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Enantioselective dearomatization of alkyl pyridiniums by N-heterocyclic carbene-catalyzed nucleophilic acylation

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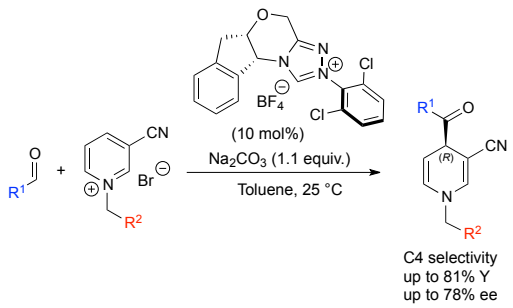


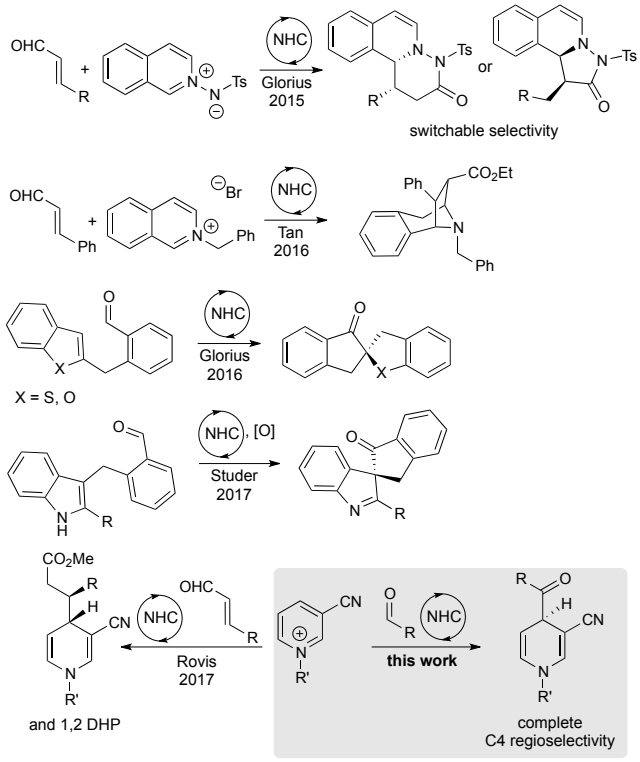
Abstract: A chiral-NHC-catalyzed dearomatizing reaction of activated N-alkylpyridinium salts with aliphatic aldehydes is described. The resulting acylated 1,4-dihydropyridines have been obtained with complete C4 regioselectivity and enantioselectivities in the range of 52-78% ee. The (4*R*) absolute configuration of the synthesized compounds has been determined by TD-DFT simulation of the Electronic Circular Dichroism spectra.

Introduction

The development of robust methodologies for the catalytic enantioselective formation of C-C bonds is one of the most investigated topic in organic chemistry to rapidly access enantioenriched structural motifs.[1] Within this realm, the catalytic asymmetric dearomatization reaction has gained increasing attention over the recent years due to the wide availability of cheap and versatile substrates such as phenols, indoles, pyrroles, pyridines, and (iso)quinolines.[2] Despite the high synthetic potential of this strategy, a main challenge associated with enantioselective dearomatization is the poor reactivity of substrates toward nucleophilic additions because of the resonance stability energy of the aromatic nucleus as well as the difficult control of the regio- and stereoselectivity in the formation of the target three-dimensional products. A number of transition metal-catalyzed reactions have been reported for the effective enantioselective dearomatization of (hetero)aromatic compounds,[3] whereas the utilization of organocatalytic approaches are less investigated.[4-8] After the pioneering works of McMillan,[4a] Jørgensen,[4b] Jacobsen[4c] and their co-workers on the dearomatization of furans and isoquinolinium salts, only a few contributions have appeared in the literature dealing with the dearomatization of (iso)quinolines,[4b,d] indoles,[5] and of the more demanding pyridines[6] by conventional organocatalytic strategies (amino, hydrogen-bonding, and anion-binding catalysis).[7] Umpolung (polarity reversal) catalysis by the use of N-heterocyclic carbenes (NHCs) as organocatalysts[9] has also been applied to the asymmetric dearomatization of (hetero)aromatic compounds but in a very limited number of recent examples,[8] mainly involving α,β-unsaturated aldehydes (enals) as the nucleophiles (homoenolate chemistry)[9] and/or intramolecular processes (Scheme 1).

The group of Glorius in 2015 developed the dearomatizing annulation reaction of N-imino(iso)quinolinium ylides using NHC-generated homoenolates or enolates with elegant switchable reactivity.[8a] Later on, simple N-alkyl isoquinolinium salts were demonstrated by Tan and co-workers as suitable substrates for chiral-NHC-catalyzed dearomatizing double Mannich reactions leading to tropanes with four contiguous stereocenters.[8b] In addition, the intramolecular dearomatization of benzofurans/benzothiophenes by hydroacylation, and of indoles by oxidative NHC catalysis were efficiently achieved by the groups of Glorius-Neugebauer[8c] and Studer,[8d] respectively. During the preparation of this manuscript, Rovis and Flanigan disclosed the enantio- and diastereoselective addition of enals to N-alkyl pyridinium salts promoted by NHC catalysts (a^3-d^3 umpolung)[10] to prepare 1,4-dihydropyridines (DHPs) with good regioselectivity (preferential C-4 functionalization of the pyridine ring).[8e] Notably, 1,4-DHPs are privileged structures with a broad spectrum of medicinally relevant properties, including antihypertensive, anticancer, and antimicrobial activity.[11] In this work, we report a complementary NHC-based approach for the

intermolecular dearomatization of pyridines relying on the a^1-d^1 umpolung[10] of aliphatic aldehydes and leading to enantioenriched C4-acylated 1,4-DHPs with complete regiocontrol over the 1,2-addition product and opposite C4 configuration compared to DHPs prepared in the Rovis study (Scheme 1).



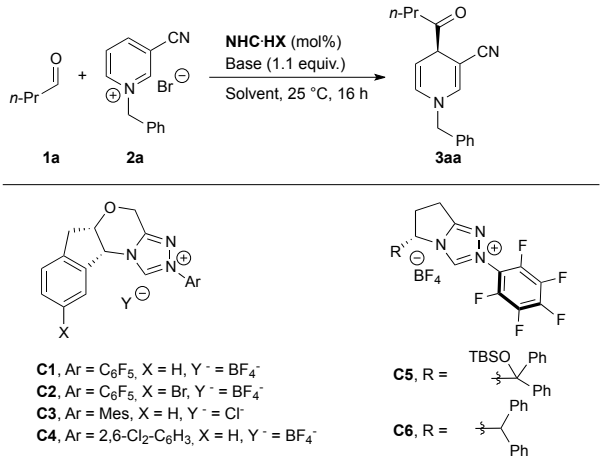
Scheme 1. Enantioselective dearomatizations by NHC catalysis

Results and Discussion

We commenced our study by subjecting *n*-butanal **1a** and the readily available N-benzylpyridinium salt **2a** bearing a cyano group at the 3-postion to a catalytic amount (10 mol%) of the Rovis triazolium salt **C1** and K_3PO_4 in toluene (Table 1, entry 1). Gratifyingly, the 1,4-DHP **3aa** formed with complete regioselectivity, high yield (90%), and encouraging enantiomeric excess (53% ee). Hence, the catalyst substituent effect was investigated and we found that the use of the newly synthesized promoter **C2** determined a slightly improved reaction outcome (entry 2), while the Bode precatalyst **C3** produced a remarkable increase of enantioselectivity (78% ee) accompanied, however, by a critical drop of conversion efficiency (entry 3). Pleasantly, the amino-indanol derived triazolium salt **C4** provided **3aa** in 81% yield and 69% ee (entry 4). Switching to the pyrrole derived triazolium salt **C5** and to its newly prepared analogue **C6** resulted in lower enantioselectivity (entries 5-6), being the precatalyst **C5** completely inactive. The solvent screening with **C4** indicated that an increase of the medium polarity caused a reduction of reaction efficiency (entries 7-9); on the other hand, the use of apolar

CCl_4 restored the enantiocontrol by the catalyst (74% ee), albeit at the expense of a diminished yield of **3aa** likely due to the low solubility of **2a** (entry 10). We next replaced K_3PO_4 and observed that nitrogen bases such as diisopropylethylamine (DIPEA) were unable to promote the reaction (entry 11); Na_2CO_3 performed better than Cs_2CO_3 in terms of enantioselectivity (entries 12-13), thus indicating a sort of influence of the hard/soft character of the metal on the stereochemical outcome of the dearomatization process.

Table 1. Reaction Optimization[a]

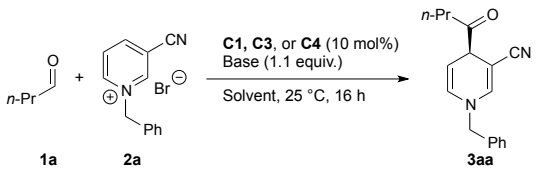


Entry	NHC·HX (mol%)	Solvent	Base	Yield [%][b]	ee [%][c]
1	**C1** (10)	Toluene	K_3PO_4	90	53
2	**C2** (10)	Toluene	K_3PO_4	93	58
3	**C3** (10)	Toluene	K_3PO_4	9	78
4	**C4** (10)	Toluene	K_3PO_4	81	69
5	**C5** (10)	Toluene	K_3PO_4	-	n.d.
6	**C6** (10)	Toluene	K_3PO_4	91	31
7	**C4** (10)	C_6H_5Cl	K_3PO_4	80	68
8	**C4** (10)	DCM	K_3PO_4	62	42
9	**C4** (10)	THF	K_3PO_4	-	n.d.
10	**C4** (10)	CCl_4	K_3PO_4	25	74
11	**C4** (10)	Toluene	DIPEA	-	n.d.
12	**C4** (10)	Toluene	Na_2CO_3	80	70
13	**C4** (10)	Toluene	Cs_2CO_3	81	62
14[d]	**C4** (10)	Toluene	Na_2CO_3	77	70
15[e]	**C4** (10)	Toluene	K_3PO_4	74	70
16[f]	**C4** (10)	Toluene	K_3PO_4	33	70
17	**C4** (5)	Toluene	K_3PO_4	29	78
18[g]	**C4** (10)	Toluene	Na_2CO_3	84	70

[a]Reaction conducted with 1.5 equiv. of **1a** (0.30 mmol) and 1.0 equiv. of **2a** in the stated solvent (0.15 M). [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction run in the presence of LiCl (0.5 equiv.). [e]Reaction run at 0 °C. [f]Reaction run at -30 °C. [g]Reaction run with 2 mmol of **1a**.

The addition of LiCl (50 mol%) as a cooperative Lewis catalyst[12] and lowering the reaction temperature left almost unaffected the stereoselectivity (entries 14-16), while the reduction of the catalyst loading to 5 mol% afforded **3aa** with lower yield but significantly higher ee (78%, entry 17). This result led us to suppose the reversibility of the dearomatization reaction and/or the occurrence of a partial racemization promoted by the basic catalyst. These hypotheses were excluded by a control experiment (see the Supporting Information), which showed the maintenance of the (stereo)chemical integrity of an authentic sample of **3aa** under the optimized reaction conditions of entry 12. Remarkably, the reaction could be scaled up to 2 mmol of **1a** without affecting the yield and enantioselectivity of **3aa**, which could be conveniently recovered by simple filtration through a short pad of silica (entry 18). The whole set of investigated conditions of the optimization study including the use of different bases and solvents for the more effective catalysts **C1**, **C3**, and **C4** are reported in Table 2.

Table 2. Additional conditions screened in the optimization study[a]



1a **2a** **3aa**

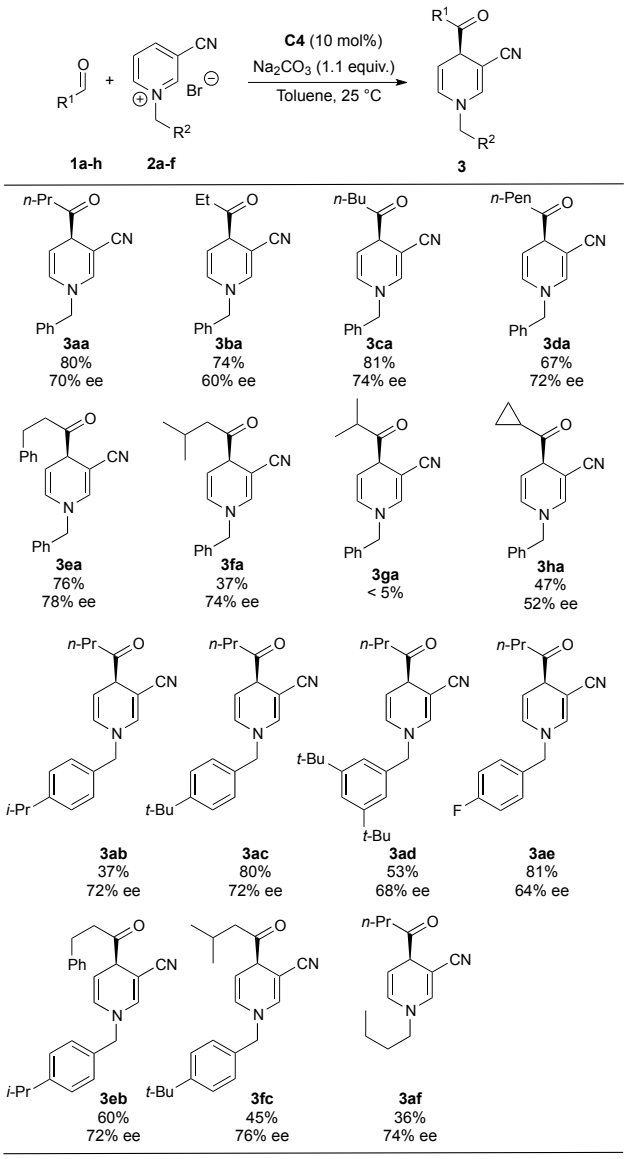
Entry	NHC·HX	Solvent	Base	Yield [%][b]	ee [%][c]
1	**C1**	Toluene	Cs_2CO_3	91	40
2	**C1**	Toluene	NaOAc	91	49
3	**C1**	Toluene	Et_3N	-	n.d.
4	**C1**	Toluene	KHMDS	-	n.d.
5	**C1**	Toluene	K_3PO_4	90	53
6	**C1**	Toluene	DBU	-	n.d.
7	**C1**	Toluene	DIPEA	-	n.d.
8	**C3**	Toluene	Na_2CO_3	11	75
9	**C3**	Toluene	Cs_2CO_3	12	69
10	**C4**	DCM	Na_2CO_3	58	49
11	**C4**	THF	Na_2CO_3	-	n.d.
12	**C4**	CCl_4	Na_2CO_3	-	n.d.
13	**C4**	*t*-AmOH	Na_2CO_3	80	Rac
14	**C4**	C_6H_5Cl	Na_2CO_3	90	53
15	**C4**	DMF	Na_2CO_3	-	n.d.
16	**C4**	cyclohexane	Na_2CO_3	-	n.d.

[a]Reaction conducted with 1.5 equiv. of **1a** (0.30 mmol) and 1.0 equiv. of **2a** in the stated solvent (0.15 M). [b]Isolated yield. [c]Determined by chiral HPLC.

Investigation of the scope of the reaction (Table 3) revealed that short-chained aliphatic aldehydes **1a-c** (*n*-propanal **1b**, *n*-pentanal **1c**) reacted with **2a** affording the corresponding 1,4-DPHs in good

yields and with increasing enantioselectivity (from 60 to 74% ee), in agreement with the increase of steric hindrance of the linear alkyl substituent. This trend reversed with the medium-chained *n*-hexanal **1d** (72% ee), likely because of a less restricted conformational freedom of the *n*-pentyl group in the reaction transition state. Aldehydes **1e** and **1f** bearing substituents at the β-carbon performed equally well with slightly improved enantioselectivity compared to linear aldehydes. On the other hand, the α-branched isobutyraldehyde **1g** was not a competent substrate, while cyclopropanecarboxaldehyde **1h** was well tolerated furnishing the 1,4-DHP **3ha** in satisfactory yield and enantioselectivity.

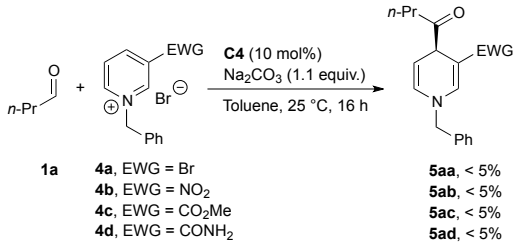
Table 3. Reaction Scope[a]



[a]Reactions conducted with 0.40 mmol of **2**, 1.5 equiv. of **1**, 1.1. equiv. of anhydrous sodium carbonate, 10 mol% of **C4** in anhydrous Toluene (2 mL).

The effect of the N-substituent on reactivity of the N-alkyl-3-cyanopyridinium core was also explored with substrates **2b-f**. Apparently, it was found a no clear correlation between stereoselectivity and bulkiness of the pyridinium nitrogen group as can be evinced by comparison of the enantiomeric excess within the series of analogous products **3aa**, **3ab**, **3ac**, and **3ad**. It is important to emphasize that high selectivities were observed in all the substrate combinations of Table 3; in fact, the moderate yields registered for some 1,4-DHPs **3** were always associated with low conversions of the corresponding substrates **1** and **2**.

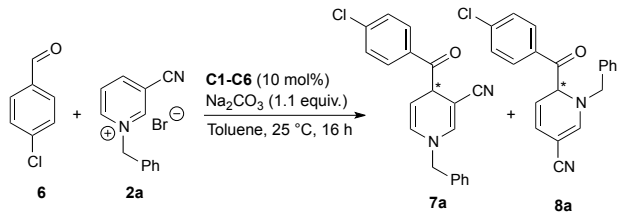
Limitations of the disclosed methodology were next investigated considering as reaction partners either pyridiniums salts with different C3 substituents or a model aromatic aldehyde. Indeed, variations of the electron withdrawing group (EWG) at the C3 position of the N-benzylpyridinium ring (compounds **4a-d**; EWG = Br, NO_2, CO_2Me, $CONH_2$) resulted in no conversion into the corresponding DHPs **5** using *n*-butanal **1a** as the nucleophile (Scheme 2).



Scheme 2. Dearomatization of pyridinium salts 4 displaying different C3 substituents

Additionally, the utilization of *p*-chlorobenzaldehyde **6** in the dearomatization of pyridinium salt **2a** produced the corresponding 1,4-DHP **7a** with low levels of enantioselectivity (up to 50% ee) using the pre-catalysts **C1-C6** and Na_2CO_3 as the base (Toluene, RT; Table 4). Interestingly, the formation of a small portion (ca. 5%) of the 1,2-addition product **8a** could be detected in the **2a**/**6** coupling, which was better performed using the newly synthesized catalyst **C2** (entry 2). On the other hand, the dearomatization of **2a** with either benzaldehyde or *p*-anisaldehyde under the conditions of entry 2 (not shown) proved to be impractical because of the poor conversion efficiency (<10%) of the nucleophilic acylation process. Overall, these results confirmed the lower efficacy of aromatic aldehydes in the disclosed dearomatization method.

Table 4. Dearomatization of pyridinium salt 2a with *p*-chlorobenzaldehyde 6[a]

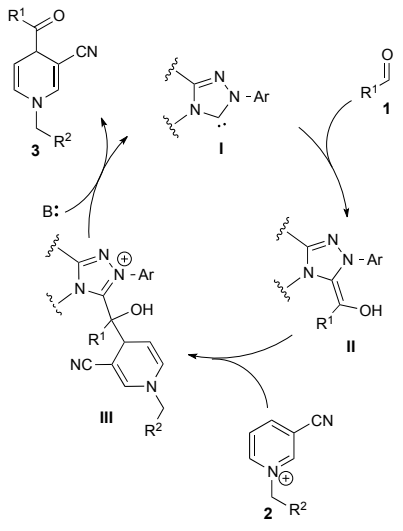


Entry	NHC·HX	Yield [%][b]	**7a** : **8a**[c]	ee [%][d]
1	**C1**	87	95 : 5	46
2	**C2**	88	95 : 5	50
3	**C3**	-	-	n.d.
4	**C4**	-	-	n.d.
5	**C5**	-	-	n.d.
6	**C6**	88	94 : 6	29

[a]Reactions conducted with 0.20 mmol of **2a**, 1.5 equiv. of **6** in anhydrous Toluene (1 mL). [b]Combined yield of **7a** and **8a**. [d]Determined by ^{1}H NMR of the unpurified reaction mixture. [c]Determined by chiral HPLC.

All the attempts to obtain good enantiopure crystals of the prepared DHPs **3** were not successful. For this reason, the absolute configuration was determined by a combination of conformational analysis and theoretical simulations of chiro-optical spectra. Accordingly, the (4*R*) stereochemistry of two representative compounds (**3ba** and **3af**) was determined by means of Time-Dependent Density Functional Theory (TD-DFT) simulation of the corresponding Electronic Circular Dichroism (ECD) spectra as duly detailed in the Supporting Information.[13]

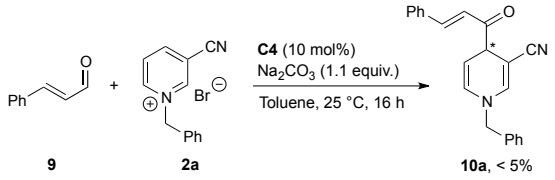
A proposed mechanism for the disclosed dearomatization process is shown in Scheme 3. The NHC **I** generated by deprotonation of triazolium salt **C4** reacts with the aldehyde **1** to give the corresponding Breslow intermediate **II**, which then intercepts the pyridinium salt **2** to afford the adduct **III**. Deprotonation by the base then leads to the product **3** and catalyst turnover.



Scheme 3. Postulated Mechanism

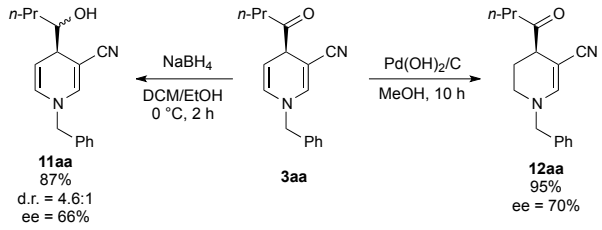
The consumptive off-cycle addition of pyridinium **2** to carbene **I** reported by the Rovis group in the NHC-catalyzed dearomatization of pyridiniums with enals could be reasonably excluded in our dearomatization process because the presence of acetic acid, which was used in the Rovis study as a necessary additive to regenerate the carbene catalyst, left unchanged the reaction outcome of the model **1a**/**2a** coupling in terms of both conversion efficiency and stereoselectivity. This result can be explained by the higher affinity of carbene **I** for aliphatic aldehydes **1** compared to α,β-unsaturated counterparts.

Since the conditions reported by the Rovis group for the a^3-d^3 umpolung of enals are quite different from those disclosed in this work, the possible formation of a chiral enol intermediate of type **II** (a^1-d^1 umpolung) from representative cinnamaldehyde **9** was tested in the dearomatization of **2a** leading to the DHP **10a** (Scheme 4). This control experiment showed no conversion of **2a** and, consequently, no reactivity of cinnamaldehyde via both homoenolate and enolate chemistry under our optimized conditions.



Scheme 4. Dearomatization of pyridinium salt 2a with cinnamaldehyde 9

The C4-acylated 1,4-DHPs **3** display a carbonyl functionality, two enamine-type double bonds, and a cyanide group amenable to further synthetic elaborations for increasing the molecular diversity of the DHP scaffold. As selected modifications, Scheme 5 reports on the chemoselective reductions of **3aa** leading to the 1,4-DHP **11aa** ($NaBH_4$) and tetrahydropyridine **12aa** (H_2, $Pd(OH)_2$).[14]



Scheme 5 Derivatization of 1,4-DHP 3aa

In conclusion, we have described an organocatalyzed nucleophilic acylation reaction for the dearomatization of activated N-alkylpyridinium salts with simple aliphatic aldehydes under chiral NHC catalysis. The process displays complete C4 regioselectivity and good levels of enantioselectivity allowing the straightforward synthesis of a small collection of hitherto unreported C4-acylated 1,4-DHPs with (4*R*) absolute configuration as established by CD analysis.

Experimental Section

General Experimental Methods. ^{1}H, ^{19}F and ^{13}C-NMR spectra were recorded on 300 and 400 MHz spectrometers in $CDCl_3$ and acetone-d_6 at room temperature. ^{13}C NMR spectra were acquired with ^{1}H broad-band decoupled mode and chemical shifts (δ) are reported in ppm relative to residual solvents signals. Reactions were monitored by TLC on Silica gel 60 F_{254} with detection by charring with Phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230-400 mesh). IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 500. High-resolution mass spectra (HRMS) were recorded in positive ion mode by Agilent 6520 HPLC-Chip Q/TF-MS nanospray using a time-of-flight, a quadrupole or a hexapole unit to produce spectra. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}. The enantiomeric ratios were determined by chiral stationary phase HPLC (Phenomenex Lux Amylose 2 250 × 4.6 mm, particle size: 5μm), using an UV detector operating at 254 nm. All commercially available reagents were used as received without further purification, unless otherwise stated. Solvents were distilled from appropriate drying agents. Liquid aldehydes **1a-h** and bases (DBU, TEA, DIPEA) were freshly distilled before their utilization. Inorganic bases were dried (100-120 °C, 5 mmHg, 6 hours) and stored in a chamber with phosphorus pentoxide (P_2O_5). Pyridinium salts **2a-f** were synthesized as reported in literature from 3-cyanopyridines and the respective benzyl and alkyl bromides.[15] Catalysts **C1** and **C3** were purchased from Sigma Aldrich and used as received. Catalysts **C2** and **C6** were prepared following a modified literature procedure.[16,17] Catalysts **C4**[17a,b] and **C5**[17c,d] are known compounds and were prepared as described.[17]

*(5aS,10bR)-9-Bromo-2-(perfluorophenyl)-5a,10b-dihydro-4H,6H-indeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate (**C2**).* To a flame-dried round-bottomed flask with (4a*R*,9a*S*)-6-bromo-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2H)-one (1.00 g, 3.7 mmol, 1.0 equiv.) in dichloromethane (25 mL), trimethyloxonium tetrafluoroborate (0.55 g, 3.7 mmol, 1.0 equiv.) was added in one portion. The suspension was stirred until a homogeneous was achieved (5-6 hours), then (perfluorophenyl)hydrazine (0.73 g, 3.7 mmol, 1.0 equiv.) was added and the reaction was allowed to stir an additional 16 h at which point the reaction was concentrated. After installing a reflux

condenser, triethyl orthoformate (2.00 mL, 18.5 mmol, 5.0 equiv.) and chlorobenzene (25 mL) were added and the mixture was heated to reflux in an oil bath for 48 h. The solution was concentrated, triturated with DCM/Et_2O for 4 h, and filtrated to afford the desired triazolium salt **C2** (1.00 g, 49%) as a tan solid. $[\alpha]_D$ = -44.4 (*c* 1.0, acetone); m.p. (°C): 191-193; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.27 (s, br, 1H), 7.76 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 6.40 (d, J = 4.1 Hz, 1H), 5.44 (d, J = 16.5 Hz, 1H), 5.28 (d, J = 16.5 Hz, 1H), 5.22 – 5.18 (m, 1H), 3.52 (dd, J = 17.3, 4.1 Hz, 1H), 3.27 (d, J = 17.3 Hz, 1H). ^{13}C{1H} NMR (101 MHz, acetone-d_6) δ 151.6, 146.3, 140.4, 139.6, 137.7, 132.6, 129.4, 127.7, 127.5, 120.1, 77.5, 62.2, 60.1, 36.7. ^{19}F NMR (376 MHz, acetone-d_6) δ -146.42 – -146.88 (m, 2F), -149.58 (tt, J = 18.0, 2.5 Hz, 1F), -151.94 (s, 4F), -161.63 (ddd, J = 20.9, 18.0, 2.5 Hz, 2F). FT-IR (neat, cm^{-1}): ν_{max} 3126, 1664, 1595, 1518, 1479, 1326, 1241. HRMS (ESI) *m/z*: $[M - BF_4]^+$ Calcd for $C_{18}H_{10}BrF_5N_3O$ 457.9922; Found 457.9939.

*(5aS,10bR)-2-(2,6-Dichlorophenyl)-4,5a,6,10b-tetrahydroindeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-2-ium tetrafluoroborate (**C4**).* $[\alpha]_D$ = -68.4 (*c* 1.0, acetone); m.p. (°C): 197-201; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.20 (s, br, 1H), 7.94 – 7.88 (m, 3H), 7.67 (d, J = 7.6 Hz, 1H), 7.53 – 7.37 (m, 3H), 6.41 (d, J = 4.1 Hz, 1H), 5.41 (d, J = 16.3 Hz, 1H), 5.30 (d, J = 16.3 Hz, 1H), 5.26 – 5.24 (m, 1H), 3.58 (dd, J = 17.2, 4.9 Hz, 1H), 3.30 (d, J = 17.2 Hz, 1H). ^{13}C{1H} NMR (101 MHz, acetone-d_6) δ 152.4, 146.6, 141.9, 136.7, 135.6, 134.1, 131.2, 130.7, 130.6, 128.4, 126.7, 124.6, 78.4, 63.6, 61.0, 38.2. ^{19}F NMR (376 MHz, acetone-d_6) δ -151.5 (s, 4F). FT-IR (neat, cm^{-1}): ν_{max} 3127, 3090, 1595, 1571, 1431, 1352, 1230. HRMS (ESI) *m/z*: $[M - BF_4]^+$ Calcd for $C_{18}H_{14}Cl_2N_3O$ 358.0508; Found 358.0527.

*(S)-5-(((tert-Butyldimethylsilyl)oxy)diphenylmethyl)-2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**C5**).* $[\alpha]_D$ = -93.5 (*c* 0.40, acetone); m.p. (°C): 214-216; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.00 (s, br, 1H), 7.66 – 7.58 (m, 2H), 7.52 – 7.45 (m, 6H), 7.39 – 7.34 (m, 2H), 6.38 (d, J = 9.0, 2.5 Hz, 1H), 3.45 – 3.30 (m, 1H), 3.13 – 3.04 (m, 1H), 2.01 – 1.87 (m, 1H), 0.96 (s, 9H), -0.22 (s, 3H), -0.29 (s, 3H). ^{13}C{1H} NMR (101 MHz, acetone-d_6) δ 165.0, 143.7, 139.9, 129.5, 129.1, 129.0, 128.6, 128.5, 82.5, 67.6, 25.6, 20.7, 18.5, -4.0. ^{19}F NMR (376 MHz, acetone-d_6) δ -146.68 – -146.73 (m, 2F), -149.33 (m, 1F), -151.97 (s, 4F), -161.90 (m, 2F). FT-IR (neat, cm^{-1}): ν_{max} 2950, 2936, 1538, 1520, 1100. HRMS (ESI) *m/z*: $[M - BF_4]^+$ Calcd for $C_{30}H_{31}F_5N_3OSi$ 572.2151; Found 572.2127.

*(S)-5-benzhydryl-2-(perfluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**C6**).* To a flame-dried round-bottomed flask with the (*S*)-5-benzhydrylpyrrolidin-

2-one (0.5 g, 2.00 mmol, 1 equiv.) in dichloromethane (20 mL), trimethyloxonium tetrafluoroborate (0.33 g, 2.20 mmol, 1.1 equiv.) was added and the reaction mixture was stirred overnight at room temperature. Then, (perfluorophenyl)hydrazine (0.44 g, 2.20 mmol, 1.1 equiv.) was added to the mixture, which was stirred overnight and then concentrated. After installing a reflux condenser, triethyl orthoformate (1.1 mL, 10 mmol, 5.0 equiv.) and acetonitrile (15 mL) were added and the reaction mixture was heated at reflux and stirred at this temperature overnight. The solvent was removed in vacuo and the product was precipitated from EtOAc/hexane to give **C6** (0.63 g, 57%) as an off-white powder. $[\alpha]_D$ = +52.1 (*c* 1.1, acetone); m.p. (°C): 232-234; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.01 (s, br, 1H), 7.69 – 7.53 (m, 4H), 7.47 – 7.37 (m, 4H), 7.36 – 7.24 (m, 2H), 6.18 (ddd, J = 11.1, 7.8, 5.4 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 3.59 – 3.33 (m, 2H), 3.23 – 3.02 (m, 1H), 2.83 – 2.66 (m, 1H). ^{13}C{1H} NMR (101 MHz, acetone-d_6) δ 164.6, 142.4, 140.2, 139.9, 129.6, 129.1, 128.2 (2C), 128.1, 127.6, 65.2, 54.8, 32.7, 21.3. ^{19}F NMR (376 MHz, acetone-d_6) δ -146.69 – -147.21 (m, 2F), -149.93 (tt, J = 15.0, 3.0 Hz, 1F), -151.93 (s, 4F), -161.87 – -162.42 (m, 2F). FT-IR (neat, cm^{-1}): ν_{max} 3126, 1598, 1526, 1509, 1456, 1365, 1286, 1175, 999. HRMS (ESI) *m/z*: $[M - BF_4]^+$ Calcd for $C_{24}H_{17}F_5N_3$ 442.1337; Found: 442.1363.

General procedure for the dearomatization of pyridinium salts 2 with aldehydes 1. *Procedure A (Asymmetric).* To a stirred suspension of pyridinium salt **2** (0.40 mmol, 1 equiv.) and pre-catalyst **C4** (0.04 mmol, 0.1 equiv.) in anhydrous Toluene (2 mL), freshly distilled aldehyde **1** (0.60 mmol, 1.5 equiv.) was added under Argon followed by addition of anhydrous sodium carbonate (0.44 mmol, 1.1 equiv.) under an argon environment. The resulting suspension was vigorously stirred at room temperature for 16 hours, then diluted with CH_2Cl_2 (2 mL), and filtered through a short pad of silica gel. The resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture) to afford the DHP **3**.

Procedure B (Racemic). To a stirred suspension of pyridinium salt **2** (0.40 mmol, 1 equiv.) and commercially available (Sigma-Aldrich) 6,7-dihydro-2-pentafluorophenyl-5*H*-pyrrolo[2,1-*c*]-1,2,4-triazolium tetrafluoroborate pre-catalyst (0.04 mmol, 0.1 equiv.) in anhydrous Toluene (2 mL), freshly distilled aldehyde **1** (0.60 mmol, 1.5 equiv.) was added under Argon followed by addition of anhydrous sodium carbonate (0.44 mmol, 1.1 equiv.) under an argon environment. The resulting suspension was vigorously stirred at room temperature for 16 hours, then diluted with CH_2Cl_2 (2 mL), and filtered through a short pad of silica gel. The resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture) to afford the racemic DHP **3** with comparable yield to that of the enantiopure counterpart.

*(R)-1-Benzyl-4-butyryl-1,4-dihydropyridine-3-carbonitrile (**3aa**)*. Following the general procedure A **3aa** (85 mg, 80%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 19.5, t_{min} = 26.2, e.r. 85:15; $[\alpha]_D$ = -23.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 3H), 7.23 – 7.12 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.1 Hz, 1H), 4.77 (dd, J = 8.1, 4.8 Hz, 1H), 4.36 (s, 2H), 3.96 (d, J = 4.8 Hz 1H), 2.57 (t, J = 8.0, 2H), 1.63 (tq, J = 8.0, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (76 MHz, $CDCl_3$) δ 207.6, 143.6, 136.0, 129.7, 129.4, 128.6, 127.4, 120.7, 101.2, 78.5, 57.9, 47.3, 41.5, 17.1, 14.0. FT-IR (neat, cm^{-1}): ν_{max} 2928, 2857, 2196, 1708, 1662, 1585, 1459, 1399, 1371, 1184. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{18}N_2NaO$ 289.1317; Found: 289.1325.

*(R)-1-Benzyl-4-propionyl-1,4-dihydropyridine-3-carbonitrile (**3ba**)*. Following the general procedure A **3ba** (75 mg, 74%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 7.4 min, t_{min} = 8.4 min, e.r. 80:20; $[\alpha]_D$ = -20.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 3H), 7.22 – 7.13 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.78 (dd, J = 8.0, 4.8 Hz, 1H), 4.35 (s, 2H), 3.97 (d, J = 4.8 Hz, 1H), 2.61 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 208.1, 143.4, 135.7, 129.4, 129.1, 128.4, 127.2, 120.5, 101.0, 78.2, 57.6, 46.8, 32.6, 7.6. FT-IR (neat, cm^{-1}): ν_{max} 2924, 2863, 2195, 1721, 1643, 1583, 1465, 1414, 1353, 1172. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{16}N_2NaO$ 275.1160; Found 275.1147.

*(R)-1-Benzyl-4-pentanoyl-1,4-dihydropyridine-3-carbonitrile (**3ca**)*. Following the general procedure A **3ca** (91 mg, 81%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7.5:2.5); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 16.6 min, t_{min} = 18.3 min, e.r. 87:13; $[\alpha]_D$ = -18.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 3H), 7.22 – 7.15 (m, 2H), 6.78 (s, 1H), 5.98 (d, J = 8.0 Hz 1H), 4.78 (dd, J = 8.0, 4.8 Hz, 1H), 4.36 (s, 2H), 3.97 (d, J = 4.8 Hz, 1H), 2.58 (t, J = 7.0 Hz, 2H), 1.64 – 1.55 (m, 2H), 1.42 – 1.23 (m, 2H), 0.90 (t, J = 7.2, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 207.6, 143.5, 135.8, 129.5, 129.2, 128.4, 127.2, 120.5, 101.0, 78.3, 57.7, 47.2, 39.2, 25.6, 22.4, 14.0. FT-IR (neat, cm^{-1}): ν_{max} 2922, 2857, 2196, 1718, 1646, 1590, 1461, 1401, 1362, 1196. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{20}N_2NaO$ 303.1473; Found 303.1481.

*(R)-1-Benzyl-4-hexanoyl-1,4-dihydropyridine-3-carbonitrile (**3da**)*. Following the general procedure A **3da** (79 mg, 67%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2); HPLC (Phenomenex Lux Amylose 2) *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 16.2 min, t_{min} = 19.4 min, e.r. 86:14; $[\alpha]_D$= -21.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 3H), 7.22 – 7.13 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.77 (dd, J = 8.0, 4.8 Hz, 1H), 4.36 (s, 2H), 3.96 (d, J = 4.8 Hz, 1H), 2.57 (t, J = 7.8, 2H), 1.65 – 1.54 (m, 2H), 1.37 - 1.22 (m, 4H), 0.88 (t, J = 7.4, 3H); $^{13}C\{1H\}$ NMR (76 MHz, $CDCl_3$) δ 207.7, 143.6, 136.0, 129.6, 129.3, 128.6, 127.4, 120.7, 101.2, 78.5, 57.9, 47.3, 39.6 31.6, 23.4, 22.7, 14.2. FT-IR (neat, cm^{-1}): ν_{max} 2929, 2859, 2196, 1710, 1651, 1590, 1455, 1411, 1360, 1180. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{22}N_2NaO$ 317.1630; Found 317.1615.

*(R)-1-Benzyl-4-(3-phenylpropanoyl)-1,4-dihydropyridine-3-carbonitrile (**3ea**)*. Following the general procedure A **3ea** (100 mg, 76%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7.5:2.5); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 28.5 min, t_{min} = 34.5 min, e.r. 89:11; $[\alpha]_D$ = -21.3 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 7.22 – 7.12 (m, 5H), 6.76 (s, 1H), 5.91 (d, J = 8.0 Hz, 1H), 4.71 (dd, J = 8.0, 4.8 Hz, 1H), 4.34 (s, 2H), 3.95 (d, J = 4.8 Hz, 1H), 2.92 (s, 4H); $^{13}C\{1H\}$ NMR (76 MHz, $CDCl_3$) δ 206.3, 143.5, 140.9, 135.7, 129.6, 129.1, 128.5, 128.4, 128.4, 128.4, 127.1, 126.1, 100.6, 78.1, 57.7, 47.3, 41.1, 29.6. FT-IR (neat, cm^{-1}): ν_{max} 2962, 2934, 2197, 1717, 1674, 1455, 1261. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{20}N_2NaO$ 351.1473; Found 351.1480.

*(R)-1-Benzyl-4-(3-methylbutanoyl)-1,4-dihydropyridine-3-carbonitrile (**3fa**)* Following the general procedure A **3fa** (41 mg, 37%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 14.8 min, t_{min} = 18.8 min, e.r. 87:13; $[\alpha]_D$ = -34.7 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 3H), 7.22 – 7.14 (m, 2H), 6.77 (s, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.75 (dd, J = 8.0, 4.8 Hz, 1H), 4.36 (s, 2H), 3.94 (d, J = 4.8 Hz, 1H), 2.45 (d, J = 6.8 Hz, 2H), 2.26 – 2.10 (m, 1H), 0.92 (d, J = 6.5 Hz, 6H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 206.8, 143.4, 135.8, 129.5, 129.1, 128.4, 127.1, 120.4, 100.7, 78.2, 57.6, 48.3, 47.4, 24.2, 22.6, 22.6. FT-IR (neat, cm^{-1}): ν_{max} 2959, 2871, 2196, 1710, 1673, 1590, 1465, 1408, 1363, 1179. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{20}N_2NaO$ 303.1473; Found 303.1487.

*(R)-1-Benzyl-4-(cyclopropanecarbonyl)-1,4-dihydropyridine-3-carbonitrile (**3ha**)*. Following the general procedure A **3ha** (50 mg, 47%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 21.6 min, t_{min} = 33.5 min, e.r. 76:24; $[\alpha]_D$ = -18.7 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 3H), 7.23 – 7.12 (m, 2H), 6.77 (s, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.86 (dd, J = 8.0, 4.6 Hz, 1H), 4.36 (s, 2H), 4.17 (d, J = 4.6 Hz, 1H), 2.14 (tt, J = 7.0, 6.5 Hz, 1H), 1.14 – 1.05 (m, 2H), 1.02 – 0.92 (m, 2H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.1, 143.4, 135.8, 129.4, 129.1, 128.3, 127.1, 120.5, 100.9, 78.3, 57.6, 47.6, 29.7, 18.1, 12.1, 11.8. FT-IR (neat,

cm^{-1}): ν_{max} 2923, 2854, 2197, 1715, 1674, 1591, 1412, 1387. HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{17}H_{16}N_2NaO$ 287.1160; Found 287.11579.

*(R)-4-Butyryl-1-(4-isopropylbenzyl)-1,4-dihydropyridine-3-carbonitrile (**3ab**)*. Following the general procedure A **3ab** (46 mg, 37%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 13.3 min, t_{min} = 15. 5min, e.r. 84:16; $[\alpha]_D$ = -13.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.23 (d, J = 6.5 Hz, 2H), 7.10 (d, J = 6.5 Hz, 2H), 6.76 (s, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.76 (dd, J = 8.0, 4.8 Hz, 1H), 4.32 (s, 2H), 3.96 (d, J = 4.8 Hz, 1H), 2.97 – 2.84 (m, 1H), 2.56 (d, J = 7.4 Hz, 2H), 1.70 – 1.61 (m, 2H), 1.24 (d, J = 4.6 Hz, 6H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 207.4, 149.1, 143.4, 133.0, 129.5, 127.2, 127.1, 120.5, 100.7, 78.0, 57.4, 47.1, 41.2, 33.8, 23.9, 16.9, 13.7. FT-IR (neat, cm^{-1}): ν_{max} 2961, 2873, 2196, 1712, 1672, 1589, 1409, 1179, 1120. HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{20}H_{24}N_2NaO$ 331.1786; Found 331.1811.

*(R)-1-(4-(tert-Butyl)benzyl)-4-butyryl-1,4-dihydropyridine-3-carbonitrile (**3ac**)*. Following the general procedure A **3ac** (103 mg, 80%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 6.3 min, t_{min} = 6.9 min, e.r. 86:14; $[\alpha]_D$ = -20.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.39 (d, J = 6.5 Hz, 2H), 7.11 (d, J = 6.5 Hz, 2H), 6.76 (s, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.76 (dd, J = 8.0, 4.8 Hz, 1H), 4.32 (s, 2H), 3.96 (d, J = 4.8 Hz, 1H), 2.55 (d, J = 7.5 Hz, 2H), 1.64 (tq, J = 7.5, 7.4 Hz, 2H), 1.31 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) *δ* 207.4, 151.5, 143.4, 132.7, 129.6, 126.9, 126.0, 126.0, 120.6, 100.8, 78.0, 57.3, 47.1, 41.3, 34.6, 31.3, 31.3, 16.9, 13.7, 13.6. FT-IR (neat, cm^{-1}): ν_{max} 2964, 2870, 2196, 1719, 1674, 1592, 1415, 1180, 1115. HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{21}H_{26}N_2NaO$ 345.1943; Found 345.1961.

*(R)-4-Butyryl-1-(3,5-di-tert-butylbenzyl)-1,4-dihydropyridine-3-carbonitrile (**3ad**)*. Following the general procedure A **3ad** (82 mg, 53%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8.5:1.5); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 6.3 min, t_{min} = 6.8 min, e.r. 84:16; $[\alpha]_D$ = -39.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.38 (s, 1H), 6.98 (s, 2H), 6.78 (s , 1H), 6.00 (d, J = 8.0 Hz, 1H), 4.78 (dd, J = 8.0, 4.8 Hz, 1H), 4.35 (s, 2H), 3.97 (d, J = 4.8 Hz, 1H), 2.58 (t, J = 7.2 Hz, 2H), 1.62 (qt, J = 7.4, 7.2 Hz, 2H), 1.31 (s, 18H), 0.92 (t, J = 7.4 Hz, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) *δ* 207.3, 151.8, 143.6, 134.9, 129.6, 122.3, 121.1, 120.6, 100.7, 77.9, 58.2, 47.2, 41.1, 34.9, 31.4, 16.9, 13.7. FT-IR (neat, cm^{-1}): ν_{max} 2959, 2873, 2191, 1731, 1664, 1591, 1406, 1182, 1131. HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{34}N_2NaO$ 401.2569; Found: 401.2553.

*(R)-4-Butyryl-1-(4-fluorobenzyl)-1,4-dihydropyridine-3-carbonitrile (**3ae**).* Following the general procedure A **3ae** (92 mg, 81%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7:3); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 18.5 min, t_{min} = 20.9 min, e.r. 82:18; $[\alpha]_D$ = -19.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.13 – 7.00 (m, 2H), 6.77 (s, 1H), 5.93 (d, J = 8.0 Hz, 1H), 4.79 (dd, J = 8.0, 4.8 Hz, 1H), 4.34 (s, 2H), 3.97 (d, J = 4.8 Hz, 1H), 2.56 (d, J = 7.2 Hz, 2H), 1.66 (qt, J = 7.4, 7.2 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 207.3, 163.9, 161.4, 143.3, 131.6, 129.3, 129.0, 120.4, 116.3, 116.1, 101.1, 78.5, 57.0, 47.1, 41.4, 17.0, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.37 - -113.44 (m, 1F). FT-IR (neat, cm^{-1}): ν_{max} 2965, 2934, 2197, 1670, 1650, 1604, 1509, 1223, 1159. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{17}FN_2NaO$ 307.1223; Found: 307.1235.

*(R)-1-(4-isoPropylbenzyl)-4-(3-phenylpropanoyl)-1,4-dihydropyridine-3-carbonitrile (**3eb**).* Following the general procedure A **3eb** (89 mg, 60%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 7.5:2.5); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 20.5 min, t_{min} = 26.3 min, e.r. 86:14; $[\alpha]_D$ = -33.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.16 (m, 5H), 7.13 – 7.01 (m, 4H), 6.74 (s, 1H), 5.91 (d, J = 8.0 Hz, 1H), 4.70 (dd, J = 8.0, 4.8 Hz, 1H), 4.30 (s, 2H), 3.95 (d, J = 4.8 Hz, 1H), 2.87 – 2.75 (m, 5H), 1.24 (d, J = 5.0, 6H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 206.4, 149.2, 143.5, 132.9, 129.7, 128.5, 128.5, 128.4, 127.2, 127.2, 126.1, 120.5, 100.5, 77.2, 57.5, 47.4, 41.1, 33.8, 29.6, 23.9. FT-IR (neat, cm^{-1}): ν_{max} 2959, 2926, 2196, 1716, 1672, 1589, 1409, 1179, 1120. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{26}N_2NaO$ 393.1943; Found 393.1958.

*(R)-1-(4-(tert-Butyl)benzyl)-4-(3-methylbutanoyl)-1,4-dihydropyridine-3-carbonitrile (**3fc**).* Following the general procedure A **3fc** (60 mg, 45%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 9.4 min, t_{min} = 12.8 min, e.r. 88:12; $[\alpha]_D$ = -27.9 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.16 – 7.07 (m, 2H), 6.76 (s, 1H), 5.96 (d, J = 8.0 Hz, 1H), 4.75 (dd, J = 8.0, 4.8 Hz, 1H), 4.32 (s, 2H), 3.94 (d, J = 4.8 Hz, 1H), 2.46 (d, J = 6.8 Hz, 2H), 2.13 – 2.21 (m, 1H), 1.31 (s, 9H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 206.9, 151.4, 143.4, 132.7, 129.6, 126.9, 126.0, 120.5, 100.6, 77.3, 57.4, 48.3 47.5, 34.6, 31.3, 24.2, 22.6. FT-IR (neat, cm^{-1}): ν_{max} 2959, 2871, 2197, 1711, 1672, 1589, 1408, 1362, 1179, 1117. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{28}N_2NaO$ 359.2099; Found 359.2107.

*(R)-1-Butyl-4-butyryl-1,4-dihydropyridine-3-carbonitrile (**3af**).* Following the general procedure A **3af** (33 mg, 36%) was obtained as a yellow oil after column chromatography on silica gel (cyclohexane/EtOAc = 8:2); HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0

mL/min, λ = 254 nm, t_{maj} = 12.3 min, t_{min} = 13.6 min, e.r. 87:13; $[\alpha]_D$ = -19.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (s, 1H), 5.90 (d, J = 7.9 Hz, 1H), 4.73 (dd, J = 8.0, 4.8 Hz, 1H), 3.94 (d, J = 4.8 Hz, 1H), 3.16 (t, J = 7.1 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.69 – 1.48 (m, 4H), 1.38 – 1.25 (m, 2H), 0.98 – 0.88 (m, 6H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 207.6, 1433, 129.2, 120.8, 100.5, 77.3, 54.2, 47.0, 41.2, 31.9, 29.7, 19.4, 16.9, 13.7, 13.6. FT-IR (neat, cm^{-1}): ν_{max} 2961, 2929, 2194, 1712, 1676, 1588, 1415, 1217, 1137. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{20}N_2NaO$ 255.1473; Found: 255.1454.

*(R)-1-Benzyl-4-(4-chlorobenzoyl)-1,4-dihydropyridine-3-carbonitrile (**7a**).* To a stirred suspension of pyridinium salt **2a** (0.20 mmol, 1 equiv.) and pre-catalyst **C1-C6** (0.02 mmol, 0.1 equiv.) in anhydrous Toluene (1 mL), *p*-chlorobenzaldehyde **6** (42 mg, 0.30 mmol, 1.5 equiv.) was added under Argon followed by addition of anhydrous sodium carbonate (23 mg, 0.22 mmol, 1.1 equiv.) under an argon environment. The resulting suspension was vigorously stirred at room temperature for 16 hours, then diluted with CH_2Cl_2 (2 mL), and filtered through a short pad of silica gel. The resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc = 8:2) to afford the 1,4-DHP **7a** contaminated by the 1,2-DHP **8a** (see Table 4 for yields and ratios). For **7a** of entry 2: HPLC (Phenomenex Lux Cellulose 4): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 20.5 min, t_{min} = 30.6 min, e.r. 75:25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.48 – 7.44 (m, 2H), 7.41 – 7.33 (m, 3H), 7.22 – 7.19 (m, 2H), 6.88 (s, 1H), 5.96 (d, J = 8.0 Hz, 1H), 4.91 (d, J = 4.6 Hz, 1H), 4.74 (dd, J = 8.0, 4.6 Hz, 1H), 4.39 (s, 2H); ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 194.6, 143.8, 140.4, 135.9, 133.3, 130.6, 130.0, 129.4, 129.4, 128.6, 127.4, 120.5, 100.4, 78.2, 57.9, 42.9. FT-IR (neat, cm^{-1}): ν_{max} 2925, 2854, 2229, 1670, 1587,1264, 1091. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{15}ClN_2NaO$ 357.0771; Found: 357.0793; **8a** ^{1}H NMR (300 MHz, $CDCl_3$; selected data) δ 7.83 – 7.80 (m, 2H), 5.87 (d, J = 8.0 Hz, 1H).

*(R)-1-Benzyl-4-(1-hydroxybutyl)-1,4-dihydropyridine-3-carbonitrile (**11aa**).* To a cooled (0 °C), stirred solution of DHP **3aa** (53 mg, 0.20 mmol, 1 equiv.) in DCM/EtOH 3:1 (2 mL), $NaBH_4$ (9 mg, 0.24 mmol, 1.2 equiv.) was added in one portion. The resulting mixture was vigorously stirred at 0 °C for 2h, then a saturated NH_4Cl solution was added drop by drop until the release of gas stopped. After this point, the solution was extracted with DCM (3 × 5 mL). The combined organic phases were collected, dried (anhydrous Na_2SO_4), and purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture 7.5:2.5) to afford **11aa** (45 mg, 87%, d.r. 82:18) as a yellow oil; HPLC for the major diastereoisomer (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 12.17 min, t_{min} = 13.06 min, e.r. 83:17); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.15

(m, 5H), 6.80 – 6.71 (m, 1H), 6.02 – 5.92 (m, 1H), 4.73 (dd, J = 8.1, 4.4 Hz, 0.15H_{min}) 4.65 (dd, J = 8.1, 4.4 Hz, 0.85H_{maj}), 4.32 (s, 2H), 3.62 – 3.53 (m, 0.85H_{maj}), 3.52 – 3.49 (m, 0.15H_{min}), 3.33 – 3.30 (m, 0.15H_{min}) 3.29 – 3.23 (m, 0.85H_{maj}), 1.59 – 1.29 (m, 4H), 0.99 – 0.90 (m, 3H); $^{13}C\{1H\}$ NMR (101 MHz, CDCl3) δ 144.3, 144.1, 136.1, 130.6, 129.6, 129.0, 128.2, 127.1, 121.0, 103.0, 100.8, 80.5, 76.8, 75.5, 74.0, 57.5, 39.9, 34.8, 34.6, 20.4, 19.3, 14.1. FT-IR (neat, cm^{-1}): ν_{max} 3461, 2961, 2958, 2930, 2871, 2191, 1673, 1591, 1455, 1414, 1181. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO$ 291.1473; Found: 291.1459.

*(R)-1-Benzyl-4-butyryl-1,4,5,6-tetrahydropyridine-3-carbonitrile (**12aa**)*. A vigorously stirred mixture of DHP **3aa** (53 mg, 0.20 mmol, 1 equiv.), $Pd(OH)_2/C$ (20 % w/w, 20 mg), and MeOH (3 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The mixture was vigorously stirred at room temperature for 10 h, then filtered on Celite, and concentrated; the resulting residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc mixture 8:2) to afford **12aa** (50 mg, 95%) as a yellow oil; HPLC (Phenomenex Lux Amylose 2): *n*-hexane/*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_{maj} = 15.5 min, t_{min} = 17.3 min, e.r. 85:15); $[\alpha]_D$ = - 39.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 2H), 7.20 – 7.12 (m, 2H), 7.03 (s, 1H), 4.28 (s, 2H), 3.24 – 3.18 (m, 1H), 3.13 (dd, J = 12.2, 3.8 Hz, 1H), 3.06 – 2.95 (m, 1H), 2.78 – 2.51 (m, 2H), 2.16 (ddt, J = 13.4, 3.8, 2.8 Hz, 1H), 1.71 – 1.50 (m, 3H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 209.9, 148.0, 135.7, 129.0, 128.2, 127.4, 123.2, 69.7, 59.7, 43.7, 43.3, 42.5, 21.6, 17.1, 13.7. FT-IR (neat, cm^{-1}): ν_{max} 2961, 2874, 2182, 1709, 1617, 1423, 1360, 1124. HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2NaO$ 291.1473; Found: 291.1487.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
compound characterization data, TD-DFT simulations of ECD spectra (PDF)

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