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Suzuki Cross-Coupling in Aqueous Media

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We report a simple and efficient procedure for the ligand-free as well as ligand-assisted Suzuki reaction in both pure water and aqueous media. The cross-coupling reactions proceed successfully using phenylboronic acid or potassium phenyltrifluoroborate as nucleophilic coupling partner. The method can be effectively applied to both activated and deactivated aryl halides yielding quantitative conversions. The catalytic activity of couplings performed in pure water increases utilizing supramolecular additives, however, decreases under standard phase-transfer conditions. Finally, the palladium loading is reducible from 3.0 mol% to 0.4 mol% without the loss of conversion.

Introduction

The palladium-catalyzed Suzuki cross-coupling reaction between organoboron compounds and organic halides is one of the most powerful tools for forming carbon-carbon bonds, particularly for the synthesis of biaryls.[1,2] Owing to the fact that the aryl-aryl structure motif is an important building block in organic chemistry, the Suzuki reaction is widely applied in academic research as well as in industrial synthesis of fine chemicals and highly complex pharmaceuticals.[3] The wide application of the reaction results from the broad functional group tolerance, the commercially availability and low toxicity of the organoborons, mild reaction conditions, ease of handling of products and by-products, and the possibility of using water as solvent or co-solvent.[4,5]

The utilization of water as suitable reaction medium has received increasing attention over the last decades. In comparison with organic solvents that are commonly used in the palladium-catalyzed Suzuki cross-coupling reaction, water is not inflammable, cheap, non-toxic, and abundant.[6,7] Besides, inorganic reagents, which are often highly soluble in water, can be easily separated from the organic product.[8] Indeed, a clear drawback of the aqueous catalysis is the disposal of contaminated wastewater, which can in turn be decimated by the reduction of the catalyst loading or the recycling of the catalyst. However, an efficient Suzuki catalysis in aqueous media is often restricted due to limited substrate solubility or the decreased stability of the catalyst in water. Therefore, phase-transfer reagents are employed to solubilize the non-polar substrates and increase their concentration in the reaction medium. In order to enhance the catalytic activity, additives like inverse phase-transfer catalysts (PTC, e.g., calix[*n*]arenes) or surfactants (e.g., tetrabutylammonium bromide (TBAB), sodium dodecyl sulfate (SDS))have already been successfully utilized.[9–12] Latter can also serve as protective agents stabilizing colloidal palladium suspensions.[13–16] In this context, water-soluble PEG-tagged compounds, which efficiently stabilize palladium nanoparticles (NP), showed to be an effective and recoverable catalytic system for the Suzuki cross-coupling reaction in aqueous media as well as pure water. [17,18]

Another possibility to improve the efficiency of the Suzuki catalysis in water is the employment of hydrophilic ligands. The modification of the pre-built catalyst $Pd(PPh_3)_4$ has been frequently studied. However, despite their large application range, ligands including phosphines are often moisture and air sensitive, toxic, and hard to separate from the organic products.[9] Alternatively, electron-rich *N*-heterocyclic carbenes (NHC) have established as effective ligands for Suzuki cross-coupling reactions.[19–25] The catalytically active species is either formed *in-situ* from a NHC precursor, a palladium source, and a base[4,26–31] or pre-built palladium-NHC complexes[32,33] are utilized to catalyze the cross-coupling reaction.Nevertheless, the interest in phosphine-free and moreover ligand-free cross-coupling reactions has grown over the past decade.[10,11,34–37] Ligand-free catalysts allow the reaction to occur in aqueous and aerobic media as well as under mild reaction conditions. Indeed, a successful conversion of sterically hindered, or the less reactive aryl chlorides, is still a problem that is frequently studied.

In general, boronic acids or esters are used in the Suzuki cross-coupling reaction. However, tetra-coordinated organoborates gained increased popularity due to their ready availability and ease of handling.[5,38–42] Especially organotrifluoroborates offer substantial benefits. They are air and moisture stable and can be easily prepared and purified,[5,43] however the use as substrates in Suzuki reactions is only marginally exploited.

Herein, we report our recent results including ligand-free Suzuki cross-coupling reactions in aqueous media and within this context the utilization of potassium phenyltrifluoroborate as alternative coupling partner. The efficiency of the catalysis in pure water should be improved by utilizing imidazolium salts as NHC ligand precursors, phase-transfer catalysts, and sulfocalix[*n*]arenes as both solubilizing and mass transfer agents. In addition, optimization studies were carried out, containing pH fine tuning and the reduction of the catalyst loading revealing the Suzuki coupling to be successful reducing the palladium loading from 3.0 mol% down to 0.4 mol%.

Results and Discussion

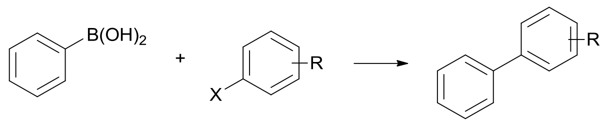
Ligand-free Suzuki Cross-Coupling Reactions

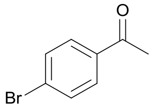
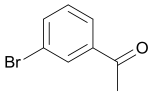
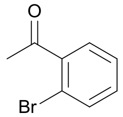
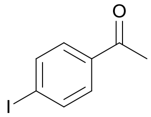
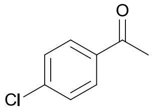
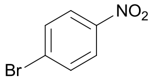
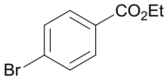
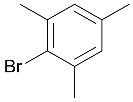
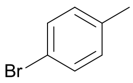
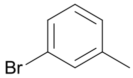
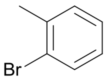
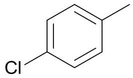
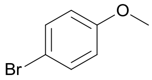
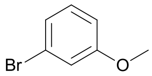
At the outset, the ligand-free catalytic system consisting of palladium acetate and potassium carbonate was tested for its scope and limitations. Therefore, the nucleophilic phenylboronic acid as well as potassium phenyltrifluoroborate was coupled with a variety of differently functionalized aryl halides, screening both activated aryl halides containing electron-withdrawing substituents and deactivated aryl halides containing electron-donating substituents (cf. table 1 and 2). Aside from electronic characteristics, the effect of steric hindrance and different halogen substituents was investigated. The substrate screenings were carried out under aerobic conditions in diverse solvents, which were 1,4-dioxane, water, 1,4-dioxane/water (1:1), and ethanol/water (1:1).

From the data compiled in table 1 and 2 one can deduce a couple of general trends that are valid for different solvents as well as for both organoboron nucleophiles. Firstly, the less expensive, but unreactive chlorobenzene derivatives **5** and **12** did not show an efficient Suzuki coupling under this reaction conditions. As expected, the reaction rate of the cross-couplings with the acetophenones bearing Cl **5**, Br **1**, or I **4** in *para* position increased strongly in the sequence Cl << Br, I. A certain distinction of the reactivity between 4'-bromo- and 4'-iodoacetophenone could not be stated. Secondly, the activated bromoacetophenones **1-3** as well as the deactivated bromotoluenes **9-11** and bromoanisoles **13-15** showed conversions dependent on the position of their substituents. The higher the steric hindrance, the lower was the conversion. This dependency was also mirrored in the low conversions of the extremely sterically hindered 2-bromomesitylene **8**. Thirdly, the substrate screenings with phenylboronic acid as organoboron coupling partner resulted in overall higher conversions compared to the couplings with potassium phenyltrifluoroborate. Last, but not least, the catalytic activity of the Suzuki cross-couplings increased with respect to the reaction media in the sequence 1,4-dioxane < water < 1,4-dioxane/water (1:1) < ethanol/water (1:1).

A closer look at the cross-coupling reactions with phenylboronic acid reveals notable distinctions of the conversions between different reaction media (Table 1). The couplings in pure water resulted in good yields with respect to the activity and steric demand of the aryl halides. It is notable that the result of the conversion of 3-bromoanisole **14b** (61%) falls completely out of alignment being more sterically hindered, but yielding nearly twice the conversion of 4-bromoanisole **13b** (36%). The highest conversions were received by the activated electrophiles 4'-bromoacetophenone **1b** (82%), 4-bromo-1-nitrobenzene **6b** (83%), and ethyl 4-bromobenzoate **7b** (85%) as well as the deactivated aryl bromides 4- **9b** and 3-bromotoluene **10b** (88% and 86%).

Table 1 Average conversions of ligand-free Suzuki cross-couplings of phenylboronic acid with aryl halides **1-15** in different solvents[a]



		Conversion [%][b]			
Entry	ArX	a) Dioxane	b) H_2O	c) Dioxane/H_2O (1:1)	d) EtOH/H_2O (1:1)
1		63, 69[c]	82	> 99 (**97**)	98
2		44	63	72	93 (**78**)
3		0	28	15	26 (**29**)
4		n.d.	78	> 99 (**98**)	99
5		0	3	3	9
6		79	83	> 99 (**74**)	89
7		n.d.	85	> 99 (**71**)	> 99
8		0	3	14	30
9		20	88	> 99	> 99 (**78**)
10		15	86	88	> 99 (**95**)
11		0	74	93	> 99 (**87**)
12		0	0	0	0
13		0	36	70	86 (**98**)
14		n.d.	61	66	> 99 (**60**)

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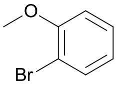
15		n.d.	23	24	89 (**83**)

[a] *Reaction conditions*: phenylboronic acid (1.50 mmol), aryl halide (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), K_2CO_3 (4.88 mmol), solvent (3 mL), solvent/H_2O (4 mL), 15 h, 40 °C. Conversions determined by ^{1}H-NMR, average values of 3-5 single measurements, general deviation ≤ 7%. [b] Isolated yields in parentheses. [c] With IMes×HCl (6.0 mol%).

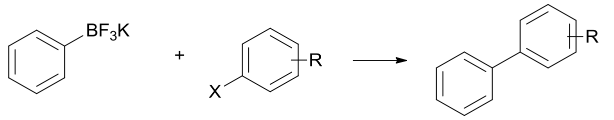
The replacement of water with 1,4-dioxane led to overall lower conversion values. Although the substrate solubility is decreased in water, the base potassium carbonate is, compared to the suspension in 1,4-dioxane, completely dissolved in water, which might contribute to the rate enhancement. The addition of the ligand IMes×HCl (Figure 1) to the coupling of 4'-bromoacetophenone **1a** increased the conversion from 63% to 69%.

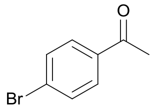
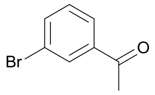
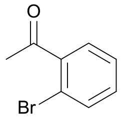
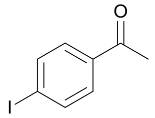
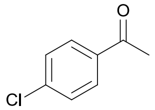
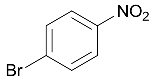
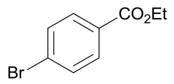
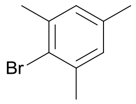
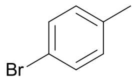
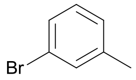
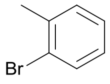
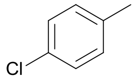
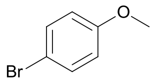
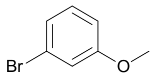
The utilization of a solvent mixture of 1,4-dioxane/water at a ratio of 1:1 resulted in high to excellent yields. The combination of the beneficial effect of water and the dissolution of the substrates by 1,4-dioxane increased the efficiency of the Suzuki couplings. The cross-coupling reactions with 4'-bromo- **1c** and 4'-iodoacetophenone **4c**, 4-bromo-1-nitrobenzene **6c**, ethyl 4-bromobenzoate **7c**, and 4-bromotoluene **9c** now all yielded quantitative conversions (> 99%). Most noticeable is the doubling of the conversion of 4-bromoanisole **13c** increasing from 36% in neat water to 70%. Besides, the conversions of the deactivated bromoanisoles **13c**-**15c** decreased with higher steric hindrance from 70%, over 66% to 24%. The activated bromoacetophenones **1c**-**3c** showed the same conversion dependence with regard to the steric disturbance of their substituents ranging from > 99%, over 72%, to 15%. Even the highly sterically hindered 2-bromomesitylene **8c** displayed a conversion increase from 3% in pure water to 14%. The bromotoluenes **9c**-**11c** exhibited excellent conversion values ranging from 88% to > 99%, however, not maintaining the conversion dependency on the steric demand of their substituents.

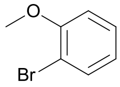
The application of the more environmentally benign solvent mixture ethanol/water (1:1) revealed superior conversions for most of the aryl halides. A special rate enhancement could be assigned to the coupling of 3-bromoanisole **14d**, now resulting in a quantitative conversion (> 99%), and 2-bromoanisole **15d** showing a nearly fourfold increase in conversion from 23% in pure water to 89%. Especially the high conversions of all three deactivated bromotoluenes **9d**-**11d** (> 99%) raised the question about the quality of the conversion values determined by ^{1}H-NMR spectroscopy. There is a chance that one compound, either the substrate (aryl halide), or the product (biaryl), is preferentially extracted from the ethanol/water mixture, i.e., the preferential extraction of the biaryl would result in a higher conversion than it really is. For this purpose, extraction blank tests for both ethanol/water (1:1) and 1,4-dioxane/water (1:1) were carried out, which ruled out such a possibility. Additionally, the isolated yields (Table 1 in parentheses) were in good agreement with the conversion values, which underline their quality.

In conclusion, one can state, that the catalytic activity of the Suzuki cross-couplings with phenylboronic acid increases with the examined reaction media in the order 1,4-dioxane < water < 1,4-dioxane/water (1:1) < ethanol/water (1:1).

Table 2 Average conversions of ligand-free Suzuki cross-couplings of potassium phenyltrifluoroborate with aryl halides **1-15** in different solvents[a]



Entry	ArX	Conversion [%]			
		a) Dioxane	b) H_2O	c) Dioxane/H_2O (1:1)	d) EtOH/H_2O (1:1)
1		0, 10[b]	82	78	96
2		0	19	48	47
3		0	18	19	13
4		n.d.	58	84	98
5		0	6	6	15
6		0	61	78	72
7		n.d.	29	52	53
8		0	0	24	16
9		0	19	90	> 99
10		0	16	86	> 99
11		0	8	88	> 99
12		0	0	6	0
13		0	11	73	86
14		n.d.	69	68	94

15		n.d.	16	21	69

[a] *Reaction conditions*: potassium phenyltrifluoroborate (1.50 mmol), aryl halide (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), K_2CO_3 (4.88 mmol), solvent (3 mL), solvent/H_2O (4 mL), 15 h, 40 °C. Conversions determined by ^1H-NMR, average values of 3-5 single measurements, general deviation ≤ 7%. [b] With IMes×HCl (6.0 mol%).

The substrate screenings with potassium phenyltrifluoroborate as nucleophile resulted in overall lower conversion values demoting the advantages of using the boron-containing salt as alternative coupling partner (Table 2). In addition, ^1H-NMR experiments showed that potassium phenyltrifluoroborate partly converted to phenylboronic acid in aqueous solution anyway, thus, raising the question which nucleophile ultimately reacts with the electrophilic aryl halide in a Suzuki cross-coupling.

However, when choosing water as reaction medium, the best conversion was achieved by the coupling with 4'-bromoacetophenone **1b** (82%). The conversions of the bromoacetophenones further decreased in dependence of the steric hindrance of the acetyl group from 19% **2b** to 18% **3b**. The other activated aryl halides bearing substituents in *para* position only gave low to modest conversions ranging from 29% (ethyl 4-bromobenzoate **7b**) to 58% (4'-iodoacetophenone **4b**) and 61% (4-bromo-1-nitrobenzene **6b**). The bromotoluenes **9b-11b** displayed a decrease in conversion analog to the substitution pattern ranging from 19% over 16% to 8%. Most notable is the modest conversion of 69% resulting from the coupling with 3-bromoanisole **14b**, which is six times larger than the conversion emerging from the reaction with the less sterically hindered 4-bromoanisole **13b** (11%).

The conduction of the substrate-screening in pure 1,4-dioxane brought about no conversions at all emphasizing the higher catalytic activity in water despite poorer solubility of the substrates. The addition of the ligand IMes×HCl to the cross-coupling reaction with 4'-bromoacetophenone **1a** resulted in a conversion increase from 0% to 10%.

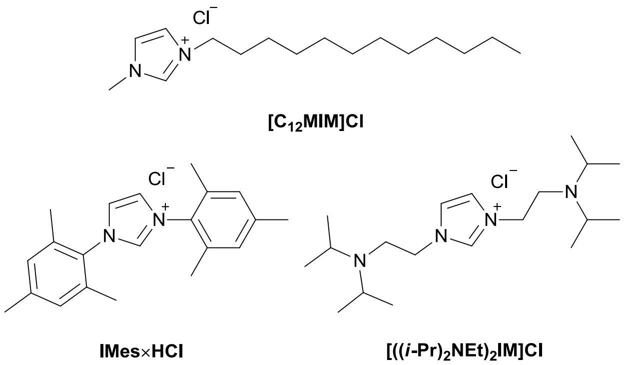
The application of the solvent mixture 1,4-dioxane/water (1:1) resulted in higher conversions than in pure water. Owing to the former results that the substrate screening in neat 1,4-dioxane provided absolutely no conversion, it seems that now 1,4-dioxane facilitates to dissolve the substrates, but water significantly contributes to an efficient cross-coupling, which is, amongst other things, achieved by the completely dissolution of the base. The most significant rate enhancements were achieved by the three deactivated bromotoluenes **9c-11c** gaining conversions in the range of 86% to 90% as well as by 4-bromoanisole **13c** yielding a sevenfold higher conversion (73%). Besides, the activated aryl halides 3'-bromoacetophenone **2c**, 4'-iodoacetophenone **4c**, 1-bromo-4-nitrobenzene **6c**, and ethyl 4-bromobenzoate **7c** underwent an increase in conversion by 24% on average.

The replacement of 1,4-dioxane with ethanol in the one-to-one mixture with water led to overall superior conversions. The deactivated bromotoluenes **9d-11d** converted quantitatively and even the also less electrophilic bromoanisoles **13d-15d** yielded conversions in the range of 69% to 94%. Furthermore, an almost quantitative conversion was achieved by the reaction with activated 4'-bromo- **1d** (96%) and 4'-iodoacetophenone **4d** (98%). Only the activated ethyl 4-bromobenzoate **7d** broke ranks keeping the moderate conversion of 53% and thus being half the conversion of the reaction with phenylboronic acid (> 99%).

Here, too, the catalytic activity increases with respect to the reaction media in the order 1,4-dioxane << water < 1,4-dioxane/water (1:1) < ethanol/water (1:1).

Ligand-assisted Suzuki Cross-Coupling Reactions

The ligand-free Suzuki cross-couplings in pure water presented before, resulted in moderate to high conversions, thus, leaving room for improvement. One possibility to enhance the catalytic activity is the utilization of imidazolium salts. These imidazolium salts can be simply added to a Suzuki cross-coupling reaction in order to form *N*-heterocyclic carbene ligands *in situ*.[4] The generated palladium complex carries two substantial benefits. On the one hand, NHC ligands are strong σ-donors, hence increasing the electron density on the palladium and accelerating the oxidative addition of the catalyst to the electrophilic aryl halide. On the other hand, bulky NHC ligands destabilize the transmetallated complex, therefore facilitating the reductive elimination.



[C$_{12}$MIM]Cl

IMes×HCl

[((*i*-Pr)$_2$NEt)$_2$IM]Cl

Fig. 1 Utilized imidazolium salts for the *in situ* preparation of *N*-heterocyclic carbene ligands

Within this study the imidazolium salts (Figure 1) 1,3-bis(2-(diisopropylamino)ethyl)-1*H*-imidazol-3-ium chloride (**[((*i*-Pr)$_2$NEt)$_2$IM]Cl**) and 1-dodecyl-3-methylimidazolium chloride (**[C$_{12}$MIM]Cl**) were tested for their capability to improve the catalytic activity in pure water (Table 3). Latter does not only serve as NHC ligand, but is also able to solubilize lipophilic substrates, increase their concentration in water, and, thus, enhance the cross-coupling reaction. The amphiphilic imidazolium salt [C$_{12}$MIM]Cl is structurally closely related to the surfactant SDS, which has been frequently used to promote cross-coupling reactions.

Initially, substrate screenings with both phenylboronic acid and potassium phenyltrifluoroborate were carried out utilizing [C$_{12}$MIM]Cl as ligand precursor. Besides, the imidazolium salt was applied in two different concentrations 0.6 mol% and 6.0 mol%, respectively. Table 3 shows three distinct trends only including a few exceptions. Firstly, the ligand-assisted Suzuki cross-couplings did result in higher conversions than the couplings without a ligand precursor. The conversions increased with the ligand concentration, i.e., the higher the concentration, the higher the conversions. Secondly, the more cost-efficient aryl chlorides **5** and **12** could still not be successfully converted.

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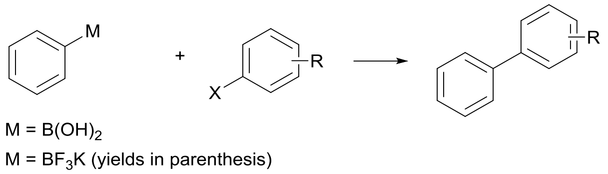
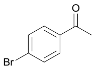
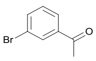
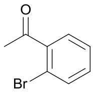
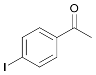
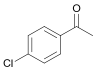
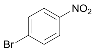
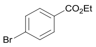
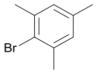
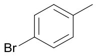
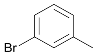
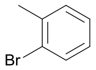
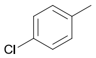
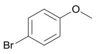
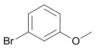
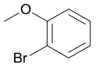
Table 3 Ligand-assisted Suzuki cross-couplings of both phenylboronic acid and potassium phenyltrifluoroborate with aryl halides **1-15** and 1-dodecyl-3-methylimidazolium chloride as ligand precursor in pure water[a]



Entry	ArX	Conversion [%][b]		
		a) Ligand-free	b) [L] = 0.6 mol%	c) [L] = 6.0 mol%
1		82 (82)	93 (91)	97 (89)
2		63 (19)	85 (39)	96 (88)
3		28 (18)	20 (17)	79 (56)
4		78 (58)	79 (62)	85 (78)
5		3 (6)	5 (7)	10 (6)
6		8 (61)	91 (93)	88 (84)
7		85 (29)	> 99 (83)	> 99 (85)
8		3 (0)	7 (6)	14 (18)
9		88 (19)	83 (45)	> 99, > 99[c] (97)
10		86 (16)	> 99 (40)	> 99 (93)
11		74 (8)	> 99 (29)	> 99 (98)
12		0 (0)	0 (0)	0 (0)
13		36 (11)	54 (27)	62, 59[c], 59[d] (41)
14		61 (69)	66 (80)	87 (82)
15		23 (16)	23 (15)	46 (27)

[a] *Reaction conditions*: phenylboronic acid (1.50 mmol), aryl halide (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), $[C_{12}MIM]Cl$ (0.6, 6.0 mol%), K_2CO_3 (4.88 mmol), H_2O (3 mL), 15 h, 40 °C. [b] Conversions of couplings with potassium phenyltrifluoroborate in parentheses. [c] Conversion of coupling with $[((i\text{-Pr})_2NEt)_2IM]Cl$ (6.0 mol%) as ligand precursor. [d] Twofold volume of H_2O (6 mL).

The same applied to the reaction with the highly sterically hindered 2-bromomesitylene **8**. Thirdly, the conversions of the cross-couplings with the alternative organoboron potassium phenyltrifluoroborate remained lower compared to the couplings with phenylboronic acid.

Taking a closer look at the substrate screenings with phenylboronic acid, some conversions clearly stand out. Most noticeable is the quantitative conversion of ethyl 4-bromobenzoate **7b** and **7c**, 3-bromo- **10b** and **10c**, and 2-bromotoluene **11b** and **11c** for both ligand concentrations. By contrast, 4-bromotoluene **9c** only converted quantitatively when the ligand concentration was 6.0 mol%. The deactivated bromoanisoles **13-15** showed a steadily rate enhancement with higher $[C_{12}MIM]Cl$ concentration revealing an overall increase of conversion by 25% on average. Although not converting quantitatively, the most significant difference between the conversion of the ligand-free Suzuki coupling and the reaction with 6.0 mol% $[C_{12}MIM]Cl$ was yielded by 3'-bromo- **2c** (63% → 96%) and 2'-bromoacetophenone **3c** (28% → 79%).

The conversions of the cross-couplings with potassium phenyltrifluoroborate were not similarly high, but for many of the aryl bromides a larger rate enhancement could be realized regarding the conversion difference between the reaction without and with 6.0 mol% imidazolium salt. This difference was most significant for the reaction of deactivated bromotoluenes **(9-11)** causing an increase of 82% on average. A likewise high enhancement was obtained by some activated aryl bromides, now yielding conversions from 56% (2'-bromoacetophenone **(3c)**), over 85% (ethyl 4-bromobenzoate **(7c)**), to 88% (3'-bromoacetophenone **(2c)**). However, modest conversion improvements were gained by deactivated 4-bromoanisole **(13c)** (11% → 41%) as well as activated 4'-iodoacetophenone **(4c)** (58% → 78%) and 4-bromo-1-nitrobenzene **(6c)** (61% → 84%), whereby latter yielded a higher conversion of 93% **(6b)** using only 0.6 mol% ligand precursor.

The capability of the second imidazolium salt $[((i\text{-Pr})_2NEt)_2IM]Cl$ (6.0 mol%) to enhance the catalytic activity in pure water was tested by the coupling of phenylboronic acid with 4-bromotoluene as well as 4-bromoanisole (Table 3). This imidazolium salt does not feature the same surfactant characteristics, but definitively accelerates the reductive elimination step regarding its bulky substituents. The conversions of both Suzuki cross-couplings did not much differ from the results of the reactions with $[C_{12}MIM]Cl$ of the same concentration. 4-Bromotoluene **9c** converted quantitatively and 4-bromoanisole **13c** gained a conversion increase from 36% without ligand precursor to 59%.

In conclusion, it can be noted that the catalytic activity of the Suzuki cross-coupling in neat water as environmentally benign solvent, is efficiently promoted utilizing the imidazolium salts $[C_{12}MIM]Cl$ as well as $[((i\text{-Pr})_2NEt)_2IM]Cl$ as ligand precursors.

Phase-Transfer Catalysis

We next examined the reaction behaviour of the Suzuki cross-couplings with potassium phenyltrifluoroborate under phase-transfer conditions in comparison to the afore studied reaction in pure aqueous media (Table 4). For our test reactions we kept the reaction protocol in principle, but added TBAB as standard PTC and 18-crown-6 to capture the potassium counter ion, which should facilitate the dissociation of the ion pair by shielding the positive charge and therefore enhancing the catalytic activity.

We then screened the catalysis for different substrates and

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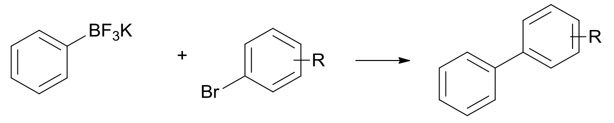
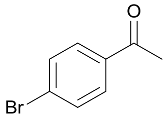
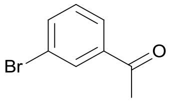
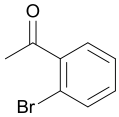
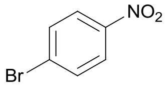
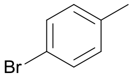
solvents. The results follow the same trends observed in the Suzuki couplings without PTC, see table 4 right column. The bromoacetophenones provided yields decreasing with higher steric influence from 79% **1** over 9% **4** to 6% **5**. The activated 4-bromo-1-nitrobenzene **6** revealed a conversion of 52%, whereas the deactivated 4-bromotoluene **7** converted with a yield of 10%. By changing the solvent from CH_2Cl_2 to toluene **3** we observed a decrease of conversion about 24%. Finally, we replaced the borate with phenylboronic acid and tested the coupling with the activated 4'-bromoacetophenone **2** in CH_2Cl_2, yielding a conversion of only 44%.

Table 4 Phase-transfer catalysis of ligand-free Suzuki cross-coupling between potassium phenyltrifluoroborate and different aryl halides[a]



Entry	ArX	Conversion [%]	Conversion [%][b]
1, 2, 3		79, 44[c], 55[d]	82
4		9	19
5		6	18
6		52	61
7		10	19

[a] *Reaction conditions*: potassium phenyltrifluoroborate (1.50 mmol), aryl halide (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), 18-crown-6 (10.0 mol%), TBAB (10.0 mol%), K_2CO_3 (4.88 mmol), H_2O/DCM (3 mL/3 mL), 15 h, 30 °C. [b] Without PTC in pure water. [c] With phenylboronic acid as organoboron, without 18-crown-6. [d] With toluene as co-solvent.

All in all the conversions under phase-transfer conditions using TBAB or 18-crown-6 are lower than similar reactions in water without added phase-transfer catalysts. Therefore, in this specific case this methodology is not ecologically justified taking the additional waste stemming from the PTC into account.

Suzuki Cross-Coupling Reactions Using Supramolecular Additives

Another possibility to facilitate the Suzuki cross-coupling reaction in pure water is the utilization of sulfocalix[*n*]arenes (SC[*n*] Figure 2). On the one hand, these supramolecular additives are effective solubilizing agents. Owing to the sulfonate groups at the upper rim, they are water soluble themselves and can solubilize the nonpolar substrates by encapsulating them in their cavities through non-covalent interactions.[12] Additionally, sulfocalix[*n*]arenes, especially when alkylated at the lower rim, possess surface activities and can therefore serve as amphiphilic mass transfer agents helping the lipophilic substrates through bulk water.

In a first experiment, octylated sulfocalix[8]arene (SC8C_8) was added to the ligand-free Suzuki cross-couplings of 4-bromotoluene with phenylboronic acid as well as potassium phenyltrifluoroborate in pure water (Table 5). The small concentration of 0.5 mol% of the macrocycle was sufficient to promote both reactions. Phenylboronic acid **1** and 4-bromotoluene reacted quantitatively, whereas the coupling with the organoborate **2** yielded an about fivefold higher conversion compared to the reaction without additive (19% → 86%).

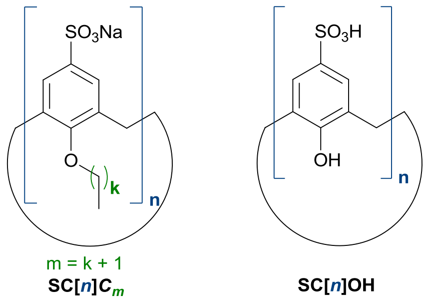
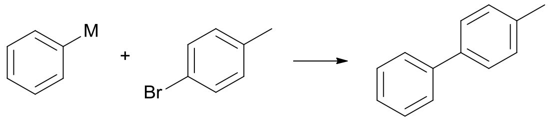


Fig. 2 General structure of utilized sulfocalix[*n*]arenes

Table 5 Ligand-free Suzuki cross-couplings of both phenylboronic acid and potassium phenyltrifluoroborate with 4-bromotoluene using SC8C$_8$ in pure water[a]



Entry	M	Conversion [%]	Conversion [%][b]
1	$B(OH)_2$	> 99	88
2	BF_3K	86	19

[a] *Reaction conditions*: organoboron (1.50 mmol), 4-bromotoluene (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), K_2CO_3 (4.88 mmol), SC8C_8 (0.5 mol%), H_2O (3 mL), 15 h, 40 °C. [b] Without SC8C_8.

While the catalytic activity of the ligand-free cross-coupling could be readily facilitated by SC8C_8, the question arised how the combination of a supramolecular additive and a *N*-heterocyclic carbene precursor would affect the catalysis. Therefore, different sulfocalix[*n*]arenes were added to the ligand-assisted cross-coupling reaction between phenylboronic acid and deactivated 4-bromoanisole with $[((i\text{-}Pr)_2NEt)_2IM]Cl$ serving as ligand precursor. Table 6 shows that the conversion increased from left to right for alkylated sulfocalix[*n*]arenes. More precisely, the addition of SC4C_3 **1b**, SC4C_8 **2b**, and SC8C_8 **4b**, respectively, resulted in overall higher conversion values as compared to the conversion of 36% **a** of the ligand-free coupling without additive. However, these results could be exceeded by the blank ligand-assisted Suzuki reaction (59%) **c**. Finally, the combination of supramolecular additive and ligand yielded the highest conversions, whereas the utilization of SC4C_8 **2d** rendered the

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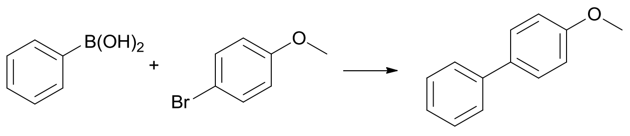
largest rate enhancement (66%). Looking at the results of the cross-couplings with SC4OH the opposite is the case, i.e. the ligand-free coupling yielded a higher conversion (64%) **3b** than the ligand-assisted reaction (58%) **3d**.

Table 6 Ligand-assisted Suzuki cross-couplings of phenylboronic acid with 4-bromoanisole using sulfocalix[*n*]arenes as additive and 1,3-bis(2-(diisopropylamino)ethyl)-1*H*-imidazol-3-ium choride as ligand precursor in pure water[a]



Entry	SC[*n*]	Conversion [%]			
		a)[b]	b)[c]	c)[d]	d)
1	SC4C_3	36	56	59	61
2	SC4C_8		58		66
3	SC4OH		64		58
4	SC8C_8		52		n.d.

[a] *Reaction conditions*: phenylboronic acid (1.50 mmol), 4-bromoanisole (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), K_2CO_3 (4.88 mmol), SC8C_8 (0.5 mol%), $[((i\text{-}Pr)_2NEt)_2IM]Cl$ (6.0 mol%), H_2O (3 mL), 15 h, 40 °C. [b] Ligand-free coupling without SC[*n*]. [c] Ligand-free coupling. [d] Coupling without SC[*n*].

These initial reactions showed that all sulfocalix[*n*]arenes were able to promote the Suzuki cross-coupling, whereat the influence of different additives was rather low. 0.5 mol% of the calixarenes were sufficient to achieve an average conversion increase of 22%, while the addition to a ligand-assisted Suzuki cross-coupling reaction yielded a conversion increase of 26% on average.

Optimization Studies

Conversion Dependence on pH Value

With the substrate screenings in hand, we were further interested in optimizing the Suzuki reaction towards water as suitable reaction medium. Various reaction parameters, including variation of the base, have already been investigated.[2] Owing to the fact, that any base forms hydroxide ions in aqueous media, it is rather interesting to know what effect the pH adjustment has on the catalytic activity. Therefore, we chose the coupling of potassium phenyltrifluoroborate with 4-bromo-1-nitrobenzene as test reaction (Table 7). The reaction conditions were kept constant except for the variation of K_2CO_3 concentration. The conversions resulted in a Gaussian-like progression (Figure 3) with increasing pH and a maximum conversion of 67% at which the K_2CO_3 equivalents (4.88 mmol) **3** according to literature were employed.[44] For very small hydroxide concentrations ($2.90 \cdot 10^{-3}$ mmol) **1**, less activated organoboron was produced, which is required during the transmetallation step, causing an extremely low conversion of 6%. Using an amount of base near its maximal solubility (21.7 mmol) **5**, the reactants did not convert at all. A possible reason for this is the inhibition of the formation of the catalytically active zerovalent palladium species due to a ligand exchange of acetate with hydroxide ions in the first place. In summary, the optimal pH for an effective coupling is already found by this study.

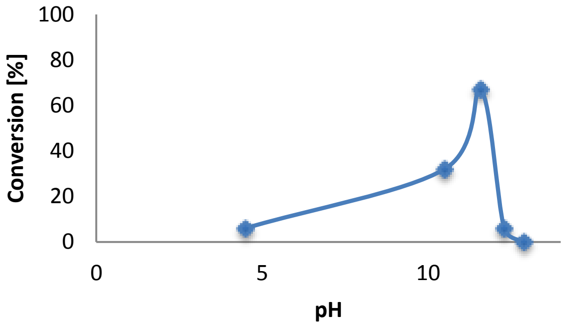
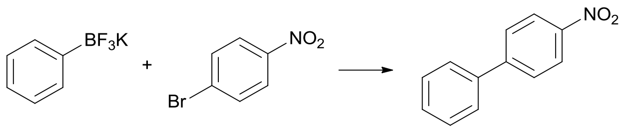


Fig. 3 Conversion dependence on the pH value

Table 7 Examination of the conversion dependence on the pH value using the ligand-free Suzuki cross-coupling between potassium phenyltrifluoroborate and 1-bromo-4-nitrobenzene in pure water[a]



Entry	K_2CO_3 [mmol]	pH[b]	Conversion [%]
1	$2.90 \cdot 10^{-3}$	4.5	6
2	0.36	10.5	32
3	4.88	11.6	67
4	12.1	12.3	6
5	21.7	12.9	0

[a] *Reaction conditions*: potassium phenyltrifluoroborate (1.50 mmol), 4-bromo1-nitrobenzene (1.00 mmol), $Pd(OAc)_2$ (3.0 mol%), K_2CO_3, H_2O (3 mL), 15 h, 40 °C. [b] pH value of K_2CO_3 and $Pd(OAc)_2$ dissolved in H_2O.

Reduction of the Catalyst Loading

If a specific synthetic transformation is more sustainable just by using water as solvent is an ongoing issue, because the disposal of contaminated wastewater has to be taken into consideration, but is often neglected in the discussion.[6] A clear way to improve the ecology of a catalysis is the reduction of the catalyst loading. We studied this by means of the ligand-free Suzuki cross-coupling reaction between phenylboronic acid and 4'-bromoacetophenone in pure water (Table 8, Figure 4). The application of the initial $Pd(OAc)_2$ loading of 3.0 mol% **1** resulted in an average conversion of 82% with a standard deviation of ± 1%. At first, the catalyst loading was reduced from 3.0 mol% to 1.0 mol% **1-5** in 0.5 mol% steps. Owing to the fact that the coupling with 1.0 mol% $Pd(OAc)_2$ **5** yielded a greater conversion (85%) than the initial one, further reductions from 1.0 mol% to 0.5 mol% **5-10** were carried out in steps of 0.1 mol%. The utilization of 0.5 mol% $Pd(OAc)_2$ **10** afforded a conversion of 82%, thus the remaining reductions down to 0.05 mol% **11-19** were chosen in steps of 0.05 mol% to guarantee a thorough investigation. The Suzuki cross-coupling reaction with an ultra-low catalyst loading of 0.05 mol% **19** still resulted in a moderate conversion of 74%. However, the last time the conversion was greater or equal than the initial one, was achieved by using 0.4 mol% $Pd(OAc)_2$ **12** (83%).

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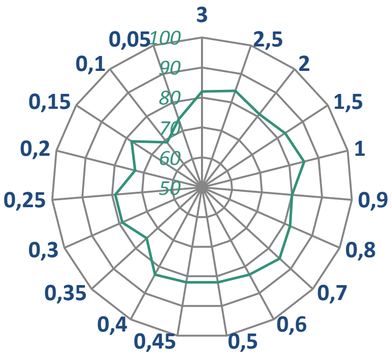
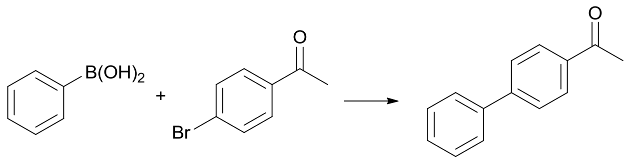


Fig. 4 Spider chart of the reduction of the $Pd(OAc)_2$ loading using the ligand-free Suzuki reaction between phenylboronic acid and 4'-bromoacetophenone. *Abscissa (circumference): $Pd(OAc)_2$ loading [mol%]; ordinates: conversion [%]*

Table 8 Reduction of the $Pd(OAc)_2$ loading using the ligand-free Suzuki reaction between phenylboronic acid and 4'-bromoacetophenone[a]



Entry	$Pd(OAc)_2$ [mol%]	Conv. [%]	Entry	$Pd(OAc)_2$ [mol%]	Conv. [%]
1	3.0	82 ± 1	11	0.45	82
2	2.5	84	**12**	**0.4**	**83**
3	2.0	81	13	0.35	75
4	1.5	83	14	0.3	79
5	1.0	85	15	0.25	79
6	0.9	80	16	0.2	73
7	0.8	82	17	0.15	78
8	0.7	85	18	0.1	69
9	0.6	83	19	0.05	74
10	0.5	82			

[a] *Reaction conditions*: phenylboronic acid (1.50 mmol), 4'-bromoacetophenone (1.00 mmol), $Pd(OAc)_2$ (3.0 → 0.05 mol%), K_2CO_3 (4.88 mmol), H_2O (3 mL), 15 h, 40 °C.

For comparison, the reduction of the $Pd(OAc)_2$ loading was also carried out by means of the ligand-assisted Suzuki cross-coupling between phenylboronic acid and 4'-bromoacetophenone in pure water, whereat $[C_{12}MIM]Cl$ served as ligand precursor (Table 9, Figure 5). The initial conversion of 97%, achieved by the application of 3.0 mol% $Pd(OAc)_2$ **1** was already higher than the conversion yielded by the ligand-free coupling (82 ± 1%). Here also, the catalyst loading was at first reduced in 0.5 mol% steps from 3.0 mol% to 0.5 mol% **1-6**. However, this time the limit when the conversion was for the last time higher than the initial one, was already reached by applying 1.5 mol% $Pd(OAc)_2$ **4** (98%), which prompted us not to thoroughly examine further reduction of the catalyst loading below 1.0 mol%. The utilization of 1.0 mol% **5** and 0.5 mol% **6** $Pd(OAc)_2$ resulted in a conversion decrease of 10%. Finally, the Suzuki cross-coupling with 0.25 mol% catalyst **7** yielded a conversion of 85%.

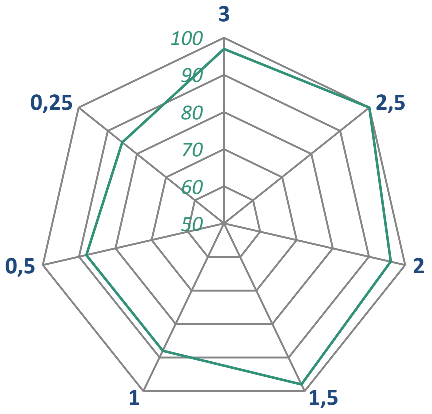
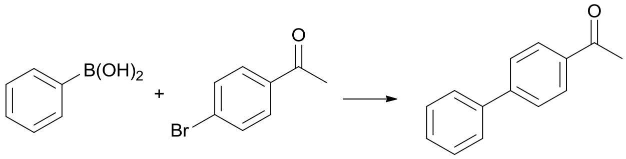


Fig. 5 Spider chart of the reduction of the $Pd(OAc)_2$ loading using the ligand-assisted Suzuki reaction between phenylboronic acid and 4'-bromoacetophenone. *Abscissa (circumference): $Pd(OAc)_2$ loading [mol%]; ordinates: conversion [%]*

Table 9 Reduction of the $Pd(OAc)_2$ loading using the ligand-assisted Suzuki reaction between phenylboronic acid and 4'-bromoacetophenone[a]



Entry	$Pd(OAc)_2$ [mol%]	Conversion [%]
1	3.0	97
2	2.5	100
3	2.0	96
4	**1.5**	**98**
5	1.0	88
6	0.5	88
7	0.25	85

[a] *Reaction conditions*: phenylboronic acid (1.50 mmol), 4'-bromoacetophenone (1.00 mmol), $Pd(OAc)_2$ (3.0 → 0.25 mol%), $[C_{12}MIM]Cl$ (6.0 mol%), K_2CO_3 (4.88 mmol), H_2O (3 mL), 15 h, 40 °C.

In conclusion, though working with extremely low catalyst loadings, which also made high demands on the weighing scale, the conversion values clearly displayed stability for both test series. In comparison, for the ligand-free coupling the $Pd(OAc)_2$ loading could be reduced from 3.0 mol% to 0.4 mol% without the loss of conversion, whereas for the ligand-assisted coupling the limit was reached at a catalyst loading of 1.5 mol%. However, the application of 0.5 mol% catalyst to the ligand-assisted Suzuki coupling still resulted in a higher conversion (88%) than any yielded by the ligand-free coupling, thus raising the question if a greater catalyst loading plus an ancillary additive can be accepted for a higher conversion.

Conclusions

In conclusion, we have shown that an efficient, broadly applicable and moreover sustainable Suzuki catalysis in pure water is possible with a palladium loading of 0.4 mol% and without the need for a ligand or any organic co-solvent. Besides, the easy to handle and air-stable potassium phenyltrifluoroborate

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can be effectively employed for the ligand-free Suzuki cross-coupling in aqueous media, however, not realizing the conversions achieved by analog couplings with phenylboronic acid as nucleophile. The simple reaction protocol had been successfully applicable to a range of activated as well as deactivated aryl halides. The catalytic activity of the Suzuki cross-coupling in pure water was increased by applying NHC ligand precursors and/or supramolecular sulfocalix[*n*]arenes as iPTC. The modification of the reaction conditions by means of standard phase transfer catalysis, respectively, has proven to be not more effective than the reaction in pure aqueous solution. Furthermore, pH adjustment experiments have outlined the optimal base concentration. Finally, the palladium loading of a ligand-free Suzuki-coupling in pure water was successfully reduced more than sevenfold without the loss of conversion, while the catalyst loading of the analog ligand-assisted reaction was halved yielding nearly quantitative conversion.

Acknowledgment

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Experimental section

General

Chemicals were purchased from commercial sources and used without further purification. Potassium phenyltrifluoroborate, IMes×HCl, $[((i\text{-Pr})_2\text{NEt})_2\text{IM}]\text{Cl}$, and alkylated sulfocalix[*n*]arenes were prepared according to the published procedure.[43–47] ^{1}H-NMR spectra were recorded on a Bruker Avance 400 operating at 400.13 MHz. Chemical shifts δ are indicated in parts per million (ppm) with respect to the internal standard TMS ($\delta = 0$ ppm). The conversions of the Suzuki couplings were determined by comparing the integrated proton signals of product and starting material. Blind extraction tests of biaryls and aryl halides verified the correlation of yields with product/starting material ratios. The ^{1}H-NMR spectra were calibrated on TMS in $CDCl_3$.

Suzuki Cross-Coupling Reaction Protocols

Ligand-free Suzuki Cross-Coupling in H_2O

K_2CO_3 (675 mg, 4.88 mmol) and $Pd(OAc)_2$ (6.73 mg, 0.03 mmol, 3.00 mol%) were dissolved in H_2O (3 mL) and stirred for 30 min at 40 °C. After cooling down to room temperature (rt), the aryl halide (1.00 mmol) and subsequently potassium phenyltrifluoroborate (276 mg, 1.50 mmol) or phenylboronic acid (183 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 µL), the mixture was centrifuged. 600 µL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

Ligand-free Suzuki Cross-Coupling in H_2O with Additives

K_2CO_3 (675 mg, 4.88 mmol, 4.9 eq) and $Pd(OAc)_2$ (6.74 mg, 0.03 mmol, 3.00 mol%) were dissolved in H_2O (3 mL) and stirred for 30 min at 40 °C. At first, a sulfocalixa[n]arene (0.50 mol%, 5.00 µmol), then the aryl halide (1.00 mmol) and subsequently phenylboronic acid (183 mg, 1.50 mmol) or potassium phenyltrifluoroborate (276 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 µL), the mixture was centrifuged. 600 µL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

Ligand-assisted Suzuki Cross-Coupling in H_2O

K_2CO_3 (675 mg, 4.88 mmol, 4.9 eq), $Pd(OAc)_2$ (6.74 mg, 0.03 mmol, 3.00 mol%) and an imidazolium salt were dissolved in H_2O (3 mL) and stirred for 30 min at 40 °C. At first the aryl halide (1.00 mmol) and subsequently phenylboronic acid (183 mg, 1.50 mmol) or potassium phenyltrifluoroborate (276 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 µL), the mixture was centrifuged. 600 µL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

Ligand-assisted Suzuki Cross-Coupling in H_2O with Additives

K_2CO_3 (675 mg, 4.88 mmol, 4.9 eq), $Pd(OAc)_2$ (6.74 mg, 0.03 mmol, 3.00 mol%) and 1,3-bis(2-(diisopropylamino)ethyl)-1*H*-imidazol-3-ium chloride (6.00 mol%, 60.0 mmol, 21.5 mg) were dissolved in H_2O (3 mL) and stirred for 30 min at 40 °C. At first a sulfocalixa[n]arene (0.50 mol%, 5.00 µmol), then the aryl halide (1.00 mmol) and subsequently phenylboronic acid (183 mg, 1.50 mmol) or potassium phenyltrifluoroborate (276 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 µL), the mixture was centrifuged. 600 µL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

Ligand-free Suzuki Cross-Coupling in Dioxane[44]

K_2CO_3 (675 mg, 4.88 mmol) and a 0.05 M solution of $Pd(OAc)_2$ (600 µL, 3.00 mol%) in dioxane were dissolved in dioxane (2.40 mL) and stirred for 30 min at 40 °C. At first the aryl halide (1.00 mmol) and subsequently potassium phenyltrifluoroborate (276 mg, 1.50 mmol) or phenylboronic acid (183 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. After cooling down to rt, an aliquot of 300 µL was filled up with $CDCl_3$ to 600 µL and used for ^{1}H-NMR analysis.

Ligand-assisted Suzuki Cross-Coupling in Dioxane[44]

K_2CO_3 (675 mg, 4.88 mmol), the IMes×HCl ligand precursor (6.00 mol%), and a 0.05 M solution of $Pd(OAc)_2$ (600 µL, 3.00 mol%) in dioxane were dissolved in dioxane (2.40 mL) and stirred for 30 min at 100 °C. At first 4’-bromoacetophenone (0.20 g, 1.00 mmol) and subsequently potassium phenyltrifluoroborate (276 mg, 1.50 mmol) or phenylboronic acid (183 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. After cooling down to rt, an aliquot of 300 µL was filled up with $CDCl_3$ to 600 µL and used for ^{1}H-NMR analysis.

Ligand-free Suzuki Cross-Coupling in Dioxane/H_2O (1:1)

K_2CO_3 (675 mg, 4.88 mmol) and a 0.05 M solution of $Pd(OAc)_2$ (600 µL, 3.00 mol%) in dioxane were dissolved in H_2O (1 mL) and stirred for 10 min at 40 °C. At first the aryl halide (1.00 mmol) and subsequently potassium phenyltrifluoroborate (276 mg, 1.50 mmol) or phenylboronic acid (183 mg, 1.50 mmol), respectively, were added. After another addition of H_2O (1 mL) and dioxane (1.40 mL), the sample was stirred for 15 h at 40 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 µL), the mixture was centrifuged. 600 µL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

Ligand-free Suzuki Cross-Coupling in Ethanol/H_2O (1:1)

K_2CO_3 (675 mg, 4.88 mmol) and $Pd(OAc)_2$ (6.73 mg, 0.03 mmol, 3.00 mol%) were dissolved in H_2O (2 mL) and stirred for 30 min at 40 °C. At first ethanol (2 mL), then the aryl halide (1.00 mmol) and subsequently potassium phenyltrifluoroborate (276 mg, 1.50 mmol) or phenylboronic acid (183 mg, 1.50 mmol), respectively, were added. The sample was stirred for 15 h at 40 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 μL), the mixture was centrifuged. 600 μL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

PTC; General Procedure

K_2CO_3 (675 mg, 4.88 mmol) and $Pd(OAc)_2$ (6.73 mg, 0.03 mmol, 3.00 mol%) were dissolved in H_2O (1 mL) and an organic solvent (2 mL) and stirred for 15 min at 40 °C. At first, the aryl halide (1.00 mmol) and subsequently potassium phenyltrifluoroborate (276 mg, 1.50 mmol) or phenylboronic acid (183 mg, 1.50 mmol), respectively, and the phase-transfer catalyst (0.10 mmol, 10.0 mol%) were added. After another addition of H_2O (2 mL) and the organic solvent (1 mL), the sample was stirred for 15 h at 30 °C. The reaction mixture was cooled down to rt. After adding $CDCl_3$ (2 × 600 μL), the mixture was centrifuged. 600 μL of the organic phase were extracted with a pasteur-pipette and used for ^{1}H-NMR analysis.

Preparative Catalysis

General Procedure

The reaction was set according to the catalysis protocols for the respective solvent and aryl halide (1.00 mmol) with phenylboronic acid (183 mg, 1.50 mmol) as organoboron coupling partner. After heating at 40 °C for 15 h the sample was cooled down to rt, centrifuged and extracted with $CHCl_3$ (3-4 × 600 μL). The organic phase was purified over celite or flash column chromatography on silica gel. The product was concentrated and dried in high vacuum.

Characterization

*4'-Phenylacetophenone (**1c**)*

Purification over celite afforded 97% of a colourless solid; mp 115-116 °C (Lit.:[48] 116-117 °C); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 8.02 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 7.1 Hz, 2H), 7.45 (t, J = 7.7 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 2.62 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 197.97, 145.96, 140.05, 136.03, 129.14, 129.10, 128.42, 127.45, 127.40, 26.83 ppm.

*3'-Phenylacetophenone (**2d**)*

Elution with Cyclohexane/EtOAc (4:1) afforded 78% of a yellow oil; ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 8.18 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 7.9 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 2.66 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 198.30, 141.95, 140.40, 137.86, 131.96, 129.26, 129.14, 128.02, 127.41, 127.40, 127.18, 26.98 ppm.

*2'-Phenylacetophenone (**3d**)*

Elution with Cyclohexane/EtOAc (98:2) afforded 29% of a yellow oil. The product could not be separated from the aryl bromide. The yield was determined by setting the conversion against weight.

*4'-Phenylacetophenone (**4c**)*

Elution with Cyclohexane/EtOAc (9:1) afforded 98% of a colourless solid; mp 119-120 °C (Lit.:[48] 116-117 °C); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 8.03 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 6.9 Hz, 2H), 7.47 (t, J = 7.3 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 2.63 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 197.94, 145.97, 140.07, 136.05, 129.15, 129.11, 128.43, 127.47, 127.42, 26.86 ppm.

*4-Nitrobiphenyl (**6c**)*

Elution with Cyclohexane/EtOAc (4:1) afforded 74% of a light brown solid; mp 108-109 °C (Lit.:[49] 114-115 °C); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 8.31 (d, J = 8.9 Hz, 2H), 7.74 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 6.9 Hz, 2H), 7.50 (t, J = 7.2 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 147.79, 147.25, 138.92, 129.33, 129.10, 127.96, 127.55, 124.27 ppm.

*Ethyl biphenyl 4-carboxylate (**7c**)*

Elution with Cyclohexane/EtOAc (9:1) afforded 71% of a white solid; mp 49-50 °C (Lit.:[50] 48-49 °C); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 8.11 (d, J = 8.5 Hz, 2H), 7.67-7.59 (m, 4H), 7.46 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 166.70, 145.71, 140.25, 130.25, 129.45, 129.10, 128.29, 127.46, 127.19, 61.15, 14.55 ppm.

*2,4,6-Trimethylbiphenyl (**8d**)*

Elution with Cyclohexane/EtOAc (98:2) and Kugelrohr distillation could not afford the pure biaryl.

*4-Phenyltoluene (**9d**)*

Elution with Cyclohexane/EtOAc (4:1) afforded 78% of a colourless crystalline solid; mp 44.3 °C (Lit.:[49] 47-48 °C); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 7.57 (d, J = 7.4 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 2.38 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 141.37, 138.57, 137.21, 129.69, 128.92, 127.20, 127.18, 21.30 ppm.

*3-Phenyltoluene (**10d**)*

Purification over celite afforded 95% of a yellow oil; ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 7.55 (d, J = 6.8 Hz, 2H), 7.41-7.34 (m, 4H), 7.28 (t, J = 7.5 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 2.37 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 141.58, 141.46, 138.53, 128.90, 128.87, 128.21, 128.20, 127.39, 127.37, 124.49, 21.76 ppm.

*2-Phenyltoluene (**11d**)*

Elution with Cyclohexane/EtOAc (4:1) afforded 87% of a yellow oil; ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 7.40-7.33 (m, 2H), 7.32-7.26 (m, 3H), 7.25-7.18 (m, 4H), 2.25 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 142.18, 142.15, 135.55, 130.51, 130.00, 129.40, 128.27, 127.45, 126.97, 125.96, 20.67 ppm.

*4-Phenylanisole (**13d**)*

Elution with Cyclohexane/EtOAc (4:1) afforded 98% of a colourless solid; mp 81-83 °C (Lit.:[49] 92-94 °C); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 7.57-7.51 (m, 4H), 7.41 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 9.0, 2H), 3.85 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 159.36, 141.05, 134.01, 128.93, 128.38, 126.96, 126.87, 114.41, 55.56 ppm.

*3-Phenylanisole (**14d**)*

Elution with Cyclohexane/EtOAc (98:2) afforded 60% of a light yellow oil; ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 7.56 (d, J

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= 6.8 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.27-7.34 (m, 2H), 7.15 (d, J = 7.6 Hz, 1H), 7.11 (s, 1H), 6.86 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 160.13, 142.92, 141.26, 129.92, 128.90, 127.57, 127.35, 119.83, 113.07, 112.83, 55.38 ppm.

*2-Phenylanisole (**15d**)*

Elution with Cyclohexane/EtOAc (98:2) afforded 83% of a light yellow oil; ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 7.52 (d, J = 8.3 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.33-7.29 (m, 3H), 7.03 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H) ppm; ^{13}C-NMR (100.62 MHz, $CDCl_3$, 298 K): δ = 156.66, 138.74, 131.09, 130.92, 129.74, 128.80, 128.17, 127.10, 121.02, 111.42, 55.73 ppm.

1-Dodecyl-3-methylimidazolium Chloride[51]

1-Methyl imidazole (4.78 mL, 60.0 mmol) and 1-chlorododecane (18.4 mL, 78.0 mmol) were refluxed at 70 °C for three days. After cooling down to rt, the upper layer was discarded. The ionic liquid was dissolved in water and washed with EtOAc (30 mL). Once the solvent was evaporated, the obtained solid was again washed with EtOAc (4 × 20 mL) and redissolved in CH_2Cl_2. After evaporating the solvent of, the light yellowish solid was dried in high vacuum. 5.94 g (20.7 mmol, 35%); light yellowish solid; mp 50 °C; IR (ATR): $\tilde{\nu}$ (cm-1) = 3083 (m, Aryl, $\nu_{C\text{-}H}$), 3050 (m, Aryl, $\nu_{C\text{-}H}$), 2950 (w, $-CH_2-$, $\nu_{C\text{-}H}$), 2915 (s, $-CH_2-$, $\nu_{C\text{-}H}$), 2850 (m, $-CH_2-$, $\nu_{C\text{-}H}$), 1571 (m, Aryl, $\nu_{C=C}$), 1472 (m, $-CH_2-$, $-CH_3-$, $\delta_{C\text{-}H}$), 1426 (w, $-CH_2-$, $-CH_3$, $\delta_{C\text{-}H}$), 1383 (w, $-CH_3$, $\delta_{sC\text{-}H}$), 859 (m, Aryl, $\nu_{C\text{-}H}$), 800 (m, Aryl, $\nu_{C\text{-}H}$), 714 (m, $-CH_2-$, $\rho_{C\text{-}H}$); further absorption bands: 3459 (m), 3409 (m), 1636 (m), 1176 (s), 663 (w), 622 (s), 506 (br), 476 (s); ^{1}H-NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 10.45 (s, 1H), 7.50 (t, J = 1.5 Hz, 1H), 7.32 (t, J = 1.6 Hz, 1H), 4.25 (t, J = 7.4 Hz, 2H), 4.06 (s, 3H), 1.83 (qu, J = 7.3 Hz, 2H), 1.26-1.18 (m, 18H), 0.81 (t, J = 6.9 Hz, 3H) ppm; ^{13}C-NMR (100.62 MHz, CDCl3, 298 K): δ = 138.17, 123.65, 121.81, 50.24, 36.75, 32.00, 30.44, 29.70, 29.61, 29.49, 29.43, 29.12, 26.39, 22.78, 14.23 ppm; MS (EI): calc. for $C_{16}H_{31}N_2^+$: 251.25, found: m/z = 251 [M^+].

Notes and references

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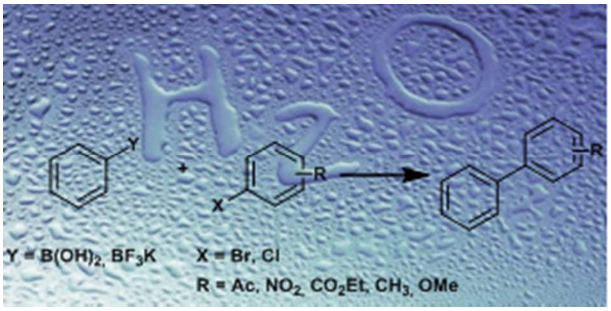

Efficient and general applicable ligand-less and ligand-supported Suzuki coupling reactions in pure water under aerobic conditions