

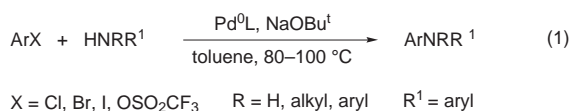
# Palladium-catalyzed amination of aromatic halides in water-containing solvent systems: a two-phase protocol

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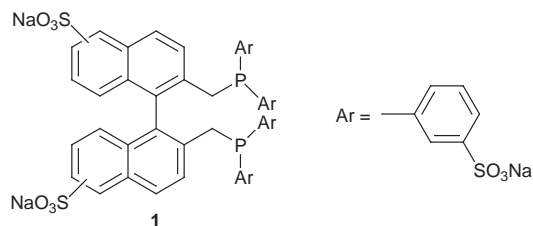
The use of the six-fold sulfonated ligand BINAS-6 **1** permits the Pd<sup>0</sup>-catalyzed amination of aromatic halides in water containing single- or two-phase systems.

Following the initial investigations of Kosugi *et al.*,<sup>1</sup> both Buchwald<sup>2</sup> and Hartwig<sup>3</sup> and their co-workers have developed in recent years a new methodology for the amination of aromatic halides and triflates (ArX: X = Cl, Br, I, OSO<sub>2</sub>CF<sub>3</sub>) with amines RR<sup>1</sup>NH to yield aromatic amines of the type ArNRR<sup>1</sup>.<sup>4</sup> ArX and RR<sup>1</sup>NH were reacted with (di)phosphine-complexed palladium [Pd<sup>0</sup>L, 1–5 mol%] and sodium *tert*-butoxide (1.4 equiv.) in PhMe at 80–100 °C under homogeneous reaction conditions [eqn. (1)].



Under such conditions reapplication of the Pd<sup>0</sup> catalyst would be difficult as is reuse of the relatively expensive (di)phosphine ligand L. In contrast, by using a two-phase protocol, the separation of products (and unreacted starting material) from the catalyst and subsequent reapplication of the catalyst in further reactions is made facile.<sup>5</sup> For this reason there is increasing interest in two-phase catalysis both in the laboratory<sup>6,7</sup> and for industrial applications.<sup>8</sup> Here we report on a two-phase protocol of the aforementioned Pd<sup>0</sup>-catalyzed amination reaction.

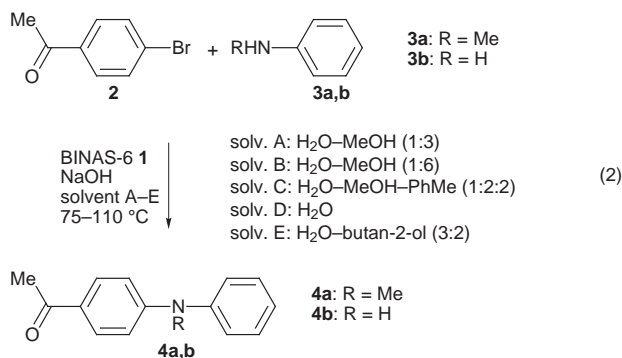
The ligand used here is the six-fold sulfonated 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl **1** (BINAS-6) dissolved in water.<sup>9</sup>



The reaction of 4-bromoacetophenone **2** with *N*-methylaniline **3a** in water–MeOH (1:3; solvent A) using NaOH as the base and the aforementioned catalyst Pd<sup>0</sup>-**1** afforded 1-[4-(*N*-methylanilino)phenyl]ethan-1-one **4a** in 88% yield [eqn. (2); Table 1, entry 1].

Reacting **2** with **3b** in the presence of Pd<sup>0</sup>-**1** and NaOH as the base in water–MeOH (1 : 6; solvent B) resulted in the formation of 1-(4-anilinophenyl)ethan-1-one **4b** in 91% yield [eqn. (2); Table 1, entry 2]. The Pd<sup>0</sup>-**1** catalyst, which is dissolved in the aqueous phase, can be reused after separation of the products. The reaction was repeated under similar conditions. The following yields were achieved: second reaction 85% **4b**, (5 h); third reaction 53% **4b**, (7 h); fourth reaction 36% **4b**, (7 h).

The use of a two-phase H<sub>2</sub>O–MeOH–PhMe system (1 : 2 : 2; solvent C) in the reaction of **2** with **3a** afforded only low yields



(36%) of **4a** [eqn. (2); Table 1, entry 3]. The use of emulsifying agents like tetradecyltrimethylammoniumbromide did not increase the yield of **4a**, but resulted in considerable problems during product recovery. With only water as the solvent (solvent D) **4a** was obtained in 36% yield [eqn. (2); Table 1, entry 4].

Butan-2-ol and water form a biphasic system with good miscibility of the two solvents. Thus in the reaction of **2** with **3b** in the presence of Pd<sup>0</sup>-**1** and water–butan-2-ol (3 : 2, solvent E) the product **4b** was obtained in 89% yield [eqn. (2); Table 1, entry 5]. NaOH was found to give the best results as compared to other group I hydroxides. The catalyst Pd<sup>0</sup>-**1** remains in the aqueous phase while the products can be collected conveniently by separation of the organic layer. Only small amounts of

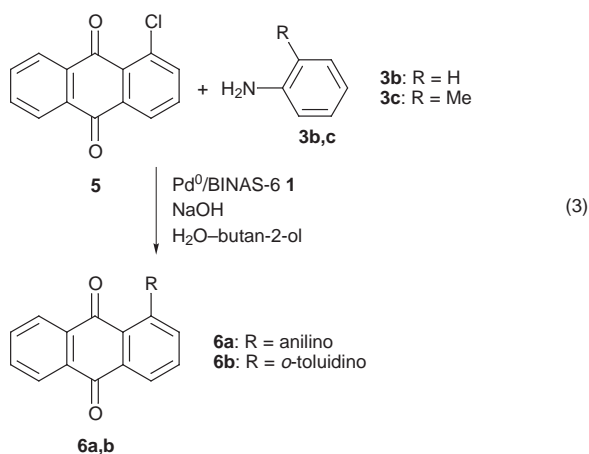
**Table 1** Pd<sup>0</sup>-**1** catalysed aminations of ArX in water-containing solvent systems. All reactions were carried out under argon with degassed solvents and starting materials. **1** was applied in an aqueous solution (140 mmol l<sup>-1</sup>). Physical and spectroscopic data of the products were consistent with those reported previously in the literature.

Entry <sup>a</sup>	Halide	Amine	Solvent	Reaction time/h	Product	Yield (%)
1	<b>2</b>	<b>3a</b>	A	2	<b>4a</b>	88
2	<b>2</b>	<b>3b</b>	B	3	<b>4b</b>	91
3	<b>2</b>	<b>3a</b>	C	32	<b>4a</b>	36
4	<b>2</b>	<b>3a</b>	D	25	<b>4a</b>	36
5	<b>2</b>	<b>3b</b>	E	6	<b>4b</b>	89
6	<b>5</b>	<b>3b</b>	E	6	<b>6a</b>	81
7	<b>5</b>	<b>3c</b>	E	8	<b>6b</b>	71

<sup>a</sup> Details of entries 1–7. 1: 160 μmol **1**, 20 μmol Pd(OAc)<sub>2</sub>, 3 ml MeOH, 1 mmol ArX, 1.3 mmol amine, 1.3 mmol NaOH, 75 °C; products were extracted with Et<sub>2</sub>O. 2: 70 μmol **1**, 9 μmol Pd(OAc)<sub>2</sub>, 6 ml MeOH, 1 mmol ArX, 1.3 mmol amine, 1.4 mmol NaOH, 75 °C; products were extracted with Et<sub>2</sub>O. 3: 840 μmol **1**, 100 μmol Pd(OAc)<sub>2</sub>, 12 ml MeOH, 12 ml PhMe, 6 ml water, 2 mmol ArX, 2.4 mmol amine, 2.8 mmol NaOH, 70 °C; products were collected by separation of the organic layer. 4: 840 μmol **1**, 100 μmol Pd(OAc)<sub>2</sub>, 12 ml water, 2 mmol ArX, 2.4 mmol amine, 2.8 mmol NaOH, 90 °C; products were extracted with Et<sub>2</sub>O. 5–7: 80 μmol **1**, 11 μmol Pd(OAc)<sub>2</sub>, 3 ml water, 2 ml butan-2-ol, 1 mmol ArX, 1.3 mmol amine, 1.3 mmol NaOH, 110 °C; products were collected by separation of the organic layer.

product (<5%) remain in the aqueous phase. In this solvent system the catalyst can be reused as well.

Reacting 1-chloroanthraquinone **5** with aniline **3b** in the presence of Pd<sup>0</sup>-**1** and NaOH in water–butan-2-ol (3 : 2) allowed amination of **5**, affording 1-anilinoanthraquinone **6a** in 81% yield [eqn. (3); Table 1, entry 6]. The use of *o*-toluidine **3c** under similar conditions gave 1-(*o*-toluidino)anthraquinone **6b** in 71% yield [eqn. (3); Table 1, entry 7].



In conclusion, it has been demonstrated that the Pd<sup>0</sup>-catalyzed amination of aromatic halides with amines can be performed by means of a two-phase protocol with NaOH instead of the expensive NaOBu<sup>t</sup> as the base. Further advantages are the facile catalyst/product separation and the reusability of the water-soluble Pd<sup>0</sup>/BINAS-6 catalyst. The catalyst system is also suitable for the preparation of substituted anthraquinones, which are important in dye stuff production.<sup>10</sup> Further work is being conducted to optimise the reaction conditions and to perform selective single amination reactions of dichloro-substituted anthraquinones.

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