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Pd-Catalyzed Asymmetric Allylic Alkylation of Glycine Imino Ester Using a Chiral Phase-Transfer Catalyst

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Pd-catalyzed asymmetric allylic alkylation of the glycine imino ester **1a** has been developed using a chiral quaternary ammonium salt **3d** without chiral phosphine ligands. The proper choice of the achiral Pd ligand, $P(OPh)_3$, is important to achieve high enantioselectivity. By this method with the dual catalysts, numerous enantiomerically enriched α-allylic amino acids **4a**−**h** could be prepared with comparable to higher enantioselectivity than that of the conventional asymmetric alkylation of **1a**. In addition, the Pd-catalyzed reaction of **1a** with 1-phenyl-2-propenyl acetate **2i** afforded the branch product **6** with high enantio- and diastereoselectivity (>95% de, 85% ee).

Introduction

Chiral α-alkyl and α,α-dialkyl-α-amino acids are an important class of nonproteogenic amino acids and have attracted considerable attention in biological and pharmacological studies, because introduction of these amino acids to peptides induces conformational constraints and enhances metabolic stability.[1] As a result, thus far, a number of diastereoselective synthetic methods of α-alkylated amino acids using various chiral auxiliaries have been reported.[2] Recently, catalytic asymmetric synthesis has been intensively studied, and some efficient methods have been developed other than the asymmetric hydrogenation of dehydroamino acids.[3−6] The asymmetric alkylation of glycine imino esters by a chiral phase-transfer catalyst (PTC) would be a versatile method in terms of operational simplicity and high enantioselectivity.[3] However, the PTC-mediated reaction suffers from the limitation of the allylic halide sources, and it is difficult to extend this procedure to construct contiguous chiral centers in α-alkylated amino acids. On the other hand, the asymmetric allylation of the glycine imino ester through a chiral π-allyl palladium(II) complex can construct two stereogenic centers on both the allylic substrate and the prochiral nucleophile, albeit the stereoselectivity of the latter chiral center might be low.[4] In general, the enantioselective nucleophilic attack of a prochiral nucleophile to give a π-allyl complex is not easily controlled by a chiral ligand on the palladium atom located at the opposite side of the π-allyl carbon structure from the approching nucleophile.[7] To overcome the problems incurred in this reaction, several ingenious ligands for constructing an effective chiral environment around the π-allyl−palladium(II) complex have been developed.[8] With the aim of establishing a different methodology, we examined the palladium-catalyzed nucleophilic substitution in the presence of a chiral PTC as

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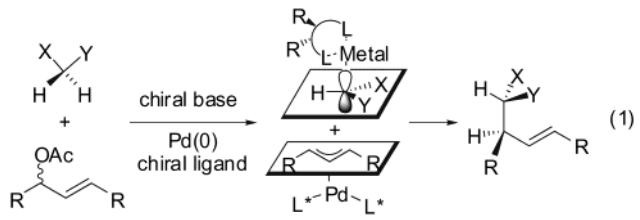
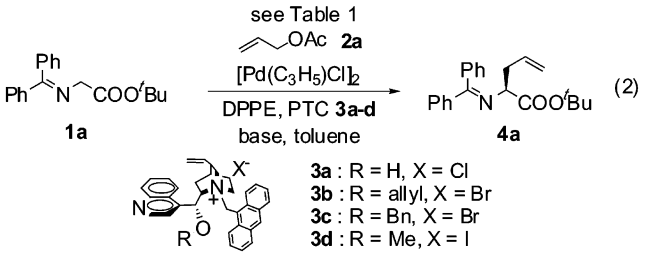
cocatalyst, which might construct an effective chiral environment around a prochiral nucleophile (eq 1).



In this paper, we present a full account of our investigation into the enantioselective allylic alkylation (up to 96% ee) of *tert*-butyl *N*-(diphenylmethylene)glycinate **1a** with several allylic acetates **2a**−**j**, catalyzed by the achiral metal complex [Pd(π-allyl)Cl]$_2$/(PhO)$_3$P in the presence of the chiral *O*-methyl cinchonidinium salt **3d**.[9] The results of the double asymmetric induction by the combination of a chiral PTC and chiral Pd ligand are also described.

Results and Discussion

Asymmetric Allylic Alkylation of 1a with Allyl Acetate in the Presence of Chiral PTCs 3a−d. The first attempt for asymmetric Pd-mediated allylation of **1a** with allyl acetate **2a** was carried out in toluene in the presence of the cinchonidinium salts **3a**−**d** (0.1 equiv) and various achiral phosphine or phosphite ligands (Table 1). These representative results are shown in Table 1 (eq 2).



The Pd-catalyzed reaction of **1a** in the presence of **3a**, 1,2-bis(diphenylphosphino)ethane (DPPE), and solid KOH (1.5 equiv) was completed in 6 h to give the corresponding allylated product **4a**[10a] in good yield but with low enantioselectivity (3% ee, entry 1). Similar reactions with *O*-alkylated PTCs **3b**−**d** afforded the same product **4a** with slightly improved enantioselectivity (entries 2−4).

We next examined the effect of Pd ligands other than DPPE on the enantioselectivity. Whereas the addition of *n*-Bu$_3$P in place of DPPE decreased the enantioselectivity, that of Ph$_3$P, (EtO)$_3$P, and (PhO)$_3$P gave the desired product **4a** in 50−82% ee at the expense of the chemical yield, respectively (entries 5−8). Furthermore, it was revealed that the best result (82% yield, 94%ee) was obtained when the reaction was performed at 0 °C with 3 equiv of a 50% aqueous KOH solution in the presence of **3d** and (PhO)$_3$P (entry 9). In addition, it is revealed that 1,2-bis(diphenylphosphino)ethane monooxide [DPPE(O)][11] could be employed for the preparation of **4a** with the same enantioselectivity as (PhO)$_3$P (entry 10). From the result that (*S*)-**4a** was always obtained as the major product in the reaction with the cinchonidine-derived ammonium salt **3d**, the Pd-catalyzed allylic alkylation of **1a** with **2a** would proceed in a similar chiral environment constructed by **3d** as the PTC-catalyzed alkylation of **1a** with allyl bromide.[3]

TABLE 1. Asymmetric Allylation of 1a under PTC Conditions[a]

entry	PTC	ligand (mol %)	base	yield, %[b]	ee, %[c]
1	**3a**	DPPE (8)	KOH	83	3
2	**3b**	DPPE (8)	KOH	71	12
3	**3c**	DPPE (8)	KOH	91	9
4	**3d**	DPPE (8)	KOH	74	24
5	**3d**	*n*-Bu$_3$P (16)	KOH	69	4
6	**3d**	Ph$_3$P (16)	KOH	32	59
7	**3d**	(EtO)$_3$P (16)	KOH	25	50
8	**3d**	(PhO)$_3$P (16)	KOH	19	82
9[d]	**3d**	(PhO)$_3$P (16)	50% KOH	82	94
10[d]	**3d**	DPPE(O) (10)	50% KOH	83	93

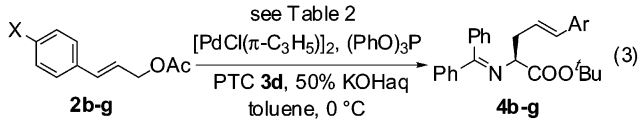
[a] All reactions were carried out in toluene at room temperature. The ratio of **1a**:**2a**:base:[Pd(π-allyl)Cl]$_2$:PTC was 100:200:150:3.5:10, unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis with a Daicel Chiral Pack OD-H column. [d] The reaction was carried out with 50% aqueous KOH (3 equiv) at 0 °C.

TABLE 2. Allylic Alkylation of 1a with Various Allylic Acetate 2b−g[a]

entry	acetate (X)	time, h	yield, %[b]	ee, %[c]
1	**2b** (X = H)	3	89	96
2	**2c** (X = Cl)	7	85	93
3	**2d** (X = F)	6	83	93
4	**2e** (X = NO$_2$)	5	47	91
5	**2f** (X = Me)	9	67[d]	91
6	**2g** (X = OMe)	23	39[d]	96

[a] All reactions were carried out in toluene at 0 °C. The ratio of **1a**:**2b**−**g**:50% aq KOH:[Pd(π-allyl)Cl]$_2$:(PhO)$_3$P:PTC was 100:200:300:9:0−36:10. [b] Isolated yield. [c] Determined by HPLC analysis with a Daicel Chiral Pack OD-H column. [d] The starting material **1a** was not consumed completely.

Asymmetric Allylic Alkylation of 1a with Various Allylic Acetates 2b−h Using the Chiral PTC 3d. Having established higher levels of enantioselectivity, the allylic alkylation of **1a** with some allylic substrates **2b**−**h** was examined using a combination of [(allyl)PdCl]$_2$/(PhO)$_3$P and **3d**, and the representative results are summarized in Table 2 (eq 3).



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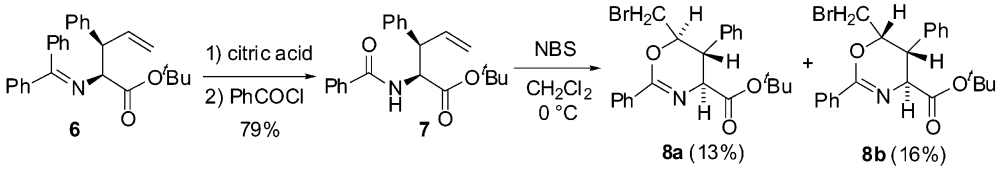
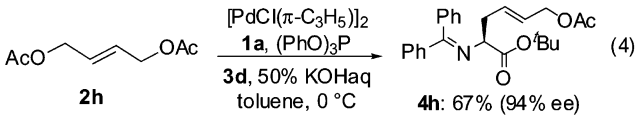
SCHEME 1

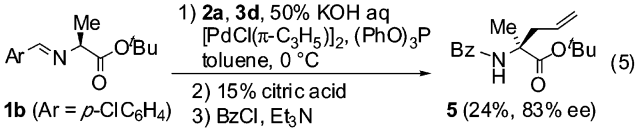


Various enantiomerically enriched allylation products **4b**−**h** were obtained with 91−96% ee in moderate to good yields. The allylation of **1a** with γ-substituted allylic substrate **2b**−**g** provided selectively the corresponding products **4b**−**g** without accompanying regio- and (*Z*)-geometrical isomers. Noteworthy is that the enantioselectivity of **4b**−**g** was not affected by the para-substituent of the aromatic ring of **2b**−**g**, while the reaction rate decreased with increasing the electron-donating ability of the substituent. In addition, similar treatment of **1a** with 1,4-diacetoxypropene **2h** gave rise to the monosubstituted product **4h** in 69% yield with 94% ee (eq 4).



(4)

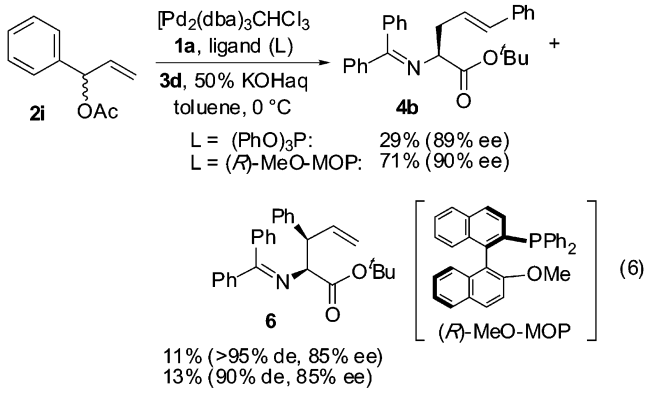
In this case, the bis-substituted product could not be obtained, even with excess of the imino ester **1a**. To extend the applicability of this method, we next investigated the asymmetric synthesis of the α,α-disubstituted amino acid derivatives (eq 5).



(5)

The Pd-mediated reaction of the *tert*-butyl *N*-(4-chlorobenzylidene)alaninate **1b** with allyl acetate **2a** proceeded smoothly to afford the desired product **5** after subjecting the crude product to subsequent hydrolysis and benzoylation. Although the chemical yield was moderate, due to the volatile intermediate, the enantioselectivity of **5** was good. The enantiomeric excess and absolute configuration of the known products **4b**, **4d**, **4f**, and **5** were determined by HPLC analysis on comparison with the authentic samples obtained from the chiral PTC-catalyzed alkylation.[10b−d] The absolute configuration of **4c**, **4e**, **4g**, and **4h** was assumed to be the same as that observed for **4b**−**g**. In addition, it is interesting to note that the PTC-mediated allylic alkylation of **1a** was dramatically influenced by the ratio of $(PhO)_3P$/Pd. When the reaction of **1a** with **2b** was carried out in the presence of 1 or 2 equiv of $(PhO)_3P$ to palladium, the desired product **4b** was obtained in good yield (56−89%) with high enantioselectivity (>95% ee). However, no desired product **4b** could be obtained without the ligand or with more than 3 equiv of $(PhO)_3P$ to palladium.

Asymmetric Allylic Alkylation of 1a with Racemic 1-Phenyl-2-propenyl Acetate. The regio- and stereocontrol of **2b** and its regioisomer **2i** in the transition-metal-catalyzed allylic alkylation is an important research topic in organometallic chemistry. To clarify the different reactivity between **2b** and **2i**, we next examined the Pd/PTC dual-catalyzed allylic alkylation of **1a** with the racemic acetate **2i** (eq 6).



(6)

The Pd-catalyzed reaction of **1a** with **2i** under the optimal conditions described above afforded the same product, (*S*)-**4b**, as that obtained with **2b** with nearly identical enantioselectivity (29% yield, 89% ee). The moderate chemical yield is attributed to the production of the regioisomer **6** (11%).[12] Interestingly, the regioisomer **6** was obtained with high enantio- and diastereoselectivity (>95% de, 85% ee). Then, expecting to synthesize **6** as a major product, we performed the same reaction of **2i** in the presence of **3c** and the chiral Pd ligand [(*R*)-MeO-MOP]. Hayashi reported that the MeO-MOP ligand promotes an inner attack of nucleophiles to the π-allylpalladium(II) complex generated from **2i**, producing the terminal alkene such as **6** predominantly.[12b] In contrast to their results, the (*R*)-MeO-MOP ligand only promoted the generation of the linear product **4b** (71% yield, 90% ee), giving rise to **6** as a minor diastereomer (13% yield, 90% de, 85% ee). The absolute configuration of the C1 center of **6** is assumed to be *S*, the same as that observed for other allylic acetates **4a**−**g**. The relative stereochemistry of **6** was determined by the chemical transformation of **6** into the cyclic compounds **8a**,**b** (Scheme 1). Namely, the sequential subjection of **6** to hydrolysis and benzoylation gave the amido ester **7**, which was converted to the 5,6-dihydro-4*H*-[1,3]oxazines **8a** and **8b** by the reaction with NBS. The NOE experiment of **8a,b** revealed that both **8a** and **8b** possess (4*S*,5*R*)-configuration (Figure 1). Although the regio- and enantioselectivity should be improved in the future, the result suggests that the chiral Pd/PTC-mediated asymmetric allylic alkylation would be a useful alternative to the chiral Pd−ligand-mediated reaction for constructing contiguous stereogenic centers.

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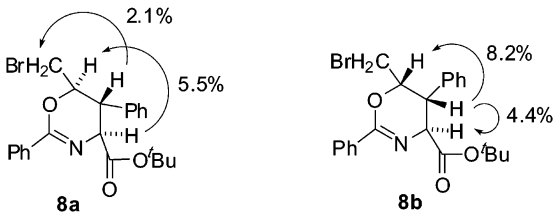
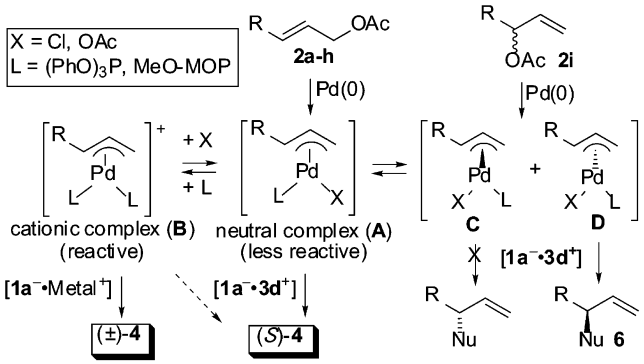


FIGURE 1. NOE experiment of **8a** and **8b**.

SCHEME 2. Plausible Reaction Mechanisms for the Asymmetric Allylic Alkylation of 1a with 2a−i Mediated by the Chiral PTC 3d



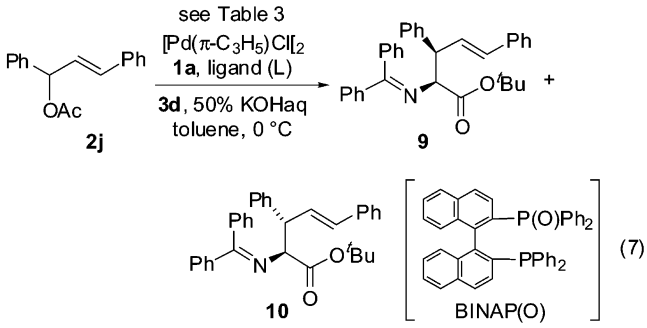
The Reaction Mechanism of the Allylic Alkylation under the PTC Conditions. From the fact that the reaction did not proceed without the palladium catalyst and the same product (*S*)-**4a** was obtained similarly to the asymmetric alkylation of **1a** with **3a**−**d**, the chiral ion-pair of the enolate of **1a** and **3d**, which seems to be the most reactive nucleophile,[3] would react with the π-allylpalladium complex **A**, giving the chiral product **4a** with high enantioselectivity (Scheme 2). It is known that the cationic complex **B** is more reactive than the neutral complex **A** for the following nucleophilic substitution.[13] Therefore, if the more σ-donating ligands such as DPPE and *n*-Bu_3P are used, the active cationic complex **B** might be formed predominantly, and any achiral enolates as well as the chiral ion pair of the enolate of **1a** and **3d** can react with **B**, resulting in poor enantioselectivity. In contrast, when the more π-accepting ligand such as $(PhO)_3P$ is used, the less reactive complex **A** might be formed exclusively, and complete suppression of the racemic reactions with achiral enolates leads to the highly enantiomeric pure product.[14] On the other hand, the reaction of **2i** with Pd(0) initially generates another type of π-allylpalladium complexes **C** and **D** (L = $(PhO)_3P$, MOP).[12b] It is reasonably considered that nucleophilic attack takes place selectively on the carbon trans to the phosphite (or phosphine) ligand because of its stronger trans influence than that of X (chloride or acetate). Furthermore, the chiral ion pair of the enolate of **1a** and **3d** effectively discriminates between the racemic π-allyl complexes **C** and **D**, giving the branch product **6** with high diastereo- and enantioselectivity. However, the nucleophilic attack of the enolate of **1a** at the secondary carbon center of the complex **D** probably proceeds slowly due to the severe steric hindrance and then the isomerization from **C** and **D** into **A** via exchange of the coordination site of L and X would occur more rapidly. Consequently, the linear product **4b** was obtained predominantly in a highly stereoselective manner.

TABLE 3. Allylic Alkylation of 1a with 2j under PTC Conditions[a]

entry	ligand	yield, %[b]	de, %[c]	ee **9**, %[d]	ee **10**, %[d]
1	$(PhO)_3P$	0			
2	DPPE	97	46	0	0
3	DPPE(O)	76	70	51 (*S*,*R*)	42 (*S*,*S*)
4	(*R*)-BINAP(O)	61	32	57 (*R*,*S*)	77 (*S*,*R*)
5	(*S*)-BINAP(O)	33	33	72 (*S*,*R*)	70 (*R*,*S*)
6[e]	(*R*)-BINAP(O)	33	33	43 (*R*,*S*)	55 (*S*,*R*)

[a] All reactions were carried out in toluene at 0 °C. [b] Isolated yield. [c] Calculated from the isolated yields. [d] Determined by HPLC analysis with a Daicel Chiral Pack AD column.

Dual Asymmetric Induction in the Presence of the Chiral PTC 3d and Chiral Pd Ligand. Since we have succeeded in the enantioselective synthesis of the branch product **6**, we next investigated the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **2j** under the PTC conditions (eq 7).



(7)

In this case, there is no need to take the regioselectivity of the reaction into consideration. Unfortunately, the same reaction of **1a** with **2j** using $(PhO)_3P$ and MOP as a Pd ligand did not proceed, resulting in recovery of the starting material (Table 3, entry 1). Then, more effective bidentate ligands bearing bis-phosphine and phosphine−phosphineoxide were employed to enhance the reactivity of the π-allylpalladium complexes. Among the ligands examined, DPPE(O)[11] ligand gave the best results (entries 2 and 3), but stereoselectivities (70% de and 51% ee) were still moderate. To overcome the problem, we undertook the dual asymmetric inductive method using dual chiral catalysts: chiral PTC **3d** and chiral Pd ligand [BINAP(O)][11] (entries 4−6). In fact, the enantioselectivity of the diastereomers **9** and **10**[15] was enhanced by the dual addition of the chiral PTC **3d** and (*R*)- or (*S*)-BINAPO, but the results were very complicated and could not be explained. We should look for a more suitable combination of the chiral anion host and the chiral Pd ligand for the dual asymmetric induction.

Conclusion

We have succeeded in the first highly enantioselective allylic alkylation of the prochiral nucleophile **1a** by using

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the chiral PTC **3d** but not a chiral Pd ligand. The combination of the chiral PTC **3d** and achiral Pd/$(PhO)_3P$ complex is the choice of the dual catalysts to achieve high enantioselectivity. By the asymmetric reaction using the dual catalysts, numerous enantiomerically enriched α-allylic amino acids **4a**−**h** could be prepared with comparable to higher enantioselectivity than that of the asymmetric alkylation of **1** with **3a** or **3b** at 0 °C to room temperature. In addition, the Pd-catalyzed reaction of **1a** with 1-phenyl-2-propenyl acetate **2i** afforded the branch product **6** with high enantio- and diastereoselectivity (>95% de, 85% ee). This means that the Pd-catalyzed asymmetric allylic alkylation with a chiral PTC would be a useful alternative to the chiral Pd−ligand-mediated reaction for constructing contiguous stereogenic centers.

Experimental Section

General Procedure for Asymmetric Allylic Alkylation. *tert*-Butyl (2*S*)-2-[(Diphenylmethylene)amino]-5-(4-chlorophenyl)-4-pentenate (4c) (Entry 2). To a suspension of **1a** (50.0 mg, 0.169 mmol), **3d** (10.6 mg, 0.0169 mmol), $[PdCl(p\text{-}C_3H_5)]_2$ (5.4 mg, 0.015 mmol), and triphenyl phosphite (21.0 mg, 0.677 mmol) in toluene (0.28 mL) were successively added a solution of *p*-chlorocinnamyl acetate (35.7 mg, 0.169 mmol) in toluene (0.56 mL) and an aqueous 50% KOH solution (66.4 mg, 0.591 mmol) at 0 °C under an argon atmosphere. After being stirred vigorously at 0 °C for 7 h, the mixture was diluted with ether (15 mL). The organic phase was washed with aqueous saturated $NaHCO_3$ (3 × 5 mL) and brine (5 mL). The extract was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography [basic silica gel, hexane/AcOEt (300/1)] to give 66.1 mg (85%) of **4c** as colorless crystals. The enantioselectivity was determined by chiral HPLC [Chiralcel OD-H column, 0.5% 2-propanol/hexane, 1.0 mL/min, $\lambda = 254$ nm, retention times: *S* (major) 10.8 min, *R* (minor) 17.3 min]. Anal. Calcd for $C_{28}H_{28}ClNO_2$: C, 75.41; H, 6.33; Cl, 7.95; N, 3.14. Found: C, 75.12; H, 6.45; N, 3.05. Mp 109−110 °C (hexane); $[\alpha]^{28}_D = -32°$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.69−2.84 (m, 2H), 4.08 (dd, 1H, $J = 4.9$ Hz, 7.6 Hz), 6.07 (ddd, 1H, $J = 7.6$ Hz, 7.6 Hz, 15.9 Hz), 6.35 (d, 1H, $J = 15.9$ Hz), 7.09−7.66 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 37.3, 66.0, 81.2, 127.2, 127.3, 127.9, 128.0, 128.4, 128.55, 128.60, 128.8, 130.3, 131.2, 132.6, 136.0, 136.6, 139.6, 170.3, 170.8; IR ($CHCl_3$) ν 1726, 1622, 1486, 1450, 1155, 970 cm^{-1}; MS (FAB) *m*/*z* 446 (MH^+, 100), 390 (92), 238 (98), 193 (35), 149 (35), 57 (36).

***tert*-Butyl (2*S*)-2-[(Diphenylmethylene)amino]-5-(4-nitrophenyl)-4-pentenate (4e) (Entry 4).** The enantioselectivity was determined by chiral HPLC [Chiralcel OD-H column, 0.6% 2-propanol/hexane, 0.75 mL/min, $\lambda = 254$ nm, retention times: *S* (major) 16.9 min, *R* (minor) 21.5 min]. Anal. Calcd for $C_{28}H_{28}N_2O_4 \cdot 5H_2O$: C, 73.23; H, 6.21; N, 6.10. Found: C, 73.16; H, 6.29; N, 6.07. Brown crystals; mp 161−162 °C (hexane/Et_2O); $[\alpha]^{23}_D = -8°$ (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.77−2.87 (m, 2H), 4.12 (dd, 1H, $J = 5.2$, 7.4 Hz), 6.34 (td, 1H, $J = 7.3$, 15.8 Hz), 6.48 (d, 1H, $J = 15.8$ Hz), 7.11−8,15 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 37.4, 65.6, 81.4, 124.0, 126.4, 127.8, 128.0, 128.5, 128.7, 128.8, 130.4, 130.6, 132.0, 136.5, 139.4, 143.9, 146.6, 170.5; IR ($CHCl_3$) ν 2981, 1727, 1596, 1518, 1344 cm^{-1}; MS (FAB) *m*/*z* 457 (MH^+, 90), 401 (100), 355 (35), 238 (60).

***tert*-Butyl (2*S*)-2-[(Diphenylmethylene)amino]-5-(4-methoxyphenyl)-4-pentenate (4g) (Entry 6).** The enantioselectivity was determined by chiral HPLC [Chiralcel OD-H column, 0.5% 2-propanol/hexane, 1.0 mL/min, $\lambda = 254$ nm, retention times: *S* (major) 20.5 min, *R* (minor) 26.7 min]. Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.88; H, 7.08; N, 3.17. Found: C, 78.81; H, 7.15; N, 3.17. A colorless oil; $[\alpha]^{23}_D = -28°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.68−2.83 (m, 2H), 3.78 (s, 3H), 4.06 (dd, 1H, $J = 5.2$ Hz, 7.4 Hz), 5.93 (ddd, 1H, $J = 7.4$ Hz, 7.4 Hz, 15.6 Hz), 6.34 (d, 1H, $J = 15.6$ Hz), 6.81 (d, 2H, $J = 8.9$ Hz), 7.09−7.44 (m, 10H), 7.64 (d, 2H, $J = 7.3$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 37.3, 55.2, 66.3, 81.0, 113.9, 124.2, 127.1, 127.9, 128.0, 128.4, 128.5, 128.8, 130.2, 130.4, 131.8, 136.7, 139.7, 158.8, 170.2, 170.9; IR ($CHCl_3$) ν 1725, 1614, 1454, 1156, 969 cm^{-1}; MS (FAB) *m*/*z* 442 (MH^+, 92), 386 (60), 238 (100), 149 (77), 57 (43).

***tert*-Butyl (2*S*)-6-Acetoxy-2-[(diphenylmethylene)amino]-4-pentenate (4h).** The enantioselectivity was determined by chiral HPLC [Chiralcel OD-H column, 1% 2-propanol/hexane, 0.55 mL/min, $\lambda = 254$ nm, retention times: *S* (major) 11.5 min, *R* (minor) 13.5 min]. A colorless oil; $[\alpha]^{31}_D = -70°$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.95 (s, 3H), 2.55−2.67 (m, 2H), 3.98 (dd, $J = 5.2$, 7.3 Hz, 1H), 4.45 (d, $J = 5.5$ Hz, 2H), 5.56−5.69 (m, 2H), 7.12−7.63 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.8, 28.0, 36.5, 64.8, 65.6, 81.1, 126.7, 127.9, 127.9, 128.4, 128.5, 128.8, 130.2, 132.0, 136.6, 139.6, 170.3, 170.6, 170.7; IR ($CHCl_3$) n 3029, 1729, 1445, 1154, 970 cm^{-1}; MS (FAB) *m*/*z* 408 (MH^+, 100), 352 (41), 306 (41), 238 (95), 292 (26), 238 (39), 165 (22); HRMS (FAB) calcd for $C_{25}H_{30}NO_4$ (MH^+) 408.2175, found 408.2163.

***tert*-Butyl (2*S*,3*R*)-2-[(Diphenylmethylene)amino]-3-phenyl-4-pentenate 6.** To a suspension of 1-phenylpropenyl acetate (30.0 mg, 0.170 mmol), **1a** (75.5 mg, 0.256 mmol), **3d** (10.7 mg, 0.0170 mmol), $[Pd_2(dba)_3CHCl_3]$ (16.0 mg, 0.0153 mmol), and triphenyl phosphite (9.5 mg, 0.0307 mmol) in toluene (0.57 mL) was added an aqueous 50% KOH solution (57.3 mg, 0.511 mmol) at 0 °C under an argon atmosphere, and the resulting mixture was stirred vigorously at 0 °C for 3 h. After the usual workup, the crude was purified by column chromatography [basic silica gel, hexane/AcOEt (300/1)] to give 19.8 mg (29%) of **4b** and 7.6 mg (11%) of **6** as a colorless oil. **6**: The enantioselectivity was determined by chiral HPLC [Chiralcel OD-H column, 0.4% 2-propanol/hexane, 0.75 mL/min, $\lambda = 254$ nm, retention times: (*S*,*R*) (major) 11.7 min, (*R*,*S*) (minor) 12.4 min]. A colorless oil; $[\alpha]^{23}_D = -165°$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 9H), 4.05−4.11 (m, 1H), 4.22 (d, 1H, $J = 6.1$ Hz), 5.12−5.18 (m, 2H), 6.23−6.33 (m, 1H), 6.82−7.64 (m, 15H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 53.7, 70.9, 81.0, 117.0, 126.4, 127.8, 127.9, 128.1, 128.2, 128.3, 128.6, 128.9, 130.1, 136.5, 137.8, 139.6, 141.3, 169.9, 170.6; IR (CHCl3) ν 3008, 1726, 1623 cm^{-1}; MS (FAB) *m*/*z* 412 (MH+, 100), 356 (43), 310 (22), 238 (69); HRMS (FAB) calcd for $C_{28}H_{30}NO_2$ (MH+) 412.2277, found 412.2285.

(4*S*,5*R*,6*RS*)-6-Bromomethyl-2,5-diphenyl-5,6-dihydro-4*H*-[1,3]oxazine-4-carboxylic Acid *tert*-Butyl Ester (8a and 8b) To a solution of **6** (13.4 mg, 0.033 mmol) in THF (0.5 mL) was added a 15% citric acid solution (0.10 mL) at room temperature and the mixture was stirred for 12 h. After being washed with ether, the mixture was neutralized with solid K_2CO_3 and extracted with AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. To a solution of the residue in THF (0.3 mL) were successively added Et_3N (4.9 mg, 0.050 mmol) and benzoyl chloride (5.0 mg, 0.036 mmol) at 0 °C. After being stirred for 5 h, the mixture was quenched with a saturated NH_4Cl solution and extracted with AcOEt. The combined extracts were washed with a saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and then concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane/AcOEt (7/1)] to give **7** (8.4 mg, 76%). To a solution of **7** (8.4 mg, 0.024 mmol) in CH_2Cl_2 (0.3 mL) was added NBS (9.7 mg, 0.055 mmol) at 0 °C and the mixture was stirred for 7 h at 50 °C. After evaporation of the solvent, the obtained residue was purified by column chromatography [silica gel, hexane/AcOEt (10/1)] to give **8b** (5.7 mg, 53%) and **8a** (3.8 mg, 36%). **8b**: a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) d 1.50 (s, 9H), 3.21 (dd, $J = 6.7$, 10.4 Hz, 1H), 3.35 (dd, $J = 7.0$, 10.4 Hz, 1H), 3.61 (dd, $J = 2.4$, 3.6 Hz, 1H), 4.53 (d, $J = 2.4$ Hz, 1H), 4.76 (ddd, $J = 3.6$, 6.7, 7.0 Hz, 1H), 7.21−7.50 (m, 8H),

8.05 (d, J = 7.0 Hz, 2H); IR ($CHCl_3$) ν 2982, 2360, 1728, 1653, 1495, 1152 cm^{-1}; MS (FAB) m/z 432 (MH^+, 84), 430 (86), 376 (60), 105 (100); HRMS (FAB) calcd for $C_{22}H_{25}{}^{79}BrNO_3$ 430.1018, found 430.1005. **8a**: a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 9H), 3.21 (dd, J = 10.7, 11.0 Hz, 1H), 3.30 (dd, J = 5.5, 11.3 Hz, 1H), 3.56 (dd, J = 2.5, 11.3 Hz, 1H), 4.42 (d, J = 11.0 Hz, 1H), 4.56 (ddd, J = 2.5, 5.5 Hz, 10.7, 1H), 7.24−7.48 (m, 8H), 8.05 (d, J = 7.3 Hz, 2H); IR ($CHCl_3$) ν 2982, 2360, 1732, 1655, 1495, 1153 cm^{-1}; MS (FAB) m/z 432 (MH^+, 73), 430 (74), 376 (67), 105 (100); HRMS (FAB) calcd for $C_{22}H_{25}{}^{79}BrNO_3$ (MH^+) 430.1018, found 430.1027.

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Supporting Information Available: Synthetic procedures and characterization for **3d**, **4a, 4b**, **4d**, **4f**, **5**, **9**, and **10**; ^1H NMR spectra for all new compounds **4c**, **4e**, **4g**, **4h**, **6,** and **8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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