Sulfonated N-heterocyclic carbenes for Suzuki coupling in water†

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Sulfonated, water-soluble imidazolium and imidazolinium salts were synthesized and the respective Pd-complexes with *N,N′*-bis(2,6-dialkyl-4-SO_3^--phenyl)imidazol-2-ylidene and *N,N′*-bis(2,6-dialkyl-4-SO_3^--phenyl)-4,5-dihydroimidazol-2-ylidene ligands were applied in aqueous Suzuki coupling reactions of aryl chlorides.

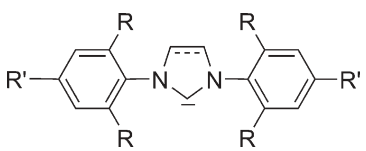
From an environmental as well as from an economic point of view, the use of volatile organic compounds as solvents for chemical transformations is under critical discussion and alternatives such as $scCO_2$,[1,2] ionic liquids[3] or water[4] are actively studied.[5]

Water especially as a cheap and non-toxic solvent has been receiving special attention[6] since the Ruhrchemie/Rhone-Poulenc hydroformylation process is carried out in an aqueous–organic solvent mixture,[7] facilitating the recovery of the valuable rhodium catalyst. The need to replace organic solvents by water is more important in the fine chemicals industry since a much larger amount of waste per mass unit of product is generated[8]—of which the majority are solvents.[9]

Obviously catalytic reactions in water require water-soluble catalysts and it is a typical strategy to modify transition metal complexes by attaching phase tags which infer the desired solubility properties.[10,11] The most prominent solubilizing group in this respect is the sulfonato group; consequently, TPPTS [tri(*m*-sulfonyl)triphenylphosphine; triphenylphosphine, trisulfonated] is the most important ligand among numerous other water-soluble phosphines.[12–16]

Primarily due to their unique electron-donating abilities and the stability of the resulting metal complexes, N-heterocyclic carbenes are beginning to replace phosphines in a number of catalytic processes.[17–22] The most important class of NHC-ligands for catalytic applications is depicted in Scheme 1.

Two of the most important transition-metal catalyzed reactions, the Ru-mediated olefin metathesis and the large group of Pd-mediated cross-coupling reactions, rely on this class of NHC-ligands, as exemplified by the work of Grubbs[23] and Nolan *et al.*[17,24]



Scheme 1 R = Me or *i*Pr, saturated or unsaturated ring.

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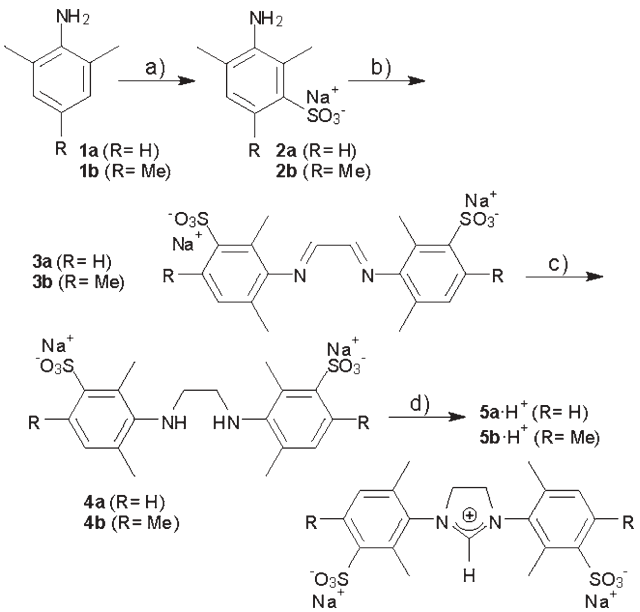
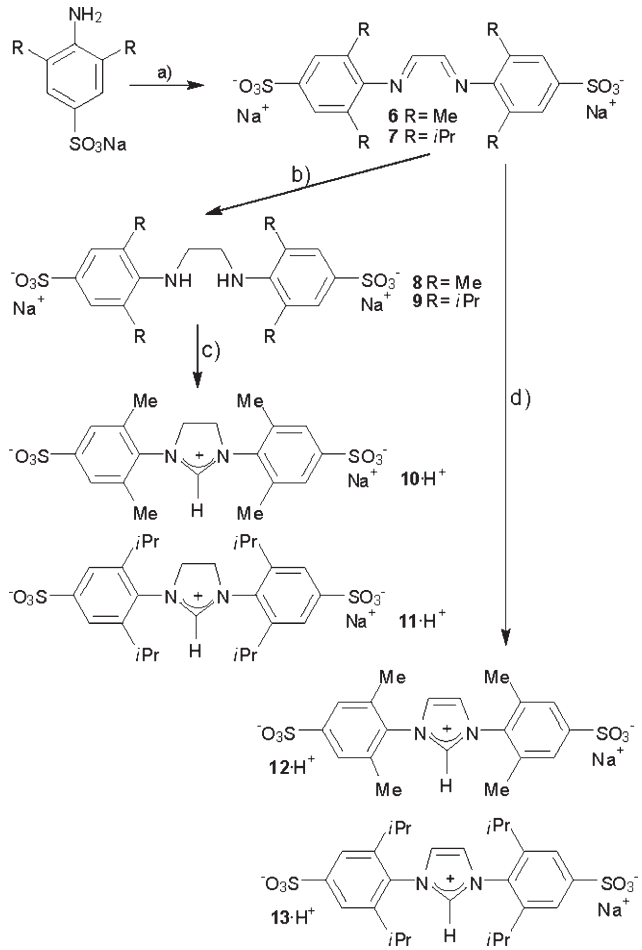
It is therefore surprising that to the best of our knowledge NHC-based relatives of TPPTS have not been described in the literature. A few hydrophilic NHC compounds are known[25,26] and have been used for cross-coupling reactions.[27,28] Recently, Grubbs utilized a PEG-decorated NHC for aqueous olefin metathesis.[29,30]

We wish to present here the synthesis of disulfonated N-heterocyclic imidazolium and imidazolinium salts (Schemes 2 and 3).‡ Starting from 2,6-dimethyl-3-(sulfonato-Na^+)aniline, which was prepared according to a procedure by Courtin *et al.*,[31] the condensation with glyoxal under carefully controlled reaction conditions generates the diimine **3a** in 72% yield. It should be noted here that in our hands the synthesis of **2a** is not reliable; since often a mixture of mono- and disulfonated aniline is formed. Fortunately, these problems can be avoided by applying the same sulfonation reaction conditions to 2,4,6-trimethylaniline, resulting in the monosulfonated aniline **2b**. Diimines **3** can be reduced under hydrogen pressure to generate the diamines **4**, which were cyclized to give the respective disulfonated imidazolinium salts **5**·H^+.

For the synthesis of the 4-sulfonato-substituted NHC-ligands a related approach was chosen. However, the formation of the respective diimines **6** and **7** is difficult when using a 40% aq. solution of glyoxal. The diimines are formed in good yields (>75%), but invariably contain a significant amount (>15%) of



Scheme 2 *Reagents and methods*: (a) 20% oleum; (b) ethanol, glyoxal, HCOOH; (c) MeOH, H_2, Pd/C; (d) EtOH, $HC(OEt)_3$, NH_4Cl, HCOOH.



Scheme 3 *Reagents and methods*: (a) Ethanol, 1,4-dioxane-2,3-diol, HCOOH; (b) MeOH, H_2, Pd/C; (c) EtOH, $HC(OEt)_3$, HCOOH; (d) chloromethyl pivalate, dmso.

unreacted aniline. Obviously, the equilibrium for the formation of the diimine and water is unfavourable. However, the diimine can be obtained in excellent yields when using 1,4-dioxane-2,3-diol, the anhydrous adduct of ethylene glycol and glyoxal. The Pd/C-catalyzed reduction of the pure diimines **6** and **7** in methanol with H_2 resulted in the formation of the desired diamines **8** and **9**. Again diamine **8** is contaminated with the respective aniline due to the facile hydrolysis of diimine **6**. This reduction proceeds cleanly only with strict exclusion of water. The cyclization of the diamines **8** and **9** to the respective imidazolinium salts, **10**·H^+ and **11**·H^+, utilizes $HC(OEt)_3$ according to standard procedures. The synthesis of the two imidazolium salts **12**·H^+ and **13**·H^+ was effected using chloromethyl pivalate as a C_1-building block.

In order to probe the catalytic performance of **5b** in Pd-mediated aqueous cross-coupling reactions,[32] we studied the Suzuki coupling of several aryl chlorides with a catalyst formed *in situ* from **5b**·H^+ and Na_2PdCl_4 in water with KOH as the base (Table 1). While the deprotonation of imidazolium or imidazolinium salts in protic solvents is not possible due to insufficient acidity,[33] the respective Pd–NHC complexes are directly obtained using palladium salts in the presence of base and the sulfonated carbene precursor **5b**·H^+ in pure water. The coupling procedure consists of mixing the respective NHC-precursor, Na_2PdCl_4 and KOH in water, stirring for 30 min to first allow for the formation

Table 1 Aqueous Suzuki coupling reaction of aryl chlorides utilizing azolium salts **5b**, **11** and **13**

Ar-Cl + Ar'-B(OH)$_2$ → (Na_2PdCl_4, NHC·H^+, 3 equiv. KOH, water, 100 °C, 12-16 h) → Ar-Ar'

Entry	Aryl chloride	Boronic acid	Catalyst	NHC	Conv.[a]
1	4-Chlorotoluene	4-Tolyl	1 mol%	**5b**	>99%
2	4-Chloroanisole	4-Tolyl	1 mol%	**5b**	>99%
3	4-Chloroacetophenone	4-Tolyl	1 mol%	**5b**	>99%
4	4-Chlorobenzonitrile	4-Tolyl	1 mol%	**5b**	>99%
5	4-Chlorotoluene	4-Tolyl	0.5 mol%	**5b**	84%
6	4-Chloroacetophenone	4-Tolyl	1 mol%	**11**	63%
7	4-Chlorotoluene	4-Tolyl	1 mol%	**11**	56%
8	4-Chlorotoluene	4-Tolyl	1 mol%	**13**	>99%
9	4-Chlorotoluene	4-Tolyl	0.1 mol%	**13**	91%
10	4-Chloroacetophenone	4-Tolyl	0.1 mol%	**13**	>99%
11	4-Chlorobenzene-sulfonamide	4-Tolyl	0.1 mol%	**13**	>99%
12	4-Chloroanisole	4-Tolyl	0.1 mol%	**13**	74%
13	4-Chloroaniline	4-Tolyl	0.5 mol%	**13**	80%
14	2-Chloropyridine	4-Tolyl	0.1 mol%	**13**	>99%
15	2-Chloropyridine	1-Naphthyl	0.5 mol%	**13**	>99%
16	4-Amino-2-chloro-pyridine	1-Naphthyl	1 mol%	**13**	85%
17	2-Chloro-4-methyl-quinoline	1-Naphthyl	0.5 mol%	**13**	>99%

[a] Average of two runs.

of the NHC–Pd complex followed by addition of the substrates. A set of four aryl chlorides (Table 1, entries 1–4) was reacted with tolylboronic acid at 100 °C using 1 mol% of the Pd catalyst during 12 h to result in the near quantitative formation of the respective coupling products. However, when the Pd-catalyst concentration is lowered to 0.5 mol%, the limits of catalysts based on **5b** become apparent as only 84% of product is formed (entry 5).

*i*Pr-substituted NHC-ligands tend to be more active in cross-coupling reactions than their Me-substituted relatives. Consequently, we studied the imidazolinium salt **11**·H^+ and the imidazolium salt **13**·H^+ in Pd-catalyzed cross-coupling reactions. To our surprise, the saturated NHC-ligand **11** is less efficient than **5b**; even at 1 mol% catalyst loading the respective Pd complexes gave only 63% and 56% conversion with 4-chloroacetophenone and 4-chlorotoluene, respectively (entries 6 and 7). With ligand **11** the formation of a black Pd precipitate was observed during the first few minutes of the catalytic reaction, which is normally indicative of catalyst decomposition. Therefore we stopped screening this ligand. Fortunately, the Pd complex of **13** turned out to be a much more active catalyst. At 1 mol%, 4-chlorotoluene is converted in >99% yield and even at 0.1 mol% catalyst loading 91% of this coupling product is formed (entries 8 and 9). Activated aryl chlorides give full conversion at 0.1 mol% (entries 10 and 11), while the deactivated chloroaniline (entry 13) requires 0.5 mol% catalyst for an 80% conversion.

Remarkably, nitrogen-containing heterocycles are coupled with high efficiencies (entries 14–17). Not only 2-chloropyridine, but also difficult substrates such as 4-amino-2-chloropyridine or the related quinoline derivative are reacted in excellent yields with tolylboronic or naphthylboronic acid. These results compare favourably with catalysts published by Buchwald *et al.*,[32] Fu *et al.*,[34] and Guram *et al.*[35]

Consequently, even the first generation of water-soluble NHC–Pd complexes is comparable in activity to the phosphines described in the literature for aqueous Suzuki reactions.[16,36]

In conclusion, the successful synthesis of sulfonated imidazolium and imidazolinium salts opens the door to the aqueous organometallic chemistry of NHC-ligands. In a preliminary study we have demonstrated the utility of sulfonated NHC-ligands in the aqueous Suzuki coupling of aryl chlorides; additional optimization of the catalytic performance in water will be undertaken in the future.

Notes and references

‡ All NMR spectra were recorded in dmso-d_6 at 300 MHz (^{1}H NMR) and 75.5 MHz (^{13}C NMR).

2,6-Dimethyl-3-(sulfonato-Na$^+$)aniline (**2a**). ^{1}H-NMR: δ 2.06 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.45 (s, 2H, NH_2), 6.73 (d, 1H, ArH, J = 9 Hz), 7.01 (d, 1H, ArH, J = 9 Hz). ^{13}C-NMR: δ 14.2 (CH_3), 17.9 (CH_3), 115.0 (aryl-CH), 118.2 (aryl-CH), 121.9 (aryl-CMe), 125.6 (aryl-CMe), 144.1 (aryl-CSO_3Na), 144.5 (aryl-CNH_2).

N,N′-(Ethane-1,2-diylidene)-bis[2,6-dimethyl-3-(sulfonato-Na$^+$)]aniline (**3a**). In a round-bottom flask the sulfonated aniline **2a** (10.0 g, 44.8 mmol) was dissolved in methanol (2500 mL). Then glyoxal (4.1 mL, 22.4 mmol) was added dropwise to the solution, followed by the addition of two drops of formic acid. The reaction mixture was stirred overnight at room temperature and then for 24 h at 50 °C. A yellow solid precipitated which was filtered off and then dried *in vacuo*. Yield: 8.1 g (16.1 mmol, 72%). ^{1}H-NMR: δ 2.08 (s, 6H, CH_3), 2.32 (s, 6H, CH_3), 7.05 (d, 2H, CH, $J_{H–H}$ = 9 Hz), 7.53 (d, 2H, CH, $J_{H–H}$ = 9 Hz), 8.10 (s, 2H, CH). ^{13}C-NMR: δ 14.8 (CH_3), 18.0 (CH_3), 123.0 (HC_{aryl}), 123.9 (HC_{aryl}), 125.9 (C_{aryl}-Me), 126.4 (C_{aryl}-Me), 144.9 (C-SO_3Na), 150.2 (C_{aryl}-N), 163.9 (HC_{imine}). HR-MS calcd for $C_{18}H_{18}N_2NaO_6S_2$ (M − NaCl) 445.0504; found: 445.0509.

N,N′-Ethane-bis[2,6-dimethyl-3-(sulfonato-Na$^+$)]aniline (**4a**). 5.0 g (10.0 mmol) of the diimine **3a** was dissolved in methanol (120 mL) in an autoclave flask. Then Pd/C 10% (1.13 g, 1.2 mmol) was added to the solution and the mixture was stirred for 3 h under 7 bar H_2 pressure. The Pd/C was filtered off through celite and the solution was evaporated under reduced pressure to obtain the diamine as a white solid. Yield: 4.1 g (8.1 mmol, 84%). ^{1}H-NMR: δ 2.20 (s, 6H, CH_3), 2.43 (s, 6H, CH_3), 3.00 (s, 4H, CH_2), 6.86 (d, 2H, CH, $J_{H–H}$ = 9 Hz), 7.32 (d, 2H, CH, $J_{H–H}$ = 9 Hz). ^{13}C-NMR: δ 14.8 (CH_3), 18.5 (CH_3), 48.5 (H_2C_{amine}), 120.4 (HC_{aryl}), 126.3 (HC_{aryl}), 127.9 (C_{aryl}-Me), 130.8 (C_{aryl}-Me), 144.6 (C-SO_3Na), 146.8 (C_{aryl}-N). HR-MS calcd for $C_{18}H_{22}N_2NaO_6S_2$ (M − NaCl) 449.08173; found: 449.08208.

1,3-Bis[2,6-dimethyl-3-(sulfonato-Na$^+$)phenyl]imidazolinium chloride (**5a**). To a solution of the diamine (**4a**) (1.5 g, 3.0 mmol) in ethanol (30 mL), were added triethylorthoformate (20 mL), NH_4Cl (0.16 g, 3.0 mmol) and a single drop of formic acid. The reaction mixture was refluxed for 2 d. The precipitated solid was filtered, washed with ether and then dried under vacuum. Yield: 0.87 g (1.7 mmol, 52%). ^{1}H-NMR: δ 2.38 (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 4.49 (s, 4H, CH), 7.23 (d, 2H, CH, $J_{H–H}$ = 9 Hz), 7.83 (d, 2H, CH, $J_{H–H}$ = 9 Hz), 9.11, 9.15 (Im-CH). ^{13}C-NMR: δ 14.6 (CH_3), 17.5 (CH_3), 50.9 (CH_2), 127.4 (HC_{aryl}), 128.1 (HC_{aryl}), 133.9 (C_{aryl}-Me), 136.3 (C_{aryl}-Me), 145.7 (C-SO_3Na), 145.9 (C_{aryl}-N), 160.5 (HC_{im}-N). HR-MS calcd for $C_{19}H_{21}N_2NaO_6S_2$ (M − NaCl) 483.06368; found: 483.06274.

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