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Multistep Mechanochemical Synthesis of PZ-1190, a Multitarget Antipsychotic Agent

Vittorio Canale,* Michał Kamiński, Wojciech Trybała, Michał Abram, Krzysztof Marciniak, Xavier Bantreil, Frédéric Lamaty, Jan Rodriguez Parkitna, and Paweł Zajdel



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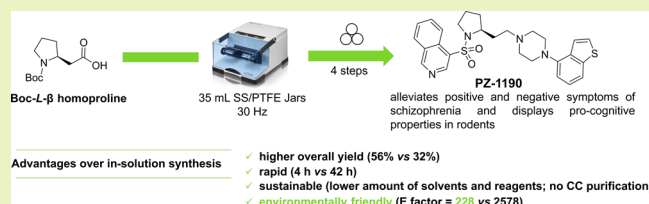
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ABSTRACT: A solid-state approach was used to synthesize compound **PZ-1190**, a multitarget ligand for serotonin and dopamine receptors with potential antipsychotic activity in rodents. Compared to the classical batch synthesis approach, the developed multistep mechanochemical protocol improved the overall yield (from 32% to 56%), reduced the reaction time (from 42 to 4 h), and decreased the use of toxic reagents and organic solvents. All synthesized intermediates and **PZ-1190** were isolated in high purity by extraction without the requirement of chromatographic purification. **PZ-1190** was obtained in high enantiomeric purity ($\geq 99\%$ ee) with no impact of grinding processes on the integrity of the stereocenter. The described procedures represent rare examples of mechanochemical reduction of a carboxylic function, which might open up the possibility of obtaining crucial β - and γ -amino alcohols in a sustainable manner. The oxidation of an aliphatic alcohol into an aldehyde using mechanochemistry has also been reported for the first time. The obtained results confirmed the suitability of mechanochemistry as a sustainable and efficient method for synthesizing candidates for preclinical development.

KEYWORDS: Azinesulfonamide derivatives, Multistep mechanochemical synthesis, Medicinal mechanochemistry, Green chemistry, Antipsychotic agents



INTRODUCTION

In the last two decades, mechanochemical methods, in particular ball milling, have emerged as alternative techniques for the synthesis of organic compounds.^{1–5} The growing interest in this solid-state approach has been pursued because of its methodological advantages over classical thermal methods and to address the need for sustainable development goals.^{6,7}

A substantial number of organic transformations to synthesize active pharmaceutical ingredients (APIs) have been successfully adapted for mechanochemical or biocatalytic mechanochemical protocols.^{8–10} This trend led to coining of the term “medicinal mechanochemistry”,^{11,12} to highlight the ongoing evolution of solid-state processes from a screening technique in pharmaceutical materials science to a sustainable and versatile methodology to produce pharmaceuticals.

Extending the concept of medicinal mechanochemistry, we have recently demonstrated the suitability of the mechanochemical approach to provide lead structures for preclinical evaluation and for obtaining focused libraries for biological screening.^{13,14} Continuing our efforts on the development of greener chemical routes for biologically active compounds, we optimized a multistep mechanochemical approach to synthesize (S)-4-[(2-[2-[4-(benzo[b]thiophen-4-yl)piperazin-1-yl]ethyl]pyrrolidin-1-yl)sulfonyl]isoquinoline (**PZ-1190**). This

compound acts as a potent multitarget serotonin and dopamine ligand and has promising antipsychotic properties.

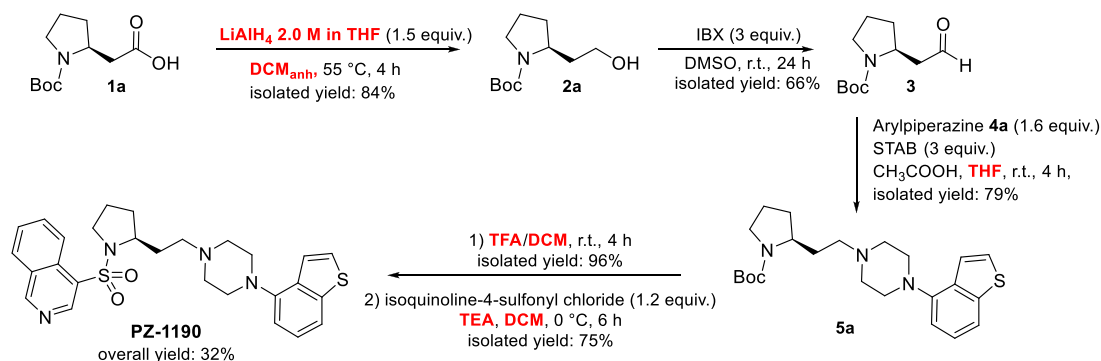
It alleviates positive and negative symptoms of schizophrenia and shows pro-cognitive properties in rodents.¹⁵ According to previously published procedures,¹⁵ the batch synthesis of **PZ-1190** comprised the following five steps: (1) reduction of Boc-L- β -homoproline **1a**, in the presence of lithium aluminum hydride, (2) oxidation of the obtained primary alcohol **2a** to the corresponding aldehyde by using 2-iodoxybenzoic acid (IBX), followed by (3) reductive amination of intermediate **3** with commercially available 1-(benzo[b]thiophene-4-yl)piperazine **4a**, (4) removal of the Boc protecting group, and (5) sulfonylation of the secondary amine to obtain the final compound with an overall yield of 32% (Scheme 1).

The main limitations of this synthetic procedure are the use of environmentally toxic solvents (e.g., dichloromethane [DCM], tetrahydrofuran [THF]), hazardous reagents (e.g., LiAlH_4), and the need for column chromatography purification for most of the synthetic steps. Based on the advantage of

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Scheme 1. Five-Step Synthesis Process for Compound PZ-1190 in Solution^a

^a LiAlH_4 = lithium aluminum hydride; THF = tetrahydrofuran; DCM = dichloromethane; IBX = 2-iodoxybenzoic acid; DMSO = dimethyl sulfoxide; STAB = sodium triacetoxyborohydride; TFA = trifluoroacetic acid; TEA = triethylamine.

mechanochemistry over the in-batch method, a multistep solid-state approach was used to synthesize compound PZ-1190. The elaborated protocol aimed to limit the use of toxic reagents and solvents, improve the overall yield, reduce the reaction time, facilitate product purification, and increase process efficiency.

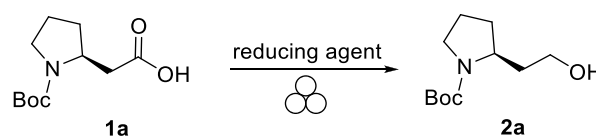
RESULTS AND DISCUSSION

Once a lead structure has been identified, the development of an efficient and scalable synthetic pathway is critical to provide the desired compound in sufficient amounts for further pharmacological/toxicological assessments and preclinical development. While optimizing the synthetic protocol for PZ-1190, we investigated the application of a mechanochemical procedure based on the original conditions for the in-solution protocol. The optimization started with the reduction of the carboxylic function of **1a** to the corresponding alcohol derivative **2a**.

Traditional in-solution protocols require the use of an excess amount of strong reducing agent (i.e., diborane, LiAlH_4 , or diisobutylaluminum hydride) with a highly flammable and explosive property, which limits their application under the mechanochemical condition. According to the literature data on the safe reduction of aldehyde, ketone, and ester functions in the solid state,¹⁶ the strong reducing agent lithium borohydride generated *in situ* from sodium borohydride (NaBH_4) and lithium chloride (LiCl) was initially tested in a 10 mL stainless steel (SS) jar containing a 1.5 cm diameter ball by using a vibratory ball mill (vbm) operated at 30 Hz (Table 1).

The evaluation of different amounts of NaBH_4 and LiCl revealed that a stoichiometric ratio of 1:3 provided optimal efficiency (entry 3 vs entries 1, 2, and 9, Table 1) after 4 h of milling. A prolonged milling time slightly increased the formation of the alcohol derivative **2a** without reaching full conversion (58–65%). To enhance the overall mixing, the use of a liquid additive was evaluated. Regardless of the nature of the organic solvent used, the conversion kinetics were slower than those observed in neat grinding. Thus, to increase the reactivity of the substrate, we applied a two-stage procedure involving *in situ* formation of a mixed anhydride followed by reduction to the corresponding alcohol in the presence of 1.5 equiv of NaBH_4 (Table 2). A screening of activating agents revealed that only 1,1'-carbonyldiimidazole (CDI) could achieve very high conversion (up to 97%) in only 30 min of

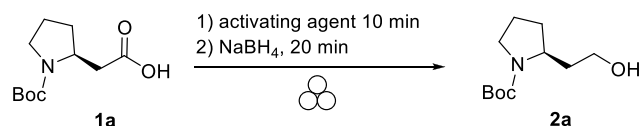
Table 1. Optimization of Milling Conditions for the Reduction of Boc-L-β-homoproline into an Alcohol Derivative^a



entry	reducing agent (equiv)	milling time (min)	conv. ^a (%)
1	$\text{NaBH}_4 + \text{LiCl}$ (1 + 2)	160	12
2	$\text{NaBH}_4 + \text{LiCl}$ (1.5 + 2)	160	25
3	$\text{NaBH}_4 + \text{LiCl}$ (1.5 + 4.5)	160	55
4 ^b		160	50
5		220	57
6		280	60
7		340	65
8		400	65
9	$\text{NaBH}_4 + \text{LiCl}$ (1.5 + 6)	160	47
10 ^b		160	45
11		220	52
12		280	57
13		340	58

^aReaction conditions: vbm 30 Hz, 10 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 125 mg, milling load = 15 mg/mL. ^b75 μL ($\eta = 0.6$ $\mu\text{L}/\text{mg}$) of MeTHF or MeOH were added. ^cConversions were determined by HPLC analysis.

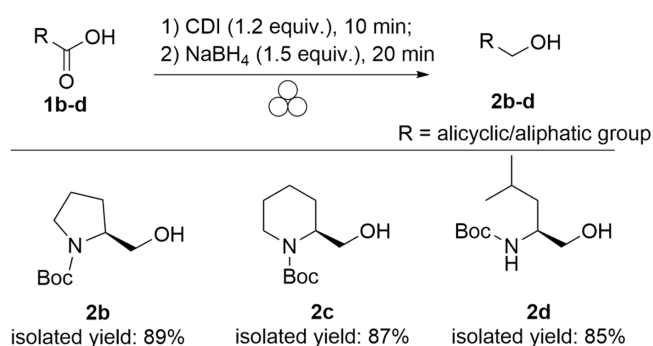
milling, while the use of methanesulfonyl chloride or isobutyl chloroformate limited the formation of product to 67% and 71%, respectively. Moreover, decreasing the amount of the reducing agent from 1.5 to 1.2 or 1 equiv was less favorable (entries 5 and 6 vs entry 7, Table 2). Then, the impact of different milling frequency and jar material on reaction kinetics was additionally investigated. Results revealed that performing the reaction at lower frequencies (20 and 25 Hz) reduced the conversion rate to 78 and 86%, respectively (Table S3). Similar effect was observed when the reduction was carried out in 10 mL PTFE jars (Table S3), confirming that grinding the reagents in SS jars was more efficient. Under these optimized conditions, the reaction was performed on a gram scale by using 35 mL SS jars to afford product **2a** with a yield of 86% (entry 8, Table 2). The enantiomeric purity of intermediate **2a** was assessed by chiral RP-HPLC analysis, confirming that mechanochemical reduction of Boc-L-β-homoproline occurred without racemization of the stereocenter (Figures S1–S4).

Table 2. Optimization of Milling Conditions for the Reduction of Boc-L-β-homoproline into an Alcohol Derivative^a

entry	activating agent (equiv)	NaBH ₄ (equiv)	milling time (min.)	conv. ^c /yield ^d (%)
1	methanesulfonyl chloride (1)	1.5	30	67/–
2	isobutyl chloroformate (1)	1.5	30	71/–
3	1,1'-carbonyldiimidazole (1)	1.5	30	80/–
4		1.5	50	82/–
5	1,1'-carbonyldiimidazole (1.2)	1	30	67/–
6		1.2	30	78/–
7		1.5	30	97/88
8 ^b		1.5	30	94/86

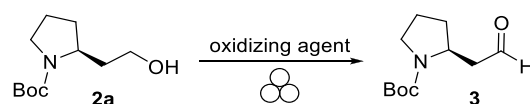
^aReaction conditions: vbm 30 Hz, 10 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 125 mg, milling load = 15 mg/mL. ^b35 mL SS jar, total mass of reagents = 1.5 g, milling load = 45 mg/mL. ^cConversions were determined by HPLC analysis. ^dIsolated yields calculated after workup procedure.

Considering the versatility of β-amino alcohols as chiral auxiliaries for the synthesis of biologically active compounds¹⁷ or ligands in various asymmetric syntheses,^{18,19} the development of green synthetic routes for the synthesis of vicinal amino alcohols remains a hot topic of research. In this context, the mechanochemical conditions were found to successfully reduce the carboxylic function of *N*-protected α-amino acids to corresponding β-amino alcohols in very high purity and yields (85–89%), thus confirming the versatility of the protocol (Scheme 2).

Scheme 2. Optimized Milling Conditions for the Reduction of α-Amino Acids into β-Amino Alcohol Derivatives^a

^aReaction conditions: vbm 30 Hz, 35 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 500 mg, milling load = 15 mg/mL. Isolated yields calculated after work-up procedure.

The oxidation of pharmaceutical intermediates often represents a bottleneck for the synthesis of biologically active compounds, thereby forcing pharmaceutical industries to develop environmentally and economically sustainable procedure suitable for the large-scale production of APIs.²⁰ In our case, there are only few available protocols reporting the oxidation of aromatic alcohols to aldehydes or ketones in a ball mill mainly by using 2-iodoxybenzoic acid (IBX) as the oxidizing agent.^{21,22} To extend this protocol to aliphatic primary alcohols, we investigated the possibility of oxidizing intermediate 2a in the presence of IBX or the more reactive Dess-Martin Periodinane (DMP) under mechanochemical conditions (Table 3).

Table 3. Optimization of Milling Conditions for the Oxidation of Primary Alcohol into an Aldehyde^a

entry	oxidizing agent (equiv)	milling time (min)	conv. ^c /yield ^d (%)
1	IBX (0.5)	30	80/–
2		45	88/–
3	DMP (0.5)	30	100/73
4		45	100/75
5 ^b		30	100/76

^aReaction conditions: vbm 30 Hz, 10 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 125 mg, milling load = 15 mg/mL. ^b35 mL SS jar, total mass of reagents = 1.5 g, milling load = 45 mg/mL. ^cConversions were determined by HPLC analysis. ^dIsolated yields calculated after workup procedure.

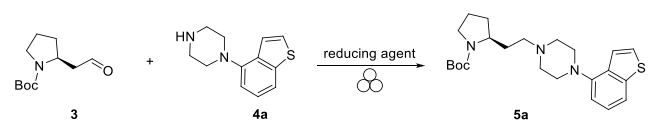
Milling of intermediate 2a after the addition of 0.5 equiv of IBX for 45 min resulted in 88% conversion of the substrate into the corresponding aldehyde. An increase in the amount of the oxidizing agent to 1 equiv enabled the full formation of the desired intermediate 3. In contrast, the use of 0.5 equiv of DMP was sufficient to ensure the complete consumption of the substrate in high yield (75%). Although the initial conditions were maintained for 45 min, the reaction time could be reduced to 30 min without affecting both conversion and yield; this finding was consistent with a highly efficient solid-state oxidation process. This optimized procedure involving DMP was then applied on a larger scale in 35 mL SS vessels to obtain aldehyde 3 in high purity and yield (76%).

The amine moiety is frequently present in various biologically active compounds because of its ability to stabilize the ligand-protein complex by the formation of an ionic interaction. It may also induce aqueous solubility, which guarantees favorable physicochemical properties and facilitates API formulation. One of methods used for the introduction of an amine moiety in the chemical template via the formation of the C–N bond involves the reductive amination.^{23,24} Of note, the reductive amination reaction represents a synthetic step to easily achieve antipsychotic drugs bearing the arylpiperazine/arylperidine motif, for example, quetiapine, lurasidone, and

risperidone.^{25–27} Although this reaction is practically relevant, rare examples of the application of reductive amination in a ball mill have been reported thus far.²⁸

Adapting the mechanochemical procedure from the literature, intermediate **3** and commercially available 1-(benzo[*b*]thiophene-4-yl)piperazine **4a** were milled in the presence of a commonly used reducing agent (1 equiv) in a 10 mL SS jar for 1 h (Table 4). The results showed that sodium

Table 4. Optimization of Milling Conditions for the Reductive Amination Reaction^a



entry	reducing agent (equiv)	milling time (min)	conv. ^e /yield ^f (%)
1	NaBH(OAc) ₃ (1)	60	64/–
2		135	71/–
3	NaBH ₃ CN (1)	60	83/–
4		135	87/–
5		200	87/–
6 ^b		135	96/–
7 ^{b,c,d}		135	100/91

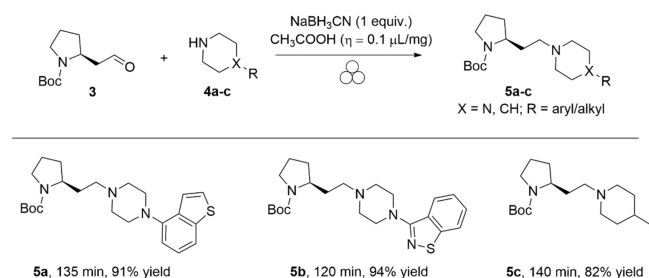
^aReaction conditions: compound **4a** (1 equiv), vbm 30 Hz, 10 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 125 mg, milling load = 15 mg/mL. ^bAldehyde was introduced in two equal portions, after 1 h of milling. ^c35 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 1.5 g, milling load = 45 mg/mL. ^d $2 \times 150 \mu\text{L}$ of CH₃COOH ($\eta = 0.2 \mu\text{L}/\text{mg}$). ^eConversions were determined by HPLC analysis. ^fIsolated yield calculated after workup procedure.

cyanoborohydride (NaBH₃CN) provided higher conversion than sodium triacetoxyborohydride (NaBH(OAc)₃) with milder reducing properties (83% vs 64%). An increase in the milling time did not or only slightly improved the formation of product **5a**, probably due to the degradation of the aldehyde function during the mechanochemical reaction. The addition of intermediate **3** in two portions within a 1 h interval successfully increased the conversion rate up to 96%. Next, quick optimization of the scale-up process in a 35 mL SS jar using the LAG condition was required to obtain complete conversion, leading to the production of intermediate **5a** in a very high yield (91%).

To investigate the substrate scope for the optimized mechanochemical protocol, selected arylpiperazine or alicyclic amine derivatives (**4b** and **4c**, respectively) were then subjected to reductive amination on a larger scale. The obtained derivatives **5b** and **5c** were produced in very good yields (94% and 82%, respectively) and purities comparable to those obtained using classical thermal methods (Scheme 3), thus demonstrating the versatility of the mechanochemical approach.

In line with our previously published procedures,^{13,14,29} the secondary amine, obtained following the treatment of Boc-protected intermediate **5a** with gaseous HCl, was mechanochemically reacted in a 35 mL SS jar with isoquinoline-4-sulfonyl chloride,³⁰ to yield the sulfonamide derivative **PZ-1190**. Although the excellent conversion rate was achieved very fast (within 5 min) by using a small excess of a sulfonylating agent (1.1 equiv) and a nontoxic inorganic base (K₂CO₃, 3 equiv), the isolated yield after the workup procedure was unsatisfactory (<85%).

Scheme 3. Optimized Milling Conditions for the Coupling of Boc-L-β-homoprolinal **3** with Different Amines^a



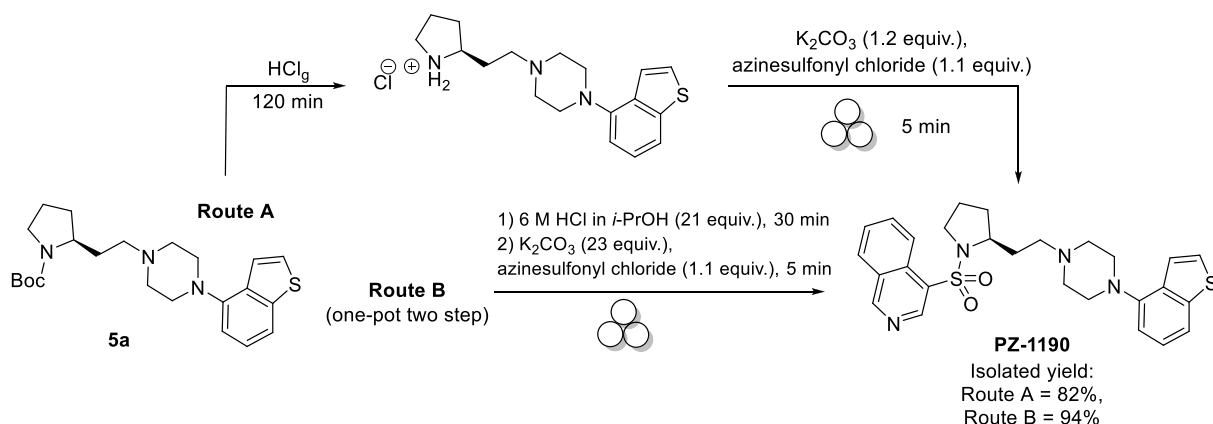
^aReaction and conditions: different aryl/alkyl amines **4a–c** (1 equiv), vbm 30 Hz, 35 mL SS jar, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 500 mg, milling load = 15 mg/mL. Aldehyde and CH₃COOH (50 μL , $\eta = 0.1 \mu\text{L}/\text{mg}$) were introduced in two equal portions, after 1 h of milling. Isolated yields calculated after work-up procedure.

This result prompted us to optimize this synthetic step by using an alternative deprotection/sulfonylation protocol completely performed in a ball mill with acid-resistant 35 mL PTFE jars as the milling medium (Scheme 4). Following this newly elaborated procedure, a secondary amine intermediate, generated by the simple milling of a Boc-protected derivative with 6 M HCl solution in isopropanol (*i*Pr-OH), was prior neutralized by using K₂CO₃ as a grinding auxiliary and then directly subjected to sulfonylation with azinesulfonyl chloride. Thus, the simplified one-pot two-step protocol ensured that the final compound **PZ-1190** was obtained in higher purity and higher isolated yield than that achieved through the sequential two-step procedure (94% vs 82%).

Furthermore, HPLC analysis confirmed that the chirality of the stereocenter was retained during the whole multistep mechanochemical procedure yielding **PZ-1190** in high enantiomeric purity ($\geq 99\%$ ee; Figures S5–S8). Finally, the sustainability of the newly developed approach was assessed by the green chemistry metrics Ecoscale and E factor (for more details, see Tables S1 and S2 in the Supporting Information).^{31,32} Apart from the reductive amination reaction, the use of the solid-state protocol, resulted in good Ecoscale scores (>65) for each synthetic step (Scheme 5). In contrast, most of the synthetic procedures previously performed in solution did not meet the Ecoscale criteria (scores < 50). Moreover, a comparison of the calculated E factor values for the synthesis of compound **PZ-1190** revealed an 11-fold decrease (from 2578 vs 228) when switching from the thermal method to mechanochemistry (Scheme 5).

CONCLUSIONS

By using a multistep mechanochemical approach, compounds **PZ-1190**, a potent multitarget ligand for serotonin and dopamine receptor with promising antipsychotic activity in rodents, were synthesized on a gram scale in high purity (100%) with an overall yield of 56%. Moreover, the elaborated solid-state procedure enabled rapid preparation of the desired lead compound (milling time of 4 h), while substantially limiting the use of environmentally toxic solvents and reagents (e.g., DCM, THF, trifluoroacetic acid, LiAlH₄, and triethylamine) and simplifying reaction conditions and workup protocols (Figure 1). Indeed, all intermediates and **PZ-1190** were obtained by simple extraction without the need for purification or crystallization.

Scheme 4. Deprotection/Sulfonylation Reaction Conditions: Two-Step (Route A) vs One-Pot, Two-Step (Route B) Procedures^a

^aReaction and conditions (Route A): $\text{HCl}_{(g)}$, 120 min then vbm 30 Hz, 35 mL SS jars, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 3 g, milling load = 90 mg/mL, 5 min. Reaction and condition (Route B): vbm 30 Hz, 35 mL PTFE jars, $\phi_{\text{ball}} = 1.5$ cm, total mass of reagents = 3 g, milling load = 90 mg/mL, 35 min.

Scheme 5. Optimized Mechanochemical Protocol and Related Green Metric Values for the Synthesis of PZ-1190

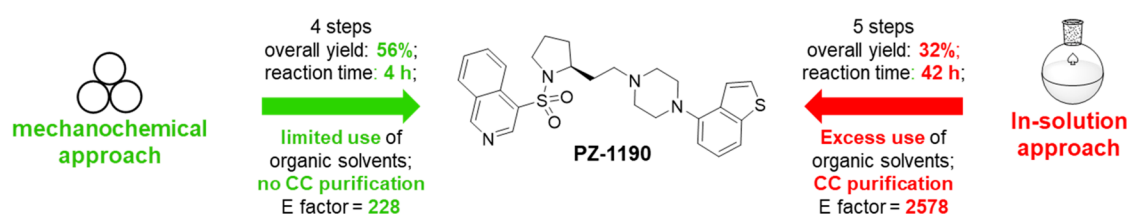
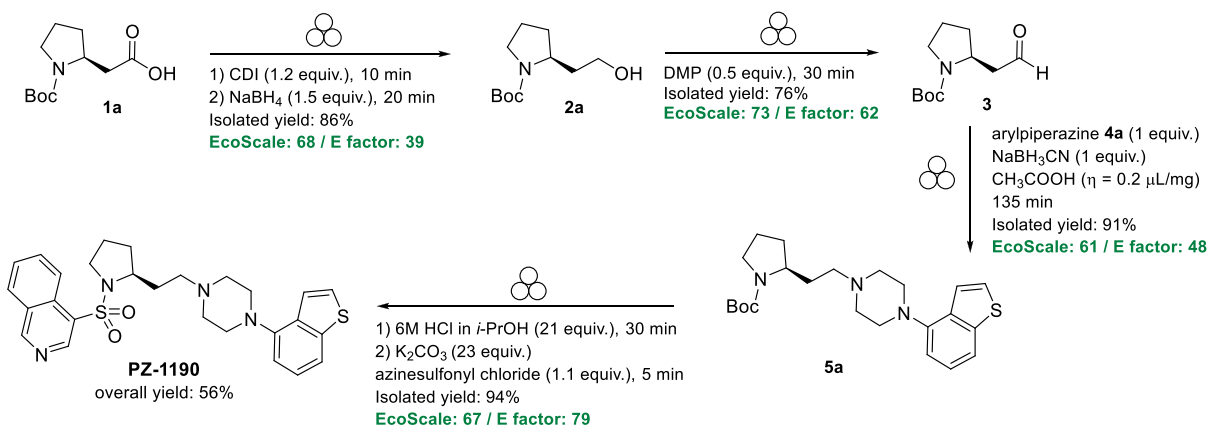


Figure 1. Mechanochemical vs in-solution multistep synthesis of PZ-1190.

A noteworthy finding is that the unexplored mechanochemical reduction of the carboxylic function of *N*-protected α - and β -amino acids was successfully performed with high yields (85–89%). Moreover, to the best of our knowledge, the described procedure represents a rare example of the oxidation of alcohol into aldehyde and deprotection of Boc function under milling conditions. Of note, The use of mechanochemical force provided **PZ-1190** in high enantiomeric purity ($\geq 99\%$ ee) with no impact of stereocenter integrity. The advantages of the mechanochemical approach over classic thermal methods were finally confirmed by assessment with the commonly used green chemistry metrics Ecoscale (<50 vs >65) and E factor (2578 vs 228). The obtained results confirmed the suitability of mechanochemistry as a sustainable

and efficient method for the multistep synthesis of biologically active compounds and could facilitate the integration of medicinal mechanochemistry as a key component of preclinical development programs.

EXPERIMENTAL SECTION

General Chemical Methods. All commercially available reagents were of the highest purity from Fluorochem, Across Organic, AmBeed, and Sigma-Aldrich. All mechanochemical reactions were carried out in a vibratory ball-mill Retsch Mixer Mill MM 400 operated at 30 Hz. Reactions were conducted in stainless steel or PTFE jars with a volume of 10 or 35 mL, containing one stainless steel ball ($\phi_{\text{ball}} = 1.5$ cm). Milling load is defined as the sum of the mass of the reactants per free volume in the jar and was equal to 15, 45, or 90 mg/mL. Total mass of reagents used was 125 mg (10 mL

jar) or alternatively 500 mg, 1.5 or 3 g (in a 35 mL jar). All of the reactions using vibratory ball-mill were performed under air and ambient temperature.

HPLC analysis was performed by using Alliance Waters 2695 System (Waters Corporation, Milford, MA, U.S.A.) equipped with a UV/vis Waters 2998 PDA spectrophotometric detector. Spectra were analyzed in the 200–800 nm range with 1.2 nm resolution. Chromatographic separations were carried out using a Chromolith SpeedROD RP 18 column; 4.6 × 50 mm and 1.7 μm particle size. The column was maintained at 30 °C, and eluted under gradient conditions from 100% to 0% of eluent A over 3 min, at a flow rate of 5 mL min⁻¹. Eluent A: water/TFA (0.1%, v/v); eluent B: acetonitrile/TFA (0.1%, v/v).

Mass spectra were recorded on a UPLC-MS/MS system consisting of a Waters Acquity Premier coupled to a Waters Xevo TQ-S Cronos mass spectrometer (electrospray ionization mode ESI). Chromatographic separations were carried out using the Acquity UPLC BEH (bridged ethylene hybrid) C18 column; 2.1 × 100 mm, and 1.7 μm particle size, equipped with Acquity UPLC BEH C18 VanGuard precolumn; 2.1 × 5 mm, and 1.7 μm particle size. The column was maintained at 40 °C, and eluted under gradient conditions from 95% to 0% of eluent A over 10 min, at a flow rate of 0.3 mL min⁻¹. Eluent A: water/formic acid (0.1%, v/v); eluent B: acetonitrile/formic acid (0.1%, v/v). Chromatograms were recorded using a Waters e1 PDA detector. Spectra were analyzed in the 200–500 nm range with 1.2 nm resolution and sampling rate 20 points/s. MS detection settings of Waters Xevo TQ-S Cronos mass spectrometer were as follows: source temperature 150 °C, desolvation temperature 350 °C, desolvation gas flow rate 600 L h⁻¹, cone gas flow 100 L h⁻¹, capillary potential 3.00 kV, cone potential 30 V. Nitrogen was used for both nebulizing and drying gas. The data were obtained in a scan mode ranging from 50 to 1000 *m/z* in time intervals of 0.5 s intervals. Data acquisition software was MassLynx V 4.2 (Waters).

HRMS analyses were performed on a UPLC Acquity H-Class from Waters hyphenated to a SynaptG2-S mass spectrometer with a dual ESI source from Waters.

¹H and ¹³C NMR spectra were recorded on a JEOL JNM-ECZR500 RS1 (ECZR version) at 500 and 126 MHz, respectively and were reported in ppm using deuterated solvent for calibration (CDCl₃). The *J* values were reported in hertz (Hz), and the splitting patterns were designated as follows: br. s. (broad singlet), s (singlet), d (doublet), t (triplet), dd (doublet of doublets), t (triplet of triplets), ddd (doublet of doublet of doublets), and m (multiplet).

The enantiomeric purity and the specific optical rotation ($[\alpha]_D^{20}$) of intermediates **2a–d** and final compound **PZ-1190** were determined on a Jasco p-2000 polarimeter p-2000 (Jasco Inc. Easton, MD). For these purposes, 1% solutions of compounds in methanol were prepared.

Chiral HPLC assays were conducted on Shimadzu Prominence-i LC-2030C 3D plus (Shimadzu Corporation, Kyoto, Japan) equipped with a Lux Cellulose-3 (Phenomenex), column (5 μm, 150 × 4.6 mm), or CHIRAL ART Amylose-C (YMC), column (5 μm, 250 × 4.6 mm) for **2a** and **PZ-1190**, respectively. Standard solutions (1 mg/mL) of each compound were prepared in acetonitrile. A volume of 10 μL was injected. The following conditions water/acetonitrile/TFA = 90/10/0.1 (v/v), flow rate 0.7 mL/min, detection at λ = 203 nm, and column oven temperature 30 °C were applied for **2a**, while acetonitrile/methanol = 75/25 (v/v), flow rate = 1.4 mL/min, detection at λ = 223 nm, and column oven temperature 25 °C were employed for final compound **PZ-1190**.

Elemental analyses for C, H, N and S were carried out using the elemental Vario EL III Elemental Analyzer (Hanau, Germany). All values are given as percentages and were within ±0.4% of the calculated values.

General Procedure for the Reduction of the Carboxylic Function of Boc-L-β-homoproline in Ball Mill. Boc-L-β-homoproline **1a** (715.35 mg, 3.112 mol, 1 equiv) and 1,1'-carbonyldiimidazole (CDI; 607.49 mg, 3.746 mmol, 1.2 equiv) were introduced in two 35 mL stainless steel jars (milling load = 45 mg/mL), each one charged with a stainless steel ball (ϕ_{ball} = 1.5 cm), and milled for 10 min.

Subsequently NaBH₄ was added (177.16 mg, 4.683 mmol, 1.5 equiv), and the reaction was carried out for additional 20 min. The resulting mixture from both jars was then solubilized in AcOEt (25 mL) and the organic layer was washed with 5% aqueous HCl solution (2 × 5 mL) and water (2 × 5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure.

tert-Butyl (S)-2-(2-Hydroxyethyl)pyrrolidine-1-carboxylate (2a) [CAS: 220312–34–5]. Light yellow oil (1.16 g, yield 86%). Molecular formula: C₁₁H₂₁NO₃; MW: 215.29; monoisotopic mass: 215.15; UPLC/MS: *t*_R = 5.86 min, purity = 100%, [M + H]⁺ = 216.2. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.39–1.42 (m, 10H), 1.53–1.72 (m, 2H), 1.80–1.89 (m, 2H), 1.89–2.01 (m, 1H), 3.24–3.36 (m, 2H), 3.47–3.66 (m, 2H), 4.07–4.15 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ ppm 23.5, 28.5, 31.3, 38.4, 46.5, 53.7, 59.3, 79.9, 156.4. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₁H₂₂NO₃, 216.1594; found, 216.1594. Chiral HPLC ≥ 99% ee (*t*_R = 16.538 min). $[\alpha]_D^{20}$ = +31.3 (c 0.1, MeOH). Elemental analysis calculated for C₁₁H₂₁NO₃: C, 61.37%; H, 9.83%; N, 6.51%. Found: C, 61.58%; H, 10.11%; N, 6.73%.

General Procedure for the Reduction of the Carboxylic Function of N-Boc-Protected α-Amino Acids in Ball Mill.

Different N-Boc-protected α-amino acids **1b–d** (1 equiv) and 1,1'-carbonyldiimidazole (CDI, 1.2 equiv) were introduced in two 35 mL stainless steel jars (milling load = 15 mg/mL), each one charged with a stainless steel ball (ϕ_{ball} = 1.5 cm) and milled for 10 min. Subsequently, NaBH₄ was added (1.5 equiv), and the reaction was carried out for an additional 20 min. The resulting mixture from both jars was then solubilized in AcOEt (25 mL) and the organic layer was washed with 5% aqueous HCl solution (2 × 5 mL), water (2 × 5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure.

tert-Butyl (S)-2-(Hydroxymethyl)pyrrolidine-1-carboxylate (2b) [CAS: 170491–63–1]. General procedure was followed with Boc-L-proline (230.67 mg, 1.072 mol, 1 equiv), CDI (208.52 mg, 1.286 mmol, 1.2 equiv), and NaBH₄ (60.81 mg, 1.607 mmol, 1.5 equiv) to afford the primary alcohol as a light yellow oil (383.92 mg, yield 89%).

Molecular formula: C₁₀H₁₉NO₃; MW: 201.27; monoisotopic mass: 201.14; UPLC/MS: *t*_R = 5.20 min, purity = 98%, [M + H]⁺ = 202.1. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.45 (s, 9H), 1.53–1.62 (m, 1H), 1.70–1.87 (m, 2H), 1.94–2.04 (m, 1H), 3.30 (s, 1H), 3.40–3.47 (m, 1H), 3.53–3.64 (m, 2H), 3.90–3.97 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ ppm 24.1, 28.5, 28.8, 47.5, 60.2, 67.7, 80.2, 157.2. HRMS (ESI): *m/z* [M + Na] calcd for C₁₀H₁₉NNaO₃, 224.1263; found, 224.1252. $[\alpha]_D^{20}$ = +53.5 (c 0.1, MeOH). Elemental analysis calculated for C₁₀H₁₉NO₃: C, 59.68%; H, 9.52%; N, 6.96%. Found: C, 59.82%; H, 9.57%; N, 6.82%.

tert-Butyl (S)-2-(Hydroxymethyl)piperidine-1-carboxylate (2c) [CAS: 118811–03–3]. General procedure was followed with Boc-L-pipecolic acid (238.53 mg, 1.040 mol, 1 equiv), CDI (202.43 mg, 1.248 mmol, 1.2 equiv), and NaBH₄ (59.03 mg, 1.561 mmol, 1.5 equiv) to afford primary alcohol as a white solid (389.72 mg, yield 87%).

Molecular formula: C₁₁H₂₁NO₃; MW: 215.29; monoisotopic mass: 215.15; UPLC/MS: *t*_R = 5.92 min, purity = 100%, [M + H]⁺ = 216.1. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.34–1.42 (m, 1H), 1.42–1.46 (m, 9H), 1.53–1.62 (m, 3H), 1.62–1.69 (m, 1H), 2.20–2.30 (m, 1H), 2.80–2.88 (m, 1H), 3.58 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.79 (dd, *J* = 10.9, 9.1 Hz, 1H), 3.88–3.96 (m, 1H), 4.23–4.31 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ ppm 19.7, 25.3, 28.5, 40.0, 52.6, 61.8, 79.9, 156.4. HRMS (ESI): *m/z* [M + Na] calcd for C₁₁H₂₁NNaO₃, 238.1419; found, 238.1414. $[\alpha]_D^{20}$ = +42.0 (c 0.1, MeOH). Elemental analysis calculated for C₁₁H₂₁NO₃: C, 61.37%; H, 9.83%; N, 6.51%. Found: C, 61.25%; H, 10.21%; N, 6.30%.

tert-Butyl (S)-2-(1-Hydroxy-4-methylpentane-2-yl)carbamate (2d) [CAS: 142121–48–0]. General procedure was followed with Boc-L-leucine (239.62 mg, 1.036 mol, 1 equiv), CDI (201.59 mg, 1.243 mmol, 1.2 equiv), and NaBH₄ (58.79 mg, 1.554 mmol, 1.5 equiv) to afford primary alcohol as a light yellow oil (382.73 mg, yield 85%).

Molecular formula: $C_{11}H_{23}NO_3$; MW: 217.31; monoisotopic mass: 217.17; UPLC/MS: $t_R = 6.46$ min, purity = 100%, $[M + Na]^+ = 240.4$. 1H NMR (500 MHz, $CDCl_3$) δ ppm 0.91 (dd, $J = 6.6, 2.4$ Hz, 6H), 1.22–1.36 (m, 2H), 1.43 (s, 9H), 1.59–1.71 (m, 1H), 2.14–2.53 (m, 1H), 3.48 (dd, $J = 10.9, 6.0$ Hz, 1H), 3.60–3.66 (m, 1H), 3.67–3.74 (m, 1H), 4.36–4.78 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 22.3, 23.1, 24.9, 28.5, 40.7, 51.2, 66.6, 79.8, 156.7. HRMS (ESI): m/z $[M + Na]$ calcd for $C_{11}H_{23}NNaO_3$, 240.1576; found, 240.1570. $[\alpha]_D^{20} = -23.8$ (c 0.1, MeOH). Elemental analysis calcd for $C_{11}H_{23}NO_3$: C, 60.80%; H, 10.67%; N, 6.45%. Found: C, 60.97%; H, 10.82%; N, 6.58%.

General Procedure for the Oxidation of Primary Alcohol in Ball Mill. Intermediate **2a** (755.41 mg, 3.511 mmol, 1 equiv) and oxidating agent DMP (744.59 mg, 1.756 mmol, 0.5 equiv) were introduced in two 35 mL stainless steel jar jars (milling load = 45 mg/mL), each one charged with a stainless steel ball ($\phi_{ball} = 1.5$ cm). After 30 min of milling, the contents of the jars was solubilized in AcOEt (30 mL) and the organic layer was washed with saturated solution of $Na_2S_2O_3$ (2×10 mL), water (2×10 mL), dried over Na_2SO_4 , filtered, and concentrated.

tert-Butyl (S)-2-(2-Oxoethyl)pyrrolidine-1-carboxylate (3) [CAS: 170491–62–0]. Light yellow oil (1.14 g, yield 76%). Molecular formula: $C_{11}H_{19}NO_3$, MW: 213.28; monoisotopic mass: 213.14. UPLC/MS: $t_R = 7.15$ min, purity = 98%, $[M + H]^+ = 214.2$. 1H NMR (500 MHz, $CDCl_3$) δ ppm 1.36–1.47 (m, 9H), 1.56–1.69 (m, 1H), 1.82 (t, $J = 7.0$ Hz, 2H), 2.00–2.15 (m, 1H), 2.38–2.51 (m, 1H), 2.71–2.95 (m, 1H), 3.31 (br. s., 2H), 4.12–4.29 (m, 1H), 9.74 (t, $J = 2.0$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.3, 27.9, 31.9, 46.1, 49.1, 51.9, 79.0, 154.1, 200.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{20}NO_3$, 214.1438; found, 214.1438. Elemental analysis calcd for $C_{11}H_{19}NO_3$: C, 61.95%; H, 8.98%; N, 6.57%. Found: C, 62.03%; H, 9.09%; N, 6.64%.

General Procedure for the Reductive Amination in Ball Mill. Different amines **4a–c** (1 equiv), aldehyde **3** (0.9 equiv), $NaBH_3CN$ (1 equiv), and glacial CH_3COOH (50 μ L, $\eta = 0.1$ μ L/mg) were introduced in two 35 mL stainless steel jars (milling load = 15 mg/mL), each one charged with a stainless steel ball ($\phi_{ball} = 1.5$ cm) and milled for 60 min. Then, a second portion of aldehyde and glacial CH_3COOH was added and the reaction was left to mill for another 60–80 min. Next, the resulting mixture from both jars were solubilized in AcOEt (25 mL) and the organic layer washed with saturated $NaHCO_3$ solution (2×10 mL), water (2×10 mL), saturated NaCl solution (1×10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure.

tert-Butyl (S)-2-[2-[4-(Benzo[b]thiophen-4-yl)piperazin-1-yl]ethyl]pyrrolidine-1-carboxylate (5a). General procedure was followed with 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride **4a** (544.77 mg, 2.138 mmol, 1 equiv), aldehyde **3** (821.86 mg, 3.85 mmol, 1.8 equiv), $NaBH_3CN$ (134.36 mg, 2.138 mmol, 1 equiv), and 2×150 μ L of glacial CH_3COOH ($\eta = 0.2$ μ L/mg). Reaction was carried out for 135 min (milling load = 15 mg/mL) to afford intermediate **5a** as light yellow oil (1.62 g, yield 91%).

Molecular formula: $C_{23}H_{33}N_3O_2S$; MW: 415.60; monoisotopic mass: 415.23. UPLC/MS: $t_R = 6.08$ min, purity = 99%, $[M + H]^+ = 416.4$. 1H NMR (500 MHz, $CDCl_3$) δ ppm 1.35–1.58 (m, 11H), 1.64–2.10 (m, 6H), 2.45 (br. s., 2H), 2.71 (br. s., 4H), 3.17 (br. s., 4H), 3.31 (br. s., 2H), 3.76–3.89 (m, 1H), 6.88 (d, $J = 7.7$ Hz, 1H), 7.23–7.30 (m, 1H), 7.34–7.42 (m, 2H), 7.53 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 23.1, 28.7, 29.8, 31.0, 31.5, 46.1, 52.2, 53.8, 55.8, 56.0, 79.3, 112.3, 117.1, 122.0, 125.0, 126.2, 134.2, 141.2, 148.5, 154.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{34}N_3O_2S$, 416.2366; found, 416.2367. Elemental analysis calcd for $C_{23}H_{33}N_3O_2S$: C, 66.47%; H, 8.00%; N, 10.11%; S, 7.71%. Found: C, 66.66%; H, 8.32%; N, 10.33%; S, 8.09%.

tert-Butyl (S)-2-[2-[4-(Benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl]pyrrolidine-1-carboxylate (5b). General procedure was followed with 3-(piperazin-1-yl)benzo[d]isothiazole **4b** (164.63, 0.751 mmol, 1 equiv), aldehyde **3** (288.19 mg, 1.351 mmol, 1.8 equiv), $NaBH_3CN$ (47.17 mg, 0.751 mmol, 1 equiv), and 2×50 μ L of glacial CH_3COOH ($\eta = 0.1$ μ L/mg). Reaction was carried out for

120 min (milling load = 15 mg/mL) to afford tertiary amine as a light yellow oil (587.92 mg, yield 94%).

Molecular formula: $C_{22}H_{32}N_4O_2S$; MW: 416.58; monoisotopic mass: 416.22; UPLC/MS: $t_R = 5.33$ min, purity = 100%, $[M + H]^+ = 417.23$; 1H NMR (500 MHz, $CDCl_3$) δ ppm 1.39–1.62 (m, 11H), 1.64–1.74 (m, 1H), 1.76–2.01 (m, 4H), 2.36–2.78 (m, 5H), 3.26–3.46 (m, 2H), 3.49–3.66 (m, 4H), 3.81 (d, $J = 19.1$ Hz, 1H), 7.33 (ddd, $J = 8.1, 7.1, 0.9$ Hz, 1H), 7.41–7.49 (m, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.1, 28.7, 30.4, 31.8, 46.1, 50.1, 53.2, 55.7, 55.9, 79.2, 120.6, 124.0, 127.6, 128.1, 152.8, 154.7, 154.8, 163.9. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{22}H_{32}N_4O_2S$: 417.2319; found: 417.2320. Elemental analysis calcd for $C_{22}H_{32}N_4O_2S$: C, 63.43%; H, 7.74%; N, 13.45%; S, 7.70%; found: C, 63.69%; H, 8.06%; N, 13.83%; S, 7.99%.

tert-Butyl (S)-2-[2-(4-Methylpiperidin-1-yl)ethyl]pyrrolidine-1-carboxylate (5c). General procedure was followed with 4-methylpiperidine **4c** (90.84 mg, 0.916 mmol, 1 equiv), aldehyde **3** (351.61 mg, 1.649 mmol, 1.8 equiv), $NaBH_3CN$ (57.55 mg, 0.916 mmol, 1 equiv), and 2×50 μ L of glacial CH_3COOH ($\eta = 0.1$ μ L/mg). Reaction was carried out for 140 min (milling load = 15 mg/mL) to afford intermediate **5c** as light yellow oil (550.52 mg, yield 82%). Molecular formula: $C_{17}H_{32}N_2O_2$; MW: 296.46; monoisotopic mass: 296.25; UPLC/MS: $t_R = 5.07$ min, purity = 100%, $[M + H]^+ = 297.0$. 1H NMR (500 MHz, $CDCl_3$) δ ppm 0.86–0.91 (m, 3H), 1.16–1.27 (m, 3H), 1.28–1.37 (m, 1H), 1.43 (br. s., 9H), 1.59 (dd, $J = 12.5, 1.9$ Hz, 2H), 1.62–1.68 (m, 1H), 1.71–2.06 (m, 6H), 2.29 (d, $J = 6.4$ Hz, 2H), 2.23–2.24 (m, 2H), 2.88 (d, $J = 11.1$ Hz, 2H), 3.27 (br. s., 2H), 3.71 (br. s., 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 22.0, 23.1, 28.6, 29.8, 30.9, 31.6, 32.1, 34.3, 46.0, 54.2, 55.8, 56.3, 79.2, 154.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{32}N_2O_2$, 297.2537; found, 297.2537. Elemental analysis calcd for $C_{17}H_{32}N_2O_2$: C, 68.88%; H, 10.88%; N, 9.45%. Found: C, 69.13%; H, 10.99%; N, 9.74%.

General Procedure for Deprotection of Boc Functionality in Solid State and Sulfonylation of Secondary Amine in a Ball Mill. Intermediate **5** (750 mg, 1.91 mmol) was subjected to $HCl(g)$ for 2 h at room temperature following previously published procedures.^{13,29} The secondary amine obtained as hydrochloride salt (229.06 mg, 0.651 mmol, 1 equiv), isoquinoline-4-sulfonyl chloride (162.99 mg, 0.716 mmol, 1.1 equiv) and K_2CO_3 (107.94 mg, 0.781 mmol, 1.2 equiv) were introduced in two 35 mL stainless steel jars (milling load = 15 mg/mL), each one charged with a stainless steel ball ($\phi_{ball} = 1.5$ cm) and milled for 5 min. Next, the resulting mixture from both jars were solubilized in AcOEt (25 mL) and the organic layer washed with saturated with $KHSO_4$ solution with pH = 3.5 (3×5 mL), saturated NaCl solution (1×5 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure.

General Procedure for One-Pot, Two-Step Deprotection/Sulfonylation of Secondary Amine in Ball Mill for Obtaining PZ-1190. Intermediate **5** (270.43 mg, 0.651 mmol, 1 equiv) was introduced into two 35 mL PTFE jars (milling load = 90 mg/mL) each one charged with a stainless steel ball ($\phi_{ball} = 1.5$ cm) followed by addition of 6 M HCl solution in isopropanol (759.1 μ L, 4.55 mmol, 7 equiv) in 3 portions after 10 min of milling. After completion of Boc removal, K_2CO_3 (2.0 g, 14.96 mmol, 23 equiv) and isoquinoline-4-sulfonyl chloride (162.95 mg, 0.716 mmol, 1.1 equiv) were added. The reaction was carried out for 5 min and the resulting powder from both jars was washed with water (4×10 mL) to yield final compound. The procedure was repeated twice.

(S)-4-[(2-[2-[4-(Benzo[b]thiophen-4-yl)piperazin-1-yl]ethyl]pyrrolidin-1-yl)sulfonyl]isoquinoline (PZ-1190). Beige powder (1.24 g, yield 94%). Molecular formula: $C_{27}H_{30}N_4O_2S_2$; MW: 506.68; monoisotopic mass: 506.18. UPLC/MS: $t_R = 6.58$ min, purity = 100%, $[M + H]^+ = 507.0$. 1H NMR (500 MHz, $CDCl_3$) δ ppm 1.60–1.76 (m, 4H), 1.81–1.91 (m, 1H), 2.06–2.17 (m, 1H), 2.50 (d, $J = 6.2$ Hz, 2H), 2.59–2.83 (m, 4H), 3.20 (br. s., 4H), 3.39–3.47 (m, 2H), 4.05 (tt, $J = 7.8, 4.1$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 7.23–7.28 (m, 1H), 7.38 (s, 2H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 7.5$ Hz, 1H), 7.86–7.91 (m, 1H), 8.07 (d, $J = 8.2$ Hz, 1H), 8.84 (d, $J = 8.7$ Hz, 1H), 9.10 (s, 1H), 9.39 (s, 1H). ^{13}C NMR (126 MHz,

CDCl₃) δ ppm 24.4, 31.1, 32.8, 48.6, 51.9, 53.6, 55.2, 58.6, 112.4, 117.2, 121.9, 124.7, 125.1, 125.2, 128.5, 128.7, 129.0, 129.1, 131.8, 132.7, 134.1, 141.2, 145.2, 148.3, 157.7. HRMS (ESI): m/z [M + H]⁺ calcd for C₂₇H₃₁N₄O₂S₂, 507.1883; found, 507.1884. Chiral HPLC > 99% ee (t_R = 5.712 min). $[\alpha]_D^{20}$ = -66.1° (c 0.1, MeOH). Elemental analysis calcd for C₂₇H₃₀N₄O₂S₂: C, 64.00%; H, 5.97%; N, 11.06%; S, 12.65%. Found: C, 63.61%; H, 5.60%; N, 10.87%; S, 13.04%.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.3c04023>.

Green metrics calculation, assessment of the specific optic rotation values, chiral HPLC chromatograms, and ¹H and ¹³C NMR spectra for all synthesized compounds (PDF)

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Author Contributions

V.C., M.K., and W.T. carried out the experiments; M.K. and W.T. characterized all intermediates and final compound; K.M. synthesized and characterized the reagent isoquinoline-4-sulfonyl chloride; X.B. and F.M. performed HRMS analysis and contributed to assess green metric values; M.A. performed the chiral HPLC experiments; V.C. conceived the study, analyzed the results; V.C. and P.Z. wrote the manuscript; J.R.P. and P.Z. acquired the fundings. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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