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Access to Highly Enantioenriched Donepezil-like 1,4-Dihydropyridines as Promising Anti-Alzheimer Prodrug Candidates via Enantioselective Tsuji Allylation and Organocatalytic Aza-Ene-Type Domino Reactions

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Article

Access to highly enantioenriched donepezil-like 1,4-dihydropyridines as promising anti-Alzheimer prodrug candidates via enantioselective Tsuji allylation and organocatalytic aza-ene-type domino reactions

Mihaela-Liliana TINTAS, Rabah Azzouz, Ludovic Peauger, Vincent GEMBUS, Emilie Petit, Laetitia Bailly, Cyril Papamicaël, and Vincent Levacher

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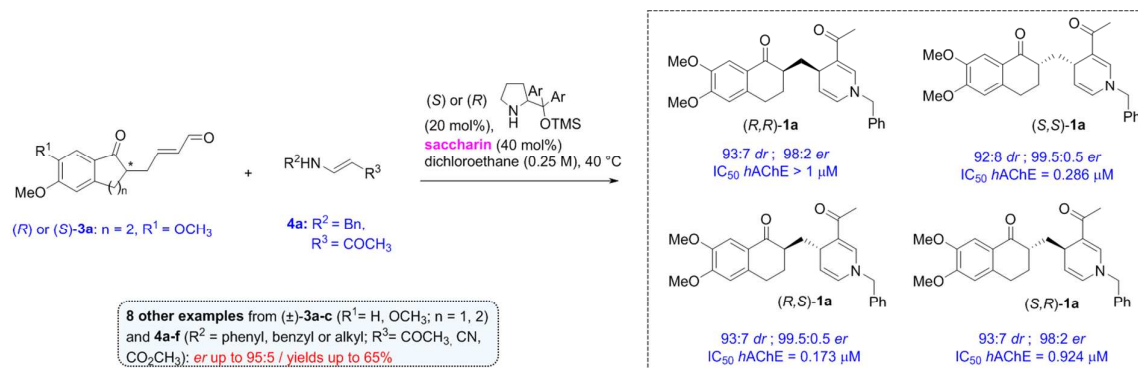
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3 **Access to highly enantioenriched donepezil-like 1,4-**
4 **dihydropyridines as promising anti-Alzheimer prodrug candidates**
5 **via enantioselective Tsuji allylation and organocatalytic aza-ene-**
6 **type domino reactions**
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45 **ABSTRACT**

46 This work aims at exploiting both the enantioselective Tsuji allylation of allyl carbonate **6** and
47 an organocatalytic aza-ene-type domino reaction between enal **3a** and β-enaminone **4a** to
48 develop a straightforward access to all of the four possible stereoisomers of a donepezil-like
49 1,4-dihydropyridine **1a** (*er* up to 99.5:0.5; overall yield up 64%); an anti-Alzheimer prodrug
50 candidate. This strategy was extended to the preparation of other enantioenriched 1,4-
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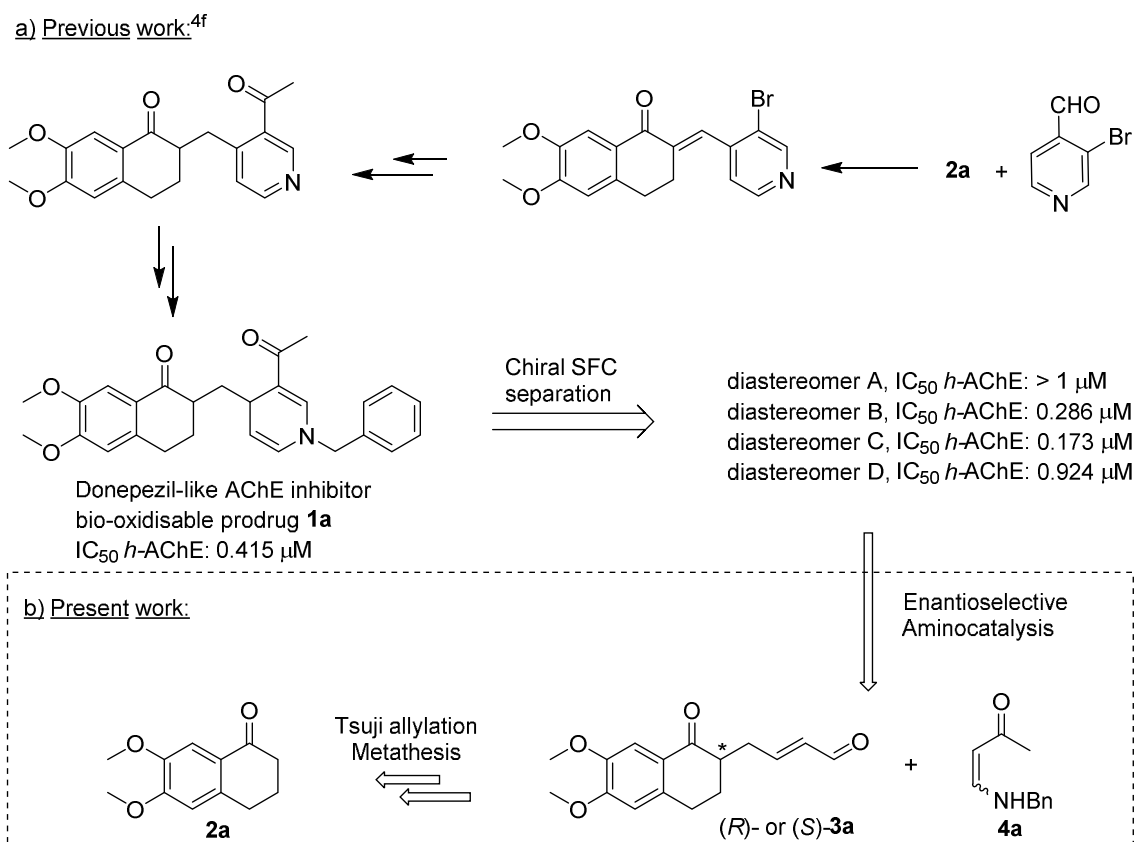
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3 dihydropyridines **1b-i** (8 examples), highlighting its potential in the development of these
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5 chiral AChE inhibitors.
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10 INTRODUCTION

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12 1,4-dihydropyridine nucleus (DHPs) is viewed as a privileged scaffold due to its virtue for
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14 selectively modulating diverse receptors, channels and enzymes, when conveniently
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16 substituted.¹ Particularly, these compounds are closely related to the NADH (\rightleftharpoons NAD⁺)
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18 coenzyme by mimicking its oxido-reductive activity. Bodor *et al.* took advantage of these
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20 redox properties to develop a brain targeting chemical delivery system (CDS) based on the
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22 1,4-dihydrotrigonelline \leftrightarrow trigonelline system.^{2,3} For several years, our group has been
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24 interested in this approach,⁴ and as part of our Alzheimer's disease research program, we
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26 have recently described the design and preparation of several prodrugs of donepezil
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28 analogues based on a bio-oxidisable strategy and tested their inhibitory activities against
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30 human acetyl cholinesterase (*hAChE*).^{4g,f} In most of cases, the designed drugs displayed
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32 high inhibitory activities although, as expected, the corresponding prodrugs were inactive.
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34 However, during these research investigations, we highlighted that some of the obtained 1,4-
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36 dihydropyridine (1,4-DHP) derivatives showed nonetheless a significant inhibitory activity.
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38 One of the most active 1,4-DHP, the compound **1a**, displayed a three-digit nanomolar activity
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40 against *hAChE* (Scheme 1a, IC₅₀ = 0.415 μ M). The tested 1,4-DHPs are issued from a non-
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42 stereocontrolled synthesis (Scheme 1a), affording a mixture of the all four possible
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44 stereomers due to the presence of two chiral carbons at both tetralone and 1,4-
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46 dihydropyridine rings. Obviously, it is well known that enantiomers of a chiral drug may
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48 display marked differences in their pharmacological behavior arising from strong differences
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50 in their interactions with enzymes, proteins, receptors and other chiral molecules in living
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52 systems.⁵ Keeping this in mind, we turned our interest toward the investigation of the
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54 structure-activity relationship of each stereoisomers A-D of **1a** with *hAChE*. To address this
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56 issue, all the four stereoisomers A-D were isolated by super critical fluid chromatography on
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3 a chiral stationary phase. An *in vitro* evaluation of the so-obtained four stereoisomers A-D
4 highlighted a striking disparity of the biological activity (*i.e.* IC₅₀, Scheme 1a).^{4f} To complete
5 our investigation, it was necessary to attribute the absolute configuration at both stereogenic
6 centers of each stereoisomer A-D and we naturally turned our attention to enantioselective
7 synthesis of the target chiral 1,4-DHPs **1a**. Although the racemic preparation of 4-substituted
8 1,4-DHPs is well documented in the literature,⁶ only a few catalytic asymmetric approaches
9 are reported. These are either based on the organocatalytic asymmetric construction of 1,4-
10 DHPs⁷ or more recently on regioselective organocatalytic 1,4-addition of enolate derivatives
11 to N-alkyl pyridinium salts.^{7f-g} Taking the structure of our target **1a** into account, the
12 organocatalytic aza-ene-type cascade reaction described by Kanger *et al.* appeared to be
13 the most appropriate approach to provide access to highly enantioenriched donepezil-like
14 1,4-dihydropyridine prodrugs.^{7e} It involves an iminium activation of α,β -unsaturated aldehyde
15 by means of Jørgensen-Hayashi catalyst in the presence of β -enaminones or β -enamino
16 esters to furnish the desired 1,4-DHPs in good yields (45-86%) along with moderate to very
17 good enantioselectivities (62-96%). According to this approach, the enantioenriched enal **3a**
18 precursor would be accessible by an enantioselective Tsuji allylation⁸ / cross-metathesis
19 sequence from α -tetralone **2a**, whereas the starting enaminone **4a** would be prepared by
20 condensation of benzylamine with *trans*-methoxy-3-buten-2-one (Scheme 1b). Herein, we
21 report a straightforward access to donepezil-like 1,4-dihydropyridine prodrugs **1a-i** and an
22 asymmetric approach allowing the preparation of each of the four possible stereoisomers *via*
23 an aminocatalyzed cyclisation as the key step.
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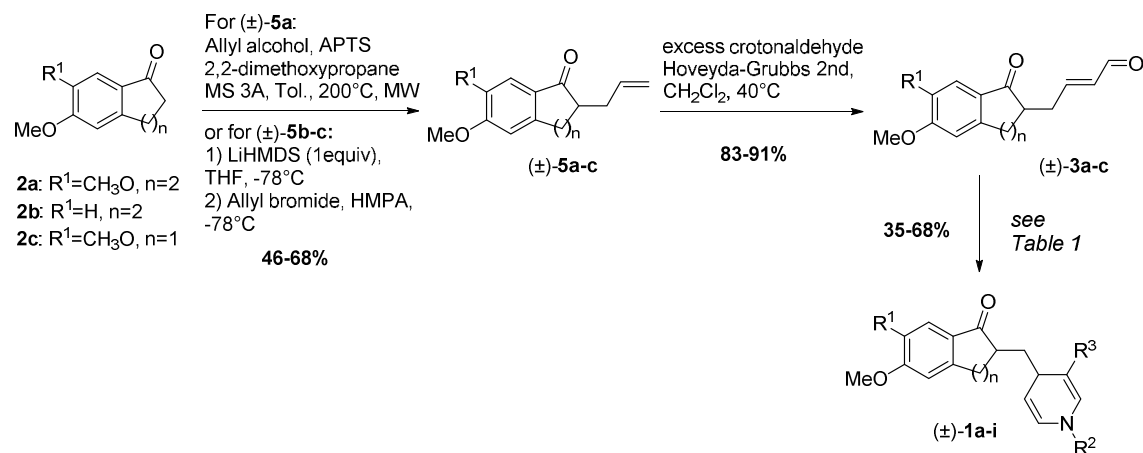
47 **Scheme 1. (a) Previous non-stereocontrolled route to donepezil-like 1,4-dihydropyridine**
48 **prodrug 1a; (b) Asymmetric approach developed in this work**
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RESULTS AND DISCUSSION

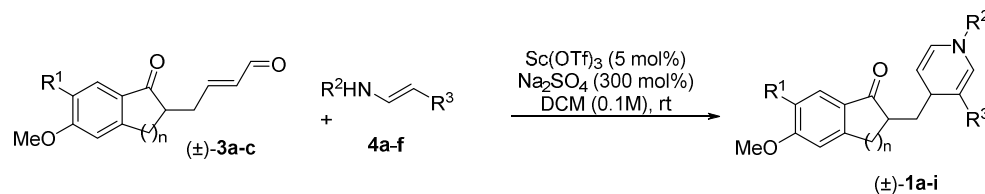
First of all, we set out to explore the scope of this new straightforward route to prepare donepezil-like 1,4-dihydropyridine prodrugs **1a-i** in a non-stereocontrolled fashion.⁶ To this end, the required enals (\pm)-**3a-c** were prepared in a two-step sequence by allylation of arylketones **2a-c**⁹ affording the corresponding α -allylated arylketones (\pm)-**5a-c** in 46-68% yields followed by cross-metathesis in the presence of an excess of crotonaldehyde (Scheme 2). Thus, Hoveyda-Grubbs 2nd generation catalyst (2.5 mol%) in dichloromethane at reflux overnight were used to afford the expected racemic enals (\pm)-**3a-c** in good to excellent yields (83-91%).

Scheme 2. Preparation of enals (\pm)-**3a-c**



Following the reaction conditions described by Renaud *et al.*,^{6g} the desired dihydropyridine **1a** was obtained by reacting enal (±)-**3a** with enaminone **4a** in the presence of scandium triflate as a catalyst in dichloromethane (Table 1, entry 1). Besides the preparation of the target **1a**, a representative panel of 1,4-DHPs **1b-g** was also prepared by reacting various enamine derivatives **4a-f** with enals (±)-**3a-c**. Except β-enamino nitrile **4f** which failed to react (entries 9-10), all other 1,4-DHPs **1a-g** were obtained in fair to good yields (up to 68%) after purification by flash chromatography (Entries 1-8). Compared to our previously reported synthesis depicted in scheme 1a,^{4f} this new route provides a more convergent and direct access to 3,4-disubstituted 1,4-DHPs with fair overall yields.

Table 1. Preparation of (±)-1,4-DHPs 1a-i^a



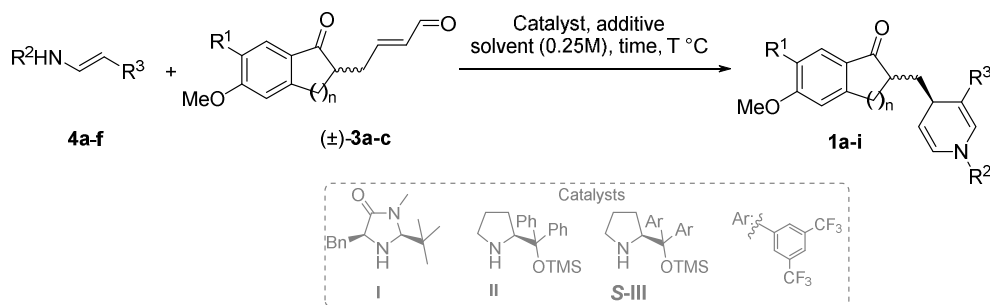
Entry	(±)- 3	R ¹	n	4	R ²	R ³	Cpd	Yield (%)
1	3a	CH ₃ O	2	4a	benzyl	C(O)CH ₃	1a	62
2	3b	H	2	4a	benzyl	C(O)CH ₃	1b	35
3	3b	H	2	4b	(2'-methyl)-benzyl	C(O)CH ₃	1c	59
4	3b	H	2	4c	phenyl	C(O)CH ₃	1d	65
6	3b	H	2	4d	<i>n</i> -propyl	C(O)CH ₃	1e	45
7	3c	CH ₃ O	1	4a	benzyl	C(O)CH ₃	1f	55
8	3c	CH ₃ O	1	4e	(2'-methyl)-benzyl	CO ₂ CH ₃	1g	68
9	3c	CH ₃ O	1	4f	benzyl	CN	1h	0 ^b

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10 **3b** H 2 **4f** benzyl CN **1i** 0^b
^a Reaction conditions: reactions performed at room temperature (21°C) under argon atmosphere with **3a-c** (1.0 equiv), **4a-f** (1.0 equiv), Sc(OTf)₃ (5 mol%), Na₂SO₄ (3.0 equiv.) in CH₂Cl₂ (0.1M). ^b No reaction occurred with 5 mol% or 1.1 equiv of Sc(OTf)₃.

With enals (\pm)-**3a-c** and enamines **4a-f** in hands, a general screening was performed to find the optimal reaction conditions for the enantioselective tandem aza-ene type reaction/cyclization cascade as one-pot entry to enantiomerically enriched 1,4-DHPs **1a-i** (Table 2). We first investigated the reaction between enal (\pm)-**3a** and enamine **4a** in the presence of MacMillan's catalyst **I** with trifluoroacetic acid (TFA) and Na₂SO₄ (Table 2, entry 1).¹⁰ After 16h of reaction at room temperature, no trace of 1,4-DHP **1a** could be observed by conducting a ¹H NMR analysis from the crude mixture. Similarly, the use of an admixture of catalyst **II** (20 mol%) and benzoic acid (BA) (20 mol%) in toluene at room temperature was disappointing since a very low catalytic activity was observed giving only traces of **1a** (Table 2, entry 2). A great stride forward was next reached by the use of the more bulky catalyst **S-III** in combination with BA. Thus, the expected 1,4-DHP **1a** was obtained in up to 30% yield and a good enantiomeric ratio (*er*= 88:12) for both diastereomers, however with a poor reproducibility (Table 2, entry 3). Only traces of **1a** was obtained when decreasing the catalyst loading from 30 to 10 mol% (Table 2, entries 4-5). Addition of 3Å molecular sieves as water scavengers provided reproducible yields up to 35% and a similar enantiomeric ratio (Table 2, entry 6). One may note that 4Å molecular sieves turned out to be even more efficient, furnishing **1a** in up to 49% yield (Table 2, entry 7). To our delight, when mixing catalyst **S-III** with the more acidic saccharin in toluene at 40 °C, 1,4-DHP **1a** was isolated in a satisfactory 60% yield after only 0.5h along with similar enantiomeric ratios (*er*= 84:16 and 85:15) (Table 2, entry 8). Finally, by using dichloroethane (DCE) as solvent, the enantiomeric ratio of both diastereomers could be somewhat improved (*er*= 92:8 and 88:12) without erosion of the yield (Table 2, entry 9).

Table 2. Screening reaction conditions for asymmetric aminocatalyzed cascade synthesis of 1,4-DHPs 1a-i^{a,b}



Entry	3	4	Cat.	Additive	Solvent	Time (h)	Cpd	Yield (%)	<i>dr</i> ^j major /minor	<i>er</i> ^k major /minor
1 ^c	3a	4a	I	TFA, Na ₂ SO ₄	DCE	16	1a	-	-	-
2 ^d	3a	4a	II	BA	toluene	18	1a	traces	-	-
3 ^d	3a	4a	(S)-III	BA	toluene	18	1a	10-30 ^h	-	88:12 / 88:12
4 ^e	3a	4a	(S)-III	BA	toluene	36	1a	traces	-	-
5 ^f	3a	4a	(S)-III	BA	toluene	36	1a	30	52/48	88:12 / 87:13
6 ^d	3a	4a	(S)-III	BA, MS 3Å ⁱ	toluene	18	1a	35	52/48	87:13 / 86:14
7 ^d	3a	4a	(S)-III	BA, MS 4Å ⁱ	toluene	18	1a	49	51/49	88:12 / 88:12
8 ^g	3a	4a	(S)-III	Saccharin	toluene	0.5	1a	60	55/45	84:16 / 85:15
9 ^g	3a	4a	(S)-III	Saccharin	DCE	2	1a	61	60/40	92:8 / 88:12
10 ^g	3b	4a	(S)-III	Saccharin	DCE	2	1b	45	52/48	93:7 / 93:7
11 ^g	3b	4b	(S)-III	Saccharin	DCE	2	1c	55	58/42	93:7 / 95:5
12 ^g	3b	4c	(S)-III	Saccharin	DCE	4	1d	47	57/43	89:11 / 88:12
13 ^g	3b	4d	(S)-III	Saccharin	DCE	8	1e	65	55/45	92:8 / 91:9
14 ^g	3c	4a	(S)-III	Saccharin	DCE	4	1f	56	53/47	90:10 / 91:9
15 ^g	3c	4e	(S)-III	Saccharin	DCE	2	1g	62	51/49	92:8 / 92:8
16 ^g	3c	4f	(S)-III	Saccharin	DCE	2	1h	54	52/48	88:12 / 94:6
17 ^g	3b	4f	(S)-III	Saccharin	DCE	2	1i	52	55/45	87:13 / 90:10
18 ^g	3c	4f	(R)-III	Saccharin	DCE	4	1h ^l	51	53/47	84:16 / 86:14
19 ^g	3b	4f	(R)-III	Saccharin	DCE	4	1i ^l	52	58/42	86:14 / 89:11

^a Configuration assigned according to the predicted model reported by Kanger^{7e}. ^b Reaction conditions: all reactions were performed under argon atmosphere. ^c **3** (1.4 equiv), **4** (1.0 equiv), **I** (40 mol%), TFA (40 mol%), Na₂SO₄ (3.0 equiv.), rt. ^d **3** (1.0 equiv), **4** (1.0 equiv), catalyst (20 mol%), benzoic acid (20 mol%), rt. ^e 10 mol% of catalyst was used. ^f 30 mol% of catalyst was used. ^g **3** (1.0 equiv), **4** (1.0 equiv), **III** (20 mol%), Saccharin (40 mol%), 40°C. ^h reaction performed in triplicate. ⁱ Molecular sieves (0.4 g /mmol). ^j Diastereomeric ratio determined by HPLC. ^k Enantiomeric ratio determined by chiral HPLC. ^l Opposite configuration was obtained.

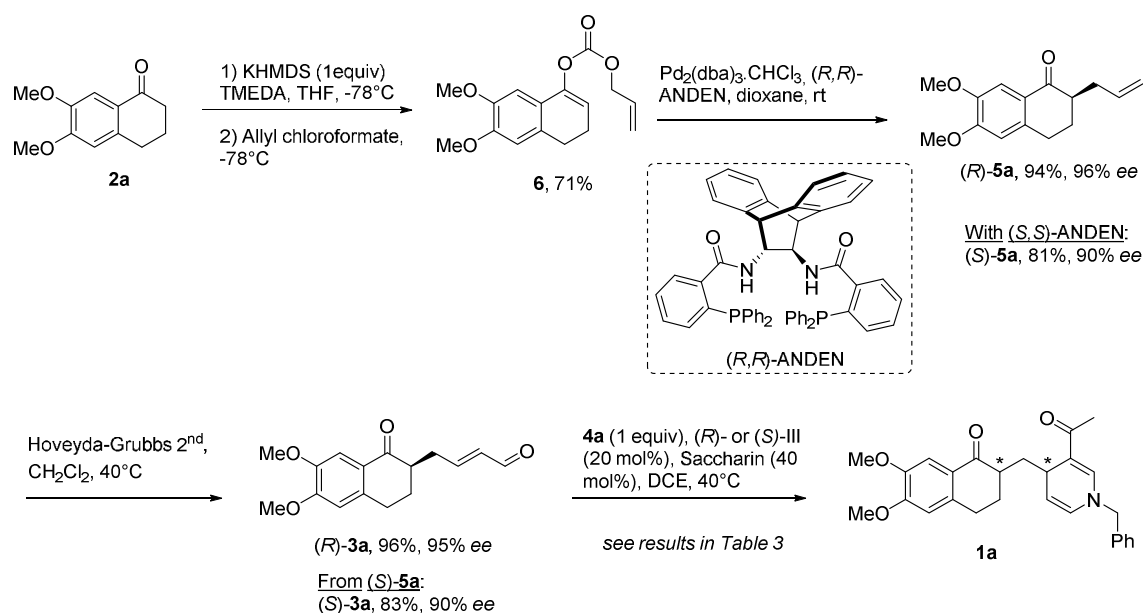
Having determined the optimal conditions, we next examined the scope of the reaction by reacting enamines **4a-f** with enals (±)-**3b-c** (Entries 10-19). Firstly, enamines **4a-d** with either a benzyl, phenyl or *n*-propyl group reacted efficiently with racemic aldehyde (±)-**3b** to lead to the corresponding 1,4-DHPs **1b-e** in 45 to 65% yields and good enantiomeric ratios ranging from 88:12 to 95:5 (Table 2, entries 10-13). Comparable yield (56%) and enantiomeric ratios (*er*= 90:10 and 91:9) were obtained by reacting enal (±)-**3c** possessing an indanone moiety and enamine (±)-**4a** (Table 2, entry 14). Pleasingly, the method was efficiently applied to the preparation of 1,4-DHPs having an ester or a nitrile functional group at the C-3 position (Table 2, entries 15-19). Thus, when the β-enamino ester **4e** was reacted with enal (±)-**3c**,

the 1,4-DHP **1g** was isolated in 62% yield and an enantiomeric ratio up to 92:8 (Table 2, Entry 15).

Similarly, the reaction between β -enamino nitrile **4f** and enal (\pm)-**3b** or (\pm)-**3c** afforded the corresponding DHPs **1h,i** in 45-52% yields and enantiomeric ratios ranging from 87:13 to 94:6 (Table 2, entries 16-17). Unsurprisingly, when **R-III** catalyst was used instead of **S-III** catalyst, DHPs **1h,i** were obtained with comparable yields (51-52%) and an inversion of the enantiomeric ratios ranging from 84:16 to 89:11 (Entries 18-19).

To achieve our initial goal, namely the asymmetric synthesis of each of the four stereoisomers of 1,4-DHP **1a**, both enals (**S**)-**3a** and (**R**)-**3a** were prepared in a three-step sequence including an enantioselective Tsuji allylation as key step (Scheme 3). Thus, the required allyl carbonate **6** was prepared in a good yield (71%) by adding allyl chloroformate to a mixture of α -tetralone **2a** previously treated with KHMDS and TMEDA in THF at -78°C .¹¹

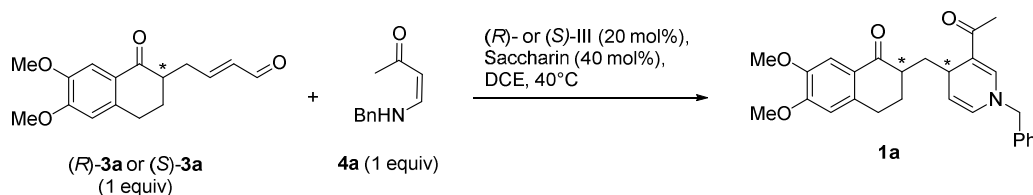
Scheme 3. Synthesis of the four stereoisomers of the target prodrug **1a**



The so-obtained carbonate **6** was subjected to a palladium-catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA) reaction to yield the α -allyl ketones **5a**.¹² So, a

solution of Pd₂(dba)₃ and (*R,R*)- or (*S,S*)-ANDEN Trost ligand in 1,4-dioxane was stirred for 30 minutes at room temperature prior to cannulation of the resulting mixture into a solution of allyl carbonate **6**. Following this procedure, α -allyl ketones (*R*)-**5a** and (*S*)-**5a** were obtained in very good yields (81-94%) and high enantiomeric ratios (*er*= 98:2 and 95:5 respectively). Both α -allyl ketones (*R*)-**5a** and (*S*)-**5a** were subjected to cross-metathesis furnishing enals (*R*)-**3a** and (*S*)-**3a** in good yields (96 and 83% respectively) without affecting enantiomeric ratios (*er*= 98:2 and 95:5 respectively). Lastly, enals (*R*)-**3a** and (*S*)-**3a** were engaged in the enantioselective organocatalytic aza-ene-type domino reaction with enaminone **4a** in presence of (*S*)- or (*R*)-Jørgensen-Hayashi catalyst **III** and saccharin as cocatalyst (Table 3).

Table 3. Enantioselective organocatalytic aza-ene type domino reaction with enals (*S*)- or (*R*)-3a****



Entry	3	III	1a ^a	Yield (%) ^b	<i>dr</i> ^c	<i>er</i> ^c major /minor	IC ₅₀ ^d (μM)
1	(<i>R</i>)- 3a	(<i>S</i>)	(<i>R,R</i>)- 1a	64	93:7	98:2	nd ^e
2	(<i>S</i>)- 3a	(<i>R</i>)	(<i>S,S</i>)- 1a	48	92:8	99.5:0.5	0.286
3	(<i>S</i>)- 3a	(<i>S</i>)	(<i>S,R</i>)- 1a	59	90:10	99.5:0.5	0.173
4	(<i>R</i>)- 3a	(<i>R</i>)	(<i>R,S</i>)- 1a	42	91:9	99:1	0.924

^a Configuration assigned according to the predicted model reported by Kanger^{7e}. ^b isolated yield. ^c determined by chiral SFC. ^d *In vitro* inhibition test of hAChE. ^e nd: not determined (% inhibition of hAChE < 50% at 10 μM)

Therefore, using (*S*)- or (*R*)-**III** catalyst, enal (*R*)-**3a** afforded, respectively diastereomers (*R,R*)-**1a** and (*R,S*)-**1a** in good yields (64% and 42% respectively) with excellent diastereomeric and enantiomeric ratios (*dr*= 93:7 and *er*= 98:2; and *dr*= 91:9 and *er*= 99:1 respectively). Then, in presence of (*S*)- or (*R*)-**III**, enal (*S*)-**3a** led respectively to the formation of diastereomers (*S,R*)-**1a** and (*S,S*)-**1a** in good yields (59% and 48% respectively) along with excellent diastereomeric and enantiomeric ratios (*dr*= 91:9 and *er*= 99.5:0.5; and *dr*= 91:9 and *er*= 99.5:0.5 respectively). Thus, the absolute configuration of the four

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3 stereoisomers A-D previously isolated by chiral super critical fluid chromatography was
4 assigned affording valuable informations on the structure-activity relationship. Firstly, the
5 configuration of the chiral center carried by the dihydropyridine moiety appears to have a
6 minor impact on the inhibitory activity against *hAChE* (Table 3, entries 1 vs 4 / entries 2 vs 3).
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8 On the contrary, the tetralone's stereogenic center seems to have a greater influence on the
9 capacity of **1a** to inhibit the enzyme activity. Whereas the diastereomers (*S,S*)-**1a** and (*S,R*)-
10 **1a** display low IC₅₀ values (Table 3, entries 2 and 3), much weaker inhibitory activity is
11 observed for the stereomers with the (*R*) configuration at the carbon atom adjacent to the
12 carbonyl group of the tetralone (Table 3, entries 1 and 4).
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23 CONCLUSION

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26 In conclusion, an asymmetric approach toward a family of chiral donepezil-like 1,4-
27 dihydropyridines **1**, highly sought-after as anti-Alzheimer prodrugs, was developed by
28 implementing two highly stereoselective key steps; *i.e.* a catalytic enantioselective Tsuji
29 allylation from enol carbonate **6** and an enantioselective organocatalytic aza-ene-type
30 domino reaction between enals **3a-c** and β -enaminones or β -enamino esters **4a-f**. It should
31 be noticed that the reaction conditions initially reported by Kanger *et al.*^{7e} had to be adapted
32 by means of saccharin as co-catalyst to boost the yield (45-65%) and dichloroethane as
33 solvent to increase the enantiomeric ratio of 1,4-DHPs **1** (*er* up to 95:5). This stereoselective
34 route toward chiral donepezil-like 1,4-dihydropyridine prodrugs **1** provides a useful extension
35 of known asymmetric transformations to the development of promising chiral prodrug
36 prototypes.^{4e-f} In addition, the opportunity to have a robust access to all stereoisomers of
37 prodrugs **1** will enable us to accelerate the lead optimization phase while securing the
38 chemical development of this new class of anti-Alzheimer drugs.
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54 EXPERIMENTAL SECTION

General Information: All commercial reagents were used without further purification. The solvents were dried with appropriate desiccants and distilled prior to use or were obtained anhydrous from commercial suppliers. Silica gel (60, 230–400 mesh or 70–230 mesh) was used for column chromatography. Reactions were monitored by thin layer chromatography on silica gel precoated aluminium plates. UV light at 254 nm or KMnO₄ stains were used to visualize TLC plates. ¹H, ¹³C{¹H} NMR spectra were recorded using a spectrometer operating at 300 and 75 MHz respectively. Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, br: broad and m: multiplet. Coupling constants *J* are in Hz and chemical shifts are given in ppm and calibrated with DMSO-*d*₆ or CDCl₃ (residual solvent signals). ¹H NMR spectra obtained in CDCl₃ were referenced to 7.26 ppm and in DMSO-*d*₆ were referenced to 2.50 ppm. ¹³C{¹H} NMR spectra obtained in CDCl₃ were referenced to 77.16 ppm. High resolution mass spectra were measured by ESI. Microwave experiments were conducted in a monomode cavity with a microwave power delivery system ranging from 0 to 850 W allowing pressurized reactions (0 to 30 bars) to be carried out in sealed glass vials (4 to 30 mL) equipped a snap cap and a silicon septum. The temperature (0 to 300 °C) was monitored via a contact-less infrared sensor and was calibrated with a ruby Thermometer. Diastomeric ratios were determined by reversed-phase HPLC using Accucore C18 column (150x2.1mm, 2.6 μm, flow= 0.3 mL.min⁻¹) with UV detection using a gradient (20 to 55%) of acetonitrile in ammonium acetate buffer (20 mM).

2-allyl-6,7-dimethoxy-tetralone-1-one ((±)-5a). In a microwave vial, to a solution of **2a** (412.5 mg, 2.0 mmol) and allyl alcohol (0.68 mL, 10.0 mmol) in dry toluene (3 mL) were added freshly distilled 2,2-dimethoxypropane (0.37 mL, 3.0 mmol), *p*-toluenesulfonic acid (68.8 mg, 0.4 mmol) and 3 Å molecular sieves (ca. 600 mg). The vial was sealed and heated in a microwave reactor at 200 °C for 1.5 h. The cooled reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed successively with saturated aqueous solution of NaHCO₃ and brine. The combined organic phase was dried over MgSO₄ and concentrated to dryness. The residue was purified by column chromatography (Petroleum ether/EtOAc = 3:1) to afford the

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3 title compound (\pm)-**5a** as a colorless oil (247.1 mg, 50%). ^1H NMR (300 MHz, CDCl_3) δ 7.51
4 (s, 1H), 6.64 (s, 1H), 5.91-5.76 (m, 1H), 5.12-5.04 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 2.95-
5 2.85 (m, 2H), 2.78-2.71 (m, 1H), 2.55-2.40 (m, 1H), 2.32-2.14 (m, 2H), 1.92-1.78 (m, 1H). ^{13}C
6 NMR (75 MHz, CDCl_3) δ 198.4, 153.4, 147.9, 138.9, 136.4, 125.7, 116.8, 110.1, 108.8, 56.0,
7 55.9, 46.5, 34.2, 28.3, 28.2. HRMS (ESI $^+$) calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{19}\text{O}_3$ m/z 247.1334, found
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15 **2-allyl-6-methoxy-tetralone-1-one ((\pm)-**5b**)**. To a solution of LiHMDS (4.15 g, 24.8 mmol) in
16 THF (20 mL) cooled at -78°C was added slowly a solution of **2b** (3.5 g, 19.86 mmol) in dry
17 THF (60 mL). After the addition was complete, the solution was stirred at -78°C for 30
18 minutes, then HMPA (7 mL, 40.2 mmol) was added slowly and stirred for other 5 minutes
19 followed by the addition of a solution of allyl bromide (2.6 mL, 30.08 mmol) in dry THF (10
20 mL) at the same temperature. The mixture was left to warm slowly to room temperature (2-
21 3h) and quenched at 0°C with aqueous 1N HCl (20 mL), and then extracted with diethyl ether
22 (3x). The combined organic phase was dried over MgSO_4 and concentrated to dryness. The
23 residue was purified by column chromatography (Petroleum ether/EtOAc = 95:5) to afford the
24 title compound (\pm)-**5b** as a colorless oil (2.9 g, 68%). ^1H NMR (300 MHz, CDCl_3) δ 8.01 (d, J
25 = 8.8 Hz, 1H), 6.82 (dd, J = 8.7, 2.5 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 5.97-5.73 (m, 1H),
26 5.13-5.04 (m, 2H), 3.85 (s, 3H), 2.95-2.93 (m, 2H), 2.81-2.67 (m, 1H), 2.58-2.42 (m, 1H),
27 2.34-2.13 (m, 2H), 1.94-1.74 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 198.4, 163.5, 146.7,
28 136.6, 130.0, 126.3, 116.9, 113.2, 112.6, 55.6, 46.9, 34.3, 29.1, 28.1. HRMS (ESI $^+$) calcd for
29 $[\text{M}+\text{Na}]^+$ $\text{C}_{14}\text{H}_{16}\text{O}_2\text{Na}^+$ m/z 239.1048, found 239.1043.
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45 **2-allyl-5,6-dimethoxy-indan-1-one ((\pm)-**5c**)**. From LiHMDS (0.8 g, 4.78 mmol) in THF (40
46 mL), **2c** (1.0g, 5.2 mmol) in THF (40 mL), HMPA (1.7 mL, 9.56 mmol), allyl bromide (0.86
47 mL, 7.17 mmol) diluted in THF (5 mL) and following the procedure described for the
48 synthesis of compound (\pm)-**5b**, the title compound (\pm)-**5c** was obtained as a colorless oil (0.5
49 g, 46%) after purification by column chromatography on silica gel (Petroleum ether/EtOAc =
50 2:1). ^1H NMR (300 MHz, CDCl_3) δ 7.13 (s, 1H), 6.83 (s, 1H), 5.83-5.68 (m, 1H), 5.13-5.00 (m,
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2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.15 (dd, $J = 17.7, 8.0$ Hz, 1H), 2.79-2.57 (m, 3H), 2.29-2.12 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 206.9, 155.6, 149.4, 149.1, 135.6, 129.4, 116.9, 107.4, 104.3, 56.2, 56.1, 46.8, 35.8, 31.8. HRMS (ESI⁺) calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{17}\text{O}_3$ m/z 233.1178 found 233.1175.

General procedure for the synthesis of enal derivatives 3a-c: Under Argon atmosphere, crotonaldehyde (20 mmol) was added to a solution of the corresponding allyl derivative **5a-c** (5.0 mmol) in degassed CH_2Cl_2 (10.0 mL). Hoveyda-Grubbs' 2nd (2.5% mol) was then added, and the reaction mixture was heated to 40 °C overnight. After cooling at room temperature, the reaction mixture was filtered over Celite[®] and the filtrate was concentrated to dryness and purified by column chromatography on silica gel to give the expected aldehydes **3a-c**.

(E)-4-(6,7-dimethoxy-1-oxo-tetralon-2-yl)but-2-enal ((±)-3a). From crotonaldehyde (182.0 mg, 2.6 mmol), (±)-**5a** (160.0 mg, 0.65 mmol), Hoveyda-Grubbs' 2nd (10 mg, 5% mol) and CH_2Cl_2 (5.0 mL). Purification by column chromatography on silica gel (Petroleum ether/EtOAc = 1:1) gave (±)-**3a** as an off-white powder (146.0 mg, 82%). ^1H NMR (300 MHz, CDCl_3) δ 9.51 (d, $J = 7.9$ Hz, 1H), 7.49 (s, 1H), 6.98-6.88 (m, 1H), 6.65 (s, 1H), 6.17 (dd, $J = 15.7, 7.9$ Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.05-2.85 (m, 3H), 2.71-2.52 (m, 2H), 2.21-2.12 (m, 1H), 1.95-1.78 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.1, 193.8, 156.5, 153.6, 148.0, 138.8, 134.5, 125.2, 110.1, 108.6, 56.1, 56.0, 46.0, 33.4, 29.0, 28.5. HRMS (ESI⁺) calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{19}\text{O}_4$ m/z 275.1283, found 275.1279.

(E)-4-(6-methoxy-1-oxo-tetralon-2-yl)but-2-enal ((±)-3b). From crotonaldehyde (1.43 g, 20.3 mmol), (±)-**5b** (1.1 g, 5.09 mmol), Hoveyda-Grubbs' 2nd (80.0 mg, 2.5% mol) and CH_2Cl_2 (1.0 mL). Purification by column chromatography on silica gel (Petroleum ether/EtOAc = 4:1) gave (±)-**3b** as an off-white powder (1.1 g, 88%). ^1H NMR (300 MHz, CDCl_3) δ 9.52 (d, $J = 7.9$ Hz, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 7.01-6.82 (m, 2H), 6.69 (d, $J = 2.4$ Hz, 1H), 6.19 (dd, $J = 15.6, 7.9$ Hz, 1H), 3.86 (s, 3H), 3.04-2.91 (m, 3H), 2.71-2.52 (m, 2H), 2.29-2.09 (m, 1H), 1.99-1.76 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.1, 194.0, 163.8, 156.7, 146.5, 134.7,

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3 130.1, 125.9, 113.5, 112.6, 55.6, 46.6, 33.5, 29.4, 28.9. HRMS (ESI⁺) calcd for [M+Na]⁺
4 C₁₅H₁₆O₃Na *m/z* 267.0997 found 267.1003.
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7 **(E)-4-(5,6-dimethoxy-1-oxo-indan-2-yl)but-2-enal ((±)-3c)**. From crotonaldehyde (0.63 mg,
8 0.75 mL, 8.99 mmol), (±)-**5c** (0.5 g, 2.15 mmol), Hoveyda-Grubbs' 2nd (17.0 mg, 2.5% mol)
9 and dichloromethane (15 mL). Purification by column chromatography on silica gel
10 (Petroleum ether/EtOAc = 1:1) gave (±)-**3c** as a yellow solid (0.51 g, 91%). ¹H NMR (300
11 MHz, CDCl₃) δ 9.51 (d, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 7.02-6.78 (m, 2H), 6.19 (dd, *J* = 15.7,
12 7.8 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.27 (dd, *J* = 16.9, 7.4 Hz, 1H), 3.02-2.83 (m, 2H),
13 2.71 (dd, *J* = 17.0, 3.3 Hz, 1H), 2.62-2.47 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 205.5, 193.9,
14 156.1, 155.3, 149.8, 148.7, 134.6, 129.0, 107.5, 104.5, 56.5, 56.3, 46.0, 34.7, 32.1. HRMS
15 (ESI⁺) calcd for [M+H]⁺ C₁₅H₁₇O₄ *m/z* 261.1126, found 261.1131.
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25 **General procedure for the synthesis of enamines 4a-f**: A mixture of the corresponding
26 commercial enol ether (5.0 mmol) and commercial amine (5.0 mmol) was heated under
27 vacuum. The methanol by-product was eliminated as it forms, affording only the expected
28 enamines **4a-f** which were used without further purification.
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33 **(Z)-4-(benzylamino)but-3-en-2-one (4a)**. From 4-methoxy-3-buten-2-one (500.0 mg, 5.0
34 mmol) and benzylamine (535.0 mg, 5.0 mmol). The mixture was heated to 60°C for 50 min to
35 give enaminone **4a** as a yellow oil (875.0 mg, 100%). ¹H NMR (300 MHz, CDCl₃) δ 10.07
36 (br s, 1H), 7.37-7.24 (m, 5H), 6.71 (dd, *J* = 12.7, 7.4 Hz, 1H), 5.06 (d, *J* = 7.4 Hz, 1H), 4.38
37 (d, *J* = 6.1 Hz, 2H), 2.08 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 197.8, 152.4, 138.0, 128.9,
38 128.8, 127.8, 127.5, 127.1, 94.5, 52.5, 29.1. HRMS (ESI⁺), calcd for C₁₁H₁₄NO 176.10699
39 found 176.10685.
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48 **(Z)-4-((2-methylbenzyl)amino)but-3-en-2-one (4b)**. From 4-methoxy-3-buten-2-one (801.0
49 mg, 8.0 mmol) and 2-methylbenzylamine (969.0 g, 8.0 mmol). The mixture was heated to
50 60°C for 30 min to give enaminone **4b** as a yellow oil (1.50 mg, 99%). ¹H NMR (300 MHz,
51 CDCl₃) δ 10.05 (s, 1H), 7.25-7.02 (m, 4H), 6.67 (dd, *J* = 12.7, 7.4 Hz, 1H), 5.04 (d, *J* = 7.4
52 Hz, 1H), 4.35 (d, *J* = 5.9 Hz, 2H), 2.31 (s, 3H), 2.06 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ
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3 197.8, 152.3, 136.0, 135.8, 130.7, 128.0, 127.9, 126.5, 94.5, 50.7, 29.2, 19.2. HRMS (ESI⁺)
4 calcd for [M+H]⁺ C₁₂H₁₆NO *m/z* 190.1231, found 190.1232.

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7 **(Z)-4-(phenylamino)but-3-en-2-one (4c)**. From 4-methoxy-3-buten-2-one (1.0 g, 10.0 mmol)
8 and aniline (931.0 mg, 10.0 mmol). The mixture was heated to 60°C for 40 min to give
9 enaminone **4c** as a red oil (1.52 g, 94%). ¹H NMR (300 MHz, CDCl₃) δ 11.60 (br s, 1H), 7.33-
10 7.18 (m, 3H), 7.06-7.00 (m, 3H), 5.29 (d, *J* = 7.7 Hz, 1H), 2.15 (s, 3H). ¹³C NMR (75 MHz,
11 CDCl₃) δ 199.0, 143.1, 140.4, 129.8, 123.5, 116.2, 97.5, 29.7. HRMS (ESI⁺) calcd for [M+H]⁺
12 C₁₀H₁₂NO *m/z* 162.0919, found 162.0911.

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19 **(Z)-4-(propylamino)but-3-en-2-one (4d)**. From 4-methoxy-3-buten-2-one (1.0 g, 10.0 mmol)
20 and *n*-propylamine (591.0 mg, 10.0 mmol). The mixture was heated to 60 °C for 2h to give
21 enaminone **4d** as a deep orange oil (1.25 g, 98%). ¹H NMR (300 MHz, CDCl₃) δ 9.81 (br s,
22 1H), 6.62 (dd, *J* = 12.8, 7.3 Hz, 1H), 4.94 (d, *J* = 7.3 Hz, 1H), 3.15-3.09 (m, 2H), 2.02 (s, 3H),
23 1.65-1.46 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 197.3, 152.8, 93.5,
24 50.9, 29.0, 24.4, 11.2. HRMS (ESI⁺) calcd for [M+H]⁺ C₇H₁₄NO *m/z* 128.1075, found
25 128.1075.

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34 **(E)- and (Z)-methyl 3-((2-methylbenzyl)amino)acrylate (4e)**. From methyl *trans*-3-
35 methoxyacrylate (581.0 mg, 5.0 mmol) and 2-methylbenzylamine (606.0 g, 5.0 mmol). The
36 mixture was heated to 60°C for 16h to give compound **4e** (*Z/E* = 1:1) as an off-white gel
37 (875.0 mg, 85%). ¹H NMR (300 MHz, CDCl₃) δ 8.06 (s, 0.5H), 7.58 (dd, *J* = 13.3, 7.8 Hz,
38 0.5H), 7.22-7.14 (m, 4H), 6.66 (dd, *J* = 13.1, 8.0 Hz, 0.5H), 4.82 (d, *J* = 13.2 Hz, 0.5H), 4.60
39 (br s, 0.5H), 4.54 (d, *J* = 8.0 Hz, 0.5H), 4.33 (d, *J* = 5.8 Hz, 1H), 4.17 (d, *J* = 5.2 Hz, 1H), 3.66
40 (s, 1.5H), 3.64 (s, 1.5H), 2.31 (s, 1.5H), 2.31 (s, 1.5H). ¹³C NMR (75 MHz, CDCl₃) δ 171.2,
41 170.0, 152.2, 136.6, 136.3, 136.0, 130.8, 130.6, 128.6, 128.3, 127.9, 127.8, 126.5, 126.4,
42 82.4, 50.7, 50.4, 50.3, 43.6, 19.2, 19.0. HRMS (ESI⁺) calcd for [M+H]⁺ C₁₂H₁₆NO₂ *m/z*
43 206.1181, found 206.1174.

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54 **(Z)-3-(benzylamino)acrylonitrile (4f)**. From 3-methoxyacrylonitrile (415.0 mg, 2.0 mmol) and
55 benzylamine (535.0 mg, 5.0 mmol). The mixture was heated to 110 °C for 4h to give a yellow
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oil (789.0 mg, 100%). ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.28 (m, 5H), 7.11 (dd, $J = 13.8, 7.5$ Hz, 1H), 4.58 (br s, 1H), 4.17 (d, $J = 5.4$ Hz, 2H), 4.03 (d, $J = 13.8$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 151.0, 136.3, 128.5, 127.5, 127.1, 122.2, 61.3, 47.2. HRMS (ESI $^+$) calcd for $[\text{M}+\text{H}]^+ \text{C}_{10}\text{H}_{11}\text{N}_2$ m/z 159.0922, found 159.0924.

General procedure for the synthesis of 1,4-DHPs 1a-g by scandium triflate catalysis

(Method A). To a suspension of $\text{Sc}(\text{OTf})_3$ (49.1 mg, 10 mol%), Na_2SO_4 (0.42 g, 3 equiv) in dry CH_2Cl_2 (3.5 mL) were added a solution of enamine freshly prepared **4a-f** (1.0 mmol, 1 equiv) and enal (\pm)-**3a-c** (1.0 mmol, 1 equiv) in dry CH_2Cl_2 (1.5 mL). The mixture was stirred at room temperature (21°C) until total consumption of enal (TLC). The reaction solution was filtered on Celite $^{\text{®}}$ and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel to afford the 1,4-DHPs **1a-g**.

General procedure for the synthesis of 1,4-DHPs 1a-i by enantioselective aminocatalysis (Method B).

Under argon atmosphere, a mixture of the enal **3a-c** (1.0 mmol, 1 equiv), saccharin (73.2 mg, 40 mol%), (*R*)- or (*S*)-**III** (65.1 mg, 20 mol%) and the enamine **4a-f** (1.0 mmol, 1 equiv) in dry dichloroethane (0.25M) was stirred at 40°C until total consumption of enal (TLC). Upon completion of the reaction and cooling to room temperature, the mixture was diluted with dichloromethane. The resulting solution was then filtered over Celite $^{\text{®}}$ and concentrated to dryness. The crude residue was directly purified column chromatography on silica gel to give the desired 1,4-dihydropyridines **1a-i**.

2-((3-acetyl-1-benzyl-1,4-dihydropyridin-4-yl)methyl)-6,7-dimethoxy-3,4-

dihydronaphthalen-1(2H)-one (1a). **Method A:** From enamine **4a** (140. mg, 0.8 mmol), (\pm)-**3a** (242.0 mg, 0.88 mmol). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave **1a** as a yellow oil (118.1 mg, 62%). **Method B:** From enamine **4a** (70.1 mg, 0.4 mmol), (\pm)-**3a** (110.0 mg, 0.4 mmol) and (*S*)-**III** (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched DHP **1a** (103.5 mg, 60%). HPLC Chiralpak $^{\text{®}}$ IE column; 60/33/7 heptane/DCM/isopropanol; flow rate = 1 mL.min $^{-1}$; t_1 = 26.07 min (minor), t_2 = 28.4 min

(minor), $t_3 = 30.4$ min (major), $t_4 = 43.1$ min (major); $dr = 60:40$; er major = 95:5; er minor = 85:5. ^1H NMR (300 MHz, CDCl_3) δ 7.51 (s, 0.5H), 7.49 (s, 0.5H), 7.47-7.11 (m, 6H), 6.65 (s, 0.5H), 6.62 (s, 0.5H), 5.98-5.93 (m, 1H), 5.09-5.04 (m, 1H), 4.45 (s, 1H), 4.44 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.73-3.68 (m, 1H), 3.21-3.08 (m, 0.5H), 2.91-2.84 (m, 1.5H), 2.73-2.64 (m, 0.5H), 2.60-2.48 (m, 0.5H), 2.40-2.05 (m, 5H), 1.95-1.81 (m, 1H), 1.65-1.51 (m, 0.5H), 1.44-1.32 (m, 0.5H). ^{13}C NMR (75 MHz, CDCl_3) δ 199.9, 199.7, 195.4, 194.2, 153.2, 153.1, 147.7, 142.9, 142.8, 138.9, 138.7, 136.8, 136.7, 128.9, 128.0, 127.9, 127.8, 126.9, 126.8, 125.6, 125.3, 113.7, 113.3, 110.2, 110.1, 108.7, 108.6, 108.2, 57.8, 57.7, 56.0, 55.9, 43.4, 42.3, 38.1, 37.7, 29.4, 28.3, 28.1, 27.2, 26.8, 24.6, 24.4. HRMS (ESI⁺) calcd for $[\text{M}+\text{H}]^+$ $\text{C}_{27}\text{H}_{30}\text{NO}_4$ m/z 432.2175, found 432.2182.

2-((3-acetyl-1-benzyl-1,4-dihydropyridin-4-yl)methyl)-6-methoxy-3,4-

dihydronaphthalen-1(2H)-one (1b). Method A: From enamine **4a** (140.0 mg, 0.8 mmol), (\pm)-**3b** (200.0 mg, 0.8 mmol). Purification by column chromatography on silica gel (EtOAc gradient in Petroleum ether) gave **1b** as a yellow oil (110.0 mg, 35%). **Method B:** From enamine **4a** (71.8 mg, 0.41 mmol), (\pm)-**3a** (102.6 mg, 0.42 mmol) and (S)-III (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched DHP **1b** (74.1 mg, 45%). HPLC analytic separation: Chiralpak[®] IC column; 80/20 heptane/ethanol; flow rate = 1 mL.min⁻¹; $t_1 = 28.08$ min (major), $t_2 = 32.6$ min (minor), $t_3 = 34.6$ min (major), $t_4 = 37.3$ min (minor); $dr = 52:48$; er major = 93:7; er minor = 93:7. ^1H NMR (300 MHz, CDCl_3) δ 7.96-7.92 (m, 1H), 7.41-7.16 (m, 6H), 6.82-6.78 (m, 1H), 6.71-6.68 (m, 1H), 5.97-5.92 (m, 1H), 5.08-5.02 (m, 1H), 4.47 (s, 2H), 3.81 (s, 3H), 3.73-3.63 (m, 1H), 3.13 (ddd, $J = 16.8, 7.1, 4.3$ Hz, 0.5H), 2.91-2.79 (m, 1.5H), 2.72-2.60 (m, 0.5H), 2.57-2.47 (m, 0.5H), 2.39-2.22 (m, 1H), 2.19 (s, 1.5H), 2.16 (s, 1.5H), 2.15-1.74 (m, 2H), 1.63-1.50 (m, 0.5H), 1.45-1.36 (m, 0.5H). ^{13}C NMR (75 MHz, CDCl_3) δ 199.9, 199.8, 195.6, 195.0, 163.3, 163.2, 146.7, 146.6, 143.1, 142.9, 136.8, 136.8, 129.8, 129.0, 129.0, 128.1, 128.0, 127.98, 127.0, 126.9, 126.2, 113.8, 113.3, 113.1, 113.0, 112.3, 110.2, 108.3, 57.9,

57.8, 55.4, 43.9, 42.7, 38.1, 37.7, 29.2, 28.9, 28.3, 28.1, 27.7, 27.0, 24.7, 24.5. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₆H₂₈NO₃ *m/z* 402.2069, found 402.2064.

2-((3-acetyl-1-(2-methylbenzyl)-1,4-dihydropyridin-4-yl)methyl)-6-methoxy-3,4-

dihydronaphthalen-1(2H)-one (1c). Method A: From enamine **4b** (140. mg, 1.1 mmol), (±)-**3b** (266.0 mg, 1.1 mmol). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave **1c** as a yellow oil (269.6 mg, 59%). **Method B:** From enamine **4b** (94.6 mg, 0.50 mmol), (±)-**3b** (122.0 mg, 0.50 mmol) and (S)-III (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched DHP **1c** (207.6 mg, 55%). HPLC Chiralpak[®] IA-3 column; 90/10 heptane/(isopropanol/ethanol = 1:1); flow rate = 1.5 mL.min⁻¹; *t*₁ = 19.94 min (minor), *t*₂ = 23.1 min (minor), *t*₃ = 26.8 min (major), *t*₄ = 37.6 min (major); *dr* = 52:48; *er* major = 92:8; *er* minor = 95:5. ¹H NMR (300 MHz, CDCl₃) δ 7.97-7.91 (m, 1H), 7.25-7.03 (m, 5H), 6.79-6.75 (m, 1H), 6.67-6.64 (m, 1H), 5.91-5.86 (m, 1H), 5.05-5.00 (m, 1H), 4.43 (s, 1H), 4.41 (s, 1H), 3.83 (s, 3H), 3.70-3.65 (m, 1H), 3.19-3.05 (m, 0.5H), 2.98-2.78 (m, 1.5H), 2.72-2.58 (m, 0.5H), 2.58-2.44 (m, 0.5H), 2.43-2.25 (m, 1H), 2.28 (s, 3H), 2.15 (s, 1.5H), 2.12 (s, 1.5H), 2.12-1.98 (m, 1H), 1.92-1.82 (m, 1H), 1.68-1.45 (m, 0.5), 1.43-1.37 (m, 0.5H). ¹³C NMR (75 MHz, CDCl₃) δ 199.9, 199.7, 195.6, 195.0, 163.3, 163.2, 146.7, 146.6, 143.0, 142.8, 135.9, 134.5, 134.4, 130.8, 129.7, 128.2, 128.1, 127.9, 127.6, 126.6, 126.5, 126.4, 126.0, 113.8, 113.4, 113.1, 113.0, 112.4, 110.1, 108.2, 56.0, 55.9, 55.4, 43.9, 42.8, 38.4, 37.9, 29.1, 28.9, 28.4, 28.2, 27.7, 27.0, 24.6, 24.4, 19.2. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₇H₃₀NO₃ *m/z* 416.2226 found 416.2227.

2-((3-acetyl-1-phenyl-1,4-dihydropyridin-4-yl)methyl)-6-methoxy-3,4-

dihydronaphthalen-1(2H)-one (1d). Method A: From enamine **4c** (161.4. mg, 1.1 mmol), (±)-**3b** (268.2 mg, 1.1 mmol). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave **1d** as a yellow oil (277.0 mg, 65%). **Method B:** From enamine **4c** (80.6 mg, 0.50 mmol), (±)-**3b** (122.0 mg, 0.50 mmol) and (S)-III (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether)

gave the enantio-enriched DHP **1d** (91.4 mg, 47%). HPLC Chiralpak[®] IA-3 column; 80/20 heptane/(isopropanol/ethanol = 1:1); flow rate = 1.0 mL.min⁻¹; *t*₁ = 15.8 min (major), *t*₂ = 18.0 min (minor), *t*₃ = 22.6 min (major), *t*₄ = 24.6 min (minor); *dr* = 57:43; *er* major = 89:11; *er* minor = 88:12. ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, *J* = 8.7 Hz, 0.5H), 7.95 (d, *J* = 8.7 Hz, 0.5H), 7.51 (s, 0.5H), 7.46 (s, 0.5H), 7.40-7.35 (m, 2H), 7.21-7.15 (m, 3H), 6.79-6.75 (m, 1H), 6.68 (d, *J* = 2.4 Hz, 0.5H), 6.65 (d, *J* = 2.4 Hz, 0.5H), 6.47-6.41 (m, 1H), 5.21-5.16 (m, 1H), 3.82 (s, 1.5H), 3.81 (s, 1.5H), 3.76-3.66 (m, 1H), 3.21-3.08 (m, 0.5H), 2.97-2.84 (m, 1.5H), 2.75-2.64 (m, 0.5H), 2.62-2.51 (m, 0.5H), 2.45-2.18 (m, 3H), 2.26 (s, 1.5H), 2.23 (s, 1.5H), 1.69-1.57 (m, 0.5H), 1.54-1.40 (m, 0.5H). ¹³C NMR (75 MHz, CDCl₃) δ 199.8, 199.6, 196.2, 195.6, 163.4, 163.3, 146.6, 146.5, 143.8, 140.0, 139.9, 129.9, 129.8, 126.6, 126.3, 126.2, 126.0, 125.4, 125.3, 120.1, 120.0, 116.7, 116.5, 113.2, 113.0, 112.4, 111.4, 109.6, 55.4, 44.0, 43.0, 38.3, 37.9, 29.2, 28.9, 28.5, 28.3, 27.8, 27.1, 24.9, 24.7. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₅H₂₆NO₃ *m/z* 388.1913, found 388.1907.

2-((3-acetyl-1-propyl-1,4-dihydropyridin-4-yl)methyl)-6-methoxy-3,4-

dihydronaphthalen-1(2H)-one (1e). Method A: From enamine **4d** (63.6 mg, 0.5 mmol), (±)-**3b** (122.0 mg, 0.5 mmol). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave **1e** as a yellow oil (79.6 mg, 45%). **Method B:** From enamine **4d** (104.3 mg, 0.82 mmol), (±)-**3b** (200.0 mg, 0.82 mmol) and (S)-III (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched DHP **1e** (188.3 mg, 65%). HPLC Chiralpak[®] IB column; 80/20 heptane/isopropanol; flow rate = 1.0 mL.min⁻¹; *t*₁ = 8.8 min (major), *t*₂ = 10.8 min (minor), *t*₃ = 11.4 min (major), *t*₄ = 12.3 min (minor); *dr* = 55:45, *er* major = 92:8; *er* minor = 91:9. ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, *J* = 8.7 Hz, 0.5H), 7.93 (d, *J* = 8.7 Hz, 0.5H), 7.07 (s, 0.5H), 7.01 (s, 0.5H), 6.78-6.75 (m, 1H), 6.67-6.64 (m, 1H), 5.91-5.86 (m, 1H), 5.07-4.90 (m, 1H), 3.81 (s, 3H), 3.70-3.48 (m, 1H), 3.31-3.01 (m, 2.5H), 2.89 (m, 1.5H), 2.70-2.58 (m, 0.5H), 2.52-2.38 (m, 1H), 2.28-2.23 (m, 0.5H), 2.18 (s, 1.5H), 2.15 (s, 1.5H), 2.09-1.94 (m, 1H), 1.81-1.73 (m, 1H), 1.68-1.48 (m, 2.5H), 1.34-1.28 (m, 0.5H), 0.92 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75

MHz, CDCl₃) δ 200.1, 199.9, 195.4, 194.8, 163.4, 163.3, 146.8, 146.7, 143.0, 142.9, 129.8, 127.9, 127.7, 126.3, 126.1, 113.2, 113.0, 112.5, 112.4, 109.9, 108.0, 56.4, 55.5, 43.9, 42.8, 38.3, 37.8, 29.1, 29.0, 28.2, 28.1, 27.6, 26.9, 24.7, 24.5, 23.6, 23.5, 11.0. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₂H₂₈NO₃ *m/z* 354.2069, found 354.2069.

2-((3-acetyl-1-benzyl-4H-pyridin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one

(1f). Method A: From enamine **4a** (84.1 mg, 0.48 mmol), (±)-**3c** (122.3 mg, 0.47 mmol).

Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave **1f** as a yellow oil (107.9 mg, 55%). **Method B:** From enamine **4a** (175.2 mg, 1.0 mmol), (±)-**3c** (260.1 mg, 1.0 mmol) and (*S*)-**III** (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched DHP **1f** (233.7 mg, 56%). HPLC Chiralpak[®] IC column; 40/50/10 heptane/DCM/isopropanol; flow rate = 1.0 mL.min⁻¹; *t*₁ = 9.4 min (major), *t*₂ = 15.2 min (minor), *t*₃ = 16.9 min (major), *t*₄ = 19.2 min (minor); *dr* = 53:47; *er* major = 89:11; *er* minor = 90:10. ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.11 (m, 7H), 6.88 (s, 0.5H), 6.84 (s, 0.5H), 6.01-5.91 (m, 1H), 5.12 (dd, *J* = 7.6, 5.2 Hz, 0.5H), 4.95 (dd, *J* = 7.6, 5.5 Hz, 0.5H), 4.47 (s, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.78-3.71 (m, 0.5H), 3.68-3.64 (m, 0.5H), 3.33-3.02 (m, 1.5H), 2.85-2.61 (m, 1.5H), 2.22 (s, 1.5H), 2.17 (s, 1.5H), 2.00-1.88 (m, 1H), 1.58-1.36 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 208.5, 208.3, 195.5, 194.95, 155.5, 155.4, 149.7, 149.4, 143.3, 142.8, 136.8, 129.5, 129.2, 129.1, 128.3, 128.2, 127.1, 127.0, 114.0, 113.3, 110.1, 108.5, 107.7, 107.5, 104.4, 104.3, 58.0, 57.9, 56.3, 56.2, 45.2, 44.2, 41.2, 40.4, 34.0, 32.7, 29.8, 29.4, 24.7, 24.6. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₆H₂₈NO₄ *m/z* 418.2018, found 418.2021.

Methyl 4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)-1-(2-methylbenzyl)-1,4-dihydropyridine-3-carboxylate (1g). Method A: From enamine **4f** (133.4 mg, 0.65

mmol), (±)-**3c** (161.0 mg, 0.62 mmol). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave **1g** as a yellow oil (304.3 mg, 68%). **Method B:** From enamine **4f** (98.5 mg, 0.48 mmol), (±)-**3c** (125.1 mg, 0.48 mmol) and (*S*)-**III** (20 mol%). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether)

gave the enantio-enriched DHP **1g** (124.6 mg, 58%). HPLC Chiralpak[®] IA-3 column; 80/20 heptane/(isopropanol/ethanol = 1:1); flow rate = 1.0 mL.min⁻¹; t₁ = 16.6 min (major), t₂ = 19.2 min (minor), t₃ = 24.1 min (major), t₄ = 26.0 min (minor); *dr* = 51:49; *er* major = 92:8; *er* minor = 92:8. ¹H NMR (300 MHz, CDCl₃) δ 7.28-7.16 (m, 6H), 6.87 (s, 0.55H), 6.85 (s, 0.45H), 5.96-5.86 (m, 1H), 5.01 (dd, *J* = 7.8, 5.1 Hz, 0.55H), 4.84 (dd, *J* = 7.5, 5.1 Hz, 0.45H), 4.40 (s, 1.1H), 4.39 (s, 0.9H), 3.98 (s, 3H), 3.90 (s, 3H), 3.70 (s, 1.35H), 3.67 (s, 1.65H), 3.55-3.49 (m, 0.45H), 3.33-3.18 (m, 1.55H), 3.01-2.72 (m, 2H), 2.31 (s, 1.65H), 2.30 (s, 1.35H), 2.13-1.98 (m, 1H), 1.64-1.45 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 208.4, 208.2, 168.9, 168.5, 155.5, 155.4, 149.6, 149.5, 149.4, 149.3, 142.0, 141.5, 136.2, 136.1, 134.8, 134.7, 130.8, 129.5, 128.8, 128.5, 128.1, 127.8, 126.5, 108.2, 107.6, 107.5, 106.7, 104.4, 101.6, 101.3, 56.3, 56.2, 51.1, 51.0, 45.1, 44.1, 41.8, 40.5, 34.3, 32.8, 30.8, 30.6, 29.8, 19.3, 19.2. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₇H₃₀NO₅ *m/z* 448.2124, found 448.2111.

1-benzyl-4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)-1,4-

dihydropyridine-3-carbonitrile (1h). Method B: From enamine **4f** (77.5 mg, 0.49 mmol), (±)-**3c** (128.0 mg, 0.49 mmol) and (S)-**III** (20 mol%) (or (R)-**III**). Purification by column chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched DHP **1h** as a yellow oil (105.9 mg, 54%). HPLC Chiralpak[®] IE column; 60/33/7 heptane/DCM/isopropanol; flow rate = 1 mL.min⁻¹; t₁ = 15.4 min (major), t₂ = 17.5 min (minor), t₃ = 20.1 min (major), t₄ = 21.8 min (minor); With (S)-**III** : *dr* = 50:40; *er* major = 88:12; *er* minor = 94:6; With (R)-**III** : *dr* = 55:45; *er* major = 85:15; *er* minor = 85:15. ¹H NMR (300 MHz, CDCl₃) δ 7.53-7.24 (m, 6H), 6.96 (s, 1H), 6.78 (m, 1H), 5.98 (m, 1H), 4.94 (dd, *J* = 8.1, 4.4 Hz, 0.5H), 4.84 (dd, *J* = 8.0, 4.4 Hz, 0.5H), 4.43 (s, 1H), 4.42 (s, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 3.64-3.57 (m, 0.5H), 3.47-3.30 (m, 1.5H), 3.13-2.82 (m, 2H), 2.40-2.21 (m, 1H), 1.80-1.65 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 207.6, 207.2, 155.6, 155.5, 149.6, 149.5, 149.3, 148.9, 143.4, 143.0, 136.3, 136.2, 129.2, 129.1, 128.9, 128.4, 128.3, 128.3, 127.2, 127.1, 121.6, 121.2, 107.5, 107.4, 106.2, 105.0, 104.4, 104.3, 82.9, 82.5, 57.6, 57.5, 56.4, 56.2,

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3 44.3, 43.7, 41.5, 40.0, 33.8, 33.1, 32.2, 32.1, 29.7. HRMS (ESI⁺) calcd for [M+H]⁺ C₂₅H₂₅N₂O₃
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5 *m/z* 401.1865, found 401.1852.

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7 **1-benzyl-4-((6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)-1,4-**

8
9 **dihydropyridine-3-carbonitrile (1i). Method B:** From enamine **4f** (79.1 mg, 0.5 mmol), (±)-
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11 **3b** (122.1 mg, 0.5 mmol) and (*S*)-**III** (20 mol%) (or (*R*)-**III** (20 mol%)). Purification by column
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13 chromatography on silica gel (EtOAc gradient in petroleum ether) gave the enantio-enriched
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15 DHP **1i** as a yellow oil (101.0 mg, 52%). HPLC Chiralpak[®] IE column; 60/33/7
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17 heptane/DCM/isopropanol; flow rate = 1 mL.min⁻¹; t₁ = 12.7 min (major), t₂ = 13.9 min
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19 (major), t₃ = 16.4 min (minor), t₄ = 17.5 min (minor); With (*S*)-**III** : *dr* = 55:45; *er* major = 87:13;
20
21 *er* minor = 90:10; With (*R*)-**III** : *dr* = 58:42; *er* major = 86:14; *er* minor = 89:11. ¹H NMR (300
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23 MHz, CDCl₃) δ 7.99 (d, *J* = 2.9 Hz, 0.5H), 7.96 (d, *J* = 3.0 Hz, 0.5H), 7.39-7.29 (m, 3H), 7.21-
24
25 7.15 (m, 2H), 6.83-6.79 (m, 1H), 6.70-6.62 (m, 2H), 5.88-5.79 (m, 1H), 4.81-4.77 (m, 1H),
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27 4.31 (s, 1H), 4.30 (s, 1H), 3.85 (s, 1.5H), 3.84 (s, 1.5H), 3.47-3.30 (m, 1H), 3.00-2.89 (m,
28
29 2H), 2.88-2.76 (m, 0.5H), 2.72-2.62 (m, 0.5H), 2.40-2.15 (m, 2H), 1.96-1.80 (1H), 1.69-1.47
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31 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 198.9, 198.8, 163.5, 163.4, 146.4, 146.3, 143.3, 142.9,
32
33 136.4, 129.9, 129.1, 129.0, 128.3, 128.2, 127.1, 113.3, 113.2, 112.4, 106.4, 105.3, 82.9,
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35 82.2, 57.5, 57.4, 55.5, 43.1, 43.0, 39.3, 38.2, 31.2, 31.1, 31.0, 29.4, 29.0, 28.6, 28.4. HRMS
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37 (ESI⁺) calcd for [M+H]⁺ C₂₅H₂₅N₂O₂ *m/z* 385.1916, found 385.1917.

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39 **Allyl (6,7-dimethoxy-3,4-dihydronaphthalen-1-yl) carbonate (6).** To a solution of KHMDS
40
41 (1.0 M solution in THF, 1.5 g, 5.82 mmol) and TMEDA (0.88 mL, 5.82 mmol) cooled at -78 °C
42
43 was added dropwise a solution of 6,7-dimethoxy-1-tetralone **2a** (1.0 g, 4.85 mmol) in 10 mL
44
45 of dry THF over a period of 30 minutes. The mixture was stirred at this temperature for 1
46
47 hour, and then was diluted with 10 mL of dry THF. When the temperature was settled at -78
48
49 °C, allyl chloroformate (0.62 mL, 6.64 mmol) was added slowly over the slurry and left to stir
50
51 for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl, then extracted 3
52
53 times with diethyl ether. The combined extracts were dried over MgSO₄ and concentrated in
54
55 vacuum. The crude residue was purified by column chromatography on silica gel (Petroleum
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58
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2 ether/EtOAc = 3:1) to give the title enol carbonate **6** as a colorless oil (1.0 g, 71%). ¹H NMR
3 (300 MHz, CDCl₃) δ 6.74 (s, 1H), 6.69 (s, 1H), 6.03-5.95 (m, 1H), 5.69 (t, *J* = 4.7 Hz, 1H),
4 5.40 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1H), 5.30 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.70 (dt, *J* = 5.8, 1.2 Hz,
5 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.78 (t, *J* = 8.2 Hz, 2H), 2.47-2.37 (m, 2H). ¹³C NMR (75 MHz,
6 CDCl₃) δ 153.4, 148.8, 147.5, 146.0, 131.4, 129.4, 123.0, 119.4, 112.7, 111.5, 104.9, 69.0,
7 56.2, 56.1, 27.2, 22.2. HRMS (ESI⁺) calcd for [M+H]⁺ C₁₆H₁₉O₅ *m/z* 291.1232, found
8 291.1223.
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17 **General procedure for Pd-DAAA:** Two oven-dried 5 mL vials were individually charged with
18 a magnetic stirring bar. One vial was loaded with Pd₂(dba)₃CHCl₃ (2.5 mol%) and the
19 corresponding chiral Anden Trost ligand (5.5 mol%); the other one was loaded with the
20 corresponding enol carbonate **6** (0.35 mmol). The vials were sealed and connected with a
21 transfer cannula. The system flushed with argon, then 1.0 mL of degassed dry 1,4-dioxane
22 was added to both vials. After stirring for 20 min, the deep red solution containing the catalyst
23 was transferred *via* cannula into the vial containing the enol carbonate **6**, and stirring was
24 continued for other 2 hours. The reaction mixture was concentrated *in vacuo* and the residue
25 was purified by column chromatography on silica gel to afford the title compound. The
26 attribution of the configuration of the novel stereocenter was done in accordance with the
27 literature data.
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39 **(*R*)-2-allyl-6,7-dimethoxy-tetralone-1-one ((*R*)-5a).** From **6** (100.0 mg, 0.35 mmol),
40 Pd₂(dba)₃CHCl₃ (15 mg, 2.5 mol %), (*R,R*)-Anden Trost ligand (26.0 mg, 5.5 mol %) and
41 2x1.0 mL of degassed dry 1,4-dioxane. Purification by column chromatography on silica gel
42 (Petroleum ether/EtOAc = 49:1) afforded the title compound (77.0 mg, 94%) as yellowish oil.
43 Spectral data (¹H and ¹³C NMR) were identical to the racemic compound. HPLC (Chiralpak®
44 IC column; 95:5 Heptane / Isopropanol; flow rate = 1 mL.min⁻¹; *t*₁ = 16.44 min (minor), *t*₂ =
45 19.49 min (major), 96% *ee*).
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53 **(*S*)-2-allyl-6,7-dimethoxy-tetralone-1-one ((*S*)-5a).** From **6** (300.0 mg, 1.03 mmol),
54 Pd₂(dba)₃CHCl₃ (45.0 mg, 2.5 mol %) (*S,S*)-Anden Trost ligand (78.0 mg, 5.5 mol %) and 2 x
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3 mL of degassed dry 1,4-dioxane. Purification by column chromatography on silica gel (petroleum ether/EtOAc = 49:1) afforded the title compound (200.0 mg, 81%) as yellowish oil. Spectral data (^1H and ^{13}C NMR) was identical to the racemic compound. HPLC (Chiralpak[®] IC column; 95:5 Heptane / Isopropanol; flow rate = 1 mL.min⁻¹; t_1 = 16.33 min (major), t_2 = 19.6 min (minor), 90% ee).

(*R,E*)-4-(6,7-dimethoxy-1-oxo-tetralon-2-yl)but-2-enal ((*R*)-3a). Following the general procedure for the metathesis reaction, from crotonaldehyde (91.0 mg, 1.29 mmol), (***R***)-5a (70.0 mg, 0.32 mmol), Hoveyda-Grubbs' 2nd (5 mg, 2.5% mol) and CH₂Cl₂ (3.0 mL). Purification by column chromatography on silica gel (Petroleum ether/EtOAc = 1:1) gave an off-white powder (76.0 mg, 96%). Spectral data (^1H and ^{13}C NMR) were identical to the racemic compound. HPLC (Chiralpak[®] IC column, 9:1 MTBE/ isopropanol, flow rate = 1 mL.min⁻¹, t_1 = 13.06 min (minor), t_2 = 16.81 min (major), 95% ee).

(*S,E*)-4-(6,7-dimethoxy-1-oxo-tetralon-2-yl)but-2-enal (*S***)-3a.** Following the general procedure for the metathesis reaction, from crotonaldehyde (207.0 mg, 2.95 mmol), (***S***)-5a (140.0 mg, 0.74 mmol), Hoveyda-Grubbs' 2nd (10 mg, 2.5% mol) and CH₂Cl₂ (8.0 mL). Purification by column chromatography on silica gel (Petroleum ether/EtOAc = 1:1) gave an off-white powder (150.0 mg, 83%). Spectral data (^1H and ^{13}C NMR) were identical to the racemic compound. HPLC: Chiralpak[®] IC column, 9:1 MTBE/ isopropanol, flow rate = 1 mL.min⁻¹, t_1 = 12.93 min (major), t_2 = 16.91 min (minor), 90% ee).

(*R*)-2-(((*R*)-1-benzyl-3-(prop-1-en-2-yl)-1,4-dihydropyridin-4-yl)methyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one ((*R,R*)-1a)

Following the general procedure for the synthesis of 1,4-DHPs by enantioselective aminocatalysis (Method B). From enal (***R***)-3a (50 mg, 0.18 mmol), saccharin (14 mg, 0.073 mmol, 40%), (***S***)-Jørgensen catalyst III (22 mg, 0.036 mmol) and enamine **4a** (32 mg, 0.18 mmol) and dichloroethane (0.8 mL). Purification by chromatography on silica gel (Petroleum ether/ EtOAc = 1:1) gave 1,4-DHP (***R,R***)-1a (50 mg, 64%) as a light-yellow oil. $[\alpha]_D^{25}$ -207.4 (c 0.43 CHCl₃). ^1H NMR (300 MHz, CDCl₃) δ 7.47 (d, J = 4.7 Hz, 1H), 7.38-7.18 (m, 6H),

6.62 (s, 1H), 5.93 (d, $J = 5.5$ Hz, 1H), 5.03 (dd, $J = 7.6, 5.5$ Hz, 1H), 4.46 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.72-3.69 (dd, $J = 12.0, 5.6$ Hz, 1H), 2.87 (t, $J = 6.0$ Hz, 2H), 2.60-2.42 (m, 1H), 2.42-2.29 (m, 1H), 2.18 (s, 3H), 2.14-2.05 (m, 1H), 1.89-1.78 (m, 1H), 1.45-1.19 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 199.9, 195.7, 153.2, 147.8, 143.1, 138.9, 136.9, 129.1, 128.1, 128.0, 127.1, 125.8, 113.5, 110.3, 110.2, 108.8, 58.0, 56.2, 56.1, 43.55, 38.3, 29.6, 28.5, 28.4, 24.8. SFC analytic separation: Chiralpak[®] IA column; 30% Ethanol/Isopropanol (70:30), flow rate = 4 mL.min⁻¹; $t_{R,R} = 4.92$ min; $dr = 93:7$; $er = 98:2$.

(S)-2-(((S)-1-benzyl-3-(prop-1-en-2-yl)-1,4-dihydropyridin-4-yl)methyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one ((S,S)-1a)

From enal (S)-**3a** (50 mg, 0.18 mmol, ee 94%), saccharin (14 mg, 0.073 mmol, 40%), (*R*)-Jørgensen catalyst III (22 mg, 0.036 mmol) and enamine **4a** (32 mg, 0.18 mmol) and dichloroethane (0.8 mL). Purification by chromatography on silica gel (Petroleum ether/EtOAc = 1:1) gave 1,4-dihydropyridine (S,S)-**1a** (38 mg, 48%) as a light-brown oil. $[\alpha]_{\text{D}}^{25} +214.4$ (c 0.43 CHCl_3). Spectral data (^1H and ^{13}C NMR) were identical to the compound (*R,R*)-**1a**. SFC analytic separation: Chiralpak[®] IA column; 30% Ethanol/Isopropanol (70:30), flow rate = 4 mL.min⁻¹; $t_{S,S} = 5.22$ min; $dr = 92:8$; $er = 99.5:0.5$.

(S)-2-(((R)-1-benzyl-3-(prop-1-en-2-yl)-1,4-dihydropyridin-4-yl)methyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one ((S,R)-1a)

From enal (S)-**3a** (50 mg, 0.18 mmol, ee 98%), saccharin (14 mg, 0.073 mmol, 40%), (*S*)-Jørgensen catalyst III (22 mg, 0.036 mmol) and enamine **4a** (32 mg, 0.18 mmol) and dichloroethane (0.8 mL). Purification by chromatography on silica gel (Petroleum ether/EtOAc = 1:1) gave 1,4-DHP (S,R)-**1a** (46 mg, 59%) as a yellow oil. $[\alpha]_{\text{D}}^{25} -203.7$ (c 0.43 CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.47 (s, 1H), 7.39-7.08 (m, 6H), 6.65 (s, 1H), 5.91 (d, $J = 6.9$ Hz, 1H), 5.03 (dd, $J = 7.7, 5.2$ Hz, 1H), 4.44 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.70-3.58 (m, 1H), 3.1-3.07 (m, 1H), 2.85-2.79 (m, 1H), 2.69-2.61 (m, 1H), 2.32-2.23 (m, 1H), 2.15 (s, 3H), 2.12-1.98 (m, 1H), 1.89-1.80 (m, 1H), 1.53-1.63 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 200.2, 195.1, 153.3, 147.8, 142.9, 139.1, 136.8, 129.1, 128.2, 128.1, 127.0, 125.5, 114.0,

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3 110.3, 108.8, 108.4, 57.9, 56.1, 56.0, 42.5, 37.8, 28.3, 27.3, 27.0, 24.6. SFC analytic
4 separation: Chiralpak[®] IA column; 30% Ethanol/Isopropanol (70:30), flow rate = 4 mL.min⁻¹;
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6 $t_{S,R} = 6.08$ min; $dr = 90:10$; $er = 99.5:0.5$.
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9 **(*R*)-2-(((*S*)-1-benzyl-3-(prop-1-en-2-yl)-1,4-dihydropyridin-4-yl)methyl)-6,7-dimethoxy-**
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11 **3,4-dihydronaphthalen-1(2H)-one ((*R,S*)-1a)**
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13 From enal (*R*)-**3a** (5 mg, 0.18 mmol), saccharin (14 mg, 0.073 mmol, 40%), (*R*)-Jørgensen
14 catalyst III (22 mg, 0.036 mmol) and enamine **4a** (32 mg, 0.18 mmol) and dichloroethane (0.8
15 mL). Purification by chromatography on silica gel (petroleum ether/EtOAc = 1:1) gave 1,4-
16 DHP (*R,S*)-**1a** (33 mg, 42%) as a yellow oil. $[\alpha]_D^{25} +198.3$ (c 0.43 CHCl₃). Spectral data (¹H
17 and ¹³C NMR) were identical to the compound (*S,R*)-**1a**. SFC analytic separation: Chiralpak[®]
18 IA column; 30% Ethanol/Isopropanol (70:30), flow rate = 4 mL.min⁻¹; $t_{R,S} = 10.0$ min; $dr =$
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91:9; $er = 99:1$.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information: Copies of ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra, HPLC and SFC chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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