Energetic assessment of the Suzuki–Miyaura reaction: a curtate life cycle assessment as an easily understandable and applicable tool for reaction optimization†

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Received 19th May 2009, Accepted 31st July 2009
First published as an Advance Article on the web 10th September 2009
DOI: 10.1039/b915744c

The solvent-less Pd-catalyzed Suzuki–Miyaura cross coupling of different aryl halides with phenylboronic acid and an *in situ* generated solid base was investigated in order to study the influence of different modes of energy entry. For this reason reactions were performed in two different ball-milling set-ups and also different techniques of microwave irradiation have been applied. Combination of reaction data (yield, selectivity, batch size) with energetic data (line power consumption) was used to generalize the results as a curtate life cycle assessment (cLCA), breaking down the reaction to the reaction step, neglecting up- and downstream processes. Thus cLCA was applied for early-level reaction optimization and as decision guidance for constitutive experiments. Under the applied reaction and boundary conditions applied for the solvent-free Suzuki–Miyaura reaction ball milling is proven to be a more effective tool for energy entry than microwave irradiation.

Introduction

The field of solid-state and solvent-free organic synthesis[1-6] has gained growing interest in recent years and will become more and more important with regard to green or sustainable chemistry.[7-9] These reactions are advantageous over classical synthetic procedures: due to the absence of solvents during the course of the reactions these do not have to be provided in the recommended purity, they are not required to be heated-up or cooled down, and, the most important issue, energy can be saved since used solvents do not have to be worked-up or purified for additional use or disposal. The chemical literature reports many examples for solvent-free reactions performed either under classical heating conditions (oil or water bath) or carried out using alternative modes of energy entry (microwave irradiation,[10,11] ultrasound,[12] grinding).[6,13-20] Despite the fact that many researchers dealt with this topic pointing out the (dis)advantages of non-classical modes of activation over well-established classical techniques, there are no reports covering the topic of energy efficiency of these approaches compared to each other. As far as green and sustainable chemistry are concerned this knowledge is a prerequisite for the validation of these processes.[7,8]

Direct comparisons of different modes of energy entry have only been published in a few cases.[12,16,21,22] The investigations of Cravotto *et al.* are focused on experiments carried out under the influence of microwave and ultrasound irradiation, whereby the combination of both techniques proved to be unsatisfactory in the case of the coupling of aryls and the reductive coupling of nitroaromatics to azo dyes.[12,21] Due to the mode of energy entry, these types of reaction can only be accomplished in solvents.

A comparison of the modes of energy entry in solvent-free (solid-state) reactions under ball-milling conditions or grinding (performance of the reaction in standard glass ware using a magnetic stirring bar for mixing) was published by Bolm *et al.* recently.[16] However, the considerations made by the authors are somewhat unsatisfactory, since the techniques of grinding with a magnetic stirring bar and high-energy ball-milling conditions are hardly comparable. In the case of treatment in ball mills, the amount of energy transferred to the reaction mixture, the energy density and energy transmission capacity are magnitudes higher than for "gentle" stirring, recognizable when comparing the surface reaction temperatures immediately after the reaction. Trotzki *et al.* gave examples of two-component Knoevenagel condensations of various benzaldehydes with malononitrile performed in a solvent-free (solid-state) manner in which ball milling was more energy efficient than microwave irradiation (monomode).[22]

This notwithstanding, it seems to be important to dig deeper and intensify the research in this direction. Therefore, within this study an evaluation of a solvent-free reaction from the viewpoint of energy efficiency is presented. Suzuki–Miyaura coupling of phenylboronic acid (**2**) with five different aryl bromides (**1**) yielding substituted biphenyls (**3**, Scheme 1) was used as model reaction to evaluate the influence of different activation techniques: mechanochemical activation (grinding)

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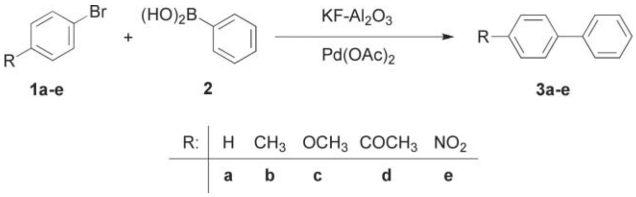
† Electronic supplementary information (ESI) available: Experimental procedures for treatments according to Table 1 apart from that for **BM1**; correlation of rpm, Y, E_1, and E_2 for **BM1** using stainless steel milling balls; temperature effect for **MW1**. See DOI: 10.1039/b915744c



Scheme 1 Suzuki–Miyaura reaction of aryl bromides (**1**) with phenylboronic acid (**2**) yielding biaryls (**3**).

and microwave irradiation.[23,24] KF–Al_2O_3 was used as solid support for the *in situ* generation of the base needed for the reaction and as a catalyst $Pd(OAc)_2$ was applied.[25] Short reaction times and the avoidance of solvent were achieved by carrying out this kind of C–C-coupling reaction with mortar and pestle, in a high speed ball mill or under the influence of microwave irradiation.[25] Table 1 presents an overview of the different equipment used and the reaction conditions for the respective energy treatments.

To compare different reaction/production pathways or the completion of reactions the methods of life cycle assessment (LCA) or eco balances (EB) can be used.[26] For the present investigations a curtate version of LCA without the focus on the up- and down-stream processes is applied (cLCA). Providing an easily understandable and applicable method for early-stage reaction optimization, the energy efficiency of a reaction/process can be considered. To achieve this goal different paths can be followed: (i) comparison of different methodologies under comparable reaction conditions, (ii) comparison of best (optimized) conditions in term of yield for each methodology, and (iii) parametrization on the basis of energy efficiency. For early-stage decisions a robust and simple method is needed, so herein a combination of approaches (i) and (iii) have been applied (*cf.* Results and discussion).

Results and discussion

On the one hand it is possible to perform solid-state reactions by grinding using traditional mortar and pestle equipment and on the other hand new, more reliable tools like high energy (ball) mills are available for mechanochemical treatment. Fig. 1 shows the results of the Suzuki–Miyaura coupling reaction of **1d** with **2** yielding **3d** induced by grinding with mortar and pestle and ball milling (**BM1**). Results indicate that the mortar and pestle experiments strongly depend on the gender of the person performing the experiment. Male test persons achieve significantly better results than female ones, most likely as a result of greater physical strength (rather than technique). For reason of reproducibility of reactive grindings it is absolutely necessary to perform the experiments with equipment allowing discrete control of energy entry and reaction time (ball mills). Only in case of very fast reactions with low activation energies and short reaction times the technique of mortar and pestle is applicable and leads to authentic results independent of the gender or physical fitness of the experimentalist. As shown in Fig. 1 revolutions per minute (rpm) of the ball mill also strongly influences the reaction, since the yield of the desired product **3d** increases together with the raise of rotational frequency.[15,19]

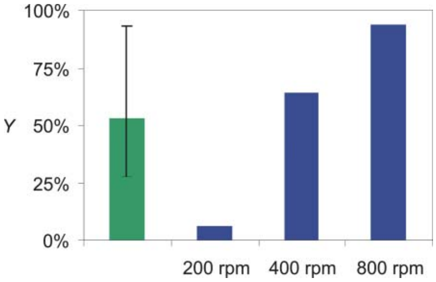


Fig. 1 Yield of coupling product **3d** (*Y*) from Suzuki–Miyaura reaction of **1d** (5 mmol) with **2** (124 mol%) induced by grinding using either mortar and pestle or ball milling (**BM1;** base: KF–Al_2O_3; catalyst: 3.6 mol% $Pd(OAc)_2$; reaction conditions *cf.* Table 1; milling time for both types of experiment: 5 min).

The Suzuki–Miyaura reaction of **2** with different aryl bromides **1a–e** to substituted biaryls **3a–e** is shown in Scheme 1. Three different treatments were applied for the performance of the Suzuki–Miyaura coupling: microwave irradiation (multimode: **MW1** and monomode: **MW2**), ball milling (planetary ball mill: **BM1** and swing/mixer mill: **BM3**), and also the combination of these two techniques was tested (**COMB**; Table 1), meaning that the samples after grinding in the ball mill were subsequently irradiated by microwave energy. Yields of the Suzuki–Miyaura coupling products as a function of the different reaction techniques are presented in Table 2. All ball milling experiments were carried out at 800 rpm (13.3 Hz) for 10 min.

For the different substituents of aryl bromides (**1a–e**) characteristic effects appear, typical for the substituent influence on the activity of aromatics for the second substitution. For instance, the acetyl group activates the Br–C bond and therefore the substrate (**1d**) is more prone to reaction with **2** resulting in good to excellent yields of the desired product (**3d**). The activation in case of the methyl group in the *p*-position (**1b**) is lower, leading to moderate yields of the desired product (**3b**) compared to **1a**, **1c** and **1d**. However it has to be stated that

Table 1 Overview of the used apparatus

Treatment	Apparatus	Reaction condition	Abbreviation
Ball milling (**BM**)[a]	Pulverisette 7[b]	$V_{\text{beaker}} = 45$ mL; $d_{\text{balls}} = 15$ mm	**BM1**
	Pulverisette 5[b]	$V_{\text{beaker}} = 250$ mL; $d_{\text{balls}} = 30$ mm	**BM2**
	MM 301[c]	$V_{\text{beaker}} = 50$ mL; $d_{\text{balls}} = 12$ mm	**BM3**
Microwave irradiation (**MW**)[d]	Praktika	multimode, $P = 300$ W	**MW1**
	Discover	monomode, $P = 150$ W	**MW2**
BM followed by **MW**		**BM1+MW1**	**COMB**

[a] Two stainless steel grinding beakers, six agate milling balls per beaker. [b] Planetary ball mill. [c] Mixer or swing mill. [d] 15 min, 150 °C.

Table 2 Yield of coupling products **3** from Suzuki–Miyaura reaction of **1** with **2** (Scheme 1) induced by microwave irradiation (**MW1**, **MW2**), ball milling (**BM1**, **BM3**) or ball milling followed by microwave irradiation (**COMB**)[a]

	Yield of **3a–e** (%) for treatment[b]				
Aryl halide	**BM1**[c]	**BM3**[c]	**MW1**	**MW2**	**COMB**
1a	92	99	78	60	98
1b	74	63	65	54	82
1c	93	56	80	49	96
1d	89	45	80	70	94
1e	78	83	75	66	80

[a] Phenylboronic acid (124 mol%), KF/Al$_2$O$_3$ support (5 g; 32 wt% KF), and Pd(OAc)$_2$) (3.56 mol-%). [b] For details *cf*. Table 1. [c] 800 rpm; 10 min.

Table 3 Comparison of amounts of electrical energy necessary for the performance of the Suzuki–Miyaura reaction of **1d** with **2** (Scheme 1)[a]

Treatment[b]	Batch size[c]	Yield (%)	E_1[d]/kWh mol^{-1}	E_2[e]
BM1[f]	2 × 5 mmol	89	1.7	1.9
BM1[g]	2 × 5 mmol	95	3,2	3,4
BM2[f]	2 × 50 mmol	95	4.6	4.8
BM3[f]	2 × 5 mmol	5	0.6	12
BM3[g]	2 × 5 mmol	85	1,0	1,2
MW1	5 mmol	80	40	50
MW2	5 mmol	59	7.6	12.9
COMB	5 mmol	91	42.8	46.2

[a] Phenylboronic acid (124 mol%), KF/Al$_2$O$_3$ support (5 g/50 g; 32 wt% KF), and Pd(OAc)$_2$) (3.56 mol-%). [b] Details *cf.* Table 1. [c] Regarding **1d**. [d] Amount of electrical energy used for one reaction run normalized for moles of aryl halide (eqn (1)). [e] Amount of electrical energy used for one reaction run normalized for moles of coupling product formed (eqn (2)). [f] 300 rpm (5 Hz), 10 min. [g] 800 rpm (13.3 Hz), 10 min.

the classical order of substituent effect is superseded in case of solventless reactions by another phenomena: mass transport limitations. To achieve good to excellent results of the Suzuki–Miyaura reaction a uniform dispersion of the reactants is needed, especially under ball milling conditions. Regarding this, the physical properties of reactants and products (the melting point) have to be considered.‡ During the milling process under the chosen reaction parameters (800 rpm, 10 min, steel beakers with agate milling balls) *T* raises from room temperature up to 50–70 °C.§ This leads to the effect such that the substrates **1a**, **1b**, and **1c** liquids under the chosen parameters result in an excellent dispersion of the substrates. In these cases the outcome of the reaction is controlled by the reactivity of the aryl halides. *p*-Bromoacetophenone (**1d**) and *p*-bromonitrobenzene (**1e**) are solids under the conditions in the reactions were carried out. Therefore their high activity is decreased since the reaction is mass-transport limited.

Table 2 shows the effect of the different reaction techniques. The comparison of the two micowave irradiation types leads to the conclusion that the multimode irradiation (**MW1**) afforded better results for the Suzuki–Miyaura reaction for all tested substrates than the monomode type (**MW2**). The comparison of the two different ball mills turns out to be much more difficult, because of the different energy input. The results, which were obtained with the planetary ball mill (**BM1**) are generally better than the results of the swing/mixer mill (**BM3**; Table 2). The combination of **MW1** and **BM1** leads to an increase of the desired products.

Regarding the influence of reaction technique, Table 2 also shows a specific order of the yield of the Suzuki–Miyaura coupling product: **MW** < **BM** < **COMB**. For all examples studied, microwave irradiation results in product mixtures with the lowest yields of **3**. Ball milling treatment leads to better results than microwave irradiation in any case. This is due to the fact that in the case of grinding techniques the mixing of the reactants is always coupled with the mode of energy entry, whereas the performance of solid-state microwave-assisted reactions the option for mixing of samples can be lacking.[27] The combination of the two mentioned techniques is hence the best choice for the solvent-free Suzuki–Miyaura reaction.

In order to investigate the influence of different grinding and microwave apparatus, the Suzuki–Miyaura coupling of *p*-bromoacetophenone (**1d**) with **2** yielding *p*-acetylbiphenyl (**3d**) as the only coupling product was performed with the apparatus listed in Table 1. Results of these experiments are presented in Table 3 revealing a strong influence of the mode of energy entry on the course of reaction. In order to compare the tested ball milling equipment all experiments were carried out with 300 rpm (1 Hz = 60 rpm) and for 10 min. For comparison of the effect of increasing rpm, experiments have been carried out with 800 rpm for 10 min (**BM1** and **BM3**).¶

For the planetary ball mills **BM1** and **BM2** the grinding sample is comminuted by high-energy impacts from grinding balls and friction between balls and balls or balls and the grinding beaker's wall. The grinding jars of the swing/mixer mill (**BM3**; Table 3) perform radial oscillations in a horizontal position only, resulting in significant lower yields of **3d**, than observed for the planetary ball mills. The inertia of the grinding balls causes them to impact with high energy on the sample material at the rounded ends of the grinding jars and pulverizes it, without any impact on the reaction. The technique of planetary ball mills is therefore advantageous over the concurring technique due to the presence of radial and vertical movements of the milling balls.[13] However, increase of vibration frequency in case of **BM1** and **BM3** leads to increased yields (*cf.* Table 3 and Fig. 1).[13,15,19] Both methods have in common that the movement of the grinding jars combined with the movement of the balls results in an intensive mixing of the sample without the appliance of any other mixing device.

If the same reaction is performed in microwave devices, two different possibilities for energy dispersion exist: a multimode

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‡ Bromobenzene (**1a**): mp = 31–30 °C. *p*-Methylbromobenzene (**1b**): mp = 26–29 °C. *p*-Bromoanisole (**1b**): mp = 9–15 °C. *p*-Bromoacetophenone (**1d**): mp = 45–52 °C. *p*-Bromonitrobenzene (**1e**): mp = 125–127 °C. Phenylboronic acid (**2**): mp = 216–219 °C. Biphenyl (**3a**): mp = 67–70 °C. *p*-Methylbiphenyl (**3b**): mp = 47–51 °C. *p*-Methoxybiphenyl (**3c**): mp = 86–82 °C. *p*-Acetylbiphenyl (**3d**): mp = 118–125 °C. *p*-Nitrobiphenyl (**3e**): mp = 113–115 °C.

§ These temperatures were measured immediately **after** the reaction on the surface of the reaction mixture and they are not comparable with bulk reaction temperature (*e.g.* fibre-optical *T*-measurement for microwaves). Comparison is possible with surface-sensitive IR-measurement of *T* for microwaves. To the best of the authors knowledge ball mills are still lacking of systems for *in-situ* *T*-measurement (*cf.* ESI†).

¶ The maximal rotation frequency of **BM2** is restricted to 300 rpm.

irradiation (**MW1**) in comparison to a monomode one (**MW2**; Tables 2 and 3) leads to better yields of the coupling product. Using a monomode apparatus, the microwaves are reflected by the cavity walls and only one standing wave is produced resulting in field inhomogenities.[28-31] Performing liquid-phase experiments in such an inhomogeneous environment, the reaction mixture is agitated by intensive stirring eliminating this disadvantage.[30,31] In case of solid-state reactions mixing is often impossible, which leads to lower yields reported for **MW2** compared to **MW1** (Table 3). In contrast, the multimode device generates an almost homogeneous field due to internal reflecting of the microwaves on a rotating metal cone.[28-31] The microwave field is homogenized more strongly and the sample is uniformly heated. The combination of ball milling and microwave irradiation (**COMB**; Tables 2 and 3) leads to a small increase of **3d** in comparison to microwave irradiation treatment or ball milling only (Table 3). But the energy consumption of this variation of the Suzuki–Miyaura reaction is higher compared to ball milling (**BM**) or microwave irradiation (**MW**).[22] Similar results were found for the other substrates also.

Differences between efficiency of the reaction methods also manifest themselves in the energy use (Table 3). The energy consumption has been calculated according to eqn (1) and 2, whereby E_1 is the overall energy consumption normalized with regard to the batch sizes listed in Table 3. In contrast, E_2 represents that amount of energy hypothetically needed for complete conversion of the substrates using different modes of energy entry (**BM**, **MW**, **COMB**). On the basis of these calculations it should be possible to directly compare the effectiveness of energy conversion to product yield regardless of the batch size.

$$E_1 = \frac{E_{\text{line power}}[\text{kWh}]}{\text{batch size}[\text{mol}]} \qquad (1)$$

$$E_2 = \frac{E_1}{Y_{3\text{d}}} \qquad (2)$$

Interestingly, the energy demand for the ball milling experiments is lower than for the application of microwave irradiation, independently of the device used for grinding and batch size. This remarkable fact is believed to be due to the operation mode of the grinding apparatus. Due to the high mass of the grinding jars and balls the inertia of these towards alteration in speed is low: the energy supplied to the system is efficiently transformed into rotational energy comparable to the balance wheel in a clock. Transformation of electrical into microwave energy is less efficient leading to a lower degree of efficiency and therefore to higher energy demand. Data compiled in Table 3 also indicate that the combination of both types of energy entry (**COMB**) is disadvantageous due to the small change in yield and the high energy consumption for **MW1**.

Under the chosen reaction conditions ball milling yields the best results regarding yield and energy consumption. As shown in Table 3 up-scaling of the reaction in the case of planetary ball milling is possible without negative effects on the reaction parameters accompanied by a slight increase of the energy consumption. However, this increase in energy consumption is not linear compared to scale-up factor of the accomplished coupling reaction. Under microwave conditions the energy demand for the C–C coupling reaction is considerably higher and up-scaling would directly influence the energy efficiency since the penetration depth is important for the efficiency of transformation of microwave energy to kinetic energy in the bulk reaction mixture. An up-scaling of the Suzuki–Miyaura reaction under the conditions performed herein (solvent-free) would lead to an increase of the energy consumption. This increase of energy input is higher than the comparable effect in case of ball milling.

In Fig. 2 the yields of **3d** of the Suzuki–Miyaura reaction depending on the rotation (ν_{rot}; **BM1**) or vibration frequency (ν_{vib}; **BM3**) including the energy consumption are presented. The important conclusion can be drawn that an increase of the desired product (**3d**) can be achieved by raising of the vibration frequency of the used ball mill as already demonstrated for **BM1** in Fig. 1.[15,19] Also, the fact that energy consumption (E_1; eqn (1)) based on the substrate increases linearly with the step-up of ν_{rot} or ν_{vib} is demonstrated (for the use of the grinding materials listed in Table 1 only):

$$E_{1;\mathbf{BM1}} = 0.214 \cdot \nu_{\text{rot}} \cdot \frac{\text{kWh}\cdot\text{s}}{\text{mol}} + 0.710 \cdot \frac{\text{kWh}}{\text{mol}} \qquad (3)$$
$$R^2 = 0.993$$

$$E_{1;\mathbf{BM3}} = 0.041 \cdot \nu_{\text{vib}} \cdot \frac{\text{kWh}\cdot\text{s}}{\text{mol}} + 0.436 \cdot \frac{\text{kWh}}{\mathit{mol}} \qquad (4)$$
$$R^2 = 0.985$$

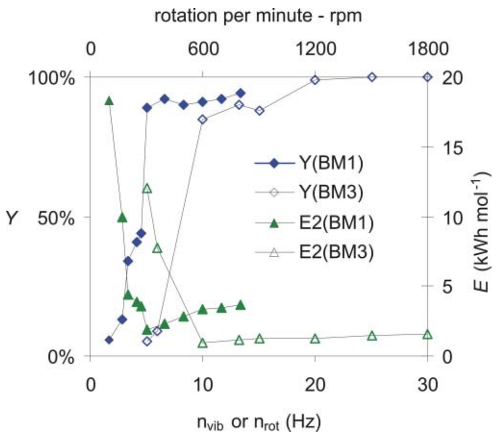

Fig. 2 Yield of coupling products **3d** (Y) from Suzuki–Miyaura reaction of **1d** (5 mmol) with **2** (124 mol%) induced by ball milling (**BM1** and **BM3**) (milling time: 10 min) and demand of electrical energy used for reaction (E_2 calculated according to eqn (2); base: KF–Al_2O_3; catalyst: 3.6 mol% $Pd(OAc)_2$).

This effect is due to the higher energy demand for acceleration and horizontal oscillation or rotation of the grinding jars with a higher frequency. The kinetic energy of a classical oscillator or rotator is defined as:

$$E_{\text{kin}}(\text{rot or osz}) = \frac{1}{2} \cdot I \cdot \omega^2 = 2\pi \cdot I \cdot \nu^2 \qquad (5)$$

with I, ω, and ν as the moment of inertia, angular velocity, and angular frequency, respectively. According to classical mechanics in eqn (5) the line power of ball mills theoretically

Table 4 Regression function for 2nd-order polynomic regression of E_1 (eqn (1)) and ν for **BM1** and **BM3**[a]

$E_{1;i} = a \cdot \nu^2 + b \cdot \nu + c$ x

i	a/kWh s^2 mol^{-1}	b/kWh s mol^{-1}	c/kWh mol^{-1}	R^2
BM1[b]	-0.0002	0.217	0.702	0.993
BM3[c]	-0.0005	0.059	0.325	0.993

[a] For conditions listed in Table 1. [b] $\nu = \nu_{\text{rot}}$. [c] $\nu = \nu_{\text{vib}}$.

has to be proportional to $(\nu_{\text{vib}})^2$ or $(\nu_{\text{rot}})^2$. 2nd-Order polynomic regression of E_1 leads to coefficients of determination R^2 for **BM1** and **BM3** of 0.993 (Table 4). Comparing both the linear regression (eqn (3) and 4) and the 2nd-order polynomic regression data leads to the conclusion that the overall energy demand for the planetary ball mill **BM1** is higher than for the mixer mill **BM3**. This is due to the fact that the translatory inertia is magnitudes higher for the planetary ball mill than for the mixer mill.

Fig. 2 reveals huge differences in yield and energy consumption between the two types of ball mills tested: planetary ball mill (**BM1**) and mixer mill (**BM3**). Generally, the performance in the former is more effective, since maximal conversion is reached at lower ν_{rot} (90% at 5 Hz = 300 rpm) as compared to **BM3** (85% at 10 Hz = 600 rpm).

In the range below 5 and 10 Hz for **BM1** and **BM3**, respectively, the phenomenon can be observed that with increasing yield of **3d** the energy consumption E_2 drops, whereas at higher frequencies the energy demand in case of E_2 is comparable with E_1 (Fig. 2). This is due to the pronounced increase of the yield. Performing grinding experiments at low frequencies results in an inefficient mixing of the reactants. This leads to the result that for experiments in the swing/mixer mill you have to work with optimised reaction conditions: The Suzuki–Miyaura reaction should be carried out at 20 Hz for 10 min to obtain excellent results under an acceptable energy consumption. However it is critical to speak of "optimized reaction conditions" since it has recently been shown that the performance of ball milling experiments is influenced by various variables (time, grinding material, number and size of milling balls,. . .).[15,19,22,25a]

The energetic assessment of the reactions presented herein are somehow comparable to a curtate life cycle assessment (cLCA). Focusing on a single reaction step the herein presented method of normalized energy demand (E_2 *cf.* eqn (2)) is comparable to a "gate-to-gate" LCA.[32] Of course, for holistic LCA up- and down-stream processes have to be considered describing the entire life cycle of a process or product from "cradle-to-grave" or from "cradle-to-cradle".[26,33] The overall energy, which is used for the supply of the required chemicals and for the work-up procedure is comparable for the Suzuki–Miyaura reaction procedures presented and compared herein. Different batch sizes have been taken into account by normalizing the energy demand (eqn (1)), allowing for cut-off of up- and down-stream processes in the energy balance. The differences are due to the kind of energy input of the used devices for the performance of the C–C-coupling reaction, but this is the major point of the investigations presented herein. For a more comprehensive assessment of the solvent free reaction presented herein in form of LCA or EB it has to be considered that the apparatus used for the reaction have different durabilities mainly influencing investment costs and overhead.

Conclusion

In conclusion, we report an efficient method for a solvent-free Suzuki reaction in the presence of an inorganic solid support (KF–Al_2O_3) and the use of alternative energy forms (mechanochemical treatment (grinding with mortar and pestle and ball milling) and microwave irradiation). Differences between reaction efficiency of the methods for reaction treatment manifest themselves in the energy use and in the yield of the desired product of the C–C coupling reaction. Ball milling is more efficient (regarding the energy consumption) than microwave irradiation or the combination of both methods under the chosen reaction conditions. Simplicity of reaction, tolerance toward atmospheric oxygen, favourable safety aspects, high yields and fast reaction times let us conclude that the described experimental method is a well applicable version of the Suzuki reaction and an attractive method of study.

Furthermore, an easily understandable and applicable method is presented which can be applied as decision guidance in early-stage optimization processes for chemical reactions considering both reaction variables (yield, selectivity, batch size) and energy demand. Within given boundary conditions (similar up- and down-stream processes) reactions/processes are able to be assessed in a form of a curtate life cycle assessment (cLCA) describing the electrical line-power conversion to product yield.

Experimental

All reagents were purchased from commercial suppliers and used without further purification. The purity of all compounds was checked prior to use by capillary gas chromatography. Reactions in ball mills were conducted using a Fritsch Planetary Micro Mill model "Pulverisette 7" (classic line), model "Pulverisette 5", and the mixer mill "MM 301" from Retsch GmbH. Experiments under microwave irradiation were performed with the multimode device "Praktika" (MLS GmbH) and in the monomode apparatus "Discover" (CEM GmbH). Experiments with mortar and pestle were carried out using devices made of china. Except for stainless steel grinding beakers, all used reaction vessels were purified with *aqua regia* prior to use to avoid any contamination or memory effects.

Blank experiments with stainless steel grinding beakers and agate grinding balls without catalysts resulted in yields of the respective coupling product below 2%, which is in the range of experimental error.

A meter of the brand Energy Check 3000 from the company Voltcraft, Germany, was used to measure the line power consumption.

Preparation of the inorganic support material

In a 250 mL Erlenmeyer flask, potassium fluoride (0.275 mol, 16 g) was dissolved in deionized water (25 mL) for the preparation of the support mixture. Subsequently, alumina (α-Al_2O_3, 63–200 µm, basic; 0.333 mol, 34 g) and further deionized water (25 mL) were added to the solution under slow stirring. Stirring was maintained for 1 h. The solvent was then evaporated *in vacuo* and the remaining residue (KF–Al_2O_3 with 32 wt% KF) stored in a desiccator over potassium hydroxide.

Synthesis details

Experimental procedures for different modes of energy entry (Table 1) differ mainly in the batch size. Exemplarily the experimental procedure for grinding in the planetary ball mill "Pulverisette 7" (**BM1**) is given. For the other procedures *cf.* the ESI.†

Ball milling **BM1**: Inorganic support material (5 g), aryl halides (5 mmol), phenylboronic acid (6.2 mmol, 0.755 g), $Pd(OAc)_2$ (0.18 mmol, 0.04 g, 3.6 mol%) were added in the milling beaker (volume: 45 mL; material: stainless steel; six 15 mm agate milling balls per beaker) of the planetary ball mill "Pulverisette 7" Fritsch GmbH. The mixtures were subsequently milled with the chosen reaction parameters for rpm and milling time. Samples were extracted with 2 ml of deionized water and 3 ml of the corresponding solvent (**1a–c**: *tert*-butylmethylether; **1d**, **le**: ethyl acetate) and were analyzed by gas chromatography.

Measurement and analysis details

The analyses of the reaction mixtures were carried out by GC-FID (HP 5890 Series II) and GC-MSD (Agilent Technologies 6890 N Network GC System). GC-FID: HP 5, 30 m × 0,32 mm × 0,25 µm, H_2–12 psi, program: 50 °C (hold for 3 min), 30 K min^{-1} up to 280 °C (hold for 5 min), injector temperature: 280 °C, detector temperature: 300 °C. GC-MSD: HP 5, 30 m × 0, 32 mm × 0, 25 µm, H_2–12 psi, program: 50 °C (hold for 3 min), 30 K min^{-1} up to 280 °C (hold for 5 min), injector temperature: 280 °C, excitation: EI (70 eV, total ion mode). All product yields reported herein are GC-determined yields and are comparable with the isolated ones. Nevertheless, the reported yields were corrected by means of different FID-sensitivity for substrate and product. The reported yields are mean values from at least two independent experimental runs.

Notes and references

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