[1] a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim, 1993; b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; c) H.-U. Blaser, B. Pugin, F. Spindler in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, 1996, p. 992.

[2] Recent review: B. L. Feringa, A. H. M. de Vries in *Advances in Catalytic Processes, Vol. 1* (Ed: M. D. Doyle), JAI, CT, USA, 1995, p. 151.

[3] a) Q.-L. Zhou, A. Pfaltz, *Tetrahedron* 1994, 50, 4467; b) M. van Klaveren, F. Lambert, D. J. F. M. Eijkelkamp, D. M. Grove, G. van Koten, *Tetrahedron Lett.* 1994, 35, 6135; c) M. Spescha, G. Rihs, *Helv. Chim. Acta* 1993, 76, 1219; d) M. Kanai, K. Tomioka, *Tetrahedron Lett.* 1995, 36, 4275; e) K. Soai, T. Hayasaka, S. Ugajin, S. Yokoyama, *Chem. Lett.* 1988, 1571; f) C. Bolm, M. Ewald, *Tetrahedron Lett.* 1990, 31, 5011; g) A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* 1994, 50, 4479; h) A. H. M. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* 1997, 8, 1377.

[4] An excellent review on recent progress in organocopper chemistry: N. Krause, A. Gerold, *Angew. Chem.* 1997, 109, 194; *Angew. Chem. Int. Ed. Engl.* 1997, 36, 187.

[5] a) A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem.* 1996, 108, 2526; *Angew. Chem. Int. Ed. Engl.* 1996, 35, 2374; b) one other example of an enantioselective copper-catalyzed addition of Et_2Zn to cyclohexenone (ee 30%) has been reported: A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* 1993, 4, 2427.

[6] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* 1995, 107, 1159; *Angew. Chem. Int. Ed Engl.* 1995, 34, 1059.

[7] a) Mismatched ligand S,S,S-1 afforded 4a with 82% yield and 75% ee; b) the introduction of substituents at the 3,3'-positions of the binaphthol moiety only marginally affected the enantioselectivities.

[8] The spectral and analytical data for all new compounds were in agreement with the indicated structures.

[9] Cu^I-catalyzed addition of functionalized organozinc reagents; B. H. Lipshutz, M. R. Wood, R. Tirado, *J. Am. Chem. Soc.* 1995, 117, 6126.

[10] F. Langer, A. Devasagayaraj, P.-Y. Chavant, P. Knochel, *Synlett* 1994, 410.

[11] P. Knochel, R. D. Singer, *Chem. Rev.* 1993, 93, 2117.

[12] a) C. Ullenius, B. Christenson, *Pure Appl. Chem.* 1988, 60, 57; b) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* 1985, 26, 6015; c) N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* 1994, 116, 381; d) J. P. Snyder, *Angew. Chem.* 1995, 107, 80; *Angew. Chem. Int. Ed. Engl.* 1995, 34, 80.

[13] a) For a catalytic asymmetric tandem Michael–aldol reaction, see T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem.* 1996, 108, 103; *Angew. Chem. Int. Ed. Engl.* 1996, 35, 104; b) M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Tetrahedron Lett.* 1996, 37, 5141.

[14] The X-ray structural analysis of compound 6b was performed by Dr. A. L. Spek (Utrecht University). Details will be reported separately.

[15] Synthesis of 10: G. L. Buchanan, R. A. Raphael, R. Taylor *J. Chem. Soc. Perkin 1* 1972, 373, and references therein.

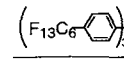[16] A. Alexakis, J. C. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* 1993, 4, 2431.

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

Bodo Betzemeier and Paul Knochel*

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

[*] Prof. Dr. P. Knochel, Dipl.-Chem. B. Betzemeier
Fachbereich Chemie der Universität
Hans-Meerwein-Strasse, D-35032 Marburg (Germany)
Fax: Int. code + (6421) 282-189
e-mail: knochel@ps1515.chemie.uni-marburg.de

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 Horvárth,[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) ([$Pd(dba)_2$], 0.15 mol%)[7] with 1-bromoperfluorooctane ($C_8F_{17}Br$) 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.

$$Ar^1\text{-}ZnBr + Ar^2\text{-}I \quad \xrightarrow[\substack{[Pd(dba)_2]\ (0.15\ mol\%) \\ toluene\ /\ C_8F_{17}Br \\ 60\,°C,\ 0.2-0.5\ h}]{\left(F_{13}C_6\text{-}\bigcirc\text{-}\right)_3 P\ (3,\ 0.6\ mol\%)} \quad Ar^1\text{-}Ar^2$$

Entry	Ar^1	Ar^2	Product 4	Yield [%] [a]
1	Ph	$4\text{-}AcOC_6H_4$	4a	93
2	$4\text{-}ClC_6H_4$	$4\text{-}NO_2C_6H_4$	4b	93
3	$4\text{-}ClC_6H_4$	$3\text{-}EtO_2CC_6H_4$	4c	97
4	$3\text{-}CF_3C_6H_4$	$4\text{-}MeOC_6H_4$	4d	89
5	$3\text{-}CF_3C_6H_4$	$4\text{-}BrC_6H_4$	4e	92
6	2-thienyl	$3\text{-}MeOC_6H_4$	4f	98
7	2-thienyl	$4\text{-}NO_2C_6H_4$	4g	87
8	$4\text{-}TIPS\text{-}OC_6H_4$ [b]	$3\text{-}EtO_2CC_6H_4$	4h	97
9	$4\text{-}TIPS\text{-}OC_6H_4$	$4\text{-}BrC_6H_4$	4i	99

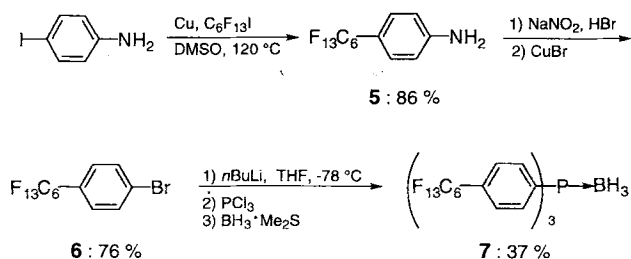[a] Yield of isolated product. [b] TIPS = iPr_3Si.

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 $(C_6F_{13}C_2H_4)_3P$.[5,10] The new phosphane 3 was prepared in three steps from 4-iodoaniline. Treatment of 3 with copper and $C_6F_{13}I$ 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 nBuLi 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 [$Pd(dba)_2$] in $C_8F_{17}Br$ to afford an orange solution of [$Pd\{P(C_6H_4\text{-}C_6F_{13})_3\}_4$] (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

Scheme 1. Synthesis of perfluorinated phosphane 7.

recovered from the toluene phase, whereas the palladium catalyst remains in the fluorous 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 [Pd(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$_2$R, CF$_3$, and iPr$_3$SiO. Furthermore, in the case of 4-bromoiodobenzene, 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).
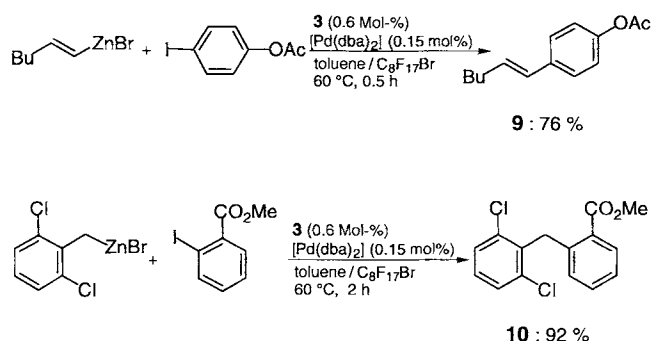
Scheme 2. Cross-coupling with an alkenyl- and a benzylzinc bromide.

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 fluorous phosphane **3** is currently underway.

Experimental Section

Typical procedure: 4-acetoxybiphenyl (**4a**). A 10 mL Schlenk flask was charged with a solution of **8** (1.2 μmol, 0.15 mol%, prepared in situ) in C$_8$F$_{17}$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 occured immediatly. The orange perfluorinated phase containing the catalyst **8** was recovered and could be used for further experiments. The organic phase was diluted with Et$_2$O and washed with a saturated aqueous solution of NH$_4$Cl. 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).

[1] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585; c) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905; d) I. Klement, M. Rottländer, C. E. Tucker, T. N. Majid, P. Knochel, *Tetrahedron* **1996**, *52*, 7201.

[2] For the use of highly efficient catalytic systems, see a) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem. Int. Ed. Engl.* **1995**, *35*, 1844; b) M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Brossmer, *ibid.* **1995**, *107*, 1992 and **1995**, *35*, 1848; c) J. Lourie, J. F. Hartwig, *ibid.* **1996**, *108*, 2531 and **1996**, *36*, 2359.

[3] I. Klement, H. Lütjens, P. Knochel, *Angew. Chem.* **1997**, *109*, 1605; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1496.

[4] I. Klement, P. Knochel, *Synlett* **1995**, 1113; *ibid.* **1996**, 1004.

[5] a) I. T. Horvárth, J. Rábai, *Science* **1994**, *266*, 72; b) S. M. Pereira, G. P. Savage, G. W. Simpson, *Synth. Commun.* **1995**, *25*, 1023; c) R. P. Hughes, H. A. Trujillo, *Organometallics* **1996**, *15*, 286; d) D. P. Curran, S. Hadida, *J. Am. Chem. Soc.* **1996**, *118*, 2531; e) D. P. Curran, M. Hoshino, *J. Org. Chem.* **1996**, *61*, 6480; f) D. P. Curran, *Chemtracts. Org. Chem.* **1996**, *9*, 75.

[6] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) M. Kobayashi, E. Negishi, *J. Org. Chem.* **1980**, *45*, 5223; c) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; Y. Tamaru, H. Ochiai, T. Nakamura, Z. Yoshida, *Tetrahedron Lett.* **1986**, *27*, 955.

[7] M. F. Rettig, P. M. Maitlis, *Inorg. Synth.* **1977**, *17*, 134.

[8] C. E. Tucker, T. N. Majid, P. Knochel, *J. Am. Chem. Soc.* **1992**, *114*, 3983.

[9] L. Brandsma, H. Verkruijsse, *Preparative Polar Organometallic Chemistry 1*, Springer, Heidelberg, **1987**, p. 125.

[10] F. Langer, K. Püntener, R. Stürmer, P. Knochel, *Tetrahedron: Asymmetry* **1997**, *8*, 715.

[11] a) Q. Y. Chen, Z. Y. Yang, Y. B. He, *J. Fluorine Chem.* **1987**, *37*, 171; b) N. Yoshino, M. Kitamura, T. Seto, Y. Shibata, M. Abe, K. Ogino, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2141.

[12] a) T. Imamoto, T. Kusomoto, N. Suzuki, K. Sato, *J. Am. Chem. Soc.* **1985**, *107*, 5301; b) A. Börner, J. Ward, W. Ruth, J. Holz, A. Kless, D. Heller, H. B. Kagan, *Tetrahedron Lett.* **1994**, *50*, 10419.

[13] S. C. Berk, M. C. P. Yeh, N. Jeong, P. Knochel, *Organometallics* **1990**, *9*, 3053.