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Direct Asymmetric α-Allylation of α-Branched Aldehydes by Two Catalytic Systems with an Achiral Pd Complex and a Chiral Primary α-Amino Acid

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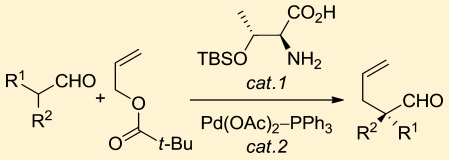
Supporting Information

ABSTRACT: Direct α-allylation of α-branched aldehydes was successfully carried out with a readily available allyl ester by combined use of two catalytic systems: Tsuji−Trost allylation reaction with an achiral palladium complex and enamine catalysis with a chiral primary α-amino acid. A quaternary carbon stereogenic center was constructed stereoselectively to give various 2,2-disubstituted pent-4-enals in good yields with high enantioselectivity.



INTRODUCTION

Stereoselective construction of a quaternary carbon stereogenic center is frequently required in the synthesis of complex organic molecules such as natural organic compounds and pharmaceuticals. Therefore, various synthetic methodologies for constructing a stereocontrolled quaternary carbon center have been developed.[1,2] We recently reported that a primary α-amino acid lithium salt was an effective catalyst for asymmetric Michael addition of α-branched aldehydes to nitroalkenes to synthesize γ-nitroaldehydes possessing a quaternary carbon atom with high enantioselectivity.[3,4] For obtaining other types of synthetically useful organic molecules having a stereocontrolled quaternary carbon atom, we decided to continue studying the primary amino acid salt-catalyzed asymmetric synthesis by using α-branched aldehydes as substrates.

Tsuji−Trost allylation reaction is recognized as one of the most important carbon−carbon bond formation reactions, since an allyl group, which is a useful substituent for further transformation reaction, can be introduced directly under mild reaction conditions.[5,6] The allylation reaction involves generation of a π-allyl palladium complex that reacts with various carbon nucleophiles. As a nucleophile for the Tsuji−Trost allylation reaction, enolate is an attractive candidate, since a synthetically useful α-allylated carbonyl compound can be obtained.[5−7] An asymmetric version of this allylation reaction was achieved by using palladium catalysts with chiral ligands, and it has been documented in detail in previous papers; however, it is still a challenge to achieve α-allylation of α-branched aldehydes by asymmetric catalysis for constructing a quaternary carbon stereogenic center with high enantioselectivity.[6,7]

In recent years, combined use of organocatalysis and transition-metal catalysis has been attempted to open a new field of organic synthesis.[8] As for allylation reactions, Córdova's group achieved direct α-allylation of aldehydes by using a multicatalyst system consisting of a palladium complex and a secondary amine, while there was no substrate scope for α-branched aldehydes.[9a] After that, List's group succeeded in carrying out asymmetric direct α-allylation of α-branched aldehydes by using a palladium complex and a chiral Brønsted acid as catalysts.[9b,c] Since reports of highly enantioselective direct α-allylation of α-branched aldehydes are scarce, it is worthwhile to investigate asymmetric direct α-allylation of α-branched aldehydes with readily available reagents.

In this context, we attempted to carry out Tsuji−Trost allylation reaction of α-branched aldehydes by employing enamine-based organocatalysis with a primary amino acid.[10]

RESULTS AND DISCUSSION

As the first approach, we examined the reaction of 2-phenylpropionaldehyde (**1a**) with allyl acetate (**2a**) in the presence of a catalytic amount of L-phenylalanine lithium salt (**3a**-OLi), which was an efficient catalyst in our previous work regarding asymmetric Michael addition of α-branched aldehydes to nitroalkenes[4] and tetrakis(triphenylphosphine)-palladium(0) [$Pd(PPh_3)_4$, **4a**] (Scheme 1). After the reaction was carried out in benzene for 24 h at 25 °C, the desired allylated product, 2-methyl-2-phenylpent-4-enal (**5a**), was obtained in a moderate yield (43%) with a low enantiomeric excess of (*R*)-enantiomer (37% ee).[11] Fortunately, we found that the allylation reaction proceeded more smoothly and cleanly by using a simple amino acid, L-phenylalanine (**3a**), as a catalyst instead of its salt, **3a-OLi**, to give the product **5a** in a better chemical yield (70%), although no improvement was observed in enantioselectivity.

To improve the enantioselectivity of the allylation reaction, we then examined a detailed optimization of the reaction conditions. First, we carried out a solvent screen for the

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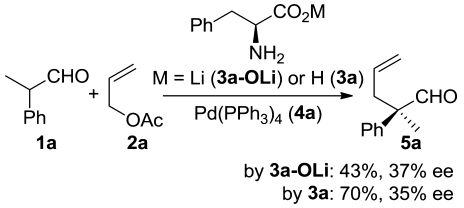
Scheme 1. α-Allylation of an α-Branched Aldehyde Catalyzed by a Palladium Complex and a Primary Amino Acid or Its Lithium Salt[a]



[a]Reagents and conditions: **1a** (0.5 mmol), **2a** (1 mmol), **3a**-OLi or **3a** (0.1 mmol), **4a** (0.05 mmol), benzene (1 mL), 25 °C, 24 h, under Ar.

allylation reaction of aldehyde **1a** with allyl ester **2a** in the presence of amino acid **3a** and palladium catalyst **4a** (Table 1).

Table 1. Solvent Screen for the Allylation Reaction of 1a with 2a in the Presence of 3a and 4a[a]

entry	solvent	yield[b] (%)	ee[c] (%)
1	benzene	70	35
2	AcOH	trace	
3	MeOH	68	26
4	MeCN	55	16
5	DMF	76	2
6	DMSO	84	5
7	THF	87	17
8	Et_2O	86	7
9	CH_2Cl_2	71	30
10	$CHCl_3$	54	42
11	$(CH_2Cl)_2$	72	24

[a]The reaction was carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), **3a** (0.1 mmol), and **4a** (0.05 mmol) in a solvent (1 mL) at 25 °C for 24 h under an Ar atmosphere. [b]Isolated yield of **5a** based on **1a**. [c]Determined by chiral HPLC analysis.

It was found that the allylation reaction hardly proceeded in an acidic solvent (AcOH), while a neutral protic solvent (MeOH) gave allylated product **5a** in a moderate yield (68%) with low enantioselectivity (26% ee) (entries 2 and 3). The use of aprotic polar solvents such as MeCN, DMF, DMSO, and ethers also resulted in poor enantioselectivity, though good chemical yields were obtained (Table 1, entries 4–8). After further screening of solvents, we found that $CHCl_3$ was a preferable solvent for obtaining **5a** with better enantioselectivity (42% ee) (Table 1, entry 10).

Next we screened allylating reagents **2** possessing various leaving groups (Table 2). The use of allyl methyl carbonate (**2b**) instead of acetate **2a** gave the allylated product **5a** with poor enantioselectivity, since the allylation reaction can be promoted independently of amino acid catalyst **3a** by generation of an enolate from **1a** with methoxide which was generated from methyl carbonate **2b** (Table 2, entry 1). Allyl compounds having a highly acidic leaving group (**2c–e**) were found to be unsuitable for the present reaction, since only a trace amount of allylated product **5a** was obtained along with a large amount of the starting material **1a** (Table 2, entries 2–4). In contrast, allyl compounds having a lower acidic leaving group, allyl isobutyrate (**2g**) and pivalate (**2h**), gave better results in both chemical yield and enantioselectivity of **5a** than those of **2a** (Table 2, entries 6 and 7). We found that the enantiomeric excess of **5a** could be improved slightly (53% ee)

Table 2. Screening of 2 for the Allylation Reaction of 1a in the Presence of 3a and 4a[a]

entry	2	yield[b] (%)	ee[c] (%)
1	allyl-OCO_2Me (**2b**)	52	5
2	allyl-Br (**2c**)	trace	
3	allyl-$OCOCF_3$ (**2d**)	trace	
4	allyl-OSO_2-4-MeC_6H_4 (**2e**)	trace	
5	allyl-OCOPh (**2f**)	48	49
6	allyl-OCO-*i*-Pr (**2g**)	60	46
7	allyl-OCO-*t*-Bu (**2h**)	71	51
8	**2h**[d]	83	53

[a]Unless otherwise mentioned, the reaction was carried out with **1a** (0.5 mmol), **2** (1.0 mmol), **3a** (0.1 mmol), and **4a** (0.05 mmol) in $CHCl_3$ (1 mL) at 25 °C for 24 h under an Ar atmosphere. [b]Isolated yield of **5a** based on **1a**. [c]Determined by chiral HPLC analysis. [d]A reduced amount of **2h** (0.6 mmol) was used, and the reaction was carried out for 48 h.

by reducing the amount of allyl ester **2h**, and a chemical yield of 83% was achieved by carrying out the reaction for 48 h (Table 2, entry 8).

We then carried out screening of palladium catalysts **4** and their ligands for the allylation reaction of aldehyde **1a** with allyl ester **2h** in the presence of amino acid catalyst **3a** (Table 3). The use of a palladium catalyst, $Pd(OAc)_2$ (**4b**) or $Pd(dba)_2$

Table 3. Screening of 4 and Its Ligands for the Allylation Reaction of 1a with 2h in the Presence of 3a[a]

entry	4 (concn, mol %)	ligand (concn, mol %)	yield[b] (%)	ee[c] (%)
1	**4a** (10)	none	83	53
2	$Pd(OAc)_2$, **4b** (10)	PPh_3 (40)	72	54
3	$Pd(dba)_2$, **4c** (10)	PPh_3 (40)	82	52
4	**4b** (10)	P(2-furyl)$_3$ (40)	84	54
5	**4b** (10)	P(*o*-Tol)$_3$ (40)	trace	
6	**4b** (10)	$P(OPh)_3$ (40)	11	44
7	**4b** (10)	PCy_3[d] (40)	trace	
8	**4b** (10)	P(*n*-C_4H_9)$_3$ (40)	trace	
9	**4b** (10)	dppe[e] (20)	12	47
10	**4b** (10)	dppp[f] (20)	22	64
11	**4b** (10)	dppb[g] (20)	13	50
12	**4b** (10)	dppf[h] (20)	80	49
13	**4b** (10)	(±)-binap[i] (20)	68	52
14	**4a** (5)	none	81	55
15	**4b** (5)	PPh_3 (20)	80	54
16	**4c** (5)	PPh_3 (20)	84	52
17	**4b** (5)	P(2-furyl)$_3$ (20)	56	45
18	**4b** (5)	PPh_3 (15)	80	56
19[j]	**4b** (5)	PPh_3 (15)	77	55
20[k]	**4b** (5)	PPh_3 (15)	68	50
21[l]	**4b** (5)	PPh_3 (15)	24	
22[m]	none	none	nr	

[a]Unless otherwise mentioned, the reaction was carried out with **1a** (0.5 mmol), **2h** (0.6 mmol), **3a** (0.1 mmol), **4**, and a ligand in $CHCl_3$ (1 mL) at 25 °C for 48 h under an Ar atmosphere. [b]Isolated yield of **5a** based on **1a**. nr = no reaction. [c]Determined by chiral HPLC analysis. [d]Tricyclohexylphosphine. [e]1,2-Bis(diphenylphosphino)-ethane. [f]1,3-Bis(diphenylphosphino)propane. [g]1,4-Bis-(diphenylphosphino)buthane. [h]1,1′-Bis(diphenylphosphino)-ferrocene. [i]2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. [j]A reduced amount of **3a** (0.075 mmol) was used. [k]A reduced amount of **3a** (0.05 mmol) was used. [l]The reaction was carried out without **3a**. [m]The reaction was carried out without **4** and a ligand.

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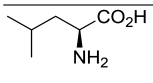
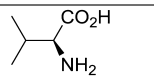
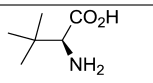
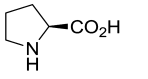
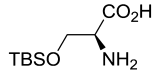
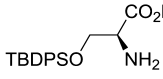
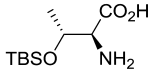
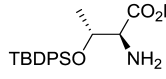
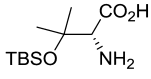
(**4c**), with PPh_3 gave results similar to those for **4a** (Table 3, entries 1−3). On the other hand, allylation reactions using **4b** with various phosphine ligands indicated that both the chemical yield and enantioselectivity of allylated product **5a** greatly depend on the phosphine ligands. For example, P(2-furyl)$_3$ gave good results similar to those of PPh_3; however, other monodentate ligands, P(*o*-Tol)$_3$, P(OPh)$_3$, PCy_3, and P(*n*-C_4H_9)$_3$, could not promote the allylation reaction efficiently (Table 3, entries 4−8). Although several bidentate ligands, dppe, dppp, dppb, dppf, and binap, were also examined, they did not provide better results than those for PPh_3 and P(2-furyl)$_3$ (Table 3, entries 9−13). Optimization of palladium catalyst loading indicated that the amount of palladium catalyst could be reduced to 5 mol % without significant loss of chemical yield or enantioselectivity of **5a** when the allylation reaction was carried out in the presence of a palladium catalyst possessing PPh_3 as a ligand (Table 3, entries 14−17). After optimization of the ratio of PPh_3 to palladium catalyst **4b**, the best result was obtained by using 15 mol % PPh_3 and 5 mol % **4b** (Table 3, entries 15 and 18). In addition, it was revealed that an amino acid catalyst concentration of at least 20 mol % was required to carry out the allylation reaction efficiently and that a palladium catalyst was necessary to promote the allylation reaction (Table 3, entries 18−22).

Next we carried out screening of amino acid catalysts **3** for the allylation reaction (Table 4). Examination using **3b−d** indicated that the enantiomeric excess of allylated product **5a** is affected by the bulkiness of a side chain of amino acids, and a relatively sterically hindered amino acid gave better enantioselectivity. A secondary amino acid, L-proline (**3e**), could not promote the enamine catalysis of an α-branched aldehyde efficiently, and a large amount of the starting material **1a** was recovered.[4] With these results in mind, we prepared some sterically hindered primary amino acids (**3f−j**), including *O*-silylated L-serines, L-threonines, and 3-hydroxy-D-valine.[12] Among these amino acid catalysts, the most sterically hindered catalyst, *O*-TBS-3-hydroxy-D-valine (**3j**), gave the best enantioselectivity as expected; however, the reaction was slower than that using the other catalysts. By considering the balance between the chemical yield and enantiomeric excess of **5a**, *O*-TBS-L-threonine (**3h**) was chosen as an appropriate amino acid catalyst for further investigation. Fortunately, it was found that both the chemical yield and enantioselectivity could be improved slightly by using a small amount of $MgSO_4$ as an additive. Thus, we obtained allylated product **5a** in a good yield (78%) with high enantioselectivity (86% ee) under the reaction conditions.

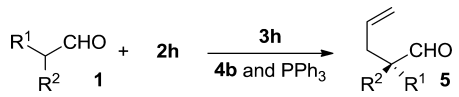
Under the optimized reaction conditions, we then carried out the allylation reaction by employing several types of α-branched aldehydes **1** as substrates (Table 5). The allylation reactions with an aldehyde possessing a methyl or chloro group on the *para*- or *meta*-position of the aryl group proceeded as well as that with **1a** to give allylated products in good yields with high enantioselectivity; however, that with *ortho*-substituted aldehydes resulted in no reaction (Table 5, entries 2−7). Likewise, 2-(4-fluorophenyl)propionaldehyde (**1h**) and 2-(naphthalen-2-yl)propionaldehyde (**1i**) successfully gave the corresponding allylated products **5h** and **5i**, respectively (Table 5, entries 8 and 9). The use of a heteroaryl-substituted substrate, 2-(thiophene-2-yl)propionaldehyde (**1j**), resulted in a good yield, though the enantioselectivity was moderate (Table 5, entry 10). 2-Phenylbutyraldehyde (**1k**) was also found to be a good substrate for obtaining allylated product **5k** with high enantioselectivity; however, the reaction was very slow, and a large amount of the starting material **1k** was recovered (Table 5, entry 11). By the present allylation reaction, α-allylated mandelic acid derivative **5l** could be synthesized enantioselectively from 2-methoxy-2-phenylacetaldehyde (**1l**),[13] though there is room for improvement in both of the chemical yield and enantioselectivity (Table 5, entry 12). Our method can be

Table 4. Screening of 3 for the Allylation Reaction of 1a with 2h in the Presence of 4b and PPh_3[a]

Amino acid catalysts **3**, Yield of **5a**,[b] ee[c]		
		
3b, 78%, 52% ee	**3c**, 79%, 60% ee	**3d**, 87%, 76% ee
		
3e, trace	**3f**[d], 53%, 64% ee	**3g**[e], 56%, 80% ee
		
3h, 65%, 84% ee	**3i**, 74%, 80% ee	**3j**, 48%, 85% ee[g]
(78%, 86% ee)[f]		

[a]Unless otherwise mentioned, the reaction was carried out with **1a** (0.5 mmol), **2h** (0.6 mmol), **3** (0.1 mmol), **4b** (0.025 mmol), and PPh_3 (0.075 mmol) in $CHCl_3$ (1 mL) at 25 °C for 72 h under an Ar atmosphere. [b]Isolated yield of **5a** based on **1a**. [c]Determined by chiral HPLC analysis. [d]TBS = *tert*-butyldimethylsilyl. [e]TBDPS = *tert*-butyldiphenylsilyl. [f]$MgSO_4$ (0.1 mmol) was used as an additive. [g]ee of the (*S*)-enantiomer.

Table 5. Substrate Scope[a]



entry	aldehyde **1** (R^1, R^2)	yield of **5**[b] (%)	ee[c] (%)
1	**1a** (Me, Ph)	78 (**5a**)	86
2	**1b** (Me, 4-MeC_6H_4)	79 (**5b**)	84
3	**1c** (Me, 3-MeC_6H_4)	89 (**5c**)	82
4	**1d** (Me, 2-MeC_6H_4)	nr	
5	**1e** (Me, 4-ClC_6H_4)	85 (**5e**)	87
6	**1f** (Me, 3-ClC_6H_4)	82 (**5f**)	86
7	**1g** (Me, 2-ClC_6H_4)	nr	
8	**1h** (Me, 4-FC_6H_4)	80 (**5h**)	84
9	**1i** (Me, naphthalen-2-yl)	76 (**5i**)	85
10	**1j** (Me, thiophene-2-yl)	88 (**5j**)	70
11	**1k** (Et, Ph)	36 (**5k**)	84
12	**1l** (OMe, Ph)	48 (**5l**)	46
13	**1a**	71 (**6**)[d]	70
14	**1m** (Me, cyclohexyl)	nr	
15	**1n** (Me, *n*-C_3H_7)	nr	

[a]The reaction was carried out with **1** (0.5 mmol), **2h** (0.6 mmol), **3h** (0.1 mmol), **4b** (0.025 mmol), PPh_3 (0.075 mmol), and $MgSO_4$ (0.1 mmol) in $CHCl_3$ (1 mL) at 25 °C for 72 h under an Ar atmosphere. [b]Isolated yield of **5** based on **1**. nr = no reaction. [c]Determined by chiral HPLC analysis. [d]*trans*-Cinnamyl pivalate (**2i**; 1.0 mmol) was used instead of **2h**.

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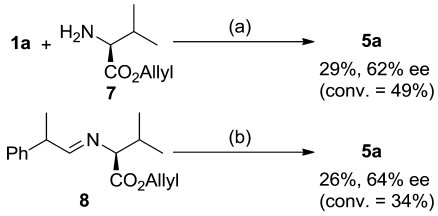
applied for the reaction of **1a** with a substituted allyl ester, *trans*-cinnamyl pivalate (**2i**), and (*E*)-2-methyl-2,5-diphenyl-pent-4-enal (**6**) was obtained in a good yield with moderate enantioselectivity (Table 5, entry 13). In this reaction, no generation of the regio- and geometric isomers was observed. In contrast to the successful results shown above, no reaction was observed when α,α-dialkylacetaldehydes 2-cyclohexylpropionaldehyde (**1m**) and 2-methylvaleraldehyde (**1n**) were employed as substrates (Table 5, entries 14 and 15).

To gather information on the reaction mechanism, we carried out allylation reactions with L-valine allyl ester (**7**) and with imine **8** generated from **7** and aldehyde **1a** (Scheme 2).

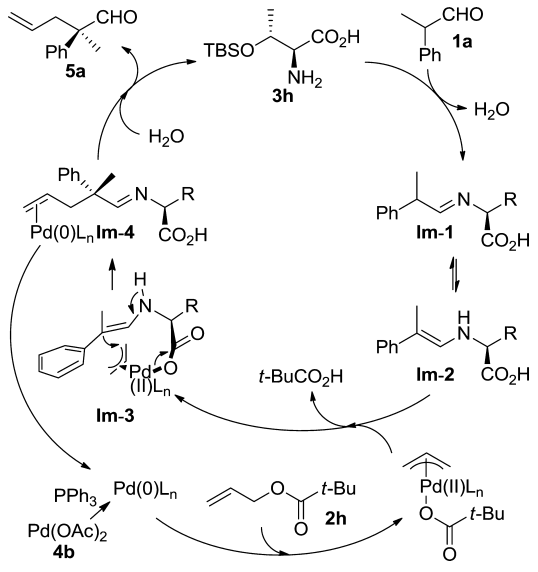
Scheme 2. Allylation Reaction with Valine Allyl Ester 7 and with Imine 8 Generated from 7 and Aldehyde 1a[a]



[a]Reagents and conditions: (a) **1a** (0.5 mmol), **7** (0.5 mmol), **4b** (0.025 mmol), PPh_3 (0.075 mmol), $CHCl_3$ (1 mL), 25 °C, 18 h, under Ar; (b) **8** (0.5 mmol), **4b** (0.025 mmol), PPh_3 (0.075 mmol), $CHCl_3$ (1 mL), 25 °C, 18 h, under Ar.

Since enantioselectivity similar to that of the allylation reaction of **1a** in the presence of amino acid **3c** was observed (Table 4), an imine intermediate would be formed and involved deeply in the induction of enantioselectivity of the allylation reaction.[14] With these results in mind, we estimated a plausible reaction mechanism of the allylation reaction of aldehyde **1a** with amino acid catalyst **3h** (Scheme 3). Initially, amino acid catalyst **3h** reacted with aldehyde **1a** to give imine **Im-1**, which can generate enamine **Im-2** by tautomerization. On the other hand, Pd(II) catalyst **4b** was reduced to Pd(0) in the reaction conditions,[15] and then Pd(0) reacted with allyl ester **2h** to give a π-allyl Pd(II) complex by oxidative addition. In the next step, the pivalate ion of the π-allyl complex was exchanged with the carboxyl group of **Im-2** to give intermediate **Im-3**. Then intramolecular nucleophilic addition of the enamine to the π-allyl complex occurred to generate imine **Im-4**. Finally, Pd(0) was released and following hydration of **Im-4** provided the allylated product **5a** and amino acid catalyst **3h**.

Scheme 3. Plausible Reaction Mechanism



CONCLUSION

We found that a primary amino acid, *O*-TBS-L-threonine, was an effective asymmetric catalyst for the Tsuji–Trost allylation reaction of α-branched aldehydes with a readily available allylating reagent, allyl pivalate. The allylation reaction smoothly proceeded with construction of a quaternary carbon stereogenic center, and various 2,2-disubstituted pent-4-enals were synthesized with high enantioselectivity.

EXPERIMENTAL SECTION

Materials. Aldehyde **1a** is commercially available. Other aldehydes, **1b–k**,[16] **1l**,[17] and **1m,n**,[16] were prepared according to the literature. Allyl esters **2a–f** are commercially available. Allyl isobutyrate (**2g**) was prepared according to the literature.[18] Allyl pivalate (**2h**) and *trans*-cinnamyl pivalate (**2i**) were synthesized by esterification of pivalic acid. Amino acids **3a–e** are commercially available. *O*-Silylated L-serines **3f** and **3g** and L-threonines **3h** and **3i** were synthesized according to the literature.[12] 3-(*tert*-Butyldimethylsiloxy)-D-valine (**3j**) was synthesized from L-serine. Palladium catalysts **4** and phosphine ligands were purchased and were used without purification. Aldehydes **1**, allyl esters **2**, and solvents were used after distillation.

Synthesis of Allyl Pivalate (2h) and *trans*-Cinnamyl Pivalate (2i). To a mixture of K_2CO_3 (31.1 g, 225 mmol) and DMF (75 mL) in a round-bottomed flask were successively added pivalic acid (15.3 g, 150 mmol) and allyl bromide (18 mL). After the mixture was stirred for 5 h at room temperature, the resulting solution was poured into water (300 mL) and extracted with Et_2O (100 mL × 3). The combined organic phase was washed with H_2O (200 mL × 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give almost pure allyl pivalate (**2h**) in 81% yield (17.3 g, 122 mmol). Spectroscopic data are in agreement with the published data.[19a] *trans*-Cinnamyl pivalate (**2i**) was also synthesized in the same manner.[19b]

Synthesis of 3-(*tert*-Butyldimethylsiloxy)-D-valine (3j). To a mixture of $NaHCO_3$ (8.40 g, 100 mmol), H_2O (40 mL), and 1,4-dioxane (5 mL) in a round-bottomed flask was added L-serine (5.25 g, 50 mmol). After cessation of gas evolution, benzyl chloroformate (12.0 g, 56 mmol) was added dropwise at 0 °C while the reaction vessel was cooled in an ice–water bath, and the whole reaction mixture was stirred for 0.5 h at the same temperature. The ice–water bath was then removed, and the reaction mixture was stirred overnight at room temperature. The resulting reaction mixture was washed with Et_2O (50 mL × 2) and acidified to pH 2 with aq 3 N HCl. The obtained solution was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the residue in the flask were added DMF (50 mL), K_2CO_3 (13.8 g, 100 mmol), and methyl iodide (14.2 g, 100 mmol) at room temperature. After the mixture was stirred for 15 h at room temperature, the resulting solution was poured into water (200 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude material was purified by column chromatography (silica gel; hexane/ethyl acetate, 1:1) to give *N*-[(benzyloxy)carbonyl]-L-serine methyl ester in 76% yield (two steps, 9.61 g, 38 mmol). In a three-necked round bottomed flask equipped with a condenser, magnesium (3.0 g, 125 mmol) was dried under a nitrogen atmosphere. Dry Et_2O (100 mL) and 1,2-dibromoethane (0.2 mL) were successively added to the reaction vessel, and the slurry was stirred for 5 min. Methyl iodide (7.5 mL, 120 mmol) was then added dropwise, and the mixture was stirred for 1 h at room temperature. The reaction mixture was then cooled to 0 °C with an ice–water bath, and a dry Et_2O solution (20 mL) of *N*-

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[(benzyloxy)carbonyl]-L-serine methyl ester (5.06 g, 20 mmol) was added dropwise to the reaction mixture. The ice−water bath was removed, and the mixture was then stirred for 4 h at room temperature. After addition of 3 N HCl (100 mL) to the reaction mixture at 0 °C, the resulting mixture was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude material was purified by column chromatography (silica gel; hexane/ethyl acetate, 1:1) to give (*S*)-2-[[(benzyloxy)-carbonyl]amino]-3-methyl-1,3-butanediol in 50% yield (2.53 g, 10 mmol). To a solution of (*S*)-2-[[(benzyloxy)carbonyl]amino]-3-methyl-1,3-butanediol (2.53 g, 10 mmol) in MeCN (40 mL) were added phosphate buffer solution (pH 6.7, 30 mL) and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl; 1.56 g, 1 mmol) at room temperature. After the reaction mixture was warmed to 35 °C, a H_2O solution (10 mL) of $NaClO_2$ (1.8 g, 20 mmol) and an aqueous NaClO solution (0.83%, 6 mL) were added to the reaction mixture at the same time with stirring for 1 h. The reaction mixture was additionally stirred for 4 h at 35 °C, and then the resulting solution was acidified to pH 2 with citric acid. The obtained mixture was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the obtained crude *N*-[(benzyloxy)-carbonyl]-3-hydroxy-D-valine in a flask were added DMF (50 mL), K_2CO_3 (2.76 g, 20 mmol), KI (166 mg, 1 mmol), and benzyl bromide (2.56 g, 15 mmol). After being stirred for 15 h at room temperature, the resulting solution was poured into water (200 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude material was purified by column chromatography (silica gel; hexane/ethyl acetate, 4:1) to give *N*-[(benzyloxy)carbonyl]-3-hydroxy-D-valine benzyl ester in 63% yield (two steps, 2.25 g, 6.3 mmol). To a solution of *N*-[(benzyloxy)-carbonyl]-3-hydroxy-D-valine benzyl ester (0.36 g, 1 mmol) in dry DMF (4 mL) were added 2,6-lutidine (0.75 g, 7 mmol) and (TBS)OTf (0.63 g, 3 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 3 h at 0 °C and then additionally for 8 h at room temperature. The resulting solution was poured into water (20 mL) and extracted with Et_2O (20 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After the obtained crude material was roughly purified by column chromatography (silica gel; hexane/ethyl acetate, 8:1), the obtained *N*-[(benzyloxy)carbonyl]-3-(*tert*-butyldimethylsiloxy)-D-valine benzyl ester was dissolved in MeOH (8 mL), and the solution was added onto Pd/C (10%, 60 mg) under a nitrogen atmosphere in a round-bottomed flask. After the atmosphere in the flask was replaced with hydrogen, the reaction mixture was stirred for 6 h under a hydrogen atmosphere at room temperature. Pd/C was filtered with Celite, and the filtrate was concentrated under reduced pressure. The obtained white solid was washed with Et_2O and hexane and dried in air to give pure 3-(*tert*-butyldimethylsiloxy)-D-valine (**3j**) in 70% yield (two steps, 173 mg, 0.7 mmol) as a white solid: mp 114−115 °C; $[\alpha]_D^{21}$ = +11.5° (*c* = 1.0, MeOH); NMR (CD_3OD) δ_H 0.17 (3H, s), 0.18 (3H, s), 0.91 (9H, s), 1.31 (3H, s), 1.54 (3H, s), 3.38 (1H, s); NMR (CD_3OD) δ_C 18.9, 25.4, 26.4, 29.4, 65.8, 74.8, 171.6; IR (KBr) ν/cm^{-1} 1637 (C═O); HR ESI-MS *m*/*z* calcd for $C_{11}H_{25}NO_3Si$ + H (M + H) 248.1677, found (M^+ + H) 248.1675.

Typical Procedure for the Allylation Reaction. $Pd(OAc)_2$ (**4b**; 5.6 mg, 0.025 mmol), PPh_3 (19.7 mg, 0.075 mmol), *O*-TBS-L-threonine (**3h**; 23.3 mg, 0.1 mmol), $MgSO_4$ (12 mg, 0.1 mmol), and $CHCl_3$ (1 mL) were placed in a 7 mL vial, and the atmosphere in the vial was replaced with argon. After addition of 2-phenylpropionaldehyde (**1a**; 67 mg, 0.5 mmol) and allyl pivalate (**2h**; 85 mg, 0.6 mmol) to the reaction mixture with stirring, the vial was charged with argon again and capped tightly. Then the reaction mixture was stirred for 72 h at 25 °C. The resulting mixture was filtered through a small plug of silica gel, eluted with Et_2O (2 mL × 3), and concentrated under reduced pressure. (*R*)-2-Methyl-2-phenylpent-4-enal (**5a**) was isolated by column chromatography (silica gel, hexane−Et_2O, 19:1) in 78% yield (67.9 mg) as a clear oil. The enantioselectivity was determined by chiral HPLC analysis (86% ee). The absolute configuration was determined by comparison of the specific rotation with that of the literature:[9b,c,14b] $[\alpha]_D^{20.0}$ = −69.5° (*c* = 1.0, $CHCl_3$, 86% ee), −35.0° (*c* = 1.0, MeOH, 86% ee). NMR ($CDCl_3$) data for **5a**: δ_H 1.44 (3H, s), 2.60−2.72 (2H, m), 5.01−5.08 (2H, m), 5.49−5.60 (1H, m), 7.24−7.31 (3H, m), 7.37−7.41 (2H, m), 9.52 (1H, s); δ_C18.7, 40.5, 53.5, 118.5, 127.0, 127.2, 128.7, 133.1, 139.3, 201.7. The spectroscopic data of **5b**,[9b] **5c**,[9b] **5e**,[9c] **5i**,[9b] **5j**,[9b] and **6**[9b] are in agreement with the published data.

Data for 2-methyl-2-(4-methylphenyl)pent-4-enal (5b):[9b] 79% yield (74.3 mg); clear oil; $[\alpha]_D^{20.0}$ = −55.7° (*c* = 1.0, $CHCl_3$, 84% ee); NMR ($CDCl_3$) δ_H 1.42 (3H, s), 2.34 (3H, s), 2.58−2.71 (2H, m), 5.01−5.08 (2H, m), 5.50−5.60 (1H, m), 7.13−7.14 (2H, m), 7.19−7.21 (2H, m), 9.50 (1H, s); NMR ($CDCl_3$) δ_C 18.8, 20.9, 40.5, 53.2, 118.5, 127.1, 129.6, 133.3, 136.3, 137.1, 202.0.

Data for 2-methyl-2-(3-methylphenyl)pent-4-enal (5c):[9b] 89% yield (83.7 mg); clear oil; $[\alpha]_D^{25.0}$ = −72.8° (*c* = 1.0, $CHCl_3$, 82% ee); NMR ($CDCl_3$) δ_H 1.43 (3H, s), 2.36 (3H, s), 2.59−2.72 (2H, m), 5.02−5.09 (2H, m), 5.50−5.61 (1H, m), 7.05−7.12 (3H, m), 7.28−7.30 (1H, m), 9.50 (1H, s); NMR ($CDCl_3$) δ_C 18.8, 21.6, 40.5, 53.5, 118.5, 124.1, 127.9, 128.1, 128.7, 133.3, 138.5, 139.3, 202.0.

Data for 2-(4-chlorophenyl)-2-methylpent-4-enal (5e):[9c] 85% yield (88.7 mg); clear oil; $[\alpha]_D^{24.8}$ = −66.9° (*c* = 1.0, $CHCl_3$, 87% ee); NMR ($CDCl_3$) δ_H 1.43 (3H, s), 2.58−2.69 (2H, m), 5.03−5.08 (2H, m), 5.46−5.57 (1H, m), 7.17−7.19 (2H, m), 7.34−7.37 (2H, m), 9.49 (1H, s); NMR ($CDCl_3$) δ_C 18.8, 40.6, 53.3, 119.0, 128.6, 129.0, 132.7, 133.4, 137.9, 201.4.

Data for 2-(3-chlorophenyl)-2-methylpent-4-enal (5f): 82% yield (85.6 mg); clear oil; $[\alpha]_D^{24.7}$ = −65.0° (*c* = 1.0, $CHCl_3$, 86% ee); NMR ($CDCl_3$) δ_H 1.44 (3H, s), 2.58−2.70 (2H, m), 5.04−5.10 (2H, m), 5.47−5.58 (1H, m), 7.11−7.14 (1H, m), 7.24−7.34 (3H, m), 9.51 (1H, s); NMR ($CDCl_3$) δ_C 18.8, 40.6, 53.6, 119.1, 125.5, 127.4, 127.6, 130.0, 132.6, 134.9, 141.6, 201.2; IR (neat) ν/cm^{-1} 1726 (C═O); HR EI-MS *m*/*z* calcd for $C_{12}H_{13}ClO$ (M) 208.0655, found (M^+) 208.0651.

Data for 2-(4-fluorophenyl)-2-methylpent-4-enal (5h): 80% yield (76.9 mg); clear oil; $[\alpha]_D^{22.2}$ = −68.0° (*c* = 1.0, $CHCl_3$, 84% ee); NMR ($CDCl_3$) δ_H 1.44 (3H, s), 2.58−2.70 (2H, m), 5.03−5.08 (2H, m), 5.48−5.58 (1H, m), 7.05−7.09 (2H, m), 7.21−7.25 (2H, m), 9.49 (1H, s); NMR ($CDCl_3$) δ_C 20.3, 42.1, 54.5, 117.1 (d, *J* 21.7 Hz), 120.2, 130.3 (d, *J* 7.9 Hz), 134.3, 136.5 (d, *J* 3.0 Hz), 163.4 (d, *J* 246.3 Hz), 203.0; IR (neat) ν/cm^{-1} 1725 (C═O); HR ESI-MS *m*/*z* calcd for $C_{12}H_{13}FO$ + H (M + H) 193.1023, found (M^+ + H) 193.1024.

Data for 2-methyl-2-(naphthalen-2-yl)pent-4-enal (5i):[9b] 76% yield (85.2 mg); clear oil; $[\alpha]_D^{24.7}$ = −107.0° (*c* = 1.0, $CHCl_3$, 85% ee); NMR ($CDCl_3$) δ_H 1.56 (3H, s), 2.70−2.85 (2H, m), 5.02−5.11 (2H, m), 5.52−5.62 (1H, m), 7.36−7.38 (1H, m), 7.48−7.52 (2H, m), 7.71−7.72 (1H, m), 7.83−7.87 (3H, m), 9.59 (1H, s); NMR ($CDCl_3$) δ_C 18.9, 40.5, 53.8, 118.7, 125.0, 126.26, 126.28, 126.4, 127.5, 128.0, 128.6, 132.4, 133.1, 133.4, 136.8, 202.0.

Data for 2-methyl-2-(thiophene-2-yl)pent-4-enal (5j):[9b] 88% yield (79.0 mg); clear oil; $[\alpha]_D^{22.3}$ = −13.2° (*c* = 1.0, $CHCl_3$, 70% ee); NMR ($CDCl_3$) δ_H 1.51 (3H, s), 2.69 (2H, d, *J* 7.2 Hz), 5.09−5.16 (2H, m), 5.60−5.71 (1H, m), 6.92 (1H, dd, *J* 1.2, 3.6 Hz), 7.04 (1H, dd, *J* 3.6, 5.2 Hz), 7.31 (1H, dd, *J* 1.2, 5.2 Hz), 9.49 (1H, s); NMR ($CDCl_3$) δ_C 19.9, 41.4, 52.1, 119.2, 125.2, 125.4, 127.4, 132.5, 144.1, 199.6.

Data for 2-ethyl-2-phenylpent-4-enal (5k): 36% yield (33.9 mg); clear oil; $[\alpha]_D^{20.0}$ = −46.5° (*c* = 1.0, $CHCl_3$, 84% ee); NMR ($CDCl_3$) δ_H 0.82 (3H, t, *J* 7.3 Hz), 1.96−2.06 (2H, m), 2.66−2.79 (2H, m), 5.03−5.12 (2H, m), 5.49−5.60 (1H, m), 7.23−7.42 (5H, m), 9.52 (1H, s); NMR ($CDCl_3$) δ_C 7.9, 24.5, 36.1, 57.4, 118.3, 127.3, 127.6, 128.7, 132.9, 138.4, 202.4; IR (neat) ν/cm^{-1} 1724 (C═O); HR ESI-MS *m*/*z* calcd for $C_{13}H_{16}O$ + H (M + H) 189.1274, found (M^+ + H) 189.1275.

Data for 2-methoxy-2-phenylpent-4-enal (5l): 48% yield (45.6 mg); clear oil; $[\alpha]_D^{20.0}$ = −59.5° (*c* = 1.0, $CHCl_3$, 46% ee); NMR ($CDCl_3$) δ_H 2.83−2.89 (1H, m), 3.03−3.09 (1H, m), 3.34 (3H, s), 5.08−5.18 (2H, m), 5.59−5.70 (1H, m), 7.30−7.41 (5H, m), 9.52 (1H, s); NMR ($CDCl_3$) δ_C 35.4, 51.5, 86.1, 118.8, 126.9, 128.3, 128.8,

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131.5, 136.1, 200.3; IR (neat) ν/cm^{-1} 1731 (C=O); HR ESI-MS m/z calcd for $C_{12}H_{14}O_2$ + Na (M + Na) 213.0886, found (M^+ + Na) 213.0888.

Data for (*E*)-2-methyl-2,5-diphenylpent-4-enal (6):[9b] 71% yield (88.3 mg); clear oil; $[\alpha]_D^{23.8} = -87.3°$ (c = 1.0, $CHCl_3$, 70% ee); NMR ($CDCl_3$) δ_H 1.50 (3H, s), 2.76−2.87 (2H, m), 5.94 (1H, dt, J 7.5, 15.9 Hz), 6.41 (1H, d, J 15.9 Hz), 7.17−7.34 (8H, m), 7.39−7.44 (2H, m), 9.58 (1H, s); NMR ($CDCl_3$) δ_C 18.9, 39.9, 54.1, 124.9, 126.1, 127.17, 127.24, 127.4, 128.5, 128.9, 133.6, 137.2, 139.4, 202.0.

Synthesis of L-Valine Allyl Ester (7) and Imine 8. L-Valine allyl ester hydrogen chloride was synthesized from *N*-Boc-L-valine by general transformation reaction according to the literature.[20] To a Et_2O solution (10 mL) of L-valine allyl ester hydrogen chloride (96.8 mg, 0.5 mmol) was added satd aq $NaHCO_3$ (10 mL). After the resulting solution was stirred for 15 min, the organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give **7**. Then **7** and aldehyde **1a** (67 mg, 0.5 mmol) were dissolved in benzene (10 mL), and the solution was refluxed in a round-bottomed flask equipped with a Dien−Stark trap. After 4 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure to give imine **8**.[14b]

Allylation Reaction with L-Valine Allyl Ester (7) and with Imine 8. $Pd(OAc)_2$ (**4b**; 5.6 mg, 0.025 mmol), PPh_3 (19.7 mg, 0.075 mmol), and $CHCl_3$ (0.5 mL) were placed in a 7 mL vial, and the atmosphere in the vial was replaced with argon. After addition of aldehyde **1a** (67 mg, 0.5 mmol) and a $CHCl_3$ (0.5 mL) solution of **7**, or merely a $CHCl_3$ (0.5 mL) solution of imine **8**, to the reaction mixture with stirring, the vial was charged with argon again and capped tightly. Then the reaction mixture was stirred for 18 h at 25 °C. To the resulting mixture was added H_2O (1 mL), and the whole reaction mixture was stirred vigorously. The organic phase was separated, filtered through a small plug of silica gel, eluted with Et_2O (2 mL × 3), and concentrated under reduced pressure. Pure allylated product **5a** was obtained after purification by column chromatography.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC data of **5** and **6** and ^{1}H and ^{13}C NMR spectra of **3j**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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