Mechanochemical reductive amination of aldehydes and ketones: solid-state synthesis of the antiparkinsonian drugs rasagiline and safinamide

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ABSTRACT: A general two-step, one-pot mechanochemical procedure for carrying out reductive amination under solvent-free conditions is described. The method involves milling the starting materials in stainless steel jar and balls in the presence of zinc chloride and sodium cyanoborohydride, and was applied to a broad range of carbonyl compounds, including aromatic and aliphatic aldehydes and ketones, and also two drug molecules (benzocaine and sulphathiazole) and four natural products (vainillin, menthone, cinnamaldehyde, tryptamine). Its use in target-oriented synthesis was demonstrated by the fully mechanochemical preparation of

two active pharmaceutical ingredients, the anti-Parkinson monoamino oxidase B inhibitors rasagiline and safinamide, with improved green metrics in comparison with solution chemistry.

1. INTRODUCTION

Secondary amine is a widespread motif in drug molecules in all therapeutic areas. They are also frequently used as versatile intermediates in the synthesis of pharmaceuticals and medicinal compounds. Among the methods for synthesizing secondary amines, reductive amination is one of the most widely employed and plays a fundamental role in medicinal chemistry.[1] In this transformation, an aldehyde or ketone reacts with an amine to form an imine intermediate, which is subsequently reduced to yield the corresponding secondary amine. Reductive amination is particularly useful for the selective modification of primary amines, helping to avoid issues related to nitrogen polyalkylation. Additional advantages of this method include mild reaction conditions, methodological simplicity, wide substrate availability, and compatibility with various functional groups.

In recent years, the chemical and pharmaceutical industries have increasingly focused on developing processes that minimize the use and generation of environmentally hazardous substances. In this context, mechanochemical processes have been recognized by IUPAC as one of the top ten emerging technologies in chemistry.[2] Specifically, mechanochemistry has emerged as a valuable tool for the synthesis of Active Pharmaceutical Ingredients (APIs), often providing more efficient, sustainable, safe, and versatile approaches to producing pharmaceutical compounds. This has led to the rise of a new field described as "medicinal mechanochemistry".[3,4,5,6,7]

Although some literature reports on reductive amination using mechanochemistry exist, the available methods present several limitations. For instance, Cho and Kang conducted reductive amination using a mortar and pestle with H_3BO_3-activated $NaBH_4$ as the reducing agent.[8] However, this manual approach compromises reproducibility, as key parameters—such as

grinding frequency, duration, and applied force—are highly dependent on the operator. More recently, Moores *et al.* reported a reductive amination method employing liquid-assisted grinding (LAG) to functionalize chitosan with aldehydes, resulting in the formation of synthetic biopolymers. Nevertheless, the study did not explore the broader synthetic scope of the method.[9] Additionally, Porcheddu investigated a few examples of mechanochemical reductive amination using Bertagnini's salts (bisulfite adducts of aldehydes).[10] However, this approach adds a step, since it requires the prior preparation of the starting materials from the corresponding carbonyl compounds, and was not extended to ketones.

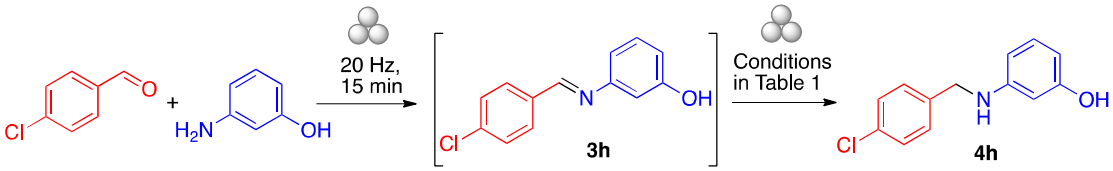
Against this backdrop, we report here a general procedure for carrying out reductive amination under solvent-free conditions using a vibratory mill. Our study explores the scope of the method, including its application to the late-stage functionalization of drug molecules, and demonstrates its application to the synthesis of two monoamine oxidase B inhibitors used as anti-Parkinson drugs: rasagiline and safinamide. One challenge in developing a general, mechanochemical protocol for reductive amination arises from the large number of amines and carbonyl substrates that exist in the liquid state, which may hinder milling efficiency by dampening impact forces, reducing particle-particle contact and limiting the energy transfer between grinding media and reactants. In order to solve this problem, the addition of salts or other inert grinding auxiliaries is a well-documented strategy in mechanochemical synthesis, particularly when liquid reagents are used. By improving mixture rheology and converting viscous pastes into free-flowing solids, these additives maintain effective energy transfer from ball impacts and thereby enhance reaction efficiency.[11,12,13] In other cases, a solid reagent present in the mixture serves also as a grinding auxiliary, enabling the use of liquid reagents.[14,15,16]

2. RESULTS AND DISCUSSION

Optimization

Our optimization work was based on a model reaction yielding the N-aryl secondary amine **4h** from *p*-chlorobenzaldehyde and *m*-aminophenol under vibratory milling conditions, using stainless steel jar and balls. We planned our method as a two-step, one-pot reaction and therefore, after verifying by ^{1}H-NMR that the intermediate imine was formed after milling the starting materials for 15 min at 20 Hz, we started the screening of reducing agents (Scheme 1 and Table 1). We first milled the intermediate imine **3h** and the reducing agents (sodium borohydride or sodium cyanoborohydride) for 30 min at 20 Hz without catalyst, but no conversion into **4h** was observed (Table 1, entries 1 and 2). We next assayed the addition of several acidic promoters such as montmorillonite K10, *p*-toluenesulfonic acid, boric acid, benzoic acid or silica gel, with moderate to good conversions (entries 3 to 12). An improved 91% conversion was achieved by adding zinc chloride as a Lewis acid to sodium borohydride (entry 13), and it increased again to 95% when sodium cyanoborohydride was used instead (entry 14). Furthermore, we studied how the amount of the catalyst and reductive agent affected the reactivity. The use of 1.1 equivalents of $NaBH_3CN$ and 1.5 equivalents of $ZnCl_2$ decreased the conversion to **4h** (entry 15). Similarly, when we maintained the amounts of $NaBH_3CN$ and decreased the quantity of catalyst (1.1, 0.1 or 0.05 equivalents) we also obtained a lower conversion (entries 16-18).

An attempt to perform the reductive amination in a one-step, one-pot protocol, by including the reducing agent and the catalyst from the beginning was thwarted by competing reduction of the carbonyl group.



Scheme 1. Model reaction for the optimization study

Table 1. Optimization of the reaction conditions

Entry	Reducing agent	Eqs	Catalyst	Eqs	Time (min)	Frequency (Hz)	Conversion (%) [a]
1	$NaBH_4$	1.5	-	-	30	20	0
2	$NaBH_3CN$	1.5	-	-	30	20	0
3	$NaBH_4$	1.5	Montmorillonite K10	1.5	30	20	29
4	$NaBH_3CN$	1.5	Montmorillonite K10	1.5	30	20	72
5	$NaBH_4$	1.5	*p*-TsOH	1.5	30	20	70
6	$NaBH_3CN$	1.5	*p*-TsOH	1.5	30	20	46
7	$NaBH_4$	1.5	H_3BO_3	1.5	30	20	25
8	$NaBH_3CN$	1.5	H_3BO_3	1.5	30	20	61
9	$NaBH_4$	1.5	Benzoic acid	1.5	30	20	30
10	$NaBH_3CN$	1.5	Benzoic acid	1.5	30	20	45
11	$NaBH_4$	1.5	SiO_2	1.5	30	20	-
12	$NaBH_3CN$	1.5	SiO_2	1.5	30	20	25
13	$NaBH_4$	1.5	$ZnCl_2$	1.5	30	20	91
14	**$NaBH_3CN$**	**1.5**	**$ZnCl_2$**	**1.5**	**30**	**20**	**95**
15	$NaBH_3CN$	1.1	$ZnCl_2$	1.5	30	20	78
16	$NaBH_3CN$	1.5	$ZnCl_2$	1.1	30	20	75
17	$NaBH_3CN$	1.5	$ZnCl_2$	0.1	30	20	-

18	$NaBH_3CN$	1.5	$ZnCl_2$	0.05	30	20	-

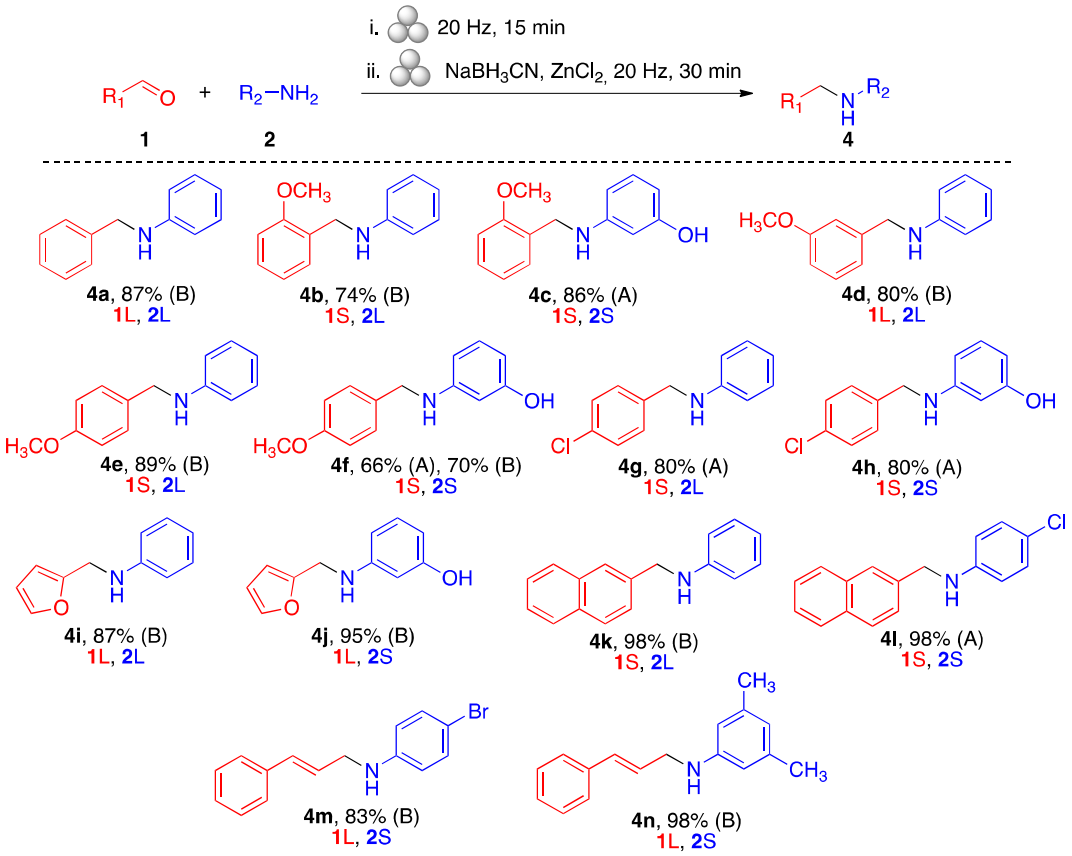
[a] The conversion rate was determined from the ^{1}H-NMR spectra by comparison of the integrals of the methylene signal of the product and the CHO signal of the remaining starting aldehyde.

Scope of the mechanochemical reductive amination

With the optimized conditions in hand (table 1, entry 14), we started our exploration of the scope of the mechanochemical reductive amination (Scheme 2) by examining the reactions of anilines with benzaldehyde (compound **4a**) and with benzaldehyde derivatives bearing either electron-donating (compounds **4b**–**4f**) or electron-withdrawing substituents (compounds **4g** and **4h**). In all cases, the desired products were obtained in good yields, regardless of the electronic nature or steric hindrance of the substituents—as illustrated by comparing the results for the *o*-, *m*-, and *p*-methoxy derivatives (**4b**, **4d** and **4e**). We also investigated variations in the aromatic aldehyde component, including 2-furfural (compounds **4i** and **4j**) and naphthalene-2-carbaldehyde (compounds **4k** and **4l**). Due to the importance of allylamines as synthetic intermediates and in medicinal chemistry,[17] our study of the scope of the reaction also included reductive aminations using cinnamaldehyde, an α,β-unsaturated aldehyde, as the substrate. This afforded the corresponding secondary allylamines (compounds **4m** and **4n**) in good to excellent isolated yields.

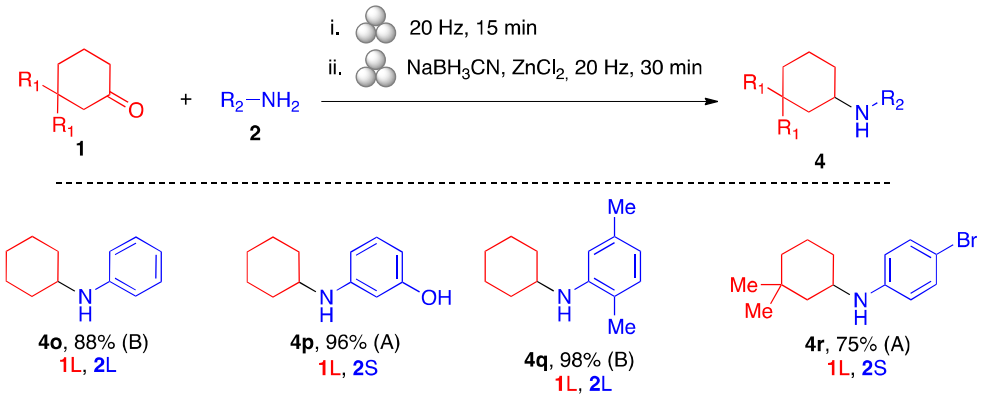
When both starting materials were solid, we used neat grinding conditions (method A). In reactions involving a low-viscosity liquid component or where both reagents were liquids, the addition of anhydrous sodium sulfate as a solid grinding assistant was necessary to facilitate effective mixing and grinding (method B). The choice of this particular grinding assistant was guided by the expectation that it should help displace the imine formation equilibrium by

withdrawing water from the reaction medium. Method B turned out to be more general, as it could be also applied to solid starting materials, as shown by the case of **4f**, but it has the disadvantage of increased residue generation.



Scheme 2. Reductive amination reactions from aromatic amines and aromatic or vinyl aldehydes. Method A: aldehyde (100 mg) and amine (1 eq), 20 Hz for 15 minutes in stainless-steel jar and balls, then $NaBH_3CN$ (1.5 eq) and $ZnCl_2$ (1.5 eq), 20 Hz for 30 minutes. Method B: same conditions, with the addition of 0.5 g of anhydrous Na_2SO_4 at the first step. The solid or liquid nature of the reagents is indicated by S and L, respectively.

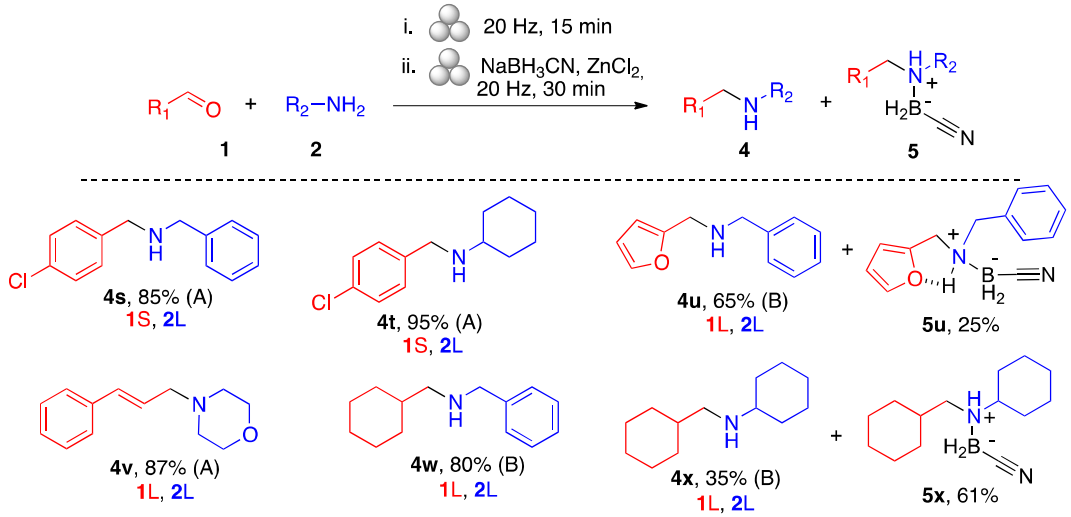
We next investigated briefly the use of ketones as starting materials in the reactions with aromatic amines, as shown in Scheme 3. Electronic effects had a modest influence on the reaction outcomes: electron-withdrawing substituents on the aromatic ring led to lower yields (compound **4r** *vs.* **4o**), whereas electron-rich anilines provided the highest yields (compounds **4p** and **4q**).



Scheme 3. Reductive amination from aromatic amines and ketones. Method A: ketone (100 mg) and amine (1 eq), 20 Hz for 15 minutes in stainless steel; then, $NaBH_3CN$ (1.5 eq) and $ZnCl_2$ (1.5 eq), 20 Hz for 30 minutes. Method B: same conditions, with the addition of 0.5 g of Na_2SO_4 at the first step. The solid or liquid nature of the reagents is indicated by S and L, respectively.

We then turned our attention to the reactivity of benzylic and cyclic aliphatic primary amines in combination with either aromatic or aliphatic aldehydes (Scheme 4). In most cases, the corresponding secondary amines **4** were obtained in good yields without complications (compounds **4s**, **4t**, **4v**, **4w**). However, in two instances, significant amounts of cyanoborane adducts[18] **5u** and **5x** were isolated. These adducts proved to be particularly stable and resisted

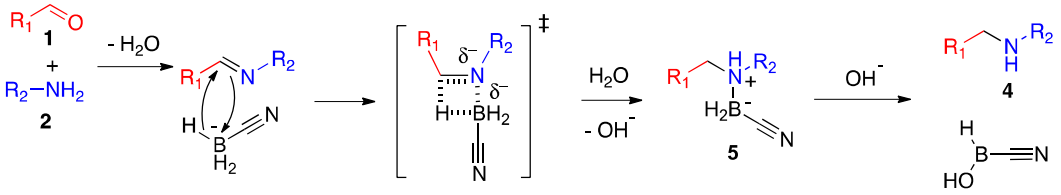
several reported conditions for cleaving the B–N bond in borane–amine complexes, including refluxing in aqueous HCl,[19] or treatment with 10% Pd/C,[20] iodine[21] or cesium fluoride and sodium carbonate in ethanol[22] (Scheme 4).



Scheme 4. Reductive amination of benzylic or cyclic aliphatic primary amines with aromatic or aliphatic aldehydes. Method A: aldehyde (100 mg) and amine (1 eq), 20 Hz for 15 minutes in stainless-steel jar and balls, then $NaBH_3CN$ (1.5 eq) and $ZnCl_2$ (1.5 eq), 20 Hz for 30 minutes. Method B: same conditions, with the addition of 0.5 g of anhydrous Na_2SO_4 at the first step. The solid or liquid nature of the reagents is indicated by S and L, respectively.

The cyanoboranes **5** can be considered intermediates in the reductive amination mechanism (Scheme 5), and they are typically cleaved during the course of the reaction to yield the final products **4**. The unusually high hydrolytic stability observed for compounds **5u** and **5x** can be attributed to specific structural features: in the case of **5u**, stabilization is likely to arise from the formation of an intramolecular hydrogen bond involving the furan oxygen; this is consistent with the chemical shift of the NH signal in **5u**, which is observed at a δ value about 1 ppm higher than

that of **5x**. In the case of the latter compound, steric hindrance resulting from α-branching in the amine moiety may hamper cleavage of the B–N bond.

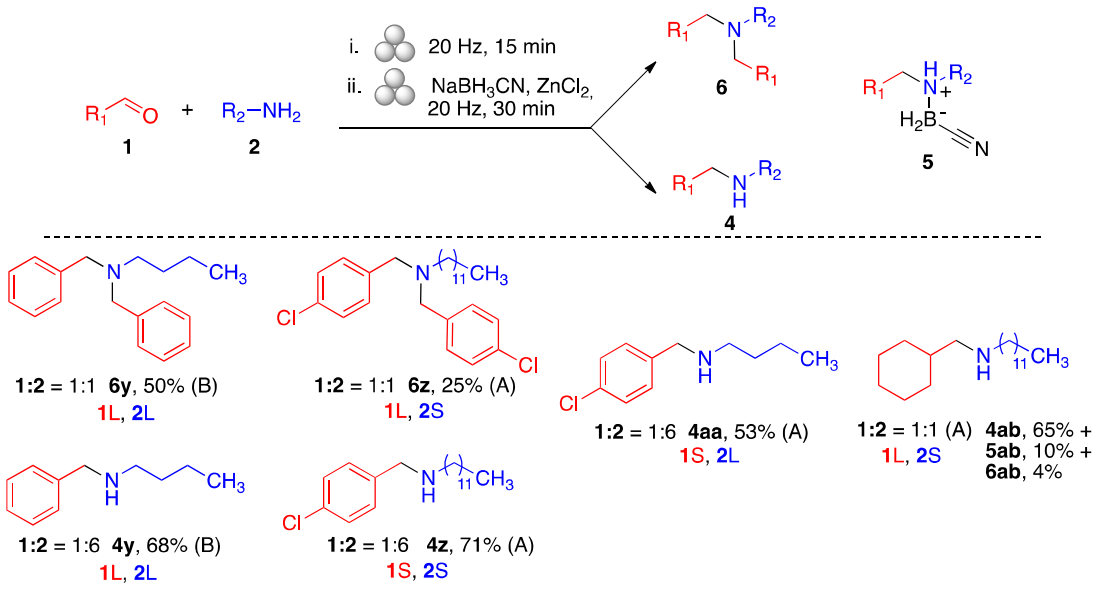


Scheme 5. Mechanistic explanation of the reductive amination process.

The reductive amination of aliphatic amines and aromatic or aliphatic aldehydes was next studied, as summarized in Scheme 6. In the reaction between butylamine and benzaldehyde, the tertiary amine **6y** was the sole isolated product when the amine and aldehyde were used in a 1:1 ratio, due to overalkylation of the highly reactive and relatively unhindered intermediate **4y** by the aldehyde. In contrast, employing a six-fold excess of amine led exclusively to the formation of the secondary amine **4y**. A similar trend was observed in the reaction between dodecylamine and *p*-chlorobenzaldehyde, which yielded the tertiary amine **6z** in modest yield under equimolar conditions, or the secondary amine **4z** when excess amine was used. The versatility of this approach for synthesizing benzyl alkyl secondary amines was further demonstrated by the successful preparation of compound **4aa** from butylamine and *p*-chlorobenzaldehyde.

An experiment involving an aliphatic aldehyde revealed a different reactivity profile: the reaction between cyclohexanecarbaldehyde and dodecylamine predominantly yielded the secondary amine **4ab**, with only trace amounts of the double alkylation product **6ab** and a minor quantity of the cyanoborane intermediate **5ab**. The limited formation of **6ab** suggests that **4ab** is

less prone to a second reductive alkylation, likely due to the increased steric hindrance associated with the cyclohexane ring, as compared to the more planar and less hindered benzene ring.

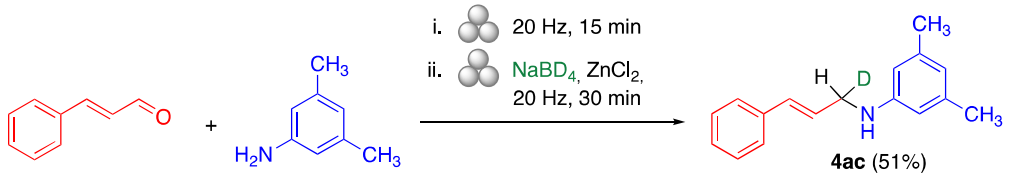


Scheme 6. Reductive aminations from linear aliphatic amines and aromatic or aliphatic aldehydes. All reactions were performed using method A: aldehyde (100 mg) and amine (1 eq), 20 Hz for 15 minutes in stainless-steel jar and balls, then $NaBH_3CN$ (1.5 eq) and $ZnCl_2$ (1.5 eq), 20 Hz for 30 minutes.

Deuteration by reductive amination

In contemporary drug discovery, there is a considerable interest in the incorporation of deuterium atoms to enhance the metabolic stability of drug candidates.[23,24] Consequently, the development of efficient synthetic methodologies for deuterium labeling has become highly relevant.[25] In spite of this interest, mechanochemical deuteration methods are scarce and generally involve metal-based dehalogenative deuteration of aryl[26,27] or alkyl[28] halides, although a mechanochemical silver-catalyzed direct H/D exchange on heteroarenes has also been described.[29]

In this context we examined briefly the application of our mechanochemical method to synthesize α-deuterated amines, using cinnamaldehyde and 3,5-dimethylaniline as starting materials. Although it is not the best reducing agent according to our optimization study, we decided to employ sodium borodeuteride rather than the much more expensive sodium cyanoborodeuteride. Pleasingly, our standard reaction conditions afforded the expected monodeuterated compound **4ac** in 51% yield (Scheme 7).

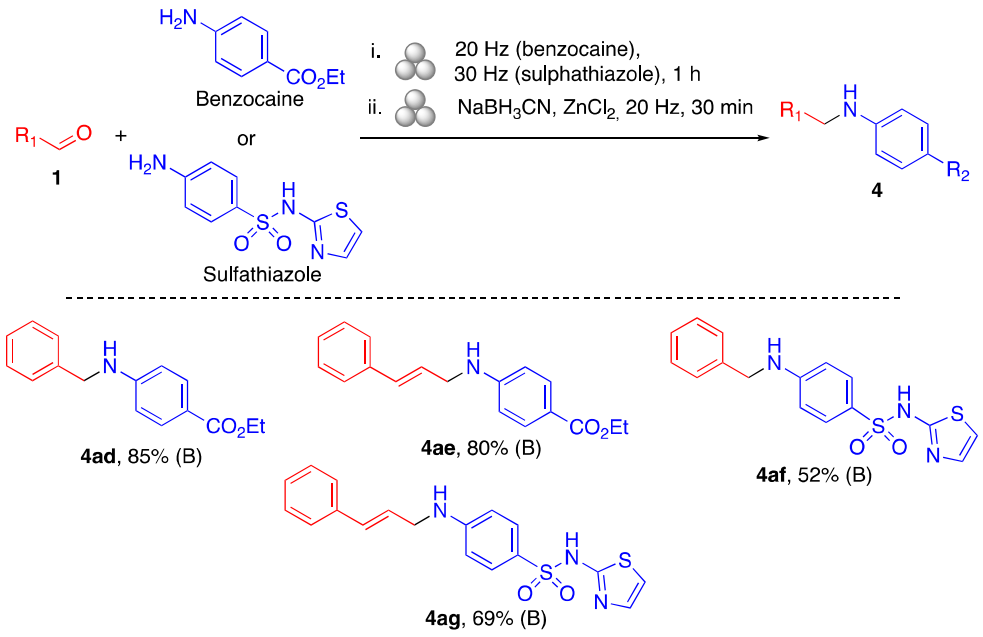


Scheme 7. Synthesis of an α-monodeuterated amine by mechanochemical reductive amination.

Drug molecules and natural products as substrates for reductive amination

Late-stage functionalization has become an increasingly valuable strategy in drug discovery, as it often reduces the synthetic effort required for library generation.[30,31] Similarly, the preparation of prodrugs is most efficient when carried out on the drug itself rather than on an intermediate. For these reasons, evaluating the applicability of new synthetic protocols directly on drug molecules is of considerable interest. Beyond its practical relevance, late-stage functionalization provides insight into the functional group tolerance of novel methodologies, given the dense and diverse functionalization typical of drug compounds. Moreover, the ability to perform reactions on drug substrates is particularly useful in the construction of hybrid systems such as multitarget-directed ligands or antibody–drug conjugates.

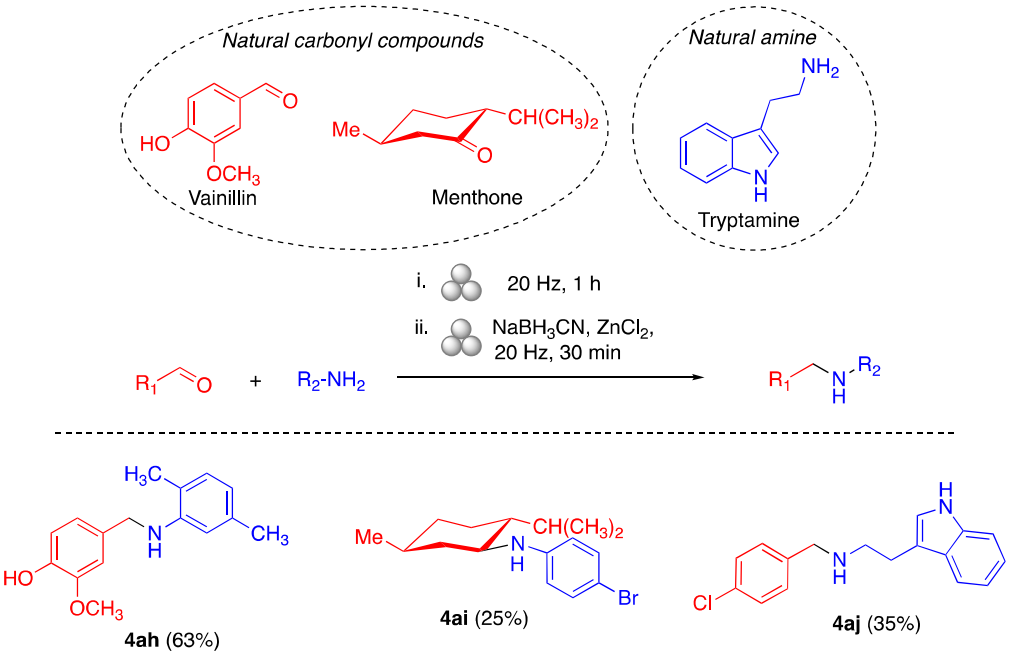
With these considerations in mind, we investigated reductive aminations of the local anesthetic benzocaine and the antibacterial sulfathiazole (Scheme 8). The reactions of benzocaine with benzaldehyde and cinnamaldehyde proceeded smoothly under our standard conditions, despite the presence of an electron-withdrawing group para to the nucleophilic amine, yielding compounds **4ad** and **4ae** in good yields. The reactions starting from sulfathiazole were less efficient and required ball milling at 30 Hz, providing the target compounds **4af** and **4ag** in 52% and 69% yield respectively, a result that could not be improved by increasing the reaction time. The lower efficiency is likely due to competing, reversible reactions between the aldehydes and the sulfonamide nitrogen, which may hinder the desired reaction at the aromatic amine.



Scheme 8. Late-stage functionalization of two drug molecules (benzocaine and sulfathiazole) *via* mechanochemical reductive amination. All reactions were performed using method B: aldehyde

(100 mg), amine (1 eq) and 0.5 g of Na_2SO_4, 20 Hz for 15 minutes in stainless steel, then $NaBH_3CN$ (1.5 eq) and $ZnCl_2$ (1.5 eq), 20 Hz for 30 minutes.

Natural products have long been a cornerstone of drug discovery. Although their structural diversity is inherently restricted, an almost unlimited number of hybrid molecules can be created by linking natural product fragments with each other or with other pharmacophores. This concept of natural product hybrids has therefore gained significant attention as a promising strategy in modern drug discovery programs.[32,33] With these ideas in mind, we also explored some reductive amination reactions starting from natural products, choosing as natural carbonyl compounds vainillin, the main component of the ethanolic extract of the vanilla bean, and menthone, a chiral monoterpene found in the essential oils of several plants belonging to the *Mentha* and *Geranium* genera, among others. We also examined the use of a natural primary amine as the substrate for a mechanochemical reductive amination and chose for this purpose tryptamine, a metabolite of the amino acid tryptophan that is found in the mammalian brain. From these starting materials, we obtained compounds **4ah**, **4ai** and **4aj** in moderate to good yields (Scheme 9). The reaction starting from menthone afforded a 9:1 mixture of diastereomers, from which only the major component **4ai** could be isolated; this structure corresponds to the more stable diastereomer of the molecule and its configuration is in agreement with literature findings on similar menthone derivatives.[34] Moreover, cinnamaldehyde, the starting material for the preparation of compounds **4am**, **4an**, **4ac**, **4ae** and **4ag**, is also a natural product, responsible for the flavor and odor of cinnamon, a well-known spice obtained from the barks of several species of the genus *Cinnamomun*.

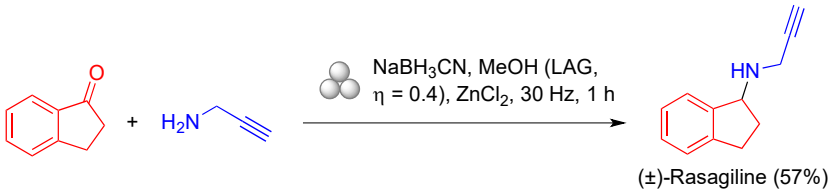


Scheme 9. Synthesis of natural product derivatives by mechanochemical reductive amination.

Synthesis of active pharmaceutical ingredients: rasagiline and safinamide

Finally, we applied the mechanochemical method developed in this study to the synthesis of active pharmaceutical ingredients, selecting the antiparkinsonian drugs rasagiline and safinamide as targets. Rasagiline is used in the treatment of Parkinson's disease due to its activity on dopaminergic neurons, functioning as a monoamine oxidase B (MAO-B) inhibitor. Beyond its primary mechanism, rasagiline also exerts neuroprotective effects by reducing oxidative stress caused by MAO-generated reactive oxygen species (ROS), as well as through MAO-independent pathways. Owing to this promising pharmacological profile, numerous rasagiline-based hybrid compounds have been explored as multitarget-directed ligands for neurodegenerative diseases.[35,36] Several synthetic strategies for rasagiline have been reported, including conventional methods, biocatalysis,[37,38] mechanoenzymatic reactions[39] and flow chemistry.[40]

When we attempted the reductive amination of 1-indanone with propargylamine under the previously established conditions, the starting materials were recovered unchanged, likely due to the low reactivity of the aromatic ketone. This limitation was overcome by increasing the milling frequency to 30 Hz, extending the reaction time to 1 hour, and adding a small amount of methanol to enable liquid-assisted grinding (LAG) with η = 0.4. Here, η is defined as the volume of liquid additive (in μL) per mass of solid (in mg) in the milling jar, and values below 2 qualify as LAG conditions. Under these modified parameters, rasagiline was successfully obtained in 57% yield (Scheme 10). It is relevant to note that, unlike previous experiments, the rasagiline synthesis could be performed as a one-pot, one-step procedure without competing reduction of the starting carbonyl compound, likely due to the lower reactivity of its carbonyl.

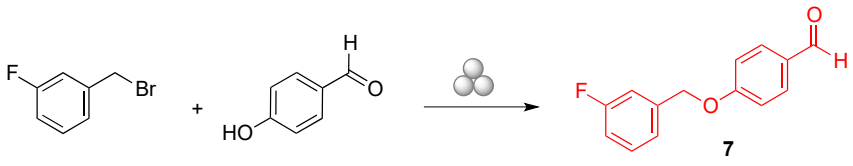


Scheme 10. Mechanochemical synthesis of rasagiline.

Safinamide, introduced in the last decade for the treatment of mid- to advanced-stage Parkinson's disease with motor fluctuations, offers several mechanistic advantages over other anti-Parkinsonian drugs, being the first approved molecule with dual dopaminergic and non-dopaminergic mechanisms of action. Specifically, safinamide functions as a reversible MAO-B inhibitor, restoring dopamine levels in the brain, and also blocks voltage-dependent sodium channels.[41] To date, synthetic strategies giving access to safinamide have primarily involved the formation of a Schiff base, followed by reduction using various agents under conventional,[42] phase-transfer [43] or microwave-assisted[44] conditions. Alternative approaches to safinamide include the Fukuyama N-alkylation method[45] and solid-phase synthesis.[46] While these methods

are relatively straightforward, they present several limitations from the sustainablility point of view, including the generation of toxic impurities during large-scale production,[43] lengthy reaction times, and the use of large volumes of solvent for both reaction and purification steps.

Our synthetic route began with a Williamson ether synthesis, a transformation with limited precedent under mechanochemical conditions.[47] To explore this reaction, we investigated the formation of compound **7** from commercially available *m*-fluorobenzyl bromide and *p*-hydroxybenzaldehyde (Scheme 11 and Table 2). Initially, various bases—potassium hydroxide and carbonate, sodium hydroxide and carbonate, and cesium carbonate—were tested under mechanochemical conditions using a vibratory ball mill. However, in all cases, the starting materials were recovered unchanged (entries 1–5) indicating the need for a catalyst, and we introduced for this purpose copper chloride or zinc chloride, which proved superior (entries 7 and 8). Cesium carbonate was chosen as the base in view of the results summarized in entries 6 and 8, which demonstrated superior performance compared to potassium carbonate. Subsequent optimization of reaction parameters, including milling frequency, reaction time, number of balls per jar, and catalyst loading (entries 6-13), enabled the successful formation of compound **7** with good conversion (entry 10). It is interesting to note that zinc chloride has not been previously described as a catalyst for the Williamson ether synthesis.



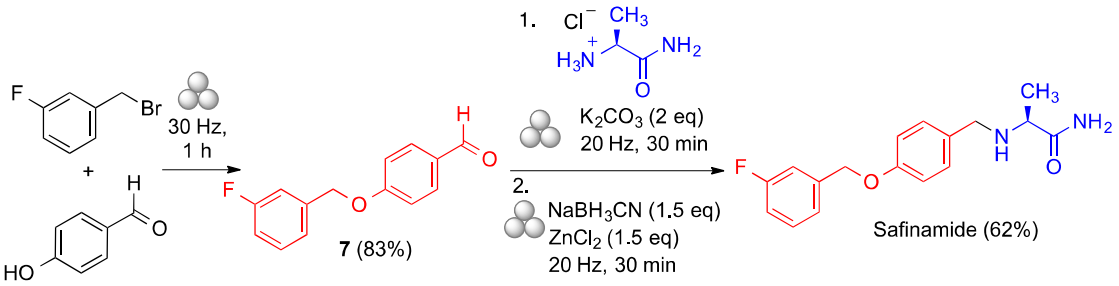
Scheme 11. First step of the synthesis of safinamide: Williamson ether synthesis

Table 2. Optimization of the reaction conditions in the Williamson synthesis of intermediate **7**.

Entry	Base	Catalyst	Nr. of balls [a]	Frequency, Hz	Time	Conversion (%) [b]
1	KOH (2 eq)	-	1	20	20 min	-
2	K_2CO_3 (2 eq)	-	1	20	20 min	-
3	Na_2CO_3 (2 eq)	-	1	20	20 min	-
4	NaOH (2 eq)	-	1	20	20 min	-
5	Cs_2CO_3 (2 eq)	-	1	30	1 h	-
6	K_2CO_3 (2 eq)	$ZnCl_2$ (2 eq)	1	30	1 h	-
7	Cs_2CO_3 (2 eq)	$CuCl_2$ (2 eq)	1	30	1 h	10
8	Cs_2CO_3 (2 eq)	$ZnCl_2$ (2 eq)	1	30	1 h	59
9	Cs_2CO_3 (2 eq)	$ZnCl_2$ (0.5 eq)	1	30	1 h	57
10	**Cs_2CO_3 (2 eq)**	**$ZnCl_2$ (0.5 eq)**	**5**	**30**	**1 h**	**89** [c]
11	Cs_2CO_3 (2 eq)	$ZnCl_2$ (1 eq)	5	30	1 h	35
12	Cs_2CO_3 (2 eq)	$ZnCl_2$ (1 eq)	1	30	2 h	53
13	Cs_2CO_3 (2 eq)	$ZnCl_2$ (2 eq)	1	30	2 h	31

[a] A 15 mm diameter stainless steel ball was used in all cases, except for entries 10 and 11 (5 stainless steel balls, 10 mm diameter). [b] Conversions were determined from the crude ^{1}H-NMR spectra, using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield was 83%.

With compound **7** in hand, we proceeded to study its reductive amination with alaninamide hydrochloride, using the previously established reductive amination process with some modifications. To facilitate imine formation, the reaction time was extended to 30 minutes, and potassium carbonate was added to release the amino acid from its salt. Subsequently, $NaBH_3CN$ and $ZnCl_2$ were added to the reaction mixture, ultimately affording safinamide in a 62% isolated yield (Scheme 12).



Scheme 12. Mechanochemical synthesis of safinamide

Green metrics

Several parameters have been described to evaluate the cost-effectiveness of a synthetic process in terms of economy and sustainability.[48,49,50] Among them, we have focused on the determination of Process Mass Intensity (PMI), defined as total mass in process / mass of product, as it is generally considered a good metric to determine the efficiency of a chemical process.[51] We have performed a dual evaluation of the PMI parameter, initially focusing on the reaction parameters, and then extending the analysis to include the full process including workup, extraction and purification. To study the mechanochemical synthesis of safinamide, both steps are analyzed separately in Tables 3 and 4 for our method, a microwave-assisted method[44] and a solution protocol found in the patent literature.[52] We employed the ACS Green Chemistry tool for all calculations,[53] and full details can be found in the Supporting Information.

For the first step (Williamson ether synthesis), and considering only the reaction itself, the ball milling and the solution method gave similar PMIs, with a slightly better result for the microwave-assisted protocol. When isolation and purification processes were included, the solution-based method was clearly superior. However, it is relevant to consider that the

differences in scale among the methods hinder a meaningful comparison of the metrics, as small-scale processes often use larger-than-necessary volumes to facilitate experimental handling.[54]

For the reductive amination step, the PMI values are better for the ball milling and microwave-assisted methods, with a slight advantage for the ball-milling procedure, both for the reaction alone and when the isolation and purification processes are considered, due to the use of large volumes of solvents in the solution method. When considering both steps in the aggregate, again ball milling has a slight advantage over the microwave-assisted method in terms of the PMI parameter (Figure 1). For the numerical data employed to construct the graphics in Figure 1, see Tables S5, S6, S11 and S12 in the Supporting Information.

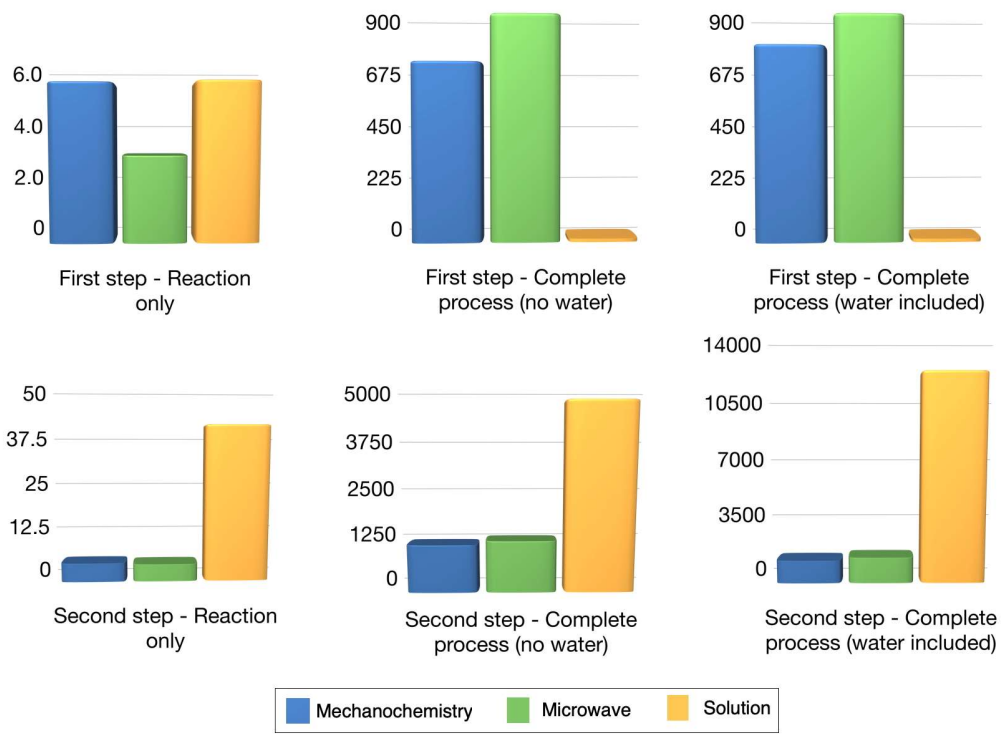


Figure 1. Compared PMI (Process Mass Intensity) values for the safinamide synthesis. "Complete process" includes the reaction itself, the workup and any extraction and/or purification stages.

Although energy requirements are not as widely used as the mass-based metrics, energy consumption is clearly a relevant aspect that should be taken into account to improve the sustainability of pharmaceutical synthetic processes. In this respect, the mechanochemical process has benefits compared with the conventional solution method, since it permits a reduction of reaction times from 48 to 2 hours, and it does not require the input of energy for external heating or cooling while the solution methods require to heat to 70-130 ºC (microwave conditions[44]) or 110-115 ºC (conventional method[52]). When establishing a comparison to the microwave-assisted reactions, which were carried out at a similar scale, it is relevant to note that the energy consumption of the Retsch MM400 mixer mill is 165 W, while the Anton Paar Monowave 300 microwave reactor, used for the work described in reference 44, features a maximum microwave output power of 850 W.

3. EXPERIMENTAL SECTION

General experimental information

Mechanochemical syntheses were carried out in a Retsch MM400 vibratory ball mill operating at a frequency of 5 to 30 Hz, using a 10 mL stainless steel milling jar and a single ball 15 mm in diameter made of the same material. All reagents, purchased from Sigma Aldrich, were of synthetic grade (95-99% purity) and were used as received. Solvents were obtained from Scharlau and Fischer. Reactions were monitored by thin layer chromatography on aluminum plates coated with silica gel and fluorescent indicator (Merck Silica gel 60 F_{254}). Chromatographic separations were carried out by column chromatography, using Thermo Scientific silica gel 60A, with 0.035-0.070 mm particle size, as the stationary phase. Infrared spectra were recorded as thin films with an Agilent Cary630 FTIR ATR spectrophotometer

equipped with a diamond accessory; wavenumbers are given in cm^{-1}. NMR spectroscopic data were recorded using a Bruker Avance spectrometer maintained by the Magnetic Resonance Unit, Universidad Complutense, operating at 250 MHz for ^{1}H-NMR and 63 MHz for ^{13}C-NMR; chemical shifts are given in (δ) parts per million and coupling constants (*J*) in Hertz. Combustion microanalyses were carried out by the Elemental Microanalysis Unit at Universidad Complutense, using a Leco 932 CHNS combustion instrument. High-resolution mass spectra (HRMS) were recorded on a quadrupole mass spectrometer fitted with electrospray ionization (ESI), at the Mass Spectrometry Unit (Universidad Complutense).

General procedure for reductive amination

Method A. A mixture of the suitable aldehyde (100 mg) and amine (1 eq.) was placed in a 10 mL stainless steel jar; a 15 mm diameter ball of the same material was added and the reaction was milled at 20 Hz for 15 minutes (30 Hz for compounds **4ae** and **4af**). Subsequently, sodium cyanoborohydride (1.5 eq.) and zinc chloride (1.5 eq.) were added to the reaction mixture and the mixture was again subjected to ball milling at 20 Hz for 30 minutes. After this time, the mixture was diluted with a saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (15 mL, in three portions). The resulting organic phase was dried over anhydrous sodium sulfate and evaporated to dryness yielding a crude that was purified by chromatography on silica gel or recrystallization.

Method B. The same protocol was used, with addition of anhydrous sodium sulfate (0.5 g) to the mixture of amine and aldehyde.

***N*-Benzylaniline (4a):** Purification conditions: chromatography eluting with a mixture of dichloromethane and petroleum ether (1:10), affording a colorless oil (87%). The spectral data match those reported in the literature.[55] Rf 0.53 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR

(250 MHz, $CDCl_3$) δ 7.52 – 7.32 (m, 5H), 7.32-7.20 (m, 2H), 6.82 (tt, 1H, J = 7.1 and 1 Hz), 6.77 – 6.65 (m, 2H), 4.41 (s, 2H), 4.09 (br s, 1H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ 148.0, 139.3, 129.2, 128.6, 127.4, 127.1, 117.5, 112.8, 48.2 ppm. IR: ν (cm^{-1}) 3415, 3022, 2921, 2850, 1599, 1502.

***N*-(2-Methoxybenzyl)aniline (4b):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:20), affording compound **4b** as white crystals (74%). The spectral data match those reported in the literature.[56] Rf 0.42 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.53 – 7.24 (m, 4H), 7.15 – 6.95 (m, 2H), 6.94 – 6.68 (m, 3H), 4.49 (s, 2H), 4.20 (br s, 1H), 3.98 (s, 3H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ 157.4, 148.4, 129.21, 128.9, 128.3, 127.3, 120.5, 117.3, 113.1, 110.2, 55.3, 43.4 ppm. IR: ν (cm^{-1}) 3405, 1596, 1510.

***N*-(2-Methoxybenzyl)-3-hydroxyaniline (4c):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:6), affording a brown oil (86%). Rf 0.5 (ethyl acetate, petroleum ether 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.38-7.21 (m, 2H), 7.04 (t, 1H, J = 8.0 Hz), 6.95 (td, 2H, J = 7.6 and 1 Hz), 6.30 (ddd, 1H, J = 8.1, 2.2, 0.8 Hz), 6.22 (ddd, 1H, J = 8.1, 2.2, 0.8 Hz), 6.17 (t, 1H, J = 2.2 Hz), 4.73 (br s, 1H), 4.32 (s, 2H), 3.89 (s, 3H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ 157.3, 156.6, 149.7, 130.1, 128.9, 128.3, 126.9, 120.5, 110.2, 106.3, 104.8, 100.4, 55.2, 43.6 ppm. IR: ν (cm^{-1}) 3410, 3049, 1598, 1491. HRMS (ESI): m/z calc. for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176; found: 230.1177.

***N*-(3-Methoxybenzyl)aniline (4d):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:20), affording compound **4d** as a yellow oil (80%). The spectral data match those reported in the literature.[57] Rf 0.40 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.39 – 7.14 (m, 3H), 7.08 – 6.93

(m, 2H), 6.87 (dd, 1H, *J* = 8.1, 2.7 Hz), 6.77 (t, 1H, *J* = 7,3 Hz), 6.90 (dd, 2H, *J* = 8.5 and 0.8 Hz), 4.36 (s, 2H), 4,11 (br s, 1H), 3.85 (s, 3H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 159.9, 148.1, 141.1, 129.6, 129.2, 119.7, 117.6, 113.0, 112.8, 112.6, 55.2, 48.3 ppm. IR: ν (cm^{-1}) 3412, 2933, 1597, 1502.

***N*-(4-Methoxybenzyl)aniline (4e):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:20), affording a yellow oil (89%). The spectral data match those reported in the literature.[56] Rf 0.40 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.34 (d, 2H, *J* = 8.4 Hz), 7.30 – 7.16 (m, 2H), 6.95 (d, 2H, *J* = 8.4), 6.78 (t, 1H, *J* = 7.5 Hz), 6.70 (d, 2H, *J* = 7.5 Hz), 4.31 (s, 2H), 4,02 (br s, 1H), 3.86 (s, 3H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 158.9, 148.3, 131.5, 129.3, 128.9, 117.6, 114.1, 112.9, 55.4, 47.9 ppm. IR: ν (cm^{-1}) 3410, 2832, 1600, 1503.

3-((4-Methoxybenzyl)amino)phenol (4f): Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:6), affording a brown oil (66% method A, 70% method B). Rf 0.4 (ethyl acetate, petroleum ether 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.34 – 7.23 (m, 2H), 7.04 (t, 1H, *J* = 8.0 Hz), 6.97 – 6.83 (m, 2H), 6.24 (tdd, 2H, *J* = 8.5, 2.2, 0.7 Hz), 6.14 (t, 1H, *J* = 2.2 Hz), 4.38 (br s, 1H), 4.22 (s, 2H), 3.84 (s, 3H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 158.7; 156.7; 149.5; 131.1; 130.1; 128.8; 113.9; 105.9; 104.7; 99.9; 55.2; 47.7 ppm. HRMS (ESI): m/z calc. for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176; found: 230.1170.

***N*-(4-Chlorobenzyl)aniline (4g):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:4), affording a yellow oil (80%). The spectral data match those reported in the literature.[58,59] Rf: 0.44 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.36 (s, 4H), 7.30 – 7.16 (m, 2H), 6.80 (tt, 1H, *J* = 7.5 and 1 Hz), 6.72 – 6.60 (m, 2H), 4.36 (s, 2H), 4.09 (br s, 1H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ:

147.7, 137.9, 132.7, 129.2, 128.7, 128.6, 117.7, 112.8, 47.5 ppm; IR: ν (cm^{-1}) 3413, 3047, 2847, 1599, 1502.

3-((4-Chlorobenzyl)amino)phenol (4h): Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:4), affording a pale brown solid (80%). Rf 0.51 (ethyl acetate, petroleum ether 1:2). Mp, 101-102 ºC. ^{1}H NMR (250 MHz, acetone-d_6) δ: 8.01 (s, 1H), 7.52 – 7.27 (m, 4H), 7.06 – 6.78 (m, 1H), 6.38 – 5.89 (m, 3H), 5.48 (br s, 1H), 4.33 (d, *J* = 5.8 Hz, 2H) ppm; ^{13}C-NMR (63 MHz, acetone-d_6) δ: 159.1, 150.85, 140.4, 132.6, 130.5, 129.6, 129.1, 105.5, 104.8, 100.4, 47.3 ppm. IR: ν (cm^{-1}): 3402, 1590. HRMS (ESI): m/z calc. for $C_{13}H_{13}ClNO$ $[M+H]^+$: 234.0680*;* found: 234.0673.

***N*-(Furan-2-ylmethyl)aniline (4i):** Purification conditions: chromatography on silica gel, eluting with a mixture of DCM and petroleum ether (1:10), affording an orange oil (87%). The spectral data match those reported in the literature.[60] Rf: 0.42 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.40 (dd, 1H, *J* = 1.8, 0.8 Hz), 7.27 – 7.14 (m, 2H), 6.84 – 6.65 (m, 3H), 6.36 (dd, 1H, *J* = 3.2 and 1.8 Hz), 6.27 (dd, 1H, *J* = 3.2 and 0.8 Hz), 4.36 (s, 2H), 4.08 (br s, 1H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ 152.7, 147.6, 142.0, 129.3, 118.1, 113.2, 110.4, 107.0, 41.5 ppm. IR: ν (cm^{-1}) 3407, 2920, 1600, 1501.

3-((Furan-2-ylmethyl)amino)phenol (4j): Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether from 1:6 to 1:4, affording a yellow oil (95%). Rf 0.44 (ethyl acetate, petroleum ether 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.36 (dd, 1H, *J* = 1.6, 0.6 Hz), 7.06 (t, 1H, *J* = 8.0 Hz), 6.43 – 6.18 (m, 4H), 6.15 (t, 1H, *J* = 2 Hz), 4.27 (s, 2H), 4,07 (br s, 2H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ 156.6, 152.3, 149.0, 141.9, 130.2, 110.3, 107.1, 106.3, 105.3, 100.4, 41.3 ppm. IR: ν (cm^{-1}) 3398, 1592, 1494. HRMS (ESI): m/z calc. for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0863; found: 190.0859.

***N*-(Naphthalen-2-ylmethyl)aniline (4k):** Purification conditions: chromatography on silica gel, eluting with a mixture of dichloromethane and petroleum ether (1:5), affording a pink powder (98%). The spectral data match those reported in the literature.[60] Rf 0.43 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.94 – 7.77 (m, 4H), 7.60 – 7.44 (m, 3H), 7.27-7.15 (m, 2H), 6.85 – 6.66 (m, 3H), 4.54 (s, 2H), 4.21 (br s, 1H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ 148.1, 136.9, 133.5, 132.7, 129.2 (2C), 128.3, 127.7, 127.7, 126.1, 125.9, 125.7 (2C), 117.6, 112.9 (2C), 48.5 ppm. IR: ν (cm^{-1}) 3398, 3047, 1596, 1498.

4-Chloro-*N*-(naphthalen-2-ylmethyl)aniline (4l): Purification conditions: recrystallization in ethanol to yield a white solid (98%). The spectral data match those reported in the literature.[61] Rf 0.75 (DCM, MeOH 2:1). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.94-7.75 (m, 4H), 7.54-7.40 (m, 3H), 7.16-7.07 (m, 2H), 6.65-6.55 (m, 2H), 4.47 (d, 2H, *J* = 5.0 Hz), 4.19 (br s, 1H); ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 146.7, 136.5, 133.5, 132.9, 129.2, 128.6, 127.87, 127.86, 126.3, 126.0, 125.9, 125.6, 122.3, 114.1, 48.6 ppm.

4-Bromo-*N*-cinnamylaniline (4m): Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9.85:0.15), affording a white solid (83%). The spectral data match those reported in the literature.[62] Rf 0.18 (hexane-ethyl acetate 9.85:0.15). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 7H), 6.68 – 6.50 (m, 3H), 6.29 (dt, 1H, *J* = 15.9 and 5.7 Hz), 3.91 (dd, 2H, *J* = 5.7, and 1.6 Hz) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 147.0, 136.7, 131.9, 131.7, 128.6, 127.7, 126.5, 126.4, 114.6, 109.2, 46.1 ppm.

***N*-Cinnamyl-3,5-dimethylaniline (4n)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9.95:0.05), affording a yellow oil (98%). The spectral data match those reported in the literature.[63] Rf 0.21 (hexane-ethyl acetate 9.95:0.05). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.47 – 7.17 (m, 5H), 6.62 (d, 1H, *J* = 15.9 Hz), 6.45 – 6.23 (m,

4H), 3.92 (dd, 2H, *J* = 5.7, 1.6 Hz), 2.25 (s, 6H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 148.2, 138.9, 137.0, 131.4, 128.6, 127.5, 127.3, 126.4, 119.7, 111.1, 46.3, 21.6 ppm.

***N*-Cyclohexylaniline (4o):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:4), affording a yellow oil (88%). The spectral data match those reported in the literature.[56] Rf 0.63 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.21(m, 2H), 6.86 (tq, 1H, *J* = 7.6 and 1.4 Hz), 6.77 (dd, 2H, *J* = 7.6 and 0.8 Hz), 3.63 (s, 1H), 3.51-3.30 (m, 1H), 2.43 – 2.11 (m, 2H), 2.11 – 1.76 (m, 3H), 1.76 – 1.14 (m, 5H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 147.20, 129.05, 116.58, 112.93, 51.42, 33.25, 25.78, 24.87 ppm. IR: ν (cm^{-1}) 3397, 2923, 2849, 1598, 1500.

3-(Cyclohexylamino)phenol (4p): Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:10) increasing polarity until (1:4), affording a yellow solid (96%) The spectral data match those reported in the literature.[64] Rf 0.51 (ethyl acetate-petroleum ether 1:2). Mp, 93.7-94.5 ºC. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.03 (t, 1H, *J* = 8.0 Hz), 6.22 (td, 2H, *J* = 8.0 and 2.2 Hz), 6.13 (t, 1H, *J* = 2.2 Hz), 4.66 (br s, 2H), 3.21 (tt, 1H, *J* = 10.1 and 3.7 Hz), 2.18 – 1.93 (m, 2H), 1.93 – 1.54 (m, 3H), 1.52 – 0.93 (m, 5H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 156.7, 148.5, 130.1, 106.7, 104.7, 100.8, 52.1, 33.2 (2C), 25.8, 24.9 (2C) ppm. IR: ν (cm^{-1}): 3298, 2926, 2851, 1592, 1492. HRMS (ESI): m/z calc. for $C_{12}H_{18}NO$ $[M+H]^+$: 192.138; found: 192.1380.

***N*-Cyclohexyl-2,5-dimethylaniline (4q)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9.85:0.15), affording an orange oil (98%). The spectral data match those reported in the literature.[65] Rf 0.55 (hexane-ethyl acetate 9.85:0.15). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.97 (d, 1H, *J* = 7.3 Hz), 6.58 – 6.33 (m, 2H), 3.35 (tt, 1H, *J* = 9.9 and 3.7 Hz), 2.33 (s, 3H), 2.19 – 2.05 (m, 5H), 1.88 – 1.63 (m, 3H), 1.56 – 1.06 (m,

5H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 145.1, 136.6, 130.1, 118.6, 117.0, 111.0, 51.4, 33.7, 26.1, 25.1, 21.6, 17.1 ppm.

4-Bromo-*N*-(3,3-dimethylcyclohexyl)aniline (4r). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9.85:0.15), affording a white oil (75%). Rf 0.29 (hexane-ethyl acetate 9.85:0.15). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J* = 8.8 Hz), 6.45 (d, 2H, *J* = 8.8 Hz), 4.82 (br s, 1H), 3.34 (tt, 1H, *J* = 11.4 and 3.8 Hz), 2.08 (d, 1H *J* = 12.7 Hz), 1.83 – 1.71 (m, 1H), 1.70 – 1.46 (m, 2H), 1.45 – 1.22 (m, 2H), 1.11 (td, 1H, *J* = 13.2 and 4.9 Hz), 1.03 – 0.81 (m, 7H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 146.5, 132.0, 114.7, 108.2, 48.8, 46.4, 38.7, 33.5, 33.2, 31.8, 24.9, 21.5 ppm. IR: ν (cm^{-1}) 3404, 1591, 1492, 808. HRMS (ESI): m/z calc. for $C_{14}H_{21}BrN$ $[M+H]^+$: 282.0852; found: 282.0847.

***N*-Benzyl-1-(4-chlorophenyl)methanamine (4s)**. Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:2), affording a colourless oil (85%). The spectral data match those reported in the literature.[56] Rf 0.55 (DCM, MeOH 2:1). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.35-7.12 (m, 9H), 3.72 (s, 2H), 3.71 (s, 2H), 1.70 (br s, 1H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 140.0, 138.7, 132.5, 129.4, 128.4, 128.4, 128.1, 126.9, 53.0 and 52.1 ppm. IR: ν (cm^{-1}) 3320, 3027, 2822, 1490.

***N*-(4-Chlorobenzyl)cyclohexanamine (4t):** Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:10), affording a pale yellow oil (95%). The spectral data match those reported in the literature.[68] Rf 0.43 (ethyl acetate, petroleum ether 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.29-7.19 (m, 4H), 3.77 (s, 2H), 2.53-2.35 (m, 1H), 1.98-1.82 (m, 2H), 1.79-1.64 (m, 2H), 1.64-1.47 (m, 1H), 1.33-0.97 (m, 5H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 139.4, 132.3, 129.4, 128.4, 56.1, 50.2, 33.5, 26.1, 24.9 ppm. IR: ν (cm^{-1}) 3330, 2926, 2853, 1490.

***N*-Benzyl-1-(furan-2-yl)methanamine (4u)**. The reductive amination between benzylamine (100 mg, 0.93 mmol) and 2-furanecarbaldehyde (1.01 eq) was carried out following the general procedure. When the grinding time finished, the milling jar was washed with a mixture of 10 mL of 0.1 M aqueous of HCl and 10 mL of ethyl acetate. The two phases were separated in a separatory funnel and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and evaporated to dryness, yielding 52 mg (25%) of **5u** as a yellow solid (see its characterization data below). On the other hand, the aqueous phase was basified to pH 9 with 0.1 M aqueous NaOH and extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and evaporated to dryness affording 109 mg (63%) of **4u** as a colorless oil.

Characterization of **4u**: The spectral data match those reported in the literature.[66] Rf 0.55 (DCM, MeOH 2:1) ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 0.8 and 1.8, 1 H) -7.29-7.13 (m, 5H), 6.26 (dd, 1H, *J* = 1.8 and 3.1) , 6.12 (dd, 1H, *J* = 0.8 and 3.1), 3.73 (s, 4H), 1,19 (br s, 1H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 153.9, 142.0, 140.0, 128.6, 128.4, 127.2, 110.2, 107.2, 52.9, 45.5 ppm. IR: ν (cm^{-1}) 3300, 2830, 1601, 1452.

***N*-Benzyl-*N*-(furan-2-ylmethyl)amino)-λ^4-boranecarbonitrile 5u**

Characterization data: Rf 0.68 (DCM, MeOH 2:1). Mp: 126.5 -127.5 ºC. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 1.8 Hz, 1H), 7.46-7.35 (m, 3H), 7.32-7.20 (m, 2H), 6.51 (d, 1H, *J* = 3.2 Hz), 6.44 (dd, 1H, *J* = 1.8 and 3.2 Hz), 4.60-3.72 (m, 5H), 2.48-1.20 (m, 2H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 146.7, 143.9, 132.9, 130.5, 129.5, 129.4, 113.0, 111.4, 56.8, 48.6. ^{11}B-NMR (160.46 MHz, $CDCl_3$) δ: -19.43 ppm. IR: ν (cm^{-1}) 3086, 2448, 2326. HRMS (ESI) m/z calc. for $C_{13}H_{15}BN_2NaO$ (M + Na): 249.1170; found 249.1165.

4-Cinnamylmorpholine (4v). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (8:2), affording an amber oil (87%). The spectral data match those reported in the literature.[67] Rf 0.12 (hexane, ethyl acetate 8:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 5H), 6.54 (d, 1H, *J* = 15.8 Hz), 6.26 (dt, 1H, *J* = 15.8 and 6.8 Hz), 3.75 (t, 4H, *J* = 4.7 Hz), 3.17 (d, 2H, *J* = 6.8 Hz), 2.52 (t, 4H, *J* = 4.7 Hz) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 136.7, 133.3, 128.5, 127.5, 126.3, 125.9, 66.9, 61.4, 53.6 ppm.

***N*-Benzyl-1-cyclohexylmethanamine (4w)**. Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:10), affording a colorless oil (80%). The spectral data match those reported in the literature.[68] Rf 0.43 (ethyl acetate, petroleum ether 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.49-7.14 (m, 5H), 3.82 (s, 2H), 2.49 (d, 2H, *J* = 6.6 Hz), 1.85-1.62 (m, 5H), 1.61-1.41 (m, 1H), 1.39-1.06 (m, 4H), 1.04-0.8 (m, 2H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 140.3, 128.3, 128.1, 126.8, 56.0, 54.03, 37.9, 31.4, 26.6, 26.0 ppm. IR: ν (cm^{-1}) 2924, 2851, 1449.

***N*-(Cyclohexylmethyl)cyclohexanamine (4x)**. Purification conditions: chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:6), afforded compounds **4x**, as a white solid (58 mg, 35%), and **5x**, as a sticky yellow solid (128 mg, 61%). The spectral data of **4x** match those reported in the literature[69] and are the following: ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 2.64 (br s, 1H), 2.47 (d, 2H, *J* = 6.8 Hz), 2.46-2.33 (m, 1H), 1.88 (d, 2H, *J* = 11.2 Hz), 1.80-1.54 (m, 8H), 1.54-1.35 (m, 1H), 1.34-0.99 (m, 8H), 0.98-0.75 (m, 2H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 57.5, 53.8, 38.0, 33.3, 31.8, 26.9, 26.4, 26.3, 25.4 ppm.

(*N*-Cyclohexyl-*N*-(cyclohexylmethyl)amino)- λ^4-boranecarbonitrile (5x)

Characterization data: Rf 0.43 (DCM, MeOH 2:1). Mp 93.1-94.1 ºC. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 3.54-3.017 (br s, 1H), 3.09-2.87 (m, 1H), 2.84-2.50 (m, 2H), 2.01 (d, 1H, *J* = 12.2

Hz), 1.95-1.65 (m, 10 H), 1.63-0.84 (m, 12H)) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 62.5, 56.7, 34.2, 30.8, 30.5, 28.8, 28.3, 26.1, 25.4, 25.3, 25.2, 25.2, 25.1 ppm. ^{11}B-NMR (160.46 MHz, $CDCl_3$) δ: -21.35 ppm; IR: ν (cm^{-1}) 3138, 2920, 2854, 2412, 2343 and 2202. HRMS (ESI) m/z calc. for $C_{14}H_{27}BN_2Na$ $[M+Na]^+$ 257.2160; found 257.2151.

***N*-Benzylbutan-1-amine (4y)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (6:4), affording a yellowish oil (68%). The spectra data match with those reported in the literature.[70] Rf 0.46 (hexane, ethyl acetate 6:4). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 3.79 (s, 2H), 2.63 (t, 2H, *J* = 7.5 Hz), 1.60 – 1.43 (m, 2H), 1.42 – 1.23 (m, 2H), 0.91 (t, 3H, *J* = 7.2 Hz).^{13}C-NMR (63 MHz, $CDCl_3$) δ 140.7, 128.5, 128.2, 127.0, 54.2, 49.3, 32.4, 20.6, 14.1.

***N*,*N*-Dibenzylbutan-1-amine (6y)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (4:6) to afford a yellow oil (50%). The spectral data match those reported in the literature.[71] Rf 0.71 (ethyl acetate, petroleum ether 1:10). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.39-7.12 (m, 10 H), 3.52 (s, 4H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.56-1.38 (m, 2H), 1.37-1.16 (m, 2H), 0.81 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 140.0, 128.7, 128.0, 126.6, 58.2, 53.1, 29.2, 20.4, 14.0 ppm.

***N*-(4-Chlorobenzyl)dodecan-1-amine (4z)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (7:3), affording a 65% yield of **4z** as a yellow oil. Rf 0.46 (hexane, ethyl acetate 7:3). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 4H), 3.72 (s, 2H), 2.57 (t, 2H, *J* = 7.1 Hz), 1.55 – 1.38 (m, 3H), 1.34 – 1.14 (m, 18H), 0.84 (t, 3H, *J* = 6.8 Hz) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 139.2, 132.7, 129.6, 128.6, 53.5, 49.6, 32.1, 30.2, 29.8, 29.8, 29.8, 29.7, 29.5, 27.5, 22.8, 14.3 1 ppm. HRMS (ESI): m/z calc. for C19H33ClN $[M+H]^+$: 310.2296; found: 310.2283.

***N,N*-bis(4-Chlorobenzyl)dodecan-1-amine (6z)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9.95:0.05), affording compound **6z** as a yellowish oil (25%). Rf = 0.58 (hexane, ethyl acetate 9.95:0.05). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (s, 8H), 3.47 (s, 4H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.53 – 1.40 (m, 2H), 1.30 – 1.16 (m, 18H), 0.87 (t, *J* = 6.9 Hz, 3H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 138.5, 132.6, 130.1, 128.5, 57.7, 53.5, 32.1, 31.7, 29.8, 29.8, 29.8, 29.6, 29.5, 27.4, 27.1, 22.9, 14.3 ppm. HRMS (ESI): m/z calcd. for $C_{26}H_{38}Cl_2N$ $[M+H]^+$: 434.2376; found: 434.2370.

***N*-(4-Chlorobenzyl)butan-1-amine (4aa)**. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (4:6), affording **4aa** as an amber oil (53%). The spectra data match with those reported in the literature.[72] ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 4H), 3.75 (s, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 1.54 – 1.41 (m, 2H), 1.39 – 1.25 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 139.1, 132.7, 129.6, 128.6, 53.4, 49.2, 32.3, 20.6, 14.1 ppm.

***N*-(Cyclohexylmethyl)dodecan-1-amine (4ab**). Purification conditions: chromatography on silica gel, eluting with a gradient from hexane and ethyl acetate (9.5:0.5) to methanol, afforded 162 mg (65%) of **4ab** as a yellow oil, 28 mg (10%) of **5ab** as a white solid and 12 mg (4%) of **6ab**, as a yellow oil.

Characterization data of **4ab**: Rf 0.93 (ethyl acetate, petroleum ether 1:2). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 2.61 (t, 2H, *J* = 7.2 Hz), 2.47 (d, *J* = 6.6 H), 2.19 (br s, 1H), 1.85-1.61 (m, 5H), 1.59-1.40 (m, 3H), 140-1.13 (m, 23 H), 0.90 (t, 2H, *J* = 6.4 Hz, 3H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 56.6, 50.1, 37.6 (CH), 31.9, 31.42, 29.7, 29.6 (4 CH_2), 29.5, 29.3, 27.3, 26.6, 26.0, 22.6, 14.1 ppm; HRMS (ESI): m/z calc. for $C_{19}H_{40}N$ $[M+H]^+$: 282.3161; found: 282.3143. IR: ν (cm^{-1}): 3430, 3330, 2921, 2852.

((Cyclohexylmethyl)(dodecyl)amino)- λ^4-boranecarbonitrile 5ab

Characterization data: Mp: 170.2-172.2 ºC. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 3.41 (br s, 1H), 3.08-2.89 (m, 1H), 2.89-2.71 (m, 2H), 2.69-2.50 (m, 1H), 1.95-1.64 (m, 8H), 1.40-1.19 (m, 23H), 0.96-0.79 (m, 5H). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 60.2, 54.3, 33.8, 31.8, 30.6, 30.5, 29.5 (2C), 29.4, 29.3, 29.3, 29.1, 26.6, 26.0 (2C), 25.3, 25.3, 22.6, 14.1. ^{11}B-NMR (160.46 MHz, $CDCl_3$) δ: -19.69 ppm. IR: ν (cm^{-1}) 3123, 2920, 2851, 2422. HRMS (ESI): m/z calc. for $C_{20}H_{41}BN_2Na$ $[M+Na]^+$: 343.3260; found: 343.3252.

***N*,*N*-bis(cyclohexylmethyl)dodecan-1-amine 6ab**

Characterization data: Rf 0.70 (ethyl acetate, petroleum ether 1:10). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 2.28 (t, 2H, *J* = 6 Hz), 2.08 (d, 4H, *J* = 7 Hz), 1.89-1.54 (m, 11H), 1.49-1.04 (m, 29H), 0.96-0.71 (m, 5H) ppm; ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 62.6 (2C), 55.3, 36.3, 31.9 (4C), 29.7 (2C), 29.7, 29.6, 29.6, 29.4, 27.4, 27.3, 27.0, 26.3 (4C), 22.7, 14.1 (2C not resolved due to overlapped signals) ppm. IR: ν (cm^{-1}) 2925.3, 2852.7, 903.4. HRMS (ESI): m/z calc. for $C_{26}H_{52}N$ $[M+H]^+$: 378.4094; found: 378.4092.

(*E*)-3,5-dimethyl-N-(3-phenylallyl-1-D)aniline (4ac). The reaction was carried out using $NaBD_4$ as the reducing agent instead of $NaBH_3CN$. Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (4.95:0.05, Rf = 0.19), affording a greenish oil (51%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.21 (m, 5H), 6.63 (dd, *J* = 15.9, 1.5 Hz, 1H), 6.44 (m, 1H), 6.43 – 6.27 (m, 3H), 3.92 (m, 1H), 2.27 (s, 6H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ 148.1, 138.9, 137.0, 131.5, 128.6, 127.6, 127.2, 126.4, 119.9, 111.2, 46.1 (t, $J_{C\text{-}D}$ = 20.4 Hz), 21.6 ppm. HRMS (ESI): m/z calc. for $C_{17}H_{18}DN$ $[M+H]^+$: 239.1653, found: 239.1653. IR (cm^{-1}): 3400, 3194, 2106, 1184, 819, 688.

Ethyl 4-(benzylamino)benzoate (4ad). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9.5:0.5, Rf = 0.24), affording **4ad** as a white solid (85%). Mp 101.9 – 104.1 ºC. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.87 (dt, 2H, *J* = 8.9 and 2.5 Hz), 7.41 – 7.27 (m, 5H), 6.59 (dt, 2H, *J* = 8.8 and 2.6 Hz), 4,60 (br s, 1H), 4.39 (s, 2H), 4.31 (q, 2H, *J* = 7.1 Hz), 1.35 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (63 MHz, $CDCl_3$) δ 166.9, 151.8, 138.4, 131.4, 128.6, 127.3, 127.2, 118.5, 111.5, 60.1, 47.4, 14.4 ppm. IR: ν (cm^{-1}) 3378, 1675, 1597, 1272. HRMS (ESI): m/z calc. for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332; found: 256.1322.

Ethyl 4-(cinnamylamino)benzoate (4ae). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (9:1, Rf = 0.22), affording **4ae** as a white solid (80%). Mp, 134 – 136.1 ºC. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.88 (dt, 2H, *J* = 8.8 and 2.5 Hz), 7.43 – 7.17 (m, 5H), 6.71 – 6.52 (m, 3H), 6.29 (dt, 1H, *J* = 15.9 and 5.7 Hz), 4.31 (q, 3H, *J* = 7.1 Hz), 4.00 (td, 2H, *J* = 5.7 and 1.6 Hz), 1.36 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 166.9, 151.7, 136.6, 132.0, 131.5, 128.7, 127.8, 126.4, 125.9, 118.9, 111.8, 60.3, 45.5, 14.5 ppm. HRMS (ESI): m/z calc. for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1494; found: 282.1490; $[M+Na]^+$: 304.1313; found: 304.1308; $[2M+Na]^+$: 585.2729; found: 585.2711. IR: ν (cm^{-1}) 3359, 1672, 1597, 1276, 1174.

4-(Benzylamino)-*N*-(thiazol-2-yl)benzenesulfonamide (4af): Purification conditions: Vacuum filtration, followed by washing with the minimum amount of dichloromethane, affording **4af** as a white solid (52%). Rf (hexane/ethyl acetate 2:3) = 0.15. Mp: 200.6 – 202.1 ºC. ^{1}H-NMR (250 MHz, DMSO-d_6) δ 7.45 (d, 2H, *J* = 8.8 Hz), 7.31 (d, 4H, *J* = 4.5 Hz), 7.27 – 7.09 (m, 2H), 6.77 – 6.68 (m, 1H), 6.59 (d, 2H, *J* = 8.8 Hz), 4.29 (s, 2H) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ 168.0, 151.5, 139.3, 129.1, 128.4, 127.6, 127.1, 126.8, 124.3, 111.1, 107.5, 45.9 ppm. IR: ν (cm^{-}

^{1}) 3385, 1519, 1272, 1086. HRMS (ESI): m/z calc. for $C_{16}H_{16}N_3O_2S_2$ $[M+H]^+$: 346.0678; found: 346.0675.

4-(Cinnamylamino)-*N*-(thiazol-2-yl)benzenesulfonamide (4ag). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (2:3, Rf = 0.13), affording **4ag** as a white solid (69%). Mp: 205.8 – 208.9 ºC. ^{1}H-NMR (250 MHz, DMSO-d_6) δ 7.49 (d, 2H, J = 8.7 Hz), 7.43 – 7.09 (m, 6H), 6.80 – 6.48 (m, 4H), 6.30 (dt, 1H, J = 16.0 and 5.4 Hz), 3.90 – 3.85 (m, 2H). ^{13}C-NMR (63 MHz, DMSO-d_6) δ 168.0, 151.6, 136.5, 130.4, 128.6, 128.0, 127.6, 127.4, 127.0, 126.2, 124.2, 111.0, 107.5, 44.3 ppm. IR: δ (cm^{-1}) 3374, 1594, 1292, 1135. HRMS (ESI): m/z calc. for $C_{18}H_{18}N_3O_2S_2$ $[M+H]^+$: 372.0835; found: 372.0839.

4-(((2,5-Dimethylphenyl)amino)methyl)-2-methoxyphenol (4ah). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (4.75:0.25, Rf = 0.17), affording **4ag** as an orange oil (63%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.97 (t, J = 3.7 Hz, 2H), 6.89 – 6.83 (m, 2H), 6.65 – 6.55 (m, 2H), 5.60 (br s, 1H), 4.28 (s, 2H), 3.88 (s, 3H), 2.28 (s, 3H), 2.13 (s, 3H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.8, 145.1 (2 overlapped signals), 136.9, 130.7, 130.1, 121.0, 119.9, 118.9, 114.5, 112.1, 110.8, 56.0, 49.1, 21.6, 17.2 ppm. HRMS (ESI): m/z calc. for $C_{16}H_{19}NO_2$ $[M+H]^+$: 258.1489, found: 258.1490. IR (cm^{-1}): 3425, 3224, 3005, 1509, 1427, 1266, 1030, 792.

4-Bromo-*N*-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)aniline (4ai). Purification conditions: chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (4:1, Rf = 0.32), affording a brown oil (25%). Two diastereomers were obtained in a 9:1 ratio (as determined from the crude mixture), but only the major diastereomer could be isolated. ^{1}H NMR (250 MHz, CDCl3) δ 7.22 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 8.4 Hz, 2H), 3.82 – 3.59 (m, 1H), 2.03 – 1.91 (m, 1H), 1.90 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.61 – 1.41 (m, 2H), 1.19 – 1.07

(m, 2H), 1.02 – 0.88 (m, 6H), 0.85 (d, *J* = 1.9 Hz, 3H), 0.83 (d, *J* = 1.9 Hz, 3H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.8, 132.2, 114.4, 47.2, 38.3, 35.0, 29.9, 29.7, 26.5, 25.3, 22.4, 21.3, 20.8 ppm. HRMS (ESI): m/z calc. for $C_{16}H_{24}BrN$ $[M+H]^+$: 310.1165, found: 310.1154. IR (cm^{-1}): 3418, 2913, 2864, 1590, 1493, 809.

***N*-(4-Chlorobenzyl)-2-(1*H*-indol-3-yl)ethan-1-amine (4aj)**. Purification conditions: chromatography eluting with a mixture of hexane and ethyl acetate (4:1, Rf = 0.18), affording a white solid (35%). The spectral data in $CDCl_3$ match with those reported in the literature.[73] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (br, 1H, NH), 7.35 (d, *J* = 8.2, 1H), 7.20 (td, *J* = 8.2, 1.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.02 (s, 1H), 7.01 – 6.92 (m, 3H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.12 (d, *J* = 13.8 Hz, 1H), 3.63 (d, *J* = 13.8 Hz, 1H), 3.30 – 2.92 (m, 4H) ppm. ^{1}H NMR (250 MHz, MeOD) δ 11.84 (br, 1H), 8.91 – 8.75 (m, 6H), 8.64 (td, *J* = 7.5, 1.0 Hz), 8.57 (s, 1H), 8.49 (td, *J* = 7.5, 1.0 Hz, 1H), 7.75 (br s, 1H), 5.66 (dd, *J* = 13.6, 4.0 Hz, 1H), 5.36 (dd, *J* = 13.6, 8.3 Hz, 1H), 4.79 – 4.42 (m, 4H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ 136.6, 135.1, 130.6, 130.3, 129.1, 126.2, 123.3, 122.8, 120.1, 118.1, 111.6, 109.2, 57.7, 50.4, 22.2 ppm. ^{13}C NMR (63 MHz, MeOD) δ 138.2, 135.8, 133.3, 132.8, 129.9, 128.1, 123.8, 122.6, 119.9, 118.9, 112.4, 111.2, 57.8, 53.0, 22.8 ppm.

Synthesis of rasagiline

A mixture of 2,3-dihydro-1*H*-inden-1-one (50 mg, 0.38 mmol), prop-2-yn-1-amine (21 mg, 18 μL, 1 eq), methanol (100 μL), sodium cyanoborohydride (95 mg, 1.5 eq) and zinc chloride (76 mg, 1.5 eq) was placed in a 10 mL stainless steel jar together with a ball of the same material of 15 mm diameter and was milled at 30 Hz for 1 hour. After this time, the mixture in the grinding jar was diluted with a saturated aqueous sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (15 mL, in three portions). The resulting organic phase was dried over anhydrous

sodium sulfate and evaporated to dryness. The crude product was purified by silica gel chromatography, eluting with a mixture of ethyl acetate and petroleum ether (1:20) yielding rasagiline as a yellow oil (57%). The spectral data match those reported in the literature.[74] Rf 0.57 (DCM, MeOH 1:2) ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.41 – 7.31 (m, 1H), 7.32 – 7.15 (m, 3H), 4.44 (t, 1H, *J* = 5 Hz), 3.56 (dd, 2H, *J* = 2.5, 1.1 Hz), 3.16 – 2.97 (m, 1H), 2.96 – 2.74 (m, 1H), 2.52-2.32 (m, 1H), 2.28 (t, 1H, *J* = 2.5 Hz), 1.97-1.79 (m, 1H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 144.5, 143.9, 127.7, 126.3, 125.0, 124,3, 82.5, 71.5, 61.9, 36.2, 33.4, 30.5 ppm. IR ν (cm^{-1}) 3293, 2937, 1675.

Synthesis of safinamide

4-((3-Fluorobenzyl)oxy)benzaldehyde (7)

A mixture of 4-hydroxybenzaldehyde (100 mg) and 1-(bromomethyl)-3-fluorobenzene (1 eq) as placed in the 10 mL stainless steel jar together with 5 balls of the same material, 10 mm in diameter. Cesium carbonate (2 eq) and zinc chloride (0.5 eq) were added to the reaction mixture and milled at 30 Hz for 1 hour. After this time, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL, in three portions). The resulting organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The product was purified by silica gel chromatography with a mixture of ethyl acetate and petroleum ether (1:20), yielding compound **7** as a colourless oil (83 %). NMR data are in accordance to those reported in the literature.[75] ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.89 (s, 1H), 7.84, (d, 2H, *J* = 7.6 Hz), 7.43-7.28 (m, 1H), 7.24-7.10 (m, 2H), 7.10-6.9 (m, 3H), 5.14 (s, 2H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 190.7, 163.3, 162.9 (d, *J* = 245.0 Hz), 138.4 (d, *J* = 7.0 Hz), 131.9, 130.2, 130.2 (d, *J* = 1.5 Hz), 122.6, 115.1 (d, *J* = 82.5 Hz), 115.0, 114.1 (d, *J* = 21.3 Hz), 69.3 ppm.

(*S*)-2-(4-(3-Fluorobenzyloxy)benzylamino)propanamide (safinamide)

A mixture of the aldehyde **7** (100 mg, 0.44 mmol), alaninamide hydrochloride (1 eq) and potassium carbonate (2 eq) was placed in a 10 mL stainless steel jar together with a 15 mm diameter ball of the same material and the mixture was milled at 20 Hz for 15 minutes. Subsequently, sodium cyanoborohydride (1.5 eq) and zinc chloride (1.5 eq) were added and the reaction mixture was again subjected to milling at 20 Hz for 30 min. After this time, the mixture was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (15 mL, in three portions). The resulting organic phase was dried over anhydrous sodium sulfate and evaporated to dryness to give a residue that was purified by column chromatography on silica gel, eluting with ethyl acetate, to afford 81.4 mg (62%) of safinamide as a white solid. NMR data are in accordance to those reported in the literature.[75] Rf: 0.57 (DCM, MeOH 2:1). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.41 – 7.28 (m, 1H), 7.27 – 7.08 (m, 4H), 7.06 – 6.86 (m, 3H), 5.89 (br s, 1H), 5.04 (s, 2H), 3.71 (dd, 2H, *J* = 17.8 and 12.9 Hz), 3.26 (q, 1H, *J* = 6.8 Hz), 2.30 (br s, 2H) 1.33 (d, 3H, *J* = 6.8 Hz). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 178.2, 163.0 (d, *J* = 246.8 Hz), 157.8, 139.7 (d, *J* = 7.8 Hz), 131.8, 130.2 (d, *J* = 8.7 Hz), 129.5, 122.7 (d, *J* = 2.8 Hz), 114.9, 114.8 (d, *J* = 20.9 Hz), 114.5 (d, *J* = 21.8 Hz), 69.2, 57.5, 51.8, 19.5 ppm.

CONCLUSIONS

Ball milling of aldehydes or ketones and amines in the presence of sodium borohydride and zinc chloride provides a general method for reductive amination under solid-state conditions. The method is amenable to late-stage functionalization of drug molecules and natural products and has also allowed the fully mechanochemical synthesis of the anti-Parkinson MAO B inhibitors rasagiline and safinamide, with improved green metrics in comparison with solution chemistry.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge: Additional details of the green metrics calculations for safinamide synthesis and copies of NMR spectra (PDF file).

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ABBREVIATIONS

API, Active Pharmaceutical Ingredient; MAO, monoamine oxidase; PMI, Process Mass Intensity; ROS, reactive oxygen species.

NONTECHNICAL SYNOPSIS

Ball milling enables solvent-free reductive amination, allowing the efficient synthesis of antiparkinsonian drugs rasagiline and safinamide through green chemistry.

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