Retraction

The results that are described in the article entitled “Facile Palladium-Catalyzed Arylation of Heterocycles and Nonactivated Arenes with Aryl Chlorides”, for which I am the responsible corresponding author, were criticized by a very attentive reader after appearance of the article online in Early View. Quite a few of the spectroscopic data are incorrect, and the original mass spectra cannot be located. The critical reader and his co-workers were unable to reproduce our results, and we are grateful to them for bringing this to our attention. I herewith withdraw the Communication with the consent of the co-author.

Herbert Plenio

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Direct Cross-Coupling

Facile Palladium-Catalyzed Arylation of Heterocycles and Nonactivated Arenes with Aryl Chlorides**

*Jan Pschierer and Herbert Plenio**

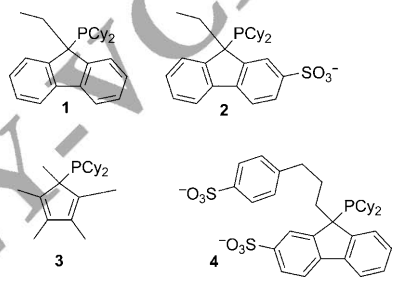
In memory of Keith Fagnou

Direct cross-coupling of heterocycles with aryl–X substrates (X = I, Br, Cl, OMs, OTs, etc.) for the synthesis of biaryl compounds through consecutive C–X and C–H activation may result in an alternative to the well-known Suzuki–Miyaura, Stille, Negishi, Kumada, or Hiyama reactions.[1] The significant progress in direct cross-coupling reactions during the last few years has been summarized in a number of recent review articles by Ackermann,[2] Daugulis,[3] Fagnou,[4] Gevorgyan,[5] Lautens[6] and others.[7] In these reactions, complexes of numerous transition metals like Pd, Cu,[8] Ni, Rh,[9] Fe, Ru, and Ir have been successfully applied.[2]

In heterocycles and in arenes with *ortho* directing groups, certain C–H bonds are activated and thus more amenable to such reactions; this also applies to the C–X bond in aryl iodides and bromides and to intramolecular C–H/C–X reactions.[10] Consequently, a large number of transformations have been reported for reactants combining these favorable properties.[11] On the other hand, substrates without activated C–H and/or C–X groups still pose significant problems in biaryl formation. Only few reports on the direct cross-coupling of aryl chlorides[12] and tosylates/mesylates[2] with heterocyclic substrates[13] or with directing groups,[14] mainly employing palladium- or nickel-based catalysts have been published. Direct arylation reactions of arene substrates not bearing directing groups are scarce.[2,15] Proch and Kempe successfully employed a rhodium-based catalyst for reactions of aryl–X compounds (X = I, Br, Cl) with arenes.[16] Meanwhile, Fagnou and co-workers reported the coupling of benzene[17] or electron-deficient arenes[18] with various aryl bromides where they employed relatively small loadings of $Pd(OAc)_2$ (2–3 mol%) and the DavePhos ligand at 120°C (DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl). However, only benzene, which needs to be present in large excess, was successfully employed. Furthermore, the reaction with benzene is restricted to aryl bromides.

Herein, we report a general and highly active catalytic system for reactions of a wide range of activated and nonactivated arenes with aryl chlorides in water (or alternatively in *n*-butanol/water mixtures for poorly water soluble substrates). This study is based on our successful application of palladium complexes of sulfonated fluorenyl phosphines[19] in the aqueous Suzuki–Miyaura coupling.[20] In particular, heterocyclic substrates turned out to be highly reactive when water was used as the solvent in the Suzuki reaction,[20a] as well as in various C–X/C–H activation reactions as demonstrated by Greaney and co-workers[21] This high reactivity was attributed to the absence of significant catalyst inhibition by heterocyclic substrates under the reported reaction conditions[20a] and motivated us to study direct cross-coupling reactions in more detail.

We first tested the reaction of benzothiazole with chlorobenzene in water or water/*n*-butanol using combinations of different bases (NaOH, K_2CO_3), palladium sources (0.05 mol% of Na_2PdCl_4, $PdCl_2$, $Pd(OAc)_2$), and various fluorenyl[20a,c] and pentamethylcyclopentadienyl (Cp*) phosphines[22] (Scheme 1).



Scheme 1. Fluorenyl and Cp* phosphine derivatives evaluated in direct cross-coupling reactions. Cy = cyclohexyl.

Several Pd/phosphine complexes were highly efficient and gave the desired coupling product in 56–89% yield, with ligand **4** being the top performer (Table S1 in the Supporting Information). With a view to the facile large-scale synthesis of the disulfonated fluorenyl phosphine cataCXium F sulf (**4**)[20a,23] and its commercial availability, it was decided to study this water-soluble phosphine in more detail for a large range of different heterocyclic substrates (Table 1). In most reactions 0.1 mol% of [Pd] was sufficient for quantitative product formation (Table 1). For comparison with the work of others, the reaction of benzothiazole with chlorobenzene serves as an instructive example (Table 1, entry 10). The use of 5 mol% of $Pd(OAc)_2$ and 10 mol% of Ad_2PnBu at 125°C in NMP (*N*-methylpyrollidone) as the solvent and K_2CO_3 as the base was reported by Chiong and Daugulis and afforded the isolated product in 63% yield.[13] However, the same reaction using 0.05 mol% of Na_2PdCl_4 and 0.1 mol% of **4** at

[*] J. Pschierer, Prof. Dr. H. Plenio
Organometallic Chemistry, Technische Universität Darmstadt
Petersenstrasse 18, 64287 Darmstadt (Germany)
E-mail: plenio@tu-darmstadt.de

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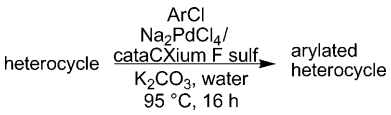
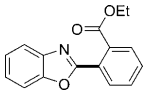
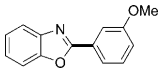
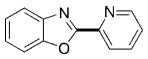
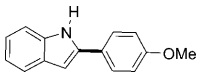
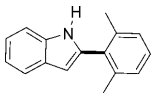
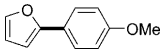
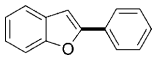
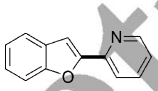
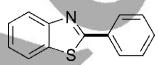
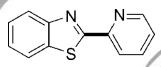
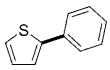
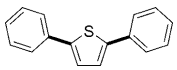
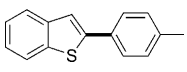
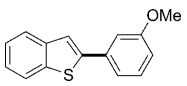
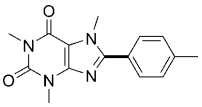
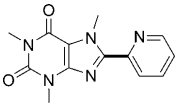
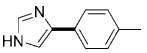
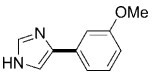
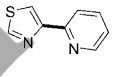
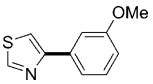
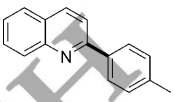
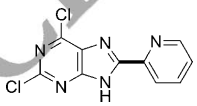
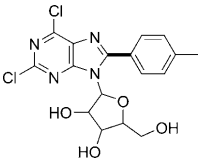
Table 1: Direct cross-coupling reactions of heterocycles and aryl chlorides in water.



Entry	Heterocycle	Product	[Pd] [mol%]	Yield [%]
1	benzoxazole		1.0 0.5 0.1	99[a] 99[b] 89[b]
2	benzoxazole		0.5 0.1	99[a] 78[b]
3	benzoxazole		0.5 0.1	99[a] 82[b]
4	indole		0.5 0.1 0.05	99[a] 99[b] 67[b]
5	indole		0.1 0.05	99[a] 71[b]
6	furan		1.0 0.5 0.1 0.05	99[a] 99[b] 86[b] 67[b]
7	benzofuran		0.5 0.1 0.05	99[a] 99[b] 47[b]
8	benzofuran		0.5 0.1 0.05	99[a] 99[b] 27[b]
9	benzothiazole		0.1 0.05 0.05 0.025 0.025	99[a] 89[b] 99[d] 38[b] 53[d]
10	benzothiazole		0.1 0.05 0.025	99[a] 73[b] 17[b]
11	thiophene		0.5 0.1	99[a] 67[b]
12	thiophene		0.5[c] 0.1[c]	99[a] 61[b]
13	benzothiophene		0.1 0.05	99[a] 80[b]
14	benzothiophene		0.1 0.05	92[a] 73[b]
15	caffeine		0.1 0.05 0.05	99[a] 67[b] 81[d]
16	caffeine		0.1 0.05	99[a] 43[b]
17	imidazole		0.1 0.05	78[a] 73[b]
18	imidazole		0.5 0.1	83[a] 26[b]
19	thiazole		0.1 0.025	99[a] 61[b]
20	thiazole		0.1 0.025	99[a] 54[b]
21	quinoline		0.1 0.05	99[a] 78[b]
22	2,6-dichloro9*H*-purine		0.1 0.05	99[a] 67[b]
23	2,6-dichloropurineribo-side		0.1 0.05	99[a] 46[b]

Reaction conditions: heterocycle (1.0 mmol), aryl chloride (1.2 mmol), K_2CO_3 (2.5 mmol), Na_2PdCl_4/cataCXium F sulf (1:2), degassed water (5.0 mL), 95 °C, 16 h. [a] Yield of isolated product. [b] Yield determined by GC analysis. [c] 2.5 mmol of aryl chloride, [d] 1.2 mmol of aryl bromide. The assignment of the isomers relies on NMR spectroscopy and comparison of the melting points to known values (see the Supporting Information).

95 °C in water and K_2CO_3 as the base provided 89% yield (Table 1, entry 9). This outcome corresponds to a 100-fold lower catalyst loading at significantly lower reaction temperatures. The present approach compares favorably with the analogous reactions using aryl bromides instead of aryl chlorides. The benzothiazole transformation with 4-bromotoluene was reported to provide the product in 91% yield, albeit using 2 mol% of $Pd(OAc)_2$, 4 mol% of PCy_3, and 30 mol% pivalic acid as an additive.[11a] The effect of this additive towards our catalytic system was tested, but no improvement was observed, even though such reactions are believed to proceed along the concerted metalation–depro-

tonation pathway.[24] Instead, simple bases such as NaOH or K_2CO_3 provided the best results.

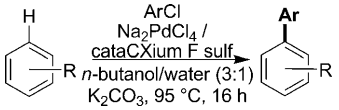
The present approach also allowed reactions with heterocyclic aryl chlorides (2-chloropyridine; Table 1, entries 3, 8, 10, 16, 19, and 22), which led to bis(heterocyclic) compounds and was highly tolerant towards additional functional groups such as unprotected amino groups in indoles (Table 1, entry 4), imidazoles (Table 1, entries 17 and 18), or purine (Table 1, entry 22), and hydroxy groups in purine ribosides (Table 1, entry 23). The selective mono- and diarylation of thiophene led to mono- and diarylated products (Table 1, entries 11 and 12). We believe that this pronounced selectivity is a result of the different water solubilities of mono- and diarylated products.

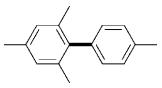
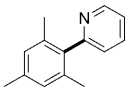
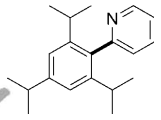
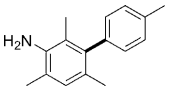
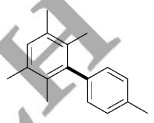
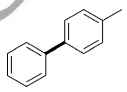
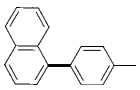
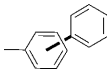
The use of water in such direct cross-coupling reactions may be seen favorably with respect to the green nature of this solvent. However, apart from superior reactivity in water, this approach also facilitates the reaction work-up procedure. The cross-coupling products tend to be poorly soluble in water and are easily separated either by phase separation (for large-scale reactions) or by extraction with *n*-butanol, while the various salts (palladium and sulfonated phosphine) remain in the aqueous phase.

Motivated by the excellent activity of Pd/cataCXium F sulf in the arylation of heterocyclic substrates, we preliminarily evaluated the reaction of the nonactivated substrate mesitylene with 4-chlorotoluene under the same reaction conditions. Initially no product formation was observed. However, while the heterocyclic substrates are characterized by a significant water solubility (especially at elevated temperatures), the same is not true for mesitylene. We therefore employed a mixture of *n*-butanol/water (3:1), which offers reasonable solubility for nonpolar substrates. This reaction of 4-chlorotoluene and mesitylene resulted in significant product formation (26% conversion) at 1 mol% catalyst loading and 95°C. A new optimization of the catalyst formulation, including tests with various other phosphines (PCy_3, *t*BuPCy$_2$, (*t*Bu)$_2$PCy, Ad$_2$P*n*Bu, and Ad$_2$PBn (Ad = 1-admantyl); Tables S2 and S3 in the Supporting Information), reestablished the superiority of **4** in combination with Na_2PdCl_4. After increasing the catalyst loading to 5 mol% of [Pd], more than 90% product formation was observed for the transformations detailed in Table 2. We note that there is no need for a massive excess of the nonactivated arene (30 equiv of benzene, as reported by Lafrance and Fagnou).[17] Instead, for all of the reactions reported here, only a small excess of the aryl chloride is required (1.1–1.2 equivalents of aryl chloride per arene).

The coupling reactions involving nonactivated arenes appear to be tolerant towards functional groups and a heterocyclic chloride, such as 2-chloropyridine, does not lead to the deactivation of the catalyst. Reaction of 2-chloropyridine with mesitylene led to the clean formation the cross-coupling product (Table 2, entry 2). Furthermore, this transformation appears to be relatively insensitive towards steric demand in the arene substrates: because the analogous reaction of 1,3,5-triisopropylbenzene with 2-chloropyridine also led to the formation of the respective coupling product in excellent yield (Table 2, entry 3).

Table 2: Direct cross-coupling reactions of nonactivated arenes and aryl chlorides.



Entry	Arene	Product	Cat. [mol%]	Yield [%]
1	mesitylene		5.0 2.5 2.5 1.0	99[b] 63[c] 62[a,c] 26[c]
2	mesitylene		5.0 2.5 1.0	99[b] 41[c] 9[c]
3	1,3,5-triisopropylbenzene		5.0 2.5 1.0	99[b] 32[c] 26[c]
4	2,4,6-trimethylaniline		5.0 2.5 2.5 1.0	99[b] 73[c] 75[a,c] 46[c]
5	1,2,4,5-tetramethylbenzene		5.0 1.0	99[b] 21[c]
6	benzene		5.0 2.5 1.0	91[b] 69[c] 21[c]
7	naphthalene		5.0 2.5 2.5 1.0	87[b,e] 43[c] 41[a,c] 12[c]
8	toluene		5.0	99%[d]

Reaction conditions: arene (1.0 mmol), aryl chloride (1.2 mmol), K_2CO_3 (2.5 mmol), Na_2PdCl_4/cataCXium F sulf (1:2), degassed water/*n*-butanol (1:3), 95°C, 16 h. [a] 1.2 mmol of aryl bromide, [b] Yield of isolated product. [c] Yield determined by GC analysis. [d] Mixture of *o*/*m*/*p* isomers (2:32:66). [e] 5% of 2-arylated product was also formed.

Normally aryl bromides and iodides are applied in direct cross-coupling reactions, while in the present set of reactions we have so far exclusively used aryl chlorides. Therefore we tested how our catalytic system responds to the use of aryl bromides instead of chlorides. For nonactivated substrates (Table 2, entries 1, 4, and 7) the same yields, regardless of the nature of the C–X bond, were observed when using aryl chlorides and bromides. This result suggests that C–H activation is rate limiting in direct cross-coupling reactions of nonactivated substrates. This hypothesis receives additional support from the analysis of the competition reaction of C_6H_6/C_6D_6 with 4-tolylchloride, which reveals a pronounced

kinetic isotope effect ($k_H/k_D = 4.6$). In the case of direct cross-coupling reactions involving heterocycles slightly higher yields for aryl bromide than for chloride were found (Table 1, entries 9 and 15); obviously for those highly C–H activated substrates, C–X activation contributes to the rate-limiting step. With a view to the mechanism of such reactions involving deprotonation of C–H bonds, it is remarkable that the often used polar aprotic solvents can be replaced by water.

In conclusion, the in situ formed Pd/cataCXium F sulf complex displays excellent activity for direct cross-coupling reactions of aryl chlorides with numerous heterocycles and various nonactivated substrates. We believe that several factors are responsible for this: 1) complexes of Pd/cataCXium F sulf are much more powerful for oxidative addition than the Pd/PCy_3 complexes[25] that are often employed in combined C–X/C–H activation reactions, 2) the use of water as the solvent relieves the catalyst inhibition by heterocyclic substrates, as heterocycles prefer to engage in hydrogen bonding to water rather than coordinate to Pd,[20a] 3) in water the primary [(L)ArPdCl] complex formed after oxidative addition might dissociate more easily to form cationic Pd species, which should be more efficient for C–H activation.[26] As a consequence of the intense research on the classic C–X cross-coupling reactions it is now well understood how to activate C–Cl bonds. The same catalysts can also be applied successfully to C–H activation, but nonetheless we still need to learn more about the factors determining the efficient activation of C–H bonds with such catalysts.

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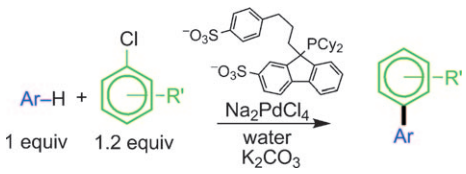
Communications

Direct Cross-Coupling

J. Pschierer, H. Plenio* ____ ■■■■–■■■■

Facile Palladium-Catalyzed Arylation of Heterocycles and Nonactivated Arenes with Aryl Chlorides



Efficient CH/CX activation in water: Arenes or various heterocycles were treated with aryl chlorides and gave the respective biaryl compounds in more than 90% yield using 0.05–5 mol% of a Pd/phosphine complex in water or water/*n*-butanol as the reaction solvent (see scheme; Cy = cyclohexyl).