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LETTER

Suzuki cross-couplings of (hetero)aryl chlorides in the solid-state

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The ultrasound-assisted cross-linking of chitosan with hexamethylene diisocyanate with the simultaneous incorporation of $Pd(OAc)_2$ resulted in a catalyst which is suitable for the solid-state Suzuki cross-coupling of poorly reactive (hetero)aryl chlorides with phenylboronic acid. Reactions were carried out solvent-free in a planetary ball mill allowing the catalyst to be recycled several times.

Introduction

Reactions in ball mills have attracted serious attention in organic synthesis circles during the last decade.[1,2] This method allows reactions to be carried out in the solid state and possibly reduces the solvent amount[3–6] which makes it attractive for other application fields as well.[7] Pd-catalyzed cross-couplings *via* the Suzuki-,[8–10] Heck-,[11] or Sonogashira-type reactions,[12,13] as well as Cu-catalyzed click reactions (CuAAC),[14] and the homo-coupling of terminal alkynes,[15] make use of metal salts or metal complexes which are difficult to separate from the solid reaction mixtures afterwards.

Additionally, the application of aryl chlorides instead of bromides or iodides as cross-coupling partners has only so far afforded zero or minor yields. An example of this is a Suzuki reaction in the presence of KF–Al_2O_3 using a planetary ball mill.[10] This inorganic solid material was used for the *in situ* generation of the base needed for the reaction and $Pd(OAc)_2$ was used as the catalyst.[10,16] The synthetic procedure was very efficient with aryl iodides and bromides but failed in the case of the poorly reactive aryl chlorides.[10] Similar observations were reported when a more reactive reagent system $Pd(PPh_3)_4$ and K_2CO_3 (catalyst and base, respectively) was used.[8] All the results reported in the literature gave no reaction or very low yields with these substrates.[8–10,16]

With the aim of finding conditions which may widen the application of this method, we realized that the physicochemical properties of the catalyst could play a fundamental role in the solid state. Our candidate for Pd-catalyzed reactions is a cross-linked chitosan/Pd(II) catalyst that has already been tested as a heterogeneous catalyst in microwave-assisted reactions.[17] Although chitosan (CS) modification requires some tricky procedures,[18] this material is cheap, stable and biodegradable, making it suitable for Pd-catalyzed Suzuki reactions.[19–21] Despite the fact that several metal-catalyzed reaction protocols for ball milling synthesis have been developed, only in one case the possibility of catalyst recycling was included.[22] These authors described the synthesis of oximes with Bi_2O_3 as a catalyst by grounding in a mortar the reacting mixture with a pestle.

Experimental

Materials

Commercially available reagents and solvents were used without further purification. Medium molecular weight CS was purchased from Sigma Aldrich.

Catalyst preparation

CS (5.0 g) was dissolved in 0.1 N HCl (350 mL) in a 1 L round-bottom cylindrical flask at 60 °C under sonication with a titanium horn (19.8 kHz, 70 W) for less than 1 h. A solution of $Pd(OAc)_2$ (2.23 mmol, 500 mg) in 0.1 N HCl (50 mL) was added after 5 min at 50 °C while the sonication was run at reduced power (50 W). Hexamethylene diisocyanate (HMDI; 37.0 mmol, 6 mL) was added dropwise at 50 °C and was sonicated for 10 min at 60 W at which point complete gelation occurred. The gel was heated for 2 h at 50 °C and a yellowish solid material formed which was then transferred to a mortar and triturated with a 0.5 N NaOH solution until pH 10 was reached. The solid residue was filtered, washed with water, acetone and diethylether (each solvent 150 mL), and dried overnight under vacuum. This procedure afforded 8.23 g of the Pd(II)-loaded urethane/urea-bridged CS derivative ≙ catalyst HMDI-CS/Pd.

Catalyst characterization

FT-IR spectra were recorded on a Perkin-Elmer model 2000 spectrometer in the 650–4000 cm^{-1} range at a resolution of 2 cm^{-1} using the ATR-method. TG-curves were recorded on the TA Instrument TGA 2050 (Shimadzu). The analyses were carried out with a constant heating rate of 10 K min^{-1}

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from 50 to 700 °C under atmospheric conditions. The metal content of the catalysts was determined by ICP-MS on a Quadrupole-ICP-MS X Series II (Thermo Fisher Scientific) after the solid catalyst samples were digested in HNO_3 and *aqua regia*. The oxidation state of the adsorbed palladium was determined by measuring the binding energy (Eb) of the Pd 3d-core level by X-ray photoelectron spectroscopy (XPS) with a Quantum 2000 (PHI Co., Chanhassen, MN, USA) using a focused monochromatic Al K_α-source (1486.7 eV). Spectra were normalized to the C 1s peak.

Catalytic testing

Ball milling was conducted using a planetary ball mill (PM100; Retsch GmbH) equipped with a single milling beaker (stainless steel, 125 mL). For the experiments 15 × 10 mm milling balls of the same material were applied. The prepared catalyst (1 g), aryl halide (0.25 mmol), phenyl-boronic acid (0.27 mmol, 33 mg), and K_2CO_3 (0.5 mmol, 69 mg) were added to the milling balls one after the other. The reaction mixture was subsequently milled at 600 min^{-1} for either 90 or 120 min. Every 30 min the direction of rotation was inverted. The reaction products were dissolved in EtOAc (3 × 15 mL). The supported catalyst, insoluble in the organic solvent, was separated by filtration and was washed with acetone (3 × 15 mL), dried under vacuum and reused in a new reaction. The products were analyzed by GC-MS. The yields determined by GC-MS were comparable with the yields of the isolated products. Purification was performed *via* flash-chromatography on a silica column (CombyFlash Rf® Teledyne ISCO) using hexane–ethyl acetate mixtures as eluents. Conversions and yields were initially determined by GC-MS and confirmed by chromatographic separation (+2%).

Product analysis

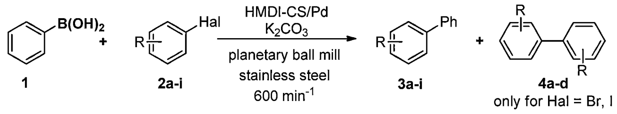
GC-MS measurements were performed on an Agilent Technologies 6850 Network GC System with a 5973 Network Mass Selective Detector using a capillary column (length 30 m, i.d. 0.25 mm, film thickness 0.25 μm). GC conditions were as follows: injection split 1 : 20, injector temperature 250 °C, detector temperature 280 °C. The temperature program ran from 50 °C (3 min) to 80 °C at 3 °C min^{-1} and 80 °C to 300 °C at 10 °C min^{-1} (30 min). Helium was used at 25 kPa as the carrier gas.

Results and discussion

The ultrasound-assisted synthesis of the CS catalyst HMDI-CS/Pd resulted in a solid material which was characterized using FT-IR, XPS-spectroscopy, and thermal analysis (TGA, DTA). The metal content of the catalysts, prior to and after their application in Suzuki cross-couplings (Scheme 1), was determined with ICP-MS analysis. The addition of HMDI to the CS solution containing $Pd(OAc)_2$ resulted in the cross-linking of the polymer chains, a regular distribution of the metal and a considerable catalytic activity.[17]

Structural properties of the catalyst

To compare the properties of CS and the catalyst, FT-IR and thermal analysis of both materials have been carried out. Fig. 1 shows the overlay of the infrared spectra for pure CS and HMDI-CS/Pd. Pure CS shows a broad band at around 3320 cm^{-1} which is caused by OH-, NH_2- as well as CONH-vibrations (amide = non-deacetylated glucosamine groups).[19] After cross-linking with HMDI and *in situ* deposition of Pd, the band appears less broad. This indicates that the diisocyanate reacted with the hydroxyl and amino groups of the polymer. The resulting urea- and urethane-linkages also contain the CONH-function, which are responsible for this band. It should be mentioned that isocyanate-groups do not necessarily react with the polymer, they can also be hydrolyzed by the solvent which would result in new amine-functions. Another indicator for successful cross-linking is the band at 2930 cm^{-1} which refers to CH_2-vibrations. After polymer cross-linking, there is a higher number of CH_2-groups in the polymer, resulting in a stronger and sharper absorption band in the IR-spectrum. New bands appear at approximately 1600 and 1260 cm^{-1} which are assigned to the urea- and urethane-functions (C=O– and C–N-vibrations) in the polymer. The absorption at 1026 cm^{-1} indicates C–O–C vibrations which are typical for carbohydrates. This band slightly decreases in intensity. This could be caused by the chain-cleavage that may occur in the acidic solvent that was used during the cross-linking under power ultrasound.



Scheme 1 Suzuki cross-coupling reaction of aryl halides in a planetary ball mill (*cf.* Table 1).

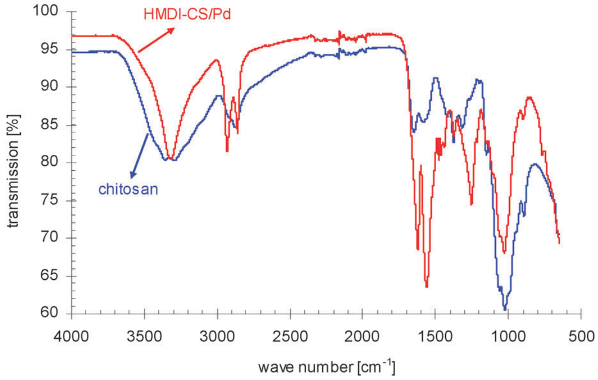


Fig. 1 FTIR-spectra of pure CS and cross-linked catalyst HMDI-CS/Pd.

Further evidence of successful cross-linking with HMDI can be found in the TGA-analysis (Fig. 2). At the beginning of the measurement, a mass loss of approximately 10% was observed. This is assigned to absorbed water. It is important to note that the two curves show different slopes. Pure CS loses the absorbed water faster than the cross-linked polymer. In fact, the modified polymer has a network-like structure which is responsible for the slower release of water. Moreover, the cross-linking caused an increased amount of polar groups in the polymer, which can absorb more water and bind it *via* hydrogen bonds. The TGA-curve shows that the cross-linked polymer indeed exhibits a greater (but slower) weight loss.

The metal loading of the catalysts was checked by ICP-analyses. Due to impurities, non-modified CS exhibited a Pd-loading of

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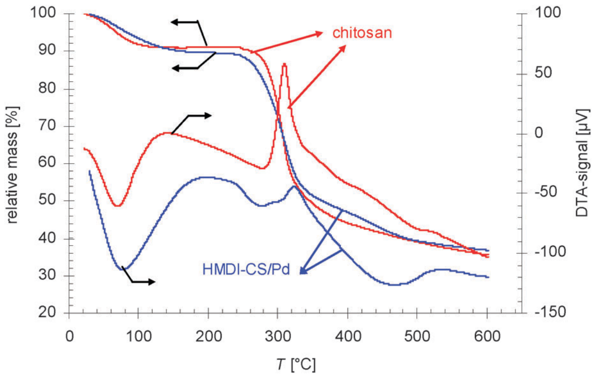


Fig. 2 TGA- and DTA-curves for pure CS and HMDI cross-linked catalyst HMDI CS/Pd; black arrows indicate type of signal: relative mass or DTA.

$<9.4 \times 10^{-4}$ wt%, which is a number of magnitudes lower than found in the prepared catalyst.

Analysis of the Pd-loaded polymer directly after catalyst preparation and after the fourth reaction cycle (*cf.* Table 1) resulted in Pd-contents of 2.3 ± 0.3 and 2.1 ± 0.3 wt%, respectively. Thus, the catalyst system proves its stability with respect to metal leaching. However, catalyst recycling entailed an average weight loss of 3.4% relative to the initial catalyst mass. XPS-analysis of the oxidation state resulted in a similar E_b, for the Pd $3d_{5/2}$ core level, to the value reported in the literature.[17]

Catalytic testing

Catalytic tests were carried out by comminuting phenylboronic acid (**1**) and several aryl halides (**2a–i**) together with the catalyst and K_2CO_3[8] which was used as the base in a stainless steel milling beaker mounted on a planetary ball mill. The reaction with unloaded CS samples led to no conversion at all.[17,19] Solid-state reactions in the presence of HMDI cross-linked CS/Pd(II) afforded the cross-coupled products (**3a–i**) and biphenyls which originated from homo-coupling of the aryl halide (**4a–d**, Ullmann reaction; Scheme 1).[23] The amount of biphenyl (**3e**) from the homo-coupling of **1** was very low (<1%) for most of the reactions. The amount of homo-coupled products **4a–d** is considerably higher for the present CS-based catalyst system (Table 1) than for other Suzuki cross-coupling procedures in ball mills using $Pd(OAc)_2$[9,10] or $Pd(PPh_3)_4$.[8] As expected, the reactions of aryl iodides (**2a**,**b**) and aryl bromides (**2c**,**d**) lead to higher reaction rates, resulting in quantitative conversion after 90 min, whereas the chlorides afforded longer reaction times (120 min). The increased formation of homo-coupling products **4** was evident in recycling experiments. Thus, with *p*-iodoanisole (**2a**), the yield of **4a** was 35% in the second run, compared to 25% after the first. *m*-Iodophenol (**2b**), however, exclusively gave the cross-coupling product **3b**. Similarly to **2a**, *p*-bromoacetophenone (**2c**) and *p*-bromoanisole (**2d**) gave 84% and 72% yields of cross-coupling adducts (**3c** and **3d** respectively) and 15%, 22% of homo-coupling products (**4c**, **4d** respectively) (Table 1). In a trial with **2c**, no reaction occurred in the absence of **1** and only a 5% yield of **4c** was isolated. The higher reactivity and selectivity of aryl bromides towards Suzuki cross-coupling, when compared to iodides, have also been reported by other authors.[8–10] The formation of the dehalogenated aromatics was observed among the side reactions.

Table 1 Suzuki reaction of aryl halides (**2a–i**; Scheme 1) with phenylboronic acid (**1**) in a ball mill using HMDI-CS/Pd as catalyst[a]

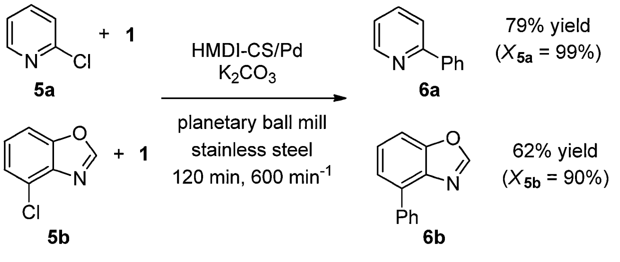
Entries 2a–i	Hal	R	Time/min	X_2 (%)	Yield (%)	Homo-coupling (%)
a	I	*p*-MeO	90	>99	74	25
a[b]			90	>99	64	35
b	I	*m*-OH	90	90	90	
c	Br	*p*-Ac	90	>99	84	15
d	Br	*p*-MeO	90	>99	72	22
e	Cl	H	120	>99	99	
f	Cl	*p*-NO_2	120	>99	84	
f[b]			120	95	75	
f[c]			120	82	64	
f[d]			120	65	50	
g	Cl	*p*-Ac	120	29	29	
h	Cl	*m*-Ac	120	40	36	
i	Cl	*o*-Ac	120	78	39	

X_2 = conversion of **2**.[a] Reaction conditions: 1 g catalyst, 0.27 mmol **1**, 0.25 mmol **2**, 0.5 mmol K_2CO_3; planetary ball mill, milling beaker (stainless steel, 125 mL), milling balls (stainless steel, 15 × 10 mm); 600 min^{-1}. Distribution from GC-MS analysis as a mean of three runs. [b] Catalyst application: 2nd run. [c] Catalyst application: 3rd run. [d] Catalyst application: 4th run.

Besides the reactions with aryl iodides and bromides, noteworthy results were also obtained with the less reactive aryl chlorides **2e–i** (Table 1). To the best of our knowledge this is the first report in which aryl chlorides have been cross-coupled with **1** in a ball mill affording >10% yield.

Reports by Schneider and Ondruschka[10] as well as Klingensmith and Leadbeater[9] reported yields of only 6% and 2% for the cross-coupling of chlorobenzene (**2e**) and *p*-chlorotoluene with **1**, respectively. Moreover, we exclusively recovered cross-coupling (**3e–i**) products in these new experiments (Table 1).

Obviously, the stronger C–Cl bond in **2e–i** favours oxidative addition to the catalyst over the dehalogenation accompanied by homo-coupling seen in **2a–d**. High conversions and high yields were obtained with **2e** and *p*-chloronitrobenzene (**2f**). With *p*-chloroacetophenone (**2g**), the reaction proceeded slowly with partial conversion but with high chemoselectivity, while higher conversions and yields were detected with the *m*- (**2h**) and *o*-isomer (**2i**). We suppose that these slight differences could arise from the coordinating effect of the carbonyl group on the palladium, stronger in the *ortho* and *meta* positions, thus favouring the oxidative addition. In the reaction with **2f**, the catalyst was recycled three times with a loss in activity. ICP-analyses of the catalyst after its application revealed that leaching is not so significant as to explain the activity loss.



Scheme 2 Solid state Suzuki cross-coupling of heteroaryl chlorides (**5**) with phenylboronic acid (**1**) in a planetary ball mill (for conditions see Table 1; X = conversion).

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Weight loss during catalyst recycling is probably responsible for the observed effect. Using heterocyclic 2-chloropyridine (**5a**) and 4-benzoxazole (**5b**) in the reaction with **1** afforded the cross-coupling products **6a** and **6b** in 79 and 62% yields, respectively (Scheme 2).

The side reaction of aryl–aryl coupling can be slightly reduced when working under argon atmosphere. This, however, is a task that cannot easily be when using a planetary ball mill. In comparison to results previously published for the cross-coupling of bromo-*N*-heteroarenes in a similar ball mill,[8] the yields obtained with the present catalyst are considerably higher, although the reaction times are longer.

Conclusions

In summary, we have reported an interesting protocol for Suzuki cross-couplings under ball milling conditions using a HMDI cross-linked CS/Pd-derivative as catalyst. The catalyst was prepared in water *via* sonochemical cross-linking with HMDI in the presence of the metal salt. This catalyst can be reused three times and shows low metal leaching during its application in the Suzuki cross-coupling of aryl chlorides. The average to high yields that were obtained with several aryl chlorides, compared with the poor results reported in the literature, may open the door to reactions with poorly reactive substrates in the ball mill and possibility to catalyst recycling.

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