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First enantioselective synthesis of 4-aminoalcohol quinoline derivatives through a regioselective S_N2 epoxide opening mechanism

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ABSTRACT

Mefloquine derivatives, contrary to chloroquine derivatives have not been widely studied to date. Consequently, mefloquine and its derivatives still remain very attractive synthetic targets. Although mefloquine is usually used clinically as a racemic mixture, some studies have shown that its (+)-enantiomer is more potent than the (−)-enantiomer. Moreover, the (−)-enantiomer is responsible for side effects due to reaction with the central nervous system adenosine receptors, while the (+)-enantiomer does no bind at this binding site. Recently, different libraries of racemic 4-aminoalcohol quinolines showed interesting antimalarial activities. Herein, we describe an enantiopure synthetic and straightforward route to prepare pure enantiomer 4-aminoalcohol quinoline derivatives through a 4-oxirane key-intermediate. A regioselective S_N2 ring opening of this epoxide, by diverse amines, allows us to obtain the corresponding (*R*) or (*S*) 4-aminoquinolines with good yields and enantiomeric excesses generally superior to 92%. The reported methodology appears suitable for the synthesis of a large number of pure enantiomer 4-aminoalcohol quinoline derivatives.

1. Introduction

Human malaria is one of the most important diseases in the world, with a corresponding mortality of more than 1 million deaths per year.[1] Four species of *Plasmodium* are responsible for malaria in human beings and among these, *Plasmodium falciparum* is the most dangerous. Antifolates (pyrimethamine, trimethoprim, and sulphonamides) and quinoline-containing drugs (quinine, mefloquine, halofantrine, chloroquine, and primaquine) are two principal classes of antimalarial drugs that have been developed during the past 50 years.[2] Newer antimalarial agents such as antibiotics (doxycycline), the hydroxynaphthoquinone derivatives (atovaquone, lumefantrine), and artemisinin (active principle of *Artemesia annua*) were introduced during this period.[3] Due to the efficiency decrease of classical medication toward the rapid extension of *P. falciparum* chloroquine-resistant strains, there is a need to develop new and effective antimalarial drugs.[4] Extensive work has been done to synthesize chloroquine analogs but with much less in regard to mefloquine derivatives. Consequently, mefloquine and its derivatives still remain very attractive synthetic targets. Mefloquine hydrochloride (Lariam®) is a highly active blood schizontocide against multi-drug resistant *falciparum* malaria strains. This quinoline methanol derivative presents two asymmetric carbon atoms (Fig. 1). Karle et al. showed that the (+)-enantiomer of the mefloquine is more potent than the (−)-enantiomer by a factor of 1.69 (IC_{50} values against Sierra Leone and Indochina *P. falciparum* strains).[5] However, mefloquine is commonly used clinically as a racemic mixture of (±)-(*R*∗,*S*∗)-α-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol which consists of individual enantiomers (+)-(11*R*,12*S*)-α-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol and (−)-(11*S*,12*R*)-α-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol. Mefloquine remains the drug of choice for US military deployments in such regions, primarily because its longer half-life (compared to those of Malarone or doxycycline)[6]

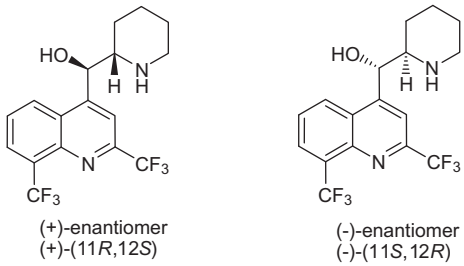

Figure 1. Mefloquine enantiomer structures.

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allows weekly administration, thereby making compliance less problematic.

However, undesirable side effects on the central nervous system (CNS) have been associated with mefloquine use. These include disturbed sleep, heightened anxiety, panic attacks, depression, and psychosis.[7,8] It has been found that the (−)-enantiomer of mefloquine binds to CNS adenosine receptors, while the (+)-enantiomer is without significant activity at this binding site. Moreover, blocking of central adenosine receptors by the (−)-enantiomer is believed to result in neuropsychiatric symptoms associated with mefloquine.[9] Further evidence suggests that the neurotoxicity of mefloquine appears to be related to the piperidine ring.[10] Previously, it was reported that the opening of the piperidine ring at the 4-position of the quinoline scaffold is associated with an improved potency and a selectivity relative to mefloquine. Recently, Dow et al. described the antimalarial potential together with the physicochemical properties, of several libraries describing racemic mixtures of mefloquine non-piperidine analogs.[11] According to these authors, mefloquine neurological effects could be limited by a lower permeability of the blood–brain barrier of new mefloquine analogs through physicochemical property modifications. From their library, an active series of diamines has been identified showing a similar metabolic stability and a lower permeability than mefloquine. The main modification of the mefloquine derivatives concerns the 4-position of the quinoline scaffold to synthesize 4-aminoalcohol quinoline.[11,12] Racemic mixtures of mefloquine analogs were synthesized and evaluated for other biological properties such as treatment of tuberculosis,[13] bacterial infections, and treatment of movement disorders (Parkinson's or Alzheimer's diseases) due to their binding affinity to the adenosine A_2 receptor.[14]

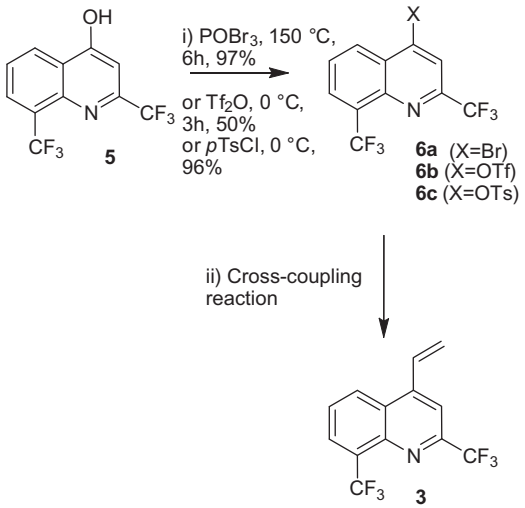
Several other approaches to reduce mefloquine neurotoxicity have been proposed: (i) reformulation of mefloquine as a pure isomer, and (ii) reengineering of mefloquine (based on physicochemical property modifications) to obtain less neurotoxic derivatives still showing an antimalarial activity. In the continuation of our precedent work concerning the synthesis of new antimalarial drugs,[15] the asymmetric synthesis of enantiopure 4-aminoalcohol quinoline mefloquine analogs has been considered as an interesting goal. These compounds should present the physiochemical properties required to achieve a balance between potency, reduced blood–brain barrier penetration, and metabolic stability. To the best of our knowledge, no enantioselective syntheses of mefloquine amino-analogs have been described. Consequently, our goal is to propose a new enantioselective pathway to mefloquine amino-analogs allowing access to new antimalarial compounds with a strong antimalarial activity and few neurological side effects.

2. Results and discussion

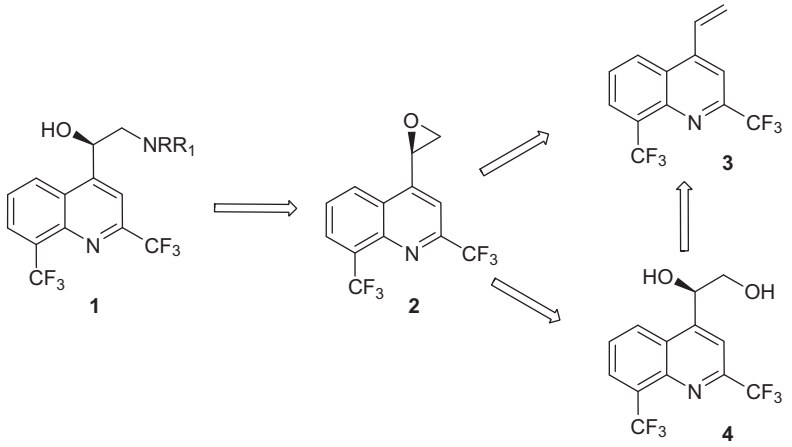
Mefloquine and its synthesis were first described by Ohnmacht et al.[16] in 1971. In 1974, a more detailed account of the synthesis along with antimalarial activity of the mefloquine isomers is given by Carroll and Blackwell.[17] More recently, Xie et al. reported a new and enantioselective synthesis of the (11*R*,12*S*)-mefloquine hydrochloride using a proline-catalyzed asymmetric direct aldol reaction and a Beckmann rearrangement as the key steps. The experimental analysis confirmed the absolute configuration of (+)-mefloquine as (11*R*,12*S*).[18]

During the synthesis of (*R*)- and (*S*)-4aminoalcohol quinoline mefloquine analogs **1**, the envisaged strategy involved enantiopure key-intermediate **2** (4-oxirane) synthesis (Scheme 1). This enantioselective epoxide can be easily diversified on position 4, through a regioselective S_N2 ring opening mechanism. The preparation of 4-oxirane **2** was carried out from 4-vinylquinoline **3** either in one step by a Jacobsen epoxidation or in two steps via a Sharpless asymmetric dihydroxylation (diol **4**).

The 4-vinylquinoline **3** has been prepared either from the corresponding 4-bromoquinoline or from 4-sulfoxyquinoline **6** (4-tosyloxy- or 4-trifluorooxy-quinoline) (Scheme 2). The 4-bromoquinoline **6a** is easily accessible by reaction of 4-hydroxyquinoline **5** with phosphorus oxybromide at 150 °C. Sulfonates **6b** and **6c** are prepared from the same alcohol **5** by the action of triflic anhydride



Scheme 2. Synthesis of 2,8-trifluoromethyl-4-vinylquinoline **3**.



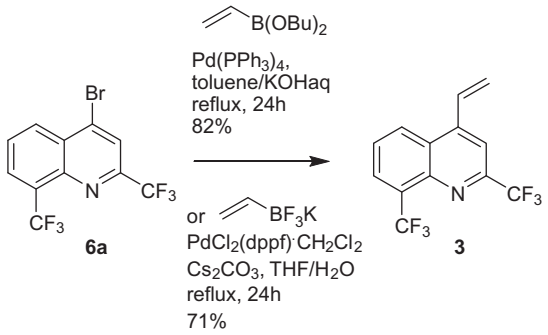
Scheme 1. Retrosynthesis of (11*R*)-enantiopure 4-aminoalcohol quinoline **1**.

(50% yield) and *p*-toluenesulfonic acid (96% yield), respectively. These different precursors will be used as an electrophile in transition-metal-catalyzed cross couplings (Hiyama, Stille and Suzuki reactions).

Using reaction conditions reported in the literature,[19] a Hiyama coupling has been performed with vinyltrimethoxysilane and 2,8-trifluoromethyl-4-bromoquinoline **6a** on water using sodium hydroxide as the activator at 120 °C. Normally, this process should give good results in the presence of a low quantity of diacetate palladium (1 mol %). Unfortunately, in our case, 4-vinylquinoline **3** is formed in only 14% yield after 16 h of reaction. In order to reduce the reaction time and to increase the yield, two others tests have been made: (i) under microwave and (ii) with 10 mol % of palladium catalyst. However, we did not succeed in improving the previous yield of 14%.

To overcome this, the Stille coupling reaction with vinyltributylstannane as a vinylating reagent has been investigated. In order to determine the optimal cross-coupling reaction conditions (solvents, catalysts, substrates and bases) a study has been carried out. The results are shown in Table 1. A first assay was performed by using the reaction conditions described by Comins et al. in 2005, slightly modified.[20] The 4-bromoquinoline **6a** was reacted with vinylstannane using the $Pd(PPh_3)_2Cl_2$ as a catalyst and tetrabutylammonium bromide as an additive at reflux of degassed acetonitrile (Table 1, entry 1). The 4-vinyl product was obtained in 46% yield with a purity of 98% determined by an HPLC. The starting material was totally converted but the reaction suffered from an instability of the catalyst, which was observable through the precipitation of black palladium over the course of the reaction. Thus, when the same reaction was performed using oven dried glassware and distilled acetonitrile: a yield increase of 20% was observed (entry 2). The comparison between three solvents (dimethylformamide, toluene and acetonitrile) revealed that acetonitrile affords the best yields (entries 2–5). Without adding tetrabutylammonium bromide (TBAB), only a 43% yield (vs 65%) of the corresponding cross-coupled product **3** was obtained (entry 5). Indeed, TBAB is known to be able to stabilize colloidal palladium nanoparticules that act as catalysts.

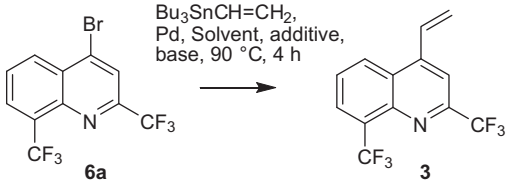
Other Pd complexes tested as catalysts were less effective than $Pd(PPh_3)_2Cl_2$ (entries 8 and 9). The addition of an inorganic base such as K_2CO_3 increases the reaction yield (entries 10 vs 2). The best yield with a satisfactory purity was obtained using $Pd(PPh_3)_2Cl_2$, TBAB, distilled acetonitrile and K_2CO_3 (75%, entry 10). When 4-tosyloxy- and 4-trifluorooxyquinoline were used in the place of 4-bromoquinoline, in the optimal conditions previously described, the yields decreased in an important way by 60% and 42%, respectively. The vinylquinoline **3** was easily prepared in good yield (82%) by a direct Suzuki–Miyaura cross-coupling reaction of 4-bromoquinoline **6a** with dibutyl vinylboronate (Scheme 3). This step has been performed in the presence of $Pd(PPh_3)_4$ as a catalyst and a 4 M aqueous solution of KOH solution.[21] The Suzuki–Miyaura-type reaction was expanded with potassium vinyltrifluoroborate and 4-bromoquinoline **6a** as coupling partners by using $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst, Cs_2CO_3 as the base, and THF–H_2O as the solvent system.[22] Consequently, this new palladium-catalyzed cross-coupling reaction led to the expected 4-vinylquinoline **3** in 71% yield.



Scheme 3. Suzuki cross-coupling.

After optimization of the 4-vinylquinoline **3** preparation, a direct asymmetric epoxidation using a chiral (salen)Mn catalyst has been envisaged although several direct methods for olefin

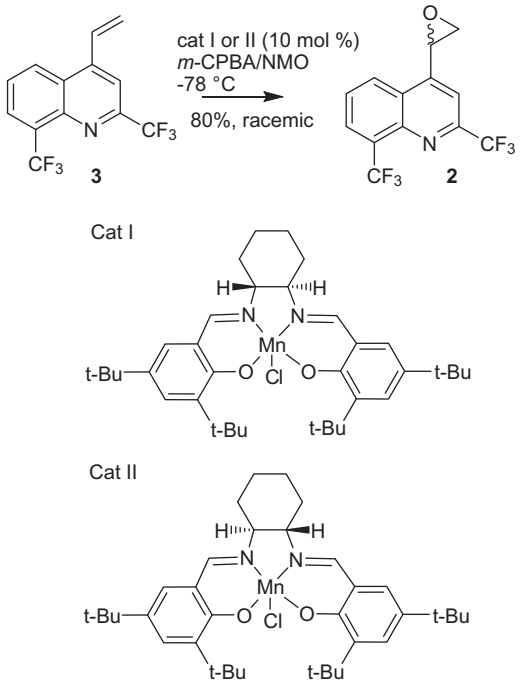
Table 1
Stille coupling conditions to prepare alkene **3**



Entry[a]	Pd catalyst (mol %)	TBAB (equiv)	Base (equiv)	Solvent[b]	Yield[d] (%)	Purity[e] (%)
1	$Pd(PPh_3)_2Cl_2$ (10)	1	—	MeCN[c]	46	98
2	$Pd(PPh_3)_2Cl_2$ (10)	1	—	MeCN	65	nd
3	$Pd(PPh_3)_2Cl_2$ (10)	1	—	Toluene	7	nd
4	$Pd(PPh_3)_2Cl_2$ (10)	1	—	DMF	13	nd
5	$Pd(PPh_3)_2Cl_2$ (10)	—	—	MeCN	43	99
6	$Pd(PPh_3)_4$ (10)	1	2	MeCN	9	nd
7	$Pd(PPh_3)_2Cl_2$ (10) + PPh_3 (20)	1	—	MeCN	16	96
8	$Pd_2(dba)_3$ (10) + PPh_3 (20)	1	—	MeCN	84	72
9	$Pd(OAc)_2$ (10)	1	—	MeCN	60	83
10	$Pd(PPh_3)_2Cl_2$ (10)	1	2	MeCN	75	100
11	$Pd_2(dba)_3$ (10)	1	2	MeCN	88	68
12	$Pd(PPh_3)_2Cl_2$ (5)	1	2	MeCN	48	96

[a] All reactions were performed with 1 equiv of **6a** and 2 equiv of $Bu_3SnCH{=}CH_2$.
[b] Performed using dry solvents.
[c] Performed using a degassed solvent.
[d] Yield obtained after flash chromatography.
[e] Determined by HPLC analysis.

epoxidation are known. In the case of "terminal" double bonds, the corresponding epoxides are often obtained with low enantiomeric excesses.[23] However, in 1994, Jacobsen et al.[24] reported the enantioselective epoxidation of styrene, at low temperatures (−78 °C), adding *m*-chloroperbenzoic acid (*m*-CPBA) and *N*-methylmorpholine-N-oxide (NMO) to the chiral (salen)Mn complexes. This effective anhydrous oxidant system was applied with success to a series of various terminal aromatic olefins with a yield of around 80% and an ee 80%.[25] More recently, Prasad et al.[26] developed a large-scale Jacobsen asymmetric epoxidation methodology to obtain a chiral dihydrobenzofuran epoxide (melatonin agonist precursor). Their best result gives the terminal epoxide with 87% yield (72% ee). In order to obtain the enantiopure 4-oxirane **2**, we used various



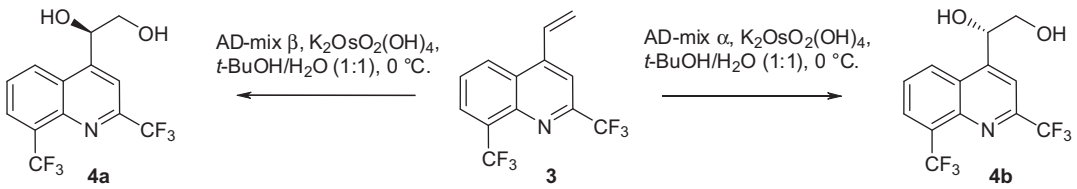
Scheme 4. Direct oxirane synthesis using the chiral (salen)Mn(III) complexes.

experimental conditions for the Jacobsen epoxidation. Each assay was run with NMO (5 equiv), *m*-CPBA (2 equiv), and chiral (salen)Mn(III) complexes (10 mol %) at −78 °C. The experiments differ by: (i) *m*-CPBA addition in solid form or in solution in absolute EtOH, (ii) DCM or DCM/THF solvent mixtures, and (iii) work-up at room temperature or at low temperature (−78 °C). Unfortunately, each experiment led to a racemic mixture of oxirane with 80% yield average (Scheme 4).

A direct epoxide synthesis being impossible, an indirect way thus appeared necessary. Our strategy consists of a two step process synthesis based on asymmetric dihydroxylation chemistry followed by a stereospecific cyclization. This cyclization can be obtained according to different literature procedures: (i) a base-mediated ring closure via selective hydroxyl activation, generally via a mesylate or tosylate form,[27] (ii) a formation of acetoxy halides and epoxide via the Sharpless acetoxonium ion[28] or (iii) a Mistunobu reaction.[29] We chose the Sharpless asymmetric dihydroxylation method followed by a cyclization via the Sharpless acetoxonium ion. We have developed the optimized conditions for the Sharpless asymmetric dihydroxylation starting from the 2,8-bis(trifluoromethyl)-4-vinylquinoline. According to the final enantiomeric alcohol expected **4a** (*R*) or **4b** (*S*) the vinylquinoline **3** is reacted with commercially available AD-mix α or AD-mix β, in a solution of *t*-BuOH/H_2O at 0 °C, with eventual addition of $K_2OsO_2(OH)_4$ and $MeSO_2NH_2$ (see Table 2).

The first assays of asymmetric dihydroxylation were carried out with 1.4 g of AD-mix α or β added to 1 equiv of methylsulfonamide (entries 1 and 2) as described by Kolb et al.[27] The corresponding oxiranes **4a** or **4b** were obtained with 40% yield average. In order to increase the yield, the quantities of AD-mix α have been increased: doubled (entry 3) or multiplied by four (entry 4), without success. However, addition of 1 mol % of $K_2OsO_2(OH)_4$ to 1.4 g of AD-mix increased significantly the yield (78% vs 43% entries 5, 2). Furthermore, we have demonstrated that the presence of methylsulfonamide is not required for the advancement of the reaction (entry 5 and 6). Finally, the treatment of vinylquinoline **3** with 1.4 g of AD-mix β in the presence of 1 mol % of oxidant $K_2OsO_2(OH)_4$ provided the corresponding (*R*)-diol {$[\alpha]_D^{20} = -52$ (*c* 0.25, DCM)} in 68% yield and 97% enantiomeric excess (ee). The (*S*)-diol {$[\alpha]_D^{20} = +62$ (*c* 0.25; DCM)} was prepared from 1.4 g of

Table 2
Reagents and conditions used to prepare enantiopure diol **4a** and **4b**



Entry	AD-mix (g)	$K_2OsO_2(OH)_4$	$MeSO_2NH_2$	Time (h)	Yield (%)	% ee[c]	$[\alpha]_D^{20}$[e]	Diol (absolute configuration)[f]
1	α (1.4)[a]	—	1 mmol	26	37	nd[d]	—	—
2	β (1.4)[b]	—	1 mmol	30	43	nd	—	—
3	α (2.5)	—	1 mmol	28	36	nd	—	—
4	α (6.4)	—	1 mmol	47	26	96	+62	**4b** (*S*)
5	β (1.4)	1 mol %	1 mmol	24	78	98	−52	**4a** (*R*)
6	β (1.4)	1 mol %	—	19	68	97	−52	**4a** (*R*)
7	α (1.4)	1 mol %	—	18	78	96	+62	**4b** (*S*)

[a] 1 g of AD-mix α corresponds to 1.0 mol % of $(DHQ)_2$-PHAL, 3 mmol of $K_3Fe(CN)_6$, 3 mmol of K_2CO_3, 0.4 mol % of $K_2OsO_2(OH)_4$.
[b] 1 g of AD-mix β corresponds to 1.0 mol % of $(DHQD)_2$-PHAL, 3 mmol of $K_3Fe(CN)_6$, 3 mmol of K_2CO_3, 0.4 mol % of $K_2OsO_2(OH)_4$.
[c] Enantiomeric excesses were determined by HPLC (Chiralpak IB column, heptane/*i*-PrOH 90:10; 1 mL/min, 210 nm) t_R (*R*) = 26 min, t_R (*S*) = 33 min.
[d] Not determined.
[e] *c* 0.25, DCM.
[f] Configuration of the major enantiomer was determined by analyzing ^1H NMR spectra of the Mosher monoesters and/or with crystallographic epoxide spectra.

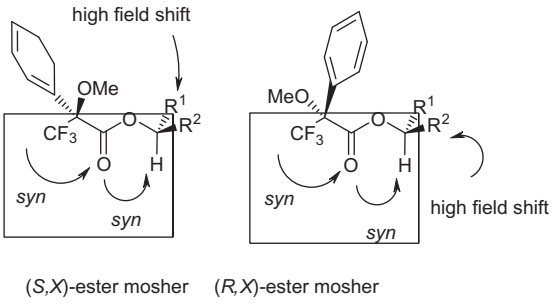
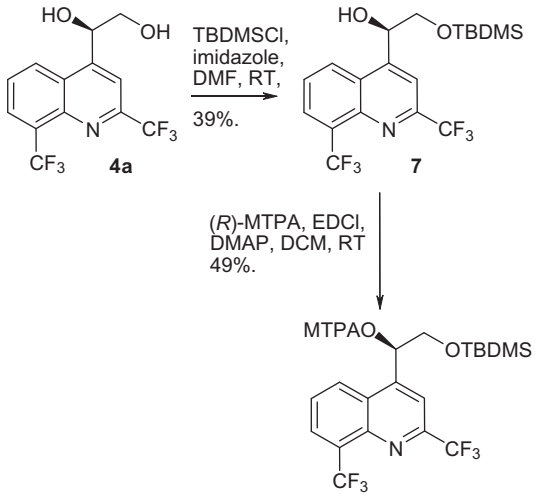


Figure 2. Preferred conformations of MTPA esters.

AD-mix α in the presence of 1 mol % of oxidant $K_2OsO_2(OH)_4$ in 78% yield and 96% ee.

The Mosher's MTPA (methoxy(trifluoromethyl)phenylacetyl) method is a well-known tool to determine the absolute configuration of chiral alcohols and primary amines since this process does not require the crystallization of compounds.[30] In MTPA esters, the aromatic substituent (phenyl group) generates a diamagnetic anisotropy effect due to the ring current induced by the external magnetic field. The proton NMR signals of the alcohol moiety facing the phenyl group on the preferred conformation are moved to a higher magnetic field (high-field shift). In ester (*S*,*X*), the protons of group R^1 feel a diamagnetic anisotropy effect, and hence their ^{1}H NMR signals show high-field shifts whereas R^2 does not (Fig. 2). Conversely, in the ester (*R*,*X*), R^2 is above the benzene plane of the MTPA moiety, and hence the protons of group R^2 show high-field shifts. The parameter $\Delta\delta$ reflecting the anisotropy is defined as $\Delta\delta = \delta(S,X) - \delta(R,X)$.

In this work, the corresponding Mosher's monoester **8** was prepared, from the diol **4a** (*R*), using (*S*)-α-methoxy-α-trifluoromethyl-phenylacetic acid or (*R*)-α-methoxy-α-trifluoromethyl-phenylacetic acid. For this purpose, the alcohol **7** was obtained with a 39% yield after selective primary alcohol protection of compound **4a** with *t*-butyldimethylsilylchloride in DMF, at room temperature. Subsequently, the two diastereomeric esters **8a** (*R*,*R*) and **8b** (*S*,*R*) were synthesized by reaction of **7** with the corresponding (*R*)- and (*S*)-Mosher's MTPA in dichloromethane with a 49% yield (Scheme 5).



Scheme 5. Preparation of Mosher's monoesters **8a** and **8b**.

The ^{1}H NMR analyses of the diastereomeric esters allowed us to establish without ambiguity the absolute configuration of the diols by combining the anisotropy effects discussed above with the definition of the $\Delta\delta$ parameter. The MTPA moiety and the methine proton of the secondary alcohol moiety are placed up in the front side and in the rear side, respectively. The substituent R^2 showing positive $\Delta\delta$ values is placed at the right side, while the substituent R^1 showing negative $\Delta\delta$ values is at the left side. So, the absolute configuration (X = *R*) of our alcohol has been determined (Fig. 3).

Concerning the epoxide formation by ring closure via Sharpless acetoxonium ion, we have chosen to use a 'one-pot' method, previously described by Sharpless for the stereospecific conversion of each (*R*)- or (*S*)-1,2-diols into their corresponding epoxides.[27] This process involves three successive steps: (i) formation of the cyclic orthoester by acid catalyzed transesterification; (ii) generation of halohydrins ester via regioselective opening of an acetoxonium ion by addition of tributyldimethylsilyl chloride, and (iii) cyclization to an epoxide by base mediated saponification in methanol. This conversion of the diol **4a** to the oxirane **2a** was accomplished with global retention of configuration because this process in-

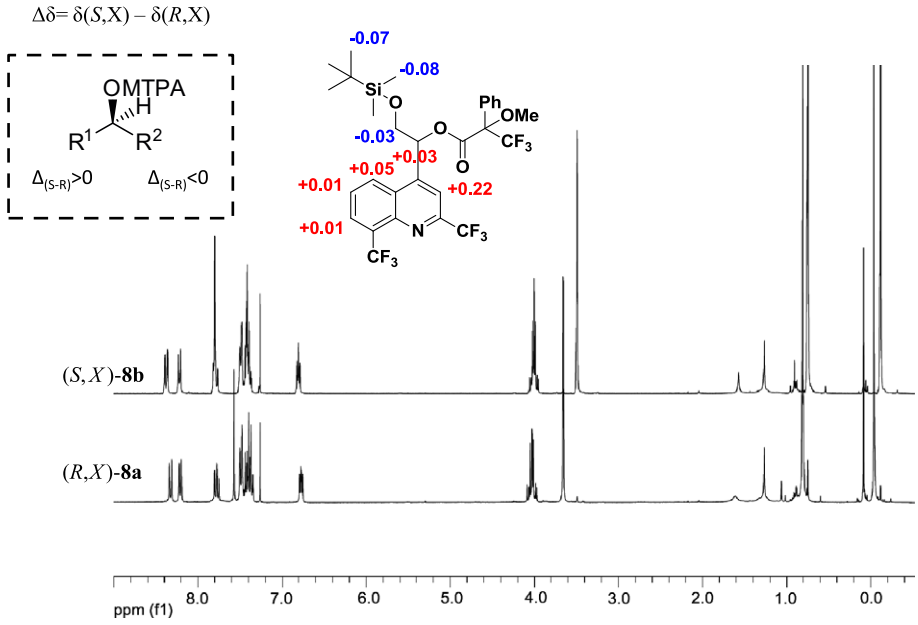
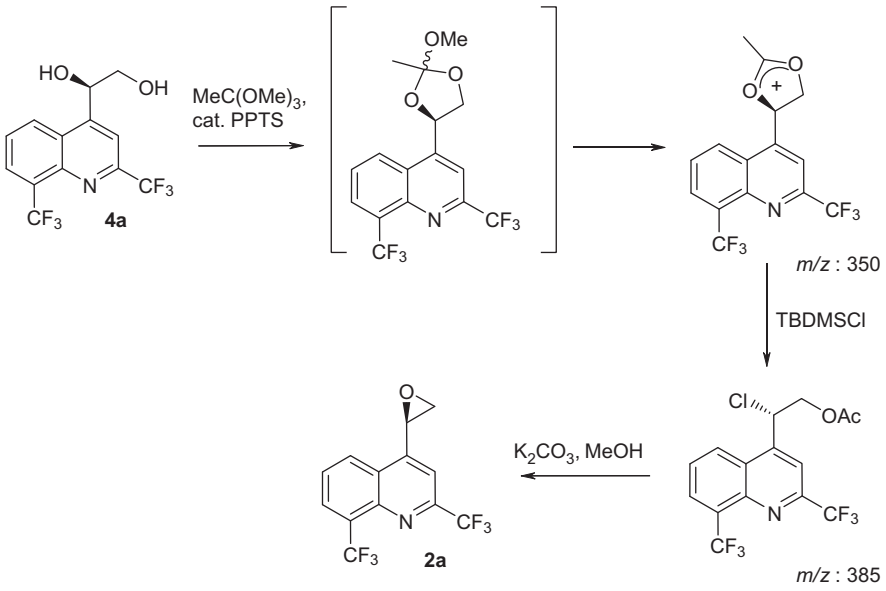


Figure 3. ^{1}H NMR analysis of the diastereomeric esters **8a** and **8b**.



Scheme 6. One-pot stereospecific conversion of the 1,2-diol **4a** into epoxide **2a** via a chlorhydrine ester.

volves two successive inversions at the same stereocenter: (i) inversion at the halide receiving stereocenter at the time of halohydrin ester formation and (ii) second inversion at the halide center during cyclization to the epoxide (Scheme 6).

All three operations have been carried out in one reaction vessel without isolation of any intermediates but each step was followed and validated by GCMS. Thus, the slightly modified Sharpless conditions applied to the conversion of diols **4a** and **4b** give the corresponding oxiranes **2a** and **2b** with retention of configuration according to the specific rotation of each compound (Table 3).

In order to confirm the structure and the absolute configuration of the synthesized quinoline epoxides **2**, X-ray studies for the two derivatives were performed. Unfortunately, suitable crystals were only obtained for compound (−)-**2a**. Its molecular structure, depicted in Figure 4, confirms the structure in the solid state as anticipated on the basis of IR and NMR data. Moreover, the configuration of (−)-**2a** was determined by observing and calculating the $F(+)/F(-)$ ratios of Bijvoet pairs using the mean F value of each independent reflection.[31] Based on these results, the absolute configuration at C-11 in (−)-**2a** is determined to be (*R*). Consequently, (−)-**2a** led us to consider that the (+)-enantiomer-**2b** should present the (*S*)-absolute configuration. Furthermore, these

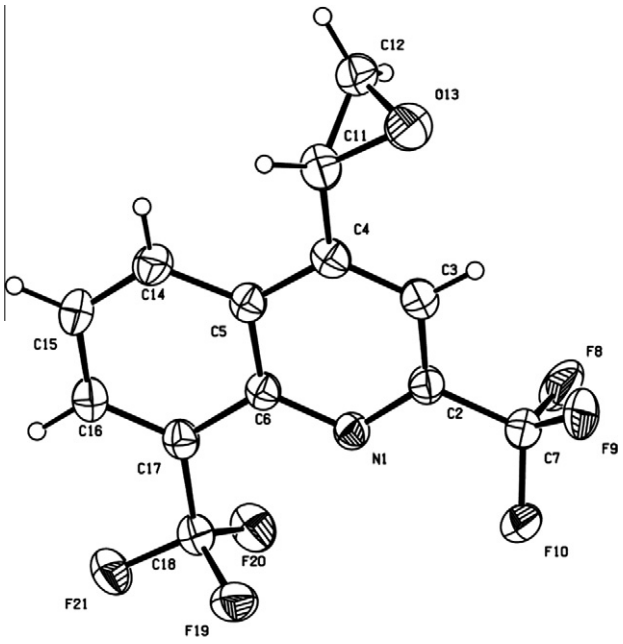
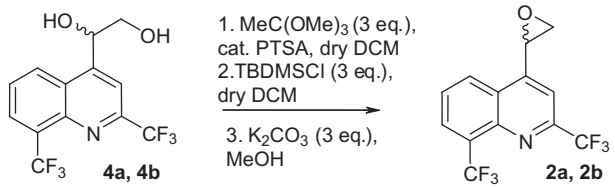


Figure 4. View of the crystal structure of (*R*)-**2a** with our numbering scheme; displacement ellipsoids are drawn at the 30% probability level.

Table 3
Substrate scope of enantioselective epoxidation



4	2	Yield (%)	ee[a] (%)	$[\alpha]_D^{20}$[b]	Absolute configuration[c]
a	**a**	68	92	−52	(*R*)
b	**b**	57	96	+45	(*S*)

[a] Enantiomeric excess was determined by GC.
[b] *c* 0.25, MeOH.
[c] Absolute configuration was determined with crystallographic epoxide spectra.

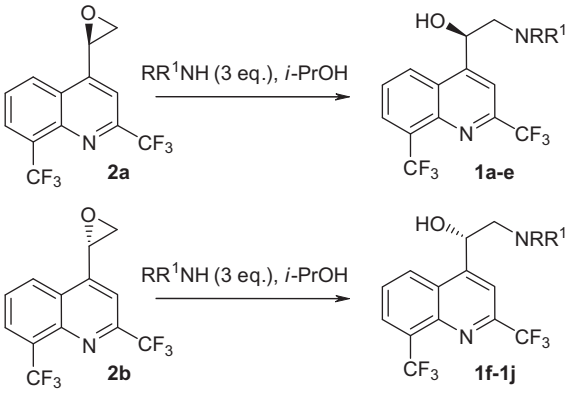
results indirectly confirm the stereochemistry of each (*R*)- or (*S*)-quinolin-4-yl-ethanediol precursors **4**.

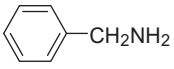
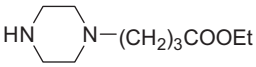
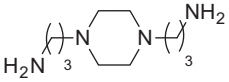
Finally, the treatment of oxirane **2a** or **2b** with diverse amines, in a regioselective S_N2 nucleophilic ring opening mechanism, provided the corresponding enantiopure 4-aminoquinolines **1a–e** (*R*) or **1f–j** (*S*) with good yield (35–96%) and ees that were generally superior to 92% (Table 4). No epimerization at the stereogenic carbon was observed, as determined by chiral HPLC analysis, using the opposite enantiomer as a standard.

3. Conclusion

Previous work by Milner et al.[12] described an exploratory 4-alcohol quinoline library meant to provide early-lead racemate

Table 4
(11*R*) Pure 4-aminoquinolines derivatives synthesis by regioselective S_N2 epoxyde opening



Entry	Substrate: RR_1NH	Product	Yield (%)	ee[a] (%)	$[\alpha]_D^T$	Absolute configuration[b]	t_R[c] (min)
1		**1a**	66	95	−34.5[d]	(*R*)	16.8
2		**1f**	89	98	+46.3[d]	(*S*)	18.9
3		**1b**	35	89	−70.7[e]	(*R*)	9.0
4		**1g**	38	97	+78.2[e]	(*S*)	20.1
5	*n*-$C_5H_{11}NH_2$	**1c**	88	94	−50.3[f]	(*R*)	21.5
6		**1h**	93	99	+49.8[f]	(*S*)	25.3
7	*n*-$C_6H_{13}NH_2$	**1d**	88	94	−47.5[f]	(*R*)	18.5
8		**1i**	85	98	+54.0[f]	(*S*)	21.4
9		**1e**	98	93	−49.6[e]	(*R*)	6.2
10		**1j**	82	92	+50.6[e]	(*S*)	7.2

[a] Enantiomeric excess was determined by Chiral HPLC.
[b] Absolute configuration was determined with epoxide crystallographic spectra.
[c] Retention time.
[d] *c* 0.25, DMSO.
[e] *c* 0.25, DCM.
[f] *c* 0.25, MeOH.

compounds. In this article we proposed an enantiopure, synthetic, and straightforward route to prepare 4-aminoquinolines derivatives through enantiopure 4-oxirane **2** synthesis. The preparation of **2** was carried out from 4-vinylquinoline **3** in two steps via a Sharpless asymmetric dihydroxylation with retention of configuration. The key-intermediate **2** has been easily diversified, on position 4, through a regioselective S_N2 ring opening mechanism with various amines, to provide the corresponding enantiopure 4-aminoquinolines **1a** (*R*) or **1b** (*S*) with good yield (35–96%) and ees generally superior to 92%. The antimalarial activity of these compounds will be tested in vitro and in vivo.

4. Experimental

4.1. General methods

All starting materials and reagents were obtained from commercial suppliers and were used without further purification. Reactions requiring anhydrous conditions were performed under a blanket of argon. All solvents were purified via literature procedures or used without further purification. Flash column chromatography was carried out on Kielselgel 60 (40–63 μm) ASTM (Merck). Routine monitoring of reactions was performed using Merck Silica Gel 60 F254 plates, thin layer chromatography (TLC) and visualized under UV light (254 nm), with ethanolic phosphomolybdic acid (PMA). Nuclear magnetic resonance (NMR) spectra were recorded using Bruker 600 MHz NMR instrument (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz) and Bruker 300 MHz NMR instrument (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz). Chemical shifts are expressed in parts per million (δ, ppm) downfield from tetramethylsilane and are referenced to the deuterated solvent. ^{1}H NMR and ^{13}C NMR data were reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet), integration, coupling constants in Hertz (Hz). High Performance Liquid Chromatography (HPLC) was carried out on a Schimadzu LC-20AD equipped with a Chiralpak IB column. Specific rotations were measured on a Jasco P1010 polarimeter. High-resolution mass spectra were obtained from a Micromass-Waters Q–TOF Ultima spectrometer. Infrared spectra were recorded with a Jasco FTIR-4200 and are reported using the frequency of absorption (cm^{-1}). Gas Chromatography–Mass Spectrometry (GCMS) was carried out on a Schimadzu GCMS-QP2010S equipped with a SLB-5 ms.

4.1.1. 4-Bromo-2,8-bis(trifluoromethyl)quinoline 6a

Phosphorous oxybromide (4 g, 14.2 mmol), under an argon atmosphere, was heated to 90 °C until complete dissolution of the solid. Compound **5** (4.08 g, 14.2 mmol) was added to this hot solution and the bath temperature was increased to 150 °C. After 6 h, the resulting mixture was allowed to cool to room temperature. The reaction mixture was quenched by addition of ice-cold water and the precipitate formed was filtered and washed with

water to afford the expected compound **6a** (4.70 g, 96%) as a white solid. R_f 0.79 (cyclohexane/Et_2O 5:1); mp: 60 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (t, J = 7.9 Hz, 1H), 8.11 (s, 1H), 8.22 (d, J = 7.3 Hz, 1H), 8.46 (d, J = 8.6 Hz, 1H), NMR data were in agreement with the lit.;[13] ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.9 (q, J = 276.0 Hz), 122.0 (q, J = 2.0 Hz), 123.6 (q, J = 273.8 Hz), 128.9, 129.4, 129.8 (q, J = 30.8 Hz), 130.5 (q, J = 5.3 Hz), 131.5, 138.5, 144.5, 148.6 (q, J = 36.1 Hz); IR ν_{max} = 1577, 1422, 1302, 1136, 1098, 1010, 876, 824 cm^{-1}; GCMS (m/z): 343; HRMS calcd for $C_{11}H_4BrF_6NNa$ $(M+Na)^+$ 365.9329, found 365.9346.

4.1.2. 2,8-Bis(trifluoromethyl)quinolin-4-yl trifluoromethanesulfonate 6b

To a solution of **5** (1.5 g, 5.34 mmol) in toluene/aqueous solution of LiOH (5%, w/v) (22 mL; 1:1, v/v) was added dropwise triflic anhydride (1.1 mL, 6.41 mmol), at 0 °C. The resulting mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was washed with water and the organic phase was dried over anhydrous sodium sulfate, and was concentrated under reduced pressure to afford **6b** (1.12 g, 50%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.95 (t, J = 8.0 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.4 (q, J = 1.7 Hz), 118.9 (q, J = 320.5 Hz), 120.4 (q, J = 275.5 Hz), 122.0 (q, J = 273.6 Hz), 125.1, 129.1(q, J = 27.3 Hz), 129.4, 130.8 (q, J = 5.0 Hz), 145.6, 149.4 (q, J = 36.8 Hz), 154.0.

4.1.3. 2,8-Bis(trifluoromethyl)quinolin-4-yl 4-methylbenzenesulfonate 6c

To a solution of **5** (500 mg, 1.78 mmol) in acetone (4 mL) was added an aqueous solution of NaOH 2 M until pH 11, and *p*-toluenesulfonyl chloride (680 mg, 3.56 mmol) at 0 °C. The reaction mixture was stirred overnight. After allowing warming to room temperature, the solvent was reduced under pressure. The resulting residue was washed with water and filtered to afford compound **6c** (746 mg, 96%) as a white solid. Mp: 107 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.95 (t, J = 7.9 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 109.4, 120.6 (q, J = 275.6 Hz), 123.2 (q, J = 273.8 Hz), 123.6, 126.1, 127.9, 130.0 (q, J = 5.2 Hz), 130.4, 131.4 (q, J = 3.9 Hz), 145.3, 147.0, 149.1 (q, J = 36.0 Hz), 154.6; HRMS calcd for $C_{18}H_{11}F_6NO_3SNa$ $(M+Na)^+$ 458.0262, found 458.0270.

4.1.4. 2,8-Bis(trifluoromethyl)-4-vinylquinoline 3

Method A: To a solution of **6a** (100 mg, 0.29 mmol), TBAB (93 mg, 0.29 mmol), K_2CO_3 (80 mg, 0.58 mmol), and $Pd(PPh_3)_2Cl_2$ (20 mg, 10 mol %) in dry MeCN (580 μL), was added tributylvinyltin (102 μL, 0.35 mmol), under an argon atmosphere. The tube was sealed and the mixture was stirred at 90 °C. After 4 h, the reaction was allowed to cool to room temperature then was filtered through a pad of Celite and washed with MeCN. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (cyclohexane/Et_2O 5:1) to afford **3** (64 mg, 75%) as a white solid. R_f 0.34 (cyclohexane/Et_2O 5:1); mp: 76 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dd, J = 11.1, 0.7 Hz, 1H), 6.09 (dd, J = 17.3, 0.7 Hz, 1H), 7.43 (dd, J = 17.3, 11.1 Hz, 1H), 7.72 (t, J = 7.9 Hz, 1H), 7.86 (s, 1H), 8.15 (d, J = 6.9 Hz, 1H), 8.33 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.1 (q, J = 2.1 Hz), 121.3 (q, J = 275.5 Hz), 123.2, 123.6 (q, J = 273.6 Hz), 127.0, 127.9, 127.8, 129.0 (q, J = 5.5 Hz), 129.2 (q, J = 30.5 Hz), 131.0, 144.0, 146.2, 148.4 (q, J = 35.6 Hz), NMR data were in agreement with the lit.;[12] IR ν_{max} = 1590, 1426, 1303, 1134, 1108, 888, 833 cm^{-1}; GCMS (m/z): 291; HRMS calcd for $C_{13}H_7F_6NNa$ $(M+Na)^+$ 314.0380, found 314.0390.

Method B: To a solution of **6a** (1.16 mmol) in toluene/aqueous solution of KOH (4 M) (9 mL; 8:1, v/v) was added dibutyl vinylboronate (1.28 mmol) and $Pd(PPh_3)_4$ (0.035 mmol), under nitrogen. The reaction mixture was stirred at reflux for 24 h. The reaction was allowed to cool to room temperature, transferred to a separating funnel, and then was washed with water (20 mL) and toluene (2 × 20 mL), the washings being added to the separating funnel. The organic layer was separated, washed with an aqueous 1 M NaOH solution, then with a brine solution, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography (cyclohexane/ether 5:1) to afford **3** (82%) as a white solid.

Method C: To a suspension of potassium vinyltrifluoroborate (1.16 mmol), cesium carbonate (3.5 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.116 mmol), and **6a** (1.16 mmol) in THF (15 mL) was added water (1.5 mL), under a nitrogen atmosphere. The reaction mixture was stirred at reflux for 24 h. The reaction was allowed to cool to room temperature, diluted with water (25 mL), and was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine and then dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/ether 5:1) to afford **3** (71%) as a white solid.

4.1.5. (*R*)-1-[2,8-Bis(trifluoromethyl)quinolin-4yl]ethane-1,2-diol 4a

To a solution of AD-mix-β (4.8 g) and $K_2OsO_2(OH)_4$ (12.7 mg, 1 mol %) in *t*-BuOH/H_2O (34.4 mL; 1:1 v/v) was added **3** (1 g, 3.44 mmol) at 0 °C and stirred overnight. The reaction was quenched at 0 °C by addition of Na_2SO_3 (5.16 g), then was warmed to room temperature and stirred for 30 min. The reaction mixture was extracted with EtOAc, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was precipitated in cyclohexane, filtered on Buchner to afford **4a** (945 mg, 84%, GCMS: 100%, and 98% ee) as a white solid. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH, 95:5; flow 1.0 mL/min, $t_R(R)$ = 26.8 min, $t_R(S)$ = 32.9 min); $[\alpha]_D^{20} = -52$ (c 0.25, DCM); mp: 130–135 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (dd, J = 11.6, 4.2 Hz, 1H), 3.89 (dd, J = 11.6, 5.2 Hz, 1H), 5.62 (dd, J = 5.9, 4.4 Hz, 1H), 7.83 (t, J = 7.9 Hz, 1H), 8.15 (s, 1H), 8.23 (d, J = 7.2 Hz, 1H), 8.54 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.9, 71.7, 116.3 (q, J = 2.1 Hz), 122.9 (q, J = 274.8 Hz), 125.1 (q, J = 272.8 Hz), 128.4, 129.3, 130.0 (q, J = 5.6 Hz), 130.1 (q, J = 29.7 Hz), 144.8, 149.2 (q, J = 34.9 Hz), 153.4; IR ν_{max} = 3266, 2937, 1605, 1587, 1308, 1128, 1102, 838 cm^{-1}; GCMS (m/z): 325; HRMS calcd for $C_{13}H_9F_6NO_2Na$ $(M+Na)^+$ 348.0435, found 348.0420.

4.1.6. (*S*)-1-[2,8-Bis(trifluoromethyl)quinolin-4yl]ethane-1,2-diol 4b

According to the same procedure for **4a**, the product **4b** was prepared starting from **3** (640 mg) to obtain **4b** (558 mg, 78%, 97% ee) as a white solid. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH, 95:5; flow 1.0 mL/min, $t_R(R)$ = 26.8 min, $t_R(S)$ = 31.8 min); mp: 130–135 °C; $[\alpha]_D^{20} = +62$ (c 0.25, DCM); ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (dd, J = 11.6, 4.2 Hz, 1H), 3.89 (dd, J = 11.6, 5.2 Hz, 1H), 5.62 (dd, J = 5.9, 4.4 Hz, 1H,), 7.83 (t, J = 7.9 Hz, 1H), 8.15 (s, 1H), 8.23 (d, J = 7.2 Hz, 1H), 8.54 (d, J = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.9, 71.7, 116.3 (q, J = 2.1 Hz), 122.9 (q, J = 274.8 Hz), 125.1 (q, J = 272.8 Hz), 128.4, 129.3, 130.0 (q, 1H, J = 5.6 Hz), 130.1 (q, J = 29.7 Hz), 144.8, 149.2 (q, J = 34.9 Hz), 153.4; IR ν_{max} = 3266, 2937, 1605, 1587, 1308, 1128, 1102, 838 cm^{-1}; GCMS (m/z): 325; HRMS calcd for $C_{13}H_9F_6NO_2Na$ $(M+Na)^+$ 348.0435, found 348.0440.

4.1.7. (*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethanol 7

To a solution of **4a** (140 mg, 0.43 mmol) in dry DMF (5 mL), under an argon atmosphere, were added TDBMSCl (64.8 mg, 0.43 mmol) and imidazole (29.2 mg, 0.43 mmol). The mixture was stirred at room temperature for 24 h. The solution was concentrated under reduced pressure, and then the residue was

dissolved in EtOAc and was washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (DCM/MeOH 99:1) to afford **7** (74 mg, 39%, 99% ee) as a colorless oil. HPLC analysis (Chiralpak IB column, heptanes/*i*-PrOH 99:1; flow 1 mL/min, $t_R(R)$ = 13.9 min, $t_R(S)$ = 16.6 min); $[\alpha]_D^{21} = -41.1$ (*c* 0.25, DCM); R_f 0.88 (DCM/MeOH 99:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 3.67 (dd, *J* = 10.3, 7.4 Hz, 1H), 4.03 (dd, *J* = 10.3, 3.7 Hz, 1H), 5.57 (dd, *J* = 7.2, 3.4 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 18.2, 25.8, 67.5, 70.3, 115.2 (q, *J* = 2.05 Hz), 121.3 (q, *J* = 275.1 Hz), 123.5 (q, *J* = 273.6 Hz), 126.8, 127.0, 127.2, 128.7 (q, *J* = 5.5 Hz), 129.2 (q, *J* = 32.7 Hz), 143.6, 148.5 (q, *J* = 36.8 Hz), 149.2; IR ν_{max} = 2956, 2932, 2861, 1604, 1586, 1431, 1308, 1144, 1108, 837, 807 cm^{-1}; HRMS calcd for $C_{19}H_{23}F_6NO_2SiNa$ $(M+Na)^+$ 462.1300, found 462.1320.

4.1.8. (*R*)-(*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8a

To a solution of **7** (43 mg, 0.098 mmol) in dry DCM (1 mL), under an argon atmosphere, were added at 0 °C (*R*)(+)-MTPA (27 mg, 0.12 mmol), EDCI (37.5 mg, 0.2 mmol), and DMAP (3.6 mg, 0.029 mmol). The mixture was stirred at room temperature for 24 h. The solution was concentrated under reduced pressure. The residue was purified by column chromatography (DCM/MeOH 99:1) to afford **8a** (38 mg, 58%, 95% ee) as a yellow oil. The ee was determined by ^{1}H NMR. $[\alpha]_D^{24} = -19.2$ (*c* 0.25, DCM); R_f 0.82 (DCM/MeOH 99:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.044 (s, 3H), −0.041 (s, 3H), 0.81 (s, 9H), 3.65 (d, *J* = 0.68 Hz, 3H), 3.99 (dd, *J* = 11.4, 4.0 Hz, 1H), 4.05 (dd, *J* = 11.4, 6.8 Hz, 1H), 6.77 (dd, *J* = 6.8, 4.0 Hz, 1H), 7.49–7.36 (m, 5H), 7.57 (s, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 8.21 (d, *J* = 7.2 Hz), 8.32 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.6 (2C), 18.1, 25.6, 55.8, 65.1, 74.3, 115.4 (q, *J* = 1.8 Hz), 120.9 (q, *J* = 275.6 Hz), 123.2 (q, *J* = 288.7 Hz), 123.4 (q, *J* = 273.7 Hz), 126.4, 126.9 (3C), 127.7, 128.6, 129.1 (q, *J* = 5.1 Hz), 129.7 (q, *J* = 30.4 Hz), 130.1, 131.7, 143.8, 145.0, 148.2 (q, *J* = 35.5 Hz), 165.9; IR ν_{max} = 2955, 2930, 2857, 1755, 1605, 1312, 1147, 1112, 1018, 837 cm^{-1}; HRMS calcd for $C_{29}H_{30}F_9NO_4SiNa$ $(M+Na)^+$ 678.1698, found 678.1688.

4.1.9. (*S*)-(*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-((*tert*-butyldimethylsilyl)oxy)ethyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8b

According to the same procedure for **8a**, the product **8b** was prepared starting from **7** (41 mg) to obtain **8b** (30 mg, 49%, 98% ee) as a yellow oil. The ee was determined by ^{1}H NMR. $[\alpha]_D^{24} = -36.7$ (*c* 0.25, DCM); R_f 0.82 (DCM/MeOH 99:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.12 (s, 3H), −0.11(s, 3H), 0.74 (s, 9H), 3.49 (d, *J* = 1.2 Hz, 3H), 3.98 (dd, *J* = 11.2, 4.6 Hz, 1H), 4.02 (dd, *J* = 11.1, 5.9 Hz, 1H), 6.80 (t, *J* = 5.19 Hz, 1H), 7.57–7.32 (m, 5H), 7.81–7.78 (m, 2H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.9, −5.8, 18.0, 25.5, 55.3, 65.0, 73.9, 115.8 (q, *J* = 1.9 Hz), 121.0 (q, *J* = 275.6 Hz), 123.3 (q, *J* = 289.0 Hz), 123.4 (q, *J* = 273.8 Hz), 126.5, 127.2, 127.4, 127.7, 128.6, 129.2 (q, *J* = 5.6 Hz), 129.7 (q, *J* = 30.7 Hz), 129.9, 131.4, 143.8, 145.4, 148.1 (q, *J* = 35.5 Hz), 165.9; IR ν_{max} = 2955, 2930, 2857, 1755, 1605, 1312, 1147, 1112, 1018, 837 cm^{-1}; HRMS calcd for $C_{29}H_{30}F_9NO_4SiNa$ $(M+Na)^+$ 678.1698, found 678.1688.

4.1.10. (*R*)-4-(Oxiran-2-yl)-2,8-bis(trifluoromethyl)quinoline 2a

To a solution of **4a** (800 mg, 0.62 mmol) in dry DCM (8.8 mL), under an argon atmosphere, were added trimethylorthoacetate (236 μL, 1.85 mmol) and PTSA (5.3 mg, 0.031 mmol). The mixture was stirred for 4 h at room temperature. The volatiles were removed in vacuo, and the flask pumped on high vacuum to remove excess MeOH. The residue was redissolved in dry DCM (8.8 mL), under argon, and was cooled to 0 °C. Trimethylsilyl chloride (234 μL, 1.85 mmol) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The volatiles were removed in vacuo, and the residue was redissolved in MeOH (8.8 mL). Then K_2CO_3 (254.8 mg, 1.85 mmol) was added, and the mixture was stirred for 5 h. The reaction was poured onto saturated aqueous solution of NH_4Cl, extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography (cyclohexane/Et_2O 1:1), to afford **2a** (513 mg, 68%, 92% ee) as a yellow solid. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH, 99:1; flow 1.0 mL/min, $t_R(S)$ = 15.1 min, $t_R(R)$ = 17.4 min); $[\alpha]_D^{20} = -52$ (*c* 0.25, DCM); R_f 0.36 (cyclohexane/Et_2O 1:1); mp: 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.42 (dd, *J* = 5.7, 4.2 Hz, 1H), 4.55 (dd, *J* = 3.6, 2.7 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): 49.2, 50.8, 113.3 (q, *J* = 2.0 Hz), 121.1 (q, *J* = 275.5 Hz), 123.4 (q, *J* = 273.6 Hz), 127.0, 127.4, 127.6, 129.1 (q, *J* = 5.5 Hz), 129.4 (q, *J* = 30.5 Hz), 143.3, 146.8, 148.7 (q, *J* = 35.5 Hz), 149.5, NMR data were in agreement with the lit.;[12] IR ν_{max} = 1606, 1587, 1431, 1308, 1276, 1213, 1102, 1069, 895, 982, 822 cm^{-1}; GCMS: 307; HRMS calcd for $C_{13}H_7F_6NONa$ $(M+Na)^+$, 330.0330, found 330.0314.

4.1.11. (*S*)-4-(Oxiran-2-yl)-2,8-bis(trifluoromethyl)quinoline 2b

According to the same procedure that **2a**, the product **2b** was prepared starting from **4b** (800 mg) to obtain **2b** (437 mg, 57%, 96% ee) as a yellow solid. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH, 99:1; flow 1.0 mL/min, $t_R(S)$ = 14.9 min, $t_R(R)$ = 17.4 min); $[\alpha]_D^{20} = +45$ (*c* 0.25, DCM); R_f 0.36 (cyclohexane/Et_2O 1:1); mp: 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.42 (dd, *J* = 5.7, 4.2 Hz, 1H), 4.55 (dd, *J* = 3.6, 2.7 Hz, 1H), 7.79 (m, 2H), 8.20 (d, *J* = 7.2 Hz, 1H), 8.39 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): 49.2, 50.8, 113.3 (q, *J* = 2.0 Hz), 121.1 (q, *J* = 275.5 Hz), 123.4 (q, *J* = 273.6 Hz), 127.0, 127.4, 127.6, 129.1 (q, *J* = 5.5 Hz), 129.4 (q, *J* = 30.5 Hz), 143.3, 146.8, 148.7 (q, *J* = 35.5 Hz), 149.5, NMR data were in agreement with the lit.;[12] IR ν_{max} = 1606, 1587, 1431, 1308, 1276, 1213, 1102, 1069, 895, 982, 822 cm^{-1}; GCMS: 307; HRMS calcd for $C_{13}H_7F_6NONa$ $(M+Na)^+$, 330.0330, found 330.0314.

4.2. General method for preparation of amino-alcohol 1

To a solution of **2a** or **2b** (50 mg, 0.16 mmol) in *i*-PrOH (3.2 mL) was added the appropriate amine (0.81 mmol). The mixture was stirred for 24 h at 90 °C. The volatiles were removed in vacuo. The crude was then purified by column chromatography.

4.2.1. (*R*)-2-(Benzylamino)-1-(2,8-bis(trifluoromethyl) quinolin-4-yl)ethanol 1a

The crude was purified by column chromatography (EtOAc/MeOH/NH_4OH 90:5:5), to afford **1a** (44 mg, 66%, 95% ee) as a white solid. HPLC analysis (Chiralpak IB column, heptane/EtOH, 90:10; flow 0.5 mL/min, $t_R(R)$ = 16.8 min, $t_R(S)$ = 18.9 min); $[\alpha]_D^{27} = -34.5$ (*c* 0.25, DMSO); R_f 0.78 (EtOAc/MeOH/NH_4OH 80:10:10); mp: 163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (dd, *J* = 12.4, 6.9 Hz, 1H), 2.88 (dd, *J* = 12.5, 3.9 Hz, 1H), 3.72, (s, 2H), 5.61 (m, 1H), 7.20 (m, 5H), 7.85 (t, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 8.32 (d, *J* = 7.3 Hz, 1H), 8.55 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 52.3, 55.4, 68.1, 114.7, 121.5 (q, *J* = 275.4 Hz), 123.3 (q, *J* = 273.1 Hz), 126.4, 126.7, 126.9 (q, *J* = 28.5 Hz), 127.4, 127.7, 127.9, 129.1, 129.4 (q, *J* = 5.5 Hz), 140.5, 142.5, 146.6 (q, *J* = 34.1 Hz), 155.0; IR ν_{max} = 1603, 1587, 1430, 1310, 1300, 1127, 1106, 903, 881, 835 cm^{-1}; HRMS calcd for $C_{20}H_{17}F_6N_2O$ $(M+H)^+$ 415.1245, found 415.1265.

4.2.2. (*S*)-2-(Benzylamino)-1-(2,8-bis(trifluoromethyl) quinolin-4-yl)ethanol 1f

The crude was purified by column chromatography (EtOAc/MeOH/NH_4OH 90:5:5), to afford **1f** (59 mg, 89%, 98% ee) as a white solid. HPLC analysis (Chiralpak IB column, heptane/EtOH, 90:10; flow 0.5 mL/min, $t_R(R)$ = 16.8 min, $t_R(S)$ = 18.9 min); $[\alpha]_D^{27} = +46.3$ (*c* 0.25, DMSO); R_f 0.78 (EtOAc/MeOH/NH_4OH 80:10:10); mp: 163 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.78 (dd, *J* = 12.4, 6.9 Hz, 1H), 2.88 (dd, *J* = 12.5, 3.9 Hz, 1H), 3.72, (s, 2H), 5.61 (m, 1H), 7.20 (m, 5H), 7.85 (t, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 8.32 (d, *J* = 7.3 Hz, 1H), 8.55 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 52.3, 55.4, 68.1, 114.7, 121.5 (q, *J* = 275.4 Hz), 123.3 (q, *J* = 273.1 Hz), 126.4, 126.7, 126.9 (q, *J* = 28.5 Hz), 127.4, 127.7, 127.9, 129.1, 129.4 (q, *J* = 5.5 Hz), 140.5, 142.5, 146.6 (q, *J* = 34.1 Hz), 155.0; IR ν_{max} = 1603, 1587, 1430, 1310, 1300, 1127, 1106, 903, 881, 835 cm^{-1}; HRMS calcd for $C_{20}H_{17}F_6N_2O$ $(M+H)^+$ 415.1245, found 415.1265.

4.2.3. (*R*)-Ethyl-4-(4-(2-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-(hydroxyethyl)piperazin-1-yl)butanoate 1b

The crude was purified by column chromatography (DCM/MeOH 90:10), to afford **1b** (29 mg, 35%, 89% ee) as a yellow oil. HPLC analysis (Chiralpak IB column, heptanes/*i*-PrOH/EDA 90:10:0.1; flow 1 mL/min, $t_R(R)$ = 9.0 min, $t_R(S)$ = 20.6 min); $[\alpha]_D^{24} = -70.7$ (*c* 0.25, DCM); R_f 0.43 (DCM/MeOH 90:10); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.88–1.78 (m, 2H), 2.85–2.26 (m, 14H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.54 (dd, *J* = 10.5, 3.2 Hz, 1H), 7.72 (t, *J* = 7.1 Hz, 1H), 8.12–8.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.1, 32.2, 53.0, 57.5, 60.3, 64.5, 65.1, 114.5 (q, *J* = 1.8 Hz), 121.2 (q, *J* = 275.6 Hz), 123.5 (q, *J* = 273.9), 126.6, 126.,7, 127.0, 128.7 (q, *J* = 5.2 Hz), 129.6 (q, *J* = 29.8 Hz), 143.6, 148.7 (q, *J* = 34.9 Hz), 151.1, 173.5; IR ν_{max} = 2941, 2818, 1731, 1604, 1585, 1430, 1308, 1140, 1108, 907 cm^{-1}; HRMS calcd for $C_{23}H_{28}F_6N_3O_3$ $(M+H)^+$ 508.2035, found 508.2056.

4.2.4. (*S*)-Ethyl-4-(4-(2-(2,8-bis(trifluoromethyl)quinolin-4-yl)-2-(hydroxyethyl)piperazin-1-yl)butanoate 1g

The crude was purified by column chromatography (DCM/MeOH 90:10), to afford **1g** (31 mg, 38%, 97% ee) as a yellow oil. HPLC analysis (Chiralpak IB column, heptanes/ *i*-PrOH/EDA 90:10:0.1; flow 1 mL/min, $t_R(R)$ = 9.1 min, $t_R(S)$ = 20.1 min); $[\alpha]_D^{23} = +78.2$ (*c* 0.25, DCM); R_f 0.43 (DCM/MeOH 90:10); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.88–1.78 (m, 2H), 2.85–2.26 (m, 14H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.54 (dd, *J* = 10.5, 3.2 Hz, 1H), 7.72 (t, *J* = 7.1 Hz, 1H), 8.12–8.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.1, 32.2, 53.0, 57.5, 60.3, 64.5, 65.1, 114.5 (q, *J* = 1.8 Hz), 121.2 (q, *J* = 275.6 Hz), 123.5 (q, *J* = 273.9), 126.6, 126.,7, 127.0, 128.7 (q, *J* = 5.2 Hz), 129.6 (q, *J* = 29.8 Hz), 143.6, 148.7 (q, *J* = 34.9 Hz), 151.1, 173.5; IR ν_{max} = 2941, 2818, 1731, 1604, 1585, 1430, 1308, 1140, 1108, 907 cm^{-1}; HRMS calcd for $C_{23}H_{28}F_6N_3O_3$ $(M+H)^+$ 508.2035, found 508.2056.

4.2.5. (*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentylamino)ethanol 1c

The crude was purified by column chromatography (DCM/MeOH 90:10), to afford **1c** (56 mg, 88%, 94% ee) as a white solid. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH/EDA, 99:1:0.1; flow 1 mL/min, $t_R(R)$ = 21.5 min, $t_R(S)$ = 25.3 min); $[\alpha]_D^{26} = -50.3$ (*c* 0.25, MeOH); R_f 0.53 (DCM/MeOH 90:10); mp: 120 °C; ^1H NMR (300 MHz, MeOD) δ 0.92 (t, *J* = 6.5 Hz, 3H), 1.36–1.21(m, 4H), 1.65–1.47 (m, 2H), 2.72–2.64 (m, 2H), 2.83 (dd, *J* = 12.30, 9.32 Hz, 1H), 2.99 (dd, *J* = 12.63, 2.20 Hz, 1H), 5.68 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.87 (t, *J* = 7.9 Hz, 1 Hz), 8.15 (s, 1H), 8.26 (d, *J* = 7.0 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) δ 14.4, 23.6, 30.2, 30.6, 50.5, 57.2, 69.4, 115.7 (q, *J* = 1.96 Hz), 122.9 (q, *J* = 274.6 Hz), 125.1 (q, *J* = 272.6 Hz), 128.0, 128.8, 129.1, 130.3 (q, *J* = 60.1 Hz), 130.3 (q, *J* = 5.7 Hz), 144.9, 149.4 (q, *J* = 34.8 Hz), 154.7; IR ν_{max} = 2934, 2841, 2357, 1604, 1586, 1432, 1303, 1119, 1104, 889, 835 cm^{-1}; HRMS calcd for $C_{18}H_{21}F_6N_2O$ $(M+H)^+$ 395.1558, found 395.1544.

4.2.6. (*S*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(pentylamino)ethanol 1h

The crude was purified by column chromatography (DCM/MeOH 90:10), to afford **1h** (56 mg, 93%, 99% ee) as a white solid. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH/EDA, 99:1:0.1; flow 1 mL/min, $t_R(R)$ = 22.2 min, $t_R(S)$ = 25.3 min); $[\alpha]_D^{26} = +49.8$ (*c* 0.25, MeOH); R_f 0.53 (DCM/MeOH 90:10); mp: 120 °C; ^1H NMR (300 MHz, MeOD) δ 0.92 (t, *J* = 6.5 Hz, 3H), 1.36–1.21(m, 4H), 1.65–1.47 (m, 2H), 2.72–2.64 (m, 2H), 2.83 (dd, *J* = 12.30, 9.32 Hz, 1H), 2.99 (dd, *J* = 12.63, 2.20 Hz, 1H), 5.68 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.87 (t, *J* = 7.9 Hz, 1 Hz), 8.15 (s, 1H), 8.26 (d, *J* = 7.0 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) δ 14.4, 23.6, 30.2, 30.6, 50.5, 57.2, 69.4, 115.7 (q, *J* = 1.96 Hz), 122.9 (q, *J* = 274.6 Hz), 125.1 (q, *J* = 272.6 Hz),128.0, 128.8, 129.1, 130.3 (q, *J* = 60.1 Hz), 130.3 (q, *J* = 5.7 Hz), 144.9, 149.4 (q, *J* = 34.8 Hz), 154.7; IR ν_{max} = 2934, 2841, 2357, 1604, 1586, 1432, 1303, 1119, 1104, 889, 835 cm^{-1}; HRMS calcd for $C_{18}H_{21}F_6N_2O$ $(M+H)^+$ 395.1558, found 395.1544.

4.2.7. (*R*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(hexylamino)ethanol 1d

The crude was purified by column chromatography (DCM/MeOH, 90:10), to afford **1d** (58 mg, 88%, 97% ee) as a white solide. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH/EDA, 99:1:0.1; flow 1 mL/min, $t_R(R)$ = 18.5 min, $t_R(S)$ = 21.4 min); $[\alpha]_D^{26} = -47.5$ (*c* 0.25, MeOH); R_f 0.58 (DCM/MeOH 90:10); mp: 108 °C; ^1H NMR (600 MHz, MeOD) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.43–1.42 (m, 6H), 1.62–1.49 (m, 2H), 2.76–2.59 (m, 2H), 2.82 (dd, *J* = 12.6, 9.1 Hz, 1H), 2.99 (dd, *J* = 12.6, 2.9 Hz, 1H), 5.68 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.88 (t, *J* = 7.2 Hz, 1H), 8.15 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.53 (d, *J* = 8.6 Hz); ^{13}C NMR (150 MHz, MeOD) δ 14.4, 23.7, 28.1, 30.5, 32.9, 50.5, 57.3, 69.4, 115.7 (q, *J* = 2.3 Hz), 122.9 (q, *J* = 274.4 Hz), 125.2 (q, *J* = 272.8 Hz), 128.0, 128.8, 129.1, 130.3 (q, *J* = 5.4 Hz), 130.3 (q, *J* = 30.3 Hz), 144.9, 149.4 (q, *J* = 35.8 Hz), 154.8; IR ν_{max} = 2928, 2858, 1603, 1586, 1432, 1304, 1119, 1103, 886, 837 cm^{-1}; HRMS calcd for $C_{19}H_{22}F_6N_2O$ $(M+H)^+$ 409.1726, found 409.1732.

4.2.8. (*S*)-1-(2,8-Bis(trifluoromethyl)quinolin-4-yl)-2-(hexylamino)ethanol 1i

The crude was purified by column chromatography (DCM/MeOH, 90:10), to afford **1f** (56 mg, 85%, 97% ee) as a white solide. HPLC analysis (Chiralpak IB column, heptane/*i*-PrOH/EDA, 99:1:0.1; flow 1 mL/min, $t_R(R)$ = 19.1 min, $t_R(S)$ = 21.4 min); $[\alpha]_D^{27} = +54.0$ (*c* 0.25, MeOH); R_f 0.58 (DCM/MeOH 90:10); mp: 108 °C; ^1H NMR (600 MHz, MeOD) δ 0.91 (t, *J* = 6.9 Hz, 3H), 1.43–1.42 (m, 6H), 1.62–1.49 (m, 2H), 2.76–2.59 (m, 2H), 2.82 (dd, *J* = 12.6, 9.1 Hz, 1H), 2.99 (dd, *J* = 12.6, 2.9 Hz, 1H), 5.68 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.88 (t, *J* = 7.2 Hz, 1H), 8.15 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.53 (d, *J* = 8.6 Hz); ^{13}C NMR (150 MHz, MeOD) δ 14.4, 23.7, 28.1, 30.5, 32.9, 50.5, 57.3, 69.4, 115.7 (q, *J* = 2.3 Hz), 122.9 (q, *J* = 274.4 Hz), 125.2 (q, *J* = 272.8 Hz), 128.0, 128.8, 129.1, 130.3 (q, *J* = 5.4 Hz), 130.3 (q, *J* = 30.3 Hz), 144.9, 149.4 (q, *J* = 35.8 Hz), 154.8; IR ν_{max} = 2928, 2858, 1603, 1586, 1432, 1304, 1119, 1103, 886, 837 cm^{-1}; HRMS calcd for $C_{19}H_{22}F_6N_2O$ $(M+H)^+$ 409.1726, found 409.1732.

4.2.9. (*R*)-*tert*-Butyl-(3-(4-(3((2-(2,8-bis(trifluoromethyl) quinolin-4-yl)-2-(hydroxyethyl)amino)propyl)piperazin-1-yl)propyl)carbamate 1e

The crude was purified by column chromatography (EtOAc/MeOH/NH_4OH, 80:10:10), to afford **1e** (88 mg, 90%, 93% ee) as a colorless oil. HPLC analysis (Chiralpak IB column, M*t*BE/EDA 100:0.3; flow 1 mL/min, $t_R(R)$ = 6.2 min, $t_R(S)$ = 7.2 min); $[\alpha]_D^{24} = -49.6$

(*c* 0.25, DCM); R_f 0.29 (EtOAc/MeOH/NH_4OH 80:10:10); ^1H NMR (300 MHz, MeOD) δ 1.38 (s, 9H), 1.64–1.59 (m, 2H), 1.67 (dt, J = 13.40, 6.76 Hz, 2H), 2.51–2.24 (m, 12H), 2.85–2.57 (m, 2H), 2.72 (dd, J = 12.41, 9.11 Hz, 1H), 3.05 (dd, J = 12.51, 2.77 Hz, 1H), 3.11 (m, 1H), 5.52 (dd, J = 8.4, 2.1 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 8.11–8.09 (m, 2H), 8.23 (d, J = 8.5 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) δ 26.2, 26.5, 28.3, 39.8, 48.0, 52.8, 53.2, 55.8, 56.5, 56.6, 67.7, 78.8, 114.5 (q, J = 1.6 Hz), 121.2 (q, J = 275.6 Hz), 123.4 (q, J = 273.8 Hz), 126.5, 126.9, 127.0, 128.6 (q, J = 5.6 Hz), 129.3 (q, J = 29.9 Hz), 143.5, 148.4 (q, J = 35.5 Hz), 152.0, 156.1; IR ν_{max} = 2940, 1433, 1307, 1132, 1104, 885, 838 cm^{-1}; HRMS calcd for $C_{28}H_{40}F_6N_5O_3$ $(M+H)^+$ 608.3035, found 608.3035.

4.2.10. (*S*)-*tert*-Butyl-(3-(4-(3((2-(2,8-bis(trifluoromethyl) quinolin-4-yl)-2-(hydroxyethyl)amino)propyl)piperazin-1-yl) propyl)carbamate 1j

The crude was purified by column chromatography (EtOAc/MeOH/NH_4OH, 80:10:10), to afford **1j** (96 mg, 98%, 92% ee) as a colorless oil. HPLC analysis (Chiralpak IB column, M*t*BE/EDA 100:0.3; flow 1 mL/min, $t_R(R)$ = 6.2 min, $t_R(S)$ = 7.2 min); $[\alpha]_D^{24} = +50.6$ (*c* 0.25, DCM); R_f 0.29 (EtOAc/MeOH/NH_4OH 80:10:10); ^1H NMR (300 MHz, MeOD) δ 1.38 (s, 9H), 1.64–1.59 (m, 2H), 1.67 (dt, J = 13.40, 6.76 Hz, 2H), 2.51–2.24 (m, 12H), 2.85–2.57 (m, 2H), 2.72 (dd, J = 12.41, 9.11 Hz, 1H), 3.05 (dd, J = 12.51, 2.77 Hz, 1H), 3.11 (m, 1H), 5.52 (dd, J = 8.4, 2.1 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 8.11–8.09 (m, 2H), 8.23 (d, J = 8.5 Hz, 1H); ^{13}C NMR (150 MHz, MeOD) δ 26.2, 26.5, 28.3, 39.8, 48.0, 52.8, 53.2, 55.8, 56.5, 56.6, 67.7, 78.8, 114.5 (q, J = 1.6 Hz), 121.2 (q, J = 275.6 Hz), 123.4 (q, J = 273.8 Hz), 126.5, 126.9, 127.0, 128.6 (q, J = 5.6 Hz), 129.3 (q, J = 29.9 Hz), 143.5, 148.4 (q, J = 35.5 Hz), 152.0, 156.1; IR ν_{max} = 2940, 1433, 1307, 1132, 1104, 885, 838 cm^{-1}; HRMS calcd for $C_{28}H_{40}F_6N_5O_3$ $(M+H)^+$ 608.3035, found 608.3035.

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31. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-780365. Copies of the data can be obtained free of charge on application to CCDC, University Chemical Lab, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: int. code +44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk.