

More than Thousand Quantitative Wasteless Syntheses in 25 Reaction Types all Across Molecular Chemistry

Gerd Kaupp*

Faculty 5, University of Oldenburg, Germany

***Corresponding author**

Gerd Kaupp, Faculty 5, University of Oldenburg, Germany,
Tel: +49 4486 8386; Fax: +49 4486 920704; E-mail: gerd.kaupp@uni-oldenburg.de.

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Abstract

Wasteless preparative molecular and ionic solid-state reactions (gas-solid and solid-solid) proceed rapidly, with definite completion, at decreased activation energy omitting catalysis and waste-producing chromatographic workup, when properly executed. They are unbeatably specific, scalable up to industrial production, and obtain otherwise not available compounds also directly pure. The already available more than thousand 100% yield reactions in 25 reaction types (not counting subdivisions) across molecular chemistry are unfortunately mostly not cited, discussed, or compared in the inferior publications that depart from the solid-state and discredit the field by extremely long milling times, unnecessary catalysis, incomplete reactions, low selectivity, chromatographic workup, etc. Thus, the lack of temperature control and/or the retrogressive adding of “a little solvent” for synthetic milling leads to melt reactions at rapidly increasing temperature (most severe with planetary mills), losing all the benefits of the molecular solid-state. It is recapitulated how the solid-state can be retained with simple means, how Schmidt’s topochemical hypothesis (“forbidding” these unbeatable solid-state syntheses) is overcome, and what the physical reasons are for long range anisotropic molecular migrations along crystallographic channels, cleavage planes, or to voids. It is again shown that local melting is not required. Staying below the lowest eutectic temperature is essential. The basic reasons and technical requirement for the wealth of thermodynamic controlled solid-state reactions (as opposed to counter-thermodynamic mechanochemistry) are summarized in this mini review with a short selection from the striking synthetic advancements to remind the mostly disregarded top of sustainability also against some habits with the 12 commandments of “green chemistry”. These do not require avoiding unnecessary catalysis (on the contrary) or solvents (“green solvents” are also deactivating), or to completely avoid (instead of “decrease”) dangerous wastes by solvent consuming chromatographic workup, etc. This holds for particularly easy gas-solid productions and to solid-solid reactions, where mills are presently often misused heating/melting devices.

Keywords: Ball-milling, Directly pure products, Environmentally benign, Gas-solid reactions, Industrial scale, Molecular packing, Solid-solid reactions, Temperature control, Unbeatable specificities, Wasteless syntheses.

Introduction

The synthetic chemistry needs clean quantitative wasteless technique for the sake of sustainability. 100% yield without workup requirement (by recrystallization or chromatography) has been amply realized with real solid-state reactions. Since 1985, we have more than 1000 of them within 25 reaction types (not counting the numerous subdivisions) and short reaction times, mostly without catalysts and other auxiliaries (except when these can be easily removed) [1]. Liquids can be frozen out. For example the liquids antimony tetrachloride, epichlorohydrine and further liquid oxiranes, N-vinylpyrrolidone, phenylisothiocyanate, and 1, 1-diphenylethene has been reacted as frozen solids at -20 or down to -60°C [1].

However, these solid-state reactions are apparently disliked and not properly cited in the literature. At best a rare citation is hidden

amidst numerous other citations claiming “greenness”, none of them having the unbeatable qualities, while only ours cannot be topped. Rather it is tried to depart from the easily reached optimal reaction conditions with the aim to try differently at the cost of admitting poor result. In fact there seems to be a desire for using chromatographic workup against the reasonable requirement for achieving best “atom economy” and only “minimizing” (rather than avoiding!) wastes. Another reason for disliking true solid-state reactions is the still widespread though erroneous belief in textbooks, advocating Schmidt’s hypothesis that is the obsolete topochemistry with their 4.2 \AA dictum of 1964. The obvious error is disregard of the internal pressure situation upon reaction. Nevertheless, the hype with Schmidt’s topochemistry would forbid all of these unbeatable syntheses without intermitting liquid phases, as is amply shown at the molecular scale with contact AFM (atomic force microscopy). However, avoiding all liquid phases along the reaction path by staying below eutectic temperatures, and avoiding addition of “a little solvent”, is a prerequisite for wasteless gas-solid or stoichiometric solid-solid reactions. These are known since the experimental results of 1986 and AFM-

measurements starting in 1992 followed by numerous lectures and publications including review articles [2,3].

Materials and Methods

Solids and frozen liquids must be pure. Products can only be as pure as the starting materials. In some cases polar or unpolar impurities can be tolerated when it is easier to remove them after reaction. The amount of impurities must be corrected for in precisely stoichiometric mixtures. Catalysts can mostly be avoided due to the considerable decrease of activation energy in solid-state reactions as compared to melt or solution ones. Gas-solid reactions require gas-tight equipment, unless in large-scale open suspension or stream bed processing (Figure 1). In closed evacuated vessels the dry gases have to be slowly added in most cases and efficient cooling and agitation is required, because these can vigorously proceed, and melting must be avoided for reaction specificity and completeness. In column processing cooling has to be achieved by admixture of inert gas and stream rate. Two columns in series are required to avoid losses at the sharp reaction front. Stoichiometric gas is only required when multiple reaction would occur. Any excessive gas is recovered by freezing out in a cold trap for further use.

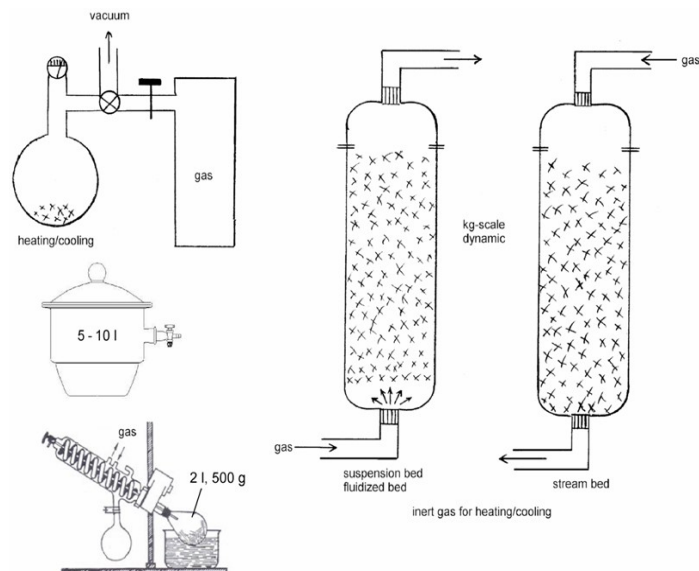


Figure 1: Typical equipment for lab-scale and larger scale (up to industrial) gas-solid reactions [4].

Waste-free solid-solid reactions require precisely stoichiometric components and temperature control. In the absence of a phase diagram, small co-grinding tests in a mortar with pestle check for melting and appropriate temperature below eutectics, so that optimal conditions may be easily found (sometimes heating, more often staying ambient, or cooling). There is not only the chemical reason for strict temperature control. The thermally activated reaction stops upon melting (losing the benefit of the lowered activation energy). When run as a melt reaction at higher or uncontrolled temperature one obtains at best incomplete reaction for long time milling with side products by kneading. The kneading is also impeded by sticky melt and scaling to industrial ball-mills (rather than kneaders) is impossible. Temperature control in solid-state chemistry is state-of-the-art since 1989.



Figure 2: Lab-size shaker ball-mill MM200[®] from Retsch GmbH; the 20 ml beaker with temperature control proper milling times are minutes to at most 1h [5].

Figure 2 shows the 2 mmol-size temperature controlled shaker mill that has been advocated and used since 1989. The temperature range is -78 to $>100^{\circ}\text{C}$. The mill provides 100% yield with otherwise never reached specificity (if there is a choice) in minutes and at most 1 h, this in case of cascade reactions. Only two balls are used and product collection is without any solvent, if necessary in a glove box (solvent less, not only “solvent-free”). When nevertheless people think they must use the mill as a heating device they lack any good result with excessive milling times, poor yields despite catalysis, and requiring chromatography, producing dangerous wastes with using organic solvents. This can be demonstrated with Figure 3. Temperature increases rapidly upon uncontrolled milling and the result is melting by misuse of the milling technique. This deters from using the unbeatable solid-state production by not citing the unbeatable state-of-the-art for virtually all reaction types without catalysts [1]. Adding “a little solvent” [6] does, of course, not help either. Don’t join that present retrogressive hype!

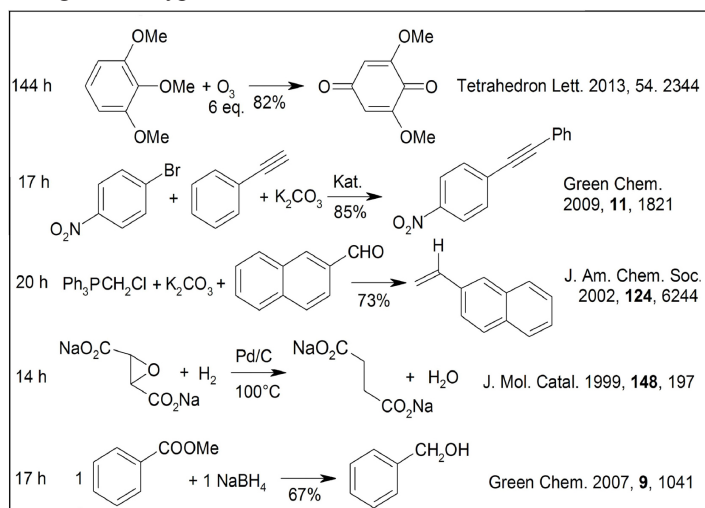


Figure 3: Undue milling times and yields in shaker/tumbler mills

of various brands without temperature control. Disgusting milling times of heated melts and poor yields despite catalysis!

The even more frequent use of planetary mills with too much impact for even more rapid heating is also deterring. There is no possibility for temperature control and clogging of the material to the walls occurs. The products have to be collected with solvent for chromatographic separation. Most authors unduly call that “green” and “solvent-free”. The degree of deterioration is shown with some examples in Figure 4. It contains also three correctly mechanochemical transformations with inorganics exhibiting melting points well above the easily reached 200°C, indicating the clogging effect. Importantly, planetary milling excludes any scaling to industrial continuous milling. Images can be found in the Internet. The reactions in Figure 4 should rather be tried by using temperature controlled shaker or rotor ball-mills without clogging at appropriate impact and strict temperature control.

Some Solid-State Milling Times in Planetary Mills

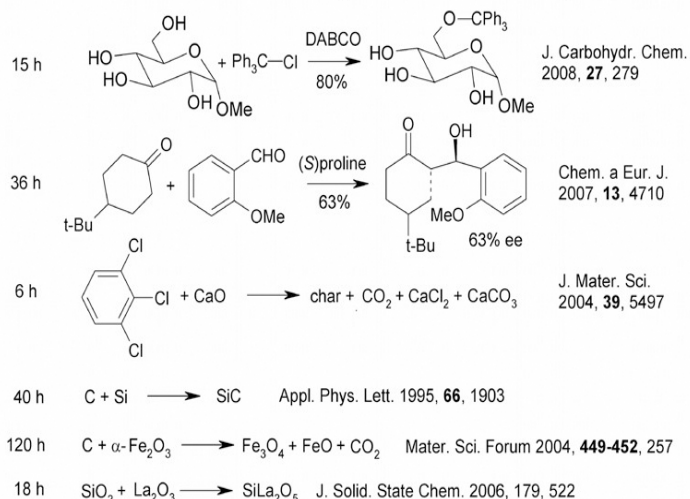


Figure 4: Some of published milling or better kneading results in planetary mills with disgusting kneading times.

Apart from the unsuitable mill, also the so-called “solvent-free” reactions with addition of “a little solvent” are a serious way back despite their present hype, giving poor yield and excessive kneading times. It is obviously tried to reinvent or revive the obsolete topochemistry, as far as solid-state reactions are concerned [6]. Solvent dependent polymorphs of salts can also be crystallized from solution. The solvent-added millings (they are not “solvent-free”!) require catalysts, provide incomplete reactions and require chromatography requiring poisonous solvents and excessive time, energy, and labor. They produce enormous amounts of dangerous wastes, do not compare with the state-of-the-art and thus do not tell yields in reviews. That is often claimed to be “green” but it is far from being sustainable! Clearly, despite the present hype with adding “a little solvent”, the so-called liquid assisted grinding “LAG” is not assisting but impeding, due to losing the bargain of the solid state. Furthermore, the continued use of the term “mechanochemical” even for “LAG” is more than confusing, because only the contacting of the components is essential (heating by milling must be prevented by temperature control) [1,4,5]. Neither solid-state nor liquid state molecular reactions with grinding or milling belong to the large and diverse

important field of mechanochemistry that covers only the breakage of intra molecular chemical bonds by mechanical impact [7]. The confusing wrong use of the term “mechanochemistry” disregards basic mechanistic knowledge and has been leading to wrong beliefs and speculations.

Industrial synthetic milling requires large mills such as temperature controlled rotor ball mills that are available from 1 to 900 liter volume of the milling chamber with rotor. The product collection is without solvent. For organic production the 2 to 20 L mills are most suitable because of materials costs beyond the 10 kg range. Temperature control is by alternative automatic milling/cooling cycles using the different operation states. Figure 5 shows a 100 L Simoloyer[®] of Zoz Ltd, and Figure 6 equipment for continuous processing with a 20 L mill.



Figure 5: 100 L production unit horizontal rotor ball mill, set for inert gas operation courtesy of Zoz Ltd. Wenden, Germany [4].



Figure 6: A 20 L Simoloyer[®] at continuous operation; courtesy of Zoz Ltd. Wenden, Germany.

With this background we know how to proceed with wasteless solid-state reactions. When crystals or amorphous solids are available these must not be dissolved, or melted, or wetted with solvents for chemical reactions. One would waste the bargain of favorable self-assembled alignment and deactivate the molecules by solvation, which is not sustainable but waste producing.

Results and Discussion

The solid-state reaction mechanism

First of all a mechanistic distinction is necessary between solid-state reactions that are thermodynamically controlled and mechanical reactions with bond breaking due to mechanical impact that lack thermodynamic control. The latter use the same mills for often sparkling tribochemical reactions forming radical-plasma when crystals of tribomaterials (e.g. quartz) are mechanically broken with light emission and carbonization of all organic material that might be reachable (from methane via the most poisonous 2,3,7,8-tetrachloro-dibenzodioxin TCDD to polymers) and numerous further applications [7]. Extremely highly activated species are formed without thermodynamic control, and they deactivate unselectively. Often care has to be taken to avoid self-sustained processes as in thermic reactions or explosions. Only if milling, shearing, cutting, grating, forging, drilling, polishing, pulling, impacting breaks chemical bonds do we have mechanical activation (and chemical follow-up reactions). In gas-solid and intra or inter solid-solid reactions we have no mechanical activation beyond comminuting. But we bring gases in contact with solids or we create repeated contacts between solid reactants by milling, which is totally different from mechanochemistry. Denying such distinction is harmful and messy. Actually, many errors in the interpretation of solid-state reactions derive from falsely calling them “mechanochemical” (for example [6] and many other publications). Recent reviews dealing correctly with that distinction are in [8- 11]. Figure 7 points out the difference.

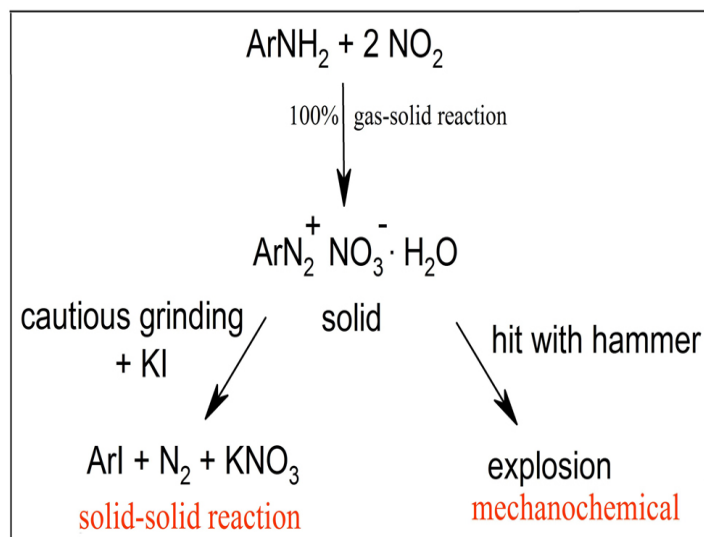


Figure 7: Distinction of molecular or salt’s solid-state reactions from mechanochemical reactions.

The solid-state mechanisms, be they thermal or photochemical, have been elucidated since 1990 with AFM. It has been found that molecules undergo anisotropic migration due to pressure formation upon photochemical or thermal reaction that must be released. This result is at variance with the strange and obsolete

Schmidt’s topochemistry hypothesis (“<4.2 Å distance, no molecular migrations within crystals”), which has nevertheless provoked an unusual hype. Such amply demonstrated anisotropic migrations are also seen with the crown witness of topochemistry, the photodimerization of α -cinnamic acid (Figure 8) [12-13]. Topochemistry is thus a misconception without any predictive power! It severely hampered the development by denial of basic physics in textbooks and also by referees, who even “forbided” gas-solid and solid-solid reactions despite the amply provided unbeatable synthetic results and AFM evidence. Molecules migrate long distances and above surfaces along crystallographic channels or in slip-planes or to crystallographic voids or to voids in amorphous solids. In the absence of such structural facts there is no chemical reaction despite < 4.2 Å distance between putative reaction centers.

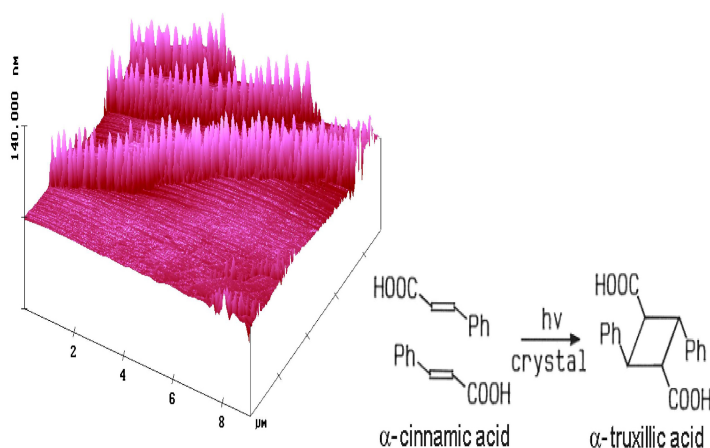


Figure 8: AFM showing molecular migrations along cleavage plane upon extremely long wavelength photo-dimerization with α -cinnamic acid [5, 14].

The cleavage planes of α -cinnamic acid and channel of solid-state reactive antipyrin are depicted for demonstration in Figure 9. This does not mean in practice that X-ray structures must be known before the solid-state syntheses are started. Channels and slip planes are quite common. Reactivity is rapidly checked (< 1 h, including IR spectroscopy).

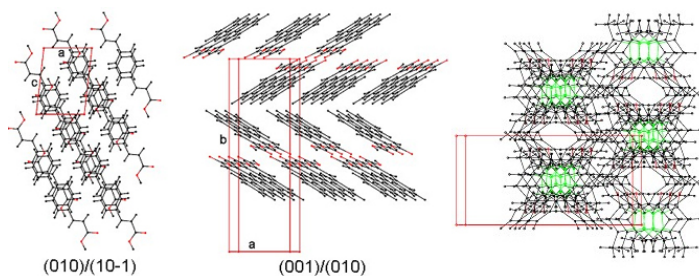


Figure 9: X-ray crystal structure projections of cleavage planes for α -cinnamic acid on (010) and (001), and channel of antipyrin along [001] [14].

An example for the AFM investigation of solid-solid reactions (contact AFM has been the most precise exclusion of local melting) is seen in Figure 10 [15]. The small crystal is laid down on the larger single crystal and time dependent scanning is close to the interface. After some time, volcano-like features grow and then augment over the surface, which has been called phase rebuilding

and thereafter all the sudden a totally changed image is scanned and it follows disintegration to create fresh surface, because the phase has transformed to the product phase. This is the ingenious three-step mechanism of all solid-state reactions (without intermediate melting!) that also explains why these reactions come to a definite completion (zero order kinetics) in the preparative or production cases. These reactions are chemically driven; everything works without mechanical impact [16].

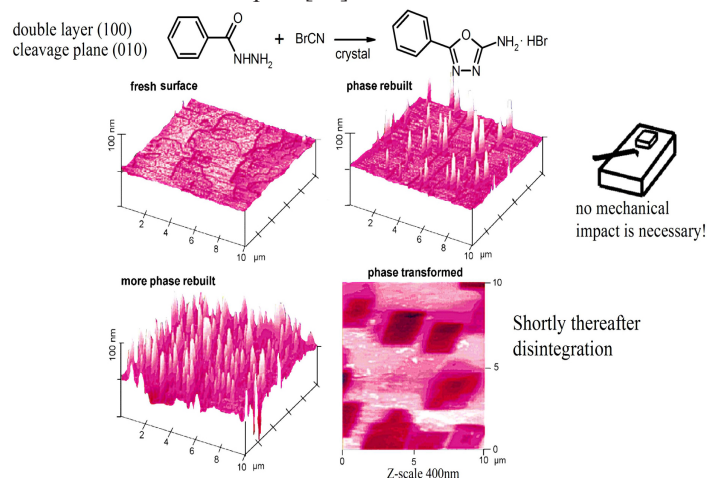


Figure 10: AFM analysis for a multistep solid-state reaction (giving 100% yield under preparative conditions), demonstrating the ingenious solid-state mechanism [16].

The efficiency of these reactions derives from the described features, leading to close to zero kinetic order, because there is always a roughly constant amount of contacts up to the definite completion. The reason for the decrease of activation energy derives from the lack of solvation. All of that has also been amply shown with AFM for gas-solid reactions on single crystals that were treated with reacting gases in-situ or ex-situ: phase rebuilding, phase transformation, and disintegration [14].

We need now the deeper insight in the principally occurring states of pressure, as involved in reactions within crystals. Geometric change upon reaction may lead to decrease of volume, unchanged volume, or increased volume. The consequences are summarized in Table 1. The molecular packing is crucial, and this systematic is of greatest importance for correct predictions [14].

Table1: Systematics of anisotropic migrations within reacting crystals [14,16].

Negative Pressure	No Pressure	Positive Pressure
shrinkage	no geometric change	expansion
migration	no migration	migration
surface features	no surface features	surface features
frequent	extremely few approved cases	very frequent

Unprecedented predictions are possible with the content of the most convincing Table 1. This has been totally overlooked by the misconception of topochemistry and their proponents and textbook writers who had made their rapid careers with it. But they disregarded all opposing evidence, despite its clarity and synthetic success. Newcomers trusted in the obsolete topochemistry

hypotheses and would also not agree that reacted molecules must migrate for pressure release despite hundredfold AFM proof of that.

We have direct contact in gas-solid reactions and must create as much as possible contacts between reacting crystals in solid-solid ones. By avoiding melting we use the bargain of the solid state. This does not involve mechanical activation beyond comminuting. It is proven by ample AFM results without milling/grinding and by the multitude of unbeatable solid-state reactions. Unsuitable crystal packing in the absence of voids, channels, or slip planes can often be engineered with different polymorphs, salt formation, and the like [1, 8, 16].

Application for reactions with negative or no pressure

Figure 11 shows an example for negative pressure, because the volume decreases upon linear dimerization of 1, 1-bis (4-tolyl)-ethene. Voids form instead of outside migration. Addition of HCl or HBr is suppressed by 3D-interlocked packing of the crystal structure for the putative HX-addition. Thus, only acid catalyzed linear head-to-tail dimerization occurs. It is quantitative without wastes under preparative conditions, as the HCl or HBr catalyst (here a necessary exception in a low melting point system) is quantitatively recovered in an evacuated cold-trap for further use. Further 1, 1-bis-aryl compounds and different acidic catalysts work as well down to -25 or even -50°C . The volumes decrease upon the linear dimerization, which can be accommodated by the crystal packing, and the imaged voids are formed [17].

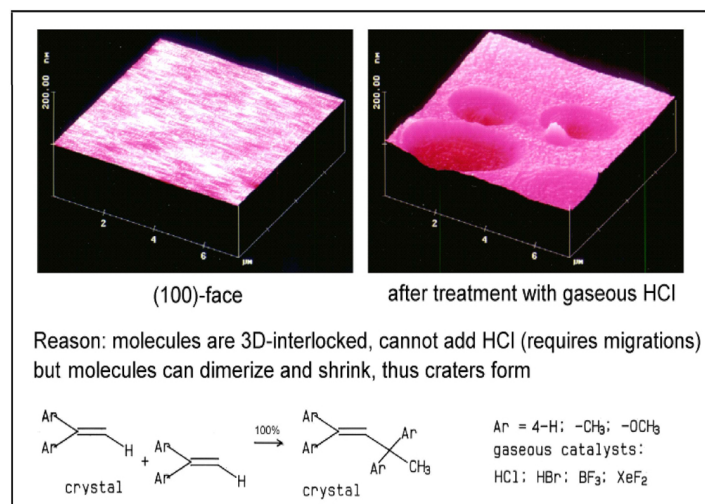


Figure11: Catalytic linear solid-state dimerization of 1, 1-bis (4-tolyl) ; AFM analysis [1].

A special case for (almost) no pressure reactions is the linear polymerization of 1, 3- diacetylenes that crystallize in columnar stacks with distances of the reactive centers below 4.2 \AA . Most of them are not reactive and the topochemistry community wasted millions of research dollars for decades, despite very complicated failing theoretical efforts. But the explanation is very easy with basic physics (Figure 12), requiring the molecular migration issue within crystals and our Table 1 that cannot be dismissed. It is clear that only molecules can migrate but polymers cannot migrate within crystals. Thus, the very few reported linear polymerizations of 1, 3-diacetylenes exhibit very close correspondence of monomer stacking and period of the polymer ($4.90\text{-}4.97$ versus $4.90\text{-}4.91$

Å). This does not produce insurmountable pressure. When the monomer stacking is larger than 4.98 Å the amount of molecular migration becomes too large, and the delicate stacks break down after a few polymerization steps, so that at best unspecific oligomers ensue. When the monomer stacking is smaller than 4.90 Å, no polymer can be formed due to excessive pressure by the larger putative polymer. Clearly, shorter distance is here detrimental. Only the self-evident migration issue provides the correct answer. No exception to these principles has been found: in one case from all of the numerous published ones with apparently not fitting stacking an initial phase transition gave the 4.90 Å polymorph before the polymerization started [14,16].

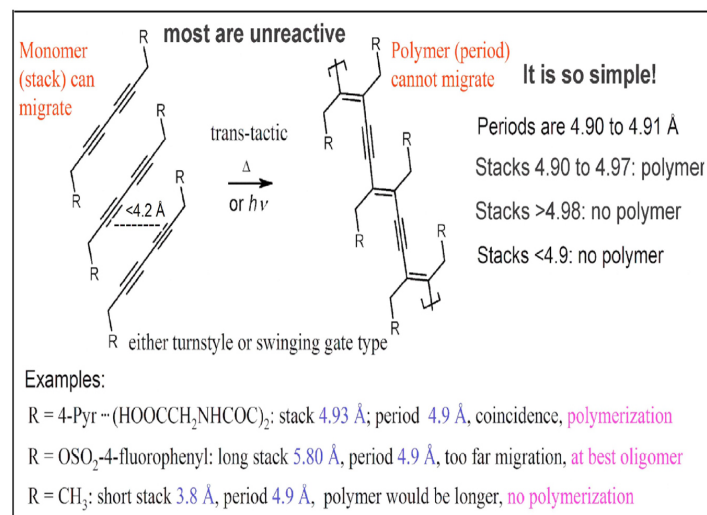


Figure 12: The explanation for the fact that the overwhelming number of 1,3-diacetylenes do not “topotactic” polymerize; these are striking and very expensive failures of topochemical pseudo problems [16].

Allowed stacking ranges for polymerization have similarly been deduced, using the same principles for explaining the reactivity/non-reactivity in the linear polymerizations of muconates (1,3-dienes) [16]. Topochemistry with its 4.2 Å distance dictum is again in severe error, non-predictive, unreasonable. Too-short distance is prohibitive. Topochemists are shocked with that but they are silent or mute, because they wasted millions of dollars by running in the false topochemistry hypothesis, instead of thinking. The reactive/not reactive question can be again decided within <math>< 10</math> min.

Application for reactions with positive pressure

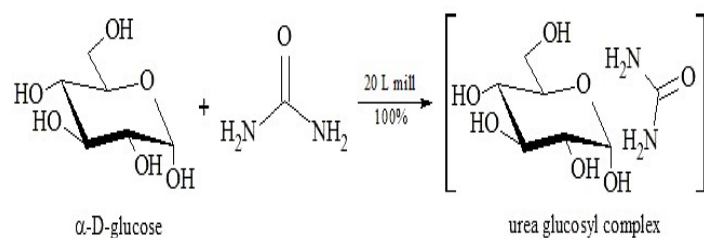
This Section deals with the overwhelming cases in solid-state chemistry. Only a few characteristic gas-solid and solid-solid syntheses or productions can be selected here from the 25 general reaction types in Table 2 that demonstrates the benefit of properly executed solid state reactions [1].

Table 2: 25 general reaction types all across molecular chemistry with more than 1000 already realized wasteless 100% yield reactions [5].

inclusion reaction	condensation of carbonyls
electron transfers	cycloadditions
proton transfers	cycloreversions

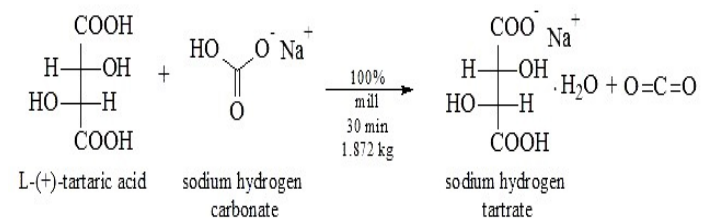
oxygen transfers	substitutions with RX
oxygenations	aromatic substitutions
hydrogenations	cyclizations
additions of RR' NH, H ₂ O, ROH	methylations
additions of halogens and HX	nitration at N and C
eliminations	diazotations
rearrangements	azocouplings
C-C bond formations	Sandmeyer reactions
carboxylations with CO ₂ catalyzed reactions	cascade reactions

The large scale production of the urea glucosyl complex (Scheme 1) [4] that was not available by crystallization without crystal seed (it required years for obtaining some mg of it from solution), is now obtained without seeding in 5 minutes in a temperature controlled (25-30°C) 20 L rotor mill at the 2 kg range.



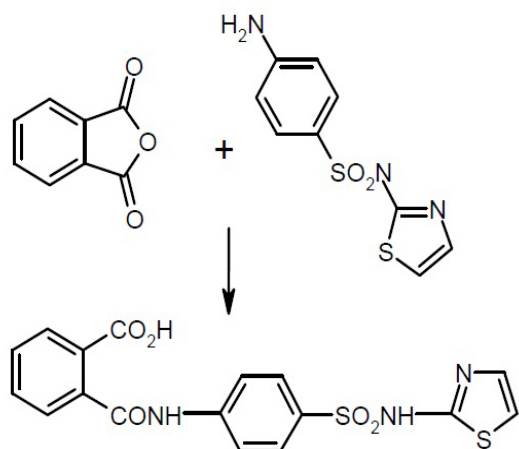
Scheme 1: Milling of α -D-glucose with urea to obtain the urea glucosyl complex [4].

The food additive sodium hydrogen tartrate from tartaric acid and sodium hydrogen carbonate with evolution of CO₂ has been upgraded from 200 g [1,4] to 1.9 kg (Scheme 2). Recently caustic sodium hydroxide (detour from NaHCO₃) in water had to be used.



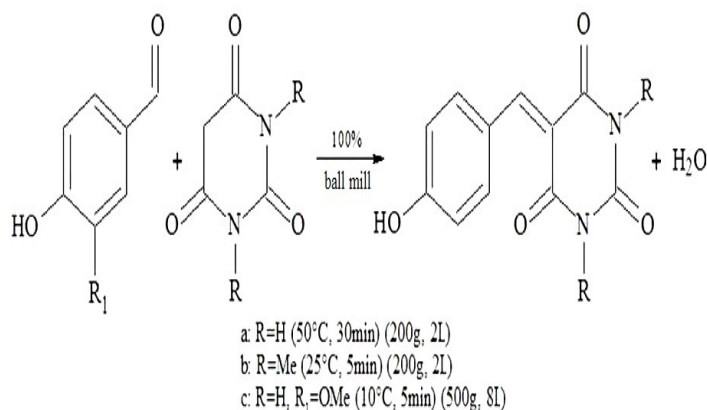
Scheme 2: Large scale dry production of sodium hydrogen tartrate monohydrate [4].

The antibacterial pharmaceutical phthalazole has been wasteless obtained in 20 min, free of imide and bisamide upon stoichiometric milling (200g batches in 2 L rotor ball-mill) at 25- 30°C (Scheme 3), whereas the side products occur upon reaction in melts or solution [1].



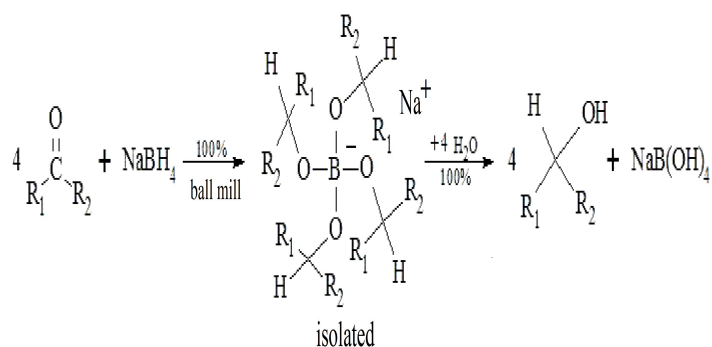
Scheme 3: Wasteless production of the antibacterial sulfonamide phthalazole by stoichiometric milling [1].

C=C-bond formations by Knoevenagel condensation under strict temperature control occurred large-scale wasteless with 100% yield upon short milling (Scheme 4), even though the couple product is the water of reaction [4]. Fortunately, it is taken up as removable crystal water by the product in all cases a-c. Entry c is close to a eutectic temperature, which indicates the excellent temperature control within the rotor mills (batches in 2 L and 8 L mills).



Scheme 4: Quantitative stoichiometric uncatalyzed Knoevenagel condensations of solid benzaldehydes with barbituric acids, using Simoloyer^(R) rotor mills (cf. Figure 5) [4].

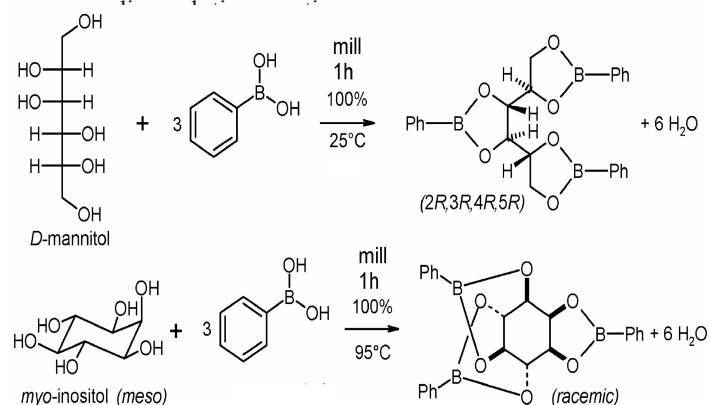
Solid-state reactions have the big advantage of particularly strict anhydrous conditions, allowing for the production of extremely sensible products. Unlike wasteful reductions of carbonyl compounds with excessive sodium borohydride where only one of the four B-H bonds is used, we isolated in 34 cases within 30 min milling each, the pure sodium tetraalkoxyboranate intermediate by using all four B-H bonds for the first time (strict 4:1 stoichiometry) and without any catalyst at 25°C. These otherwise not available salts are extremely sensitive to nucleophiles. For example with water vapor the alcohols and the easily and quantitatively separated sodium metaborate hydrate are obtained. Since the latter is a starting material for the synthesis of NaBH₄, this procedure is wasteless [18].



Scheme 5: Solid-solid wasteless reduction of ketones using all four B-H bonds of sodium borohydride in 4:1 stoichiometry without catalysis.

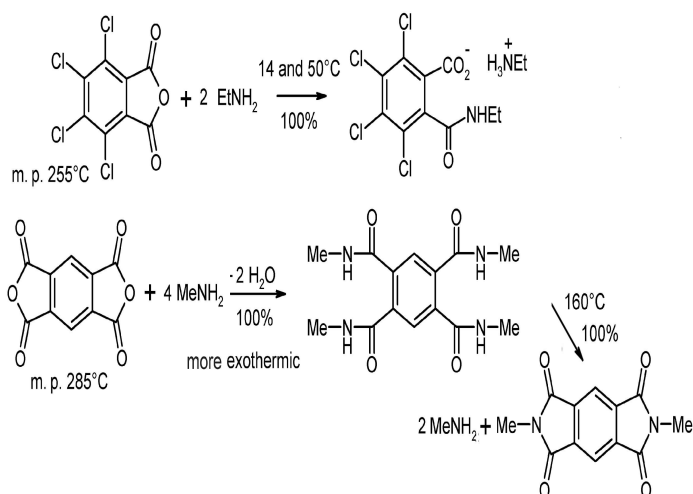
Surprisingly, this unbeatable use of NaBH₄ has not been cited in 3 later publications of the journal “Green Chemistry”, requiring large excess of NaBH₄ with catalysts, or explosive ammonia borane by calling it “green” and “environmentally benign” (incredible detour: BH₃-NH₃ from NaBH₄ + H₂ + ammonium sulfate in tetrahydrofuran). All of these use only one of the B-H bonds with poor product yields and large dangerous waste production for carbonyl reductions with (by necessity) chromatographic workup.

The enormous power of properly executed solid-state chemistry is also evident from the unbeatable stereo specificity in the protection reaction of polyols with phenylboronic acid. Only one regio- and stereo-isomer is obtained each, when one D-mannitol or myo-inositol is co-milled for 1 h with three phenylboronic acids at the given temperatures (Scheme 6). This is a “Mount Everest” in regio- and stereo-specific chemistry. The products include 6 water of reaction in their lattice that can be removed in a vacuum. The starting materials exhibit proper channels in their crystal structures. Conversely, intractable mixtures of isomers are obtained in the



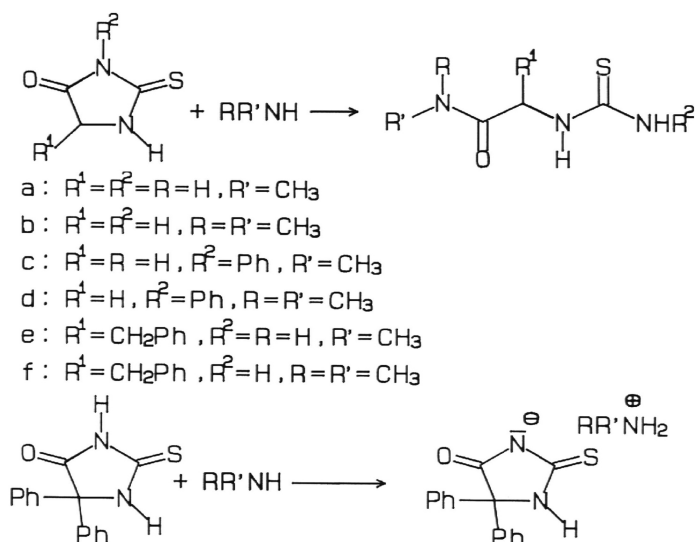
Scheme 6: Fully specific 6-cascades in the 1:3-stoichiometric milling of sugar alcohols with phenylboronic acid. [4, 19].

Surprising specificities are also obtained in small- and large-scale gas-solid reactions. A fantastic difference is shown in Scheme 7. The tetra chloro case provides only ring opening with salt formation, but the di-anhydride gives tetra-amidation. The cyclization of the tetra amide is a prominent thermal intra molecular cyclizing elimination that proceeds quantitatively without melting upon heating to 160°C [1].



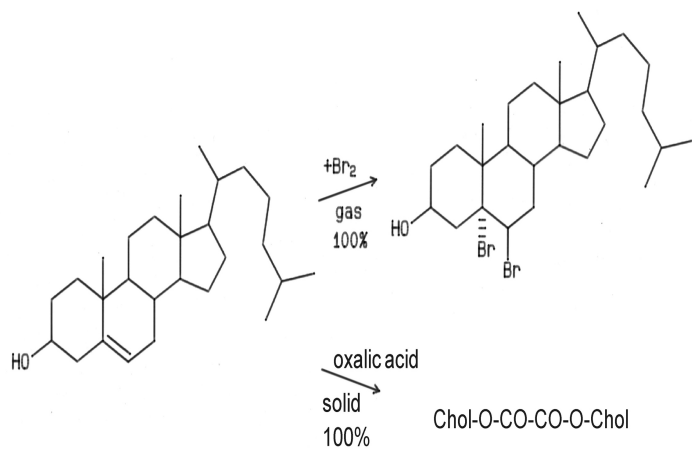
Scheme 7: Gas-solid reactions of alkylamines with anhydrides at the 500 g scale in 2 L flasks [1].

Thiohydantoines with their importance in protein syntheses react wasteless with 100% yield, when gaseous amines interact with ring opening at the 2-3 bonds, as long as the 4-position is free or mono-substituted (Scheme 8). Conversely, the diphenyl- substitution at the 4-position leads exclusively to the salt formation.



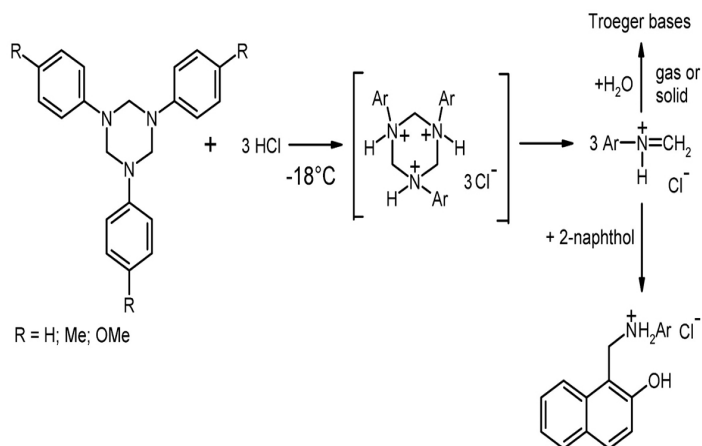
Scheme 8: Gas-solid ring opening of heterocyclic compounds in desiccator runs (see Figure 1) [1, 20].

The addition of bromine to cholesterol is the first step in the industrial production of most contraceptive hormones. The wasteless gas-solid technique is an important improvement (Scheme 9) [21]: the directly stereo-pure dibromide requires no purification as the previously one with impurities when obtained in acidic acid. The also useful wasteless solid-solid esterification by milling of cholesterol with oxalic acid cannot be stopped at the oxalic acid monoester stage. Further solid-state reactions for the production of steroid hormones have been published [22].



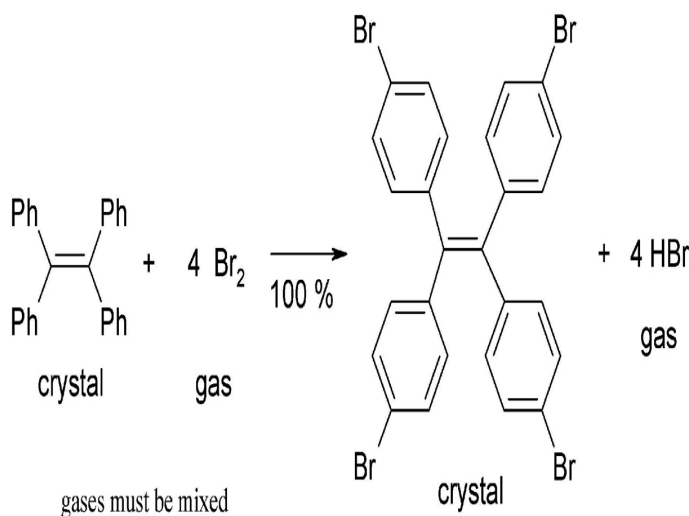
Scheme 9: Gas-solid addition of bromine to cholesterol and solid-solid esterification with oxalic acid [21].

Also otherwise inaccessible products like the first methine-iminium chlorides are available by gas-solid reaction, thanks the easily obtained extremely anhydrous conditions and the possibility to work at low temperatures. The elusive yellow, orange, and brown, respectively, products form via cautious triple protonation of triaryl-hexahydro-triazines with gaseous HCl, followed by exothermic [2+2+2]-cyclo reversion (Scheme 10). These solids are stable at -18°C (IR: 1733 and 1714 cm^{-1}). Their high reactivity has to be used at the low temperature for example for aminomethylations with 2-naphthole, etc. The corresponding tetracyclic Troeger bases are obtained with ice, or with the crystal water by grinding with $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, or upon slow warming up to ambient temperature in moist air [23].



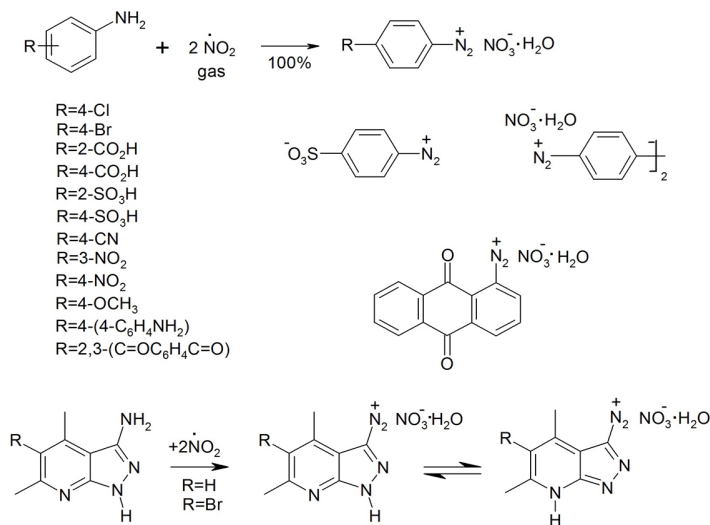
Scheme 10: Synthesis of elusive colored amino methylene hydrochlorides by gas solid reaction of 1,3,5-triaryl-hexahydro-1,3,5-triazine with HCl gas at -18°C [23].

The gas-solid tetra substitution of tetra phenylethene with bromine gas proceeds only in the para-positions without side products, as they occur in solution reactions (Scheme 11) [17]. Gas mixture by rotating the reaction flask is essential here. The valuable gaseous hydro bromide couple product is collected for use in further reactions, so this is a wasteless reaction. This highly spectacular complete specificity has provided an easy access to dendrimer syntheses. Similarly, tetra-(4-nitrophenyl)-ethene is quantitatively obtained with NO_2 as reactive gas [1, 24].



Scheme 11: Fully specific gas-solid synthesis of tetra-(4-bromophenyl)-ethene substitution from tetra phenyl-ethene with gaseous bromine [17].

Pure solid diazonium nitrate hydrates are easily obtained by gas-solid multistep reactions of aromatic amines with nitrogen dioxide (Scheme 12). Caution: these compounds are sensitive to shock and they explode at their melting points. They have been used for further quantitative gas-solid reactions (for example with amines) to give delicate triazenes that are otherwise not available in pure form [25-26], but the experimental prescriptions in the original papers should be closely followed for safety reasons. The rather stable central anthraquinonediazonium salt is used for the production of technical azo-dyes. But solid-solid-reactions with the other diazonium salts require smooth agate mortar and pestle grinding (do not mill), with slow addition of the diazonium salt to the grinded coupling component and completion with ultrasound irradiation. The specificity of the quantitatively obtained heterocyclic system is remarkable [27].



Scheme 12: Gas-solid diazotization giving 100% yield of solid diazonium nitrate hydrates from aromatic amines with NO_2 gas [1, 25, 27].

Conclusion

Properly executed gas-solid and solid-solid reactions are wasteless with lowered activation energy and thus avoiding polluting catalysts and wasteful expensive workup. They enjoy unbeatable specificity and the directly pure products are not polluted by starting materials, unwanted side products, and catalysts. These features are unbeatable and the results cannot be topped. But despite several exhaustive reviews [1, 8-11] and despite covering virtually all reaction types, these and the original publications are not cited, discussed, and compared in “green publications” with their poor results, when deviations from the state-of-the-art are tried by (often purposeful) creation of melts, due to not taking care of temperature control upon milling. In addition to that, others have been trying with addition of “a little solvent”[6], or with too high impact that clogs the materials to the walls. In all of these misuses of mills the wealth of reaching maximal numbers of contacts between powders is lost. The bargain of the solid state should however always be used. The reason for such retrogression might be the desire to accept the avoidable use of catalysts for milled or kneaded melts with poor results and time-consuming wasteful chromatographic workup. It appears as an effort to please the celebrities and referees who are still mentally caught in the misleading obsolete topochemical hypotheses. Unfortunately, that includes disregard of the basic physical facts, including the molecular ones by AFM. Such unfortunate suppression of the most sustainable syntheses and production techniques, despite the numerous available original publications and comprehensive reviews, requires now a short clarifying mini review focused on a few of the striking examples. It shall address to a larger readership, who have not the time for reading comprehensive reviews, and who had recently been flooded and disappointed with very poor milling reports, while the unbeatably benign ones were not discussed and not compared. Poor reports include excessively long milling times, poor yields despite using catalysis, poor selectivity, non-scalability, production of wastes, and even chromatographic workup requirement. Thus, only the concentrated look at the wealth of properly executed wasteless solid-state reactions (not to be confused with the counter-thermodynamic mechanochemistry) in a focused mini review can strengthen the unbeatable sustainability in chemical syntheses. Unfortunately, the “green chemistry” is discrediting the unbeatable top of sustainability by several of its 12 “commandments”, which is also counterproductive [28]. For example, unnecessary catalysis must be avoided, and “greener solvents” also deactivate and thus avoid the availability of obtaining directly pure products with insurmountable atom economy by not producing enormous dangerous wastes by chromatography. Avoiding solvents altogether is the much superior approach and wastes must not only be “decreased” (how is that possible with avoidable catalysis and chromatography?), but avoided. Also counterproductive is the discouragement of using reactive gases for clean syntheses, but advocating their transformation into detour products. Even poisonous gases can be most safely and easily handled in gas-tight equipment from lecture bottles or common steel tanks. Only the reactive gases provide the pure products specifically and wasteless. The production of detour reagents may be possible but at the expense of poor atom economy. Thus, venders of chemicals are asked to synthesize poisonous solid or liquid reagents out of these reactive gases for sale to universities or other research institutes, from where these shall be in-situ regenerated for the syntheses in question. However, such less reactive solid or liquid reagents provide all the dangerous wastes

with the final reactions giving polluted products. Again, dangerous wastes ensue by the chromatography, which could have altogether been avoided when directly using the reactive gas. Clearly, the producing industry will use the reactive gas for clean processing with wasteless gas-solid reaction for saving cost and labor. The non-polluting wasteless 100% yield gas-solid reactions are so much superior that teaching of the properly executed gas-solid and solid-solid reactions to newcomers must be started without the discouragement of “green gurus” who preach contradictory in itself commandments. Misleading concepts and counterproductive speculations are hopefully replaced by state-of-the-art gas-solid and solid-solid syntheses for a better and safer future.

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