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PAPER

Aromatic substitution in ball mills: formation of aryl chlorides and bromides using potassium peroxomonosulfate and NaX†

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Aryl chlorides and bromides are formed from arenes in a ball mill using $KHSO_5$ and NaX (X = Cl, Br) as oxidant and halogen source, respectively. Investigation of the reaction parameters identified operating frequency, milling time, and the number of milling balls as the main influencing variables, as these determine the amount of energy provided to the reaction system. Assessment of liquid-assisted grinding conditions revealed, that the addition of solvents has no advantageous effect in this special case. Preferably activated arenes are halogenated, whereby bromination afforded higher product yields than chlorination. Most often reactions are regio- and chemoselective, since *p*-substitution was preferred and concurring side-chain oxidation of alkylated arenes by $KHSO_5$ was not observed.

1. Introduction

Within the past decade numerous protocols for solvent-free reactions in ball mills have been published.[1–5] Especially, reactions between solids take advantage of ball mills as reactors. In these cases, efficient mixing and continuous particle refinement is necessary for high reaction rates due to decreased diffusion barriers. Those conditions can be realized using ball mills. Thus, several types of organic transformations have been reported so far, sometimes yielding products with unexpected selectivity compared to procedures in solutions.[6] Protocols for C–C bond-forming reactions based on carbonyls,[7–10] or the synthesis of heterocycles[11,12] are known beside examples from redox chemistry.[13–15] Amongst the methodologies for C–C bond formations metal-catalyzed homo-[16] and cross-couplings like the Suzuki,[17–19] Heck,[20] or Sonogashira reaction[21,22] have been transferred to ball milling conditions successfully. Especially for the last type of reactions, aryl halides are the substrates of choice to be coupled with organoboron reagents, activated alkenes, or terminal alkynes, respectively. However, the synthesis of such building blocks starting from readily available arenes in ball mills has not been described in the literature to the best of our knowledge.

Established industrial scale halogenation methods involve the direct use of dihalogens in combination with Lewis-acids as catalysts. Although, such processes find widespread application in industry, handling of gaseous halogens in the lab-scale is difficult due to their hazardous potential and corrosive nature. To overcome the use of these gases and with regard to the prevention of solvents some safer, solvent-free procedures, *e.g.*, under mechano-chemical conditions, have been developed. In this connection, miscellaneous reagents were published, such as (diacetoxyiodo)benzene (DIB),[23] 1,2-dipyridiniumditribromide-ethane (DPTBE),[24] iodosobenzene with HX-saturated silica gel,[25] NBS,[26] or NBS immobilized on Al_2O_3.[27] Using NBS for benzylic bromination of substituted quinolines Rahman *et al.* disclosed a method for bromination in a ball mill,[28] while most often the mentioned reactions were carried out by trituration of the reactants with mortar and pestle. However, this procedure is imprecise and the results depend strongly on the experimenter. Contrarily, reactions in ball mills allow the repeatable and precise setting of reaction conditions.[29] Thus, this technique unifies the functions of energy entry and mixing in one apparatus and is used for the present investigations.

2. Results and discussion

Herein we describe a solvent-free method for halogenation of aromatic compounds in a mixer ball mill using $KHSO_5$ (oxone)‡ and NaX (X = Cl, Br) as the reagents. Oxone is a common oxidizing agent with a large scope of application[30] and has already applied as oxidant in ball mills.[13,31,32] Several milling auxiliaries were assessed allowing the comminution of liquid reagents, which normally would distort the energy transfer to the mill charge. Furthermore the influence of milling time *t*, oscillation frequency ν_{osc}, number of milling balls n_{MB}, and the influence of additional solvents were examined. The bromination of structurally demanding mesitylene (**1**) was chosen as a model reaction (Scheme 1) for investigation of the mentioned parameters.

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‡ $KHSO_5$ was applied as its triple salt: $2KHSO_5 \times KHSO_4 \times K_2SO_4$; furthermore abbreviated as oxone.

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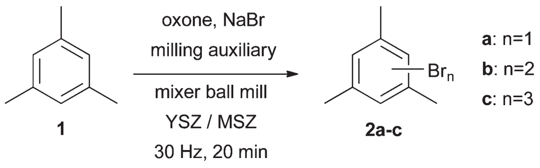

Scheme 1 Bromination of mesitylene **1** with standard reaction conditions (products from the reaction with NaCl = **3a–c**).

Table 1 Influence of the milling auxiliary on the bromination of **1**[a]

Milling auxiliary	Conversion **1** [%]	Selectivity **2a** [%]
Quartz sand	87	96
γ-Alumina (basic)	80	95
γ-Alumina (neutral)	59	7
α-Alumina (acidic)	9	66
Silica gel	71	97
Montmorillonite K-10	45	98
Na_2SO_4	5	47
NaBr	82	91

[a] Reaction conditions: 1.5 mmol **1**, 0.75 mmol oxone, 1.5 mmol NaBr, 4 g milling auxiliary, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz, t = 20 min. Conversion and selectivity were determined by GC-FID measurements of extracted products in relation to **1** (external calibration).

Reactions were carried out in a mixer ball mill equipped with milling beakers and milling balls made from yttrium- (YSZ) and magnesia-stabilized ZrO_2 (MSZ), respectively.

2.1. Influence of milling auxiliary

The first parameter which has been investigated was the influence of the milling auxiliary. In former studies it was shown that the milling auxiliary can affect the conversion and selectivity of a reaction carried out in a ball mill.[13,22,31,33] This is tracked back to different surface properties of the auxiliary solid.[13,33] As shown in Table 1 the choice of the milling auxiliary strongly affects the results, whereas the best results were obtained with quartz sand, which is proven by the high conversion and selectivity to bromomesitylene. Na_2SO_4 is not suitable as a milling auxiliary, whereas results indicate an advantageous effect of NaBr, due to the increased availability of bromide.

Three different aluminas were employed, revealing differences in both conversion and selectivity. With γ-alumina (basic and neutral) the conversion is lower but the selectivity is as high as with quartz sand. Application of acidic α-alumina results in significantly lower conversion and selectivity. For the electrophilic halogenation with $KHSO_5$ and NaX two different mechanisms can be assumed that depend on the pH: (i) halogenation with *in situ* formed bromine in acidic media

$$HSO_5^- + 2Br^- + 2H^+ \rightarrow Br_2 + HSO_4^- + H_2O \quad (1)$$

$$Ar–H + Br_2 \rightarrow Ar–Br + HBr \quad (2)$$

and (ii) with hypobromite as the halogenating species generated under the influence of bases.[34]

$$HSO_5^- + NaBr \rightarrow HSO_4^- + NaOBr \quad (3)$$

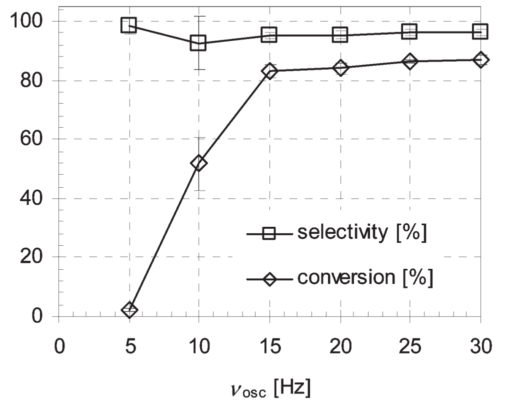

Fig. 1 Influence of oscillation frequency ν_{osc} on the solid-state bromination of **1** to **2a** (Scheme 1). Reaction conditions: 1.5 mmol mesitylene, 0.75 mmol oxone, 1.5 mmol NaBr, 4 g quartz sand, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), t = 20 min.

$$Ar–H + NaOBr \rightarrow Ar–Br + NaOH \quad (4)$$

The second mechanism seems to be more applicable, since with α-alumina (acidic) as the milling auxiliary (Table 1) a lower conversion was observed as compared with basic γ-alumina. In some cases, when deactivated aromatics where investigated the reaction mixtures turned brown, indicating the formation of bromine. This can be explained by the disproportionation of hypobromite to bromate and bromide.[35] Comproportionation of bromate and bromide results in the formation of bromine.[36]

2.2. Influence of oscillation frequency ν_{osc} and milling time t

For reactions in ball mills, process parameters like oscillation frequency ν_{osc} have to be considered. The frequency determines the kinetic energy of the milling balls and thus the dissipative energy entry into the solid reaction system.[5,13] In consequence, the temperature inside the milling vessels increases with higher ν_{osc} and, thus higher conversions can be observed.[14,29,37] Because of this, the influence of ν_{osc} on the conversion and selectivity during the bromination of **1** was examined (Fig. 1). Reactions were performed at varied operating frequencies ranging from 5–30 Hz. No influence on the selectivity of bromomesitylene (**2a**) was detectable, whereas the conversion is clearly effected by changing ν_{osc}. From 15–30 Hz a constant conversion occurred, but at decreased frequencies a significantly lower conversion of mesitylene was observed and at 5 Hz with only trace amounts of brominated product being found. Due to the decreased energy entry in combination with changes in the trajectories of the milling balls and the wear mechanisms, reactions carried out at ≤10 Hz show low performances.

Beside ν_{osc}, the milling time t has also been identified as a main influencing process parameter.[38,39] Previous studies revealed that t is a limiting factor for reactions in ball mills.[5,13,38] Thus, the reaction of **1** with NaBr was elaborated within 0.5–20 min. As Fig. 2 demonstrates, no influence on selectivity of **2a** was found over the entire period of time. In contrast, the conversion increased at t = 0.5–5 min from 12–85%. Longer reaction times showed no considerable effect on the conversion, but the conversion rate decreases. This is in accordance with

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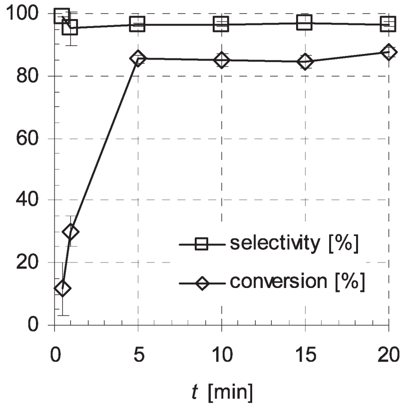

Fig. 2 Influence of milling time *t* on the solid-state bromination of **1** to **2a** (Scheme 1). Reaction conditions: 1.5 mmol mesitylene, 0.75 mmol oxone, 1.5 mmol NaBr, 4 g quartz sand, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz.

Table 2 Effect of the number of milling balls n_{MB} on the solid-state bromination of **1**[a]

n_{MB}	Σm_{MB} [g]	Conversion **1** [%]	Selectivity **2a** [%]
0	0	0	—
2	5.58	68	97
4	11.06	77	96
6	16.55	78	96
8	21.97	83	96
10	28.26	87	97

[a] Reaction conditions: 1.5 mmol **1**, 0.75 mmol oxone, 1.5 mmol NaBr, 4 g quartz sand, milling beaker (YSZ, 35 mL), milling balls (MSZ, 10 mm), ν_{osc} = 30 Hz, *t* = 20 min. Conversion and selectivity were determined by GC-FID measurements of extracted products in relation to **1** (external calibration).

other reactions in ball mills that proceed in short reaction times.[5,13,39]

2.3. Number of milling balls n_{MB}

Several studies revealed that the number of milling balls n_{MB} is a critical parameter.[13,31,38] As shown in Table 2, without any milling balls no conversion could be achieved due to the missing energy input through the trajectories and impacts of the balls. With two milling balls a conversion of 68% was observed. Further raises of the n_{MB} increases the conversion up to 87%. In accordance with the literature the selectivity is not affected by varying the number of ball mills.[31]

2.4. Influence of additional solvent: LAG

It was reported that the addition of small amounts of solvents, *e.g.*, water or acetonitrile, accelerated solvent-free mechanochemical reactions.[13,40–43] Those reaction protocols are known as liquid-assisted grinding (LAG).[44] Based on this knowledge, the influence of different solvents on the reaction of **1** with oxone and NaBr was examined. Prior to comminution, water was added in different amounts to the reaction mixture, and as shown in Table 3, where no effect on both conversion and selectivity was detectable. Water seems to be an unsuitable additive, since it is applicable for solvation of the inorganic reagents (oxone, NaBr) only. For increasing the solubility for **1** several common organic solvents were examined. Similar to water, no clear effect of the additives was observed. Obviously, additional solvents deliver no advantage for solvent-free halogenation with oxone and NaBr. A possible explanation for this behavior is that based on the solubility of the reactants, either the non-polar **1** or the inorganic hydrophilic reactants are dissolved but not all together. Since the solubility is one of the determining factors for LAG,[42] no effect was measurable in this case.

Table 3 Influence of solvents on the solid-sate bromination of **1**[a]

Solvent	Amount [μL]	Conversion **1** [%]	Selectivity **2a** [%]
No solvent	0	87	96
Water	10	89	97
	25	89	92
	50	86	97
	100	87	99
	250	87	97
Ethanol	50	88	98
MTBE	50	85	97
n-Heptane	50	90	96
Chloroform	50	88	97

[a] Reaction conditions: 1.5 mmol **1**, 0.75 mmol oxone, 1.5 mmol NaBr, 4 g quartz sand, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz, *t* = 20 min. Conversion and selectivity were determined by GC-FID measurements of extracted products in relation to **1** (external calibration).

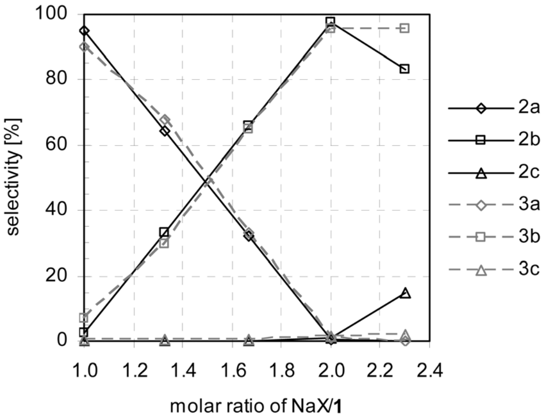

Fig. 3 Variation of the NaX/**1** molar ratio for the bromination (X = Br) and chlorination (X = Cl) of mesitylene (**1**). Reaction conditions: 1.5 mmol **1**, 2 mmol oxone, 4 g quartz sand, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz, *t* = 20 min. Products according to Scheme 1.

2.5. Influence of the NaX/reactant ratio

The reactions have been carried out with an equimolar ratio of NaBr to **1** and the selectivity to **2a** was often >90%. However, the following question might be interesting – if more than one bromine could be linked to the aromatic core? Thus, the reagent

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Table 4 Bromination of aromatic compounds using oxone and NaBr[a]

Aromatic compound	Conversion [%]	Product	Selectivity[b] [%]
Mesitylene (**1**)	85	Bromomesitylene (**2a**)	96
Benzene (**4**)	No reaction	—	—
Toluene (**5**)	95	Bromotoluene (**5a**)	99 (*o*/*p* = 1 : 2)
o-Xylene (**6**)	90	4-Bromo-1,2-dimethylbenzene (**6a**)	97
m-Xylene (**7**)	94	1-Bromo-2,4-dimethylbenzene (**7a**)	98
p-Xylene (**8**)	91	2-Bromo-1,4-dimethylbenzene (**8a**)	94
Ethylbenzene (**9**)	71	Bromoethylbenzene (**9a**)	90 (*o*/*p* = 1 : 3)
Anisole (**10**)	88	Bromoanisole (**10a**)	97 (*o*/*p* = 1 : 3)
Phenol (**11**)	81	Bromophenol (**11a**)	77 (*o*/*p* = 2 : 9)
2,3,5-Trimethylphenol (**12**)	84	Bromo-2,3,5-trimethylphenol (**12a**)	95 (*o*/*p* = 1 : 3)[c]
2,3,6-Trimethylphenol (**13**)	89	4-Bromo-2,3,6-trimethylphenol (**13a**)	96
p-Hydroxybenzaldehyde (**14**)	65	3-Bromo-4-hydroxybenzaldehyde (**14a**)	74
m-Toluidine (**15**)	91	4-Bromo-3-methylaniline (**15a**)	41
Nitrobenzene (**16**)	No reaction	—	—
Benzonitrile (**17**)	No reaction	—	—
Chlorobenzene (**18**)	No reaction	—	—
Naphthalene (**19**)	78	α-Bromonaphthalene (**19a**)	94
Anthracene (**20**)	36	9-Bromoanthracene (**20a**)	61[d]

[a] Reaction conditions: 1.5 mmol aromatic compound, 0.75 mmol oxone, 1.5 mmol NaBr, 4 g quartz sand, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz, t = 20 min. [b] Ratio of *o*- and *p*-isomers in parentheses (identified by comparison with original samples and determined by ratio of GC-MS signals). [c] With respect to the OH-group in **12**. [d] Difference to 100% selectivity accounts for 9,10-dibromoanthracene and anthraquinone.

Table 5 Chlorination of aromatic compounds using oxone and NaCl[a]

Aromatic compound	Conversion [%]	Product	Selectivity[b] [%]
Mesitylene (**1**)	85	Chloromesitylene (**3a**)	96
Benzene (**4**)	No reaction	—	—
Toluene (**5**)	92	Chlorotoluene (**5b**)	96 (*o*/*p* = 1 : 2)
o-Xylene (**6**)	76	4-Chloro-1,2-dimethylbenzene (**6b**)	93
m-Xylene (**7**)	93	1-Chloro-2,4-dimethylbenzene (**7b**)	98
p-Xylene (**8**)	80	2-Chloro-1,4-dimethylbenzene (**8b**)	91
Ethylbenzene (**9**)	75	Chloroethylbenzene (**9b**)	98 (*o*/*p* = 1 : 3)
Anisole (**10**)	86	Chloroanisole (**10b**)	96 (*o*/*p* = 1 : 3)
Phenol (**11**)	70	Chlorophenol (**11b**)	97 (*o*/*p* = 2 : 9)
2,3,5-Trimethylphenol (**12**)	64	Chloro-2,3,5-trimethylphenol (**12b**)	89 (*o*/*p* = 1 : 3)[c]
2,3,6-Trimethylphenol (**13**)	81	4-Chloro-2,3,6-trimethylphenol (**13b**)	76
p-Hydroxybenzaldehyde (**14**)	67	3-Chloro-4-hydroxybenzaldehyde (**14b**)	88
m-Toluidine (**15**)	99	4-Chloro-3-methylaniline (**15b**)	10
Nitrobenzene (**16**)	No reaction	—	—
Benzonitrile (**17**)	No reaction	—	—
Chlorobenzene (**18**)	No reaction	—	—
Naphthalene (**19**)	39	α-Chloronaphthalene (**19a**)	81
Anthracene (**20**)	19	9-Chloroanthracene (**20b**)	46[d]

[a] Reaction conditions: 1.5 mmol aromatic compound, 0.75 mmol oxone, 1.5 mmol NaCl, 4 g quartz sand, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz, t = 20 min. [b] Ratio of *o*- and *p*-isomers in parentheses (identified by comparison with original samples and determined by ratio of GC-MS signals). [c] With respect to the OH-group in **12**. [d] Difference to 100% selectivity accounts for 9,10-dichloroanthracene and anthraquinone.

ratio has been increased from 1.0–2.3. As shown in Fig. 3 while increasing the ratio of NaX, the amount of **2a** (X = Br) and **3a** (X = Cl) decreases, while more dihalogenated product (**2b**, **3b**) is formed. The maximum amount of dihalogenated mesitylene was observed with two equivalents of NaX, indicating that the amount of oxidant is not important for the halogenation, since its ratio was not changed during the reactions. Addition of more than two equivalents of NaX to the reaction mixture and ball milling for the same amount of time afforded significant amounts of tribromo (**2c**) and trichloromesitylene (**3c**). The reaction profiles are typical for a sequential process substituting one position after the other, with no significant influence on the reaction rate. Obviously the steric shielding by the flanking methyl groups is responsible for this effect.

2.6. Substrate screening

The substrate scope of the halogenation reaction with oxone and NaBr or NaCl was examined with a variety of aromatic compounds (**1**, **4**–**20**) listed in Tables 4 and 5, respectively. Results demonstrated that activated arenes can be halogenated. In most

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cases the results show good to excellent conversion and selectivity. In accordance with the literature, halogenation of deactivated aromatic compounds like nitrobenzene (**16**), benzonitrile (**17**), or chlorobenzene (**18**) failed, and no halogenation was observed.[45] Furthermore, the halogenation of heteroaromatics like pyrrol, pyridine, or 4-aminopyridine failed due to the formation quarternized heteroarenes similar to the formation of DPTBE.[24]

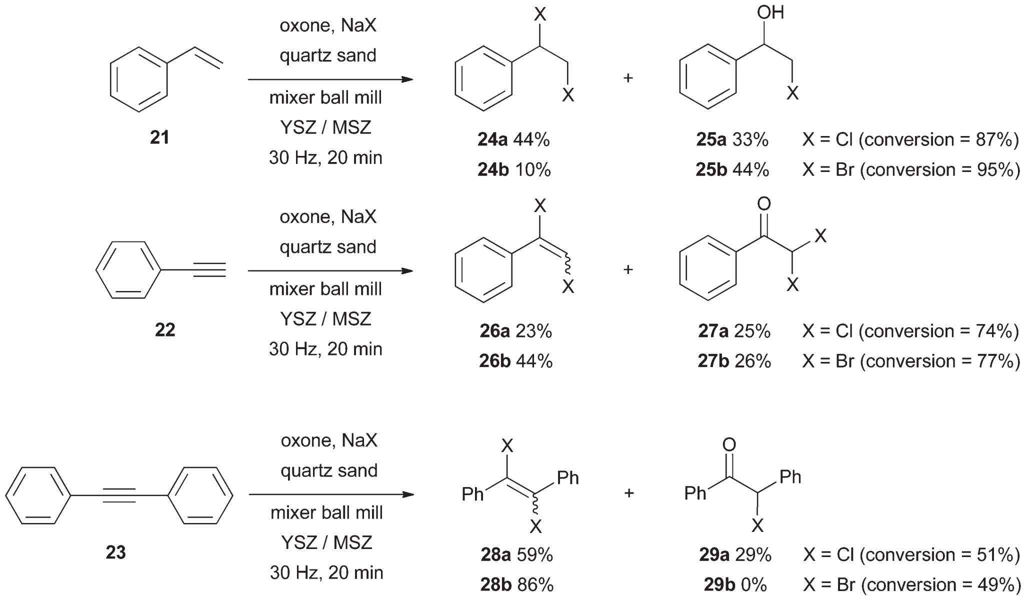
Bromination with NaBr normally results in higher conversion as respective chlorination. For most reactions tested, the monohalogenated aromatic compound was the major product and dihalogenated products occurred in small amounts only. If not stated otherwise the difference to 100% selectivity in Tables 4 and 5 accounts for the formation of such products. Reaction of anthracene (**20**) takes place with lower selectivity. Beside 9,10-dihaloanthracene as a side product, oxidation with $KHSO_5$ to anthraquinone takes place. If *m*-toluidine (**15**) is subjected to the bromination or chlorination conditions low selectivity to the halogenated product was detected despite conversion of 91 and 99%, respectively. In this case several oxidation products (azo, azoxy, nitro) have been detected in the crude reaction mixture.[46] The occurrence of these was previously observed during oxidation reactions of anilines in ball mills with different oxidants.[31] Some of the employed aromatic compounds (**5**, **9–12**) delivered a mixture of *o*- and *p*-halogenated products whereas the *p*-isomer is always favoured. The *o*/*p*-ratio varies between 1 : 2 and 2 : 9 for toluene (**5**) and phenol (**11**), respectively (Tables 4 and 5). Results are independent from the sodium halide applied for the reaction.

Of special interest is the halogenation of 2,3,6-trimethylphenol (**13**) and its 2,3,5-regioisomer (**12**) because of their importance in synthesis routes to vitamin E that start with the oxidation of trimethylphenols to trimethyl-*p*-benzoquinone.[47,48] One possible method for this reaction step is the halogenation of trimethylphenol and further oxidation to the quinoid system. Thus, *p*-halogenated trimethylphenols are valuable intermediates.[49] As shown in Tables 4 and 5 the halogenation of the regioisomeric phenols (**12**, **13**) proceeded with good conversion and selectivity. The reactivity difference between the two isomers is due to the steric shielding of two *o*-methyl groups in the case of **12** and is also known from oxidation procedures in solution. Since the *o*-positions in **13** are blocked, substitution occurs regioselectively in the *p*-position, whereas for **12** the formation of 2-chloro- (*o*-**12b**) as well as 2-bromo-3,5,6-trimethylphenol (*o*-**12a**) is indicated also.

Apart from halogenation of aromatics, it is shown that unsaturated functional groups like alkenyl (**21**) and alkynyl groups (**22**, **23**), which are tagged to a phenyl ring, are accessible for halogenation with this method (Scheme 2).[50] Aromatic compounds with these functional groups do not undergo electrophilic substitution but addition to the carbon–carbon double or triple bond occurrs. For example halogenation of phenylacetylene (**22**) provided 1,2-dibromostyrene (**26b**). In addition, the oxidation product 2,2-dibromo-1-phenylethanone (**27b**) was formed. This is in accordance with studies of Ye and Shreeve[51] and Kavala *et al.*,[24] where a similar behavior was reported. Analog reaction products were found for the halogenation of tolan (**23**). Reaction of styrene (**21**) instead afforded 1,2-dihalogenated products **24**. Spectroscopic (GC-MS) studies of the crude reaction mixtures furthermore led to the assumption that partially oxygenated products **25a** and **25b** are formed also.

2.7. Other halogenation methods

In addition to the described halogenation method with oxone and NaX (method A), two alternative reaction protocols have been developed. On the one hand the halogenation of aromatics with Cu(II)-halides as a halogen source (method B) and, on the other hand, the reaction of arylboronic acids with Cu(II)-halides or *N*-halosuccinimides (method C). Halogenation of aromatics



Scheme 2 Product distribution (selectivity) for solid-state halogenation of conjugated carbon–carbon double and triple bonds (conditions *cf.* Table 4). Products with indices **a** and **b** indicate the formation of chlorinated or brominated product, respectively. Structures **25** and **29** based on GC-MS studies.

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Table 6 Influence of the milling auxiliary for the solid-state bromination of **1** with $CuBr_2$ [a]

Milling auxiliary	Conversion **1** [%]	Selectivity **2a** [%]
Quartz sand	58	96
γ-Alumina (basic)	53	95
γ-Alumina (neutral)	51	96
α-Alumina (acidic)	39	95
Silica gel	50	93
Montmorillonite K-10	50	97
Na_2SO_4	59	98
NaBr	11	98

[a] Reaction conditions: 1.5 mmol **1**, 1.5 mmol $CuBr_2$, 4 g milling auxiliary, milling beaker (YSZ, 35 mL), 10 × 10 mm milling balls (MSZ), ν_{osc} = 30 Hz, t = 20 min. Conversion and selectivity were determined by GC-FID measurements of extracted products in relation to **1** (external calibration).

with Cu(II)-halides was performed with several milling auxiliaries (Table 6). It was observed that this kind of milling auxiliary has less of an influence, as in case of the reaction with oxone and NaBr (*cf.* Table 1). Only α-alumina (acidic) and NaBr as milling auxiliaries directed the reaction to lower conversion.

Investigation of the influence of t and n_{MB} revealed a similar behavior as was observed for the halogenation method A (oxone + NaX; Fig. 2 and Table 2). In contrast to method A, the application of copper halides is disadvantageous due to the need for two equivalents of CuX_2 for the substitution of one equivalent of a C–H function. Employment of only one equivalent is responsible for the low conversions presented in Table 6.

Murphy *et al.* described the synthesis of disubstituted aryl halides from 3,5-disubstituted boronic esters with $CuBr_2$.[52] A solvent-free method for the reaction with phenylboronic acid was developed (method C). Several aluminas were examined as milling auxiliaries. The following influence of the milling auxiliaries on the yield was observed γ-alumina (neutral) > γ-alumina (basic) > α-alumina (acidic). The yields were low for all milling auxiliaries ranging from 5–28% for α-alumina (acidic) and γ-alumina (neutral), respectively, for an equimolar use of phenylboronic acid and $CuBr_2$.

Conclusions

A fast and solvent-free method for the halogenation of aromatic compounds in a mixer ball mill was developed. It was shown that the halogenation with $KHSO_5$ (as oxone) and NaX can be performed with good results. The choice of the milling auxiliary is an important factor for the performance of the reaction and influences both conversion and selectivity. Results indicated that the oscillation frequency, milling time, and the number of milling balls are important parameters which directly affect the conversion. In contrast to the literature, addition of solvents to the reaction mixture (liquid-assisted grinding, LAG) has no significant effect on the experimental outcome for this specific ball milling reaction. The experiments referred to LAG showed no advantage compared with reactions in the complete absence of solvents.

The scope of application was shown with substrate screening and beside halogenations of aromatics, the potential for the addition to unsaturated alkenyl or alkynyl functions has been shown. In addition to the previous mentioned method, further procedures for the synthesis of halogenated aromatics were developed. The avoidance of organic solvents and the easy and fast procedure for the reaction demonstrated that this ball-milling method is an attractive alternative to other reaction protocols.

Experimental section

All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and were used as received. Reactions were accomplished in a MM400 mixer ball mill (Retsch GmbH) by using milling beakers (35 mL) made from yttrium-stabilized zirconia (YSZ). 10 × 10 mm milling balls were applied that consisted of magnesia-stabilized zirconia (MSZ). GC-FID measurements were carried out using a HP-7890A and GC-MS measurements were recorded on an Agilent Technologies GC6890N equipped with a MS detector 5973. Conditions for GC-FID: HP 5, 30 m × 0.32 mm × 0.25 mm; H_2 (12 psi), temperature 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. Conditions for GC-MS: HP 5, 30 m × 0.32 mm × 0.25 mm; He (12 psi), temperature program: 50 °C (hold for 3 min), 30 K min^{-1} up to 280 °C (hold for 8 min); injector temperature: 280 °C; detector: electron impact (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system at room temperature in chloroform-$[^2H]_3$ ($CDCl_3$). Spectral data are provided as ESI.†

Conversion and selectivity were determined by GC-FID measurements of the extracted products in relation to the substrate (external calibration). GC-MS was used for the determination of the *o*/*p*-ratio in the case of **5** and **9–12**.

General reaction procedure (method A)

The milling beakers were filled with milling balls and then milling auxiliary (4 g), oxone (0.75 mmol, 461 mg), NaX (X = Cl or Br; 1.5 mmol), and mesitylene (1.5 mmol, 180 mg) were added sequentially. Milling was performed at a specific oscillation frequency and milling time. After cooling to room temperature, the crude products were extracted on a frit with a thin silica layer by using methyl *tert*-butyl ether (MTBE, 3 × 15 mL). The solvent was evaporated in a vacuum to a volume of 2 mL; the reaction solutions were dried ($MgSO_4$) and analyzed by GC-FID and GC-MS. For NMR data the crude products were purified by column chromatography on silica gel with *n*-heptane–ethyl acetate as eluent.

General reaction procedure (method B)

The milling beakers were filled with milling balls and then the milling auxiliary (4 g), $CuBr_2$ (1.5 mmol, 335 mg), and mesitylene (**1**; 1.5 mmol, 180 mg) were added sequentially. Milling was performed at specific oscillation frequency and milling time. After cooling to room temperature, the crude products were extracted on a frit with a thin silica layer by using MTBE (3 × 15 mL). The solvent was evaporated in vacuum to a volume of

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2 mL; the reaction solutions were dried ($MgSO_4$) and analyzed by GC-FID and GC-MS.

General reaction procedure (method C)

The milling beakers were filled with milling balls and then milling auxiliary (4 g), $CuBr_2$ (1.5 mmol, 335 mg), and phenylboronic acid (1.5 mmol, 183 mg) were added sequentially. Milling was performed at specific oscillation frequency and milling time. After cooling to room temperature, the crude products were extracted on a frit with a thin silica layer by using MTBE (3 × 15 mL). The solvent was evaporated in vacuum to a volume of 2 mL; the reaction solutions were dried ($MgSO_4$) and analyzed by GC-FID and GC-MS.

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