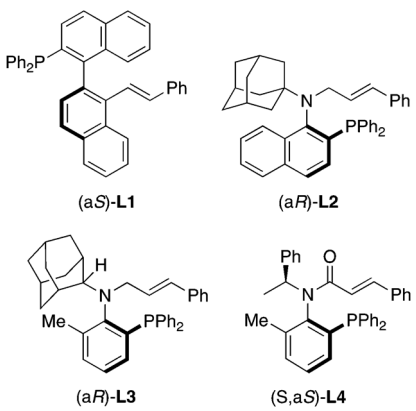

Fig. 1 Recently reported chiral ligands with axial chirality for Pd-catalyzed asymmetric allylic substitution reaction.

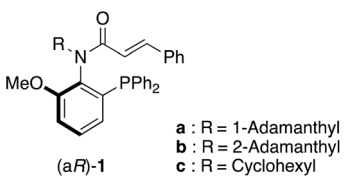

Fig. 2 *N*-Alkyl-*N*-cinnamoyl amides **1** with C–N bond axial chirality.

[a]*Graduate School of Engineering, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan. E-mail: tmino@faculty.chiba-u.jp*
[b]*Molecular Chirality Research Center, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan*
[c]*Soft Molecular Activation Research Center, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan*
[d]*Education Center, Chiba Institute of Technology, Shibazono 2-2-1, Narashino, Chiba 275-0023, Japan*

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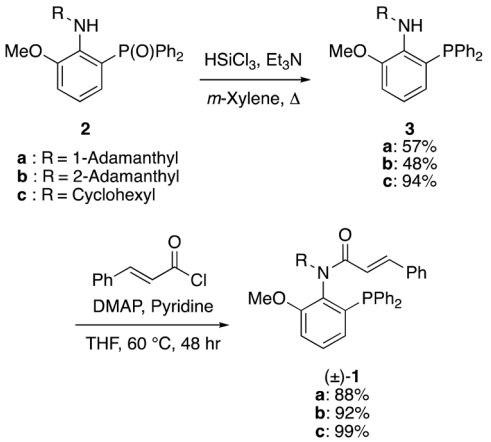
‡These authors contributed equally to this work.



Scheme 1 Preparation of cinnamoyl amide (±)-**1**.

type *N*-cyclohexylaniline compound,[4] we found that C(aryl)–N (amide) bond axial chirality exists in amide compounds **1** including *N*-cyclohexyl type compound **1c**. Next, we attempted the optical resolution of racemic compounds (±)-**1a–c** and obtained (+)-**1a–c** and (−)-**1a–c** using semi-preparative chiral HPLC on the 10 milligram scale (Scheme 2).

After the recrystallization of the optically active compound, we successfully performed the single-crystal X-ray analysis using (a*S*)-(+)-**1c** to determine the absolute configurations of **1** (Fig. 3).[6]

We also determined the racemization barriers in the axial chirality of **1a–c** in a dodecane solution. For compound **1a**, no racemization occurred in dodecane at 130 °C. On the other hand, we found that the racemization of **1b** and **1c** in dodecane occurred. We repeated this experiment at different temperatures and determined the rate constants (k_{rac}) at each temperature (see the ESI†). The rotational barrier ($\Delta G^{\ddagger}_{rac}$) of **1b** in dodecane was 27.3 kcal mol^{-1} at 25 °C (Table 1), based on Arrhenius and Eyring equations.[7] Although the half-life of *N*-cinnamyl type compound **L3** is approximately only 3 days,[4] the half-life of **1b** is about 64 days in dodecane at 25 °C. We also found that the half-life of **1c**, which has a less hindered alkyl group on a nitrogen atom than **1b**, is about 3 days at 25 °C.

We next investigated the ability of the optically active cinnamoyl amides **1** to function as chiral ligands for the Pd-catalyzed asymmetric allylic substitution reactions of allylic acetates, such as 1,3-diphenyl-2-propenyl acetate, with indoles.[1] The reaction with indole was performed using 3 mol% of [Pd(C_3H_5)Cl]$_2$ and 6 mol% of ligands **1** as a model reaction (Table 1). The reaction using (−)-**1a** as a ligand and 2 equiv. of K_2CO_3 in MeCN at 40 °C for 18 h gave the corresponding product (*S*)-**4a** in 70% yield with 88% ee (entry 1). The reaction using (−)-**1b** and (a*R*)-(−)-**1c**, respectively, gave an (*S*)-product with 82% ee and 91% ee (entries 2 and 3). We found that (a*R*)-(−)-**1c** was the best ligand among chiral ligands **1a–c**. Next, we changed the base and used other bases instead of K_2CO_3 in MeCN (entry 3 *vs.* entries 4–7). Using KOAc as a base, the enantioselectivity of (*S*)-**4a** decreased to 52% ee (entry 4). When the reaction was carried out with Cs_2CO_3, the corresponding product (*S*)-**4a** was obtained with good enantioselectivity (92% ee) and 73% yield (entry 7). When the reaction was carried out with Cs_2CO_3 using $Pd_2(dba)_3$·$CHCl_3$ instead of [Pd(C_3H_5)Cl]$_2$, the enantioselectivity of (*S*)-**4a** decreased to 87% ee (entry 8). We next investigated the effect of solvents using (a*R*)-(−)-**1c** with Cs_2CO_3 (entries 7, 9–12). Using EtOAc, DCM

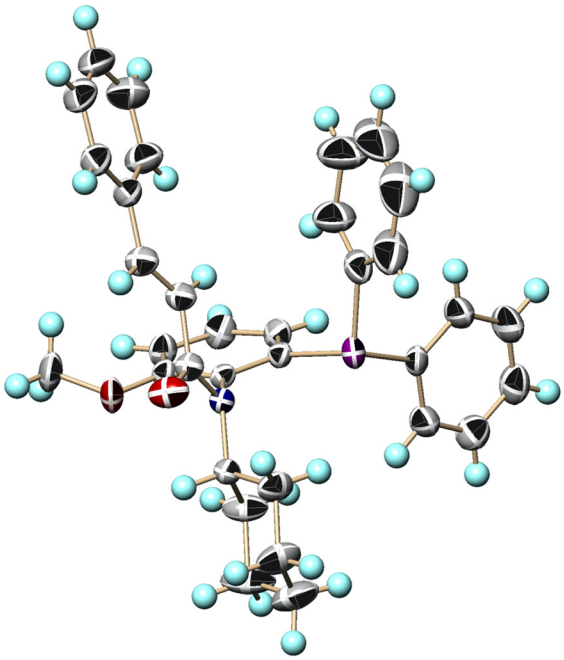
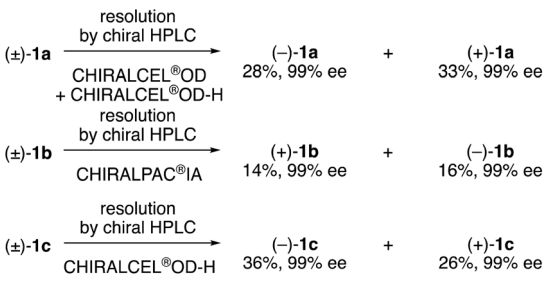


Fig. 3 X-ray structure of (a*S*)-(+)-**1c** (CCDC 2227386†). Ellipsoids are shown at the 50% probability level.

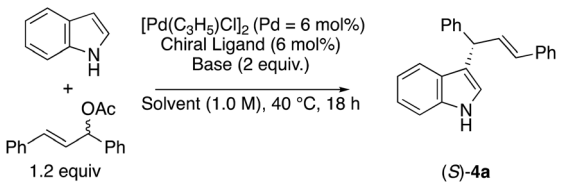
Table 1 Racemization parameters of **1b** and **1c**

Thermodynamic parameters in dodecane at 25 °C	**1b**	**1c**
Half-life (days)	64.3	3.72
K_{rac}	6.24×10^{-2}	1.08
ΔH (kcal mol^{-1})	16.8	24.0
ΔS (cal mol^{-1} K)	−35.2	−5.40
$\Delta G^{\ddagger}_{rac}$ (kcal mol^{-1})	27.3	25.6



Scheme 2 Optical resolution of (±)-**1** by semi-preparative chiral HPLC.

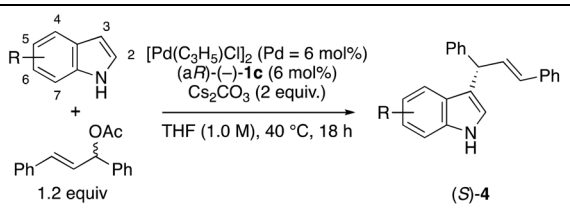
Table 2 Optimization of the Pd-catalyzed asymmetric allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate with indole[a]



Entry	Chiral ligand	Base	Solv.	Yield[b] (%)	ee[c]
1	(−)-**1a**	K_2CO_3	MeCN	70	88
2	(−)-**1b**	K_2CO_3	MeCN	67	82
3	(a*R*)-(−)-**1c**	K_2CO_3	MeCN	74	91
4	(a*R*)-(−)-**1c**	KOAc	MeCN	80	52
5	(a*R*)-(−)-**1c**	K_3PO_4	MeCN	69	88
6	(a*R*)-(−)-**1c**	Na_2CO_3	MeCN	76	74
7	(a*R*)-(−)-**1c**	Cs_2CO_3	MeCN	73	92
8[d]	(a*R*)-(−)-**1c**	Cs_2CO_3	MeCN	69	87
9	(a*R*)-(−)-**1c**	Cs_2CO_3	PhMe	87	86
10	(a*R*)-(−)-**1c**	Cs_2CO_3	EtOAc	60	89
11	(a*R*)-(−)-**1c**	Cs_2CO_3	DCM	74	91
12	(a*R*)-(−)-**1c**	Cs_2CO_3	$PhCF_3$	66	90
13	**(a*R*)-(−)-1c**	**Cs_2CO_3**	**THF**	**69**	**97**

[a] The reactions were carried out on a 0.2 mmol scale of indole in various solvents (0.2 mL) at 40 °C with 1.2 equiv. of 1,3-diphenyl-2-propenyl acetate and 2 equiv. of base, in the presence of a chiral ligand (6 mol%) and $[Pd(C_3H_5)Cl]_2$ (3 mol%; Pd = 6 mol%). [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] This reaction was carried out using $Pd_2(dba)_3{\cdot}CHCl_3$ instead of $[Pd(C_3H_5)Cl]_2$.

Table 3 Pd-catalyzed asymmetric allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate with indoles using the chiral ligand (a*R*)-(−)-**1c**[a]

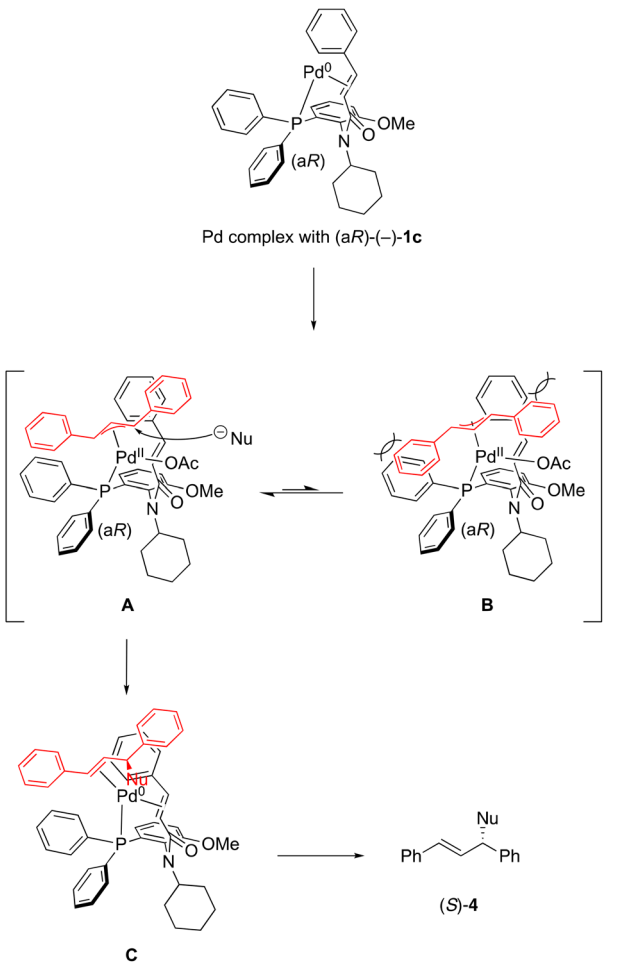


Entry	*R*	Yield[b] (%)	ee[c] (%)
1	H	69 (**4a**)	97
2	6-Br	70 (**4b**)	90
3	6-Cl	70 (**4c**)	93
4	6-F	72 (**4d**)	93
5	6-MeO	71 (**4e**)	72
6	6-BnO	77 (**4f**)	87
7	6-NO_2	26 (**4g**)	76
8	6-Me	34 (**4h**)	87
9	7-Br	64 (**4i**)	83
10	5-Br	60 (**4j**)	91
11	4-Br	68 (**4k**)	95
12	5-MeO	78 (**4l**)	91
13	2-Ph	88 (**4m**)	92

[a] The reactions were carried out on a 0.2 mmol scale of indole derivative in THF (0.2 mL) at 40 °C with 1.2 equiv. of 1,3-diphenyl-2-propenyl acetate and 2 equiv. of Cs_2CO_3, in the presence of (a*R*)-(−)-**1c** (6 mol%) and $[Pd(C_3H_5)Cl]_2$ (3 mol%; Pd = 6 mol%). [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column.

(dichloromethane), or $PhCF_3$ (benzotrifluoride) as a solvent instead of acetonitrile, we obtained the product (*S*)-**4a** with a similar level of enantioselectivities (89–91% ee) (entries 10–12). When the reaction was carried out using THF as a solvent, the corresponding product (*S*)-**4a** was obtained with the highest enantioselectivity (97% ee) and a good yield (69%) (entry 13).

With the optimized reaction conditions in hand (Table 2, entry 13), we examined the scope of the allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate with various substituted indoles using (a*R*)-(−)-**1c** in THF with Cs_2CO_3 at 40 °C (Table 3). The reactions with 6-halogenated indoles gave the corresponding products (*S*)-**4b–d** in high enantioselectivities (90–93% ee) (entries 2–4). Although the reactions using 6-nitroindole and 6-methylindole gave the products (*S*)-**4g** and (*S*)-**4h** in low yields (entries 7 and 8), the reaction with 6-methoxyindole and 6-benzyloxyindole, respectively, gave the corresponding products (*S*)-**4e** and **4f** in good yields with moderate to good enantioselectivities such as 72% ee and 87% ee (entries 5 and 6). The reaction of 7-bromoindole gave the corresponding product (*S*)-**4i** in good yield with 83% ee (entry 9). The reaction with 2-, 4-, or 5-substituted indoles also gave



Scheme 3 The possible stereochemical pathway.

the corresponding products (*S*)-**4i–m** with high enantioselectivities (entries 10–13).

According to the observed stereochemical outcome and our previous reports,[4,5] we propose a possible stereochemical pathway for the formation of (*S*)-**4** as a product. As shown in Scheme 3, Pd^{II} complexes such as W-type **A** and M-type **B** intermediates were formed from ligand (a*R*)-(−)-**1c**. Pd^{II} complex **A** was favored more than complex **B** due to a steric effect. The indole anion as a nucleophile would preferentially attack the carbon at the trans position to the phosphorus of (a*R*)-(−)-**1c** from outside.[8] Finally, the (*S*)-product **4** was obtained from Pd^{0} complex **C**.

Conclusions

We synthesized racemic *N*-alkyl-*N*-cinnamoyl amides (±)-**1a–c** from phosphine oxide **2** in two steps and successfully obtained enantiomeric isomers of **1a–c** with C(aryl)–N(amide) bond axial chirality by optical resolution using semi-preparative chiral HPLC. We also found that the optically active compound **1c** is an effective chiral ligand for the Pd-catalyzed asymmetric allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate with indoles in high enantioselectivities (up to 97% ee).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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