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Catalytic asymmetric arylation of *N*-substituted 2-pyrrolines with aryl triflates *

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Abstract

Catalytic asymmetric arylation of 1-(alkoxycarbonyl)-2-pyrrolines (**4**) with aryl triflates (**1**) in benzene in the presence of a base and a palladium catalyst, prepared *in situ* by mixing $Pd(OAc)_2$ and (*R*)-BINAP, gives optically active (*R*)-1-(alkoxycarbonyl)-5-aryl-2-pyrrolines (**5**) of up to 83% ee, together with the regioisomers 1-(alkoxycarbonyl)-5-aryl-3-pyrrolines (**6**).

Introduction

Heck-type arylation and alkenylation of olefins are versatile synthetic means for making a C–C bond [1,2]. Recently, we and other groups showed that such reactions may be made enantioselective by the use of chiral palladium catalysts [3–5]. Shibasaki and Overman independently reported an asymmetric intramolecular cyclization affording key intermediates for synthesis of natural products [3,4]. In addition, we reported a highly enantioselective intermolecular arylation of 2,3-dihydrofuran promoted by a (*R*)-BINAP-coordinated palladium catalyst, generated *in situ* from $Pd(OAc)_2$ and (*R*)-BINAP [6**], giving (*R*)-2-aryl-2,3-dihydrofuran (**2**) of over 90% ee together with a minor amount of (*S*)-2-aryl-2,5-dihydrofuran (**3**) (eq. 1) [5]. In the latter reaction, use of aryl triflates (aryl trifluoromethanesulfonates) (**1**) as arylating reagents is essential for enantioselectivity to exceed 90% ee. The use of aryl iodides instead of aryl triflates in a similar arylation system gave rise to racemic products.

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* Dedicated to our respected mentor Professor Akio Yamamoto on his retirement from the Tokyo Institute of Technology and in honor of his important contributions to organometallic chemistry.

** Reference number with asterisk indicates a note in the list of references.

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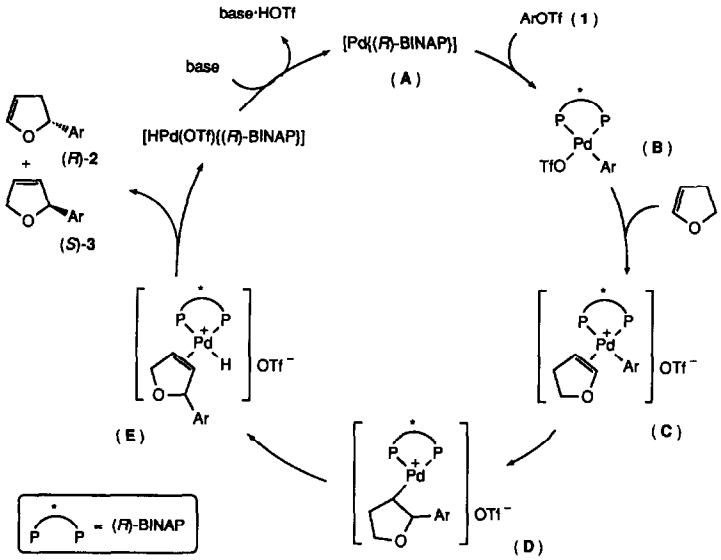
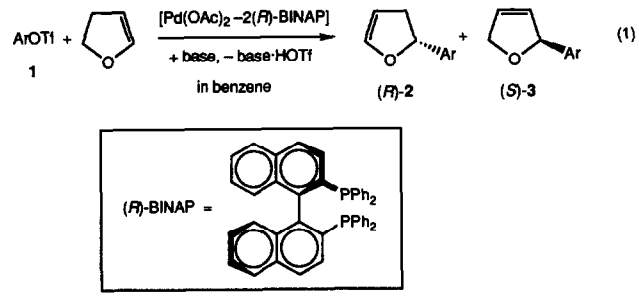


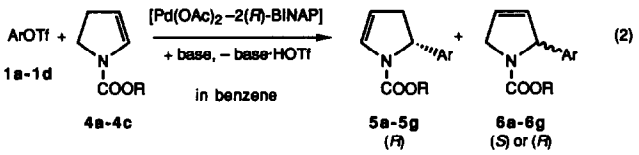
Scheme 1.



A catalytic process involving a four-coordinated cationic arylpalladium(II) olefin complex (**C**) as a key intermediate has been proposed to account for the high enantioselectivity with aryl triflates (Scheme 1). Oxidative addition of aryl triflate to a Pd^0-(*R*)-BINAP species (**A**) gives an arylpalladium complex (**B**). Coordination of 2,3-dihydrofuran on **B** gives **C**. Insertion of the dihydrofuran ligand into the Pd–Ar bond in **C** gives a σ-alkylpalladium intermediate (**D**), which subsequently undergoes a β-hydrogen elimination reaction to give a 2-aryl-2,5-dihydrofuran-coordinated palladium hydride species (**E**). Dissociation of the coordinated olefin from **E** gives 2-aryl-2,5-dihydrofuran (**3**), whereas insertion of the olefin into the Pd–H bond in **E**, followed by β-hydrogen elimination of the resulting σ-alkylpalladium species forms the thermodynamically more stable 2-aryl-2,3-dihydrofuran (**2**).

In the catalytic process in Scheme 1, the triflate ligand in **B** is a good leaving group which may easily be replaced by the olefin, giving the cationic intermediate **C**, which has a 16-electron square planar structure, convenient for the subsequent enantioselective olefin insertion [7*].

In this paper, we report that the above catalytic system using aryl triflates as arylating reagents can be applied to enantioselective arylation of *N*-substituted



1a: Ar = *p*-ClC$_6$H$_4$
1b: Ar = Ph
1c: Ar = *p*-AcC$_6$H$_4$
1d: Ar = *p*-NCC$_6$H$_4$

4a: R = Me
4b: R = Et
4c: R = Ph

5a, 6a: Ar = *p*-ClC$_6$H$_4$, R = Me
5b, 6b: Ar = *p*-ClC$_6$H$_4$, R = Et
5c, 6c: Ar = *p*-ClC$_6$H$_4$, R = Ph
5d, 6d: Ar = Ph, R = Me
5e, 6e: Ar = Ph, R = Ph
5f, 6f: Ar = *p*-AcC$_6$H$_4$, R = Me
5g, 6g: Ar = *p*-NCC$_6$H$_4$, R = Me

2-pyrrolines to give optically active 5-aryl-2-pyrroline derivatives, which have a structure that can be further elaborated to give optically active pyrrolidine alkaloids [8,9*].

Results and discussion

Catalytic asymmetric arylation

Reaction of aryl triflates (**1**) with 1-(alkoxycarbonyl)-2-pyrrolines (**4**) in benzene in the presence of tertiary or secondary amine as a base and a palladium catalyst, prepared *in situ* by mixing $Pd(OAc)_2$ and 2 equivalents of (*R*)-BINAP, gave optically active (*R*)-1-(alkoxycarbonyl)-5-aryl-2-pyrrolines (**5**) together with the regioisomers 1-(alkoxycarbonyl)-5-aryl-3-pyrrolines (**6**) (eq. 2). Compounds **5** and **6** were isolated by medium-pressure liquid chromatography and characterized by IR and NMR spectroscopy and/or high resolution mass spectrometry. The enantiomeric purities of **5** and **6** were determined by HPLC using a chiral stationary phase column (Sumipax OA-2000).

The use of 2 equiv./Pd of (*R*)-BINAP ligand is important for the catalytic reaction to succeed. The reaction did not take place with a palladium catalyst generated from $Pd(OAc)_2$ and an equimolar amount of (*R*)-BINAP. It is also noted that treatment of the catalyst precursors (*i.e.*, $Pd(OAc)_2$ and 2 equivalents of (*R*)-BINAP) with amine prior to the catalytic reaction is of particular importance for the generation of an active catalyst. Thus, on treatment of a mixture of palladium diacetate and 2 equivalents of (*R*)-BINAP in benzene with amine at 40–60°C the solution changed gradually from yellow to red. This red solution contains the catalytically active species. We recently confirmed that this color change corresponds to conversion of $Pd(OAc)_2$\{(*R*)-BINAP\} into a (*R*)-BINAP-coordinated Pd^0 species that is active in the catalytic reaction [10].

Benzene was among the most suitable solvents examined. The reaction performed in THF proceeded more slowly than that in benzene and the enantiomeric purity of major product **5** was low [11*]. The reaction did not proceed in DMF or 1,2-dichloroethane as a solvent.

Table 1 summarizes the results of the catalytic reactions with *p*-chlorophenyl triflate (**1a**) under various reaction conditions. The major product **5** was obtained as the (*R*) isomer of relatively high enantiomeric purity in every run, whereas the

Table 1

Catalytic asymmetric arylation of *N*-substituted 2-pyrrolines (**4**) with *p*-chlorophenyl triflate (**1a**) promoted by $Pd(OAc)_2$–(*R*)-BINAP catalyst [a]

Run	Substrate (**4**) (*N*-substituent)	Base [b]	Reaction temp. (°C)	Reaction time (h)	**5**/**6**	% ee [c] (config) (yield/%) [d]	
						5	**6**
1	**4a** (COOMe)	Et_3N	40	72	86/11	66 (*R*) (74)	11 (*S*) (12)
2	**4a** (COOMe)	$^iPr_2NEt$	50	33	85/15	67 (*R*) (72)	12 (*S*) (13)
3	**4a** (COOMe)	Cy_2NH	50	33	80/20	70 (*R*) (69)	8 (*S*) (17)
4	**4a** (COOMe)	$^iPr_2NH$	50	48	75/25	69 (*R*) (65)	12 (*S*) (22)
5	**4a** (COOMe)	proton sponge	50	61	56/44	83 (*R*) (19) [e]	4 (*R*) (15)
6	**4b** (COOEt)	Cy_2NH	50	48	76/24	69 (*R*) (65)	13 (*S*) (20)
7	**4c** (COOPh)	Cy_2NH	50	72	62/38	76 (*R*) (52)	7 (*R*) (32)

[a] The reaction was carried out in benzene under nitrogen. Initial conditions: **1a**/**4**/base/$Pd(OAc)_2$/BINAP = 1/5/3.3/0.03/0.06. [b] Cy_2NH: dicyclohexylamine. Proton sponge: 1,8-bis(dimethylamino)naphthalene. [c] Determined by HPLC. Optical rotations of the products are reported in Experimental section. [d] Isolated yield at 100% conversion of ArOTf unless otherwise noted. [e] 58% of ArOTf was recovered unreacted.

enantiomeric purity of regioisomer **6** was low and its absolute configuration changed with the base and the *N*-substituent of the starting pyrroline.

The relative ratio of **5** to **6** was affected by the base and the *N*-substituent. Thus, (a) amines of higher bulkiness gave higher selectivity for **6** (runs 1, 2 and 5); (b) aliphatic tertiary amines tended to give higher ratio of **5** than secondary amines (runs 1–4); and (c) alkyl carbamates **4a** and **4b** formed **5** in higher selectivity than phenyl carbamate **4c** (runs 3, 6 and 7) [12*]. It should be noted that increasing the product ratio of **6** tended to increase the enantiomeric purity of major product **5**.

Table 2 shows the results of catalytic reactions with several aryl triflates. Under appropriate conditions, 5-aryl-2-pyrroline derivatives **5** of around 70% ee were obtained in good yields.

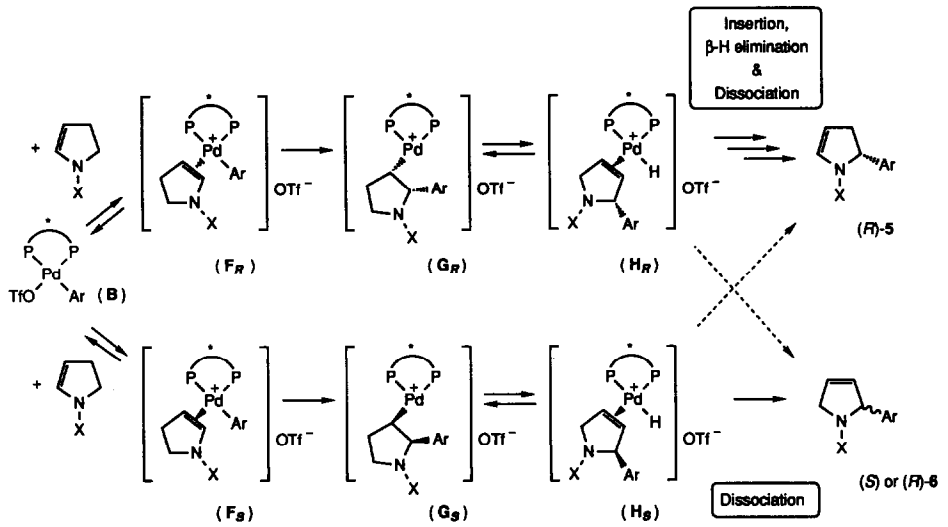
In our previous studies on the asymmetric arylation of 2,3-dihydrofuran (eq. 1) [5], we pointed out that a kinetic resolution process, that enhances the enantiomeric purity of major product (*R*)-**2** by selective elimination of (*S*)-arylation product as the minor isomer (*S*)-**3** from the catalytic cycle, is operative in the

Table 2

Catalytic asymmetric arylation of *N*-substituted 2-pyrrolines (**4**) with aryl triflate (**1**) promoted by $Pd(OAc)_2$–(*R*)-BINAP catalyst [a]

Substrates		Base [b]	Reaction temp. (°C)	Reaction time (h)	Products [% ee] [c] (yield/%) [d]	
1	**4**				**5**	**6**
1a	**4c**	$^iPr_2NEt$	60	48	(*R*)-**5c** [74] (68)	(*R*)-**6c** [10] (27)
1b	**4a**	Cy_2NH	50	41	(*R*)-**5d** [64] (81)	(*S*)-**6d** [28] (14)
1b	**4c**	$^iPr_2NEt$	60	144	(*R*)-**5e** [73] (45)	(*R*)-**6e** [29] (44)
1c	**4a**	Cy_2NH	50	39	(*R*)-**5f** [70] (70)	(*S*)-**6f** [11] (27)
1d	**4a**	Cy_2NH	50	48	(*R*)-**5g** [68] (69)	**6g** [e] (22)

[a] The reaction was carried out in benzene under nitrogen. Initial conditions: **1**/**4**/base/$Pd(OAc)_2$/BINAP = 1/5/3.3/0.03/0.06. [b] Cy_2NH: dicyclohexylamine. [c] Determined by HPLC. Optical rotations of the products are reported in Experimental section. [d] Isolated yield at 100% conversion of ArOTf. [e] Not measured.



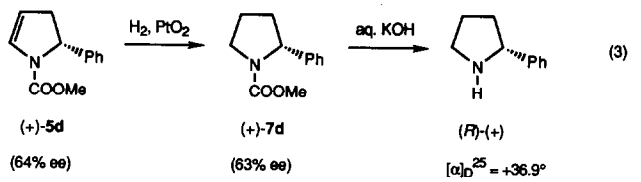
Scheme 2.

catalytic reaction. Thus, the enantiomeric purity of (*R*)-**2** increases as the product ratio of minor isomer (*S*)-**3** increases. This kinetic resolution takes place at the step where the products are released from intermediate **E** in Scheme 1. In the present reaction with 2-pyrroline derivatives, a similar relation has been observed between the enantiomeric purity of major product (*R*)-**5** and the product ratio of minor regioisomer **6** (runs 1–5, Table 1), suggesting a similar kinetic resolution process in the present system as well.

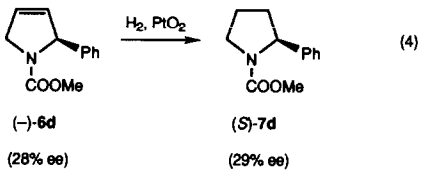
The present asymmetric arylation of *N*-substituted pyrrolines (**4**) must follow a similar catalytic cycle to that in Scheme 1. As illustrated in Scheme 2, coordination of 2-pyrroline on arylpalladium intermediate **B** forms two types of olefin-coordinated complexes, $\mathbf{F}_R$ and $\mathbf{F}_S$, depending upon the selection of enantiofaces of olefin. Both complexes undergo the subsequent olefin-insertion and β-hydrogen elimination reactions, giving a pair of diastereomers of hydridopalladium species having (*R*)-5-aryl-3-pyrroline and (*S*)-5-aryl-3-pyrroline ligands, $\mathbf{H}_R$ and $\mathbf{H}_S$, respectively. Molecular inspection using CPK models suggested that $\mathbf{H}_R$ has a more favorable structure for further olefin-insertion and β-hydrogen elimination reactions giving 5-aryl-2-pyrroline derivative **5** having (*R*) configuration. In contrast, $\mathbf{H}_S$ suffers considerable steric repulsion between the coordinated olefin and one of the phenyl groups in the BINAP ligand. Consequently, $\mathbf{H}_S$ is prone to release the coordinated 5-aryl-3-pyrroline **6**, as compared with $\mathbf{H}_R$. The overall process results in enhanced enantiomeric purity of the major product (*R*)-**5**. For example, based on the product ratio of **5** to **6** and the enantiomeric purities of both compounds, the ratio of $\mathbf{H}_R$ to $\mathbf{H}_S$ in the catalytic system of run 1 in Table 2 may be calculated as 78:22. Therefore, if both intermediates $\mathbf{H}_R$ and $\mathbf{H}_S$ afforded the same regioisomer **5** without formation of **6**, the catalytic reaction should give (*R*)-**5** of 56% ee, lower than 74% ee observed in the actual catalytic system.

Determination of absolute configurations

The configuration of the phenylation product (+)-**5d** was determined to be (*R*), by converting it into known (*R*)-(+)-2-phenylpyrrolidine (eq. 3) [13]. On the other



(3)



(4)

hand, hydrogenation of (−)-**6d** of 28% ee gave 1-(methoxycarbonyl)-2-phenylpyrrolidine (**7d**) of 29% ee, which has the opposite configuration to (*R*)-(+)-**7d** derived from (*R*)-(+)-**5d** as confirmed by HPLC using a chiral stationary phase column (eq. 4).

Similarly, phenyl carbamate (+)-**5e** was converted into (*R*)-(+)-2-phenylpyrrolidine. Hydrogenation of (+)-**5e** and (+)-**6e** gave (*R*)-(+)-1-(phenoxycarbonyl)-2-phenylpyrrolidine with the same absolute configuration.

The absolute configurations of other arylation products **5a–5c**, **5f**, **5g**, **6a–6c**, **6f**, and **6g** were assigned on the basis of the assumption that the elution order of enantiomers in HPLC using a chiral stationary phase column (Sumipax OA-2000) is the same as that of the phenylation products **5d**, **5e**, **6d**, and **6e**, for which the (*R*) enantiomer is eluted prior to the (*S*) enantiomer.

Conclusion

We have confirmed in this study that the catalytic system with aryl triflates as arylating reagents is efficient in the asymmetric arylation of *N*-substituted pyrrolines to give optically active 5-aryl-2-pyrroline derivatives. A catalytic cycle has been suggested that involves a novel kinetic resolution process enhancing the enantiomeric purity of the major regioisomer. A similar catalytic mechanism involving a kinetic resolution process may operate in related catalytic asymmetric Heck reactions of cyclic olefins.

Experimental section

General

All manipulations were carried out under nitrogen using conventional Schlenk techniques. ^{1}H NMR spectra were measured on a JEOL JNM-EX90 spectrometer. Chemical shifts are reported in δ ppm referred to $SiMe_4$ as an internal standard. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Perkin Elmer 1720X FT-IR spectrometer. High resolution mass spectra were measured on a JEOL JMS-DX-303 spectrometer at an ionization voltage of 70 eV. Enantiomeric purities were determined by HPLC using a

Shimadzu LC-9A system, equipped with a chiral stationary phase column (Sumipax OA-2000) and a UV detector. Preparative medium-pressure liquid chromatography (MPLC) was performed with a prepacked silica gel column (Kusano C.I.G. Si-10, 22 $\phi \times 300$ mm). GLC was carried out on a Shimadzu GC-7AG instrument, equipped with a FID detector and a 1-m glass-made column (3 ϕ) of 5% Silicone OV-1 on Chromosorb WAW DMCS.

Materials

Aryl triflates (**1a–1d**) and *N*-substituted 2-pyrrolines (**4a–4c**) were prepared by the reported methods [14,15]. Amines were obtained from commercial sources and used without further purification. Palladium diacetate was purchased from Johnson Matthey and purified by recrystallization from hot benzene. (*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl ((*R*)-BINAP) (Kanto Chemical) was used without further purification. THF and benzene were dried over sodium benzophenone ketyl and distilled just before using. 1,2-Dichloroethane was dried over CaH_2, distilled, and stored under nitrogen. *N*,*N*-Dimethylformamide was dried over a 4 A Molecular Sieve.

Asymmetric arylation of N-*substituted pyrrolines*

General procedure. A mixture of $Pd(OAc)_2$ (4.5 mg, 0.020 mmol), (*R*)-BINAP (26.6 mg, 0.043 mmol), and $^iPr_2NEt$ (0.35 mL, 2.0 mmol) in benzene (1 mL) was stirred at 60°C for 10 h. The initially yellow solution turned red. Benzene (5 mL), *p*-chlorophenyl triflate (0.156 g, 0.597 mmol) and 1-(phenoxycarbonyl)-2-pyrroline (0.567 g, 3.0 mmol) were added, and the homogeneous red mixture was stirred at 60°C until the reaction was complete (48 h). The completion was checked by GLC. Evaporation of the solvent gave a red oil, which was subjected to MPLC (silica gel; hexane/EtOAc = 3/1) to give 108 mg (68% yield) of (*R*)-(+)-1-(phenoxycarbonyl)-5-(4-chlorophenyl)-2-pyrroline (**5c**) (74% ee, $[\alpha]_D^{25}$ +97.9° (*c* 0.85, $CHCl_3$) and 44 mg (27% yield) of (*R*)-(+)-1-(phenoxycarbonyl)-5-(4-chlorophenyl)-3-pyrroline (**6c**) (10% ee, $[\alpha]_D^{25}$ +24.6° (*c* 1.28, $CHCl_3$)).

The reaction conditions and results are summarized in Tables 1 and 2. Enantiomeric purities of the reaction products were determined by HPLC (Sumipax OA-2000; hexane/$ClCH_2CH_2Cl$/EtOH = 300/20/1; flow rate = 1.0 mL/min; UV detector, 230 nm; column temperature = 37°C). The data for HPLC (retention time in min) are reported below, together with the spectroscopic and optical rotation data.

(R)-(+)-1-(methoxycarbonyl)-5-(4-chlorophenyl)-2-pyrroline (5a) (69% ee): $[\alpha]_D^{25}$ +109° (*c* 0.46, $CHCl_3$). HPLC: 13.6 (*R*), 16.1 (*S*). IR: 1708, 1623, and 1386 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.48 (dddd, J = 16.7, 4.4, 2.9, and 2.0 Hz, 1H, C(*H*)H), 3.26 (ddt, J = 16.7, 11.0, and 2.4 Hz, 1H, C(*H*)H), 3.64 (br, 3H, OCH_3), 5.04 (dt, J = 4.2 and 2.4 Hz, 1H, C*H*=CHN), 5.11 (dd, J = 11.0 and 4.4 Hz, 1H, NCH), 6.70 (br, 1H, NC*H*=CH), 7.24 (m, 4H, Ar). HRMS: calcd. for $C_{12}H_{12}NO_2Cl$, 237.0556; found, 237.0539.

(S)-(−)-1-(methoxycarbonyl)-5-(4-chlorophenyl)-3-pyrroline (6a) (12% ee): $[\alpha]_D^{25}$ −34.5° (*c* 0.77, $CHCl_3$). HPLC: 19.7 (*R*), 22.0 (*S*). IR: 1704, 1624, and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.57 and 3.67 (both s, *ca.* 1.5H each, OCH_3), 4.33 (br, 2H, NCH_2), 5.48 (br, 1H, NCH), 5.72 (br,d, J = 6.4 Hz, 1H, C*H*=CH), 5.92 (dq, J = 6.4 and 1.8 Hz, 1H, CH=C*H*), 7.25 (m, 4H, Ar). HRMS: calcd. for $C_{12}H_{12}NO_2Cl$, 237.0556; found, 237.0534.

*(R)-(+)-1-(ethoxycarbonyl)-5-(4-chlorophenyl)-2-pyrroline (**5b**) (69% ee):* $[\alpha]_D^{25}$ +94.8° (*c* 0.67, $CHCl_3$). HPLC: 12.0 (*R*), 13.3 (*S*). IR: 1705, 1623, and 1383 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9–1.4 (br, 3H, OCH_2CH_3), 2.49 (dddd, J = 16.9, 4.4, 2.9, and 2.0 Hz, 1H, C(*H*)H), 3.26 (ddt, J = 16.9, 11.7, and 2.2 Hz, 1H, C(*H*)H), 3.9–4.3 (br, 2H, OCH_2), 5.04 (dt, J = 4.2 and 2.9 Hz, 1H, C*H*=CHN), 5.10 (dd, J = 11.7 and 4.4 Hz, 1H, NCH), 6.74 (br, 1H, NC*H*=CH), 7.25 (m, 4H, Ar). HRMS: calcd. for $C_{13}H_{14}NO_2Cl$, 251.0713; found, 251.0702.

*(S)-(−)-1-(ethoxycarbonyl)-5-(4-chlorophenyl)-3-pyrroline (**6b**) (13% ee):* $[\alpha]_D^{25}$ −19.5° (*c* 0.43, $CHCl_3$). HPLC: 17.0 (*R*), 17.8 (*S*). IR: 1701, 1624, and 1384 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.04 and 1.24 (both t, J = 7.3 Hz, *ca.* 1.5H each, OCH_2CH_3), 4.01 and 4.09 (both q, J = 7.3 Hz, *ca.* 1H each, OCH_2), 4.34 (br, 2H, NCH_2), 5.46 (br, 1H, NCH), 5.72 (br,d, J = 7 Hz, 1H, C*H*=CH), 5.93 (br,d, J = 7 Hz, 1H, CH=C*H*), 7.26 (m, 4H, Ar). HRMS: calcd. for $C_{13}H_{14}NO_2Cl$, 251.0713; found, 251.0685.

*(R)-(+)-1-(phenoxycarbonyl)-5-(4-chlorophenyl)-2-pyrroline (**5c**) (74% ee):* $[\alpha]_D^{25}$ +97.9° (*c* 0.86, $CHCl_3$). HPLC: 17.4 (*R*), 18.9 (*S*). IR: 1723, 1624, and 1394 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.59 (br,d, J = 17 Hz, 1H, C(*H*)H), 3.36 (br,dd, J = 17 and 11 Hz, 1H, C(*H*)H), 5.18 (dt, J = 4.4 and 2.6 Hz, 1H, C*H*=CHN), 5.28 (br, 1H, NCH), 6.85 (m, 1H, NC*H*=CH), 6.7–7.4 (m, 9H, Ar). HRMS: calcd. for $C_{17}H_{14}NO_2Cl$, 299.0713; found, 299.0723.

*(R)-(+)-1-(phenoxycarbonyl)-5-(4-chlorophenyl)-3-pyrroline (**6c**) (10% ee):* $[\alpha]_D^{25}$ +24.6° (*c* 1.28, $CHCl_3$). HPLC: 25.3 (*R*), 27.1 (*S*). IR: 1728, 1626, and 1384 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.50 (m, 2H, NCH_2), 5.64 (br, 1H, NCH), 5.81 (m, 1H, C*H*=CH), 6.01 (m, 1H, CH=C*H*), 6.8–7.4 (m, 9H, Ar). HRMS: calcd. for $C_{17}H_{14}NO_2Cl$, 299.0713; found: 299.0691.

*(R)-(+)-1-(methoxycarbonyl)-5-phenyl-2-pyrroline (**5d**) (64% ee):* $[\alpha]_D^{25}$ +96.5° (*c* 1.68, $CHCl_3$). HPLC: 12.3 (*R*), 14.8 (*S*). IR: 1714, 1623, and 1386 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.49 (dddd, J = 16.7, 4.4, 2.9, and 2.0 Hz, 1H, C(H)H), 3.24 (ddt, J = 16.7, 11.0, and 2.4 Hz, 1H, C(*H*)H), 3.60 (br, 3H, OCH_3), 5.01 (dt, J = 4.2 and 2.4 Hz, 1H, C*H*=CHN), 5.12 (dd, J = 11.0 and 4.4 Hz, 1H, NCH), 6.71 (br, 1H, NC*H*=CH), 7.25 (m, 5H, Ph). HRMS: calcd. for $C_{12}H_{13}NO_2$, 203.0947; found, 203.0942.

*(S)-(−)-1-(methoxycarbonyl)-5-phenyl-3-pyrroline (**6d**) (28% ee):* $[\alpha]_D^{25}$ −58.3° (*c* 0.46, $CHCl_3$). HPLC: 17.8 (*R*), 20.1 (*S*). IR: 1706, 1623, and 1386 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.56 and 3.67 (both s, *ca.* 1.5H each, OCH_3), 4.36 (br, 2H, NCH_2), 5.46 (br, 1H, NCH), 5.73 (br, 1H, C*H*=CH), 5.94 (br, 1H, CH=C*H*), 7.25 (m, 5H, Ph). HRMS: calcd. for $C_{12}H_{13}NO_2$, 203.0947; found: 203.0939.

*(R)-(+)-1-(phenoxycarbonyl)-5-phenyl-2-pyrroline (**5e**) (73% ee):* $[\alpha]_D^{25}$ +99.4° (*c* 0.41, $CHCl_3$). HPLC: 16.1 (*R*), 18.3 (*S*). IR: 1724, 1624, and 1402 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.61 (br,d, J = 17 Hz, 1H, C(*H*)H), 3.33 (br,dd, J = 17 and 12 Hz, 1H, C(*H*)H), 5.16 (dt, J = 4.2 and 2.6 Hz, 1H, CH=CHN), 5.30 (br, 1H, NCH), 6.86 (m, 1H, NC*H*=CH), 6.7–7.4 (m, 10H, Ph). HRMS: calcd. for $C_{17}H_{15}NO_2$, 265.1103; found 265.1090.

*(R)-(+)-1-(phenoxycarbonyl)-5-phenyl-3-pyrroline (**6e**) (29% ee):* $[\alpha]_D^{25}$ +63.1° (*c* 0.53, $CHCl_3$). HPLC: 24.2 (*R*), 27.1 (*S*). IR: 1728, 1624, and 1391 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.51 (m, 2H, NCH_2), 5.65 (br, 1H, NCH), 5.81 (dq, J = 6.2 and 2.0 Hz, 1H, C*H*=CH), 5.98 (dq, J = 6.2 and 1.8 Hz, 1H, CH=C*H*), 6.8–7.4 (m, 10H, Ph). HRMS: calcd. for $C_{17}H_{15}NO_2$, 265.1103; found 265.1096.

(R)-(+)-1-(methoxycarbonyl)-5-(4-acetylphenyl)-2-pyrroline (5f) (70% ee): $[\alpha]_D^{25}$ +108° (*c* 0.56, $CHCl_3$). HPLC (hexane/$ClCH_2CH_2Cl$/EtOH = 100/20/1): 28.7 (*R*), 30.6 (*S*). IR: 1714, 1681, 1624, and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.49 (m, 1H, C(*H*)H), 2.58 (s, 3H, $COCH_3$), 3.29 (ddt, *J* = 16.8, 11.2, and 2.2 Hz, 1H, C(*H*)H), 3.67 (br, 3H, OCH_3), 5.06 (dt, *J* = 4.4 and 2.4 Hz, 1H, C*H*=CHN), 5.20 (dd, *J* = 11.2 and 4.4 Hz, 1H, NCH), 6.73 (br, 1H, NC*H*=CH), 7.35 (br,m, 2H, Ar), 7.93 (m, *J* = 8.3 Hz, 2H, Ar).

(S)-(−)-1-(methoxycarbonyl)-5-(4-acetylphenyl)-3-pyrroline (6f) (11% ee): $[\alpha]_D^{25}$ −38.7° (*c* 1.2, $CHCl_3$). HPLC (hexane/$ClCH_2CH_2Cl$/EtOH = 100/20/1): 39.5 (*R*), 40.7 (*S*). IR: 1708, 1683, 1624, and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.58 (s, 3H, $COCH_3$), 3.56 and 3.68 (both s, *ca.* 1.5H each, OCH_3), 4.37 (br, 2H, NCH_2), 5.55 (br, 1H, NCH), 5.73 (br, 1H, C*H*=CH), 5.95 (dq, *J* = 6.4 and 1.7 Hz, 1H, CH=C*H*), 7.29 and 7.38 (both m, *ca.* 1H each, Ar), 7.92 (m, *J* = 8.3 Hz, 2H, Ar).

(R)-(+)-1-(methoxycarbonyl)-5-(4-cyanophenyl)-2-pyrroline (5g) (68% ee): $[\alpha]_D^{25}$ +119° (*c* 0.65, $CHCl_3$). HPLC: 53.8 (*R*), 56.8 (*S*). IR: 2229, 1704, 1623, and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.47 (dddd, *J* = 16.7, 4.6, 2.6, and 2.0 Hz, 1H, C(*H*)H), 3.30 (ddt, *J* = 16.7, 11.2, and 2.4 Hz, 1H, C(*H*)H), 3.66 (br, 3H, OCH_3), 5.06 (dt, *J* = 4.4 and 2.4 Hz, 1H, C*H*=CHN), 5.19 (dd, *J* = 11.2 and 4.6 Hz, 1H, NCH), 6.73 (br, 1H, NC*H*=CH), 7.36 (br,d, *J* = 8.4 Hz, 2H, Ar), 7.63 (d, *J* = 8.4 Hz, 2H, Ar).

(S)-(−)-1-(methoxycarbonyl)-5-(4-cyanophenyl)-3-pyrroline (6g). IR: 2230, 1707, 1624, and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.56 and 3.68 (both s, *ca.* 1.5H each, OCH_3), 4.37 (br, 2H, NCH_2), 5.4–5.8 (br,m, 2H, NCH and C*H*=CH), 5.97 (dq, *J* = 6.2 and 2.0 Hz, 1H, CH=C*H*), 7.2–7.8 (m, 4H, Ar).

Determination of absolute configurations

(a) Conversion of (+)-5d into (R)-(+)-2-phenylpyrrolidine. (+)-1-(methoxycarbonyl)-5-phenyl-2-pyrroline (**5d**) (63% ee; 95.2 mg, 0.47 mmol) and PtO_2 (10.6 mg) were placed in a Schlenk tube equipped with a stirring bar, a rubber septum cap, and a balloon containing dihydrogen gas. Ethyl acetate (2 mL) was added, and the system was evacuated by pumping. Dihydrogen gas (1 atm) was introduced, and the mixture was stirred at room temperature for 4 h. GLC revealed the absence of **5d** from the system and the formation of 1-(methoxycarbonyl)-2-phenylpyrrolidine (**7d**) (99% selectivity). The platinum catalyst was removed by column chromatography (silica gel, AcOEt), and the eluate was concentrated to dryness to give 94.4 mg of (+)-**7d** (98% yield), which has enantiomeric purity of 63% ee as confirmed by HPLC (UV 215 nm; retention time (min): 22.7 (*R*), 28.9 (*S*)): $[\alpha]_D^{25}$ +72.0° (*c* 0.70, $CHCl_3$). IR: 1701 and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.7–2.5 (m, 4H, CH_2CH_2), 3.45–3.85 (br, 5H, OCH_3 and NCH_2), 4.94 (br,d, 1H, NCH), 7.1–7.4 (m, 5H, Ph).

To a flask containing (+)-**7d** (89.3 mg, 0.436 mmol) thus prepared were added ethylene glycol (2 mL) and a 20% aqueous KOH solution (1 mL). The mixture was heated at 100°C for 1 day. The resulting solution was diluted with brine (*ca.* 10 mL), and extracted with Et_2O (50 mL). The Et_2O-layer was then extracted three times with 10% aqueous HCl. Concentration of the organic layer gave 54.9 mg of the starting (+)-**7d** (61% recovered). The aqueous layer was made alkaline (3 M NaOH), and extracted repeatedly with Et_2O. The Et_2O-extract was washed once with brine, and dried over Na_2SO_4, and concentrated to dryness to give a pale yellow oil, which was purified by bulb-to-bulb distillation (100°C, 30 mm Hg) to

yield 9.4 mg of (*R*)-(+)-2-phenylpyrrolidine (15% yield): $[\alpha]_D^{25}$ +36.9° (*c* 0.46, $CHCl_3$) (lit. $[\alpha]_D^{17}$ +71.2° (neat) [13]). This compound exhibited ^1H NMR data in fair agreement with those in the literature [13] ($CDCl_3$): δ 1.5–2.3 (m, 4H, CH_2CH_2), 2.00 (s, 1H, NH), 2.8–3.4 (m, 2H, NCH_2), 4.11 (t, $J = 7.0$ Hz, 1H), 7.15–7.45 (m, 5H, Ph).

In a similar procedure, (+)-1-(phenoxycarbonyl)-5-phenyl-2-pyrroline (**5e**) (64% ee; 46.1 mg, 0.17 mmol) was converted into (*R*)-(+)-2-phenylpyrrolidine (73% yield): $[\alpha]_D^{25}$ +38.6° (*c* 0.79, $CHCl_3$).

*(b) Determination of absolute configuration of (+)-**6e**.* Hydrogenation of (+)-**6e** of 24% ee (42.0 mg) in ethyl acetate (2 mL) catalyzed by PtO_2 (5 mg) gave 1-(phenoxycarbonyl)-2-phenylpyrrolidine (**7e**) of 25% ee (41.8 mg), which has the same configuration as (*R*)-(+)-**7e** derived from (*R*)-(+)-**5e** (64% ee) as confirmed by HPLC (UV 215 nm; retention time (min): 31.5 (*R*), 37.7 (*S*)). (*R*)-(+)-**7e** (64% ee): $[\alpha]_D^{25}$ +57.3° (c 0.50, $CHCl_3$). IR: 1723 and 1385 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.8–2.6 (m, 4H, CH_2CH_2), 3.75 (br, 2H, NCH_2), 5.12 (br, 1H, NCH), 6.7–7.4 (m, 10H, Ph).

Similar experiments have been performed with a pair of regioisomers (*R*)-(+)-**5d** (68% ee) and (−)-**6d** (28% ee). In this case, hydrogenation of the isomers gave the pyrrolidine derivatives with the opposite configurations to each other.

(c) Other compounds. Absolute configurations of **5a–5c**, **5f**, **5g**, **6a–6c**, **6f**, and **6g** were assigned on the basis of the assumption that the elution order of enantiomers in HPLC is the same as that of the phenylation products **5d**, **5e**, **6d**, and **6e**, for which the (*R*) enantiomer is eluted prior to the (*S*) enantiomer.

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