

## Switchable Selectivity during Oxidation of Anilines in a Ball Mill

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**Abstract:** A solvent-free method for the direct oxidation of anilines to the corresponding azo and azoxy homocoupling products by using a planetary ball mill was developed. Various oxidants and grinding auxiliaries were tested and a variety of substituted anilines were investigated. It was possible to form chemoselectively either azo,

azoxy, or the nitro compounds from reaction of aromatic anilines. The selectivity of the solvent-free reaction is

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switchable by applying a combination of oxidant and grinding auxiliary. Furthermore, a comparison with other methods of energy input (microwave, classical heating, and ultrasound) highlighted the advantages of the ball mill approach and its high energy efficiency.

### Introduction

The importance of green chemistry and sustainability are becoming more important for routine organic synthesis.<sup>[1]</sup> In this regard, the omission of solvents is advantageous due to the fact that supply, purification, and disposal of potentially environmentally problematic chemicals can be omitted. The reduction of solvent waste is one of the major motivations for the development of a broad variety of solvent-free synthetic reaction protocols.<sup>[2]</sup> Furthermore, the problem of insolubility of inorganic reagents (oxidants etc.) in organic solvents can be bypassed under solvent-free conditions. Although reactions can be carried out in a solvent-free manner using classical laboratory equipment or by using microwave heating, the application of ball milling conditions is a small, but emerging field of research. Ball milling was found to be

an excellent method for some organic reactions, for example, aldol-type reactions, oxidations or reductions.<sup>[2c, g, 3]</sup>

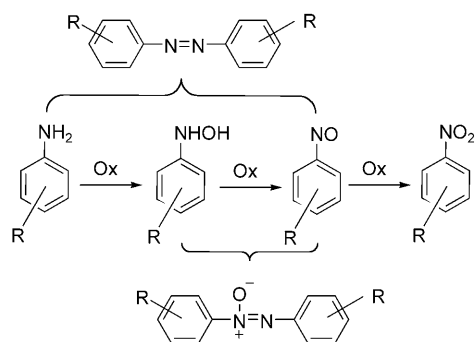
Herein we describe a solvent-free method for the chemoselective oxidation of anilines to the corresponding azo or azoxy homocoupling products using a planetary ball mill. Aromatic azo compounds are usually synthesized by coupling diazo compounds with amines or phenols,<sup>[4]</sup> coupling of primary arylamines with nitroso compounds (Mills reaction),<sup>[5]</sup> oxidation of hydrazo compounds,<sup>[6]</sup> or the reduction of nitro compounds.<sup>[7]</sup> In addition to the above-mentioned routes to azo compounds, the direct oxidation of anilines to symmetric azo compounds is also feasible.<sup>[8]</sup> Aromatic azo and azoxy compounds are important dyes and are widely used in biological and chemical analysis as chromophores. Furthermore, they are applied in chemical synthesis as reducing agents, stabilizers, and polymerization inhibitors.

An accepted mechanism for the direct oxidation describes a partial oxidation of anilines, furnishing either hydroxyl amines or nitroso compounds. Consecutive condensation of the nitroso-derivative either with remaining aniline or with hydroxyl amines afforded the azo or azoxy compounds, respectively (Scheme 1).<sup>[9]</sup> Overoxidation of the nitroso group gives rise to nitro compounds. There are many protocols for this type of reaction available in the literature whereby oxidation can be accomplished both by chemical oxidants and by electrochemical reaction. However, although there are many examples in the literature dealing with solution protocols, there is only one example for a solvent-free approach to amine oxidation.<sup>[10]</sup> In contrast, the oxidation of other compounds (aromatics, alcohols) using potassium permanga-

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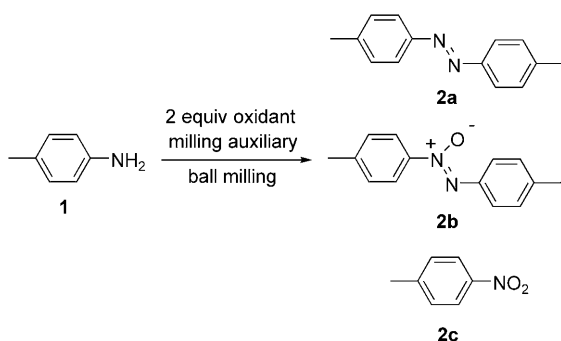
Scheme 1. Mechanism for the oxidation of primary aromatic amines.<sup>[9]</sup>

nate or other oxidants has successfully been established under solvent-free conditions.<sup>[2a,b,11]</sup> The reactions are usually initiated by classical heating or by microwave heating, whereas oxidations conducted in ball mills are rarely discussed.<sup>[31,12]</sup>

## Results and Discussion

Within this work, a solvent-free method for the selective oxidation of primary aromatic amines using a planetary ball mill was developed. Beside the oxidants, several filling materials (milling auxiliaries) were used in the milling beakers to enable work with small batch sizes. For the first experiments, milling beakers and balls made from agate (a naturally-occurring variety of quartz) were employed.

**Effects of oxidation agents and milling auxiliaries:** Various oxidants were tested to investigate their influence on the selectivity of product formation in the oxidation of *p*-toluidine (**1**; Scheme 2). Two milling auxiliaries were applied in the

Scheme 2. Oxidation of *p*-toluidine (**1**) with different oxidants and milling auxiliaries.

syntheses: fused quartz sand (denoted as SiO<sub>2</sub>) and  $\gamma$ -aluminium oxide (activity 90, neutral; denoted as Al<sub>2</sub>O<sub>3</sub>; Table 1). Surprisingly, not only were differences between the oxidants observed (e.g., KMnO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub>/urea), but also significant differences were observed for the same oxidant in combination with different grinding auxiliaries (e.g., Oxone =

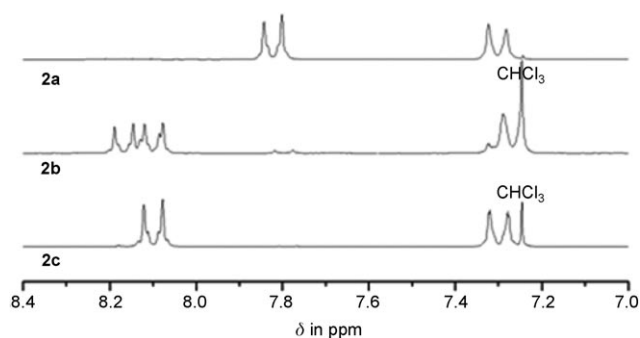
Table 1. Oxidation<sup>[a]</sup> of *p*-toluidine (**1**) with various oxidants in combination with the milling auxiliaries Al<sub>2</sub>O<sub>3</sub> and SiO<sub>2</sub>.

Oxidant	X( <b>1</b> ) [%] <sup>[b]</sup>		S( <b>2a</b> ) [%] <sup>[b]</sup>		S( <b>2b</b> ) [%] <sup>[b]</sup>		S( <b>2c</b> ) [%] <sup>[b]</sup>	
	Al <sub>2</sub> O <sub>3</sub>	SiO <sub>2</sub>	Al <sub>2</sub> O <sub>3</sub>	SiO <sub>2</sub>	Al <sub>2</sub> O <sub>3</sub>	SiO <sub>2</sub>	Al <sub>2</sub> O <sub>3</sub>	SiO <sub>2</sub>
KMnO <sub>4</sub>	96	95	95	88	2	3	2	–
K <sub>2</sub> MnO <sub>4</sub>	71	49	98	94	–	3	–	–
NaIO <sub>4</sub>	48	97	74	91	2	–	–	–
Oxone <sup>[c]</sup>	94	99	3	2	88	10	6	85
H <sub>2</sub> O <sub>2</sub> /urea	96	7	1	20	92	45	4	–
Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	29	88	83	97	6	–	1	–
sodium percarbonate <sup>[d]</sup>	84	2	4	99	84	–	11	–
K <sub>2</sub> CrO <sub>7</sub>	5	3	67	50	–	–	–	–
KIO <sub>3</sub>	3	2	50	–	–	–	–	–
KMnO <sub>2</sub>	3	3	50	50	–	–	–	–
NaBO <sub>3</sub>	6	3	50	50	–	–	–	–

[a] Reaction conditions: *p*-toluidine (2 mmol), oxidant (4 mmol), grinding auxiliary (4 g); 800 rpm, 10 min, agate beaker (45 mL), six agate milling balls (15 mm). [b] Conversion (*X*) and selectivity (*S*) were determined by GC-FID measurements of extracted products in relation to *p*-toluidine (**1**; Scheme 2). [c] Triple salt: 2 KHSO<sub>5</sub>/KHSO<sub>4</sub>/K<sub>2</sub>SO<sub>4</sub>. [d] 2 Na<sub>2</sub>CO<sub>3</sub>·3 H<sub>2</sub>O<sub>2</sub>.

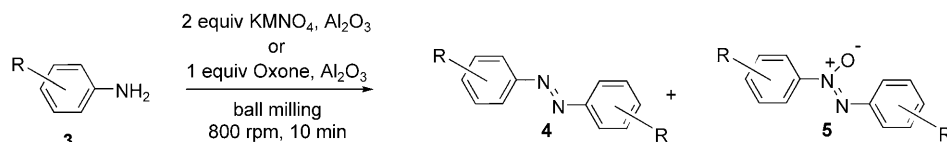
2 KHSO<sub>5</sub>/KHSO<sub>4</sub>/K<sub>2</sub>SO<sub>4</sub>, and H<sub>2</sub>O<sub>2</sub>/urea). This was very interesting because it allowed the reaction to be directed towards all three major oxidation products (azo, azoxy, nitro) by choosing the right combination of oxidant and grinding auxiliary. For example, to generate the azo product, KMnO<sub>4</sub> plus Al<sub>2</sub>O<sub>3</sub> seemed to be the best choice, whereas the application of Oxone, H<sub>2</sub>O<sub>2</sub>/urea or sodium percarbonate with Al<sub>2</sub>O<sub>3</sub> led to high selectivity for the azoxy product. In contrast, with Oxone and SiO<sub>2</sub> as the oxidant and grinding auxiliary, respectively, it was even possible to drive the reaction to the nitro product. Other common oxidants, such as K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> or NaBO<sub>3</sub> showed only very low activity. Although many more oxidants are described in literature that would be suitable for the direct oxidation of anilines,<sup>[13]</sup> the potential application of the ball mill approach to oxidation was initially assessed here with the given selection.

To verify the structure of the oxidation products, <sup>1</sup>H NMR spectroscopic analysis was considered suitable (Figure 1). Only one stereoisomer each was formed for the azo and azoxy products, presumably the more stable *Z* isomer, be-

Figure 1. <sup>1</sup>H NMR spectra of the aromatic region of the oxidation products of *p*-toluidine (**1**; Scheme 2) in CDCl<sub>3</sub> at 200 MHz.

cause otherwise the presence of further signals arising from the aromatic protons would be expected.

To further examine the influence of the milling auxiliary, experiments were conducted with  $\text{KMnO}_4$  as the oxidant (Table 2). With  $\text{Al}_2\text{O}_3$  ( $\gamma$ -modi-



Scheme 3. Solvent-free chemoselective oxidation of anilines **3** either with  $\text{KMnO}_4$  to the corresponding azobenzenes **4** or with Oxone to the respective azoxy compounds **5**.

Table 2. Oxidation<sup>[a]</sup> of *p*-toluidine (**1**) with  $\text{KMnO}_4$  varying the milling auxiliary.

Milling auxiliary	<i>X</i> ( <b>1</b> ) [%] <sup>[b]</sup>	<i>S</i> ( <b>2a</b> ) [%] <sup>[b]</sup>	<i>S</i> ( <b>2b</b> ) [%] <sup>[b]</sup>	<i>S</i> ( <b>2c</b> ) [%] <sup>[b]</sup>
quartz sand ( $\text{SiO}_2$ )	96	88	3	–
silica gel 60	98	91	1	1
$\gamma$ -alumina ( $\text{Al}_2\text{O}_3$ ) <sup>[c]</sup>	96	95	2	2
$\alpha$ -alumina <sup>[d]</sup>	83	89	3	1
$\gamma$ -alumina <sup>[e]</sup>	94	94	2	1
$\text{CeO}_2$	96	87	4	–
montmorillonite K-10	99	95	–	1
KF/ $\text{Al}_2\text{O}_3$ <sup>[f]</sup>	96	94	2	1

[a] Reaction conditions: *p*-toluidine (2 mmol),  $\text{KMnO}_4$  (4 mmol), milling auxiliary (4 g); 800 rpm, 10 min, agate beaker (45 mL), six agate milling balls (15 mm). [b] Conversion (*X*) and selectivity (*S*) were determined by GC-FID measurements of extracted products in relation to *p*-toluidine (**1**; Scheme 2). [c] Activity 150, basic. [d] Activity 90, acidic. [e] Activity 90, neutral. [f] Commercially available form, 40 wt % KF.

fication, activity 90, neutral) and montmorillonite K-10, the azo product was generated with the highest conversion and selectivity. Despite the excellent results obtained with montmorillonite K-10, its handling was very problematic due to its low material density. With regard to conversion, further experiments revealed that other materials were also applicable as grinding auxiliaries (e.g.,  $\text{CeO}_2$ , KF/ $\text{Al}_2\text{O}_3$ ). However, taking into account the selectivity towards the azo compound,  $\text{CeO}_2$ , acidic  $\alpha$ -alumina, or quartz sand could be disregarded. Comparing the influence of various oxidants on the selectivity revealed only small effects (Table 1). With regard to economic and ecological issues,  $\text{Al}_2\text{O}_3$  (activity 90, neutral) was thus chosen as the milling auxiliary of choice for further experiments.

**Formation of azo compounds from anilines:** A screening of some primary aromatic amines was performed to assess the generality of the approach. As exemplified in Table 1 for the oxidation of **1** (Scheme 2), the reaction conditions could be adjusted to form either azo, azoxy, or nitro compounds. Due to the fact that the oxidation of anilines to the aromatic nitro compounds is relatively straightforward, only the formation of azo and azoxy compounds were investigated further.

First, the oxidation was performed with  $\text{KMnO}_4$  and  $\text{Al}_2\text{O}_3$  as oxidant and grinding auxiliary, respectively, to chemoselectively transform anilines into the corresponding symmetric azo product (Scheme 3). As can be seen in Table 3, aniline and *p*-substituted amines (except *p*-amino

Table 3. Oxidation of anilines **3** with  $\text{KMnO}_4$  to the corresponding azobenzenes **4**,<sup>[a]</sup> by using agate or  $\text{ZrO}_2$  as material for milling beakers and balls.

R ( <b>3</b> ; Scheme 3)	<i>X</i> ( <b>3</b> ) [%] <sup>[b]</sup>		<i>S</i> ( <b>4</b> ) [%] <sup>[b]</sup>		<i>S</i> ( <b>5</b> ) [%] <sup>[b]</sup>	
	Agate	$\text{ZrO}_2$	Agate	$\text{ZrO}_2$	Agate	$\text{ZrO}_2$
H ( <b>3a</b> )	89	97	95	95	2	3
<i>m</i> -MeO ( <b>3b</b> )	66	80	94	91	4	3
<i>o</i> -Me ( <b>3c</b> )	81	92	84	80	2	3
<i>m</i> -Me ( <b>3d</b> )	80	93	91	89	3	3
<i>p</i> -Me ( <b>3e</b> )	96	98	95	95	2	2
<i>p</i> -Ac ( <b>3f</b> )	29	32	67	75	17	15
<i>o</i> -Cl ( <b>3g</b> )	61	79	82	85	7	5
<i>m</i> -Cl ( <b>3h</b> )	79	92	92	86	6	7
<i>p</i> -Cl ( <b>3i</b> )	97	99	93	92	4	5
<i>o</i> -Br ( <b>3j</b> )	61	76	82	78	9	10
<i>m</i> -Br ( <b>3k</b> )	78	89	86	84	6	6
<i>p</i> -Br ( <b>3l</b> )	92	98	91	88	6	6
<i>o</i> -I ( <b>3m</b> )	48	70	84	80	9	7
<i>p</i> -I ( <b>3n</b> )	77	88	92	78	3	1

[a] Reaction conditions: amine (2 mmol),  $\text{KMnO}_4$  (4 mmol),  $\gamma$ - $\text{Al}_2\text{O}_3$  (4 g; activity 90, neutral); 800 rpm, 10 min, beaker (45 mL), six milling balls (15 mm). [b] Conversion (*X*) and selectivity (*S*) were determined by GC-FID measurements of extracted products in relation to amine (**3**; Scheme 3). For isolated yields of **4a–n**, see the Supporting Information.

acetophenone) showed the highest conversions and selectivities, presumably due to the relatively low steric influence of the substituent. In contrast, *o*-substituted anilines afforded lower conversion and produced larger amounts of side products (nitro, and side-chain oxidation products). As shown in Table 3 (and also the other tables), the sum of product selectivities did not equal 100% in every case. In some cases, low amounts of side chain oxidation products (aldehydes and acids) or dehalogenated products were identified. However, the concentrations of these side products were rather low compared to those obtained when the oxidation was conducted in solution. Furthermore, the reaction conditions, especially the reaction time, were significantly more efficient than alternative procedures reported in the literature.<sup>[10,14]</sup>

A range of grinding materials for beakers and balls (tungsten carbide, agate, stainless steel,  $\text{ZrO}_2$ , corundum) can be employed in experiments with ball mills. These differ in their material properties (hardness, abrasion) and bulk density. Generally, the use of a more heavy-weight milling material, such as tungsten carbide, results in a significantly higher kinetic energy than the use of a low-density material, such as agate. Higher kinetic energy, in turn, delivers more energy to the reaction mixture through friction and impact. This energy transfer is strongly correlated to chemical con-

version.<sup>[3],15]</sup> As shown for the reaction of anilines to generate azo (Table 3) and azoxy compounds (Table 4), the conversions could be increased by changing the milling material from agate ( $\text{SiO}_2$ ;  $\rho=2.65 \text{ g cm}^{-3}$ ) to  $\text{ZrO}_2$  ( $\rho=6.5 \text{ g cm}^{-3}$ ), while keeping the other reaction conditions constant.

Table 4. Oxidation of anilines **3** with Oxone to the corresponding azoxy-benzenes **5**,<sup>[a]</sup> by using agate or  $\text{ZrO}_2$  as material for milling beakers and balls.

R ( <b>3</b> ; Scheme 3)	X( <b>3</b> ) [%] <sup>[b]</sup>		S( <b>4</b> ) [%] <sup>[b]</sup>		S( <b>5</b> ) [%] <sup>[b]</sup>	
	Agate	$\text{ZrO}_2$	Agate	$\text{ZrO}_2$	Agate	$\text{ZrO}_2$
H ( <b>3a</b> )	83	98	3	4	92	89
<i>m</i> -MeO ( <b>3b</b> )	81	96	3	5	93	87
<i>o</i> -Me ( <b>3c</b> )	79	97	3	3	89	88
<i>m</i> -Me ( <b>3d</b> )	81	97	3	4	93	88
<i>p</i> -Me ( <b>3e</b> )	94	99	3	4	88	87
<i>p</i> -Ac ( <b>3f</b> )	52	82	14	17	81	70
<i>o</i> -Cl ( <b>3g</b> )	70	94	4	3	84	89
<i>m</i> -Cl ( <b>3h</b> )	69	92	6	8	89	87
<i>p</i> -Cl ( <b>3i</b> )	76	96	5	8	86	83
<i>o</i> -Br ( <b>3j</b> )	79	95	3	4	87	87
<i>m</i> -Br ( <b>3k</b> )	67	92	3	6	86	81
<i>p</i> -Br ( <b>3l</b> )	73	95	7	8	85	76
<i>o</i> -I ( <b>3m</b> )	60	82	13	17	73	58
<i>p</i> -I ( <b>3n</b> )	61	88	16	23	69	41

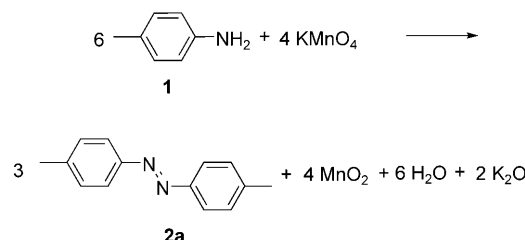
[a] Oxone = triple salt:  $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ ; reaction conditions: amine (2 mmol), Oxone (4 mmol),  $\gamma\text{-Al}_2\text{O}_3$  (4 g; activity 90, neutral); 800 rpm, 10 min, beaker (45 mL), six milling balls (15 mm). [b] Conversion (X) and selectivity (S) were determined by GC-FID measurements of extracted products in relation to amine (**3**; Scheme 3). For isolated yields of **5a–n**, see the Supporting Information.

**Formation of azoxy compounds from anilines:** When Oxone was used as oxidant instead of  $\text{KMnO}_4$  but still with  $\gamma\text{-Al}_2\text{O}_3$  (activity 90, neutral), the main product of aniline oxidation was the azoxy products, as already exemplified for *p*-toluidine (Table 1). In contrast to the reactions of anilines with  $\text{KMnO}_4$  (Table 3), no clear substituent effect could be recognized for the oxidation with Oxone (Scheme 3, Table 4).<sup>[9]</sup> The results varied more randomly and the selectivity for the target product (69–93% azoxy) was also not as high as those obtained under the previous conditions (84–95% azo). Especially for *p*-amino acetophenone (**3f**) and iodinated anilines (**3m** and **3n**), significant amounts of the azo products were identified. Lower selectivities for oxidation reactions of halogenated anilines in the presence of Oxone are known from other examples also.<sup>[9b]</sup> However, the occurrence of side reactions did not account for the observations (Table 4). Rather it seems that the oxidation potential is the limiting factor. According to the mechanism depicted in Scheme 1, the employed triple salt is clearly not able to form the hydroxyl amine for these substrates, which is a prerequisite for the subsequent condensation with the nitroso intermediate to form the azoxy product.

As mentioned above for the specific formation of azobenzenes (**4**; Table 3), the overall conversion can be increased by changing the milling material from agate to the more dense  $\text{ZrO}_2$  without a reduction in selectivity. Similar results were found for the formation of **5** from **3** (Table 4). For the

formation of both **4** and **5** in the presence of  $\text{ZrO}_2$ , the yield of the isolated product was enhanced (for isolated yields, see the Supporting Information). However, the difference between GC-based yield and isolated yield was approximately 10% in favor of the former, mainly due to the work-up procedure, which was not optimized.

**Effect of the amount of  $\text{KMnO}_4$  and the number of milling balls:** The model reaction depicted in Scheme 2 was chosen to investigate the effect of  $\text{KMnO}_4$  concentration and the number of milling balls on the course of reaction. Theoretically, a ratio of  $\text{KMnO}_4$  to *p*-toluidine (**1**) of 2:3 is sufficient for complete oxidation to the azo product, as shown in the overall redox equation for the oxidation of **1** (Scheme 4). Comparison with literature procedures describing the oxidation in solution and in the solid state revealed that those protocols require more than stoichiometric amounts of  $\text{KMnO}_4$ .<sup>[10,12f,14]</sup>



Scheme 4. General redox equation for the oxidation of *p*-toluidine (**1**) with  $\text{KMnO}_4$ .

As expected, the rate of conversion of **1** in the reaction with  $\text{KMnO}_4$  and  $\text{Al}_2\text{O}_3$  as the oxidant and the grinding auxiliary, respectively, depended on the amount of  $\text{KMnO}_4$  used (Figure 2). Interestingly, the selectivity for the main azo product remained almost unchanged; down to one equivalent of  $\text{KMnO}_4$ , a nearly linear dependence was found, whereas with less than one equivalent, the rate of conversion decreased significantly, presumably because of con-

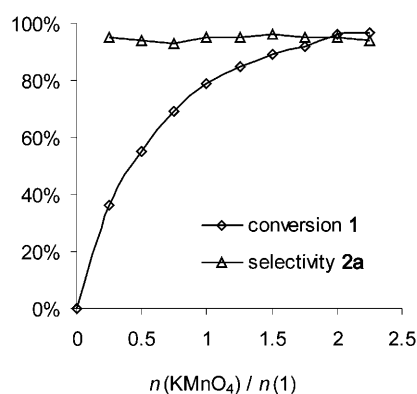


Figure 2. Influence of  $\text{KMnO}_4$  concentration on the solvent-free conversion of *p*-toluidine (**1**; 2 mmol) into the corresponding azo-compound with  $\gamma\text{-Al}_2\text{O}_3$  (activity 90, neutral; 4 g) as grinding auxiliary in a ball mill (agate beaker (45 mL), six agate milling balls (15 mm); 800 rpm; 10 min).

sumption of  $\text{KMnO}_4$  through side-reactions and self-reduction. With amounts lower than 0.66 equivalents of  $\text{KMnO}_4$ , complete oxidation of **1** is not possible, as shown in Scheme 4.

An interesting phenomenon occurred when the number of milling balls was reduced (Figure 3). The rate of conversion decreased in a linear fashion when five or four balls in-

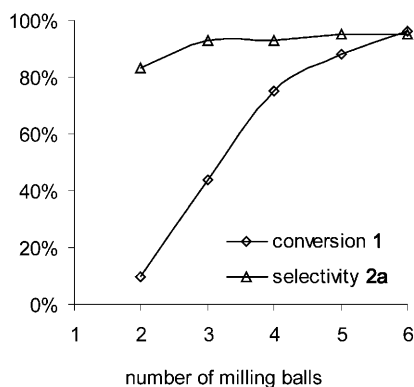


Figure 3. Effect of the number of milling balls for the solvent-free conversion of *p*-toluidine (**1**; 2 mmol) into the corresponding azo-compound with  $\text{KMnO}_4$  (4 mmol) as the oxidant and  $\gamma\text{-Al}_2\text{O}_3$  (activity 90, neutral; 4 g) as the grinding auxiliary in a ball mill (agate beaker (45 mL), agate milling balls (15 mm); 800 rpm; 10 min).

stead of six balls were used. Employing three and two balls led to a more distinct decrease in conversion. This is an indication that the conversion is only affected by temperature, whereby the energy is dispersed into the system by the input of kinetic energy of the milling balls (four or more milling balls).<sup>[31]</sup> With three or less milling balls, insufficient mixing of the reactants also influences the course of reaction. This could be a general effect that is important for the application of reactions in a planetary ball mill. In conclusion, at least four milling balls are required to ensure thorough mixing.

Measurement of the milling ball mass after each run revealed the influence of the grinding auxiliary on the deterioration of the milling balls caused by friction and impact processes. Milling with the auxiliary  $\text{SiO}_2$  led to more than threefold mass loss compared to the use of  $\text{Al}_2\text{O}_3$  as auxiliary (Table 5), in which the mass lost did not affect the reproducibility of the results. In fact, the variation in terms of conversion when using completely new milling balls compared with those obtained with older balls that had been applied more than 100 times, was less than 2%.

Table 5. Deterioration of milling balls.

Milling material	Average weight loss of milling balls per trial [wt %] <sup>[a]</sup>	
	$\text{SiO}_2$	$\gamma\text{-Al}_2\text{O}_3$ <sup>[b]</sup>
Agate	0.22	0.06
ZrO <sub>2</sub>	0.27	0.07

[a] Milling conditions for one trial: batch-sizes according to Figure 2; agate beaker (45 mL), six agate milling balls (15 mm), 800 rpm, 10 min. [b] Activity 150, basic.

**Comparison to methods in solution:** Finally, a comparison between solvent-free ball milling procedures (planetary and vibration ball mill) and four methods in solution (microwave heating, conventional heating, ultrasound) for five anilines was performed (Scheme 3; Table 6).<sup>[2f]</sup> It is clear that the solvent-free methods are competitive and even more effective than the oxidation performed in a microwave, in a round-bottom flask, or in an ultrasound reactor. Reactions in solution were performed at 80 °C and, in the case of sonication, the mixture was cooled down to 20 °C. Compared to surface temperatures measured after the reaction in the ball mills (40 °C), those temperatures are higher. In combination with the fact that the reaction time was longer, higher conversions would have been expected for the reactions conducted in solution. Clearly the heterogeneous solid-state reaction procedure was superior to classical methods. In particular, for the sterically hindered *o*-toluidine (**3c**) and the deactivated *m*-anisidine (**3b**) substrates, the yields using the

Table 6. Influence of energy input on the oxidation of anilines with  $\text{KMnO}_4$  and  $\text{Al}_2\text{O}_3$ .<sup>[a]</sup>

Amine	Conversion of amine [%]/selectivity for the azo product [%] <sup>[b]</sup>					
	solvent-free		in solution (30 mL; $\text{H}_2\text{O}$ /acetonitrile, 1:1 v/v)			
	planetary ball mill <sup>[c]</sup>	vibration ball mill <sup>[d]</sup>	conventional heating <sup>[e]</sup>	multimode microwave <sup>[f]</sup>	monomode microwave <sup>[g]</sup>	ultrasound <sup>[h]</sup>
aniline ( <b>3a</b> )	93/95	71/89	83/88	90/91	58/91	88/94
<i>m</i> -anisidine ( <b>3b</b> )	70/90	40/91	53/89	22/91	27/90	73/96
<i>o</i> -toluidine ( <b>3c</b> )	94/89	81/97	89/88	39/87	63/88	82/87
<i>m</i> -toluidine ( <b>3d</b> )	95/91	87/92	84/72	54/81	84/72	67/87
<i>p</i> -toluidine ( <b>3e</b> )	>99/96	>99/95	96/90	91/93	96/90	97/97

[a] Standard batch size: amine (2 mmol),  $\text{KMnO}_4$  (4 mmol),  $\gamma\text{-Al}_2\text{O}_3$  (4 g; activity 90, neutral). [b] Determined by GC-FID measurements of extracted products in relation to amine. [c] Fritsch Pulverisette 7 classic line: two agate beaker (45 mL), six agate milling balls per beaker (15 mm), 800 rpm, 20 min. [d] Retsch MM301: two agate beaker (50 mL), six agate milling balls per beaker (15 mm), 13.3 Hz, 20 min. [e] Round-bottom flask (100 mL); 80 °C, 60 min. [f] MLS ETHOS Plus: 80 °C ( $P_{\text{max}}=300$  W), 30 min. [g] CEM Discover: 80 °C ( $P_{\text{max}}=130$  W), 30 min. [h] Hielscher UP200 s: 33 % of standard batch size; 100 %  $P_{\text{max}}$ , 20 °C, 20 min.

solid-state approach were significant higher. One literature example that dealt with the oxidation of amines with  $\text{KMnO}_4$  using microwave and ultrasonic irradiation showed that solvent effects may also cause side reactions at higher temperatures.<sup>[16]</sup> It is remarkable that reactions conducted in an ultrasound reactor gave similar conversion and selectivity with all five amines to reactions performed with ball mills. However, it has to be considered that only one third of the standard reaction mixture (0.7 mmol instead of 2 mmol amine) was employed.

Another major advantage of the ball mill procedure is the easy workup. In the case of reactions in solution, the manga-



nese dioxide resulting from the reduction of  $\text{KMnO}_4$  tends to form a muddy mass that can be rather difficult to work up. In contrast, the ball milling procedure results in a powder that is easily extractable with an organic solvent prior to analysis or isolation. The solvent-free, conventionally heated or microwave-assisted performance of the reaction was also assessed. However, the corresponding yields were not reliable with regard to statistical spread of the results. Clearly, improper mixing of the solid reactants was responsible for this artifact. Another advantage of the use of ball mills is the intense mixing, which enables the apparatus to be used for both reaction and mixing in one device.

In addition to the comparison of chemical performance, the reaction of *p*-toluidine in different reaction environments was assessed with respect to energy conversion. Energy consumption of 0.035, 0.02, 0.38, 0.20, 0.29, and 0.015 kWh were measured for the reaction conditions listed in Table 6, respectively. Considering that both of the ball mills were operated with two equally filled milling beakers and that, in the case of sonication, a reduced batch size was used, the molar energy conversion could be calculated (Figure 4).<sup>[17]</sup> The data indicate that the solvent-free proce-

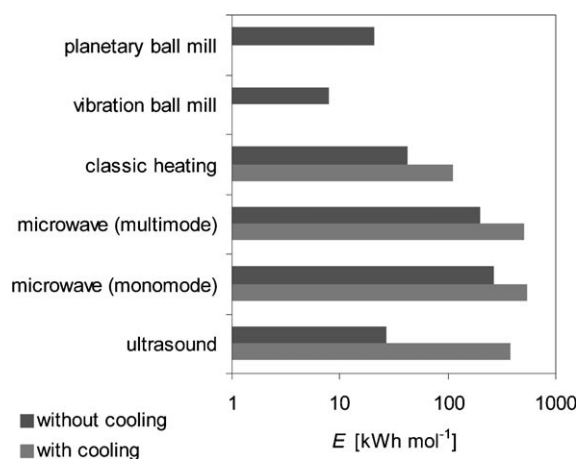


Figure 4. Energy consumption for the oxidation of *p*-toluidine (2 mmol) with  $\text{KMnO}_4$  using the reaction conditions listed in Table 6 (calculated according to Schneider et al.<sup>[17]</sup>).

dure is superior to solvent-based methods. Only the reaction performed in an ultrasound reactor had comparable energy efficiency, and only if the energy for cooling was neglected. Generally, the reactions in solution needed  $0.01 \text{ kWh min}^{-1}$  to operate the cryostat (the same cryostat was used for all processes; cryostat temperature =  $10^\circ\text{C}$ ). Including this fact, the efficiency of the ball milling procedure is highlighted even more. The lower energy efficiency of the planetary ball mill compared to the vibration ball mill was due to technical differences.<sup>[18]</sup> Because the moving masses are significantly higher for the former, a higher moment of inertia has to be overcome to provide proper movement of the milling balls. However, reaction scale-up is only possible with the planetary ball mill.

## Conclusion

A fast and solvent-free method for the oxidation of primary aromatic amines to azo and azoxy compounds in a planetary ball mill is described. It was shown that conversion and selectivities can be controlled by the choice of oxidant and grinding auxiliary. Furthermore, the experiments showed good reproducibility. Reaction screening of various anilines showed substituent effects for the oxidation with  $\text{KMnO}_4$  furnishing the azo compounds with high selectivities. Employing Oxone instead of  $\text{KMnO}_4$  afforded the corresponding azoxy compounds with similar selectivities. Again, conversion is related to the substitution of the starting materials. Compared to methods in solution (microwave, conventional heating, ultrasound), the solvent-free procedure in the ball mill is more efficient in terms of both chemical yield and energy consumption. The avoidance of organic solvents and the easy, fast, and energy-saving aspects of the reaction make this ball-milling method a real alternative to conventional reaction protocols.

## Experimental Section

**General:** Chemicals are commercially available from Sigma-Aldrich or Alfa Aesar and were used as received. Reactions were performed in a Fritsch "Pulverisette 7 classic line" planetary ball mill using 45 mL grinding beakers (agate or  $\text{ZrO}_2$ ) and milling balls ( $6 \times 15 \text{ mm}$ ; agate or  $\text{ZrO}_2$ ). All reaction vessels were cleaned with ethanolic HCl (1 M) prior to use to avoid any contamination or memory effects.

GC-FID and GC-MSD measurements were performed with a 6890-GC or a 6890N-GC-MS instrument, respectively, both from Agilent Technologies. Conditions for GC-FID: HP 5,  $30 \text{ m} \times 0.32 \text{ mm} \times 0.25 \mu\text{m}$ ,  $\text{H}_2$ -10 psi, program:  $70^\circ\text{C}$  (hold for 3 min),  $15 \text{ K min}^{-1}$  up to  $280^\circ\text{C}$  (hold for 10 min), injector temperature:  $280^\circ\text{C}$ , detector temperature:  $300^\circ\text{C}$ . Conditions for GC-MSD: HP 5,  $30 \text{ m} \times 0.32 \text{ mm} \times 0.25 \mu\text{m}$ , He-10 psi, program:  $70^\circ\text{C}$  (hold for 3 min),  $15 \text{ K min}^{-1}$  up to  $280^\circ\text{C}$  (hold for 7 min), injector temperature:  $280^\circ\text{C}$ , detector: EI (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system at RT in  $\text{CDCl}_3$  as solvent using tetramethylsilane as internal standard.

Data reported herein (conversion, selectivity) were calculated from the GC data and are comparable with those for the isolated products. The reported yields were adjusted by correcting for the different FID sensitivity for substrate and product. Isolated yields for the target products in Tables 3 and 4 are provided within the Supporting Information and are given in relation to the employed amine. Isolation was performed for those reactions in Tables 3 and 4 that were performed with  $\text{ZrO}_2$  as the grinding material.

**General reaction procedure for the oxidation of anilines:** Grinding beakers (45 mL; agate or  $\text{ZrO}_2$ ) were equipped with six milling balls of the same material ( $d = 15 \text{ mm}$ ), and the milling auxiliary (4 g), the amine (2 mmol), and the oxidant (4 mmol) were added in the given order. Milling was performed at 800 rpm for 10 min. After cooling of the grinding beakers to RT, the crude products were washed through a thin silica layer using methyl *tert*-butyl ether (MTBE;  $3 \times 10 \text{ mL}$ ). The solvent was evaporated in vacuum and the crude products were dried, redissolved in MTBE (1.5 mL) and analyzed by GC-FID and GC-MS. Analytical samples for NMR spectroscopic investigations were isolated by column chromatography using a *n*-hexane/toluene mixture as eluent. Products were identified by comparison with literature data. For analytical details of the isolated products, see the Supporting Information.

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