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Two approaches for the synthesis of levo-praziquantel†

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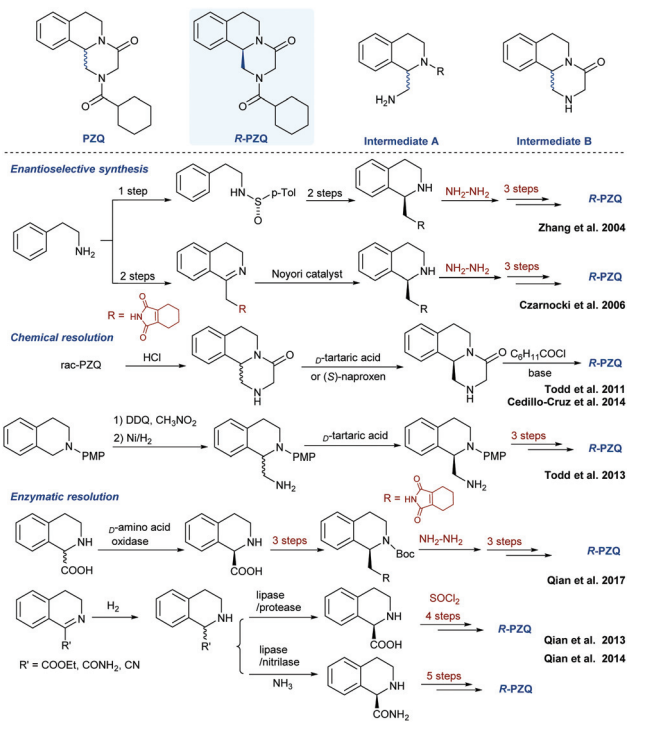
We report herein the development of two pathways for the preparation of levo-praziquantel (*R*-PZQ), which involves three-/four-step processes of a mechanochemical (asymmetric) aza-Henry/acylation reaction, a hydrogenation reaction, (chiral resolution) and a solvent-free acylation-ring closing reaction. The key intermediate (*R*)-1-aminomethyl tetrahydroisoquinoline could be obtained either by chiral resolution with a rational reuse of the *S*-isomer or by mechanochemical enantioselective synthesis that refrained from using a bulky toxic solvent. The efficiency and scalability of both the developed routes were demonstrated and desired target product was obtained in a satisfactory yield with excellent enantiopurity (>99%), offering practical, concise and environmentally friendly alternatives to access *R*-PZQ.

Introduction

Schistosomiasis is a major health concern that affects almost 240 million people worldwide. It is an acute and chronic tropical parasitic disease caused by the *Schistosoma* spp worm.[1] According to the World Health Organization (WHO) Model List of Essential Medicines 2019, praziquantel (PZQ) is indicated as the first-line drug for the treatment of schistosomiasis[2] (Scheme 1) and also to be highly effective against a broad range of cestodes and trematodes in humans and animals.[3] This small molecule drug is commonly synthesized and administered as a racemate.[4] However, only the *R*-enantiomer displays anti-parasitic activities while the *S*-enantiomer is inactive with poor taste; thus producing PZQ in an enantiopure form is necessary.[5]

As one of the important chiral nitrogen-containing heterocyclic compounds,[6] *R*-PZQ can be generated by enantioselective synthesis,[7] chemical resolution,[4,8] and enzymatic resolution[9] (Scheme 1). The asymmetric synthesis of *R*-PZQ has received little synthetic attention and few synthetic routes to their enantiomers have been published: Zhang *et al.*[7a] first reported a chiral auxiliary (Andersen reagent) mediated Pictet–Spengler reaction for the synthesis of *R*-PZQ in 2004. Subsequently, Czarnocki *et al.*[7b] introduced an asymmetric transfer hydrogenation approach which relied on the classical Noyori conditions. Despite advances, these protocols have several limitations for scaled-up preparation, for example, the requirement of a protective and deprotective process, tedious chromatographic methods, and an inevitable toxic reagent. While multistep enantioselective routes for the preparation of



Scheme 1 Synthetic routes to *R*-PZQ.

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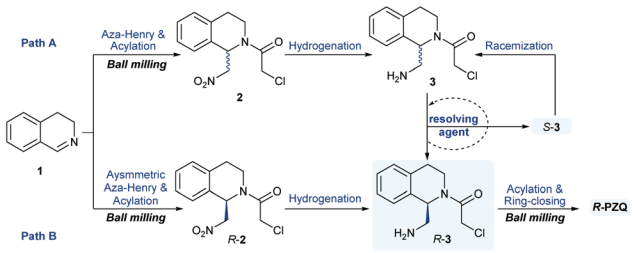


Scheme 2 Two approaches for the preparation of *R*-PZQ.

R-PZQ are reported, the classical approach of separating a single enantiomer from a racemic mixture of intermediate **A** [8a] or **B** [4,8b–c] by the formation of diastereomeric salts remains an important strategy for its construction. However, the racemization and reuse of the unwanted *S*-isomer were still a big challenge for achieving a high overall yield. Enzymatic resolution of racemic mixtures is another common way to access pure enantiomers at the laboratory and industrial scale,[10] wherein *R*-PZQ has been obtained mostly by using nitrilase, lipase, protease, and D-amino acid oxidase.[9c] These approaches effectively provide high selectivity, but always require multistep processes and environmentally unfriendly reagents (such as hydrazine hydrate and types of acyl chlorides) for the transformation of the products.

Given the limitations of existing routes, it is clear that a practical, concise and environmentally friendly alternative to synthesize *R*-PZQ is in urgent need. In this report, we described our synthetic effort to access *R*-PZQ through two approaches (Scheme 2). The key intermediate (*R*)-1-aminomethyl tetrahydroisoquinoline (*R*-**3**) could be obtained either by the resolution of a readily available racemic material or by an enantioselective synthesis.

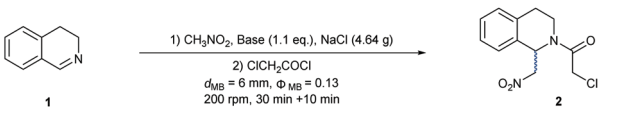
Results and discussion

Synthesis of *R*-3 *via* chiral resolution (path A)

Initially, we decided to obtain *R*-**3** by the kinetic resolution of 1-aminomethyl-2-chloracetyl tetrahydroisoquinoline **3** which itself was synthesized starting from the readily available material 3,4-dihydroisoquinoline **1** through two steps: (a) a mechanochemical aza-Henry reaction under solvent-free ball milling conditions,[11] and (b) a nitro reduction reaction by nickel catalysis (Scheme 2, path A).

Aza-Henry/acylation reaction. A mechanochemical protocol under ball-milling conditions has many advantages; for example, it can minimize the use of reagents, solvents, additives and/or catalysts to reduce operating costs, it can increase the energy efficiency of a process, and new or alternative reagents can be employed, making it an interesting tool for organic synthesis.[11] Herein, we began our investigation on the solvent-free aza-Henry reaction under ball-milling conditions at the laboratory scale. A careful screening of the substrate ratios, bases (Table 1), and the mechanochemical parameters

Table 1 Optimization of aza-Henry reaction conditions[a]



Entry	**1** : CH_3NO_2 : $ClCH_2COCl$ (eq.)	Base	Yield of **2** [b]/%
1	1 : 3.0 : 3.0	NaOH	36
2	1 : 3.0 : 3.0	$NaHCO_3$	65
3	1 : 3.0 : 3.0	Na_2CO_3	67
4	1 : 3.0 : 3.0	$(n\text{-Bu})_3N$	71
5	1 : 3.0 : 3.0	$(n\text{-Bu})_2NH$	66
6	1 : 3.0 : 3.0	Et_3N	81, 82[c]
7	1 : 2.0 : 3.0	Et_3N	81
8	1 : 1.5 : 3.0	Et_3N	82
9	**1 : 1.5 : 2.0**	**Et_3N**	**83**
10	1 : 1.5 : 1.5	Et_3N	67
11	1 : 1.0 : 2.0	Et_3N	55

[a] Reaction conditions: **1** (1 mmol, 1.0 eq.), nitromethane, base (1.1 eq.), and NaCl (4.64 g) were placed in a 50 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 6 mm, Φ_{MB} = 0.13) on a planetary mill and milled at 200 rpm for 30 min, followed by the addition of chloracetyl chloride and milling for 10 min. [b] Yield of **2** based on **1**. [c] Et_3N (1.5 eq.).

such as milling time (t), rotation speed (v_{rot}), milling ball filling degree (Φ_{MB}) and grinding auxiliary (Table S1 and Fig. S1†) were carried out to facilitate the synthesis of 1-nitromethyl-2-chloracetyl tetrahydroisoquinoline **2** [12] in a very good yield. Triethylamine (1.1 equiv.) was the preferred organic base (Table 1, entries 1–6), and using nitromethane (1.5 equiv.), chloracetyl chloride (2.0 equiv.) and NaCl (4.64 g) as the grinding auxiliary was sufficient to achieve the best product yield (Table 1, entry 10 and Fig. S1†). A mild milling rotation (200 rpm), a medium milling ball filling degree (d_{MB} = 6 cm, Φ_{MB} = 0.13) and a short reaction time (a total of 40 min) render the reaction facile and practicable (Table S1†). Moreover, a scaled-up reaction (50 mmol) was readily carried out in a 250 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 8 mm, Φ_{MB} = 0.13) and NaCl (120 g), without loss of efficiency (82% yield). In this case, the grinding auxiliary NaCl could be recycled and reused at least three times and gave a satisfactory yield (78%). In addition, the work-up procedure of this protocol only required dissolving of the reaction mixture in ethyl acetate with subsequent filtration and washing to afford the crude product as a grey powder, which could be purified by recrystallization with methanol.

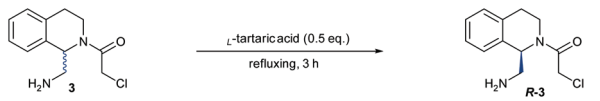
Hydrogenation reaction. The reduction of **2** was investigated with several systems, *e.g.* RANEY® Ni/H_2, $(NH_4)_2S$, Pd/C/H_2, and iron powder/NH_4Cl (Table S2†). Since mild hydrogenation conditions favour the reduction of β-nitroamines,[13] it was not surprising that RANEY® Ni, a clean, readily available and preferred commercial catalyst, together with H_2 gave promising results (Table S3†): 75% yield of 1-aminomethyl tetrahydroisoquinoline **3** was obtained for 1 mmol scale reduction by RANEY® Ni/H_2 (1 atm) in aqueous (ammonia) methanol, and 74% yield was achieved for 25 mmol scale production. Compound **3** could be reacted with DL-tartaric acid to give a

salt which is more stable and suitable for storage, thereby simplifying product purification.

Chiral resolution. Next, the resolution of **3** was attempted in MeOH/H_2O with different chiral acids, such as L-tartaric acid, D-tartaric acid, dibenzoyl L-tartaric acid and di-*p*-toluoyl-D-tartaric acid. Only L-tartaric acid formed a crystalline salt with the desired *R*-enantiomer; other chiral acids gave no solid product. Thus, the resolution using L-tartaric acid was further investigated (Table 2). MeOH/water (5 : 1) offered the best result (entry 5), while other solvents gave either a low yield or poor ee (entries 1–4). Appropriate water content of the solvent was critical for the solubility of L-tartaric acid and the resulting diastereomeric salts, thereby influencing the ee and yield of *R*-**3** dramatically (entries 6–10). The amount of the solvent and the reaction time had much less effect on the ee of *R*-**3** than its yield (entries 11–14). To our delight, the optimal product was achieved in 26% yield with >99% ee, when 0.5 equiv. of L-tartaric acid in 8 mL of MeOH/water (5 : 1) was used with refluxing for 5 h. The process could be readily scaled up to 50 mmol without significant loss of the yield (23%, 43% based on the recovery of *S*-**3**) and ee (99.7%).

Recovery of the undesired *S*-3. Analysis showed that typically around 65–75% of the unwanted *S*-**3** with 30–40% ee was left in the mother liquor, causing huge loss. To increase the overall throughput of the resolution process, we devoted our efforts toward recycling and reusing the unwanted *S*-**3**. However, the racemization of **3** enriched with *S*-**3** recovered from the mother liquor was a big a challenge since **3** was a primary aliphatic amine attached to a secondary carbon, which showed extremely low reactivity compared to those attached to tertiary carbon substrates. Several literature studies revealed that there are reports on the racemization of inactivated amines, such as thiyl radical-,[14] transition metal-,[15] strong base-,[16] or Schiff base[17]-mediated racemization of non-activated amines. Unfortunately, all these methods cannot successfully racemize *S*-**3**. To our surprise, the racemization of *S*-**3** (37.8% ee) could be accomplished after treatment with DL-tartaric acid three times to afford racemized *S*-**3** in 62% yield with 2.7% ee (Fig. 1). The resulting racemized *S*-**3** was subjected to the next cycle of the resolution to give *R*-**3** in 26% yield with ee > 97%, which was further improved to >99% by recrystallization in acetone. It should be noted that both the resolving agent (L-tartaric acid)[18] and the racemization agent (DL-tartaric acid) could be recovered and reused through a practical salting-out and liberation process with a yield of 72% and 73%, respectively.

Table 2 Optimization of resolution reaction conditions[a]



Entry	Solvent	Yield of *R*-**3** [b]/%	ee of *R*-**3** [c]/%
1	EtOH : H_2O = 5 : 1	33	72.5
2	Acetone : H_2O = 5 : 1	Trace	n.d.
3	CH_3CN : H_2O = 5 : 1	9	98.5
4	IPA : H_2O = 5 : 1	23	99.5
5	**MeOH : H_2O = 5 : 1**	**26 (47)**	**99.9**
6	MeOH : H_2O = 7 : 1	27	93.2
7	MeOH : H_2O = 10 : 1	33	51.0
8	MeOH : H_2O = 20 : 1	36	43.2
9	MeOH	36	43.1
10	MeOH : H_2O = 1 : 1	Trace	n.d.
11[d]	MeOH : H_2O = 5 : 1	18	>99.9
12[e]	MeOH : H_2O = 5 : 1	24	99.9
13[f]	MeOH : H_2O = 5 : 1	23	99.9
14[g]	MeOH : H_2O = 5 : 1	20	>99.9

[a] Reaction conditions: *rac*-**3** (3.8 mmol), L-tartaric acid (1.9 mmol), and solvent (8 mL) were placed in a 25 mL two-necked flask and refluxed for 3 h. [b] Yield of *R*-**3** based on *rac*-**3**. [c] Determined by HPLC analysis. [d] MeOH : H_2O = 5 : 1 (6 mL). [e] MeOH : H_2O = 5 : 1 (10 mL). [f] Refluxing for 4 h. [g] Refluxing for 5 h.

Synthesis of *R*-3 *via* an asymmetric reaction (path B)

Despite the synthesis of *R*-**3** *via* resolution being successfully scaled up, the process was elongated as a result of the racemization of the unwanted *S*-**3** and the recovery of the resolution agents. To address this issue, we further focused on the direct preparation of *R*-**2** *via* an asymmetric aza-Henry reaction enabled by liquid-assisted mechanical milling[19] (Table 3), a powerful technology for reactivity- and selectivity-control[11e,20]

Attempts to catalyse the reaction of **1** and nitromethane using quinine alkaloids (**C1** and **C2**) in the presence of dichloroethane (DCE) as the liquid additive (LAG)[19] and silica gel as the grinding auxiliary[21] did not show any signs of chiral induction (entries 1 and 2). Further examination with other chiral catalysts showed that **C4** was optimal for this asymmetric aza-Henry reaction (entries 3–6). Even at a reduced catalyst loading of 15 mol%, a yield of 81% with 86% ee was obtained (entry 7), while further reducing the catalyst loading to 10 mol% decreased the product ee (entry 8). Before we concluded that DCE and *n*-heptane (a less toxic solvent) were the preferred liquid additives, a number of LAGs were studied (entries 9–14). Control experiments delineated that a trace amount of a liquid additive was necessary to achieve a desired ee value (entry 15).[22] In addition, organic bases were superior to inorganic bases, among which NEt_3 gave the best result (entries 16–18). Preliminary results demonstrated that the ee of *R*-**2** could be improved to >99% after recrystallization from methanol. The robustness of this route was ascertained by a successful scaled-

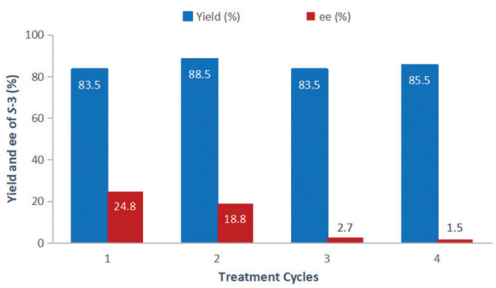
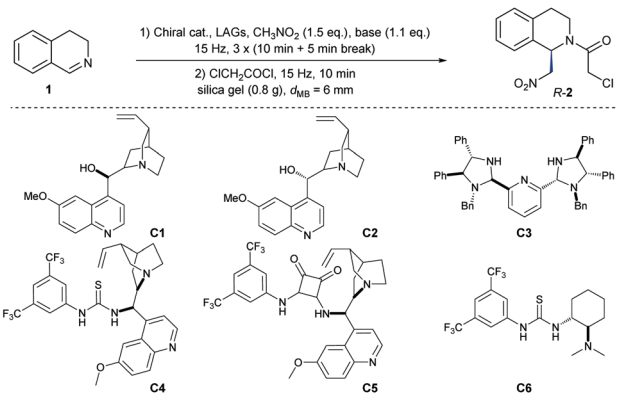


Fig. 1 Racemization of *S*-**3**.

Table 3 Optimization of conditions for the asymmetric aza-Henry reaction[a]



Entry	Cat.	LAG	Base	Yield of *R*-**2** [b]/%	ee of *R*-**2** [c]/%
1	C1	DCE	NEt_3	73	<5
2	C2	DCE	NEt_3	71	0
3	C3	DCE	NEt_3	56	11
4	C4	DCE	NEt_3	82	86
5	C5	DCE	NEt_3	76	47
6	C6	DCE	NEt_3	79	61
7[d]	C4	DCE	NEt_3	81	85
8[e]	C4	DCE	NEt_3	81	53
9	C4	Diox	NEt_3	71	73
10	C4	THF	NEt_3	69	74
11	C4	MeOH	NEt_3	34	31
12	C4	H_2O	NEt_3	31	n.d.
13[d]	C4	*n*-Hept[f]	NEt_3	80 (70)[g]	88 (99.8)[g]
14	C4	Tol	NEt_3	78	82
15	C4	—	NEt_3	81	71
17	C4	DCE	DABCO	84	83
18	C4	DCE	Na_2CO_3	56	54
19	C4	DCE	$NaHCO_3$	68	79

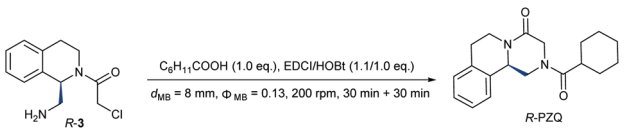
[a] Reaction conditions: **1** (1 mmol), chiral catalyst (20 mol%) and LAG (4 eq., the η parameter was not used since there were more than two kinds of liquid substrates and/or reagents) were added to a 25 mL zirconia vessel and premixed on a mixer mill at 15 Hz for 5 min. Then nitromethane (1.5 eq.), base (1.1 eq.) and silica gel (0.8 g) were added with two 10 mm zirconia balls and milled at 15 Hz for 30 min [3 × (10 min + 5 min break)], followed by the addition of chloracetyl chloride (2.0 mmol) and milling for 10 min. [b] Yield of *R*-**2** based on **1**. [c] Determined by HPLC analysis. [d] Ligand (15 mol%). [e] Ligand (10 mol%). [f] *n*-Heptane (2 eq.). [g] After recrystallization from methanol.

up production of 1-g products (68% yield, 99.6% ee). Moreover, the recovery (67% yield) and reuse of the grinding auxiliary made the process more sustainable. Further reduction of *R*-**2** could be easily achieved under Ni/H_2 conditions (see path A, reduction reaction) and *R*-**3** was obtained in 75% yield with >99% ee.

Final synthesis of levo-praziquantel (*R*-PZQ)

An acylation reaction with cyclohexyl chloride as the acylation agent and a ring-closing reaction in the presence of a base were two inevitable steps for the synthesis PZQ and *R*-PZQ in most of the reported processes.[8,9] Considering the causticity and storage security of acyl chloride, the safer and environmentally-friendly carboxylic acid together with coupling reagents[23] was envisioned to give a beneficial result.

Table 4 Optimization of chemical conditions for the synthesis of *R*-PZQ[a]



Entry	Coupling reagent/eq.	Yield of *R*-PZQ[b]/%	ee of *R*-PZQ[c]/%
1	CDI (1.0)	72	99.0
2[d]	CDI (1.0)	10	n.d.
3	DIC (1.0)	62	99.3
4	EDCI (1.0)	68	100
5	**EDCI/HOBt (1.0/1.0)**	**84**	**99.7**
6	DCC/DMAP (1.0/0.2)	55	98.5
7	DCC/DMAP/HOBt (1.0/0.2/1.0)	67	99.8

[a] Reaction conditions: cyclohexanecarboxylic acid (1.0 mmol) and a coupling reagent were placed in a 50 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 6 mm, Φ_{MB} = 0.13) on a planetary mill and milled at 200 rpm for 30 min followed by the addition of *R*-**3** (1.0 mmol) and milling for 30 min. [b] Yield of *R*-PZQ based on *R*-**3**. [c] Determined by HPLC analysis. [d] *R*-**3** (1.0 mmol), cyclohexanecarboxylic acid (1.0 mmol) and CDI (1.0 mmol) were placed in a 50 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 6 mm, Φ_{MB} = 0.13) and milled at 200 rpm for 60 min. CDI = *N*,*N*′-carbonyldiimidazole, DIC = *N*,*N*′-diisopropylcarbodiimide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, DCC = dicyclohexylcarbodiimide, and DMAP = *N*,*N*-4-dimethylaminopyridine.

Gratifyingly, a preliminary evaluation at the laboratory scale showed that an acylation/ring-closing sequence from *R*-**3** (99.7% ee) and cyclohexanecarboxylic acid proceeded smoothly in the presence of CDI (1.0 equiv.) under one-pot ball-milling conditions (Table 4, entry 1).

Further examination of the coupling reagents showed that all the tested reagents gave the corresponding *R*-PZQ in moderate to good yields (entries 1 and 3–7), among which the EDCI/HOBt combination provided the best yield of 84% with excellent preservation of enantioselectivity (99.7%). As expected, the pre-activation of carboxylic acid with the coupling reagents was necessary (entry 1 *vs.* entry 2). After a careful study of the mechanochemical parameters (Table S4†), *R*-PZQ (84% yield, 99.7% ee) was prepared by milling of cyclohexanecarboxylic acid (1.0 equiv.) and EDCI/HOBt (1.1/1.0 equiv.) at 200 rpm with a stainless-steel ball (d_{MB} = 6 mm, Φ_{MB} = 0.13) for 30 min, followed by the addition of *R*-**3** (1.0 equiv.) and milling for another 30 min. Notably, this mechanochemical protocol provided a convenient one-pot procedure for the final construction of the drug *R*-PZQ without additional bases, and even at 50 mmol scale production (80% yield and 99.3% ee). Last but not least, chromatography purification of the crude *R*-PZQ could be successfully avoided.

Conclusions

In summary, we have reported two pathways for the practical and scalable synthesis of levo-praziquantel (*R*-PZQ). The chiral resolution pathway requires no protective processes, toxic sol-

vents and chromatographic methods. Notably, the racemization of *S*-**3** is attainable by using safe, cheap and recyclable DL-tartaric acid, and the resolution agent L-tartaric acid can also be recovered and reused three times. The asymmetric synthesis pathway provides a concise and environmentally friendly route for the construction of the target chiral drug *via* three-step syntheses. In addition, the mechanochemical (asymmetric) aza-Henry reaction and the acylation-ring closing reaction endow both synthetic routes with time-saving and green properties.

Experimental

General details

Chemicals were sourced from commercial suppliers and purified by standard procedures unless otherwise noted. 2,3-Dihydroisoquinoline was prepared according to the literature report.[24] All of the ball-milling reactions were conducted in a planetary mill or mixer mill with 25 mL, 50 mL or 250 mL stainless-steel/zirconia grinding vessels and stainless-steel/zirconia milling balls, if not mentioned otherwise. TLC (Thin-Layer Chromatography) analysis was performed using pre-coated glass plates. Melting points (mp) were obtained on a digital melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker instrument (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard. Coupling constants (J) are given in Hz. Mass spectra were recorded with a high-resolution MS instrument (Bruker Daltonics micro TOF II) using an ESI ion source. HPLC was performed on Shimadzu LC-20AT apparatus, using a Daicel Chiralpak AD-H or OD-H chiral column, eluting with a mixture of hexane and isopropyl alcohol or ethanol. Optical rotations were measured with a Rudolph Autopol V polarimeter.

2-Chloro-1-(1-(nitromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-ethanone (2).[25] A mixture of **1** (0.131 g, 1.0 mmol), nitromethane (0.092 g, 1.5 mmol), triethylamine (0.111 g, 1.1 mmol) and NaCl (4.64 g) was placed in a 50 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 6 mm, Φ_{MB} = 0.13) on a planetary mill and milled at 200 rpm for 30 min followed by the addition of chloroacetyl chloride (0.226 g, 2.0 mmol) and milling at 200 rpm for 10 min. At the end of the experiment, the reaction mixture was dissolved with ethyl acetate (30 mL) and filtered. The filtrate was washed with water (3 × 5 mL) and brine (3 × 5 mL) and concentrated under vacuum, followed by purification *via* column chromatography (SiO_2, 100% hexane to 2 : 1 hexane/ethyl acetate) to give the expected compound **2** as a white solid (0.223 g, 83% yield). M.p.: 99.0–100.1 °C (lit.[23] 100–103 °C). The rotamers ratio is 3.3, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.15 (m, 4H), 6.16 (dd, J = 5.6, 5.6 Hz, 0.77 H, major), 5.72 (dd, J = 4.0, 4.0 Hz, 0.23 H, minor), 4.88–4.66 (m, 2 H), 4.34 (d, J = 12.4 Hz, 0.23 H, minor), 4.19 (d, J = 12.4 Hz, 0.77 H, major), 4.11 (d, J = 12.4 Hz, 0.77 H, major), 4.06 (d, J = 12.4 Hz, 0.23 H, minor), 3.95–3.86 (m, 1H), 3.75–3.65 (m, 1H), 3.15–2.98 (m, 1H), 2.93–2.73 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.5 major, 166.2 minor, 134.8 minor, 134.1 major, 131.0 major, 130.3 minor, 130.1 minor, 129.2 major, 128.9 minor, 128.5 major, 127.4 major, 127.3 major, 127.2 minor, 126.7 minor, 78.2 minor, 78.0 major, 55.3 minor, 52.0 major, 41.32 major, 41.26 major, 40.8 minor, 36.3 minor, 28.8 major, 27.3 minor.

1-(1-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-chloroethanone (3). To a solution of **2** (0.268 g, 1.0 mmol) in methanol/aqueous ammonia (10 : 1, 11 mL), RANEY® nickel (0.5 mL, 100 g solid in 110 mL water) was added at room temperature. The mixture was degassed with H_2 and H_2 gas was continuously passed over the solution under balloon pressure for 3 h. The reaction mixture was filtered through Celite and concentrated under vacuum, which was followed by purification *via* column chromatography (SiO_2, 100 : 0.5 DCM/Et_3N to 20 : 1 : 0.1 DCM/MeOH/Et_3N) to give the expected compound **3** as a grey yellow oil (0.179 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.11 (m, 4H), 4.90–4.83 (m, 1H), 4.80 (dd, J = 10.0, 4.4 Hz, 1H), 3.77–3.71 (m, 1H), 3.68 (d, J = 17.3 Hz, 1H) 3.53 (d, J = 17.3 Hz, 1H), 3.03–2.94 (m, 1H), 2.93–2.71 (m, 3H), 1.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 135.0, 134.2, 129.4, 127.0, 126.6, 124.7, 56.9, 50.1, 49.8, 38.8, 28.9. HRMS (ESI): $C_{12}H_{15}{}^{35}ClN_2O_2$ $[M + H]^+$: calcd 239.0946, found: 239.0936.

(*R*)-1-(1-(Aminomethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-chloroethanone (*R*-3). A mixture of **3** (0.907 g, 3.8 mmol) and L-tartaric acid (0.285 g, 1.9 mmol) in methanol/water (5 : 1, 8 mL) was stirred and refluxed for 3 h, and gradually cooled to room temperature. The resulting suspension was filtered, rinsed with ice-cold methanol (3 × 2 mL) and dried to give a white solid salt (0.399 g, 54% yield). The salt was dissolved in water (5 mL) and the pH of the mixture was adjusted to 11–12 by the addition of 5 N NaOH solution and then the mixture extracted with ethyl acetate (3 × 2 mL). The combined organic layers were concentrated under vacuum to give *R*-**3** as a white solid (0.236 g, 26% yield, 99.9% ee). M.p.: 121.7–123.2 °C. $[a]_D^{20}$ = −316.30 (c = 1, $CHCl_3$). HPLC analysis: Chiralcel AD-H column, ethanol/hexane 30 : 70, flow rate 0.7 mL min^{-1}, UV detection at 254 nm, t_{minor} = 16.2 min, t_{major} = 19.6 min, 99.9% ee.

(*R*)-2-Chloro-1-(1-(nitromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethenone (*R*-2). **1** (0.131 g, 1.0 mmol), *n*-Heptane (0.30 mL, 2.0 mmol) and **C4** (0.089 g, 15 mol%) were added to a 25 mL zirconia vessel and pre-mixed on a mixer mill at 15 Hz for 5 min. Then, nitromethane (0.09 g, 1.5 mmol), triethylamine (0.111 g, 1.1 mmol) and silica gel (0.8 g) were added with two 10 mm zirconia balls, and the mixture was milled at 15 Hz for 30 min [3 × (10 min + 5 min break)], followed by the addition of chloroacetyl chloride (0.226 g, 2.0 mmol) and milling for 10 min. At the end of the experiment, the reaction mixture was directly added to a SiO_2 chromatographic column and purified (100% hexane to 2 : 1 hexane/ethyl acetate) to give *R*-**2** as a white solid (0.215 g, 80% yield, 88% ee). The solid was then recrystallized from methanol to give 99.8% ee in a total yield of 70%. M.p.: 98.9–100.2 °C. $[a]_D^{20}$ = 56.00 (c = 1, $CHCl_3$). HPLC analysis: Chiralcel OD-H column, isopropanol/hexane

30 : 70, flow rate 1.0 mL min^{-1}, UV detection at 210 nm, t_{minor} = 16.4 min, t_{major} = 46.4 min, 88.2% ee; t_{minor} = 16.3 min, t_{major} = 46.0 min, 99.8% ee.

Synthesis of *R*-3 from *R*-2. Refer to the procedure for the synthesis of **3** from **2**. An excellent maintenance of ee was achieved (*R*-**2** of 99.8% ee resulted in *R*-**3** of 99.6% ee).

(*R*)-2-(Cyclohexanecarbonyl)-1,2,3,6,7,11*b*-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (*R*-PZQ).[4] A mixture of cyclohexanecarboxylic acid (0.128 g, 1.0 mmol), EDCI (0.192 g, 1.0 mmol) and HOBt (0.135 g, 1.0 mmol) was placed in a 50 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 8 mm, Φ_{MB} = 0.13) on a planetary mill and milled at 200 rpm for 30 min followed by the addition of *R*-**3** (0.239 g, 1.0 mmol, 99.9% ee) and milling at 200 rpm for 30 min. At the end of the experiment, the milled mixtures were rinsed with saturated aqueous sodium bicarbonate (3 × 5 mL), dissolved with 20 mL ethyl acetate, and washed with saturated aqueous sodium bicarbonate (3 × 5 mL) and brine (3 × 5 mL), respectively. The organic layers were concentrated under vacuum and purified by column chromatography (SiO_2, 100% hexane to 2 : 1 hexane/ethyl acetate) to give the expected *R*-PZQ as a white solid (0.263 g, 84% yield, 99.7% ee). M.p.: 112.0–113.0 °C (lit.[4] 113.5–114.5 °C). $[a]_D^{23}$ = −132.20 (*c* = 1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.13 (m, 4H), 5.15 (d, *J* = 13.2 Hz, 1H), 4.91–4.73 (m, 2H), 4.46 (d, *J* = 17.2 Hz, 0.77H, major), 4.36 (d, *J* = 17.2 Hz, 0.23H, minor), 4.07 (d, *J* = 17.2 Hz, 0.77H, major), 4.07 (d, *J* = 17.2 Hz, 0.23H, minor), 3.30–2.74 (m, 4H), 2.61–2.40 (m, 1H), 1.89–1.22 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 174.8, 164.4, 134.7, 132.8, 129.7 minor, 129.3 major, 127.7 minor, 127.5 major, 127.0, 125.5 major, 125.2 minor, 55.8 minor, 55.0 major, 49.6 minor, 49.0 major, 46.3 minor, 45.2 major, 40.8, 39.1 major, 38.7 minor, 29.5 minor, 29.3 major, 29.2 minor, 29.0 major, 28.9 minor, 28.7 major, 25.7. HPLC analysis: Chiralcel OD-H column, isopropanol/hexane 25 : 75, flow rate 1.0 mL min^{-1}, UV detection at 240 nm, t_{minor} = 11.5 min, t_{major} = 15.4 min, 99.7% ee.

Scaled-up synthesis of 2. A mixture of **1** (6.56 g, 50.0 mmol), nitromethane (4.58 g, 75.0 mmol), triethylamine (5.56 g, 55.0 mmol) and NaCl (120 g) was placed in a 250 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 8 mm, Φ_{MB} = 0.13) on a planetary mill and milled at 200 rpm for 30 min followed by the addition of chloroacetyl chloride (11.29 g, 100.0 mmol) and milling at 200 rpm for 10 min. At the end of the experiment, the reaction mixture was dissolved with ethyl acetate (2 × 60 mL) and filtered to give grey solid residues. The solid residues were washed with methanol and dried to afford the recovered NaCl (96 g), which can be reused directly in the next reactions three times. The ethyl acetate layers were washed with water (3 × 30 mL) and concentrated under vacuum to give the crude product as a grey powder, which was recrystallized from methanol to give **2** as a white solid (11.02 g, 82% yield). M.p.: 118.7–120.0 °C.

Scaled-up synthesis of 3. To a solution of **2** (6.72 g, 25.0 mmol) in methanol/aqueous ammonia (10 : 1, 150 mL), RANEY® nickel (12.5 mL, 100 g solid in 110 mL water) was added at room temperature. The mixture was degassed with H_2 and H_2 gas was continuously passed over the solution under 15 psi pressure in a hydrogenator for 3 h. Then, the reaction mixture was filtered through Celite and concentrated under vacuum to give the crude product (5.80 g) as a pale-yellow oil. To a solution of the crude product in methanol (40 mL), DL-tartaric acid (3.75 g) was added, stirred and refluxed for 4 h, and then gradually cooled to room temperature. The resulting suspension was filtered, rinsed with ice-cold methanol (3 × 10 mL) and dried to give a white solid salt (7.76 g, 80% yield). The salt was dissolved in water (50 mL) and the pH of the mixture was adjusted to 11–12 by the addition of 5 N NaOH solution and then the mixture extracted with ethyl acetate (3 × 40 mL). The combined organic layers were concentrated under vacuum to give **3** (4.42 g, 74% yield). The aqueous phase was retained for the recovery of DL-tartaric acid.

Scaled-up synthesis of *R*-3 *via* chiral resolution. A mixture of **3** (11.94 g, 50.0 mmol) and L-tartaric acid (3.75 g, 25.0 mmol) in methanol/water (5 : 1, 90 mL) was stirred and refluxed for 3 h, and gradually cooled to room temperature. The resulting suspension was filtered, rinsed with ice-cold methanol (3 × 10 mL) and dried to give a white solid salt (5.25 g, 54% yield). The salt was dissolved in water (40 mL) and the pH of the mixture was adjusted to 11–12 by the addition of 5 N NaOH solution and then the mixture extracted with ethyl acetate (3 × 30 mL). The combined organic layers were concentrated under vacuum to give *R*-**3** (3.20 g, 27% yield, 95.1% ee). The aqueous phase was retained for the recovery of L-tartaric acid. Further recrystallization of the product from acetone/hexane (1 : 1) gave the expected *R*-**3** in 23% yield (2.75 g) with 99.7% ee. HPLC analysis: Chiralcel AD-H column, ethanol/hexane 30 : 70, flow rate 0.7 mL min^{-1}, UV detection at 254 nm, t_{minor} = 17.0 min, t_{major} = 21.0 min, 99.7% ee.

Recovery of *S*-3. The mother liquors from the chiral resolution process were concentrated under reduced pressure and 5 N NaOH solution was added to them until pH 11–12 was reached. The solution was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were concentrated under reduced pressure to give *S*-**3** as a yellow solid (9.01 g, 37.8% ee). A mixture of *S*-**3** (9.01 g, 37.7 mmol) and DL-tartaric acid (5.66 g, 37.7 mmol) in methanol (80 mL) was stirred and refluxed for 3 h and gradually cooled to room temperature. The resulting suspension was filtered, rinsed with ice-cold methanol (3 × 10 mL) and dried to give a white solid salt. The salt was dissolved in water (60 mL) and the pH of the mixture was adjusted to 11–12 by the addition of 5 N NaOH solution and then the mixture extracted with ethyl acetate (3 × 40 mL). The combined organic layers were concentrated under vacuum to give partly racemized *S*-**3** (7.64 g, 85% yield, 24.8% ee). The aqueous phase was retained for the recovery of DL-tartaric acid. After three repeated treatment cycles with DL-tartaric acid, racemized *S*-**3** (5.56 g, 62% yield, 2.7% ee) was obtained.

Recovery of L-tartaric acid (DL-tartaric acid). To the combined basic aqueous portions from *R*-**3**, **3** or racemized *S*-**3** liberation processes, calcium chloride (25.0 mmol for *R*-**3** or **3**, 97.1 mmol for racemized *S*-**3**) was added to precipitate calcium L-tartrate or calcium DL-tartaric acid, followed by the addition

of equimolar 98% sulfuric acid (1.33 mL for *R*-**3** or **3**, 5.18 mL for racemized *S*-**3**) to liberate L-tartrate or DL-tartaric acid as a white suspension. The suspension was filtered and rinsed with ice-cold methanol (3 × 5 mL for *R*-**3** or **3**, 3 × 15 mL for racemized *S*-**3**) and dried to give L-tartaric acid (average 2.70 g, 72%) or DL-tartaric acid (average 2.74 g for **3**, 10.64 g for racemized *S*-**3**, 73%).

Scaled-up synthesis of *R*-2. **1** (0.75 g, 5.7 mmol), *n*-heptane (1.67 mL, 11.4 mmol) and **C4** (1.01 g, 1.7 mmol) were added to a 50 mL zirconia vessel and pre-mixed on a mixer mill at 15 Hz for 5 min. Then nitromethane (0.52 g, 8.6 mmol), triethylamine (0.63 g, 6.3 mmol) and silica gel (3.5 g) were added with two 12 mm zirconia balls, and the mixtures were milled at 15 Hz for 30 min [3 × (10 min + 5 min break)], followed by the addition of chloroacetyl chloride (1.29 g, 11.4 mmol) and milling for 10 min. At the end of the experiment, the reaction mixture was dissolved with ethyl acetate (30 mL) and filtered to give grey solid residues. The solid residues were washed with methanol and dried to afford the recovered silica gel (2.8 g) which can be reused with freshly added ones in the next reactions three times. The filtrates were washed with water (3 × 15 mL) and brine (3 × 15 mL), and concentrated under vacuum, followed by recrystallization from methanol to give *R*-**2** as a white solid (1.04 g, 68% yield, 99.6% ee). HPLC analysis: Chiralcel OD-H column, isopropanol/hexane 30 : 70, flow rate 1.0 mL min^{-1}, UV detection at 210 nm, t_{minor} = 16.2 min, t_{major} = 46.1 min, 99.6% ee.

Scaled-up synthesis of *R*-PZQ. A mixture of cyclohexanecarboxylic acid (6.41 g, 50.0 mmol), EDCI (9.59 g, 50.0 mmol) and HOBt (6.76 g, 50.0 mmol) was placed in a 250 mL stainless-steel vessel with a stainless-steel ball (d_{MB} = 8 mm, Φ_{MB} = 0.13) on a planetary mill, and milled at 200 rpm for 30 min followed by the addition of *R*-**3** (11.94 g, 50.0 mmol, 99.7% ee) and milling at 200 rpm for 30 min. At the end of the experiment, the milled mixtures were rinsed with saturated aqueous sodium bicarbonate (3 × 100 mL), dissolved with 150 mL ethyl acetate, and washed with saturated aqueous sodium bicarbonate (3 × 50 mL) and brine (3 × 50 mL), respectively. The organic layers were concentrated under vacuum to give the crude *R*-PZQ as a white solid. Further purification of the solid was carried out by recrystallization from acetone/hexane (1 : 1) (12.50 g, 80% yield, 99.3% ee). HPLC analysis: Chiralcel OD-H column, isopropanol/hexane 25 : 75, flow rate 1.0 mL min^{-1}, UV detection at 240 nm, t_{minor} = 11.2 min, t_{major} = 14.8 min, 99.3% ee.

Author contributions

Conceptualization: J. Yu; methodology: J. Yu, H. Shou, G. Peng; investigation: Z. He, H. Shou, G. Peng; funding acquisition: J. Yu; visualization: J. Yu, Z. He; writing – original draft: J. Yu, Z. He; writing – review and editing: J. Yu, H. Shou.

Conflicts of interest

There are no conflicts to declare.

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