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Organocatalytic Asymmetric Domino Aza-Michael−Mannich Reaction: Synthesis of Tetrahydroimidazopyrimidine Derivatives

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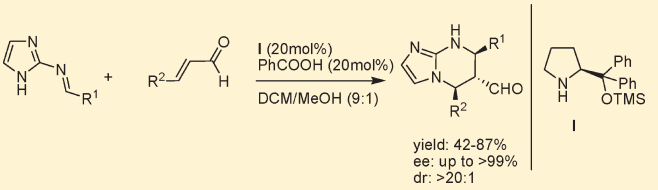
Supporting Information

ABSTRACT: Highly substituted tetrahydroimidazopyrimidine derivatives with three chiral centers have been synthesized for the first time using an organocatalytic asymmetric domino aza-Michael−Mannich reaction of α,β-unsaturated aldehydes and *N*-arylidene-1*H*-imidazol-2-amines. This efficient approach furnishes the products in good yields (42−87%) with excellent stereoselectivities (>20:1 dr, up to >99% ee).

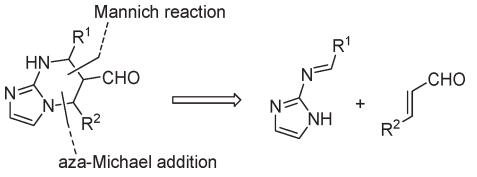


The tetrahydroimidazopyrimidine ring system is found in many naturally occurring products that have attracted attention due to the broad scope of their biological activities.[1,2] Different classes of tetrahydroimidazopyrimidine compounds have shown antidepressant[2a,b] and antihypertonia[2c] activities that have been put to pharmaceutical uses. However, syntheses of tetrahydroimidazopyrimidine derivatives are not very well documented in the literature.[2b,3] The traditional methods for their synthesis often require many synthetic manipulations and purifications, which result in low overall yields. Thus the development of novel, concise methodologies that allow the rapid construction of these tetrahydroimidazopyrimidine skeletons, preferably in a single operation, is highly desired.

Organocatalytic domino reactions[4−6] allow the sequential formation of several new bonds and chiral centers in just one operation. They have been proven to be powerful tools for the efficient and stereoselective synthesis of complex molecules[7] that are difficult to access by traditional methods. The aza-Michael addition[8] participated domino reaction provides a simple and direct way for the synthesis of nitrogen-containing heterocycles. For example, the asymmetric syntheses of 1,2-dihydroquinolines,[9] pyrrolidines,[10] tetrahydro-1,2-oxazines,[11] and isoindolines[12] have been realized. Herein, we report the first asymmetric synthesis of enantioenriched tetrahydroimidazopyrimidine derivatives through an organocatalytic domino strategy using α,β-unsaturated aldehydes and *N*-arylidene-1*H*-imidazol-2-amines as starting materials (Scheme 1).

The reactions of 2-carbonyl-substituted indoles[13] and pyrroles[14] with enals have been realized for the syntheses of pyrrolidine-fused heterocycles. However, the asymmetric synthesis of six-membered ring-fused heterocycles, such as biologically interesting tetrahydroimidazopyrimidines, through aza-Michael reaction of nitrogen heterocycles has not been reported. We would like to focus our research on this challenging task. Unlike tetrazole, triazole, and other nitrogen heterocycles,[15] the N−H group of imidazole is not acidic enough to participate in N-alkyaltion reactions. The introduction of electron-withdrawing groups, such as carbonyl or cyano, can reduce the pK_a value of this N−H group, making it possible for N-alkylation reactions[13,14,15b] to occur. The iminic group is a weak electron-withdrawing group and enables many further transformations. We envisaged that the *N*-arylidene-1*H*-imidazol-2-amines (**1**) and the α,β-unsaturated aldehydes (**2**) might be suitable substrates for the domino aza-Michael−Mannich reaction and that they would generate the highly substituted tetrahydroimidazopyrimidine derivatives (**3**). To test our hypothesis, the readily available L-proline-derived secondary amines (**I**−**IV**), which are capable of both iminium[16] and enamine[17] catalysis, were explored as catalysts for this domino reaction.

Scheme 1. Domino Aza-Michael−Mannich Reaction of α,β-Unsaturated Aldehyde and *N*-Arylidene-1*H*-imidazol-2-amine



The reaction of *N*-benzylidene-1*H*-imidazol-2-amine (**1a**) and cinnamaldehyde (**2a**) was selected as a model reaction. We first studied catalysis of the domino reaction with diphenyl prolinol silyl ether (**I**) in dichloromethane. The reaction proceeded with high stereoselectivity (97% ee, >20:1 dr) but in low yield (30%, Table 1, entry 1). There was no significant improvement in yield when using a variety of different solvents, most

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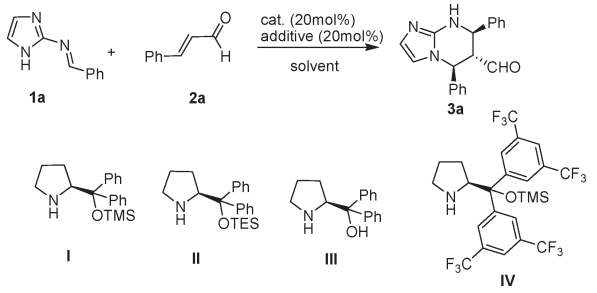
Table 1. Optimizing of the Reaction Conditions[a]



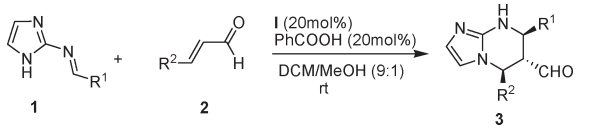
entry	catalyst	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**I**	DCM	24	30	>20:1	97
2	**I**	THF	24	30	>20:1	95
3	**I**	toluene	24	trace	ND	ND
4	**I**	ether	24	trace	ND	ND
5	**I**	$CHCl_3$	24	20	>20:1	98
6	**I**	MeOH	6	55	>20:1	96
7	**I**	DCM/MeOH (9:1)	16	73	>20:1	99
8	**I**	DCM/MeOH (1:1)	12	77	>20:1	98
9[e]	**I**	DCM/MeOH (9:1)	16	80	>20:1	>99
10[f]	**I**	DCM/MeOH (9:1)	12	73	>20:1	98
11[e]	**II**	DCM/MeOH (9:1)	24	42	>20:1	99
12[e]	**III**	DCM/MeOH (9:1)	24	NR		
13[e]	**IV**	DCM/MeOH (9:1)	24	trace	ND	ND

[a] Reactions was performed with *N*-benzylidene-1*H*-imidazol-2-amine (0.13 mmol), cinnamaldehyde (0.1 mmol), and secondary amine (0.02 mmol) in solvent (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the products. [d] Determined by HPLC analysis with the corresponding alcohol. [e] With 20% PhCOOH as additive. [f] With 20% NaOAc as additive.

likely due to the poor solubility of **1a** in these solvents. However, high stereoselectivities were retained (Table 1, entries 2−5). When methanol was used as solvent, the starting material **1a** was completely consumed in just 6 h to provide the product **3a** in 55% yield and 96% ee (Table 1, entry 6). The arylaldehyde and 2-aminoimidazole derived from the decomposition of **1a** also were detected. Those results suggested that **1a** was more active in methanol and that the use of a mixture of dichloromethane and methanol might improve the efficiency of the reaction. Experiments indicated that this was the case. After extensive screening, the best results in terms of yield (73%) and enantioselectivity (99%) were obtained using a 9:1 ratio of dichloromethane and methanol (Table 1, entry 7). The yield was improved to 80% by the addition of benzoic acid while retaining high enantioselectivity (>99% ee, Table 1, entry 9). In contrast, the addition of sodium acetate had almost no influence on the reaction (Table 1, entry 11). Other secondary amine catalysts also were examined as catalysts: the reaction proceeded in 42% yield and 99% ee when catalyst **II** (Table 1, entry 12) was used, and there were no domino reaction product detected in 24 h when catalysts **III** and **IV** were employed (Table 1, entries 13 and 14).

With the optimal reaction conditions in hand, the substrate scope of this domino aza-Michael−Mannich reaction was explored, and the results are summarized in Table 2. Various substituted aromatic enals were examined. Both electron-withdrawing and electron-donating groups on the aromatic ring were

Table 2. Substrate Scope of the Domino Aza-Michael−Mannich Reaction[a]



entry	R^1	R^2	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph (**1a**)	Ph (**2a**)	80 **3a**	>20:1	>99
2	Ph (**1a**)	3-MeC_6H_4 (**2b**)	71 **3b**	>20:1	99
3	Ph (**1a**)	3-$OMeC_6H_4$ (**2c**)	50 **3c**	>20:1	>99
4	Ph (**1a**)	3-ClC_6H_4 (**2d**)	60 **3d**	>20:1	99
5	Ph (**1a**)	3-BrC_6H_4 (**2e**)	68 **3e**	>20:1	>99
6	Ph (**1a**)	3-$NO_2C_6H_4$ (**2f**)	70 **3f**	>20:1	99
7[e]	Ph (**1a**)	4-MeC_6H_4 (**2g**)	58 **3g**	>20:1	99
8	Ph (**1a**)	4-$MeOC_6H_4$ (**2h**)	54 **3h**	>20:1	>99
9[e]	Ph (**1a**)	4-ClC_6H_4 (**2i**)	76 **3i**	>20:1	98
10[e]	Ph (**1a**)	4-BrC_6H_4 (**2j**)	72 **3j**	>20:1	98
11[e]	Ph (**1a**)	4-$NO_2C_6H_4$ (**2k**)	76 **3k**	>20:1	>99
12	Ph (**1a**)	piperonyl (**2l**)	66 **3l**	>20:1	99
13	Ph (**1a**)	2-furyl (**2m**)	49 **3m**	>20:1	99
14	Ph (**1a**)	2-thiophene (**2n**)	42 **3n**	>20:1	99
15	4-$OMeC_6H_4$ (**1b**)	4-ClC_6H_4 (**2i**)	60 **3o**	>20:1	98
16	4-$OMeC_6H_4$ (**1b**)	4-$NO_2C_6H_4$ (**2k**)	62 **3p**	>20:1	97
17[e]	4-$CF_3C_6H_4$ (**1c**)	Ph (**2a**)	85 **3q**	>20:1	99
18	4-$CF_3C_6H_4$ (**1c**)	4-ClC_6H_4 (**2i**)	87 **3r**	>20:1	99
19[e]	4-$CF_3C_6H_4$ (**1c**)	4-$NO_2C_6H_4$ (**2k**)	75 **3s**	>20:1	99

[a] Reactions was performed with *N*-arylidene-1*H*-imidazol-2-amine (0.13 mmol), α,β-unsaturated aldehyde (0.1 mmol), **I** (0.02 mmol), and PhCOOH (20 mol %) in DCM/MeOH (9:1, 0.3 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR of the products. [d] Determined by HPLC analysis with the corresponding alcohol. [e] DCM/MeOH (1:1) as solvent.

tolerated, yielding the expected products in moderate to high yields (54−80%) and excellent stereoselectivities (>97% ee, >20:1 dr, Table 2, entries 1−12). The reaction of 2-furyl and 2-thiophene enal led to the formation of **3m** and **3n** in 49 and 42% yields, respectively, both in 99% ee (Table 2, entries 13 and 14). The electronic nature of the substituent on the aromatic ring of **1** had little influence on the reaction. Extensions of this strategy to use the less reactive aliphatic enals were unsuccessful; no reaction occurred when crotonaldehyde was used.

The absolute configuration of the three new chiral centers of **3n** was assigned as 5*S*, 6*S*, and 7*R* by X-ray crystallographic analysis of **4n** (the alcohol corresponding to **3n**, Figure 1). On the basis of this observation, a plausible catalytic cycle for the reaction is proposed in Scheme 2. The reaction starts with the iminium activation of **2** by **I**, followed by aza-Michael addition of **1** to the iminium ion to give intermediate **A**. The enamine of **A** undergoes an intramolecular Mannich reaction to give **B**. The catalyst is regenerated for the next catalytic cycle through hydrolysis of **B**: **B** then hydrolyzes to give tetrahydroimidazopyrimidine **3**.

In summary, we have developed a novel organocatalytic domino aza-Michael−Mannich reaction of *N*-arylidene-1*H*-imidazol-2-amines and α,β-unsaturated aldehydes for use in the synthesis of highly substituted tetrahydroimidazopyrimidine

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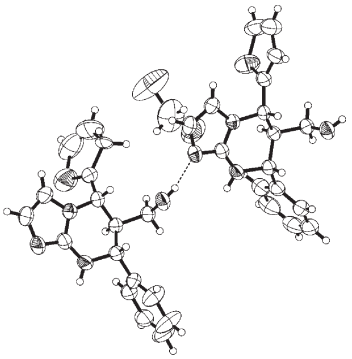
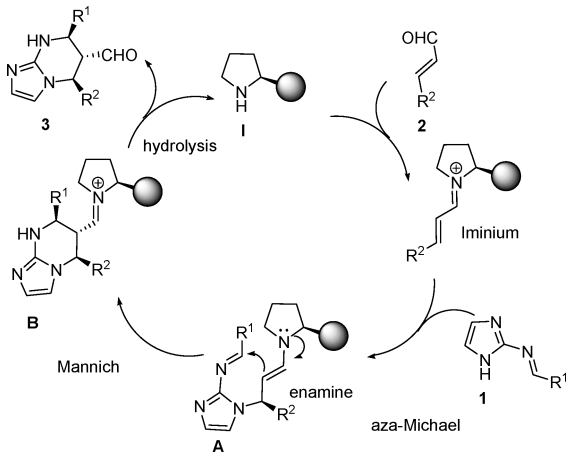


Figure 1. X-ray structure of **4n**.

Scheme 2. Proposed Catalytic Cycle of the Domino Aza-Michael−Mannich Reaction



derivatives bearing three chiral centers. The reaction is catalyzed efficiently by readily available diphenylprolinol silyl ethers with moderate to good yield (42−87%) and high stereoselectivities (>97% ee, >20:1 dr). This strategy described could be extended to the asymmetric synthesis of biologically important tetrahydropyrazolopyrimidine derivatives[18] and other tetrahydropyrimidine-fused heterocycles.

EXPERIMENTAL SECTION

General Procedure for the Preparation of 1a−1c. To a solution of benzaldehyde (1.92 mL, 18.8 mmol) in dichloromethane (15 mL) were added sequentially 2-aminoimidazole sulfate (3.7 g, 14.3 mmol), tetraisopropyl orthotitanate (6.83 mL, 23.3 mmol), and triethylamine (3.9 mL, 28.1 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was taken up in ethyl acetate and water and filtered. The filtrate was separated, and the organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was recrystallized from ethyl acetate/hexane to afford **1a**[19] in 60% yield: ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 12.23 (s, 1H), 9.15 (s, 1H), 7.95 (m, 2H), 7.58−7.50 (m, 3H), 7.15 (br s, 1H), 6.93 (br s, 1H).

***N*-(4-Methoxybenzylidene)-1*H*-imidazol-2-amine (1b).** The title compound was obtained according to general procedure described above in 50% yield: ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 12.17 (s, 1H), 9.08 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 7.0 (br s, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ 162.6, 159.2, 151.4, 130.9, 128.9, 114.9, 55.9; HR-MS (ESI) m/z 202.0979 [M + H]$^+$, calcd for $C_{11}H_{12}N_3O$, 202.0980.

***N*-(4-(Trifluoromethyl)benzylidene)-1*H*-imidazol-2-amine (1c).** The title compound was obtained according to general procedure described above in 70% yield: ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 12.49 (s, 1H), 9.24 (s, 1H), 8.14 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.19 (br s, 1H), 6.99 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, ppm) δ 157.9, 150.5, 139.7, 131.4 (q, J_{C-F} = 31.6 Hz), 129.5, 126.2, 126.1, 124.4 (q, J_{C-F} = 270.8 Hz); HR-MS (ESI) m/z 240.0743 [M + H]$^+$, calcd for $C_{11}H_9N_3F_3$, 240.0749.

General Procedure for Organocatalytic Asymmetric Aza-Michael−Mannich Reaction. To a solution of catalyst **I** (0.02 mmol), benzoic acid (0.02 mmol), and α,β-unsaturated aldehyde **2** (0.1 mmol) in 0.3 mL of DCM/MeOH (9/1) was added *N*-arylidene-1*H*-imidazol-2-amine **1** (0.13 mmol) at room temperature. After completion of the reaction as analyzed by TLC, the reaction mixture was directly purified by silica gel column chromatography to give the desired product **3**. **3** was dissolved in 2 mL of EtOH, and $NaBH_4$ (1.0 equiv) in EtOH (0.1 M) was added. The mixture was stirred under room temperature for 30 min. The volatile was evaporated under vacuum, and the residue was purified by silica gel column chromatography to give the corresponding alcohol **4** in almost quantitative yield.

(5*S*,6*S*,7*R*)-5,7-Diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3a). The title compound was obtained using the general procedure described above, in 80% yield and >99% ee: $[\alpha]^{20}_D$ = +34.9 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.22 (s, 1H), 7.49−7.46 (m, 2H), 7.38−7.26 (m, 6H), 7.20−7.15 (m, 2H), 6.26 (s, 1H), 6.01 (s,1H), 5.41 (d, J = 10.0 Hz, 1H), 4.62 (d, J = 10.0 Hz, 1H), 3.54−3.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.1, 148.3, 138.0, 137.4, 129.0, 128.9, 128.85, 128.7, 127.7, 127.5, 123.6, 112.6, 60.4, 57.9, 57.3; HR-MS (ESI) m/z 336.1708 [M + MeOH + H]$^+$, calcd for $C_{20}H_{22}N_3O_2$, 336.1712. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 10.6 min (major) and t_r = 32.5 min (minor).

(5S,6S,7R)-7-phenyl-5-m-tolyl-5,6,7,8-tetrahydroimidazo-[1,2-a]pyrimidine-6-carbaldehyde (3b). The title compound was obtained using the general procedure described above, in 71% yield and 99% ee: $[\alpha]^{20}_D$ = +38.3 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.24 (d, J = 1.2 Hz, 1H), 7.50−7.48 (m, 2H), 7.40−7.26 (m, 3H), 7.22 (dd, J = 7.6, J = 8.0 Hz 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.05−6.95 (m, 2H), 6.35 (s, 1H), 6.06 (s, 1H), 5.38 (d, J = 10.4 Hz, 1H), 4.62 (d, J = 10.4 Hz, 1H), 3.54 (ddd, J = 1.2 Hz, J = 10.4 Hz, J = 10.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.3, 148.4, 138.7, 138.1,137.6, 129.5, 129.1, 129.0, 128.8, 128.3, 127.6, 124.9, 124.6, 112.8, 60.6, 58.1, 57.6, 21.4; HR-MS (ESI) m/z 350.1866 [M + MeOH + H]$^+$, calcd for $C_{21}H_{24}N_3O_2$, 350.1869. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 8.5 min (major) and t_r = 19.8 min (minor).

(5*S*,6*S*,7*R*)-5-(3-Methoxyphenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3c). The title compound was obtained using the general procedure described above, in 50% yield and >99% ee: $[\alpha]^{20}_D$ = +35.6 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.22 (d, J = 1.6 Hz, 1H), 7.55−7.48 (m, 2H), 7.46−7.30 (m, 3H), 7.26−7.20 (m, 2H), 6.85−6.78 (m, 2H), 6.72 (s, 1H), 6.29 (s, 1H), 6.07 (d, J = 0.8 Hz, 1H), 5.39 (d, J = 10.0 Hz, 1H), 4.61 (d, J = 10.0 Hz, 1H), 3.76 (s, 3H), 3.52 (ddd, J = 1.6 Hz, J = 10.0 Hz, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.2, 159.9, 148.4, 139.7, 137.6, 129.9, 129.03, 129.0, 127.5, 124.6, 120.0, 114.1, 113.2, 112.7, 60.5, 58.0, 57.6, 55.3; HR-MS (ESI) m/z 366.1816

$[M + MeOH + H]^+$, calcd for $C_{21}H_{24}N_3O_3$, 366.1818. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate =1.0 mL/min: t_r = 12.3 min (major) and t_r = 28.3 min (minor).

(5*S*,6*S*,7*R*)-5-(3-Chlorophenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3d). The title compound was obtained using the general procedure described above, in 60% yield and 99% ee: $[\alpha]^{20}_D$ = +36.3 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.23 (d, *J* = 1.6 Hz, 1H), 7.50−7.47(m, 2H), 7.46−7.30 (m, 3H), 7.30−7.20 (m, 2H), 7.19 (s, 1H), 7.12−7.08 (m, 1H), 6.50 (d, *J* = 1.6 Hz, 1H), 6.10 (d, *J* = 1.6 Hz, 1H), 5.89 (br s, 1H), 5.46 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 10.0 Hz, 1H), 3.50 (ddd, *J* = 1.6 Hz, *J* = 10.0 Hz, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.6, 148.2, 140.2, 137.1,134.8, 130.1, 129.09, 129.07, 129.0, 127.7, 127.4, 125.0, 124.0, 112.6, 60.1, 57.2, 57.0; HR-MS (ESI) *m*/*z* 370.1323 $[M + MeOH + H]^+$, calcd for $C_{20}H_{21}N_3O_2Cl$, 370.1322. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate =1.0 mL/min: t_r = 9.6 min (major) and t_r = 37.8 min (minor).

(5*S*,6*S*,7*R*)-5-(3-Bromophenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3e). The title compound was obtained using the general procedure described above, in 68% yield and >99% ee: $[\alpha]^{20}_D$ = +36.2 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.23 (d, *J* = 1.2 Hz, 1H), 7.50−7.45 (m, 2H), 7.42−7.26 (m, 5H), 7.20−7.10 (m, 2H), 6.21 (s, 1H), 6.01(d, *J* = 1.6 Hz, 1H), 5.42 (d, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 10.0 Hz, 1H), 3.48 (ddd, *J* = 1.2 Hz, *J* = 9.6 Hz, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.8, 148.6, 140.9, 137.4, 131.8, 130.6, 130.4, 129.1, 129.0, 127.5, 126.4, 124.9, 122.9, 112.4, 60.5, 57.4, 57.0; HR-MS (ESI) *m*/*z* 414.0822 $[M + MeOH + H]^+$, calcd for $C_{20}H_{21}N_3O_2Br$, 414.0817. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 10.2 min (major) and t_r = 37.5 min (minor).

(5*S*,6*S*,7*R*)-5-(3-Nitrophenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3f). The title compound was obtained using the general procedure described above, in 70% yield and 99% ee: $[\alpha]^{20}_D$ = +9 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.27 (d, *J* = 0.8 Hz, 1H), 8.13−8.11 (m, 1H), 8.01 (s, 1H), 7.52−7.38 (m, 4H), 7.38−7.26 (m, 3H), 6.28 (d, *J* = 1.2 Hz, 1H), 6.00 (d, *J* = 1.6 Hz, 1H), 5.64 (d, *J* = 8.8 Hz, 1H), 4.68 (d, *J* = 8.8 Hz, 1H), 3.53−3.48 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.2, 148.6, 148.4, 141.1, 137.2, 133.6, 129.2, 129.0, 127.3, 125.3, 123.5, 122.5, 112.2, 60.1, 57.0, 56.4; HR-MS (ESI) *m*/*z* 381.1559 $[M + MeOH + H]^+$, calcd for $C_{20}H_{21}N_4O_4$, 381.1563. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 85:15, flow rate = 0.8 mL/min: t_r = 15.8 min (major) and t_r = 44.7 min (minor).

(5*S*,6*S*,7*R*)-7-Phenyl-5-*p*-tolyl-5,6,7,8-tetrahydroimidazo-[1,2-a]pyrimidine-6-carbaldehyde (3g). The title compound was obtained according to general procedure described above, in 58% yield and 99% ee: $[\alpha]^{20}_D$ = +44.8 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.22 (d, *J* = 1.6 Hz, 1H), 7.50−7.49 (m, 2H), 7.48−7.26 (m, 3H), 7.20−7.05 (m, 4H), 6.35 (d, *J* = 0.8 Hz, 1H), 6.05 (d, *J* = 1.6 Hz, 1H), 5.38 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 10.4 Hz, 1H), 3.52 (ddd, *J* = 1.6 Hz, *J* = 10.0 Hz, *J* = 10.4 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.3, 148.3, 138.7, 137.7,135.1, 129.6, 129.1, 129.0, 127.7, 127.6, 124.6, 112.7, 60.7, 57.9, 57.7, 21.1; HR-MS (ESI) *m*/*z* 350.1869 $[M + MeOH + H]^+$, calcd for $C_{21}H_{24}N_3O_2$, 350.1869. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 9.7 min (major) and t_r = 20.3 min (minor).

(5*S*,6*S*,7*R*)-5-(4-Methoxyphenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3h). The title compound was obtained using the general procedure described above, in 54% yield and >99% ee: $[\alpha]^{20}_D$ = +50.0 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.23 (d, *J* = 1.2 Hz, 1H), 7.51−7.48 (m, 2H), 7.40−7.30 (m, 3H), 7.13 (d, *J* = 8.4, Hz, 2H), 6.84 (d, *J* = 8.4, Hz, 2H), 6.24 (s, 1H), 6.02 (s, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 4.60 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 3H), 3.49 (ddd, *J* = 1.2 Hz, *J* = 10.0 Hz, *J* = 10.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.4, 159.7,148.5, 137.7, 130.0, 129.0, 128.9, 127.6, 124.4, 114.2, 112.4, 60.7, 57.6, 55.2; HR-MS (ESI) *m*/*z* 366.1806 $[M + MeOH + H]^+$, calcd for $C_{21}H_{24}N_3O_3$, 366.1818. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r =16.6 min (major) and t_r = 33.5 min (minor).

(5*S*,6*S*,7*R*)-5-(4-Chlorophenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3i). The title compound was obtained according to general procedure described above, in 76% yield and 98% ee: $[\alpha]^{20}_D$ = +47.8 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.21 (d, *J* = 0.8 Hz, 1H), 7.48−7.45 (m, 2H), 7.40−7.33 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 1H), 6.04 (s, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 10.0 Hz, 1H), 3.49−3.44 (m, 1H); NMR (125 MHz, $CDCl_3$, ppm) δ 199.7, 148.1, 137.0, 136.5, 134.7, 129.18, 129.15, 129.1, 128.7, 127.4, 123.9, 112.6, 60.3, 57.4, 57.1; HR-MS (ESI) *m*/*z* 370.1316 $[M + MeOH + H]^+$, calcd for $C_{20}H_{21}N_3O_2Cl$, 370.1322. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 11.0 min (major) and t_r = 31.3 min (minor).

(5*S*,6*S*,7*R*)-5-(4-Bromophenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3j). The title compound was obtained using the general procedure described above, in 72% yield and 98% ee: $[\alpha]^{20}_D$ = +64.4 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.21 (d, *J* = 1.6 Hz, 1H), 7.49−7.30 (m, 7H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 1.2 Hz, 1H), 6.04 (d, *J* = 1.6 Hz, 1H), 5.43 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 10.0 Hz, 1H), 3.47 (ddd, *J* = 1.6 Hz, *J* = 10.0 Hz, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.8, 148.4, 137.5, 137.2, 132.1, 129.4, 129.2, 127.4, 125.0, 122.8, 112.6, 60.7, 57.6, 57.2; HR-MS (ESI) *m*/*z* 414.0809 $[M + MeOH + H]^+$, calcd for $C_{20}H_{21}N_3O_2Br$, 414.0817. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 12.1 min (major) and t_r = 35.2 min (minor).

(5*S*,6*S*,7*R*)-5-(4-Nitrophenyl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3k). The title compound was obtained using the general procedure described above, in 76% yield and >99% ee: $[\alpha]^{20}_D$ = +58.0 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.25 (d, *J* = 0.8 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.48−7.45 (m, 2H), 7.39−7.26 (m, 5H), 6.24 (d, *J* = 1.6 Hz, 1H), 5.99 (d, *J* = 1.6 Hz, 1H), 5.63 (d, *J* = 9.2 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 3.45 (ddd, *J* = 0.8 Hz, *J* = 9.2 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.2, 148.7, 147.8, 146.1, 137.1, 129.2, 129.1, 128.6, 127.3, 125.3, 124.0, 112.3, 60.3, 57.4, 56.5; HR-MS (ESI) *m*/*z* 381.1554 $[M + MeOH + H]^+$, calcd for $C_{20}H_{21}N_4O_4$, 381.1563. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 80:20, flow rate = 0.8 mL/min: t_r = 14.3 min (major) and t_r = 33.7 min (minor).

(5*S*,6*S*,7*R*)-5-(Benzo[*d*][1,3]dioxol-5-yl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3l). The title compound was obtained using the general procedure described above, in 66% yield and 99% ee: $[\alpha]^{20}_{D}$ = +66.8 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.24 (d, *J* = 1.6 Hz, 1H), 7.50−7.48 (m, 2H), 7.42−7.28 (m, 3H), 6.75−6.70 (m, 2H), 6.65 (s, 1H), 6.28 (d, *J* = 1.2 Hz, 1H), 6.07 (d, *J* = 1.6 Hz, 1H), 5.94 (d, *J* = 1.2 Hz, 2H), 5.32 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 10.4 Hz, 1H), 3.48 (ddd, *J* = 1.6 Hz, *J* = 10.0 Hz, *J* = 10.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.2, 148.4, 148.2, 147.9, 137.6, 131.89, 129.1, 129.0, 127.6, 124.7, 112.5, 108.3, 107.6, 101.3, 60.7, 57.9, 57.6; HR-MS (ESI) *m*/*z* 380.1597 $[M + MeOH + H]^+$, calcd for $C_{21}H_{22}N_3O_4$, 380.1610. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 19.8 min (major) and t_r = 33.9 min (minor).

(5*S*,6*S*,7*R*)-5-(Furan-2-yl)-7-phenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3m). The title compound was obtained using the general procedure described above, in 49% yield and 99% ee: $[\alpha]^{20}_{D}$ = +52.3 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.34 (d, *J* = 1.2 Hz, 1H), 7.49−7.45 (m, 2H), 7.40−7.26 (m, 4H), 6.33−6.28 (m, 3H), 6.24 (d, *J* = 1.6 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 4.64 (d, *J* = 9.6 Hz, 1H), 3.77 (ddd, *J* = 1.2 Hz, *J* = 9.6 Hz, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.5, 149.2, 147.5, 143.2, 137.6, 129.0, 128.9, 127.4, 124.7, 112.1, 110.5, 110.0, 57.2, 55.9, 51.0; HR-MS (ESI) *m*/*z* 326.1499 $[M + MeOH + H]^+$, calcd for $C_{18}H_{20}N_3O_3$, 326.1505. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 13.1 min (major) and t_r = 40.5 min (minor).

(5*S*,6*S*,7*R*)-7-Phenyl-5-(thiophen-2-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3n). The title compound was obtained using the general procedure described above, in 42% yield and 99% ee: $[\alpha]^{20}_{D}$ = +41.9 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.29 (d, *J* = 1.6 Hz, 1H), 7.52−7.45 (m, 2H), 7.42−7.32 (m, 3H), 7.32−7.26 (m, 1H), 7.05−7.04 (m, 1H), 6.95−6.92 (m, 1H), 6.30 (d, *J* = 1.6 Hz, 1H), 6.20 (d, *J* = 1.6 Hz, 1H), 5.72 (d, *J* = 10.4 Hz, 1H), 4.60 (d, *J* = 10.0 Hz, 1H), 3.61 (ddd, *J* = 1.2 Hz, *J* = 10.0 Hz, *J* = 10.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.8, 147.8, 140.6, 137.4, 129.1, 127.9, 127.6, 126.8, 126.5, 124.7, 112.4, 60.7, 57.8, 53.6; HR-MS (ESI) *m*/*z* 342.1263 $[M + MeOH + H]^+$, calcd for $C_{18}H_{20}N_3O_2S$, 342.1276. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 12.7 min (major) and t_r = 27.0 min (minor).

(5*S*,6*S*,7*R*)-5-(4-Chlorophenyl)-7-(4-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3o). The title compound was obtained using the general procedure described above, in 60% yield and 98% ee: $[\alpha]^{20}_{D}$ = +28.6 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.22 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 1.6 Hz, 1H), 6.03 (d, *J* = 1.2 Hz, 1H), 5.43 (d, *J* = 10 Hz, 1H), 4.54 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.43 (ddd, *J* = 1.6 Hz, *J* = 10.0 Hz, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 200.0, 160.1, 148.5, 137.0, 134.6, 129.1, 128.6, 125.1, 114.5, 112.6, 60.9, 57.2, 57.1, 55.3; HR-MS (ESI) *m*/*z* 400.1422 $[M + MeOH + H]^+$, calcd for $C_{21}H_{23}N_3O_3Cl$, 400.1428. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 20.3 min (major) and t_r = 47.0 min (minor).

(5*S*,6*S*,7*R*)-7-(4-Methoxyphenyl)-5-(4-nitrophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3p). The title compound was obtained using the general procedure described above, in 62% yield and 97% ee: $[\alpha]^{20}_{D}$ = +57.4 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.23 (d, *J* = 0.8 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 1.6 Hz, 1H), 5.99 (d, *J* = 1.2 Hz, 1H), 5.62 (d, *J* = 9.6 Hz, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.44 (ddd, *J* = 0.8 Hz, *J* = 9.6 Hz, *J* = 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.4, 160.2, 148.8, 146.1, 128.8, 128.7, 128.5, 125.4, 124.0, 114.5, 112.3, 60.7, 56.8, 56.6, 55.3; HR-MS (ESI) *m*/*z* 411.1656 $[M + MeOH + H]^+$, calcd for $C_{21}H_{23}N_4O_5$, 411.1668. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 80:20, flow rate = 0.8 mL/min: t_r = 19.7 min (major) and t_r = 40.0 min (minor).

(5*S*,6*S*,7*R*)-5-Phenyl-7-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3q). The title compound was obtained using the general procedure described above, in 85% yield and 99% ee: $[\alpha]^{20}_{D}$ = +13.7 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.29 (d, *J* = 1.6 Hz, 1H), 7.62−7.60 (m, 4H), 7.32−7.26 (m, 3H), 7.17−7.14 (m, 2H), 6.19 (d, *J* = 1.6 Hz, 1H), 6.05 (d, *J* = 1.2 Hz, 1H), 5.41 (d, *J* = 9.6 Hz, 1H), 4.77 (d, *J* = 9.6 Hz, 1H), 3.53 (ddd, *J* = 1.2 Hz, *J* = 9.6 Hz, *J* = 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.7, 148.2, 142.0, 137.7, 131.0 (q, J_{C-F} = 32.5 Hz), 129.0, 128.9, 128.0, 127.5, 127.0, 125.9, 125.8, 124.4, 123.8 (q, J_{C-F} = 271.0 Hz), 112.7, 60.2, 58.0, 56.7; HR-MS (ESI) *m*/*z* 404.1569 $[M + MeOH + H]^+$, calcd for $C_{21}H_{21}F_3N_3O_2$, 404.1586. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 8.00 min (major) and t_r = 33.2 min (minor).

(5*S*,6*S*,7*R*)-5-Phenyl-7-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3r). The title compound was obtained using the general procedure described above, in 87% yield and 99% ee: $[\alpha]^{20}_{D}$ = +21.1 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.28 (d, *J* = 1.6 Hz, 1H), 7.62 (dd, *J* = 8.4 Hz, *J* = 8.4 Hz, 4H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 1.6 Hz, 1H), 6.05 (d, *J* = 1.6 Hz, 1H), 5.44 (d, *J* = 9.6 Hz, 1H), 4.74 (d, *J* = 9.6 Hz, 1H), 3.47 (ddd, *J* = 1.6 Hz, *J* = 9.6 Hz, *J* = 9.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 199.3, 148.1, 141.7, 136.3, 134.8, 131.2 (q, J_{C-F} = 36.3 Hz), 129.0, 128.9, 128.9, 127.9, 127.0, 124.8, 123.7 (q, J_{C-F} = 276.0 Hz), 112.6, 60.2, 57.2, 56.7; HR-MS (ESI) *m*/*z* 438.1192 $[M + MeOH + H]^+$, calcd for $C_{21}H_{20}ClF_3N_3O_2$, 438.1196. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 9:1, flow rate = 1.0 mL/min: t_r = 9.00 min (major) and t_r = 30.7 min (minor).

(5*S*,6*S*,7*R*)-5-Phenyl-7-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrimidine-6-carbaldehyde (3s). The title compound was obtained using the general procedure described above, in 75% yield and 99% ee: $[\alpha]^{20}_{D}$ = +33.0 (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.29 (d, *J* = 1.2 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.62 (dd, *J* = 8.4 Hz, *J* = 8.4 Hz, 4H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 1.6 Hz, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 5.68 (d, *J* = 9.2 Hz, 1H), 4.79 (d, *J* = 9.2 Hz, 1H), 3.50 (ddd, *J* = 1.2 Hz, *J* = 9.2 Hz, *J* = 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 198.5, 148.2, 147.9, 145.4, 141.4, 131.3 (q, J_{C-F} = 32.5 Hz), 128.4, 127.8, 126.1, 126.0, 125.1, 124.7, 123.3 (q, J_{C-F} = 270.0 Hz), 112.5, 59.8, 56.4, 56.3; HR-MS (ESI) *m*/*z* 449.1422 $[M + MeOH + H]^+$, calcd for $C_{21}H_{20}F_3N_4O_4$, 449.1437. The enantiomeric excess was determined by HPLC analysis of the corresponding alcohol (after treatment with $NaBH_4$) using a Daicel Chiralpak OD-H column, hexane (0.1% TEA)/*i*-PrOH = 80:20, flow rate = 0.8 mL/min: t_r = 12.7 min (major) and t_r = 26.1 min (minor).

■ ASSOCIATED CONTENT

Supporting Information. Copies of CSP-HPLC chromatograms, and ^{1}H and ^{13}C NMR spectra of the products, and X-ray crystallographic data of **4n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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