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Organocatalytic Asymmetric α-Allylation and Propargylation of α-Branched Aldehydes with Alkyl Halides

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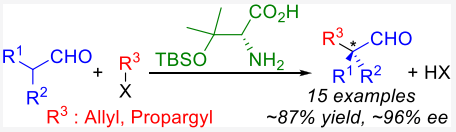
ABSTRACT: Enantioselective α-allylation and -propargylation of α-branched aldehydes with alkyl halides was successfully performed using a chiral primary amino acid organocatalyst. This alkylation reaction, involving the generation of a chiral quaternary carbon stereocenter, proceeded smoothly in a mildly basic aqueous solution of potassium hydrogen carbonate to furnish α-allylated or -propargylated aldehydes in a good yield (up to 87%) and high enantioselectivity (up to 96% ee).



Enantioselective synthesis of a quaternary carbon stereocenter is an important research topic in medicinal chemistry because chiral quaternary carbon stereocenters are found in biologically active compounds such as pharmaceuticals and agrochemicals, and their biological properties can be typically modulated by changing the configuration of the chiral carbon atoms. Various methods have been developed for the carbon−carbon bond formation at a tertiary carbon atom, which is a straightforward procedure to obtain a quaternary carbon atom. However, the development of a highly enantioselective catalytic method is challenging in organic synthesis.[1,2] Generally, an aldehyde is a useful substrate for the carbon−carbon bond formation reaction because the presence of an acidic α-proton of the formyl group enables the easy formation of an enolate, which can be used as a carbon nucleophile. However, direct α-alkylation via an aldehyde enolate typically suffers from side reactions such as *O*-alkylation and aldol reactions.[3] To avoid this, aldehydes are generally converted into enolate equivalents, such as silyl enol ethers[4] and enamines,[5] and then used as carbon nucleophiles for the α-alkylation of aldehydes. The aldehyde enolate equivalents facilitate the asymmetric formation of the carbon−carbon bond, and a number of reports on the asymmetric α-alkylation of aldehydes have been published so far.[6,7] Metal enolates of amides[8a,b] and esters[8c] are also known as useful intermediates for synthesizing α-alkylated aldehydes. In 2000, the List, Lerner, and Barbas group reported L-proline as an excellent catalyst for carrying out the intermolecular asymmetric aldol reaction.[9] Currently, organocatalytic α-alkylation of aldehydes is recognized as one of the most important methods for the asymmetric α-alkylation of aldehydes.[10] By using amino acid or amine organocatalysts, direct α-alkylation of aldehydes can be achieved via the formation of an enamine intermediate. In recent years, the combined use of organocatalysis and transition-metal catalysis for the activation of both an electrophile and a nucleophile to produce a carbon−carbon bond has attracted the attention of synthetic organic chemists.[11] We recently reported the application of readily available primary amino acids and their salts as effective catalysts for the asymmetric α-alkylation of α-branched aldehydes, leading to the generation of a chiral quaternary carbon stereocenter, e.g., conjugate addition to nitroalkenes[12a] and enones.[12b] Moreover, Tsuji−Trost allylation was achieved through synergistic catalysis using a palladium complex and a primary amino acid.[12c−f] As discussed in a previous study by the Rios group,[13] transition-metal-free enamine-based organocatalytic α-alkylation of aldehydes with alkyl halides still remains challenging since this reaction can suffer from self-aldolization of substrates and alkylation of an amine catalyst.[3,7] Despite such difficulty of the transition-metal-free amine catalyzed alkylation of aldehydes, several groups successfully carried out the alkylation by using unique substrates. For example, the List group reported that the asymmetric intramolecular α-alkylation with halo aldehydes proceeded to give cyclic compounds via the S_N2 reaction.[14a] Cascade reactions between aldehydes and halo nitroalkenes by Enders' group[14b] and that between α,β-unsaturated aldehydes and bromomalonates by Córdova's group[14c] also gave cyclic compounds with high enantioselectivity via the enamine-based organocatalysis of aldehydes. As for the intermolecular synthesis, the MacMillan group achieved asymmetric α-alkylation of aldehydes with alkyl halides by photoredox organocatalysis with an amine catalyst and a transition-metal photosensitizer.[15] The Cozzi group[16a,b] and Nishibayashi group[16c] also successfully carried out α-allylation or -propargylation of aldehydes by synergistic catalysis with an organocatalyst and a transition-metal catalyst. Although there are not many reports, transition-metal-free intermolecular α-alkylation of aldehydes was also achieved. For example, S_N1-type alkylation reactions of enamine-based organocatalysis with aldehydes were reported

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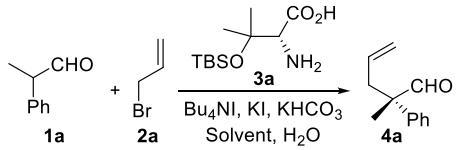
by Petrini and Melchiorre group,[17a,b] Cozzi group,[17c−e] and Jacobsen group.[17f] List group achieved α-benzylation of α-branched aldehydes by S_N2-type reaction of enamine-based organocatalysis.[18] Palomo group reported that α-allylation of aldehydes with electron-deficient allyl halides proceeded in the presence of a silyl prolinol catalyst and a stoichiometric amount of tertiary amines.[19] Among the works regarding transition-metal-free intermolecular α-alkylation of aldehydes described above, Cozzi,[17e] Jacobsen,[17f] and List[18] successfully synthesized a chiral quaternary carbon stereocenter with high enantioselectivity by alkylation of α-branched aldehydes. In the context of these pioneering works, the author turned our attention toward the transition-metal-free α-alkylation of α-branched aldehydes with simple alkyl halides through enamine-based organocatalysis. Herein, the successful development of an efficient method for the asymmetric α-alkylation of α-branched aldehydes with allyl or propargyl halides to generate a chiral quaternary carbon stereocenter through enamine-based organocatalysis by using a primary amino acid as the catalyst is described.

Initially, alkylation of 2-phenylpropionaldehyde (**1a**) with allyl bromide (**2a**) was performed in the presence of a catalytic amount of *O*-(*tert*-butyldimethylsilyl)-3-hydroxy-D-valine (**3a**).[12d] Because a stoichiometric amount of acid waste would be generated in this reaction, a base was added to the reaction mixture to neutralize it. First, a sterically hindered amine, diisopropylethylamine, was chosen as an organic base to avoid its *N*-alkylation by **2a**; however, alkylation of catalyst **3a** occurred to stall the alkylation of aldehyde **1a** (Supporting Information). In contrast, alkylation using an inorganic base such as potassium hydrogen carbonate ($KHCO_3$) in an aqueous solvent at 0 °C suppressed the catalyst alkylation to predominantly give **4a** while maintaining the enantioselectivity (Table 1, entry 1). Because the reaction mixture contained

Table 1. Organocatalytic Alkylation of 1a with 2a in the Presence of $KHCO_3$[a]



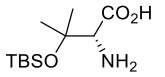
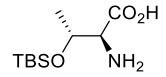
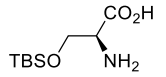
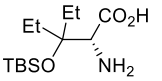
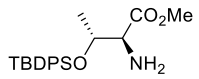
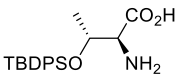
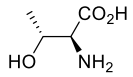
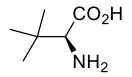
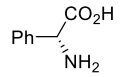
entry	Bu_4NI (equiv)	KI (equiv)	solvent	yield (%)	ee (%)
1	none	1.0	2-PrOH	20	93
2	1.0	none	2-PrOH	64	90
3	0.5	0.5	2-PrOH	60	92
4	0.5	none	2-PrOH	55	92
5[b]	0.5	0.5	2-PrOH	64	92
6[b]	0.5	0.5	*tert*-BuOH	64	92

[a]The typical reaction was performed with **1a** (0.5 mmol), **2a** (1 mmol), **3a** (0.1 mmol), $KHCO_3$ (1 mmol), KI, Bu_4NI in H_2O (1 mL) and solvent (0.6 mL) at 0 °C for 16 h under Ar. [b]Allyl methanesulfonate (**2b**) was used instead of **2a**.

immiscible organic and aqueous phases, the use of tetrabutylammonium iodide (Bu_4NI), a phase transfer catalyst, instead of KI to promote the alkylation reaction led to the formation of **4a** in higher yield (entry 2). Brief solvent screening led to the identification of 2-propanol (2-PrOH) as the optimal solvent for the alkylation reaction, furnishing **4a** in good yield and high enantioselectivity (Supporting Information). The optimal amounts of Bu_4NI and KI were also investigated, and it was found that higher enantioselectivity was obtained when the amount of Bu_4NI was low (entry 3). Although the alkylation reaction proceeded even with a catalytic amount of iodide, it occurred more smoothly when a stoichiometric amount of iodide was used (entry 4). The use of allyl methanesulfonate (**2b**) instead of **2a** led to a slight increase in the yield of **4a**. Likewise, the use of 2-PrOH and *tert*-butanol (*tert*-BuOH) as solvents was found to give a higher yield than other alcohols (entries 5 and 6).

Next, we screened for the optimal catalyst for the alkylation of **1a** with **2b** (Table 2). Compared to catalyst **3a**, the less hindered

Table 2. Catalyst Screening for the Alkylation of 1a with 2b[a]

Catalysts **3**, Yield of **4a**, ee[b]		
		
3a, 64%, 92% ee	**3b**, 63%, 83% ee[c]	**3c**, 41%, 71% ee[c]
		
3d, 46%, 83% ee	**3e**, trace, nd	**3f**, 64%, 60% ee[c]
		
3g, trace, nd	**3h**, 17%, 70% ee[c]	**3i**, trace, nd

[a]The reaction was performed with **1a** (0.5 mmol), **2b** (1 mmol), **3** (0.1 mmol), $KHCO_3$ (1 mmol), KI (0.25 mmol), Bu_4NI (0.25 mmol) in H_2O (1 mL), and 2-PrOH (0.6 mL) at 0 °C for 16 h under Ar. [b]nd = not determined [c]Enantiomer of **4a** was obtained.

amino acids **3b** and **3c** exhibited lower enantioselectivity, while a more hindered amino acid **3d** resulted in a slower reaction rate. Thus, a moderately bulky amino acid was found to be essential for the efficient catalysis of the alkylation reaction and the achievement of high enantioselectivity. Next, the methyl ester of *O*-silylated L-threonine **3e** was used as a catalyst. However, the reaction was very slow, and only a trace amount of **4a** was obtained. Because the alkylation reaction with its methyl-group-free amino acid analog, **3f**, proceeded smoothly, the carboxy group of the amino acid was determined to be important for the efficient promotion of the alkylation reaction. Siloxy-group-free amino acids **3g−i** also did not promote the alkylation reaction well, and **4a** was formed in a low yield. This poor result was possibly because the solubility of amino acids in the organic phase affected the reaction rate of the alkylation of **1a** with **2b**, and amino acids **3a−d,f**, which were soluble in the organic phase, gave a higher yield than hydrophilic amino acids **3g−i**. Consequently, amino acid **3a** was chosen as the catalyst for further investigation.

After small optimization of the reaction conditions, it was found that the increased catalyst loading to 30 mol % was required for obtaining the alkylated product in a good yield without prolonging the reaction time. By using *tert*-BuOH as an organic solvent instead of 2-PrOH, the use of H_2O and an organic solvent could be reduced to 0.6 and 0.4 mL, respectively, for the reaction with 0.5 mmol of aldehyde. Then, the substrate scope of the alkylation reaction was investigated with various α-branched aldehydes **1** and alkylating reagents **2** (Table 3). The

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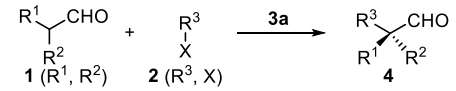
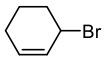
Table 3. Substrate Scope[a]



1a (Me, Ph)
1b (Me, 4-MeC$_6$H$_4$)
1c (Me, 3-MeC$_6$H$_4$)
1d (Me, 2-MeC$_6$H$_4$)
1e (Me, 4-ClC$_6$H$_4$)
1f (Me, 3-ClC$_6$H$_4$)
1g (Me, 2-ClC$_6$H$_4$)
1h (Me, 4-FC$_6$H$_4$)
1i (Me, 4-MeOC$_6$H$_4$)
1j (Me, naphthalen-2-yl)
1k (Et, Ph)
1l (Me, 2-phenylethyl)

2a (CH$_2$CH=CH$_2$, Br)
2b (CH$_2$CH=CH$_2$, OSO$_2$Me)
2c (CH$_2$CH=CH$_2$, Cl)
2d (CH$_2$CH=CMe$_2$, Br)
2e (CH$_2$CH=CHMe, Br)
2f (CH$_2$C≡CH, Br)
2g (Et, OSO$_2$Me)
2h 

entry	1	2	4	yield (%)[b]	ee (%)[c]
1	**1a**	**2b**	**4a**	80	92
2[d]	**1a**	**2b**	**4a**	31	94
3	**1a**	**2a**	**4a**	76	91
4	**1a**	**2c**	**4a**	22	92
5	**1b**	**2b**	**4b**	84	90
6	**1c**	**2b**	**4c**	84	92
7	**1d**	**2b**		nr	nd
8	**1e**	**2b**	**4e**	80	96
9	**1f**	**2b**	**4f**	77	93
10	**1g**	**2b**		nr	nd
11	**1h**	**2b**	**4h**	79	92
12	**1i**	**2b**	**4i**	82	88
13	**1j**	**2b**	**4j**	83	92
14[e]	**1k**	**2b**	**4k**	67	91
15[e]	**1l**	**2b**		nr	nd
16	**1a**	**2d**	**4m**	71	79
17	**1a**	**2e**	**4n**	81	86
18[f]	**1a**	**2f**	**4o**	87	90
19[f]	**1h**	**2f**	**4p**	80	88
20[f]	**1i**	**2f**	**4q**	85	92
21	**1a**	**2g**		nr	nd
22[g]	**1i**	**2h**	**4r**	13	87
23[h]	**1a**	**2b**	**4a**	87	94

[a]The typical reaction was performed with **1** (0.5 mmol), **2** (1 mmol), **3a** (0.15 mmol), KHCO$_3$ (1 mmol), KI (0.25 mmol), Bu$_4$NI (0.25 mmol) in H$_2$O (0.6 mL), and *tert*-BuOH (0.4 mL) at 0 °C for 24 h under Ar. [b]nr = no reaction [c]nd = not determined [d]The reaction was performed with **1a** (0.5 mmol), **2b** (1 mmol), **3a** (0.15 mmol), KHCO$_3$ (1.25 mmol), Bu$_4$NHSO$_4$ (0.25 mmol) in H$_2$O (0.6 mL), and *tert*-BuOH (0.4 mL) at 0 °C for 87 h under Ar. [e]The reaction was performed for 72 h. [f]The reaction was performed for 64 h. [g]The reaction was performed for 54 h. [h]The reaction was performed with **1** (2.5 mmol), **2** (5 mmol), **3a** (0.75 mmol), KHCO$_3$ (5 mmol), KI (1.25 mmol), Bu$_4$NI (1.25 mmol) in H$_2$O (3.0 mL), and *tert*-BuOH (2.0 mL) at 0 °C for 24 h under Ar.

alkylation reaction proceeded in a two-phase reaction mixture consisted of organic and aqueous phases under the best reaction conditions. The progress of the reaction was monitored by TLC, and workup was performed after no further change was observed. Under the optimized reaction conditions, the alkylation reaction of **1a** with **2b** was completed within 24 h and afforded **4a** in 80% yield and 92% ee (entry 1). Because the alkylation was slow in the absence of iodide ions, it is likely that the alkylation of **1a** with allyl iodide, which is presumed to be generated by the reaction of **2b** and the iodide ion, proceeded faster than that with **2b** (entry 2). Likewise, the alkylation reaction with allyl bromide **2a** in the presence of iodide ions afforded **4a** in good yield and high enantioselectivity(entry 3). However, the same reaction with allyl chloride **2c** gave **4a** in low yield, probably because of the slow conversion of **2c** to allyl iodide (entry 4). Next, the alkylation reaction was carried out with an aldehyde possessing a methyl or a chloro substituent on the aryl ring. Although no reaction was observed with *ortho*-substituted aldehydes, *para*- and *meta*-substituted aldehydes gave the alkylated products in good yield and high enantioselectivity (Entries 5−10). Likewise, the use of 2-(4-fluorophenyl)propionaldehyde (**1h**), 2-(4-methoxyphenyl)-propionaldehyde (**1i**), and 2-(naphthalen-2-yl)propion-aldehyde (**1j**) led to the formation of alkylated products **4h**, **4i**, and **4j** (entries 11−13). 2-Phenylbutyraldehyde (**1k**) was also found to be a good substrate for obtaining alkylated **4k**, although the reaction was slow (entry 14). In contrast to the above-mentioned successful results, no reaction was observed when α,α-dialkylacetaldehyde **1l** was employed as a substrate (entry 15). Some additional alkylating reagents were also used for the alkylation of **1a**. Disubstituted and monosubstituted allyl bromide **2d** and **2e** also gave the respective alkylated products **4m** and **4n** in good yield and high enantioselectivity (entries 16 and 17). Since no secondary alkylated products were observed in the reaction with **2e**, it was found that the alkylation of aldehydes would proceed via the S_N2 reaction. Propargylation with **2f** was also investigated, and alkylated products **4o−q** were synthesized in good yield and high enantioselectivity (entries 18−20). Unfortunately, no reaction was observed in the case of reaction with ethylmethanesulfonate (**2g**), probably because of the lower reactivity of a simple alkyl halide than that of allyl or propargyl halides (entry 21). Although the reaction with cyclohexenyl bromide **2h** was very slow, corresponding alkylated product **4r** was obtained with high enantioselectivity (entry 22). Finally, a larger scale synthesis was conducted, and a good yield of **4a** was obtained from 2.5 mmol of **2a** (entry 23).

The plausible reaction mechanism for the alkylation of **1a** with **2b** is proposed in Scheme 1. By comparing the specific rotation with those reported previously, it was found that **4a** was an *S*-enantiomer.[12c,17d] Initially, **3a**, the amino acid catalyst, was converted to its potassium or tetrabutylammonium salt (**3a-OM**) in the presence of KHCO$_3$ or Bu$_4$NI, respectively (Scheme 1a). Then, **3a-OM** reacted with **1a** to give imine **Im-1**, which generated enamine **Im-2** by tautomerization. Concurrently, allyl iodide was generated by the reaction of **2b** with the iodide ion. Enamine **Im-2** then underwent alkylation by allyl iodide to give imine **Im-3**, which was, in turn, converted to α-alkylated aldehyde **4a** and catalyst **3a-OM** by hydrolysis. An acid waste, hydrogen iodide (HI), generated during the alkylation of **Im-2**, was neutralized by KHCO$_3$ to generate KI. A plausible mechanism for the stereocontrol is depicted in Scheme 1b.[12f] To avoid steric repulsion between the enamine moiety and the carboxylate group, the large amino acid side chain (Y) was oriented perpendicular to the *re* face of the α-carbon atom of the enamine moiety. Consequently, the allyl iodide approached the enamine from its *si* face, assisted by an electrostatic interaction between allyl iodide and the carboxylate group to furnish the *S*-enantiomer of alkylated **4a**.

In conclusion, the asymmetric α-alkylation of α-branched aldehydes with allyl or propargyl halides was successfully achieved using *O*-(*tert*-butyldimethylsilyl)-3-hydroxy-D-valine, a chiral primary-amino-acid-based enamine organocatalyst. By carrying out the alkylation reaction in an aqueous solvent, it was found that the catalyst alkylation was suppressed to give an

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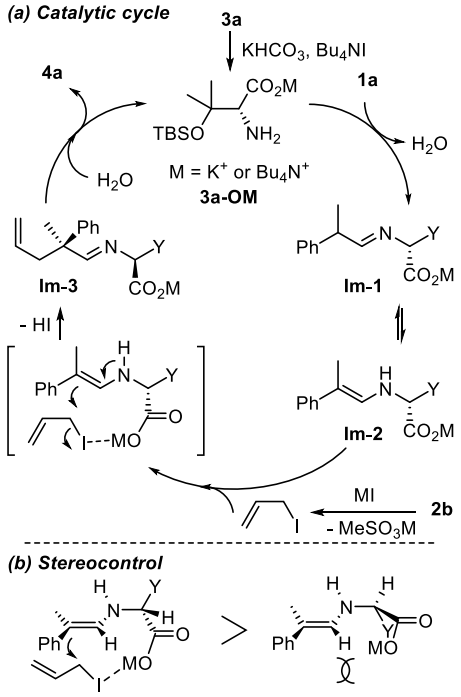
Scheme 1. Plausible Reaction Mechanism



alkylated product in a good yield. In this reaction, a chiral quaternary carbon stereocenter was generated with high enantioselectivity.

EXPERIMENTAL SECTION

Materials. Aldehydes **1**, alkylating reagents **2**, and amino acids **3** used in this study are known compounds. Aldehyde **1a** was purchased and used after column chromatography (silica gel, hexane−Et_2O 19:1); other aldehydes **1b**,[20a] **1c**,[18] **1d**,[20b] **1e**,[20c] **1f,g**,[20b] **1h**,[20c] **1i−k**,[20a] and **1l**[20d] were synthesized according to the literature procedure.[20a] Alkylating reagents **2a,c−h** were purchased and used after distillation; **2b** was synthesized from allyl alcohol and methane sulfonyl chloride by a general procedure for the transformation of an alcohol to a sulfonate.[21] *O*-Silylated amino acids **3a**,[12d] **3b,c**,[22] **3d**,[12d] **3e**,[12f] and **3f**[22] were synthesized according to the literature procedures; other amino acids **3g−i** were purchased and used without purification. Purification of alkylated products **4** was accomplished by column chromatography on Kanto Chemical Co., Inc. silica gel, 60 N (spherical, neutral; 63−210 μm). Proton NMR (^{1}H NMR), fluorine NMR (^{19}F NMR), and proton-decoupled carbon NMR [^{13}C{^{1}H} NMR] spectra were recorded on a JNM-ECS400 FT NMR unit. Chemical shifts, δ of ^{1}H NMR, and ^{13}C{^{1}H} NMR are referred to TMS and that of ^{19}F NMR was referred to CF_3CO_2H (−76.55 ppm). The specific rotation was measured by a HORIBA SEPA-500 polarimeter. HPLC was carried out using a JASCO PU-2089 Plus intelligent pump and a UV-2075 Plus UV detector. HRMS were measured on a JMS-T100-LP for **4o** and on a Thermo Scientific Exactive for **4i,n,p−r**.

Typical Procedure for the Alkylation Reaction. In a 7 mL vial, 3-(*tert*-butyldimethylsiloxy)-D-valine (**3a**, 35.1 mg, 0.15 mmol), tetrabutylammonium iodide (92 mg, 0.25 mmol), potassium iodide (42 mg, 0.25 mmol), and potassium hydrogen carbonate (100 mg, 1 mmol) were placed. The vial was capped with a rubber septum, and the atmosphere in the vial was replaced with argon. Then a bubbler was attached to the vial with a needle, a mixture of water (0.6 mL) and *tert*-butanol (0.4 mL) was added, and the mixture was stirred for 5 min at room temperature. After 2-phenylpropionaldehyde (**1a**, 67 mg, 0.5 mmol) and allyl methanesulfonate (**2b**, 136 mg, 1 mmol) were added to the mixture at 0 °C, the whole reaction mixture was stirred for 24 h at the same temperature. The resulting mixture was extracted with Et_2O (1 mL × 4), and the combined organic phase was filtered through a small plug of silica gel, eluted with Et_2O (1 mL × 3), and concentrated under reduced pressure. (*S*)-2-Methyl-2-phenylpent-4-enal (**4a**) was isolated by column chromatography (silica gel, hexane−Et_2O 19:1) in 80% yield (69.8 mg) as a colorless oil. The enantioselectivity was determined by chiral HPLC analysis (92% ee). The absolute configuration was determined by comparison of the specific rotation with those of the literatures:[12c,d] colorless oil; $[\alpha]_{589}^{16.5}$ = +53.4 (*c* 1.0, $CHCl_3$); R_f = 0.71 (*n*-hexane−EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.52 (1H, s), 7.41−7.24 (5H, m), 5.60−5.49 (1H, m), 5.09−5.02 (2H, m), 2.73−2.60 (2H, m), 1.45 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 202.0, 139.4, 133.1, 128.8, 127.3, 127.1, 118.6, 53.6, 40.5, 18.8. Spectroscopic data of **4a−h,j,k**[12c,d] and **4m**[23] are in agreement with the published data.

Larger-Scale Synthesis of 4a. In a 20 mL vial, **3a** (186 mg, 0.75 mmol), tetrabutylammonium iodide (461 mg, 1.25 mmol), potassium iodide (208 mg, 1.25 mmol), and potassium hydrogen carbonate (500 mg, 5 mmol) were placed. The vial was capped with a rubber septum, and the atmosphere in the vial was replaced with argon. Then a bubbler was attached to the vial with a needle, a mixture of water (3.0 mL) and *tert*-butanol (2.0 mL) was added, and the mixture was stirred for 5 min at room temperature. After **1a** (335 mg, 2.5 mmol) and **2b** (680 mg, 5 mmol) were added to the mixture at 0 °C, the whole reaction mixture was stirred for 24 h at the same temperature. The resulting mixture was extracted with Et_2O (5 mL × 4), and the combined organic phase was filtered through a small plug of silica gel, eluted with Et_2O (5 mL × 3), and concentrated under reduced pressure. Allylated product **4a** was isolated by column chromatography (silica gel, hexane−Et_2O 19:1) in 87% yield (376.8 mg) with 94% ee.

2-Methyl-2-(4-methylphenyl)pent-4-enal (4b): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 84% yield (78.8 mg), 90% ee, colorless oil; $[\alpha]_{589}^{16.7}$ = +72.3 (*c* 1.0, $CHCl_3$); R_f = 0.58 (*n*-hexane−EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.49 (1H,s), 7.21−7.19 (2H, m), 7.15−7.13 (2H, m), 5.60−5.50 (1H, m), 5.08−5.01 (2H, m), 2.71−2.58 (2H, m), 2.34 (3H, s), 1.42 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 202.0, 137.0, 136.2, 133.3, 129.5, 127.0, 118.5, 53.2, 40.5, 20.9, 18.8.

2-Methyl-2-(3-methylphenyl)pent-4-enal (4c): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 84% yield (78.8 mg), 92% ee, colorless oil; $[\alpha]_{589}^{16.9}$ = +77.8 (*c* 1.0, $CHCl_3$); R_f = 0.49 (*n*-hexane−EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.50 (1H, s), 7.29−7.28 (1H, m), 7.12−7.04 (3H, m), 5.60−5.50 (1H, m), 5.09−5.01 (2H, m), 2.71−2.59 (2H, m), 2.36 (3H, s), 1.43 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 202.0, 139.3, 138.5, 133.3, 128.7, 128.1, 127.9, 124.1, 118.5, 53.5, 40.5, 21.6, 18.8.

2-(4-Chlorophenyl)-2-methylpent-4-enal (4e): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 80% yield (83.0 mg), 96% ee, colorless oil; $[\alpha]_{589}^{19.0}$ = +83.0 (*c* 1.0, $CHCl_3$); R_f = 0.56 (*n*-hexane−EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.49 (1H, s), 7.37−7.34 (2H, m), 7.20−7.17 (2H, m), 5.57−5.46 (1H, m), 5.08−5.03 (2H, m), 2.69−2.57 (2H, m), 1.44 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 201.4, 137.9, 133.4, 132.6, 129.0, 128.6, 119.0, 53.2, 40.5, 18.8.

2-(3-Chlorophenyl)-2-methylpent-4-enal (4f): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 77% yield (79.9 mg), 93% ee, colorless oil; $[\alpha]_{589}^{17.1}$ = +74.1 (*c* 1.0, $CHCl_3$); R_f = 0.43 (*n*-hexane−EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.51 (1H, s), 7.34−7.25 (3H, m), 7.14−7.12 (1H, m), 5.58−5.47 (1H, m), 5.10−5.05 (2H, m), 2.70−2.58 (2H, m), 1.44 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 201.3, 141.6, 134.9, 132.5, 130.0, 127.6, 127.4, 125.4, 119.1, 53.6, 40.5, 18.8.

2-(4-Fluorophenyl)-2-methylpent-4-enal (4h): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 79% yield (75.6 mg), 92% ee, colorless oil; $[\alpha]_{589}^{21.8}$ = +71.7 (*c* 1.0, $CHCl_3$); R_f = 0.56 (*n*-hexane−EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) 9.49 (1H, s), 7.25−7.20 (2H, m), 7.10−7.05 (2H, m), 5.58−5.47 (1H, m), 5.08−5.03 (2H, m), 2.70−2.57 (2H, m), 1.44 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 201.6, 162.0 (d, *J* 246 Hz), 135.0, 132.8, 128.9 (d, *J* 7.7 Hz), 118.9, 115.7(d, *J* 21 Hz), 53.1, 40.7, 18.9; ^{19}F NMR (376 MHz, $CDCl_3$) − 116.0.

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2-Methyl-2-(4-methoxyphenyl)pent-4-enal (4i): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 82% yield (83.6 mg), 88% ee, colorless oil; $[\alpha]_{589}^{16.6}$ = +92.3 (*c* 1.0, $CHCl_3$); R_f = 0.53 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.46 (1H, s), 7.19−7.15 (2H, m), 6.94−6.90 (2H, m), 5.60−5.50 (1H, m), 5.08−5.01 (1H, m), 3.81 (3H, s), 2.70−2.57 (2H, m), 1.42 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 201.9, 158.7, 133.3, 131.1, 128.3, 118.5, 114.2, 55.2, 52.9, 40.5, 18.8.; ν(neat)/cm^{-1} 1720 (C═O); HRMS (APCI/Orbitrap) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}O_2^+$ 205.1223, found 205.1224.

2-Methyl-2-(naphthalen-2-yl)pent-4-enal (4j): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 83% yield (93.5 mg), 92% ee, colorless oil; $[\alpha]_{589}^{17.2}$ = +124.0 (*c* 1.0, $CHCl_3$); R_f = 0.54 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.59 (1H, s), 7.87−7.81 (3H, m), 7.711−7.707 (1H, m), 7.53−7.46 (2H, m), 7.38−7.35 (1H, m), 5.61−5.51 (1H, m), 5.11−5.01 (2H, m), 2.85−2.69 (2H, m), 1.55 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 202.0, 136.7, 133.3, 133.1, 132.4, 128.6, 128.0, 127.5, 126.4, 126.3, 125.0, 118.7, 53.8, 40.5, 18.9.

2-Ethyl-2-phenylpent-4-enal (4k): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 67% yield (63.0 mg), 91% ee, colorless oil; $[\alpha]_{589}^{17.4}$ = +50.8 (*c* 1.0, $CHCl_3$); R_f = 0.60 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.50 (1H, s), 7.40−7.20 (5H, m), 5.57−5.47 (1H, m), 5.10−5.02 (2H, m), 2.77−2.64 (2H, m), 2.06−1.92 (2H, m), 1.80 (3H, t, *J* 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 202.5, 138.5, 132.9, 128.8, 127.6, 127.3, 118.4, 57.5, 36.1, 24.5, 8.0.

2,5-Dimethyl-2-phenylhex-4-enal (4m): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 71% yield (72.2 mg), 79% ee. Light yellow oil; $[\alpha]_{589}^{17.5}$ = +37.1 (*c* 1.0, $CHCl_3$); R_f = 0.61 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.53 (1H, s), 7.40−7.25 (5H, m), 4.96−4.91 (1H, m), 2.67−2.56 (2H, m), 1.65 (3H, d, *J* 0.8 Hz), 1.56 (3H, s), 1.42 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 202.6, 140.0, 135.0, 128.7, 127.1, 118.6, 118.4, 54.4, 34.4, 25.9, 19.0, 17.9.

2-Methyl-2-phenylhex-4-enal (4n): obtained as a mixture of (*E*)- and (*Z*)-isomers by column chromatography (silica gel, hexane−Et_2O 19:1); 81% yield (75.7 mg), 86% ee, colorless oil; $[\alpha]_{589}^{16.8}$ = +39.3 (*c* 1.0, $CHCl_3$); R_f = 0.66 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.54 (1H, s), 9.52 (1H, s), 7.40−7.36 (2H, m), 7.31−7.23 (3H, m), 5.59−5.44 (1H, m), 5.23−5.14 (1H, m), 2.68−2.66 (2H, m), 2.62−2.60 (2H, m), 1.61−1.59 (3H, m), 1.57−1.55 (3H, m), 1.44 (3H, s), 1.41 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 202.5, 202.3, 139.8, 139.6, 129.3, 128.8, 127.24, 127.19, 127.1, 125.3, 124.5, 54.1, 53.8, 39.2, 33.2, 19.0, 18.8, 18.0, 12.9.; ν(neat)/cm^{-1} 1722 (C═O); HRMS (APCI/Orbitrap) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}O^+$ 189.1274, found 189.1276.

2-Methyl-2-phenylpent-4-ynal (4o): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 87% yield (74.6 mg), 90% ee, colorless oil; $[\alpha]_{589}^{17.5}$ = +98.9 (*c* 1.0, $CHCl_3$); R_f = 0.53 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.53 (1H, s), 7.43−7.38 (2H, m), 7.35−7.27 (3H, m), 2.85−2.71 (2H, m), 1.97 (1H, t, *J* 2.8 Hz), 1.62 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 200.4, 138.2, 128.9, 127.7, 127.0, 80.0, 71.4, 53.2, 26.3, 19.0; ν(neat)/cm^{-1} 1721 (C═O), 2119 (C≡C), 3290 (≡C—H); HRMS (ESI/TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{12}ONa^+$ 195.0780, found 195.0781.

2-(4-Fluorophenyl)-2-methylpent-4-ynal (4p): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 80% yield (76.3 mg), 88% ee, colorless oil; $[\alpha]_{589}^{16.7}$ = +87.4 (*c* 1.0, $CHCl_3$); R_f = 0.43 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.50 (1H, s), 7.27−7.22 (2H, m), 7.12−7.06 (2H, m), 2.81−2.69 (2H, m), 1.97 (1H, t, J 2.8 Hz), 1.61 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 200.1, 162.2 (d, *J* = 246 Hz), 133.9 (d, *J* = 10.9 Hz), 128.8 (d, *J* = 28.6 Hz), 115.8 (d, *J* = 82.3 Hz), 79.8, 71.6, 52.7, 26.5, 19.2; ^{19}F NMR (376 MHz, $CDCl_3$), −115.3; ν (neat)/cm^{-1} 1722 (C═O), 2120 (C≡C), 3297 (≡C—H); HRMS (APCI/Orbitrap) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{12}FO^+$ 191.0867, found 191.0868.

2-Methyl-2-(4-methoxyphenyl)pent-4-ynal (4q): isolated by column chromatography (silica gel, hexane−Et_2O 19:1); 85% yield (86.2 mg), 92% ee, colorless oil; $[\alpha]_{589}^{16.7}$ = +114.1 (*c* 1.0, $CHCl_3$); R_f = 0.49 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.47 (1H, s), 7.21−7.17 (2H, m), 6.95−6.91 (2H, m), 3.81 (3H, s), 2.81−2.68 (2H, m), 1.97 (1H, t, *J* 2.4 Hz), 1.59 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 200.3, 159.0, 129.9, 128.2, 114.2, 80.2, 71.3, 55.2, 52.5, 26.3, 19.1; ν(neat)/cm^{-1} 1722 (C═O), 2115 (C≡C), 3289 (≡C—H); HRMS (ESI/Orbitrap) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{14}O_2Na^+$ 225.0886, found 225.0886.

2-(1-Cyclohexen-3-yl)-2-phenylpropanal (4r): obtained as a mixture of diastereomers by column chromatography (silica gel, hexane−Et_2O 19:1); 81% yield (75.7 mg), 86% ee, colorless oil; $[\alpha]_{589}^{16.5}$ = +2.7 (*c* 1.0, $CHCl_3$); R_f = 0.66 (*n*-hexane−EtOAc, 9:1); ^1H NMR (400 MHz, $CDCl_3$) 9.54 (1H, s), 9.52 (1H, s), 7.40−7.36 (2H, m), 7.31−7.23 (3H, m), 5.59−5.44 (1H, m), 5.23−5.14 (1H, m), 2.68−2.66 (2H, m), 2.62−2.60 (2H, m), 1.61−1.59 (3H, m), 1.57−1.55 (3H, m), 1.44 (3H, s), 1.41 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 202.5, 202.3, 139.8, 139.6, 129.3, 128.8, 127.24, 127.19, 127.1, 125.3, 124.5, 54.1, 53.8, 39.2, 33.2, 19.0, 18.8, 18.0, 12.9; ν(neat)/cm^{-1} 1717 (C═O); HRMS (ESI/Orbitrap) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}O_2Na^+$ 267.1356, found 267.1356.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01394.

HPLC data; ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra of **4** (PDF)

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Notes

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