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Palladium-Catalyzed Cross-Coupling of Organozinc Bromides with Aryl Iodides in Perfluorinated Solvents**

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The formation of new carbon–carbon bonds by palladium-catalyzed cross-coupling has experienced a spectacular development over the past ten years.^[1] Most of these reactions require relatively large quantities of a costly palladium catalyst (1–5 mol %)^[2] and removal of traces of palladium compounds from the reaction products; this has hampered

applications of this methodology to large-scale syntheses. Recently we showed that perfluorinated solvents are a convenient medium for transition metal catalyzed oxidations with a perfluorinated metal complex as the catalyst.^[3,4] At high temperatures (ca. 60 °C) many organic solvents and reagents are soluble in perfluorinated solvents, but at room temperature organic compounds are insoluble; this leads to a two-phase system at room temperature. Fluorous biphasic catalysis, popularized by Horváth,^[5] has the advantage of easy phase separation and avoids pollution of the reaction product with the transition metal catalyst, which is only soluble in the fluorous phase and can be reused several times after simple phase separation. Here we report that palladium(0)-catalyzed cross-coupling^[6] between arylzinc bromides (Ar^1ZnBr , **1**) and aryl iodides (Ar^2I , **2**) proceeds smoothly in the presence of the perfluorinated phosphane **3** (0.6 mol %) and bis(dibenzylideneacetone)palladium(0) ($[\text{Pd}(\text{dba})_2]$, 0.15 mol %)^[7] with 1-bromoperfluorooctane ($\text{C}_8\text{F}_{17}\text{Br}$) and toluene as the solvent system to provide polyfunctional biphenyls of type **4** in high yields (Table 1).

Table 1. Palladium-catalyzed cross-coupling between arylzinc bromides **1** and aryl iodides **2** in a toluene/1-bromoperfluorooctane biphasic system.

$\text{Ar}^1\text{-ZnBr} + \text{Ar}^2\text{-I} \xrightarrow[\text{toluene / C}_8\text{F}_{17}\text{Br, 60 °C, 0.2–0.5 h}]{\text{(F}_{13}\text{C}_6\text{C}_6\text{F}_5)_3\text{P} \text{ (3, 0.6 mol \%)} \text{ [Pd(dba)}_2\text{] (0.15 mol \%)}} \text{Ar}^1\text{-Ar}^2$				
Entry	Ar ¹	Ar ²	Product 4	Yield [%] [a]
1	Ph	4-AcOC ₆ H ₄	4a	93
2	4-ClC ₆ H ₄	4-NO ₂ C ₆ H ₄	4b	93
3	4-ClC ₆ H ₄	3-EtO ₂ CC ₆ H ₄	4c	97
4	3-CF ₃ C ₆ H ₄	4-MeOC ₆ H ₄	4d	89
5	3-CF ₃ C ₆ H ₄	4-BrC ₆ H ₄	4e	92
6	2-thienyl	3-MeOC ₆ H ₄	4f	98
7	2-thienyl	4-NO ₂ C ₆ H ₄	4g	87
8	4-TIPS-OC ₆ H ₄ [b]	3-EtO ₂ CC ₆ H ₄	4h	97
9	4-TIPS-OC ₆ H ₄	4-BrC ₆ H ₄	4i	99

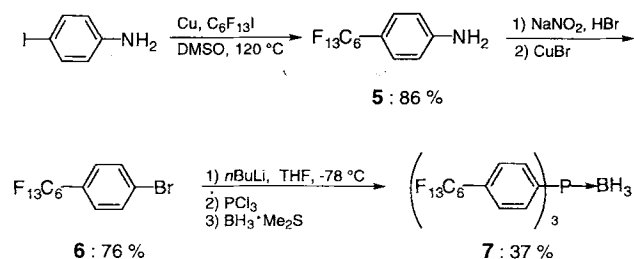
[a] Yield of isolated product. [b] TIPS = *i*Pr₃Si.

Arylzinc bromides **1** were prepared from the corresponding aryl bromides by bromine–lithium exchange followed by lithium–zinc transmetalation with zinc bromide.^[8] 2-Thienyllithium used to prepare 2-thienylzinc bromide was obtained by deprotonation of thiophene with *n*-butyllithium.^[9] The use of triarylphosphane **3**, which bears long perfluorinated chains, is essential for the success of the reaction. No activity of the palladium catalyst was observed with the previously known ($\text{C}_6\text{F}_{13}\text{C}_2\text{H}_4$)₃P.^[5,10] The new phosphane **3** was prepared in three steps from 4-iodoaniline. Treatment of **3** with copper and $\text{C}_6\text{F}_{13}\text{I}$ in DMSO (120 °C, 2 h) gave the substituted aniline **5** in 86% yield.^[11] Sandmeyer reaction of **5** [a) NaNO_2 , HBr; b) CuBr] provided the corresponding aryl bromide **6** in 76% yield. Bromine–lithium exchange with *n*BuLi in THF followed by addition of PCl_3 afforded the phosphane–borane complex **7** in 37% yield after protection with borane (Scheme 1). After **7** was purified, the borane protecting group was removed with diethylamine.^[12]

The free phosphane **3** was treated with $[\text{Pd}(\text{dba})_2]$ in $\text{C}_8\text{F}_{17}\text{Br}$ to afford an orange solution of $[\text{Pd}(\text{P}(\text{C}_6\text{H}_4\text{-C}_6\text{F}_{13})_3)_4]$ (**8**). With this catalyst (0.15 mol %), the reaction between an arylzinc bromide and an aryl iodide is complete within 0.5 h at 60 °C. At this temperature, the reaction mixture is homogeneous and a two-phase system is again obtained upon cooling to room temperature. The cross-coupling product **4** is easily

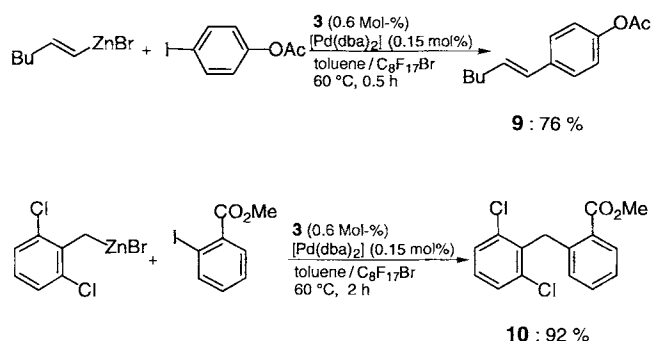
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Scheme 1. Synthesis of perfluorinated phosphane 7.

recovered from the toluene phase, whereas the palladium catalyst remains in the fluororous phase. The latter can be reused several times without significant changes in reaction yields. Thus, cross-coupling between phenylzinc bromide and 4-iodophenyl acetate in the presence of **8** (1.5 mol %) provides the biphenyl **4a** in 93 % yield. Repeating the reaction four times with the same catalyst solution gave yields of 91, 90, 86, and 89 %. Furthermore, **8** displays higher activity than $[\text{Pd}(\text{PPh}_3)_4]$, which may be due to the presence of the fluorinated carbon chain. It removes electron density from the phenyl ring to lead to an electron-deficient phosphane, and favors reductive elimination in these cross-couplings. The high activity of **8** allows the use of only 0.15 mol % of the catalyst under standard conditions. Upon further reducing the catalyst quantity to 0.07 mol %, a decrease in yield was observed (**4a** was obtained in only 76 % yield, as opposed to 93 %; Table 1, entry 1). Interestingly, these cross-coupling reactions tolerate several functional groups such as Cl, NO_2 , CO_2R , CF_3 , and $i\text{Pr}_3\text{SiO}$. Furthermore, in the case of 4-bromiodobenzene, only substitution of the iodide atom is observed; the C–Br bond is unaffected (entries 5 and 9). Cross-coupling can also be extended to alkenylzinc bromides^[8] and benzylzinc bromides^[13] to provide the styrene derivative **9** (76 %) and diarylmethane **10** (92 %), respectively (Scheme 2).



Scheme 2. Cross-coupling with an alkenyl- and a benzylzinc bromide.

We have prepared a new triarylphosphane **3** bearing perfluorinated substituents which allows efficient palladium-catalyzed cross-coupling between organozinc bromides and aryl iodides in biphasic catalysis. The simple work-up conditions and the possibility of reusing the catalyst for several reactions have been demonstrated. The performance of other transition metal catalyzed reactions of interest for organic synthesis with the new fluororous phosphane **3** is currently underway.

Experimental Section

Typical procedure: 4-acetoxibiphenyl (**4a**). A 10 mL Schlenk flask was charged with a solution of **8** (1.2 μmol , 0.15 mol %, prepared in situ) in $\text{C}_6\text{F}_{17}\text{Br}$ (2 mL).

4-Iodophenyl acetate (210 mg, 0.8 mmol) in toluene (2 mL) was added at 0 °C followed by a solution of phenylzinc bromide (0.88 mmol, 1.1 equiv) in toluene (1 mL). The reaction mixture was stirred at 60 °C for 0.5 h to provide a homogeneous solution. Upon cooling to 0 °C, phase separation occurred immediately. The orange perfluorinated phase containing the catalyst **8** was recovered and could be used for further experiments. The organic phase was diluted with Et_2O and washed with a saturated aqueous solution of NH_4Cl . The crude product obtained after evaporation of the solvent was purified by flash chromatography (hexanes/ether 19/1) to yield pure **4a** (158 mg, 0.74 mmol, 93 % yield).

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