Tetrahedron 71 (2015) 4738–4744

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novozyme 435 lipase mediated enantioselective kinetic resolution: a facile method for the synthesis of chiral tetrahydroquinolin-4-ol and tetrahydro-1*H*-benzo[*b*]azepin-5-ol derivatives

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ARTICLE INFO

Article history:
Received 7 April 2015
Received in revised form 16 May 2015
Accepted 18 May 2015
Available online 22 May 2015

Keywords:
Novozyme 435 lipase
Kinetic resolution
Biocatalytic processes
Tetrahydroquinolin-4-ol
Tetrahydro-1*H*-benzo[*b*]azepin-5-ol

ABSTRACT

Vinyl 2-chloroacetate was used as an efficient acyl donor for enantioselective acylation of racemic 1,2,3,4-tetrahydroquinolin-4-ols and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols with Novozyme 435 lipase. Two enantiocomplimentary tetrahydroquinolin-4-ol or tetrahydro-1*H*-benzo[*b*]azepin-5-ol derivatives could be smoothly obtained in good to excellent yields and ee values at the same time. Noteworthily, large scale preparation experiment was also demonstrated when amplified the reaction system to 10 g scale experiment, and products were obtained with high yields and ee values.

1. Introduction

Chiral benzylic alcohols and their derivatives are important building blocks for the synthesis of chemical materials, pharmaceuticals, and agrochemicals, which can be attributed to hydroxyl group could be readily converted to versatile intermediates.[1] Among these, enantiopure tetrahydroquinolin-4-ols and tetrahydro-1*H*-benzo[*b*]azepin-5-ols are attractive targets due to their promising biological activities and wide-ranging use as synthetic intermediates for drug candidates.[2] Accordingly, there has been a powerful inner impetus to quest efficient routes to this type of fascinating structures.

In the last few years, different methodologies for the synthesis of 1,2,3,4-tetrahydroquinolin-4-ols and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols have been established.[3–7] However, these strategies mainly rely on the chemical synthesis methods, and most of studies mainly focused on the synthesis of these two classes of compounds in their racemic form. In contrast, the methodologies to access chiral 1,2,3,4-tetrahydroquinolin-4-ols and 2,3,4,5-tetrahydro-1*H*-benzo-[*b*]azepin-5-ols are still limited.[2a,3,4a,4c] Meanwhile, from the view point of intended side-effects and pharmacological activities, pharmaceutical compounds having an asymmetric centre in the molecular are usually appropriate to be used in their optically active form instead of in racemic form. Therefore, it is much desired to develop novel and efficient methods for the synthesis of optically active 1,2,3,4-tetrahydroquinolin-4-ols and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols.

Biocatalytic processes have been intensely studied and have become a useful and green alternative in stereoselective synthesis due to their multiple advantages.[8] Among them, lipase mediated kinetic resolution has been broadly applied in the synthesis of chiral benzylic alcohol derivatives.[2a,9] Noteworthily, the biocatalytic kinetic resolution of racemic *N*-Ts-substituted 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ol was reported by Matsubara and co-workers.[2a] However, there were no examples of highly enantioselective and efficient synthesis of chiral 1,2,3,4-tetrahydroquinolin-4-ols and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols via the enzymatic process except for only one transformation of *N*-substituted-1,2,3,4-tetrahydroquinoline into corresponding benzyl alcohol with 5.4–9.4% yield and unknown ee using the fungus *Cunninghamella elegans*.[10] Moreover, even though we have discovered that *Pseudomonas plecoglossicidas* ZMU-T02 and ZMU-T06 could smoothly catalyzed the reaction for synthesis of (*R*)-1,2,3,4-tetrahydroquinolin-4-ol and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ol with 82% yield in 99% ee and 99% yield in 98% ee, respectively, the substrate concentration (2 mM) and substrate scope were also the main bottle neck for practical preparation.[11]

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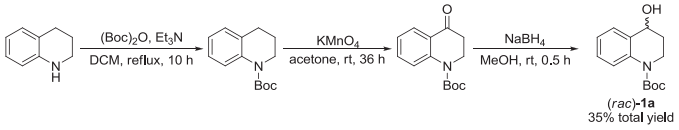
http://dx.doi.org/10.1016/j.tet.2015.05.066
0040-4020/

In this context, as a continuation of our studies on the enzymatic reactions,[11,12] we found that (*rac*)-*N*-Boc-1,2,3,4-tetrahydro quinolin-4-ol (**1a**) could be chosen as a suitable substrate for the lipase mediated enantioselective kinetic resolution, which was easily synthesized from 1,2,3,4-tetrahydroquinoline. Protection of the N–H group of 1,2,3,4-tetrahydroquinoline followed by oxidation and reduction gave (*rac*)-**1a** in 35% total yield (Scheme 1).[13] Moreover, a series of enantiocomplimentary 1,2,3,4-tetrahydro quinolin-4-ols, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols, and the corresponding esters can be obtained in excellent results with Novozyme 435 as biocatalyst and vinyl 2-chloroacetate as a novel acyl donor via highly enantioselective acylation process. It is worthwhile to note that this work represents the first example regarding vinyl 2-chloroacetate serving as highly efficient acyl donor for biocatalytic asymmetric transformation. Herein, we wish to report the results of our endeavours on this subject.



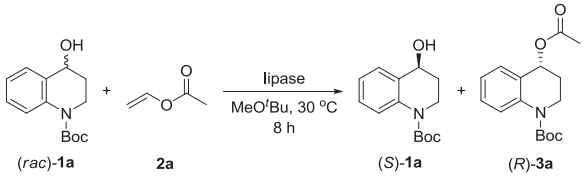
Scheme 1. Synthesis of (*rac*)-**1a**.

2. Results and discussion

Our initial studies started with the reaction of compound (*rac*)-**1a** and vinyl acetate (**2a**) in MeO^{t}Bu at 30 °C for the screening of a series of lipases (Table 1). There is no activity with the substrate (*rac*)-**1a** in the presence of Amano Type VII (Table 1, entry 1). When the reaction was performed using CAL-A as biocatalyst, the (*rac*)-**1a** was completely transformed into the racemic ester **3a** (Table 1, entry 2). Further investigations into several other lipases, including Amano lipase A, Novozyme 435, lipase RM IM, and lipase TL IM, revealed that (*S*)-**1a** and (*R*)-**3a** could be obtained in good to excellent results (Table 1, entries 3–6). Particularly, the lipase Novozyme 435 provided the highest enantioselectivity (98% and 97% ee, >200 *E* value) for the (*S*)-**1a** and (*R*)-**3a** (Table 1, entry 4).

Encouraged by these excellent results, we employed Novozyme 435 as biocatalyst to investigate the influence of various acyl donors on the activity and enantioselectivity of the resolution of (*rac*)-**1a** (Table 2). This decision was also based on the wide application of Novozyme 435 as biocatalyst for kinetic resolution and dynamic kinetic resolution of amines[15] and alcohols.[9b-e,15a,16] As shown in Table 2, it was found that the reactions were proceed smoothly to offer the desired compounds (*S*)-**1a** and (*R*)-**3a**–**c** in good conversions with excellent enantioselectivities using **2a**–**c** as acyl donors (Table 2, entries 1–3), but the acyl donors **2d** and **2e** gave poor ee for (*S*)-**1a** (Table 2, entries 4 and 5). To our great surprise, the enantioselective acylation could not occur when the R group of acyl donor was ^{t}Bu, which may be attributed to the steric effect (Table 2, entry 6). Undoubtedly, **2b** was selected as the best acyl donor to be applied in the following studies in terms of the enantiomeric ratio (>200 *E* value) and ee (99% and 99%) for the (*S*)-**1a** and (*R*)-**3b** (Table 2, entry 2).

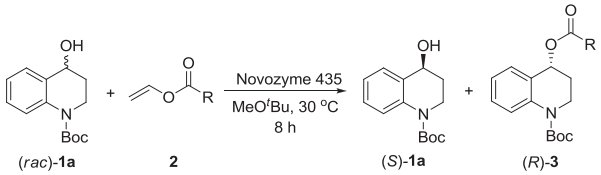
Table 1
Lipase-catalyzed acetylation of racemic **1a** with vinyl acetate[a]



Entry	Lipase	ee (%)[b]		c (%)[c]	E[d]
		(*S*)-**1a**	(*R*)-**3a**		
1	Amano Type VII	—	—	—	—
2[e]	CAL-A	—	0	100	—
3	Amano lipase A	53	99	35	>200
4	Novozyme 435	98	97	50	>200
5	lipase RM IM	58	99	37	>200
6	lipase TL IM	99	48	67	13

[a] Unless otherwise noted, the reaction mixtures of racemic **1a** (0.05 mmol, 12.5 mg), vinyl acetate **2a** (0.25 mmol, 23.0 μL) and lipase (5.0 mg) in 0.5 mL MeO^{t}Bu were shaken in orbital shaker at 300 rpm at 30 °C for 8 h.
[b] Determined by HPLC analysis.
[c] Conversion: $c=ee_S/(ee_S+ee_P)$.[14]
[d] $E=\{\ln[ee_P(1-ee_S)]/(ee_P+ee_S)\}/\{\ln[ee_P(1+ee_S)]/(ee_P+ee_S)\}$.[14]
[e] The (*rac*)-**1a** was completely transformed into the racemic ester **3a**.

Table 2
Evaluation of acyl donors of enantioselective acylation of racemic **1a**[a]



2a: R = Me
2b: R = 2-chloromethyl
2c: R = -(CH$_2$)$_5$CO$_2$CH=CH$_2$
2d: R = *n*-pentyl
2e: R = -(CH$_2$)$_9$CH$_3$
2f: R = ^{t}Bu

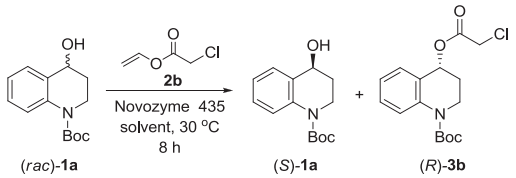
Entry	2	ee (%)[b]		c (%)[c]	E[d]
		(*S*)-**1a**	(*R*)-**3**		
1	**2a**	98	(*R*)-**3a**/97	50	>200
2	**2b**	99	(*R*)-**3b**/99	50	>200
3	**2c**	71	(*R*)-**3c**/99	42	>200
4	**2d**	23	(*R*)-**3d**/99	19	>200
5	**2e**	20	(*R*)-**3e**/99	17	>200
6	**2f**	—	—	—	—

[a] Unless otherwise noted, the reaction mixtures of racemic **1a** (0.05 mmol, 12.5 mg), **2** (0.25 mmol) and Novozyme 435 (5.0 mg) in 0.5 mL MeO^{t}Bu were shaken in orbital shaker at 300 rpm at 30 °C for 8 h.
[b] Determined by HPLC analysis.
[c] Conversion: $c=ee_S/(ee_S+ee_P)$.
[d] $E=\{\ln[ee_P(1-ee_S)]/(ee_P+ee_S)\}/\{\ln[ee_P(1+ee_S)]/(ee_P+ee_S)\}$.

To further optimize the reaction efficiency, various solvents were then examined. As shown in Table 3, kinetic resolution of racemic **1a** run in (^{i}Pr)$_2$O and CH$_3$CN gave the similar results as that performed in MeO^{t}Bu (Table 3, entries 2 and 3 vs entry 1). However, (*S*)-**1a** was obtained with dramatically decreased enantioselectivity using toluene and *n*-hexane as solvents, though both of the enantioselectivities of the ester (*R*)-**3b** were excellent (Table 3, entries 4 and 5). Moreover, the target compounds were not obtained with added water under the reaction conditions (Table 3, entry 6). Additionally, the probe into the concentration effects of Novozyme 435 revealed that a low concentration did lead to an obvious decrease in enantioselectivity and conversion (Table 3, entry 7). Thus, the above studies provided the optimal reaction conditions: the reaction mixtures of racemic **1a** (0.05 mmol), vinyl 2-chloroacetate **2b** (0.25 mmol) and Novozyme 435 (5.0 mg) in 0.5 mL MeO^{t}Bu were shaken at 300 rpm at 30 °C for 8 h (Table 3, entry 1).

After the establishment of the optimal conditions (Table 3, entry 1), substrate scope of Novozyme 435-mediated enantioselective acylation of racemic **1** was explored. As shown in Table 4, for the substrate racemic **1**, whether the substituent group is electron–deficient or –rich on the phenyl ring, the reactions proceeded smoothly and gave the corresponding alcohols (*S*)-**1b**–**d** and esters (*R*)-**3f**–**h** in excellent results (up to 48% yield, >99% ee, and >200 *E*

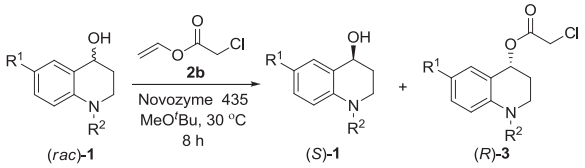
Table 3
Screening of solvents for Novozyme 435 catalyzed enantioselective acylation of racemic **1a**[a]



Entry	Solvent	ee (%)[b]		c (%)[c]	E[d]
		(S)-**1a**	(R)-**3b**		
1	MeO^{t}Bu	99	99	50	>200
2	(^{i}Pr)$_2$O	99	95	51	>200
3	CH_3CN	92	99	48	>200
4	Toluene	78	99	44	>200
5	*n*-Hexane	33	99	25	>200
6[e]	MeO^{t}Bu	—	—	—	—
7[f]	MeO^{t}Bu	73	99	42	>200

[a] Unless otherwise noted, the reaction mixtures of racemic **1a** (0.05 mmol, 12.5 mg), vinyl 2-chloroacetate **2b** (0.25 mmol, 25.3 μL) and Novozyme 435 (5.0 mg) in 0.5 mL solvent were shaken in orbital shaker at 300 rpm at 30 °C for 8 h.
[b] Determined by HPLC analysis.
[c] Conversion: c=ee$_S$/(ee$_S$+ee$_P$).
[d] E={ln[ee$_P$(1−ee$_S$)]/(ee$_P$+ee$_S$)}/{ln[ee$_P$(1+ee$_S$)]/(ee$_P$+ee$_S$)}.
[e] Water (0.55 mmol, 10.0 μL) was used.
[f] Novozyme 435 (2.0 mg) was used.

Table 4
Substrate scope of Novozyme 435-mediated enantioselective acylation of racemic **1a**–**k**[a]



1a: R^1 = H, R^2 = Boc
1b: R^1 = Cl, R^2 = Boc
1c: R^1 = Br, R^2 = Boc
1d: R^1 = OMe, R^2 = Ac
1e: R^1 = H, R^2 = CO_2Ph
1f: R^1 = H, R^2 = Cbz
1g: R^1 = H, R^2 = Ac
1h: R^1 = H, R^2 = Bz
1i: R^1 = H, R^2 = 2-furoyl
1j: R^1 = H, R^2 = SO_2Ph
1k: R^1 = H, R^2 = Bn

Entry	(*Rac*)-**1**	(*S*)-**1**/Yield (%)[b]/ee (%)[c]	(*R*)-**3**/Yield (%)[b]/ee (%)[c]	E[d]
1	**1a**	(*S*)-**1a**/45/94	(*R*)-**3b**/42/99	>200
2	**1b**	(*S*)-**1b**/48/98	(*R*)-**3f**/42/>99	>200
3	**1c**	(*S*)-**1c**/29/>99	(*R*)-**3g**/47/96	>200
4	**1d**	(*S*)-**1d**/38/>99	(*R*)-**3h**/42/92	126
5	**1e**	(*S*)-**1e**/46/96	(*R*)-**3i**/43/94	127
6	**1f**	(*S*)-**1f**/35/95	(*R*)-**3j**/37/>99	>200
7	**1g**	(*S*)-**1g**/44/>99	(*R*)-**3k**/40/95	>200
8	**1h**	(*S*)-**1h**/34/>99	(*R*)-**3l**/49/97	>200
9	**1i**	(*S*)-**1i**/40/99	(*R*)-**3m**/46/99	>200
10	**1j**	(*S*)-**1j**/34/>99	(*R*)-**3n**/40/>99	>200
11[e]	**1k**	(*S*)-**1k**/nr/—	(*R*)-**3o**/nr/—	—

[a] Unless otherwise noted, reaction mixtures of racemic **1** (5.00 mmol), vinyl 2-chloroacetate **2b** (25.00 mmol) and Novozyme 435 (0.50 g) in MeO^{t}Bu (50 mL) were shaken in orbital shaker at 300 rpm at 30 °C for 8 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] E={ln[ee$_P$(1−ee$_S$)]/(ee$_P$+ee$_S$)}/{ln[ee$_P$(1+ee$_S$)]/(ee$_P$+ee$_S$)}.
[e] Run for 24 h nr=No reaction.

value) (Table 4, entries 2–4). On the other hand, upon changing the protected group of *N*1 to other groups, such as CO_2Ph, Cbz, Ac, Bz, furoyl, and SO_2Ph, the corresponding reaction also provided the expected products in up to 49% yield with up to >99% ee and >200 *E* value (Table 4, entries 5–10). However, substrate **1k** bearing benzyl group at the *N*1 position did not provide the desired products under the standard conditions (Table 4, entry 11).

It was noteworthy that single crystal suitable for X-ray crystallographic analysis was fortunately obtained from optically pure **3j**. As shown in Fig. 1, it was determined as (*R*) configuration.[17] So it was natural that the absolute configuration of compound **1f** could be assigned as (*S*) configuration according to the absolute configuration of compound **3j**. The stereochemistry of other products in this work was assigned by analogy.

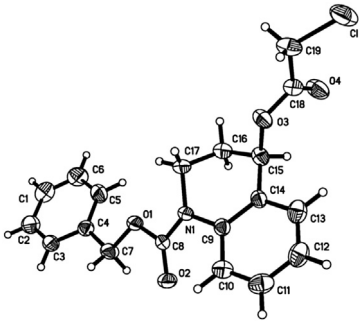
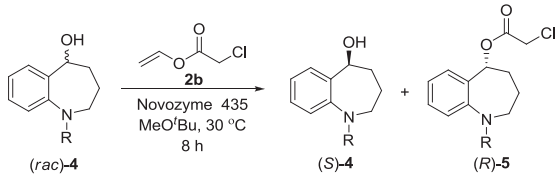


Fig. 1. X-ray crystallographic structure of optically pure **3j**.

The excellent results of enantioselective acylation of racemic 1,2,3,4-tetrahydroquinolin-4-ols (*rac*)-**1** mediated by the lipase Novozyme 435 (Table 4) prompted us to test another chiral resolution with respect to the racemic 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols (*rac*)-**4** by using the previously optimized reaction conditions (Table 3, entry 1),[18] and the results were summarized in Table 5. Different substitutions on the *N*1 position of the racemic **4**, such as Bz, 2-furoyl and Cbz, were all well tolerated to smoothly supply the corresponding alcohols (*S*)-**4** and esters (*R*)-**5** in excellent yields (up to 44%) with enantioselectivities (up to 98% ee and >200 *E* value) (Table 5, entries 1–3).

Table 5
Substrate scope of Novozyme 435-mediated enantioselective acylation of racemic **4a**–**c**[a]

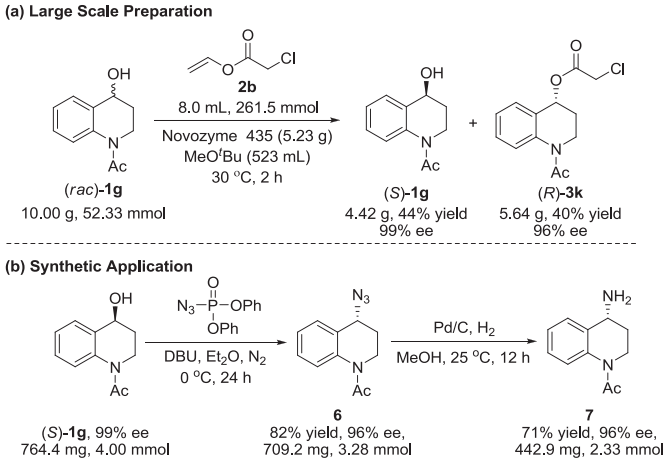


4a: R = Bz
4b: R = 2-furoyl
4c: R = Cbz

Entry	(*Rac*)-**4**	(*S*)-**4**/Yield (%)[b]/ee (%)[c]	(*R*)-**5**/Yield (%)[b]/ee (%)[c]	E[d]
1	**4a**	(*S*)-**4a**/40/98	(*R*)-**5a**/42/97	>200
2	**4b**	(*S*)-**4b**/39/96	(*R*)-**5b**/43/98	>200
3	**4c**	(*S*)-**4c**/44/90	(*R*)-**5c**/41/93	85

[a] Unless otherwise noted, reaction mixtures of racemic **4** (0.50 mmol), vinyl 2-chloroacetate **2b** (2.50 mmol) and Novozyme 435 (0.05 g) in MeO^{t}Bu (5 mL) were shaken in orbital shaker at 300 rpm at 30 °C for 8 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] E={ln[ee$_P$(1−ee$_S$)]/(ee$_P$+ee$_S$)}/{ln[ee$_P$(1+ee$_S$)]/(ee$_P$+ee$_S$)}.

To evaluate the practicability of the above methodology, the enantioselective acylation process of the racemic compound **1g** was conducted on a large more than tenfold scale with the lipase Novozyme 435 as biocatalyst. As outlined in Scheme 2, the 10 g-scale enantioselective acylation proceeded smoothly to afford the corresponding products (*S*)-**1g** and (*R*)-**3k** in the same isolated yields almost without any loss of enantioselectivities (Scheme 2, a).



Scheme 2. Large scale experiment and the transformation of (*S*)-**1g** to chiral amine **7**.

Additionally, the enantioenriched secondary alcohol (*S*)-**1g** could be transformed to (*R*)-1,2,3,4-tetrahydroquinolin-4-amine **7** with a complete inversion of stereochemistry in 58% total yield with 96% ee by treatment with diphenyl phosphorazidate, and followed by catalytic hydrogenation (Scheme 2, b).

3. Conclusion

In summary, we have developed a practical and efficient methodology for the construction of enantiocomplimentary 1,2,3,4-tetrahydroquinolin-4-ols, 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols and its corresponding esters through kinetic resolution. With the Novozyme 435 as efficient biocatalyst and vinyl 2-chloroacetate as a novel acyl donor, the enantioselective acylation of the racemic 1,2,3,4-tetrahydroquinolin-4-ols and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ols proceeded smoothly to give the corresponding chiral alcohols and esters in high yields with excellent enantioselectivities (up to 49% yield, >99% ee, and >200 E value). Furthermore, the usefulness of this protocol was demonstrated by the investigation into the 10 g-scale enantioselective acylation of the racemic 1,2,3,4-tetrahydroquinolin-4-ol, as well as the transformation of the chiral 1,2,3,4-tetrahydroquinolin-4-ol into chiral 1,2,3,4-tetrahydroquinolin-4-amine. Further biological evaluation of chiral tetrahydroquinolin-4-ol and tetrahydro-1*H*-benzo[*b*]azepin-5-ol derivatives are currently underway in our laboratory.

4. Experimental section

4.1. General

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were recorded in $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, DMSO-d_6 at 39.51 ppm).

4.2. Representative procedure for the synthesis of (*S*)-1,2,3,4-tetrahydroquinolin-4-ol (1) and (*R*)-1,2,3,4-tetrahydroquinolin-4-yl 2-chloroacetate (3)

To a solution of (*rac*)-1,2,3,4-tetrahydroquinolin-4-ol (**1**) (5.00 mmol, 1 equiv) in 50 mL MeO^{t}Bu, vinyl 2-chloroacetate (25.00 mmol, 5 equiv) and Novozyme 435 (0.50 g) were consecutively added. The reaction mixture was shaken in orbital shaker at 300 rpm at 30 °C for 8 h. After that, the mixture was filtered and concentrated, and the residue was purified by column chromatography (EtOAc/petroleum=1:5) to give (*S*)-**1** and (*R*)-**3**, respectively.

*4.2.1. (S)-tert-Butyl 4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (**1a**).* Gray solid, yield 45%; 94% *ee*, $[\alpha]_D^{25}$ −24.1 (*c* 1.00, $CHCl_3$); mp 129.1–130.8 °C. HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=95/5; 0.3 mL/min, λ=254 nm; t_{minor}=35.0 min, t_{major}=32.2 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63 (d, *J*=8.1 Hz, 1H), 7.35 (d, *J*=6.6 Hz, 1H), 7.20–7.15 (m, 1H), 7.06–7.00 (m, 1H), 5.36 (s, 1H), 4.56 (s, 1H), 3.83–3.76 (m, 1H), 3.60–3.53 (m, 1H), 1.98–1.93 (m, 1H), 1.80–1.76 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 152.9, 137.1, 132.5, 127.8, 126.7, 122.9, 122.7, 80.2, 64.1, 40.9, 32.1, 27.9; HRMS (ESI-TOF): calcd for $C_{14}H_{19}NNaO_3$ $[M+Na]^+$, 272.1257; found: 272.1269.

*4.2.2. (R)-tert-Butyl 4-(2-chloroacetoxy)-3,4-dihydroquinoline-1(2H)-carboxylate (**3b**).* Yellow oil, yield 42%; 99% *ee*, $[\alpha]_D^{25}$ 87.2 (*c* 1.04, $CHCl_3$); HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=95/5, 0.3 mL/min, λ=254 nm, t_{minor}=25.4 min, t_{major}=26.6 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J*=8.7 Hz, 1H), 7.31–7.26 (m, 2H), 7.08–7.03 (m, 1H), 6.03 (t, *J*=3.9 Hz, 1H), 4.18–4.11 (m, 1H), 4.06 (s, 2H), 3.60–3.50 (m, 1H), 2.17–2.12 (m, 2H), 1.54 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 153.4, 138.8, 129.5, 128.9, 125.1, 123.6, 123.4, 81.5, 70.0, 41.1, 40.3, 29.2, 28.3; HRMS (ESI-TOF): calcd for $C_{16}H_{20}ClNNaO_4$ $[M+Na]^+$, 348.0973; found: 348.0985.

*4.2.3. (S)-tert-Butyl 6-Chloro-4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (**1b**).* White solid, yield 48%; 98% *ee*, $[\alpha]_D^{25}$ −17.2 (*c* 0.71, $CHCl_3$); mp 132.2–133.5 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=95/5, 0.8 mL/min, λ=254 nm, t_{minor}=15.2 min, t_{major}=16.7 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 (d, *J*=9.2 Hz, 1H), 7.35 (d, *J*=2.0 Hz, 1H), 7.20 (dd, *J*=9.0 Hz, 2.6 Hz, 1H), 5.55 (d, *J*=5.5 Hz, 1H), 4.55–4.50 (m, 1H), 3.77–3.71 (m, 1H), 3.57–3.51 (m, 1H), 1.98–1.93 (m, 1H), 1.75–1.70 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.2, 136.3, 135.3, 127.4, 127.1, 127.0, 125.1, 81.1, 64.3, 41.6, 32.1, 28.3; HRMS (ESI-TOF): calcd for $C_{14}H_{18}ClNNaO_3$ $[M+Na]^+$, 306.0867; found: 306.0872.

*4.2.4. (R)-tert-Butyl-4-(2-chloroacetoxy)-3,4-dihydroquinoline-1(2H)-carboxylate (**3f**).* White solid, yield 42%; >99% *ee* $[\alpha]_D^{25}$ 76.5 (*c* 0.71, $CHCl_3$); mp 139.8–141.2 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=97/3, 0.5 mL/min, λ=254 nm, t_{minor}=30.6 min, t_{major}=24.5 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.8 Hz, 1H), 7.27–7.22 (m, 2H), 5.94 (t, *J*=4.2 Hz, 1H), 4.19–4.09 (m, 1H), 4.08 (s, 2H), 3.56–3.49 (m, 1H), 2.14–2.10 (m, 2H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 153.1, 137.3, 128.9, 128.4, 126.6, 124.9, 81.9, 69.3, 41.0, 40.3, 28.9, 28.3; HRMS (ESI-TOF): calcd for $C_{16}H_{19}Cl_2NNaO_4$ $[M+Na]^+$, 382.0583; found: 382.0574.

*4.2.5. (S)-tert-Butyl 6-bromo-4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (**1c**).* White solid, yield 29%; >99% *ee*, $[\alpha]_D^{25}$ −11.2 (*c* 0.64, $CHCl_3$); mp 174.8–176.4 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=97/3, 0.5 mL/min, λ=254 nm, t_{minor}=20.8 min, t_{major}=22.7 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (d, *J*=9.2 Hz, 1H), 7.48 (d, *J*=2.8 Hz, 1H), 7.33 (dd, *J*=9.2 Hz, 2.8 Hz, 1H), 5.55 (d, *J*=5.6 Hz, 1H), 4.55–4.51 (m, 1H), 3.77–3.70 (m, 1H), 3.56–3.50 (m, 1H), 1.99–1.93 (m, 1H), 1.73–1.70 (m, 1H), 1.44 (s, 9H); ^{13}C NMR

(100 MHz, DMSO-d_6): δ 153.1, 136.8, 135.7, 130.3, 129.8, 125.5, 115.2, 81.1, 64.3, 41.6, 32.1, 28.3; HRMS (ESI-TOF): calcd for $C_{14}H_{18}BrNNaO_3$ $[M+Na]^+$, 350.0362; found: 350.0351.

*4.2.6. (R)-tert-Butyl 6-bromo-4-(2-chloroacetoxy)-3,4-dihydroquinoline-1(2H)-carboxylate (**3g**).* Brown solid, yield 47%; 96% *ee*, $[\alpha]_D^{25}$ 55.1 (*c* 1.16, $CHCl_3$); mp 149.2–150.8 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=97/3, 0.5 mL/min, λ=254 nm, t_{minor}=32.9 min, t_{major}=26.4 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.8 Hz, 1H), 7.41–7.36 (m, 2H), 5.94 (t, *J*=4.0 Hz, 1H), 4.14–4.08 (m, 3H), 3.54–3.50 (m, 1H), 2.14–2.10 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 153.1, 137.8, 131.9, 131.8, 126.9, 125.3, 115.9, 81.9, 69.3, 41.0, 40.3, 28.8, 28.3; HRMS (ESI-TOF): calcd for $C_{16}H_{19}BrClNNaO_4$ $[M+Na]^+$, 426.0078; found: 426.0072.

*4.2.7. (S)-1-(4-Hydroxy-6-methoxy-3,4-dihydroquinolin-1(2H)-yl) ethanone (**1d**).* Colorless oil, yield 38%; >99% *ee*, $[\alpha]_D^{25}$ −189.7 (*c* 1.0, $CHCl_3$); HPLC analysis Chiralpak AD-H (hexane/*i*-PrOH=90/10, 1.0 mL/min, λ=254 nm, t_{minor}=19.1 min, t_{major}=16.6 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20–7.19 (br s, 1H), 6.97–6.96 (m, 1H), 6.79–6.76 (m, 1H), 5.47–5.46 (d, *J*=4.0 Hz, 1H), 4.50 (dd, *J*=12.0 Hz, 8.0 Hz, 1H), 3.85 (br s, 1H), 3.73 (s, 3H), 3.43–3.41 (m, 1H), 2.09–2.05 (m, 4H), 1.67 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 156.6, 130.8, 125.6, 112.7, 111.7, 64.8, 55.6, 33.4, 23.5; HRMS (ESI-TOF): calcd for $C_{12}H_{15}NNaO_3$ $[M+Na]^+$, 244.0944; found: 244.0952.

*4.2.8. (R)-1-Acetyl-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl 2-chloroacetate (**3h**).* White solid, yield 42%; 92% *ee*, $[\alpha]_D^{25}$ 71.2 (*c* 1.0, $CHCl_3$); mp 151.2–152.9 °C. HPLC analysis Chiralpak AD-H (hexane/*i*-PrOH=90/10, 1.0 mL/min, λ=254 nm, t_{minor}=22.1 min, t_{major}=19.5 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (br s, 1H), 6.87–6.85 (m, 2H), 5.93 (t, *J*=4.0 Hz, 1H), 4.05 (s, 2H), 3.97–3.94 (m, 1H), 3.77–3.71 (m, 4H), 2.21 (s, 3H), 2.19–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.9, 166.8, 157.0, 132.0, 125.8, 114.8, 113.4, 69.9, 55.6, 41.0, 39.4, 30.1, 23.0; HRMS (ESI-TOF): calcd for $C_{14}H_{16}ClNNaO_4$ $[M+Na]^+$, 320.0660; found: 320.0663.

*4.2.9. (S)-Phenyl 4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (**1e**).* White solid, yield 46%; 96% *ee*, $[\alpha]_D^{25}$ −37.6 (*c* 1.07, $CHCl_3$); mp 126.1–127.3 °C. HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=37.0 min, t_{major}=14.6 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, *J*=8.4 Hz, 1H), 7.43–7.39 (m, 3H), 7.26–7.20 (m, 4H), 7.12–7.08 (m, 1H), 5.47 (d, *J*=4.8 Hz, 1H), 4.66–4.62 (m, 1H), 4.02–3.97 (m, 1H), 3.79–3.77 (m, 1H), 2.14–2.09 (m, 1H), 1.89–1.86 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.9, 151.4, 136.8, 133.8, 129.8, 128.3, 127.5, 126.0, 124.1, 123.3, 122.4, 64.5, 42.1, 32.5; HRMS (ESI-TOF): calcd $C_{16}H_{15}NNaO_3$ $[M+Na]^+$, 292.0944; found: 292.0949.

*4.2.10. (R)-Phenyl 4-(2-chloroacetoxy)-3,4-dihydroquinoline-1(2H)-carboxylate (**3i**).* Yellow oil, yield: 43%; 94% *ee*; $[\alpha]_D^{25}$ 70.7 (*c* 1.11, $CHCl_3$); HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=28.7 min, t_{major}=35.6 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J*=8.4 Hz, 1H), 7.43–7.33 (m, 4H), 7.27–7.23 (m, 1H), 7.19–7.12 (m, 3H), 6.10 (t, *J*=4.0 Hz, 1H), 4.14–4.11 (m, 1H), 4.10 (s, 2H), 3.84–3.77 (m, 1H), 2.31–2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 153.0, 150.8, 137.9, 129.7, 129.5, 129.4, 125.9, 125.6, 124.4, 123.5, 121.7, 69.7, 41.1, 40.6, 29.1; HRMS (ESI-TOF): calcd for $C_{18}H_{16}ClNNaO_4$ $[M+Na]^+$, 368.0684; found: 368.0675.

*4.2.11. (S)-Benzyl 4-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (**1f**).* White solid, yield 35%; 95% *ee*, $[\alpha]_D^{25}$ −24.9 (*c* 1.05, $CHCl_3$); mp 110.2–111.5 °C. HPLC analysis Chiralpak AY-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=14.8 min, t_{major}=12.2 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (d, *J*=8.0 Hz, 1H), 7.41–7.31 (m, 6H), 7.19–7.16 (m, 1H), 7.07–7.03 (m, 1H), 5.42 (d, *J*=5.2 Hz, 1H), 5.18 (s, 2H), 4.58–4.56 (m, 1H), 3.90–3.85 (m, 1H), 3.67–3.65 (m, 1H), 1.99–1.96 (m, 1H), 1.80–1.78 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.2, 137.1, 136.9, 133.3, 128.9, 128.4, 128.3, 128.2, 127.4, 123.6, 123.1, 67.3, 64.5, 41.6, 32.4; HRMS (ESI-TOF): calcd for $C_{17}H_{17}NNaO_3$ $[M+Na]^+$, 306.1101; found: 306.1108.

*4.2.12. (R)-Benzyl 4-(2-chloroacetoxy)-3,4-dihydroquinoline-1(2H)-carboxylate (**3j**).* White solid, yield 37%; >99% *ee*, $[\alpha]_D^{25}$ 88.3 (*c* 1.05, $CHCl_3$); mp 90.1–91.3 °C. HPLC analysis Chiralpak AY-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=21.4 min, t_{major}=18.4 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J*=8.8 Hz, 1H), 7.42–7.26 (m, 7H), 7.11–7.07 (m, 1H), 6.03 (t, *J*=3.8 Hz, 1H), 5.26 (s, 2H), 4.25–4.20 (m, 1H), 4.05 (s, 2H), 3.69–3.61 (m, 1H), 2.19–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 154.2, 138.3, 136.0, 129.7, 129.3, 128.6, 128.3, 128.1, 125.2, 123.9, 123.4, 69.8, 67.9, 41.1, 40.5, 28.9; HRMS (ESI-TOF): calcd for $C_{19}H_{18}ClNNaO_4$ $[M+Na]^+$, 382.0817; found: 382.0823.

*4.2.13. (S)-1-(4-Hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethanone (**1g**).* Yellow oil, yield 44%; >99% *ee*, $[\alpha]_D^{25}$ −96.1 (*c* 1.09, $CHCl_3$); HPLC analysis Chiralpak AY-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=18.3 min, t_{major}=14.6 min); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50–7.41 (m, 2H), 7.24–7.19 (m, 1H), 7.16–7.11 (m, 1H), 5.43–5.42 (d, *J*=7.3 Hz, 1H), 4.58–4.53 (m, 1H), 3.91–3.84 (m, 1H), 3.54–3.50 (m, 1H), 2.16 (s, 3H), 2.13–2.04 (m, 1H), 1.78–1.71 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.3, 137.3, 127.0, 126.7, 124.1, 123.9, 64.2, 32.9, 23.3; HRMS (ESI-TOF): calcd for $C_{11}H_{13}NNaO_2$ $[M+Na]^+$, 214.0838; found: 214.0846.

*4.2.14. (R)-1-Acetyl-1,2,3,4-tetrahydroquinolin-4-yl 2-chloroacetate (**3k**).* White solid, yield 40%; 95% *ee*, $[\alpha]_D^{25}$ 78.2 (*c* 1.07, $CHCl_3$); mp 89.7–91.3 °C. HPLC analysis Chiralpak AY-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=39.3 min, t_{major}=45.0 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 3H), 7.20–7.16 (m, 1H), 6.00 (t, *J*=4.4 Hz, 1H), 4.07–4.01 (m, 3H), 3.79–3.69 (m, 1H), 2.26 (s, 3H), 2.23–2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 166.8, 139.0, 129.1, 129.0, 125.3, 124.5, 69.9, 41.0, 39.8, 30.1, 23.4; HRMS (ESI-TOF): calcd for $C_{13}H_{14}ClNNaO_3$ $[M+Na]^+$, 290.0554; found: 290.0567.

*4.2.15. (S)-(4-Hydroxy-3,4-dihydroquinolin-1(2H)-yl) (phenyl)methanone (**1h**).* White solid, yield 34%; >99% *ee*, $[\alpha]_D^{25}$ −59.9 (*c* 1.10, $CHCl_3$); mp 200.7–201.9 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=90/10, 1.0 mL/min, λ=254 nm, t_{minor}=27.4 min, t_{major}=33.5 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42–7.37 (m, 2H), 7.33–7.30 (m, 4H), 7.06–7.02 (m, 1H), 6.95–6.91 (m, 1H), 6.79–6.77 (m, 1H), 5.51 (d, *J*=5.6 Hz, 1H), 4.71–4.67 (m, 1H), 3.92–3.85 (m, 1H), 3.67–3.60 (m, 1H), 2.18–2.10 (m, 1H), 1.86–1.78 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8, 137.9, 136.9, 134.6, 130.5, 128.6, 128.5, 127.8, 126.9, 124.8, 124.5, 64.5, 42.2, 33.3; HRMS (ESI-TOF): calcd for $C_{16}H_{15}NNaO_2$ $[M+Na]^+$, 276.0995; found: 276.0998.

*4.2.16. (R)-1-Benzoyl-1,2,3,4-tetrahydroquinolin-4-yl 2-chloroacetate (**3l**).* Yellow oil, yield 49%; 97% *ee*, $[\alpha]_D^{25}$ 51.0 (*c* 1.03, $CHCl_3$); HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=90/10, 1.0 mL/min, λ=254 nm, t_{minor}=24.0 min, t_{major}=21.9 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.39 (m, 3H), 7.36–7.30 (m, 3H), 7.08–7.05 (m, 2H), 6.92–6.91 (m, 1H), 6.12 (t, *J*=4.2 Hz, 1H), 4.16–4.11 (m, 1H), 4.09 (s, 2H), 3.90–3.85 (m, 1H), 2.31–2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.9, 139.1, 135.6, 130.6, 129.2, 128.7, 128.5, 128.3, 126.5, 125.1, 124.8, 69.8, 41.3, 41.0, 29.9; HRMS (ESI-TOF): calcd for $C_{18}H_{16}ClNNaO_3$ $[M+Na]^+$, 352.0717; found: 352.0717.

*4.2.17. (S)-Furan-2-yl(4-hydroxy-3,4-dihydroquinolin-1(2H)-yl) methanone (**1i**).* Yellow oil, yield 40%; 99% *ee*, $[\alpha]_D^{25}$ −59.2 (*c* 0.60,

$CHCl_3$); HPLC analysis Chiralpak AY-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=25.4 min, t_{major}=20.3 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71–7.44 (m, 2H), 7.13–7.06 (m, 2H), 6.96 (d, *J*=7.6 Hz, 1H), 6.82 (d, *J*=3.6 Hz, 1H), 6.56–6.55 (m, 1H), 5.51 (d, *J*=5.6 Hz, 1H), 4.65–4.60 (m, 1H), 4.02–3.94 (m, 1H), 3.70–3.64 (m, 1H), 2.14–2.10 (m, 1H), 1.81–1.77 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6, 147.9, 145.4, 137.4, 134.5, 127.8, 127.1, 124.7, 123.5, 116.8, 112.0, 64.3, 42.1, 33.3; HRMS (ESI-TOF): calcd for $C_{14}H_{13}NNaO_3$ $[M+Na]^+$, 266.0788; found: 266.0794.

*4.2.18. (R)-1-(Furan-2-carbonyl)-1,2,3,4-tetrahydroquinolin-4-yl 2-chloroacetate (**3m**).* White solid, yield 46%; >99% *ee*, $[\alpha]_D^{25}$ 81.6 (*c* 1.07, $CHCl_3$); mp 110.6–112.1 °C. HPLC analysis Chiralpak AY-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=254 nm, t_{minor}=45.0 min, t_{major}=41.0 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.37 (m, 2H), 7.21–7.13 (m, 2H), 7.08–7.06 (m, 1H), 6.86 (d, *J*=3.6 Hz, 1H), 6.45–6.43 (m, 1H), 6.09 (t, *J*=4.2 Hz, 1H), 4.23–4.18 (m, 1H), 4.06 (s, 2H), 3.92–3.85 (m, 1H), 2.30–2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 159.9, 147.5, 144.5, 138.8, 129.3, 128.9, 126.8, 125.1, 123.9, 117.4, 111.6, 69.6, 41.0, 40.6, 30.0; HRMS (ESI-TOF): calcd for $C_{16}H_{14}ClNNaO_4$ $[M+Na]^+$, 342.0504; found: 342.0503.

*4.2.19. (S)-1-(Phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-4-ol (**1j**).* White solid, yield 34%; >99% *ee*, $[\alpha]_D^{25}$ 37.3 (*c* 1.04, $CHCl_3$); mp 118.1–119.7 °C. HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 0.5 mL/min, λ=254 nm, t_{minor}=22.6 min, t_{major}=20.2 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66–7.60 (m, 4H), 7.55–7.51 (m, 2H), 7.34–7.32 (m, 1H), 7.24–7.20 (m, 1H), 7.12–7.08 (m, 1H), 5.37 (d, *J*=5.2 Hz, 1H), 4.22–4.19 (m, 1H), 4.00–3.93 (m, 1H), 3.75–3.68 (m, 1H), 1.72–1.67 (m, 1H), 1.62–1.58 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 139.2, 135.7, 133.9, 133.4, 129.9, 129.5, 128.0, 127.2, 124.7, 122.5, 63.6, 43.2, 30.9; HRMS (ESI-TOF): calcd for $C_{15}H_{15}NNaO_3S$ $[M+Na]^+$, 312.0665; found: 312.0672.

*4.2.20. (R)-1-(Phenylsulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl 2-chloroacetate (**3n**).* Yellow oil, yield 40%; >99% *ee*, $[\alpha]_D^{25}$ 51.9 (*c* 1.12, $CHCl_3$); HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 0.5 mL/min, λ=254 nm, t_{minor}=35.5 min, t_{major}=33.5 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J*=8.4 Hz, 1H), 7.64–7.54 (m, 3H), 7.45–7.32 (m, 3H), 7.26–7.12 (m, 2H), 5.76 (t, *J*=3.6 Hz, 1H), 4.26–4.20 (m, 1H), 3.88 (d, *J*=4.0 Hz 2H), 3.69–3.61 (m, 1H), 1.92–1.82 (m, 1H), 1.81–1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 139.1, 136.9, 133.2, 130.4, 129.8, 129.2, 127.0, 125.6, 125.0, 123.6, 68.8, 42.2, 40.6, 27.1; HRMS (ESI-TOF): calcd for $C_{17}H_{16}ClNNaO_4S$ $[M+Na]^+$, 388.0381; found: 388.0375.

4.3. Representative procedure for the synthesis of (*S*)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ol (4) and (*R*)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl 2-chloroacetate (5)

To a solution of (*rac*)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ol (**4**) (0.50 mmol, 1 equiv) in 5 mL MeO^tBu, vinyl 2-chloroacetate (2.50 mmol, 5 equiv) and Novozyme 435 (0.05 g) were consecutively added. The reaction mixture was shaken in orbital shaker at 300 rpm at 30 °C for 8 h. After that, the mixture was filtered and concentrated, and the residue was purified by column chromatography (EtOAc/petroleum=1:5) to give (*S*)-**4** and (*R*)-**5**, respectively.

*4.3.1. (S)-(5-Hydroxy-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)(phenyl)methanone (**4a**).* White solid, yield 40%; 98% *ee*, $[\alpha]_D^{25}$ −139.1 (*c* 1.08, $CHCl_3$); mp 143.3–144.6 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=201 nm, t_{minor}=24.0 min, t_{major}=18.8 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59–7.40 (m, 1H), 7.28–7.05 (m, 6H), 6.93–6.90 (m, 1H), 6.64–6.54 (m, 1H), 5.56 (d, *J*=4.0 Hz, 1H), 4.93 (d, *J*=12.0 Hz, 1H), 4.66 (d, *J*=16.0 Hz, 1H), 2.67–2.61 (m, 1H), 2.13–2.10 (m, 1H), 1.97–1.90 (m, 1H), 1.73–1.62 (m, 1H), 1.50–1.54 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4, 142.9, 140.5, 136.7, 129.8, 128.4, 128.1, 127.9, 127.3, 127.2, 125.4, 70.1, 46.6, 36.0, 26.3; HRMS (ESI-TOF): calcd for $C_{17}H_{17}NNaO_2$ $[M+Na]^+$, 290.1151; found: 290.1151.

*4.3.2. (R)-1-Benzoyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl 2-chloroacetate (**5a**).* Colorless oil, yield 42%; 97% *ee*, $[\alpha]_D^{25}$ 78.6 (*c* 1.00, $CHCl_3$); HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=201 nm, t_{minor}=43.1 min, t_{major}=30.1 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.12 (m, 7H), 7.02–6.94 (m, 1H), 6.65–6.62 (m, 1H), 6.25–6.11 (m, 1H), 5.12–4.84 (m, 1H), 4.25 (s, 1H), 4.05–3.91 (m, 1H), 2.85 (t, *J*=12.0 Hz, 1H), 2.27–2.12 (m, 2H), 1.82–1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.3, 135.4, 131.3, 129.8, 129.4, 128.7, 128.2, 127.8, 127.6, 127.2, 123.6, 74.7, 46.4, 41.0, 31.7, 25.4; HRMS (ESI-TOF): calcd for $C_{19}H_{18}ClNNaO_3$ $[M+Na]^+$, 366.0867; found: 366.0866.

*4.3.3. (S)-Furan-2-yl(5-hydroxy-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)methan-one(**4b**).* Brown solid, yield 39%; 96% *ee*, $[\alpha]_D^{25}$ −24.9 (*c* 0.84, $CHCl_3$); mp 227.4–228.9 °C. HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=201 nm, t_{minor}=27.2 min, t_{major}=23.0 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67–7.63 (m, 2H), 7.40–7.37 (m, 1H), 7.19–7.17 (m, 1H), 7.00–6.98 (m, 1H), 6.34 (s, 1H), 5.63 (s, 1H), 5.51 (d, *J*=4.0 Hz, 1H), 4.70–4.67 (m, 1H), 4.61–4.58 (m, 1H), 2.64–2.58 (m, 1H), 2.04–2.01 (m, 1H), 1.89–1.85 (m, 1H), 1.71–1.68 (m, 1H), 1.50–1.45 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.3, 147.0, 145.4, 143.9, 140.0, 128.4, 127.9, 127.6, 125.6, 115.9, 111.6, 69.8, 46.6, 36.1, 26.3; HRMS (ESI-TOF): calcd for $C_{15}H_{15}NNaO_3$ $[M+Na]^+$, 280.0944; found: 280.0945.

*4.3.4. (R)-1-(Furan-2-carbonyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-yl 2-chloroacetate (**5b**).* White solid, yield 43%; 98% ee, $[\alpha]_D^{25}$ 37.0 (*c* 0.84, CHCl3); mp 196.4–197.9 °C. HPLC analysis Chiralpak OD-H (hexane/i-PrOH=90/10, 0.8 mL/min, λ=201 nm, tminor=40.9 min, tmajor=27.3 min); ^{1}H NMR (400 MHz, CDCl3): δ 7.52–7.41 (m, 1H), 7.37–7.26 (m, 2H), 7.08 (d, *J*=8.0 Hz, 1H), 6.20 (s, 1H), 5.92 (d, *J*=8.0 Hz, 1H), 5.72 (d, *J*=4.0 Hz, 1H), 4.98–4.95 (m, 1H), 4.23–3.28 (m, 2H), 2.86–2.83 (m, 1H), 2.44–2.31 (m, 2H), 1.84–1.71 (m, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 166.5, 157.8, 147.1, 144.4, 142.4, 135.8, 131.5, 129.8, 129.0, 128.2, 116.3, 111.1, 74.7, 47.8, 40.6, 30.1, 23.1; HRMS (ESI-TOF): calcd for C17H16ClNNaO4 [M+Na]+, 356.0660; found: 356.0670.

*4.3.5. (S)-Benzyl 5-hydroxy-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carboxylate (**4c**).* Colorless oil, yield 44%; 90% *ee*, $[\alpha]_D^{25}$ −18.0 (*c* 1.00, $CHCl_3$); HPLC analysis Chiralpak OJ-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=201 nm, t_{minor}=37.5 min, t_{major}=41.9 min); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61–7.59 (m, 1H), 7.42–7.40 (m, 1H), 7.30–7.15 (m, 7H), 5.48 (s, 1H), 5.18–5.11 (m, 1H), 5.02–4.99 (m, 1H), 4.63 (d, *J*=12.0 Hz, 1H), 4.21 (d, *J*=12.0 Hz, 1H), 2.64–2.61 (m, 1H), 2.04–2.01 (m, 1H), 1.90–1.86 (m, 1H), 1.67–1.63 (m, 1H), 1.46–1.41 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.1, 143.2, 138.9, 137.3, 128.9, 128.7, 128.3, 128.1, 127.4, 127.1, 125.3, 70.0, 66.6, 48.0, 36.1, 26.4; HRMS (ESI-TOF): calcd for $C_{18}H_{19}NNaO_3$ $[M+Na]^+$, 320.1257; found: 320.1261.

*4.3.6. (R)-Benzyl 5-(2-chloroacetoxy)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carboxylate (**5c**).* White solid, yield 41%; 93% *ee*, $[\alpha]_D^{25}$ 40.3 (*c* 1.00, $CHCl_3$); mp 104.6–105.8 °C. HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 0.8 mL/min, λ=201 nm, t_{minor}=28.8 min, t_{major}=18.2 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.34 (m, 3H), 7.29–7.19 (m, 6H), 6.00–5.92 (m, 1H), 5.31–5.02 (m, 2H), 4.48–4.09 (m, 1H), 3.73–3.50 (m, 2H), 2.88–2.74 (m, 1H), 2.36–2.13 (m, 2H), 1.74–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 154.5, 141.6, 136.6, 135.3, 130.7, 129.4, 128.5, 128.4, 128.0, 127.7, 127.3, 67.3, 66.9, 48.9, 40.6, 30.0, 23.0;

HRMS (ESI-TOF): calcd for $C_{20}H_{20}ClNNaO_4$ $[M+Na]^+$, 396.0973; found: 396.0971.

4.4. Large scale experiment for enzyme kinetic resolution of racemic 1g

To a solution of racemic alcohol **1g** (52.33 mmol, 10.00 g, 1.0 equiv) in 523.0 mL MeO^{t}Bu, vinyl 2-chloroacetate (78.50 mmol, 1.5 equiv) and Novozyme 435 (5.23 g) were consecutively added. The reaction mixture was shaken at 300 rpm at 30 °C for 2 h. After that, the mixture was filtered and concentrated, and the residue was purified by column chromatography (EtOAc/petroleum=1:1) to give (*S*)-**1g** (4.42 g, 44% yield, 99% ee) and (*R*)-**3k** (5.64 g, 40% yield, 96% ee), respectively.

4.5. Procedure for the synthesis of (*R*)-1-(4-azido-3,4-dihydroquinolin-1(2*H*)-yl)ethanone (6)

To a solution of (*S*)-**1g** (4.00 mmol, 764.4 mg, 1.0 equiv) in 40.0 mL Et_2O were consecutively added diphenyl phosphorazidate (6.00 mmol, 1.3 mL, 1.5 equiv) and DBU (0.9 mL, 1.5 equiv) at 0 °C under N_2 atmosphere. After 30 min, the reaction mixture was warmed to room temperature and continued to stir for 24 h. After quenching with water, the organic phase was separated, and the aqueous phase was extracted with EtOAc (5×10.0 mL). Then the combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and the residue was purified by flash column chromatography (EtOAc/petroleum=1:1) to give the compound **6**.

*4.5.1. (R)-1-(4-Azido-3,4-dihydroquinolin-1(2H)-yl)ethanone (**6**).* Colorless oil, 709.2 mg, yield 82%; 96% *ee*, $[\alpha]_D^{25}$ 152.3 (*c* 1.00, $CHCl_3$); HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=90/10, 1.0 mL/min, λ=254 nm, t_{minor}=15.6 min, t_{major}=12.7 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 3H), 7.22–7.18 (m, 1H), 4.58 (t, *J*=4.0 Hz, 1H) 3.97–3.92 (m, 1H), 3.80–3.75 (m, 1H), 2.25 (s, 3H), 2.21–2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 138.3, 128.6, 128.3, 128.1, 125.3, 124.7, 57.3, 40.4, 29.9, 23.4; HRMS (ESI-TOF): calcd for $C_{20}H_{20}ClNNaO_4$ $[M+Na]^+$, 239.0903; found: 239.0908.

4.6. Procedure for the synthesis of (*R*)-1-(4-amino-3,4-dihydroquinolin-1(2*H*)-yl)ethanone (7)

The compound **6** (709.2 mg, 3.28 mmol) was dissolved in MeOH (50.0 mL), and Pd/C (10%) (145.0 mg) was added into the solution at room temperature. Then the reaction mixture was stirred under H_2 atmosphere (1.0 atm) for 12 h. After completion of the reaction, as indicated by TLC, Pd/C was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (MeOH/dichloromethane/Et_3N=1:10:0.2) to give the product **7**.

*4.6.1. (R)-1-(4-Amino-3,4-dihydroquinolin-1(2H)-yl)ethanone (**7**).* Colorless oil, 442.9 mg, yield 71%; 96% *ee*, $[\alpha]_D^{25}$ 53.0 (*c* 0.80, $CHCl_3$); HPLC analysis Chiralpak OD-H (hexane/*i*-PrOH=98/2, 1.0 mL/min, λ=254 nm, t_{minor}=206.1 min, t_{major}=180.2 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J*=4.0 Hz, 1H), 7.16–7.09 (m, 3H), 3.86–3.83 (m, 2H), 3.56–3.53 (m, 1H), 2.31 (s, 2H), 2.15–2.12 (m, 1H), 2.12 (s, 3H), 1.61–1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 137.6, 136.6, 126.9, 125.7, 125.2, 124.3, 47.6, 41.0, 33.9, 23.2; HRMS (ESI-TOF): calcd for $C_{11}H_{14}N_2NaO$ $[M+Na]^+$, 213.0998; found: 213.1004.

Acknowledgements

We are grateful for financial support from Science and Technology Foundation of Guizhou Province (No. QKHSZ-2012-3078, QKHRZ-2013-47 and QKHRCTD-2014-4002), National Natural Science Foundation of China (NSFC 21162047 and 21262051) and New Century Excellent Talent of the Ministry of Education (NCET-13-1069). Special thanks are expressed to Zeli Yuan and Dabing Shi (Zunyi Medical University) for their help of single crystal analysis.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.066.

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18. The method for the synthesis of (*rac*)-tetrahydro-1*H*-benzo[*b*]azepin-5-ol (**4**) was similar to that of (*rac*)-tetrahydroquinolin-4-ol (**1**).