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Enantioselective Organocatalytic Aza-Ene-Type Domino Reaction Leading to 1,4-Dihydropyridines

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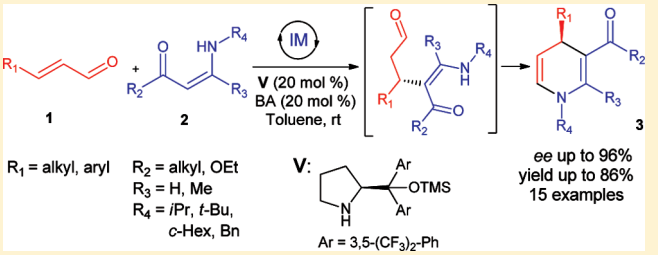
Supporting Information

ABSTRACT: A new general methodology was developed to access highly enantiomerically enriched 1,4-dihydropyridines (DHPs) **3** via an organocatalytic asymmetric aza-ene-type cascade reaction, cocatalyzed by (*S*)-diarylprolinol−TMS ether **V** and benzoic acid (BA). Both aliphatic and aryl enals **1** reacted smoothly with enaminones and *β*-enamino esters **2**, affording highly functionalized 1,4-DHPs **3** in high enantioselectivities and good yields.



INTRODUCTION

1,4-Dihydropyridines (1,4-DHPs) are a well-known class of biologically active heterocycles as well as analogues of NADH coenzymes. Probably the best known family of 1,4-DHPs are calcium channel blockers, used primarily to treat vascular disorders.[1,2] They have also been used as antitumor[3] and antidiabetic agents,[4] HIV protease inhibitors,[5] and drugs in the treatment of a number of other diseases.[6−8]

1,4-DHPs, being NADH mimics, are used as hydride sources in a wide variety of organocatalytic asymmetric reductions.[9−13] The simplest synthetic route to symmetrical 1,4-DHPs is the classical Hantzsch condensation of aryl aldehydes with ammonia or amines and 2 equiv of *β*-keto esters developed in 1882.[14] However, the methodology is not applicable for the synthesis of chiral, unsymmetrical 1,4-DHPs. Although the symmetrical DHP unit is present in many drugs, it is not always a requirement for their activity but rather a consequence of a Hantzsch condensation reaction. In many cases, chiral and/or unsymmetrical DHPs have exhibited higher or in the case of enantiomers an opposite pharmacological activity.[15,16] The value of the eudismic ratio can be as high as 1000.[17]

Although enantiomerically pure 1,4-DHPs are of great biological importance, a general methodology for accessing these types of compounds remains intangible. While a number of routes to racemic unsymmetrical DHPs have been described,[18−24] the enantiomerically pure compounds are conventionally produced either by enzymatic[25] or chemical[26−29] resolution of racemates or by the use of chiral auxiliaries.[30]

Only a few catalytic asymmetric synthesis procedures for chiral 1,4-DHPs have been reported. Takemoto et al.[31,32] developed a new Brønsted acid and novel thiourea derivative cocatalyzed method for the addition of *β*-enamino esters to enals to give access to chiral 1,4-DHPs with moderate to good enantioselectivities. However, the ee value of the products did not exceed 80%.

Gong and co-workers[33] established a one-pot protocol, using chiral phosphoric acid as a catalyst and primary amines, *β*-dicarbonyl compounds, and α,*β*-unsaturated aldehydes as starting materials to yield 1,4-DHPs, with good to excellent enantioselectivities. Aromatic enals gave high yields, whereas a *β*-alkyl-substituted unsaturated aldehyde furnished the product with a low yield and modest selectivity.

Jørgensen's aminocatalytic approach[34] was based on the activation of α,*β*-unsaturated aldehydes by diaryl prolinol silyl ether derivatives, which enabled them to direct the Michael addition of *β*-dicarbonyl compounds in a highly enantioselective manner. A primary amine was added to obtain 1,4-DHPs in a one-pot synthesis with up to 95% ee. Although the conversion of the starting materials was almost quantitative, yields of the targets remained moderate (31−60%). The last observation was explained by the reversible nature of the initial Michael addition. In addition, the simultaneous presence of the competing secondary amine as a catalyst and the primary amine as a nucleophile decreased the yield of the one-pot reaction. The established method was mostly limited to the use of aliphatic unsaturated aldehydes as it was shown that aromatic α,*β*-unsaturated aldehydes (especially with electron-donating substituents) led to the formation of product with a low yield and selectivity.

RESULTS AND DISCUSSION

As a part of our ongoing research on organocatalysis,[35−38] we set out to develop a general organocatalytic approach for the asymmetric synthesis of 1,4-DHPs. We intended to take advantage of the highly stereoselective aminocatalyst and make the catalytic cycle irreversible under the reaction conditions, using enaminones as nucleophiles. Instead of being Michael acceptors, the amine-activated double bond of the enaminone

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Scheme 1. Envisioned Cascade Reaction of Unsaturated Aldehydes with Enaminones

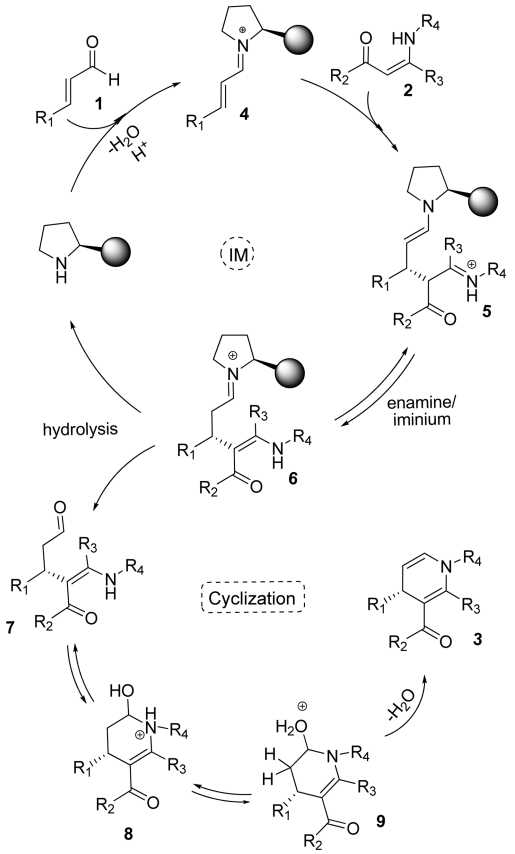
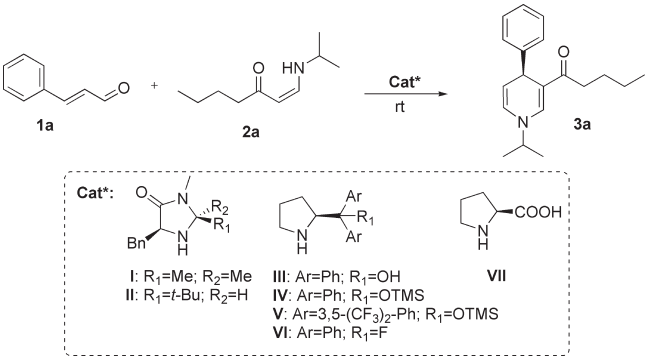


Table 1. Screening of the Catalysts



entry	cat*	additive	solvent	time (h)	yield[e] (%)	ee[f] (%)
1	**I**[a]	HCl[a]	DCE	19	19	20
2	**II**[a]		DCE	19	traces	n.d.
3	**III**[a]		DCE	72	15	*rac*
4	**IV**[a]		DCE	72	40	50
5	**IV**[b]	BA[b]	DCE	21	65	82
6	**IV**[b]	BA[b]	toluene	20	63	89
7	**IV**[b]	BA[b]	toluene	96	15[c]	64
8	**IV**[b]	TFA[b]	toluene	18	37	64
9	**IV**[b]	3,5-NO_2−BA[b]	toluene	22	45	77
10	**IV**[b]	4-NO_2−BA[b]	toluene	2	61	84
11	**V**[b]	BA[b]	toluene	20	75	93
12	**VI**[b]	BA[b]	toluene	18	70	71
13	**VII**[a]		DMF[d]	72	traces	n.d.

[a] 15 mol %. [b] 20 mol %. [c] Reaction at −20 °C. [d] Reaction at 80 °C. [e] Reaction was carried out at rt using 2 equiv of **1a** and 1 equiv of **2a**. [f] Determined by chiral HPLC.

2 (or β-enamino esters) enables a conjugate addition to α,β-unsaturated aldehydes via an iminium intermediate **4** followed by proton transfer and spontaneous iminium−enamine transformation (**5**/**6**) (Scheme 1) (a formal aza-ene-type reaction).[39] At the same time, the nucleophilicity of the amino group in compound **2** is suppressed by the electron-withdrawing properties of the neighboring α,β-unsaturated carbonyl moiety. We hypothesized that the stereoselectivity of the reaction would be determined with the first step affording stereoselectively an intermediate **5**. The following cascade of reactions involves the hydrolysis of the iminium intermediate **6** leading to a intramolecular cyclization giving rise to a six-membered heterocycle **8**. After a proton transfer has taken place, the intermediate **9** dehydrates to give an energetically more favored 1,4-DHP **3**. These considerations are outlined in Scheme 1.

Based on the considerations presented above, we investigated a reaction between (*E*)-cinnamaldehyde **1a** and *N*-*i*-Pr-enaminone **2a** catalyzed by different secondary amines in the presence or absence of a cocatalyst (Table 1). The catalysts chosen for the screening have all been efficient in iminium-catalyzed reactions.[40,41] It was found that the reaction was highly dependent on the catalyst and additives used. MacMillan's catalysts **I** and **II** and diphenylprolinol **III** were inefficient in the presence or absence of acidic additive (Table 1, entries 1−3).

Although (*S*)-diphenylprolinol−TMS ether **IV** gave the product with 50% ee after 72 h (Table 1, entry 4), the selectivity and yield were greatly improved when benzoic acid (BA) was used as a cocatalyst (Table 1, entry 5). To our delight, switching from DCE to toluene as a solvent improved the selectivity even further, affording the desired 1,4-DHP **3a** in 63% yield and 89% ee (Table 1, entry 6).

Lowering the reaction temperature to −20 °C almost stopped the reaction as well as having a detrimental effect on the selectivity (Table 1, entry 7). The use of stronger acids as additives also proved to be unproductive, as the DHP **3a** was formed with lower selectivities and yields (Table 1, entries 8−10).

Encouraged by these preliminary results with the catalyst **IV** and benzoic acid as an additive in toluene (Table 1, entry 6), we looked at the effect of a bulkier analogue of **IV** on the reaction under the same conditions. Thus, with 3,5-ditrifluoromethylphenyl prolinol−TMS ether **V** (Table 1, entry 11), the reaction proceeded with higher selectivity, as well as better yield (ee 93%; yield 75%). The fluoro-substituted catalyst **VI** gave poorer results (Table 1, entry 12), and the reaction did not proceed at all when L-proline **VII** was used as a catalyst, even at an elevated temperature (Table 1, entry 13).

With the obtained optimal reaction conditions (Table 1, entry 11) we next explored the scope of the method by testing various α,β-unsaturated aldehydes in the reaction (Table 2). Both aromatic and aliphatic aldehydes **1** reacted smoothly to undergo a cascade reaction, affording 1,4-DHPs **3** with good yields and enantioselectivities (ee from 89% to 96%). Substitution at the aryl ring of the enal **1a**−**d** had little to no effect on the yields and enantioselectivities (Table 2, entries 1−4).

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In the case of aliphatic enals **1f**−**h**, a larger excess of the aldehyde was used to ensure smooth conversion. This did not affect the enantioselectivity, as 1,4-DHPs **3f**−**h** were isolated with up to 96% ee (Table 2, entries 6−8).

To investigate further the scope of the method, different enaminones **2a**−**e** and β-enamino esters **2f**−**g** were prepared (Scheme 2) and subjected to a reaction with cinnamaldehyde **1a** or *p*-nitrocinnamaldehyde **1b** (Table 3). *N*-Cyclohexyl enaminone **2b** yielded 1,4-DHP **3i** with 76% ee (Table 3, entry 1); higher selectivity was achieved when *N*-benzyl and *N*-*tert*-butyl enaminones were subjected to the reaction conditions (Table 3, entries 2 and 3). Cyclic enaminone **2e** (prepared according to a literature procedure; for details, see Scheme 2) gave a lower yield and selectivity (Table 3, entry 4).

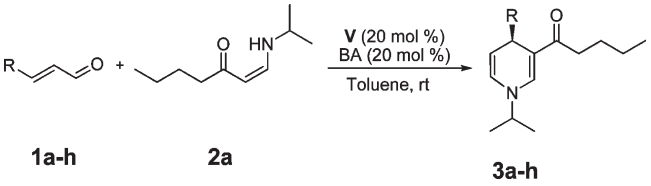
β-Enamino esters **2f**−**g** gave 1,4-DHPs **3** with moderate to good yields and enantioselectivities up to 89% ee (Table 3, entries 5−7). It should be noted that the reaction proceeded much faster than in the case of enaminones, both with aliphatic and aryl enals **1**. This tendency could be attributed to the lower electron-withdrawing effect of the ester group, which increased the nucleophilicity of the β-enamino esters **2** compared to enaminones.

The absolute configuration of the product **3n** was assigned by a comparison of the specific rotation to that described in the literature.[31] It was assumed that all products would have the same configuration (except the deviations caused by CIP rules), as reactions were run under similar conditions and only the substituents at the starting compounds were varied.

An ESI-MS analysis of the crude reaction mixture was performed in order to support the proposed reaction mechanism (Figure 1). A model reaction using (*E*)-cinnamaldehyde **1a** and enaminone **2a** was selected for the experiment. The reaction was run for 3 h at room temperature, and then the mixture was diluted with acetonitrile for direct analysis via ESI-MS. The results of the experiment are depicted in Figure 1.

All key intermediates—iminium ion **4**, addition product **5**/**6**, acyclic aldehyde **7**′ (protonated form of **7**), and/or cyclic products **8** and **9**, together with the target product **3**′—were detected. Although it is impossible to distinguish between intermediates **7**−**9** corresponding to the same mass peak 302, it can be hypothesized that all intermediates were formed during the reaction to give the final product. Although the ESI-MS experiment did not provide a definitive proof for the proposed mechanism, it correlated well with the obtained results.

Table 2. Synthesis of 1,4-DHPs with Various α,β-Unsaturated Aldehydes 1



entry	product	R	time (h)	yield (%)	ee[a] (%)
1	**3a**	phenyl	20	75[b]	93 (*S*)
2	**3b**	4-NO_2-phenyl	3	83[c,d]	89 (*S*)
3	**3c**	4-MeO-phenyl	19	86[c]	89 (*S*)
4	**3d**	4-Br-phenyl	18	80[c]	89 (*S*)
5	**3e**	2-naphthyl	24	63[c]	89 (*S*)
6	**3f**	ethyl	18	69[b]	93 (*R*)[e]
7	**3g**	butyl	17	82[b]	96 (*R*)[e]
8	**3h**	(benzyloxy)methyl	17	61[b]	93 (*R*)[e]

[a] Determined by chiral HPLC. [b] Reaction conditions: 2 equiv of α,β-unsaturated aldehyde **1**, 1 equiv of enaminone **2**, 20 mol % of **V**, and BA. [c] Reaction conditions: 1.1 equiv of α,β-unsaturated aldehyde **1**, 1 equiv of enaminone **2**, 20 mol % of **V**, and BA. [d] Reaction was carried out in DCE due to the low solubility of enal **1b** in toluene under the reaction conditions. [e] Change in configuration from *S* to *R* due to CIP rules.

CONCLUSION

We have developed a new general methodology for the synthesis of highly enantiomerically enriched 1,4-DHPs **3** via an organocatalytic aza-ene-type domino reaction, catalyzed by diarylprolinol−TMS ether **V** and benzoic acid. Both enaminones and β-enamino esters **2** reacted with aliphatic and aromatic enals **1** with good to excellent enantioselectivities (up to 96% ee) and yields (up to 86%). The described reaction has a wide scope affording 1,4-DHPs **3** with various substituents at four different positions of the ring. All reactions were carried out under mild conditions. The proposed mechanism for the reaction was supported with mass-spectrometric data of the intermediates. To the best of our knowledge, these results represent the first aza-ene-type cascade reaction of enaminones (and β-enamino esters) with enals catalyzed by chiral secondary amine.

Scheme 2. Synthesis of Enaminones and β-Enamino Esters[42−44]

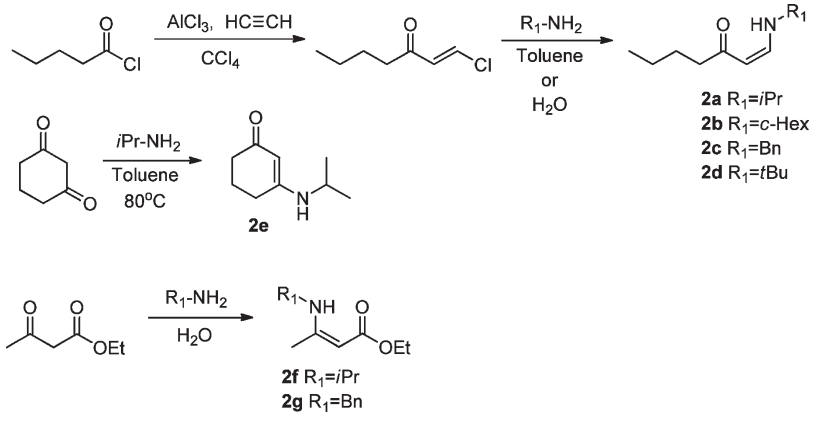


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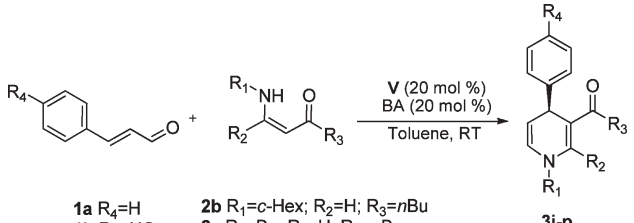
Table 3. Synthesis of 1,4-DHPs 3 with Various β-Enamino Ketones and β-Enamino Esters



1a R_4=H
1b R_4=NO_2

2b R_1=*c*-Hex; R_2=H; R_3=*n*Bu
2c R_1=Bn; R_2=H; R_3=*n*Bu
2d R_1=*t*Bu, R_2=H, R_3=*n*Bu
2e R_1=*i*Pr; R_2-R_3= -$(CH_2)_3$-
2f R_1=*i*Pr; R_2=Me; R_3=OEt
2g R_1=Bn, R_2=Me; R_3=OEt

3i-p

entry	product	time (h)	yield (%)	*ee* (%)[c]
1	**3i**	19	79[a]	76(*S*)
2	**3j**	24	54[a]	87(*S*)
3	**3k**	26	72[a]	89(*S*)
4	**3l**	23	49[a]	62(*S*)
5	**3m**	4	45[b]	84(*S*)
6	**3n**	4	70[b]	89(*S*)
7	**3p**	4	62[a]	71(*R*)[d]

[a] 2 equiv of α,β-unsaturated aldehyde **1** was used. [b] 1.1 equiv of α,β-unsaturated aldehyde **1** was used. [c] Determined by chiral HPLC. [d] Change in configuration from *S* to *R* due to CIP rules.

EXPERIMENTAL SECTION

General Methods. Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a 400 MHz instrument. Internal standard (TMS δ = 0.00) and solvent peak ($CHCl_3$ δ = 77.16) were used as chemical shift references. Mass spectra were recorded using EI (70 eV). Chiral HPLC was performed using a Chiralcel OD-H (250 × 4.6 mm) or Chiralcel OJ-H (250 × 4.6 mm) column. All reactions sensitive to moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware. Toluene was dried by distillation over Na and stored over 4 Å MS. Precoated silica gel 60 F_{254} plates were used for TLC, whereas for column chromatography silica gel KSK407100 μm was used. Commercial reagents were generally used as received. Petroleum ether used had bp 40−60 °C.

Synthesis of Starting Materials. Cinnamaldehyde **1a**, *p*-NO_2-cinnamaldehyde **1b**, *p*-MeO-cinnamaldehyde **1c**, (*E*)-2-pentenal **1f**, and (*E*)-2-heptenal **1g** were commercially available and purchased from Aldrich or Alfa-Aesar. *p*-Br-cinnamaldehyde **1d**, (*E*)-3-(naphthalen-2-yl)-acrylaldehyde **1e**, and (*E*)-4-(benzyloxy)but-2-enal **1h** were prepared according to literature procedures, and spectral data matched that of the literature.[45−47]

***p*-Br-cinnamaldehyde 1d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 7.6 Hz, 1H), 7.60−7.56 (m, 2H), 7.46−7.41 (m, 3H), 6.71 (dd, *J* = 16.0, 7.6 Hz, 1H).

(*E*)-3-(Naphthalen-2-yl)acrylaldehyde 1e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 7.7 Hz, 1H), 7.99 (s, 1H), 7.91−7.83 (m, 3H), 7.68 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.64 (d, *J* = 15.9 Hz, 1H), 7.59−7.51 (m, 2H), 6.83 (dd, *J* = 15.9, 7.7 Hz, 1H).

(*E*)-4-(Benzyloxy)but-2-enal 1h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 7.9 Hz, 1H), 7.40−7.28 (m, 5H), 6.85 (dt, *J* = 15.8, 4.1 Hz, 1H), 6.41 (ddt, *J* = 15.7, 7.9, 1.9 Hz, 1H), 4.59 (s, 2H), 4.29 (dd, *J* = 4.1, 2.0 Hz, 2H).

Synthesis of Enaminones. *N*-iPr-enamino ester **2f**, *N*-Bn-enamino ester **2g**, and *N*-iPr-enaminone **2e** were prepared according to literature procedures, and spectral data matched that of the literature.[43,44]

(*Z*)-Ethyl 3-(isopropylamino)but-2-enoate 2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 4.39 (s, 1H), 4.09 (dt, *J* = 14.2, 5.3 Hz, 2H), 3.74−3.63 (m, 1H), 1.94 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 6H).

(*Z*)-Ethyl 3-(benzylamino)but-2-enoate 2g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.37−7.23 (m, 5H), 4.53 (s, 1H), 4.42 (s, 2H), 4.10 (t, *J* = 10.7 Hz, 2H), 1.92 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

3-(Isopropylamino)cyclohex-2-enone 2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.60 (s, 1H), 3.66 − 3.51 (m, 1H), 2.31 (t, *J* = 6.5 Hz, 4H), 2.00−1.92 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 6H).

Synthesis of (*E*)-1-Chlorohept-1-en-3-one. Acetylene was bubbled through concentrated sulfuric acid to dry it and remove acetone used in storing the gas. In a 500 mL round-bottomed flask CCl_4 (300 mL) was saturated with acetylene for 5 min while the reaction flask was cooled to 4 °C. $AlCl_3$ (0.33 mol, 44.0 g, 1.1 equiv) was added, and the mixture was saturated for an additional 5 min with acetylene. Pentanoyl chloride (0.3 mol, 36.4 mL, 1 equiv) was added dropwise within 15 min. Acetylene was bubbled through the reaction mixture for 3 h. The reaction was ended by pouring the mixture into ice−water, NaCl was added, and mixture was extracted with CCl_4 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Product was purified by vacuum distillation (1.5 mbar, bp 40 °C) to yield 36 g (82%) of product as a colorless oil that darkened on standing (*E*/*Z* 9/1 by ^{1}H NMR): IR ν = 3076, 2961, 2935, 2874, 1696, 1588 cm^{-1}; MS *m*/*z* 147, 131, 112, 104, 89. For the *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 13.6 Hz, 1H), 6.53 (d, *J* = 13.6 Hz, 1H), 2.56−2.49 (m, 2H), 1.60 (ddd, *J* = 15.0, 8.5, 6.5 Hz, 2H), 1.40−1.28 (m, 2H), 0.92 (td, *J* = 7.3, 2.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 136.5, 132.5, 41.2, 26.0, 22.4, 13.9.

General Procedure for the Synthesis of Enaminones 2a−d. (*E*)-1-Chlorohept-1-en-3-one (8.15 mmol, 1.2 g, 1 equiv) was dissolved in water (**2a**,**b**) or toluene (**2c**,**d**) to give a 0.5 M solution. Primary amine (24.45 mmol, 3 equiv) was added, and the mixture was stirred at ambient temperature. The reaction was monitored by GC, and after the full conversion reaction was ended, the mixture was concentrated and directly purified on silica gel by column chromatography using a mixture of petroleum ether and ethyl acetate as eluent.

(*Z*)-1-(Isopropylamino)hept-1-en-3-one 2a: 72% yield as yellow oil with *Z*/*E* 20:1 by ^{1}H NMR; IR ν = 3275, 3054, 1638, 1571, 1388, 1146, 735 cm^{-1}; MS *m*/*z* 169, 154, 140, 127, 112, 85, 70, 43. For the *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (br s, 1H), 6.76−6.69 (m, 1H), 4.96 (d, *J* = 7.4 Hz, 1H), 3.47−3.34 (m, 1H), 2.31−2.25 (m, 2H), 1.58 (dtd, *J* = 12.8, 7.4, 5.9 Hz, 2H), 1.34 (dq, *J* = 14.6, 7.3 Hz, 2H), 1.23 (d, *J* = 6.5 Hz, 6H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 150.6, 93.0,

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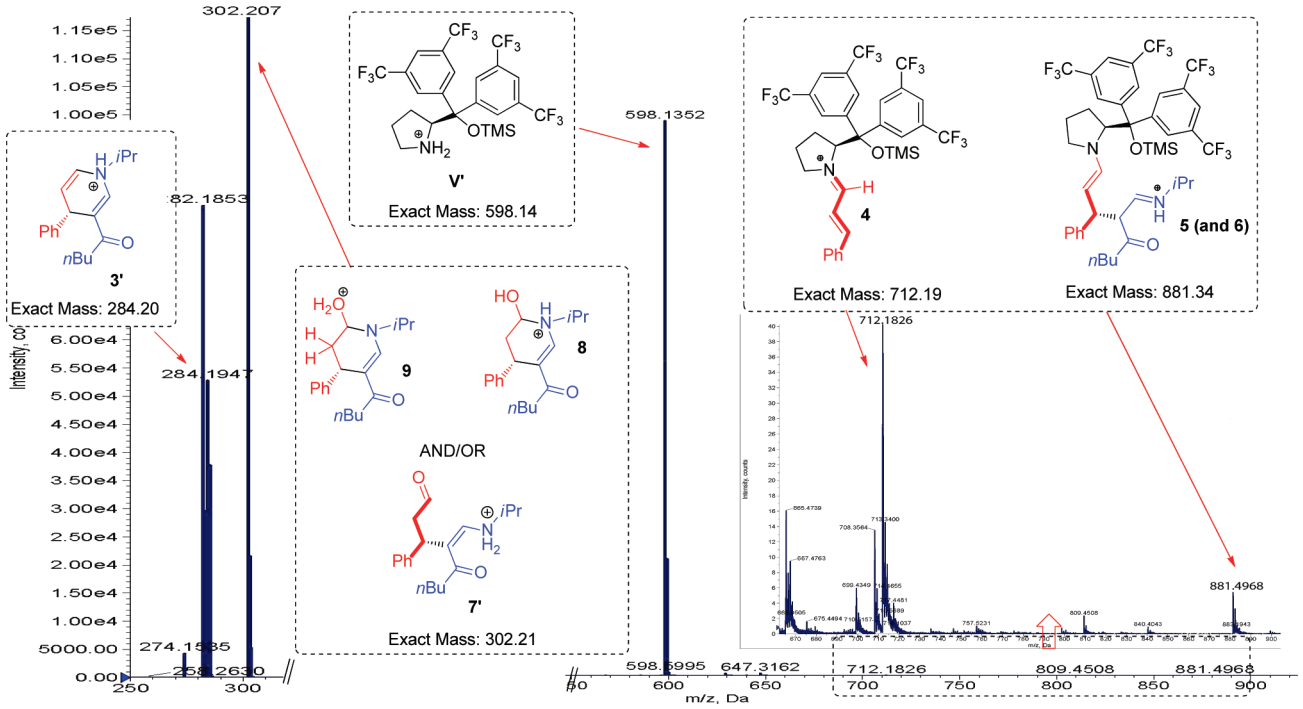

Figure 1. ESI-MS analysis of the reaction mixture (reaction time 3 h).

50.0, 41.9, 28.1, 23.9, 22.7, 14.1; HRMS $(M)^+$ $C_{10}H_{19}NO$ requires 169.1467, found 169.1466.

(*Z*)-1-(Cyclohexylamino)hept-1-en-3-one 2b: 67% yield as yellow oil with *Z*/*E* 10:1 by ^{1}H NMR; IR ν = 3275, 3051, 1638, 1573, 1389, 1145, 735 cm^{-1}; MS *m*/*z* 209, 167, 152, 134, 125, 110, 96, 70, 55, 41. For the *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 6.73 (dd, *J* = 12.9, 7.4 Hz, 1H), 4.96 (d, *J* = 7.3 Hz, 1H), 3.10−2.97 (m, 1H), 2.30−2.25 (m, 2H), 1.94−1.84 (m, 2H), 1.81−1.71 (m, 2H), 1.63−1.54 (m, 3H), 1.39−1.27 (m, 6H), 1.24−1.13 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 150.7, 93.0, 57.2, 41.9, 34.2, 28.1, 25.4, 24.7, 22.8, 14.1; HRMS $(M)^+$ $C_{13}H_{23}NO$ requires 209.1780, found 209.1785.

(*Z*)-1-(Benzylamino)hept-1-en-3-one 2c: 90% yield as yellow oil with *Z*/*E* 20:1 by ^{1}H NMR; IR ν = 3273, 3052, 1637, 1572, 1387, 1144, 735 cm^{-1}; MS *m*/*z* 217, 175, 160, 132, 91. For the *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.37−7.23 (m, 5H), 6.71 (dd, *J* = 12.6, 7.5 Hz, 1H), 5.05 (d, *J* = 7.4 Hz, 1H), 4.36 (d, *J* = 6.1 Hz, 2H), 2.33−2.25 (m, 2H), 1.64−1.52 (m, 2H), 1.39−1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 152.2, 138.0, 128.8, 127.7, 127.2, 94.0, 52.5, 41.9, 28.0, 22.6, 14.0; HRMS $(M)^+$ $C_{14}H_{19}NO$ requires 217.1467, found 217.1465.

(*Z*)-1-(*tert*-Butylamino)hept-1-en-3-one 2d: 54% yield as yellow oil with *Z*/*E* 20:1 by ^{1}H NMR; IR ν = 3277, 3052, 1638, 1570, 1387, 1144, 736 cm^{-1}; MS *m*/*z* 183, 168, 141, 126, 99, 85, 70. For the *Z*- isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (br s, 1H), 6.83 (dd, *J* = 13.3, 7.4 Hz, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 2.31−2.24 (m, 2H), 1.58 (ddd, *J* = 12.8, 8.5, 6.4 Hz, 2H), 1.35 (dt, *J* = 14.9, 7.4 Hz, 2H), 1.28 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 148.2, 93.1, 51.9, 41.9, 30.2, 28.1, 22.8, 14.1; HRMS $(M)^+$ $C_{11}H_{21}NO$ requires 183.1623, found 183.1620.

General Procedure for the Synthesis of 1,4-DHPs 3 from Aliphatic Enals and Cinnamaldehyde 1a. Prolinol−TMS ether **V** (0.1 mmol, 60 mg, 20 mol %) was dissolved in toluene (1 mL) under Ar. Benzoic acid (0.1 mmol, 12 mg, 20 mol %) was added followed by enal **1** (1 mmol, 2 equiv). After 5 min of stirring, enaminone or β-enamino ester **2** (0.5 mmol, 1 equiv) was added as a solution in toluene (0.5 mL), and the mixture was stirred at ambient temperature until TLC showed full conversion. The reaction was quenched by the addition of solid $NaHCO_3$ to the mixture, stirred for 5 min, filtered, concentrated, and directly purified by column chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate or CH_2Cl_2 and ethyl acetate as eluent. Enantiomeric purity was determined by HPLC analysis using Chiralcel OD-H or Chiralcel OJ-H column.

General Procedure for the Synthesis of 1,4-DHPs 3 from Aromatic Enals 1 (Except Cinnamaldehyde 1a). Prolinol−TMS ether **V** (0.1 mmol, 60 mg, 20 mol %) was dissolved in toluene (1 mL) under Ar. Benzoic acid (0.1 mmol, 12 mg, 20 mol %) was added followed by enal **1** (0.55 mmol, 1.1 equiv). After 5 min of stirring, enaminone or β-enamino ester **2** (0.5 mmol, 1 equiv) was added as a solution in toluene (0.5 mL), and the mixture was stirred at rt until TLC showed full conversion. The reaction was quenched by the addition of solid $NaHCO_3$ to the mixture, stirred for 5 min, filtered, concentrated, and directly purified by column chromatography on silica gel, using a mixture of petroleum ether and ethyl acetate or CH_2Cl_2 and ethyl acetate as eluent. Enantiomeric purity was determined by HPLC analysis using either a Chiralcel OD-H or a Chiralcel OJ-H column.

(*S*)-1-(1-Isopropyl-4-phenyl-1,4-dihydropyridin-3-yl)pentan-1-one 3a (Table 2, entry 1): 75% (106 mg) yield as yellow oil; 93% ee by HPLC analysis (Chiralcel OJ-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 8.24 (major) and (*R*) t_R = 17.34 (minor); $[\alpha]^{25}_D$ −432 (*c* 0.45 in MeOH); IR ν = 3060, 2959, 1666, 1629, 1575, 1490, 698 cm^{-1}; MS *m*/*z* 283, 240, 206, 164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 1.3 Hz, 1H), 7.28−7.23 (m, 4H), 7.14 (dq, *J* = 8.7, 4.2 Hz, 1H), 6.00 (d, *J* = 8.7 Hz, 1H), 5.03 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.66 (d, *J* = 5.0 Hz, 1H), 3.58 (hept, *J* = 6.7 Hz, 1H), 2.51−2.30 (m, 2H), 1.50 (qd, *J* = 7.7, 1.4 Hz, 2H), 1.33 (d, *J* = 6.7 Hz, 6H), 1.24 (dd, *J* = 14.8, 7.4 Hz, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 148.2, 138.8, 128.4, 127.7, 126.2, 124.0, 112.5, 110.4, 55.1, 38.4, 36.5, 27.6, 22.6, 22.0, 21.9, 14.1. Anal. Calcd for $C_{19}H_{25}NO$ (283.41): C, 80.52; H, 8.89; N, 4.94. Found: C, 80.22; H, 8.92; N, 4.92.

(*S*)-1-(1-Isopropyl-4-(4-nitrophenyl)-1,4-dihydropyridin-3-yl)pentan-1-one 3b (Table 2, entry 2): 83% (136 mg) yield as

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yellow solid; 89% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 9.53 (major) and (*R*) t_R = 11.21 (minor); $[\alpha]^{25}_D$ −538 (*c* 0.11 in MeOH); IR ν = 3073, 2956, 1669, 1510, 1343, 820 cm^{-1}; MS *m*/*z* 328, 285, 243, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.45−7.39 (m, 2H), 7.28 (d, *J* = 1.4 Hz, 1H), 6.08 (d, *J* = 7.8 Hz, 1H), 4.97 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.80 (d, *J* = 4.9 Hz, 1H), 3.62 (hept, *J* = 6.7 Hz, 1H), 2.45 (ddq, *J* = 22.5, 15.1, 7.5 Hz, 2H), 1.56−1.47 (m, 2H), 1.36 (d, *J* = 1.4 Hz, 3H), 1.35 (d, *J* = 1.4 Hz, 3H), 1.31−1.19 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 155.2, 146.4, 139.3, 128.6, 125.0, 123.8, 112.0, 108.9, 55.4, 38.6, 36.1, 27.7, 22.7, 22.1, 22.0, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{19}H_{24}N_2O_3)^+$ requires *m*/*z* 329.1860, found 329.1855.

(*S*)-1-(1-Isopropyl-4-(4-methoxyphenyl)-1,4-dihydropyridin-3-yl)pentan-1-one 3c (Table 2, entry 3): 86% (135 mg) yield as yellow oil; 89% ee by HPLC analysis (Chiralcel OJ-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 11.23 (major) and (*R*) t_R = 18.67 (minor); $[\alpha]^{25}_D$ −423 (*c* 0.43 in MeOH); IR ν = 3060, 2959, 1666, 1575, 1508, 1176, 1035, 830 cm^{-1}; MS *m*/*z* 313, 270, 228, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.21−7.15 (m, 2H), 6.88−6.71 (m, 2H), 5.99 (dd, *J* = 7.8, 1.0 Hz, 1H), 5.01 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.60 (d, *J* = 5.0 Hz, 1H), 3.76 (s, 3H), 3.58 (hept, *J* = 6.7 Hz, 1H), 2.51−2.28 (m, 2H), 1.55−1.45 (m, 2H), 1.33 (d, *J* = 1.4 Hz, 3H), 1.31 (d, *J* = 1.4 Hz, 3H), 1.28−1.21 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 158.0, 140.8, 138.6, 128.7, 123.8, 113.8, 112.8, 110.5, 55.3, 55.1, 37.5, 36.5, 27.7, 22.7, 22.1, 21.9, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{20}H_{27}NO_2)^+$ requires 314.2115, found 314.2108.

(*S*)-1-(4-(4-Bromophenyl)-1-isopropyl-1,4-dihydropyridin-3-yl)pentan-1-one 3d (Table 2, entry 4): 80% (145 mg) yield as yellow oil; 89% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 5.62 (major) and (*R*) t_R = 6.71 (minor); $[\alpha]^{25}_D$ −350 (*c* 0.19 in MeOH); IR ν = 3061, 2960, 1667, 1632, 1577, 1178, 842 cm^{-1}; MS *m*/*z* 364, 361, 320, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.35 (m, 2H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.16−7.12 (m, 2H), 6.02 (dd, *J* = 7.8, 0.9 Hz, 1H), 4.98 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 3.59 (hept, *J* = 6.7 Hz, 1H), 2.50−2.33 (m, 2H), 1.55−1.46 (m, 2H), 1.34 (d, *J* = 0.9 Hz, 3H), 1.32 (d, *J* = 0.9 Hz, 3H), 1.29−1.20 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 147.2, 138.9, 131.4, 129.6, 124.3, 119.9, 112.4, 109.8, 55.2, 37.9, 36.3, 27.7, 22.7, 22.1, 21.9, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{19}H_{24}BrNO)^+$ requires 362.1114, found 362.1105.

(*S*)-1-(1-Isopropyl-4-(naphthalen-2-yl)-1,4-dihydropyridin-3-yl)pentan-1-one 3e (Table 2 entry 5): 63% (105 mg) yield as yellow oil; 89% ee by HPLC analysis (Chiralcel OJ-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*R*) t_R = 15.17 (major) and (*S*) t_R = 24.28 (minor); $[\alpha]^{25}_D$ −427 (*c* 0.25 in MeOH); IR ν = 3054, 2959, 1666, 1631, 1573, 1178, 817 cm^{-1}; MS *m*/*z* 333, 290, 248, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.0, 4.1 Hz, 3H), 7.65 (d, *J* = 1.0 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.43−7.35 (m, 2H), 7.33 (d, *J* = 1.4 Hz, 1H), 6.04 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.08 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.84 (d, *J* = 5.0 Hz, 1H), 3.62 (hept, *J* = 6.7 Hz, 1H), 2.49−2.34 (m, 2H), 1.53−1.44 (m, 2H), 1.37 (d, *J* = 1.6 Hz, 3H), 1.35 (d, *J* = 1.6 Hz, 3H), 1.28−1.18 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 145.5, 138.9, 133.7, 132.4, 128.1, 128.0, 127.7, 126.7, 125.9, 125.8, 125.2, 124.2, 112.4, 110.2, 55.2, 38.6, 36.5, 27.6, 22.7, 22.1, 22.0, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{23}H_{27}NO)^+$ requires 334.2165, found 334.2153.

(*R*)-1-(4-Ethyl-1-isopropyl-1,4-dihydropyridin-3-yl)pentan-1-one 3f (Table 2, entry 6): 69% (81 mg) yield as yellow oil, 93% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 2% *i*-PrOH in hexane, 254 nm), (*R*) t_R = 6.28 (major) and (*S*) t_R = 9.76 (minor); $[\alpha]^{25}_D$ −675 (*c* 0.19 in MeOH); IR ν = 3060, 2960, 1666, 1626, 1576, 1462, 1425, 1179, 1158, 727 cm^{-1}; MS *m*/*z* 235, 220, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 1.0 Hz, 1H), 5.96 (dd, *J* = 7.9, 1.4 Hz, 1H), 4.89 (dd, *J* = 7.8, 5.2 Hz, 1H), 3.55−3.41 (m, 2H), 2.57−2.42 (m, 2H), 1.60 (ddd, *J* = 13.3, 8.5, 6.6 Hz, 2H), 1.45 (dt, *J* = 20.6, 7.2 Hz, 1H), 1.40−1.31 (m, 2H), 1.31−1.27 (m, 1H), 1.27 (d, *J* = 1.0 Hz, 3H), 1.25 (d, *J* = 1.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 140.2, 125.1, 112.1, 109.5, 54.9, 36.3, 32.6, 29.8, 28.4, 22.8, 22.0, 21.8, 14.2, 9.0; HRMS (ESI) calcd for $[M + H]^+$ $(C_{15}H_{25}NO)^+$ requires 236.2009, found 236.2009.

(*R*)-1-(4-Butyl-1-isopropyl-1,4-dihydropyridin-3-yl)pentan-1-one 3g (Table 2, entry 7): 82% (108 mg) yield as yellow oil; 96% ee by HPLC analysis (Chiralcel OJ-H column, 1 mL/min, 2% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 4.75 (minor) and (*R*) t_R = 5.21 (major); $[\alpha]^{25}_D$ −603 (*c* 0.28 in MeOH); IR ν = 3060, 2958, 2930, 2872, 1666, 1626, 1577, 1465, 1425, 1389, 1179, 1157, 732 cm^{-1}; MS *m*/*z* 263, 248, 234, 220, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 0.9 Hz, 1H), 5.93 (dd, *J* = 7.9, 1.4 Hz, 1H), 4.92 (dd, *J* = 7.8, 5.2 Hz, 1H), 3.55−3.43 (m, 2H), 2.52−2.46 (m, 2H), 1.60 (ddd, *J* = 13.1, 8.4, 6.4 Hz, 3H), 1.34 (dt, *J* = 22.2, 7.3 Hz, 4H), 1.25 (dd, *J* = 13.6, 8.2 Hz, 11H), 0.92 (t, *J* = 7.3 Hz, 4H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 140.0, 124.9, 112.7, 110.1, 54.8, 37.6, 36.3, 31.5, 28.4, 27.2, 23.0, 22.8, 22.0, 21.8, 14.4, 14.2; HRMS (ESI) calcd for $[M + H]^+$ $(C_{17}H_{29}NO)^+$ requires 264.2322, found 264.2318.

(*R*)-1-(4-((Benzyloxy)methyl)-1-isopropyl-1,4-dihydropyridin-3-yl)pentan-1-one 3h (Table 2, entry 8): 61% (100 mg) yield as yellow oil; 93% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*R*) t_R = 6.28 (major) and (*S*) t_R = 8.41 (minor); $[\alpha]^{25}_D$ −522 (*c* 0.22 in MeOH); IR ν = 3063, 3030, 2958, 2931, 2870, 1667, 1626, 1575, 1426, 1179, 735 cm^{-1}; MS *m*/*z* 327, 298, 281, 270, 254, 220, 206, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 7.17 (d, *J* = 1.3 Hz, 1H), 6.00 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.08 (dd, *J* = 7.9, 5.1 Hz, 1H), 4.51 (dd, *J* = 30.7, 12.1 Hz, 2H), 3.82 (q, *J* = 5.2 Hz, 1H), 3.51 (hept, *J* = 6.7 Hz, 1H), 3.39 (d, *J* = 0.6 Hz, 1H), 3.37 (s, 1H), 3.37−3.37 (m, 1H), 2.56−2.42 (m, 2H), 1.64−1.54 (m, 2H), 1.39−1.28 (m, 2H), 1.26 (s, 3H), 1.25 (s, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 141.0, 139.2, 128.3, 127.6, 127.4, 125.6, 109.2, 108.4, 74.8, 72.9, 55.0, 36.3, 32.9, 28.2, 22.8, 22.0, 21.8, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{21}H_{29}NO_2)^+$ requires 328.2271, found 328.2266.

(*S*)-1-(1-Cyclohexyl-4-phenyl-1,4-dihydropyridin-3-yl)pentan-1-one 3i (Table 3, entry 1): 79% (127 mg) yield as yellow oil; 76% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 5.94 (major) and (*R*) t_R = 7.84 (minor); $[\alpha]^{25}_D$ −416 (*c* 0.12 in MeOH); IR ν = 3060, 3025, 2932, 2857, 1666, 1629, 1574, 1162, 762, 698 cm^{-1}; MS *m*/*z* 323, 280, 246, 198, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 1.3 Hz, 1H), 7.26 (dd, *J* = 3.7, 0.9 Hz, 4H), 7.13 (tt, *J* = 5.0, 4.0 Hz, 1H), 6.01 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.00 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.65 (d, *J* = 5.1 Hz, 1H), 3.10 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.47−2.33 (m, 2H), 2.00−1.92 (m, 2H), 1.93−1.85 (m, 2H), 1.71 (d, *J* = 13.0 Hz, 1H), 1.56−1.43 (m, 4H), 1.42−1.29 (m, 2H), 1.29−1.19 (m, 2H), 1.19−1.10 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 148.3, 139.1, 128.4, 127.7, 126.1, 124.7, 112.4, 110.1, 63.3, 38.4, 36.5, 32.7, 32.5, 27.6, 25.8, 25.4, 22.7, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{22}H_{29}NO)^+$ requires 324.2322, found 324.2320.

(*S*)-1-(1-Benzyl-4-phenyl-1,4-dihydropyridin-3-yl)pentan-1-one 3j (Table 3, entry 2): 54% (90 mg) yield as yellow oil; 87% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 12.73 (major) and (*R*) t_R = 20.16 (minor); $[\alpha]^{25}_D$ −241 (c 0.20 in $CHCl_3$); IR ν = 3061, 3027, 2957, 2931, 2871, 1668, 1629, 1578, 1176, 730, 698 cm^{-1}; MS *m*/*z* 331, 314, 302, 288, 254, 240, 91; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.24 (m, 11H), 7.18−7.11 (m, 1H), 5.97−5.91 (m, 1H), 5.02 (dd, *J* = 7.7, 5.0 Hz, 1H), 4.67 (d, *J* = 5.0 Hz, 1H), 4.49 (s, 2H), 2.47−2.31 (m, 2H), 1.53−1.41 (m, 2H), 1.27−1.15 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 198.1, 147.8, 140.9, 137.0, 129.2, 128.5, 128.2, 127.8, 127.3, 126.7, 126.3, 113.1, 110.4, 58.1, 37.7, 36.6, 27.6, 22.6, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{23}H_{25}NO)^+$ requires 332.2009, found 332.2007.

(*S*)-1-(1-(*tert*-Butyl)-4-phenyl-1,4-dihydropyridin-3-yl)pentan-1-one 3k (Table 3, entry 3): 72% (107 mg) yield as yellow oil; 89% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 4.94 (major) and (*R*) t_R = 7.14 (minor); $[\alpha]^{25}_D$ −428 (*c* 0.32 in MeOH); IR ν = 3060, 2959, 2871, 1664, 1631, 1576, 1371, 1225, 1177, 760, 727, 698 cm^{-1}; MS *m*/*z* 297, 254, 240, 220, 198, 180, 164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.6 Hz, 1H), 7.29−7.23 (m, 4H), 7.18−7.10 (m, 1H), 6.26 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.05 (dd, *J* = 8.0, 5.1 Hz, 1H), 4.64 (d, *J* = 5.1 Hz, 1H), 2.47−2.34 (m, 2H), 1.55−1.45 (m, 2H), 1.42 (s, 9H), 1.24 (dd, *J* = 14.8, 7.4 Hz, 2H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 148.2, 137.0, 128.4, 127.7, 126.2, 123.1, 112.6, 110.4, 110.1, 56.7, 38.0, 36.6, 29.3, 27.7, 22.7, 14.1; HRMS (ESI) calcd for $[M + H]^+$ $(C_{20}H_{27}NO)^+$ requires 298.2165, found 298.2163.

(*S*)-1-Isopropyl-4-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one 3l (Table 3, entry 4): 49% (33 mg) yield as yellow oil; 62% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 254 nm), (*S*) t_R = 13.42 (major) and (*R*) t_R = 15.49 (minor); $[\alpha]^{25}_D$ −188 (*c* 0.20 in $CHCl_3$); IR ν = 3060, 3024, 2965, 1710, 1667, 1622, 1548, 1058, 731, 699 cm^{-1}; MS *m*/*z* 267, 224, 206, 190, 168, 148; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.21 (m, 4H), 7.12 (ddd, *J* = 8.6, 4.9, 2.3 Hz, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 5.19 (dd, *J* = 7.8, 5.6 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.14 (hept, *J* = 6.6 Hz, 1H), 2.70 (dt, *J* = 16.7, 5.1 Hz, 1H), 2.45−2.37 (m, 1H), 2.37−2.23 (m, 2H), 2.06−1.96 (m, 1H), 1.95−1.83 (m, 1H), 1.31 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 153.3, 147.8, 128.3, 127.6, 125.9, 122.6, 110.5, 110.3, 47.6, 36.3, 36.1, 25.8, 22.2, 21.4, 21.2; HRMS (ESI) calcd for $[M + H]^+$ $(C_{18}H_{21}NO)^+$ requires 268.1696, found 268.1691.

(*S*)-Ethyl 1-isopropyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate 3m (Table 3, entry 5): 45% (75 mg) yield as yellow oil; 84% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 215 nm), (*S*) t_R = 6.22 (major) and (*R*) t_R = 6.77 (minor); $[\alpha]^{25}_D$ −396 (*c* 0.24 in $CHCl_3$), IR ν = 3072, 2977, 2935, 1685, 1556, 1518, 1345, 1183, 1098, 827 cm^{-1}; MS *m*/*z* 330, 301, 285, 257, 215, 208, 169, 166, 138, 120; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.39−7.35 (m, 2H), 6.16 (d, *J* = 7.7 Hz, 1H), 5.01 (dd, *J* = 7.7, 5.8 Hz, 1H), 4.71 (d, *J* = 5.8 Hz, 1H), 4.21 (hept, *J* = 6.7 Hz, 1H), 4.07−3.95 (m, 2H), 2.51 (s, 3H), 1.26 (dd, *J* = 6.7, 2.4 Hz, 6H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 156.1, 149.8, 146.3, 128.1, 123.9, 123.8, 107.1, 98.8, 59.6, 47.5, 40.3, 22.4, 21.4, 15.7, 14.4; HRMS (ESI) calcd for $[M + H]^+$ $(C_{18}H_{23}N_2O_4)^+$ requires 331.1652, found 331.1649.

(*S*)-Ethyl 1-benzyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate 3n (Table 3, entry 6): 70% (132 mg) yield as yellow oil; 89% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 215 nm), (*S*) t_R = 17.76 (major) and (*R*) t_R = 22.83 (minor); $[\alpha]^{25}_D$ −341 (*c* 0.28 in $CHCl_3$); IR ν = 3064, 3032, 2980, 1688, 1562, 1518, 1346, 1171, 1103, 827 cm^{-1}; MS *m*/*z* 378, 349, 333, 305, 256, 91; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23−8.00 (m, 2H), 7.41−7.35 (m, 4H), 7.34−7.29 (m, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 6.02 (d, *J* = 7.6 Hz, 1H), 4.94 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.78 (d, *J* = 5.5 Hz, 1H), 4.64 (dd, *J* = 38.6, 16.9 Hz, 2H), 3.98 (td, *J* = 7.1, 3.5 Hz, 2H), 2.46 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 156.1, 150.0, 146.4, 137.8, 130.5, 129.1, 128.3, 127.9, 126.4, 123.8, 106.8, 99.4, 59.7, 54.0, 40.7, 16.2, 14.3; HRMS (ESI) calcd for $[M + H]^+$ $(C_{22}H_{23}N_2O_4)^+$ requires 379.1652, found 379.1645.

(*R*)-Ethyl 1-benzyl-4-butyl-2-methyl-1,4-dihydropyridine-3-carboxylate 3p (Table 3, entry 7): 62% (97 mg) yield as yellow oil; 71% ee by HPLC analysis (Chiralcel OD-H column, 1 mL/min, 10% *i*-PrOH in hexane, 215 nm), (*R*) t_R = 5.52 (major) and (*S*) t_R = 8.52 (minor); $[\alpha]^{25}_D$ −276 (*c* 0.34 in $CHCl_3$); IR ν = 3063, 3031, 2956, 2929, 2857, 1685, 1564, 1171, 1107, 729 cm^{-1}; MS *m*/*z* 313, 298, 284, 268, 256, 91; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.28−7.23 (m, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 5.91 (d, *J* = 7.5 Hz, 1H), 4.91 (dd, *J* = 7.5, 5.9 Hz, 1H), 4.56 (dd, *J* = 60.5, 17.1 Hz, 2H), 4.21−4.05 (m, 2H), 3.46−3.38 (m, 1H), 2.32 (s, 3H), 1.41−1.29 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 149.2, 138.5, 130.5, 128.9, 127.4, 126.2, 107.7, 100.6, 59.3, 53.6, 39.0, 33.3, 27.4, 23.0, 16.0, 14.6, 14.3; HRMS (ESI) calcd for $[M + H]^+$ $(C_{20}H_{28}NO_2)^+$ requires 314.2115, found 314.2110.

ESI-MS Experiment for the Determination of Reaction Intermediates. (*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl((trimethylsilyl)oxy)methyl)pyrrolidine V (0.034 mmol, 20 mg, 20 mol %) and benzoic acid (0.034 mmol, 4,2 mg, 20 mol %) were dissolved in toluene (0.4 mL) under Ar. Cinnamaldehyde **1a** (0.34 mmol, 43 μL, 2 equiv) was added followed by (*Z*)-1-(isopropylamino)hept-1-en-3-one **2a** (0.17 mmol, 29 mg, 1 equiv) in toluene (0.1 mL). The mixture was stirred at ambient temperature for 3 h, and then 0.1 mL of reaction mixture was diluted with 0.2 mL of toluene. For ESI-MS analysis, 0.1 mL of the resulting mixture was further diluted with 0.9 mL of acetonitrile. The analysis was performed in positive mode, and the results of the experiment are depicted in Figure 1.

■ ASSOCIATED CONTENT

Supporting Information. Chiral-phase HPLC data and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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