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Click Mechanochemistry: Quantitative Synthesis of "Ready to Use" Chiral Organocatalysts by Efficient Two-Fold Thiourea Coupling to Vicinal Diamines

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Abstract: Mechanochemical methods of neat grinding and liquid-assisted grinding have been applied to the synthesis of mono- and bis(thiourea)s by using the click coupling of aromatic and aliphatic diamines with aromatic isothiocyanates. The ability to modify the reaction conditions allowed the optimization of each reaction, leading to the quantitative formation of chiral bis-(thiourea)s with known uses as organocatalysts or anion sensors. Quantitative reaction yields, combined with the fact that mechanochemical reaction conditions avoid the use of bulk solvents, enabled solution-based purification methods (such as chromatography or recrystallization) to be completely avoided. Importantly, by using selected model

Introduction

Mechanochemical^[1] grinding or milling is rapidly becoming a method of choice in different areas of chemical and materials synthesis. To date, the applications of mechanochemical milling have included the crystal engineering of organic solids with pharmaceutical,^[2] luminescent,^[3] and photo- or thermoactive properties,^[4] studies of biomolecular recognition,^[5] the synthesis of supramolecular, coordination, and covalent cages,^[6] interlocked systems,^[7] coordination polymers, and metal–organic frameworks,^[8] asymmetric catalysis, and deracemization.^[9] There can be many benefits of mechanochemical milling in chemical synthesis if the reactions pro-

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reactions, we also show that the described mechanochemical reaction procedures can be readily scaled up to at least the one-gram scale. In that way, mechanochemical synthesis provides a facile method to fully transform valuable enantiomerically pure reagents into useful products that can immediately be applied in their designed purpose. This was demonstrated by using some of the mechanochemically prepared reagents as organocatalysts in a model Morita–Baylis–Hillman reac-

Keywords: click chemistry • green chemistry • mechanochemistry • milling • reaction efficiency • solvent-free reactions tion and as cyanide ion sensors in organic solvents. The use of electronically and sterically hindered ortho-phenylenediamine revealed that mechanochemical reaction conditions can be readily optimized to form either the 1:1 or the 1:2 click-coupling product, demonstrating that reaction stoichiometry can be more efficiently controlled under these conditions than in solution-based syntheses. In this way, it was shown that excellent stoichiometric control by mechanochemistry, previously established for mechanochemical syntheses of cocrystals and coordination polymers, can also be achieved in the context of covalent-bond formation.

ceed in a straightforward and clean fashion. In such cases, it is possible to obtain the desired product in high purity and quantitative yield. Milling mechanochemistry is environmentally benign^[10] as chemical transformations can be very effectively performed either under completely solvent-free conditions, or facilitated and directed by a catalytic amount of a liquid phase (liquid-assisted grinding, LAG, also known as solvent-drop grinding).^[11] Recent critical studies have established mechanochemistry to be the environmentally friendly tool of organic synthesis that combines high reaction efficiency with minimal input of energy and solvent. Mechanosynthesis has improved a variety of carbon–carbon bond-forming reactions, including Suzuki–Miyaura, Heck, and Sonogashira couplings, aldol reactions, cycloadditions, and heterocycle synthesis.^[10b,12–16]

We recognized the laboratory-scale transformations of chiral reagents to be an important, but unexplored field that could benefit from the efficiency of mechanochemical milling. In particular, we now address the laboratory-scale synthesis of modern organocatalysts, which often requires rare reagents the availability of which in a typical laboratory environment is limited by their cost, and the conversion of which necessitates the highest synthetic efficiency. We demonstrate the use of LAG mechanosynthesis to synthesize bifunctional chiral thiourea catalysts in >99% isolated yield.

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These bis(thiourea)s have been used as catalysts in many important reactions, notably the Morita–Baylis–Hillman reaction, the acetalization of aldehydes and ketones, and the Friedel–Crafts alkylation.^[17] As well as their use as organo-catalysts, thioureas have found applications as anion sensors and transporters.^[18]

As a model reaction, we used the coupling of organic isothiocyanates and amines, a known click reaction in solution.^[19] The application of milling to conduct click reactions was very recently reported by Stolle and co-workers, who performed the popular coupling of organic azides and acetylenes in this manner. Their work provided excellent yields, albeit in the presence of inert additives to counter the shock-sensitive nature of organic azides.^[20] We find thiourea coupling to be particularly suitable to mechanochemistry because it avoids shock-sensitive reagents and, therefore, does not require sample dilution. For this study, we were encouraged by the literature precedent by Kaupp et al.^[21a] on the synthesis of *N*-methyl-*N*'-aryl thioureas by milling methylisothiocyanate with three *para*-substituted anilines.

Our study was strongly motivated by the report by Li and co-workers, who conducted the mechanosynthesis of simple aromatic thioureas by using a mortar and pestle.^[21b] The high yields that were obtained through such a simple meth-

nochemical thiourea synthesis to more complex molecules, as well as optimizing the reaction yields to provide products in high purity. These products could be immediately used for the intended applications without resorting to conventional laboratory purification techniques (e.g., chromatography, flash chromatography, recrystallization) that are both wasteful of solvent^[21] and severely limit the isolated product yield in laboratory syntheses.^[23]

We now demonstrate that the application of LAG in an automated mill enables the expansion of the mechanochemical click coupling of organic amines and isothiocyanates to sterically and electronically hindered amines and diamines to provide well-known achiral (compounds 1 and 2, Scheme 1) and chiral catalysts (compounds 3-6, Scheme 1). These products are mechanochemically obtained in quantitative^[24] isolated yields, making them immediately applicable for organocatalytic or anion-binding studies. Whereas most of our initial study is conducted with only the amounts of expensive reagents that would typically be available in a research laboratory, we also demonstrate the applicability of the synthesis on a one-gram scale without loss of isolated yield. We also show a superior ability of milling synthesis relative to synthesis in solution to control reaction stoichiometry. In particular, we show the selective synthesis of the

odology led us to speculate that an automated milling approach, in which reaction parameters can be readily controlled and optimized, would allow these syntheses to be carried out in a fast and reproducible fashion. The introduction of the LAG methodology, which is conducted in a mechanical mill and utilizes substoichiometric amounts of a liquid phase to enhance and direct mechanochemical reactions, provides an opportunity to modify the mechanochemical reaction environment in a similar way to changing the solvent in traditional organic synthesis. Thus, in addition to the reaction time, milling frequency, and impact force (controlled in ball milling by varying the number and size of milling balls), LAG provides an opportunity to improve and control reactivity either by switching between different liquid phases, or by varying η ,^[22] that is, the ratio of the added liquid phase (in µL) to the weight of the reactant mixture (in mg). We expected that LAG would enable us to expand the scope of the mecha-





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non-symmetrical mono- and symmetrical bis(thiourea)s 7 and 8, respectively, simply by milling the reactants in the correct stoichiometric ratio (Scheme 1).

Results and Discussion

Monothiourea targets derived from aniline derivatives: The first targets in our study were symmetrical N,N'-bis[3,5-bis-(trifluoromethyl)phenyl]thiourea (1) and nonsymmetrical N-[3,5-bis(trifluoromethyl)phenyl]-N'-[4-chlorophenyl]thiourea (2). The LAG reaction of 3,5-bis(trifluoromethyl)phenyl iso-thiocyanate with 3,5-bis(trifluoromethyl)aniline in a 1:1 ratio by using methanol (MeOH) as the grinding liquid, quantitatively^[24] yielded 1 (Table 1). The complete forma-

Table 1. Optimized mechanochemical syntheses of thiourea-based organocatalysts by neat grinding (NG) and LAG by using MeOH in a ball mill. Literature yields are given in brackets.

	Product	Reactant state of aggregation ^[a]	Method ^[b]	Yield ^[c] [%]
1	1	liquid/liquid	LAG ^[d]	>99 (84) ^[17b]
2	1	liquid/liquid	LAG (1 g scale)	98 ^[e]
3	2	liquid/solid	LAG	>99
4	(1R, 2R)-3	liquid/solid	NG/LAG	>99 (94) ^[17a]
5	(1R, 2R)-3	liquid/solid	NG (1 g scale)	98 ^[e]
6	(15, 25) - 3	liquid/solid	NG/LAG	>99
7	(1R, 2R)-4	liquid/solid	NG/LAG	>99 (81) ^[29]
8	(1R, 2R)-5	solid/solid	NG/LAG	$>99 (89)^{[18b]}$
9	(1S, 2S) - 5	solid/solid	NG/LAG	>99
10	(<i>R</i>)-6	liquid/solid	LAG ^[f]	$>99 \ (85)^{[17f]}$
11	7	liquid/solid	$NG^{[d]}$	99 ^[h]
12	8	liquid/solid	LAG ^[g]	>99
13	8	liquid/solid	LAG (1 g scale)	99 ^[i]

[a] Isothiocyanate/(di)amine at standard temperature and pressure. [b] 20 min of ball milling by using one 12 mm diameter stainless-steel ball. [c] Based on ¹H NMR spectroscopy and HPLC. [d] 30 min grinding. [e] 180 min grinding, isolated yield. [f] 60 min grinding. [g] 180 min grinding. [h] 10 mol% excess of *ortho*-phenylenediamine was used, isolated yield after chromatography. [i] 9 h grinding, isolated yield.

tion of **1** and the absence of starting materials in the mechanochemically prepared sample was confirmed spectroscopically by using ¹H and ¹³C NMR and Fourier-transform infrared (FTIR) spectroscopy (Figure 1).

Recording the FTIR spectrum of the solid immediately after the reaction ensured that the observed quantitative transformations are not an artifact of sample preparation for NMR or HPLC analysis. Quantitative conversion of the reactant isothiocyanate was readily noted by the disappearance of the characteristic isothiocyanate stretching band between 2000 and 2200 cm⁻¹. Furthermore, reflections in the powder X-ray diffraction (PXRD) pattern of mechanochemically prepared **1** coincided with those expected for the previously reported crystal structure.^[17b,25]

Similarly, the nonsymmetrical organocatalyst $2^{[26]}$ was prepared by a mechanochemical LAG coupling of 3,5-bis(trifluoromethyl)phenyl isothiocyanate with 4-chloroaniline in >99% yield (Table 1). Again, the absence of the isothiocya-



Figure 1. FTIR spectra of the reactant isothiocyanate (top) and the (un)symmetrical thiourea catalysts **1** (middle) and **2** (bottom) immediately after milling. The absence of the isothiocyanate absorption band between 2000 and 2200 cm⁻¹ is notable, indicating the complete conversion of the isothiocyanate reactant.

nate reactant was readily verified by the absence of the characteristic isothiocyanate stretching band in the spectrum of the mechanochemical product (Figure 1).

Bis(thiourea) targets derived from ortho-phenylenediamine and 1,1'-binaphtyl-2,2'-diamine: Stoichiometric control in covalent mechanosynthesis: Following the successful synthesis of diarylmonothioureas 1 and 2, we explored the formation of bis(thiourea)s based on symmetrical ortho-phenylenediamine and asymmetrical (R)-1,1'-binaphtyl-2,2'-diamine. The click coupling reaction of these diamines with isothiocyanates is expected to be particularly hindered by steric factors. Whereas the binaphthyl-based target (R)-6 is attractive because of its established use as an asymmetric organocatalyst, we were also tempted to explore the mechanochemical reaction of ortho-phenylenediamine with phenylisothiocyanate. In particular, the inverted mechanochemical reaction by grinding of benzene-1,2-bis(isothiocyanate) with aniline has previously been explored,^[23a] and resulted in the formation of an unstable isothiocyanate-substituted monothiourea intermediate that underwent an intramolecular cyclization to form a benzimidazole thione (Scheme 2a).

We speculated that by using a 1,2-diamine instead of a 1,2-bis(isothiocyanate) as the reaction locus we could avoid the intramolecular cyclization and enable the synthesis of the nonchiral sterically congested bis(thiourea) $\mathbf{8}^{[18c]}$ through the stable intermediate **7** (Scheme 2b). Indeed, milling of *ortho*-phenylenediamine and phenyl isothiocyanate in a 1:2 ratio gave the bis(thiourea) **8** in quantitative

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Scheme 2. a) Mechanochemical coupling of a vicinal isothiocyanate with an aniline via a reactive monothiourea intermediate; b) intermolecular mechanochemical coupling of a vicinal diamine and an aromatic isothiocyanate via a stable monothiourea intermediate 7; and c) mechanochemical coupling of 1,1'-binaphtyl-2,2'-diamine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate via a stable monothiourea compound (**R**)-9.

yield within 3 h after exploring different mechanochemical reaction conditions (grinding liquid, time). Although the quantitative disappearance of the isothiocyanate reactant was verified through FTIR spectroscopy of the reaction mixture immediately after grinding (Figure 2), the ¹H NMR spectra (Figure 3) revealed that the product was pure compound **8**.

However, ¹H NMR spectroscopy (Figure 3) also revealed that with mechanochemical milling times of less than an hour the reaction mixture contained a significant amount of the intermediate amino-substituted monothiourea **7** (Figure 3 d). Consequently, we decided to explore whether monothiourea **7** could be selectively synthesized in a mechanochemical process. Indeed, milling of *ortho*-phenylenediamine with phenyl isothiocyanate in a 1:1 ratio led to clean formation of monothiourea **7** in >95 % yield (Figure 4), as established by HPLC. The yield of **7** could be further improved by using a slight excess (10 mol%) of the diamine reactant, leading to an overall isolated yield of 99% following milling and brief washing with ethyl acetate to remove the excess diamine.

The ability to synthesize and isolate both **7** and **8** in excellent yields without using a large excess of the starting materials is in stark contrast with solution-based syntheses. Specifically, we have conducted the reaction of *ortho*-phenylenediamine and phenylisothiocyanate in ratios of 1:1 and 1:2 by using conventional solution-based techniques. The 1:1 reaction yielded a solid product, the weight of which amounted to 81% of the weight of the starting materials. Analysis by ¹H NMR spectroscopy revealed that the product was



Figure 2. Optimization of the LAG synthesis (12 mm ball, methanol, $\eta = 0.25 \,\mu\text{Lmg}^{-1}$) of the *ortho*-phenylenediamine bis(thiourea) **8** monitored by FTIR spectroscopy after a) 30, b) 90, and c) 180 min. The isothiocyanate absorption band between 2000 and 2200 cm⁻¹ is still present after 30 min grinding.

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Figure 3. Optimization of the reaction conditions in the mechanosynthesis of the *ortho*-phenylenediamine bis(thiourea) **8** monitored by ¹H NMR spectroscopy (samples were taken directly from the reaction jar and dissolved in [D₆]DMSO). a) *ortho*-Phenylenediamine; b) phenyl isothiocyanate; c) a solution-based synthesis in dichloromethane at room temperature; d) NG, 30 min, 12 mm ball; e) LAG (methanol, $\eta = 0.25 \ \mu Lmg^{-1}$), 90 min, 12 mm ball; f) LAG (methanol, $\eta = 0.25 \ \mu Lmg^{-1}$), 90 min, 12 mm ball; g) LAG (methanol, $\eta = 0.25 \ \mu Lmg^{-1}$), 180 min, 12 mm ball; and h) LAG (methanol, $\eta = 0.33 \ \mu Lmg^{-1}$), 180 min, 12 mm ball; Compound **7** corresponds to the monothiourea and **8** to the bis(thiourea).

a 29:1 mixture of monothiourea **7** and bis(thiourea) **8**, respectively (Figure 4d). The 1:2 reaction yielded a solid product, the weight of which was 60% of the total starting material weight. ¹H NMR analysis revealed that the product was a mixture of **7** and **8** in a ratio of 7:1, respectively (Figure 3c).

The comparison of solution and mechanochemical experiments strongly indicates the superior ability of mechanochemistry to control the stoichiometric composition of the product. Although excellent control of product stoichiome-



Figure 4. Optimization of the reaction conditions in the mechanosynthesis of the *ortho*-phenylenediamine monothiourea **7** monitored by ¹H NMR spectroscopy (samples were taken directly from the reaction jar and dissolved in $[D_6]DMSO$). a) NG, 30 min, 2×6 mm balls; b) NG, 30 min, 8 mm ball; c) NG, 30 min, 12 mm ball, 10 mol % excess of *ortho*-phenylenediamine; and d) a solution-based synthesis in dichloromethane at room temperature. Compound **7** corresponds to the monothiourea, **8** to the bis(thiourea), and PDA to unreacted *ortho*-phenylenediamine.

try was previously observed in the contexts of hydrogenand halogen-bonded cocrystals, as well as coordination polymers, the syntheses of **7** and **8** indicates that a similar level of control is also possible for covalent-bond-forming reactions, at least in cases in which the second reaction step is significantly more sterically hindered than the first.

Similar observations were made in the mechanosynthesis of the binaphthyl-based bis(thiourea) 6, the (R)-enantiomer of which was recently used in the asymmetric catalysis of the Henry reaction, [17f] and the (S)-enantiomer of which has been reported as an organocatalyst in the Friedel-Crafts alkylation.^[17e] Neat grinding of (*R*)-1,1'-binaphtyl-2,2'-diamine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate in a 1:2 ratio for 10 min resulted in a mixture of the starting materials, the non-symmetrical monothiourea (R)-9, and the desired bis(thiourea) (R)-6 (Scheme 2c and Figure S29 in the Supporting Information). However, LAG by using MeOH as the grinding liquid $(\eta = 0.25 \,\mu L \,mg^{-1})^{[22]}$ drastically improved the conversion to the final product leaving behind only a small amount of monothiourea intermediate (R)-9 (\approx 5–6 mol%). As one of the reactants is a liquid, this improvement in mechanochemical reactivity by LAG cannot be ascribed solely to improved molecular diffusion, but is more likely a result of the modification in the chemical environment. A similar effect of the grinding liquid in a mechanochemical system that already involves a liquid reactant has previously been reported for the synthesis of three-component cocrystals.^[11a]

For the quantitative synthesis of (**R**)-6, however, we explored a variety of further reaction conditions and established that (**R**)-6 was obtained in >99% purity (based on HPLC) after 60 min of LAG (MeOH as the grinding liquid, $\eta = 0.4 \,\mu \text{Lmg}^{-1}$). In contrast to the reactions involving *ortho*-phenylenediamine, the intermediate urea (**R**)-9 was not obtained in high purity by conducting the mechanochemical reaction in a 1:1 ratio. A significant amount of bis(thiourea) (**R**)-6 was always present, which we ascribe to a more activated isothiocyanate reactant and the reduced steric hindrance on the 1,1'-binaphtyl core.

Chiral bis(thiourea) organocatalysts based on aliphatic vicinal diamines: Our next targets were the chiral bis(thiourea) organocatalysts 3–5 (Scheme 1b), in which the two thiourea moieties reside on an asymmetrical (1R,2R)- or (1S,2S)-1,2diaminocyclohexane (3 and 5) or (1R,2R)-1,2-diphenylethylene (4) backbone. Neat grinding of a 2:1 mixture of 3,5bis(trifluoromethyl)phenyl isothiocyanate and (1R,2R)- or (1S,2S)-diaminocyclohexane for 20 min afforded enantiomerically pure (1R,2R)-3^[17a] and (1S,2S)-3, respectively, in quantitative yield, as shown by FTIR analysis (Figure 5) immediately after milling and by HPLC (Table 1). The im-

cantly more activated electron pair on the amine moieties. The facile reaction between 3,5-bis(trifluoromethyl)phenyl isothiocyanate and 1,2-diaminocyclohexane was also observed in solution, as demonstrated by the ¹H NMR spectrum of a mixture of the diamine and the isothiocyanate in $[D_6]DMSO$ (see Figure S28 in the Supporting Information). Consequently, to confirm that the high reaction yields are

proved rate of product formation in comparison with reac-

tions involving aniline derivatives is consistent with a signifi-

truly the result of mechanochemical grinding, rather than an artifact of solution-based preparation of samples for HPLC or NMR analysis, we analyzed each mechanochemical product by FTIR immediately after grinding. The disappearance of the isothiocyanate stretching band at 2200 cm⁻¹ indicated the full conversion of the reactants. The analysis of the mechanochemical products by PXRD revealed significant differences in sample crystallinity depending on the mechanochemical method. In particular, the product obtained by neat grinding for 20 min exhibited a PXRD pattern with broad features, indicating poor product crystallinity and/or highly amorphous content. Crystallinity was improved, however, in cases in which the mechanochemical synthesis was conducted by LAG with MeOH. Such outcomes are consistent with previous analyses of amorphous/crystalline content in molecular cocrystals obtained by neat or liquid-assisted grinding methods.^[27] The mechanochemical synthesis of the organocatalyst (1R.2R)-3 was also readily scaled up to 1 g amounts without a noticeable loss in the isolated yield (Table 1).

The mechanochemical coupling of 3,5-bis(trifluoromethyl)phenyl isothiocyanate with (1R,2R)-1,2-diphenyl-1,2-diaminoethane by neat grinding or LAG quantitatively gave the catalyst (1R,2R)-4.^[17a,28] (Table 1). The complete disappearance of the isothiocyanate reactant was confirmed by FTIR spectroscopy. Again, PXRD indicated that the neat grinding product is poorly crystalline, whereas LAG afforded a crystalline material. Differential scanning calorimetry (DSC) analysis of the neat grinding product revealed an exothermic event at 106 °C, followed by endothermic events above 185 °C. The exothermic event is consistent with the transition from an amorphous to a crystalline phase, whereas the endothermic peaks are assigned to melting or decomposition of the compound.^[17a,28] Such conjecture is supported by subsequent PXRD measurements that show significant improvement in the crystallinity of the sample after the 106 °C exotherm, as well as by the DSC analysis of the LAG product, which displayed only the endotherms at 185°C (see the Supporting Information).

Our next targets were the bis(*para*-nitrophenyl) derivatives (**1**R,**2**R)-**5** and (**1**S,**2**S)-**5**. Racemic compound **5** has been used as a colorimetric sensor for cyanide ions in DMSO.^[18b] Both neat grinding and LAG reactions of (1R,2R)- or (1S,2S)-1,2-diaminocyclohexane with *para*-nitrophenyl isothiocyanate in a ratio of 1:2 yielded the desired (**1**R,**2**R)-**5** and (**1**S,**2**S)-**5**, respectively, in high purity and quantitative yield, surpassing earlier solution-based syntheses, as demonstrated by FTIR analysis immediately after

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(1R,2R)-4, (1R,2R)-5, and (1S,2S)-5. The absence of the isothiocyanate

absorption band between 2000 and 2200 cm⁻¹ is notable in all cases.

formula	$C_{30}H_{36}N_4O_2S_2$	Ζ	2				
$M_{ m r}$	776.8	$ ho_{ m calc} [m gcm^{-3}]$	1.431				
crystal system	monoclinic	λ [Å]	0.71073				
space group	$P2_1$	$\mu \ [\mathrm{mm}^{-1}]$	0.243				
<i>a</i> [Å]	14.321(2)	R, for all 5358 reflections	0.0826				
b [Å]	8.904(2)	w R_2 , for 4479 reflections with $I \ge 2\sigma(I)$	0.1617				
c [Å]	14.418(2)	S	1.050				
β [°]	101.323(3)	$ ho_{ m min,max} \left[{ m e} { m \AA}^{-3} ight]$	-0.69, 0.68				
V [Å ³]	1802.7(5)						

Table 2. General and crystallographic information for crystal structure analysis of compound (1R,2R)-3-2(*i*PrOH).

grinding, as well as subsequent HPLC analysis and ¹H NMR spectroscopy.

Crystal-structure analysis: For structure confirmation, (1R,2R)-3 was also obtained as single crystals by recrystallization from isopropanol (*i*PrOH). Single-crystal X-ray diffraction (Table 2) revealed that the single crystals were an *i*PrOH solvate of the (1R,2R)-3 organocatalyst (Figure 6).

The solvated crystal consist of hydrogen-bonded tapes in which a set of *i*PrOH molecules are associated with thiourea moieties through bifurcated $N-H\cdotsO$ hydrogen bonds



Figure 6. Crystal structure of (1R,2R)-3-2(*i*PrOH): a) one molecule of (1R,2R)-3 and b) a fragment of a hydrogen-bonded tape involving (1R,2R)-3 and *i*PrOH, with hydrocarbon hydrogen atoms and the disorder of trifluoromethyl groups not shown.

(N···O separations: 2.95 and 2.92 Å), and are also attached to a second set of *i*PrOH molecules by O– H···O hydrogen bonds (O···O separation: 2.76 Å). The second set of *i*PrOH molecules also links to the neighboring thiourea groups by not very common O–H···S interactions (O···S separation: 3.36 Å). Molecules of (1*R*,2*R*)-3 interact through bifurcated N–H···S contacts (N···S separations: 3.39 and 3.35 Å) that exhibit a bent geometry characteristic of thioureas in the solid state, with the angle between the planes of the hydrogen-bond donor and acceptor thiourea moieties being 69°.^[29]

Immediate applicability of mechanochemically-prepared bis-(thiourea)s and reaction scale-up: To verify the applicability of the mechanochemically prepared organocatalysts, we tested the as-prepared achiral compound 1 and chiral compound (1R,2R)-3 for nonstereoselective and asymmetric



Scheme 3. Thiourea-catalyzed Morita-Baylis-Hillman reaction.

versions of a Morita–Baylis–Hillman reaction, respectively (Scheme 3).^[17a,g,h] Following the literature procedure, benzaldehyde and 2-cyclohexene-1-one were used as the reactants and 1,4-diazabicyclo[2.2.2]octane was used as the base.^[17a] Yields of 58% in the case of the nonstereoselective reaction and 70% in the (**1***R*,**2***R*)-**3** catalyzed asymmetric Morita– Baylis–Hillman reaction were obtained (Table 3), which are comparable to the previously reported results.

Table 3. Catalytic performance of **1** and (1R,2R)-**3** in the Morita–Baylis– Hillman reaction of benzaldehyde and 2-cyclohexene-1-one. Literature values in brackets.^[17a]

	Catalyst	Method for catalyst	Yield ^[a]	ee ^[b]
		synthesis	[%]	[%]
1	1	LAG	58 (60)	_
2	(1R,2R)-3	neat grinding or LAG	70	24
3	(1R,2R)-3 EtOAc solvate	in solution ^[c]	68 (72)	25 (33) ^[d]

[a] Isolated yields after column chromatography. [b] Determined by chiral HPLC analysis (Chiralcel OJ 250×4.6 mm stationary phase). [c] Stirring in THF, then recrystallization from hexane/EtOAc.^[17a] [d] Difference from literature value can be explained by a four-fold reduction in scale.

To fully verify that the mechanochemical method of preparation does not affect the catalytic performance of the catalyst, we also prepared (1R,2R)-3 through the reported solution-based procedure involving the thiourea coupling in THF and recrystallization from a mixture of hexane and EtOAc.^[17a] The catalytic activity of the solution-prepared catalyst was identical to that of our mechanochemically synthesized material. However, ¹H NMR spectra of the solution-synthesized catalyst revealed that it was a 1:1 EtOAc



Figure 7. Comparison of ¹H NMR spectra of bis(thiourea) (1R,2R)-3 prepared by a) neat grinding and b) a solution-based reaction in THF and recrystallized from hexane/ethyl acetate. Recrystallization affords the 1:1 ethyl acetate solvate according to NMR analysis (EtOAc peaks are labeled with *).

solvate of (1R,2R)-3 (Figure 7), which was also corroborated by thermal analysis (thermogravimetric analysis (TGA) and DSC). The surprising stability of the ethyl acetate solvate was proven by the difficulty in removing it from the solution-made organocatalyst: complete removal of the solvent was accomplished only after drying the solid under high vacuum ($p = 10^{-4}$ mbar) for three hours. As established by TGA (see the Supporting Information), the EtOAc solvates of (1R,2R)-3 and (1S,2S)-3 retained 75–90% of the solvent of crystallization even after standing for two months in open air. Consequently, besides enhancing the reaction speed and efficiency, mechanosynthesis circumvented the previously unrecognized formation of a highly stable catalyst solvate in the solution-based synthesis.^[30]

To further verify the immediate applicability of our mechanochemically obtained bis(thiourea)s in areas other than organocatalysis, we explored the efficiency of the as-prepared (1*R*,2*R*)-5, (1*S*,2*S*)-5, and their racemic 1:1 mixture as colorimetric indicators for cyanide ions (Figure 8), as previously reported for the racemic form of $5^{[18b,31]}$ The results reveal the sensitivity of mechanochemically prepared enantiomeric 5 to CN⁻ is comparable to that reported for the racemate (concentration range 10^{-5} to 10^{-4} mol dm⁻³).

Although the presented mechanochemical syntheses of mono- and bis(thiourea)s have been conducted on a scale that would be expected in a typical research laboratory, we also explored the synthesis of 1, 3, and 8 on a one-gram scale. The results (Table 1) show that excellent isolated yields are retained upon scaling up of the reaction with reaction times of between three and nine hours.

Conclusion

We have shown that mechanochemical milling allows the click synthesis of known achiral and chiral thiourea catalysts in excellent yields on up to a one gram reaction scale. Short reaction times, quantitative yields, and the absence of prod-



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Figure 8. UV/Vis absorption spectrophotometric titration of a) (**1***R*,**2***R*)-**5**, b) (**1***S*,**2***S*)-**5**, and c) a 1:1 mixture of the enantiomers ($c=2.0 \times 10^{-5}$ moldm⁻³ solution in DMSO) with tetrabutylammonium cyanide. Arrows indicate the changes in the absorbances at 360 and 475 nm upon addition of cyanide ions (from 0 to 10 equivalents).

uct workup render the presented mechanosyntheses very suitable for the efficient conversion of valuable reagents in a typical chemical laboratory, illustrated here for the quantitative transformations of enantiomerically pure diamines. Preliminary tests indicate that mechanochemically prepared thioureas are as effective catalysts and anion sensors as those synthesized by traditional methods, and that mechanochemistry avoids the unwanted formation of solvated products that could serendipitously result from solution-based synthesis. Our results also demonstrate that mechanosynthesis can provide excellent yields of bis(thiourea)s based on reactants hindered by stereochemical and electronic effects. In this way, mechanochemistry is superior to established solution-based methods and we are now exploring the high-

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yielding mechanosynthesis of *ortho*-phenylenediamine bis-(thiourea)s.

Experimental Section

All chemicals were purchased from commercial sources (Sigma Aldrich or Alfa Aesar) and were used as received (except 4-nitrophenyl isothiocyanate, which was purified by column chromatography). The experiments were carried out in a Retsch MM400 mill at a frequency of 30 Hz by using a 10 cm^3 stainless steel grinding jar and a single stainless steel ball with a 12 mm diameter. Dry methanol was used as the liquid phase in all liquid-assisted grinding (LAG) experiments.

¹H and ¹³C NMR spectra were recorded on Bruker Avance (300 and 600 MHz) spectrometers with tetramethylsilane as an internal standard. IR spectra were obtained on an ABB Bomem MB102 spectrophotometer (CsI optics, DTGS detector, KBr pellet). Routine HPLC analyses were performed on a Varian ProStar Instrument with a UV/Vis detector by using Restek UltraIBD C18 (reversed phase) 5 µm, 250×4.6 mm column operated at room temperature and a flow rate of 1 mLmin⁻¹. A 90:10 methanol/acetic acid (2%) mixture was used as the eluent in all analyses. Chiral HPLC analyses were performed on a Knauer Smartline analytical system by using a Chiralcel OJ (250×4.6 mm) chiral column with *n*-hexane/2-propanol (9:1) as the mobile phase. UV spectrophotometric titrations were performed on a PG Instruments T80 plus spectrophotometer according to a literature procedure.^[18b]

Further details of the experimental procedures are given in the Supporting Information, along with individual results of ¹H and ¹³C NMR, FTIR, HPLC, PXRD, DSC, and UV/Vis measurements. CCDC-862352 (-(1*R*,2*R*)-3-2*i*PrOH) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via:

www.ccdc.cam.ac.uk/data_request/cif.

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