Fast copper-, ligand- and solvent-free Sonogashira coupling in a ball mill†

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A solvent-free method for the Sonogashira coupling reaction was established under ball milling conditions without the use of copper or additional ligands. $Pd(OAc)_2$ or $Pd(PPh_3)_4$ in combination with 1,4-diazabicyclo[2.2.2]octane (DABCO) were chosen as catalysts and base, respectively. The reaction was investigated using a variety of aryl halides and acetylenes and with different amounts of the Pd-catalyst and DABCO. Results indicated that the employment of $Pd(OAc)_2$ in combination with SiO_2 as a grinding auxiliary preferentially induces the transformation of aryl iodides to the corresponding Sonogashira coupling products. In contrast, both the substitution of SiO_2 by Al_2O_3 or replacement of $Pd(OAc)_2$ with $Pd(PPh_3)_4$ enable the reaction of aryl bromides with phenylacetylenes. The selective reaction of bis-ethynyl compounds to double-coupled products and the influence of further common bases on the reaction was also scrutinized, confirming the high reactivity of DABCO as a base for solvent-free transformations.

Introduction

Green chemistry and sustainability are becoming more and more important in everyday organic synthesis.[1] Within this subject, the elimination of solvents is advantageous, since supply, purification, and disposal of these can be omitted. The accompanying reduction of solvent waste is the major motivation for the development of a broad variety of solvent-free synthetic reaction protocols.[2] While reactions are often carried out in a solvent-free manner using classical laboratory equipment or microwave heating, the application of ball milling is a rather small, but strongly emerging field of research. Ball milling was found to be an excellent method for some organic reactions: *e.g.* aldol-type reactions, oxidation or reduction.[2e,g,3] Besides these stoichiometric reactions, metal-catalyzed and organocatalytic protocols have also been proven to work.

Within these investigations, a fast, copper-, ligand-, and solvent-free protocol for the Sonogashira coupling of aryl halides with aryl- and alkylacetylenes using a commercial planetary ball mill is described. The Sonogashira reaction is an important C–C cross-coupling reaction between sp- (aryl-, alkenyl- and alkylacetylenes) and sp^2-hybridized carbon atoms (aryl halides or triflates) catalyzed by transition metals (Pd, Au, Cu, Ni).[4] The coupling products are widely used as starting materials for the synthesis of molecular organic systems (*e.g.* electro-optical switches, conducting polymers), pharmaceuticals or natural products.[4c–g] Additionally, this synthetic transformation is the tool of choice for the construction of carbon-rich materials (*e.g.* radialenes, graphenes) from simple building blocks.[5]

The reaction is normally carried out in organic solvents under inert conditions.[4a,b] Besides the countless numbers of publications dealing with the development of new catalytic systems, a few more recent articles report experimental protocols under solvent-free conditions.[6] Compared to other Pd-catalyzed cross-coupling reactions, like the Suzuki–Miyaura or Mizoroki–Heck reactions,[7,8] only one very recent implementation in a ball mill has been published to date for the Sonogashira reaction.[9] In that work, $Pd(PPh_3)_4$ + CuI was used as the catalytic system and the reactions were accomplished with distinctly longer reaction times than described in the current work, as will be reported below.

Results and discussion

Reactions were performed under aerobic conditions using air-stable Pd(II) acetate ($Pd(OAc)_2$) and 1,4-diazabicyclo[2.2.2]-octane (DABCO) as the catalyst and basic component responsible for the deprotonation of alkynes, respectively. DABCO has been found to be an excellent base for the Sonogashira reaction,[10] and it is a solid, which is a major advantage for an implementation of the reaction in a ball mill (compared to other commonly used amine bases like triethylamine or diisopropylamine). In addition, fused quartz sand (SiO_2) was used as an inert filling material for the milling beakers to enable work with small batch sizes. In contrast to the work of Mack and coworkers,[9] no copper co-catalyst has been employed and the reaction time was restricted to 20 min of ball milling.

Sonogashira reaction between aryl iodides and phenylacetylenes

Reaction screening of different aryl iodides (**1a–f**) and conjugated acetylene derivatives (**2a–d**; Table 1) was carried out using constant reaction parameters to investigate the influence of substituents on the acetylene derivatives and aryl halides on the course of reaction.

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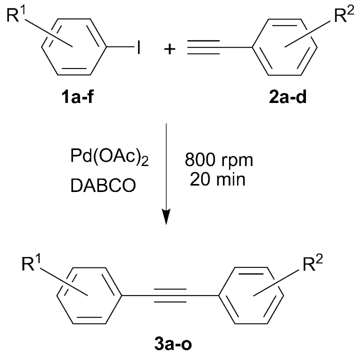
Table 1 Sonogashira reactions[a] of aryl iodides (**1**) with substituted phenylacetylenes (**2**)

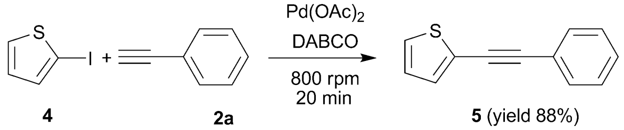


Product	Aryl iodide (R^1)	Acetylene (R^2)	X(**1**) [%][b]	S(**3**) [%][b]
3a	**1a** (H)	**2a** (H)	68	99
3a (ZrO_2)[c]	**1a** (H)	**2a**	80	99
3b	**1b** (*o*-Me)	**2a**	54	98
3c	**1c** (*p*-Me)	**2a**	47[d]	>99
3c (ZrO_2)[c]	**1c** (*p*-Me)	**2a**	74[c]	>99
3d	**1d** (*o*-MeO)	**2a**	51	98
3e	**1e** (*p*-MeO)	**2a**	58[d]	98
3f	**1f** (*p*-Ac)	**2a**	98	99
3g	**1a** (H)	**2b** (*p*-Me)	67	97
3g (ZrO_2)[c]	**1a** (H)	**2b**	83[c]	98
3h	**1c** (*p*-Me)	**2b**	55	98
3h (ZrO_2)[c]	**1c** (*p*-Me)	**2b**	77[c]	97
3j	**1e** (*p*-MeO)	**2b**	53	98
3k	**1f** (*p*-Ac)	**2b**	95	92
3l	**1e** (*p*-MeO)	**2c** (*p*-MeO)	61	>99
3m	**1f** (*p*-Ac)	**2c**	99	>99
3n	**1e** (*p*-MeO)	**2d** (*p*-F)	53	96
3o	**1f** (*p*-Ac)	**2d**	93	99

[a] Reaction conditions: 2 mmol aryl iodide (**1a–f**), 2.5 mmol acetylene compound (**2a–d**), 2.5 mmol DABCO, 5 mol% $Pd(OAc)_2$, 5 g SiO_2, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1**. [c] ZrO_2 milling beakers and balls were used instead of agate ones. [d] No change in conversion was observed when $PdCl_2$ was used instead of $Pd(OAc)_2$ in the same molar amount.

It was found that only aryl iodides **1a–f** showed noticeable conversions, whereas in the case of aryl bromides, none or only traces of the Sonogashira coupling product were found under the reaction conditions employed ($Pd(OAc)_2$ + DABCO). Similar behaviour was reported for a solvent-free microwave-assisted attempt using KF–alumina and Pd–CuI–PPh_3 as the base and catalyst system, respectively.[6a] No coupling product was found if either $Pd(OAc)_2$ or DABCO were absent, or if $Pd(OAc)_2$ was substituted by palladium powder. This suggests that either Pd(II) is the active species in the catalytic cycle, or that *in situ* reduction of Pd(II) to Pd(0) furnishes more active Pd species. The latter way may be supported by the fact that small amounts of 1,4-diarylbuta-1,3-diyne (homocoupling product of **2**) have been identified in the reaction mixture, whose concentration was independent of conversion. For some examples the application of $PdCl_2$, instead of the acetate, yielded products with similar yields and identical selectivities (**3c**,**e**; Table 1). Employment of $Pd(PPh_3)_4$ as a catalyst was investigated, enabling the transformation of aryl bromides (**1g–l**; see Tables 6 and 7 and the following text) as indicated recently by Mack and coworkers.[9]

Certain combinations of aryl halides and acetylenes tested (**1a–f** with **2a–d**) showed high selectivities for the Sonogashira coupling product related to the employed aryl halide (Table 1). Also the reproducibility was quite good; the deviation of the values of conversion and selectivity did not exceed 1–2%. Using agate, which is a relatively light-weight material, as the material for milling beakers and balls led to medium and high conversions of the aryl iodides. A more heavy-weight milling material, such as ZrO_2, resulted in significantly higher conversions for the same reaction conditions, caused by the higher energy input of the milling balls (**3a**,**c**,**g**,**h**; Table 1).[7d,11] Conversions were significantly higher for aryl iodides with electron-withdrawing substituents (*p*-iodoacetophenone, **1f**) and neutral substituents (iodobenzene **1a**) than for those with electron-donating substituents (*p*-iodotoluene and *p*-iodoanisole, **1c** and **1e**). The electron-poor 2-iodothiophene (**4**) showed high conversion and selectivity (98%) in the reaction with phenylacetylene (**2a**; Scheme 1) under the reaction conditions reported for examples listed in Table 1.



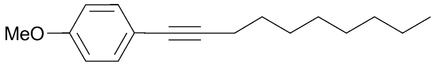
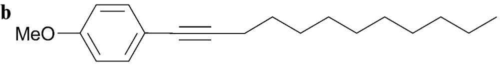
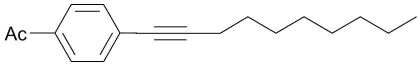
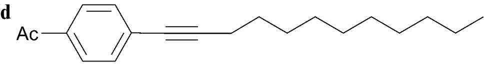
Scheme 1 Coupling reaction of 2-iodothiphene (**4**) and phenylacetylene (**2a**; for conditions see Table 1).

Sonogashira reaction between aryl iodides and alkynes

The variation of the acetylene seems to have little influence on the conversion of the aryl iodides. This suggests that the oxidative addition of the aryl iodide to the Pd-catalyst, which is faster for electron-poor aryl iodides with a weaker carbon–halogen bond than for electron-rich aryl iodides, could be the rate-determining step within the catalytic cycle of this solvent-free method. This dependency could be confirmed by employing decyne (**6a**) and dodecyne (**6b**) as the coupling component (Table 2). Sonogashira coupling of **6** with *p*-iodoanisole (**1e**) and **1f** furnished coupling products **7a–d** (Table 2) in similar yields as demonstrated in the corresponding reactions with phenylacetylenes **2a–d** (see Table 1). The treatment of alkynes **6** under the described experimental conditions did not afford any destructive bond breakage in the alkyl chain, which is due to the employment of mild reaction conditions. The application of milling materials with a higher density (steel, copper, tungsten carbide) resulted in destructive shortening of the alkyl substituents by the occurrence of stronger frictional forces and higher reaction temperatures.

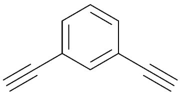
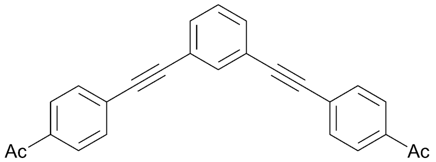
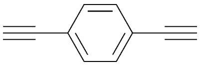
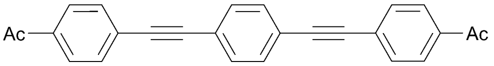
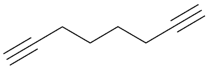
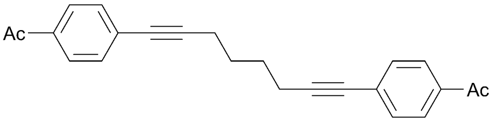
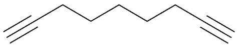
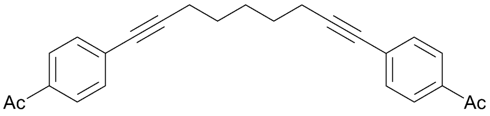
In addition to alkynes **6** bearing an alkyl chain as a substituent only, three acetylenes containing an OH-group at carbon atom 3 (**8a–c**; Scheme 2) were employed in the Sonogashira coupling with **1f**. After ball milling (agate) in the presence of 5 mol% $Pd(OAc)_2$ and 2.5 mmol of DABCO, the products (**9a–c**) were isolated in acceptable yields. The selectivities for the Sonogashira coupling products were as high as reported for the previous examples (> 98%; Tables 1 and 2). The successful coupling of **8a** is remarkable, since the 2-hydroxyprop-2-yl group is an excellent protecting group. In contrast to TMS or TIPS this end group is tolerable to fluoride ions and can easily be removed in the

Table 2 Sonogashira reactions[a] of aryl iodides (**1**) with alkynes (**6**)

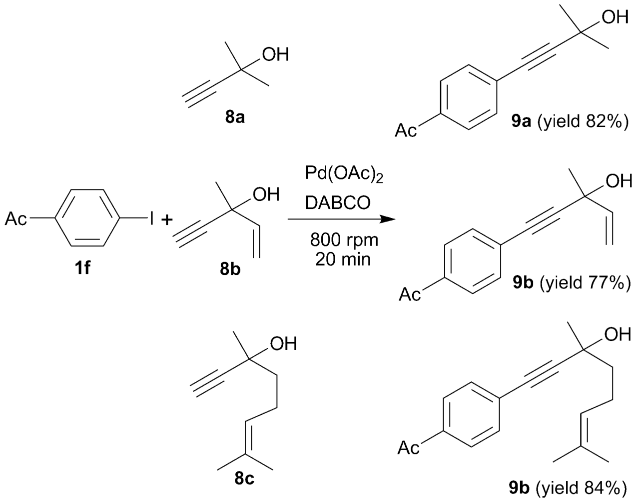
Product	Aryl iodide	Acetylene	$X(\mathbf{1})$ [%][b]	$S(\mathbf{7})$ [%][b]
7a 	*p*-Iodoanisole (**1e**)	Decyne (**6a**)	48	93
7b 	*p*-Iodoacetophenone (**1f**)	Decyne (**6a**)	92	93
7c 	*p*-Iodoanisole (**1e**)	Dodecyne (**6b**)	50	>99
7d 	*p*-Iodoacetophenone (**1f**)	Dodecyne (**6b**)	92	>99

[a] Reaction conditions: 2 mmol aryl iodide (**1e**,**f**), 2.5 mmol alkyne (**6**), 2.5 mmol DABCO, 5 mol% Pd(OAc)$_2$, 5 g SiO$_2$, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1**.

Table 3 Double Sonogashira reactions[a] of *p*-iodoacetophenone (**1f**) with bis-ethynyl compounds (**10**)

Bis-ethynyl compound	Sonogashira coupling product	Yield [%][b]
10a 	**11a** 	63
10b 	**11b** 	69
10c 	**11c** 	75
10d 	**11d** 	74

[a] Reaction conditions: 2 mmol *p*-iodoacetophenone (**1f**), 1 mmol bis-ethynyl compound (**10a–d**), 2.5 mmol DABCO, 5 mol% Pd(OAc)$_2$, 5 g SiO$_2$, 800 rpm, 20 min, ZrO$_2$ beaker (45 ml), 6 × ZrO$_2$ milling balls (15 mm). [b] Determined with ^{1}H-NMR measurements of extracted products in relation to **1f**.

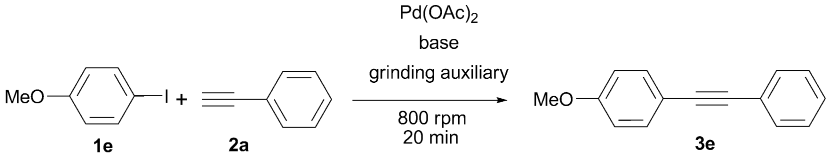


Scheme 2 Reaction of *p*-iodoacetophenone (**1f**) and 3-hydroxy-acetylenes (**8**; for conditions see Table 1).

presence of alkali hydroxides (retro-Favorski elimination). In the case of **8b**, the possible competing Mizoroki–Heck coupling reaction on the terminal double bond did not occur.

Sonogashira reaction with bis-ethynyl compounds

Surprisingly, only di-coupled products could be isolated when **1f** was applied in the Sonogashira reaction with bis-ethynyl compounds (**10**; Table 3). ZrO$_2$ beakers and milling balls were used, instead of agate ones, to achieve satisfactory results. Furthermore, the conversions of *p*-iodoacetophenone **1f** were limited by side reactions of the bis-ethynyl compounds, assumed to be oligomerization reactions. The products were not suitable for GC-FID analysis so ^{1}H-NMR analysis of the crude reaction mixture was used to determine the conversion and selectivity. Since ^{1}H-NMR spectra revealed a highly symmetrical peak distribution and there were no signals for acetylenic protons, it was clear that mono-coupled products were absent. The ^{1}H-NMR spectra of the crude and isolated products revealed no differences, apart from the absence of signals for non-converted **1f**.



Scheme 3 Sonogashira model reaction of *p*-iodoanisole (**1e**) with phenylacetylene (**2a**).

Influence of catalyst, base and grinding auxiliary

The reaction between *p*-iodoanisole (**1e**) and phenylacetylene (**2a**; Scheme 3) was taken as a model reaction for investigation of the influence of the amounts of catalyst $Pd(OAc)_2$ and DABCO on the conversion of **1e**. This reaction shows medium conversion under screening reaction conditions (Table 1), assuming that influences of the above-mentioned variations should be easily recognizable by changes in conversion.

The amount of $Pd(OAc)_2$ was varied in the range of 1–5 mol% related to *p*-iodoanisole (**1e**), whilst keeping other reaction parameters constant (Fig. 1). A nearly linear dependence of the conversion and the amount of $Pd(OAc)_2$ can be observed, while the selectivity is unaffected. The turnover-frequencies (TOF) for the coupling reactions of aryl iodides **1a–f** with phenylacetylene listed in Table 1 range from 28 to 59 h^{-1}. Compared to previous studies of solvent-free Sonogashira reactions in ball mills (TOF: ~2 h^{-1})[9] the herein-reported reaction conditions are advantageous due to short reaction times. Decreasing the Pd-concentration to 1 mol% (Fig. 1) resulted in an increase of TOF to 110 h^{-1}, which is remarkable considering the fact that the reaction has a strongly heterogeneous nature.

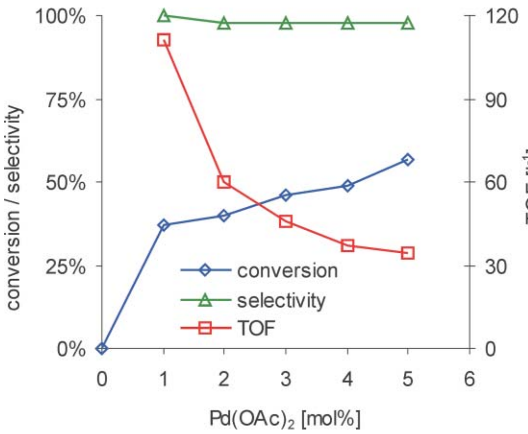


Fig. 1 Conversion of *p*-iodoanisole (**1e**; 2 mmol) in the coupling reaction with phenylacetylene (**2a**; 2.5 mmol) for different amounts of $Pd(OAc)_2$ (reaction conditions: 2.5 mmol DABCO, 5 g SiO_2; ball milling: agate beaker (45 ml), 6 × agate balls (15 mm) per beaker, 800 rpm, 20 min).

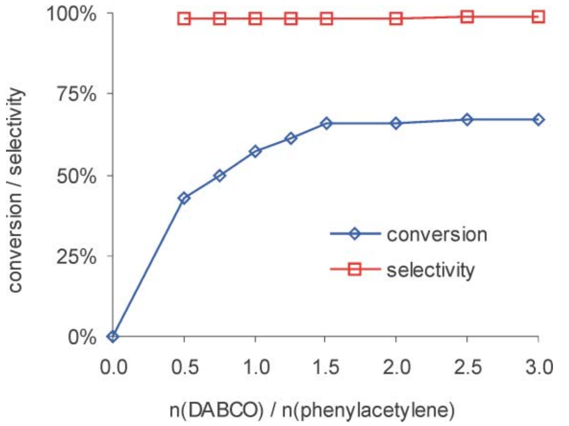


Fig. 2 Conversion of *p*-iodoanisole (**1e**; 2 mmol) in the coupling reaction with phenylacetylene (**2a**; 2.5 mmol) for different amounts of DABCO (reaction conditions: 5 mol% $Pd(OAc)_2$, 5 g SiO_2; ball milling: agate beaker (45 ml), 6 × agate balls (15 mm) per beaker, 800 rpm, 20 min).

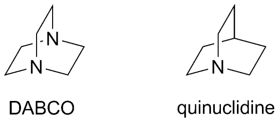
Next, the amount of DABCO was varied between 0.5–3 molar equivalents (1.25–7.5 mmol) relative to phenylacetylene (**2a**; Fig. 2). The relationship to **2a** was chosen as the determinant parameter, because the base is responsible for abstraction of the propargylic hydrogen from **2**, **6**, **8** or **10** (Schemes 1–3, Tables 1–3). Similar to the effect described in Fig. 1, a nearly linear dependence of conversion and amount of DABCO is apparent, though the selectivities remain high. A 1.5-fold molar excess (3.75 mmol) of DABCO seems to be an upper limit for this reaction, since no further increase of conversion for higher amounts of DABCO were noticed.

Compared to other common amine bases like triethylamine or diisopropylamine and inorganic bases, DABCO afforded the highest conversions for the model reaction of **1e** with **2a** (Table 4), which is in fact proof that DABCO is the best choice for the Sonogashira coupling reaction under solvent-free conditions.[10] Only quinuclidine (1-azabicyclo[2.2.2]octane) showed slightly higher conversion, which is a stronger base than DABCO (pK_a 11.0 compared to 8.8 and 3.0 for DABCO) and has a similar chemical structure (Scheme 4). But compared to DABCO, quinuclidine is much more expensive and toxic, therefore DABCO is more applicable, particularly with regard

Table 4 Sonogashira reaction[a] in the presence of different bases for the reaction of *p*-iodoanisole (**1e**) and phenylacetylene (**2a**)

Base	*X*(**1e**) [%][b]	*S*(**3e**) [%][b]
DABCO	66	98
Triethylamine	27	99
Diisopropylamine	12	99
Quinuclidine	73	97
K_2CO_3	13	99
KOH	28	99
TBAB	—	—
Triphenylamine	—	—
Tribenzylamine	—	—
4-Phenylmorpholine	—	—

[a] Reaction conditions: 2 mmol *p*-iodoanisole (**1e**), 2.5 mmol phenylacetylene (**2a**), 3.75 mmol base, 5 mol% $Pd(OAc)_2$, 5 g SiO_2, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1e**.



Scheme 4 Structures of 1,4-diazabicyclo[2.2.2]octane (DABCO) and of 1-azabicyclo[2.2.2]octane (quinuclidine).

to the principles of green chemistry (avoiding toxicity)[1a,b,d,11] and green engineering (avoiding high costs).[1c,11]

Furthermore, sterically hindered bases like triphenylamine or tribenzylamine did not initiate any reaction. The inactivity of these bases may be an indication that the base is intermittently coordinated to the catalyst. Considering the fact that *o*- and *p*-iodotoluene (**1b**,**c**) resulted in similar product yields upon coupling with **2a** (Table 1), the independence of the experimental outcomes on the variation of substituents at **2a** supports the fact that the oxidative addition of the aryl iodide is the rate-determining step. This step is obviously independent from the nature of the base, allowing the conclusion that the latter is responsible for the activation of the acetylene coupling partner. However, an acetylene–DABCO adduct could not be identified in the reaction mixture, but it could be concluded that DABCO forms an addition product (probably DABCO·HI) at the end of the reaction. The low conversions resulting from the employment of bases other than DABCO (Table 4) emphasizes its special role in Sonogashira reactions. In the case of other Pd-mediated cross-coupling reactions, the main function of the base is the interception of the HI molecules. In contrast, in the case of the Sonogashira coupling a Lewis or Brønsted basicity is essential for the abstraction of the acidic proton in **2a**.

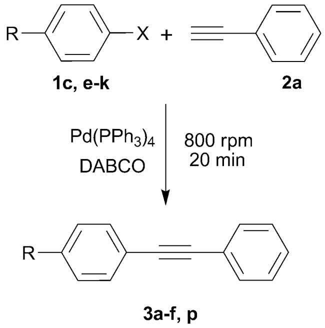
Different grinding auxiliaries were tested for their influence on the reaction of *p*-iodoanisole (**1e**) and phenylacetylene (**2a**; Table 5). The use of CeO_2 and TiO_2 led to the same conversions as for SiO_2, whereas both neutral (γ-modification) and basic alumina (α-Al_2O_3) significantly increased the conversion. The application of silica gel and KF–Al_2O_3 (32 wt% KF) revealed an opposite trend concerning the transformation to product **3e**. This negative effect is in contrast to the results reported for the solvent-free Suzuki–Miyaura reaction performed using KF–alumina as a base and under ball milling conditions.[7c–e]

Table 5 Sonogashira reaction[a] between *p*-iodoanisole (**1e**) and phenylacetylene (**2a**) in the presence of different grinding auxiliaries

Base	*X*(**1e**) [%][b]	*S*(**3e**) [%][b]
SiO_2 (fused quartz sand)	58	99
SiO_2 (silica gel)	25	99
CeO_2	58	98
TiO_2	59	99
γ-Al_2O_3 (neutral)	83	99
α-Al_2O_3 (basic)	85	99
KF–Al_2O_3 (32 wt% KF)	45	99

[a] Reaction conditions: 2 mmol *p*-iodoanisole (**1e**), 2.5 mmol phenylacetylene (**2a**), 2.5 mmol DABCO, 5 mol% $Pd(OAc)_2$, 5 g grinding auxiliary, 800 rpm, 20 min, agate beaker (45 ml), 6 × agate milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1e**.

Table 6 Screening reactions[a] of aryl halides (**1**) and phenylacetylene (**2a**) using $Pd(PPh_3)_4$ as catalyst



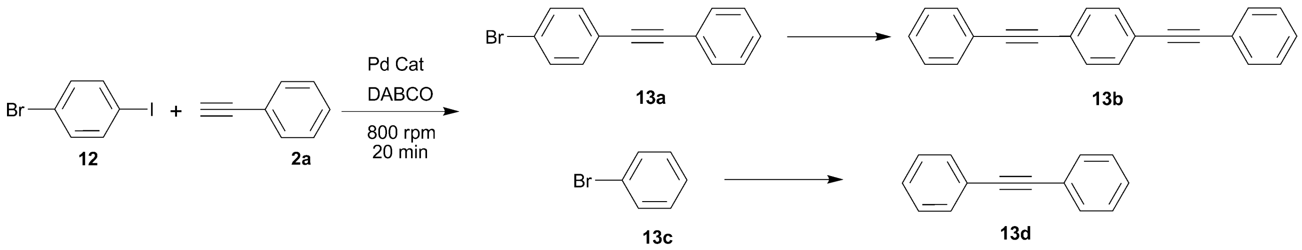
			Agate:		ZrO_2:	
Product	Aryl halide (R)	Y	*X*(**1**)[b] [%]	*S*(**3**)[b]	*X*(**1**)[b] [%]	*S*(**3**)[b]
3c	**1c** (Me)	I	24	99	99	98
3e	**1e** (MeO)	I	26	98	99	98
3f	**1f** (Ac)	I	35	99	99	99
3a	**1g** (H)	Br	4	98	71	98
3c[c]	**1h** (Me)	Br	1	98	61	99
3e	**1i** (MeO)	Br	3	99	52	98
3f	**1j** (Ac)	Br	34	99	97	98
3p	**1k** (CF_3)	Br	26	98	99	97
3q	**1l** (NO_2)	Br	94 (32)[c]	99	99	98

[a] Reaction conditions: 2 mmol aryl halide (**1c**,**e–l**), 2.5 mmol phenylacetylene (**2a**), 2.5 mmol DABCO, 5 mol% $Pd(PPh_3)_4$, 5 g α-Al_2O_3 (basic), 800 rpm, 20 min, beaker (45 ml), 6 × milling balls (15 mm). [b] Determined with GC-FID measurements of extracted products in relation to **1**. [c] $Pd(OAc)_2$ was used instead of $Pd(PPh_3)_4$.

Influence of copper, Pd(0) and grinding auxiliary

A very interesting result was obtained when the Sonogashira reaction between **1e** and **2a** was performed in the presence of 5 mol% CuI in addition to the $Pd(OAc)_2$. The conversion of **1e** decreased by 10%, caused by the increasing conversion of **2a** to the homo-coupling product 1,4-diphenylbuta-1,3-diyne (Glaser reaction). Obviously, CuI has no positive influence on the Sonogashira coupling mechanism itself under solvent-free reaction conditions. It is also worth mentioning that only traces of the coupling product **3e** were achieved if 20 mol% of PPh_3 was added to the reaction mixture (5 mol% $Pd(OAc)_2$, 2.5 mmol DABCO). However, only the respective phosphine oxide could be detected after ball milling. Apparently, *in situ* formation of $Pd(PPh_3)_4$ had not occurred. In contrast, the application of 5 mol% $Pd(PPh_3)_4$ (also containing 20 mol% of PPh_3) instead of $Pd(OAc)_2$ resulted in the formation of the Sonogashira coupling products, as indicated in Table 6. Bromides (**1g–l**) were also suitable for coupling reactions when using this Pd-complex in combination with basic α-Al_2O_3 as a grinding auxiliary, as demonstrated by Mack and co-workers, before performing the reaction in a 8000M SpexCertiprep (vibration ball mill).[9] The herein-presented reaction is also advantageous with respect to the fact that no additional copper was required, and milling balls or containers made of copper were not needed. Remarkably *p*-nitro-bromobenzene (**1l**) showed the highest conversion under the given conditions and was also suitable for coupling with $Pd(OAc)_2$, but with lower conversion than for $Pd(PPh_3)_4$.

Table 7 Reaction[a] of *p*-iodobromobenzene (**12**) and phenylacetylene (**2a**)



Pd-source	Milling material	*X*(**12**) [%][b]	*S*(**13a**) [%][b]	*S*(**13b**) [%][b]	*S*(**13c**) [%][b]	*S*(**13d**) [%][b]
$Pd(OAc)_2$	Agate	87	81	19	0	0
$Pd(PPh_3)_4$	Agate	39	100	0	0	0
$Pd(OAc)_2$	ZrO_2	91	78	20	1	1
$Pd(PPh_3)_4$	ZrO_2	99	94	2	1	3

[a] Reaction conditions: 2 mmol *p*-iodobromobenzene (**12**), 2.5 mmol phenylacetylene (**2a**), 2.5 mmol DABCO, 5 mol% Pd, 5 g Al_2O_3 (basic), 800 rpm, 20 min, beaker (45 ml), 6 × milling balls (15 mm). [b] Determined by GC-FID measurements of extracted products in relation to **12**.

The application of milling tools made of copper or tungsten carbide for Sonogashira reactions, as used in the literature, would certainly enhance the energy required, due to the higher kinetic energy of the milling balls. Indeed, the presence of ZrO_2 or agate is preferable, due to lower thermal stress which could cause side reactions especially at longer reaction times, *e.g.* dehalogenation of aryl halides. The data shown in Table 6 reveals the dependence of conversion on the density (weight) of the milling material. ZrO_2 milling balls again afforded higher conversions, whereas the selectivity remained unchanged compared to the employment of agate.

If the results for the aryl iodides with agate milling material are compared with those of the screening reactions (Table 1), it can be seen that $Pd(OAc)_2$ is more effective for the coupling of iodo-aromatics *via* ball milling than $Pd(PPh_3)_4$; not only with respect to the reaction itself but also regarding economic (price) and environmental issues (no bulky ligands).[1a–d,11]

Using this approach to perform an asymmetric coupling of *p*-iodobromobenzene (**12**) with phenylacetylene (**2a**; Table 7), the selectivity for the product **13a** was significantly higher for $Pd(PPh_3)_4$, but the conversion of **12** was distinctly lower than with the application of $Pd(OAc)_2$ as catalyst with agate milling equipment. Surprisingly, the double-coupled product 1,4-bis(phenylethynyl)benzene (**13b**) is only formed with the use of $Pd(OAc)_2$ although $Pd(PPh_3)_4$ should be more reactive for the conversions of aryl bromides, as shown for the conversion of *p*-nitro-bromobenzene (**3q**, Table 6). As indicated in Tables 1 and 6, switching to higher-weight milling equipment (ZrO_2) afforded higher conversions of **12**,[7d,12] accompanied by a decreased selectivity for **13a**. Instead, noticeable amounts of de-iodinated starting material (**13c**) and the corresponding Sonogashira coupling product of **13c** (**13d**) were found.

Conclusions

An improved copper-, ligand-, and solvent-free experimental protocol for the Sonogashira coupling of aryl halides with aryl- and alkyl-substituted acetylenes in a planetary ball mill was developed. The employment of air-stable $Pd(OAc)_2$in combination with 1,4-diazabicyclo[2.2.2]octane as a catalyst and base, respectively, allowed for the chemoselective trasformation of aryl iodides. All coupling reactions showed high selectivities according to the desired Sonogashira products. Conversions of aryl iodides were controllable *via* variation of either the amount of Pd(II)-acetate or DABCO and showed good reproducibility. Furthermore, DABCO showed higher efficiency than other commonly used bases. Modification of the standard reaction procedure by three different methodologies also allowed the transformation of aryl bromides: i) substitution of $Pd(OAc)_2$ by $Pd(PPh_3)_4$, ii) replacement of agate milling beakers and balls by higher-weight equipment made of ZrO_2 or/and iii) employment of alumina as filling material instead of fused quartz sand.

The avoidance of organic solvents and the easy, fast and energy-saving accomplishment of the reaction makes this method a real alternative to conventional reaction protocols, especially in regard to the concept of green chemistry. This was proven by the employment of unusual, but synthetically important, substrates like 3-hydroxyalkynes or bis-ethynyl compounds. The presence of terminal carbon–carbon triple and double bonds in one molecule chemoselectively afforded the Sonogashira coupling product, instead of the Mizoroki–Heck coupling product.

Experimental

General

All chemicals were purchased from Sigma Aldrich or Alfa Aesar and were used as received. Reactions were accomplished in a Fritsch "Pulverisette 7 classic line" (Fritsch GmbH, Idar-Oberstein, Germany) planetary ball mill using 45 ml grinding beakers (agate, ZrO_2) and milling balls (6 × 15 mm; agate or ZrO_2). All reaction vessels were cleaned with *aqua regia* prior to use to avoid any contamination or memory effects.

GC-FID measurements were performed on a 6890-GC and GC-MSD measurements were accomplished with a 6890N-GC-MS, both from Agilent Technologies. Measurement conditions GC-FID: HP 5, 30 m × 0.32 mm × 0.25 µm, H_2 10 psi, program: 70 °C (hold for 3 min), 15 K min^{-1} up to 280 °C (hold for

10 min), injector temperature: 280 °C, detector temperature: 300 °C. Measurement conditions GC-MSD: HP 5, 30 m × 0.32 mm × 0.25 µm, He 10 psi, program: 70 °C (hold for 3 min), 15 K min^{-1} up to 280 °C (hold for 7 min), injector temperature: 280 °C, detector: EI (70 eV). NMR spectra were recorded with a Bruker Avance 200 MHz system at room temperature in deuterochloroform ($CDCl_3$) as a solvent, using tetramethylsilane as internal standard.

All product yields reported herein are calculated from GC-data 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.

Typical reaction procedure for the Sonogashira coupling

The grinding beakers (45 ml; agate or ZrO_2) were equipped with 6 milling balls of the same material (d = 15 mm). Afterwards SiO_2 (= fused quartz sand; 5 g), the acetylene compound (2.5 mmol), 1,4-diazabicyclo[2.2.2]octane (= DABCO; 2.5 mmol, 280 mg), the aryl halide (2 mmol) and $Pd(OAc)_2$ (5 mol%, 25 mg) were added in the given order. Milling was carried out at 800 rpm for 20 min. After cooling of the grinding beakers to room temperature (10 min), the crude products were extracted on a frit with a thin silica layer using chloroform (3 × 10 ml). The solvent was evaporated in vacuum, the crude products were dried, re-dissolved in 1.5 ml of chloroform and analyzed by GC-FID and GC-MS.

Analytical samples for NMR investigations were isolated by column chromatography using a n-hexane–toluene mixture (1 : 1) as the eluent. Products were identified according to the literature data. For the analytical details of the isolated products, see the ESI.†

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