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Catalytic System for Heck Reactions Involving Insertion into Pd−(Perfluoro-organyl) Bonds

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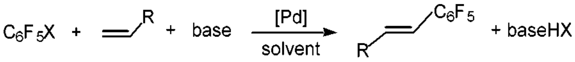
σ-Bonds between transition metals and perfluorinated groups (M−Rf) are among the strongest M−C bonds. Very few stoichiometric and, as far as we know, no *catalytic* reactions based on insertion of unsaturated molecules into M−Rf bonds have been reported. Alkene insertion into M−C bonds plays a key role in important catalytic processes such as alkene oligomerization,[1] polymerization,[1a,2] and the Heck reaction.[3] Such catalysis involving M−Rf bonds is desirable for the functionalization of perfluorinated compounds, important for the fine chemical and pharmaceutical industries.[4]

In recent years the Heck reaction has been improved by the discovery of very active catalysts based on palladacycles, or the use of new reaction conditions,[5−8] but despite the major effort in this field, perfluoro-aryl or -alkyl halides have not been reported as substrates.[9] Here we report the first *catalytic* Heck reaction, involving olefin insertion into an Rf−M bond.

Some of us had studied the insertion of dienes into the Pd−Pf bond of [Pd(Pf)Br(NCMe)$_2$] (**1**) and (NBu$_4$)$_2$[Pd$_2$(μ-Br)$_2$(Pf)$_2$Br$_2$] (**2a**) (Pf = C$_6$F$_5$) and isolated intermediates relevant in the Heck reaction.[10,11] The stoichiometric reaction of **2a** and styrene in the presence of a silver salt gave *trans*-PhCH═CHPf,[11] which encouraged us to look for catalytic conditions for it. Indeed **1** and **2a** are efficient catalyst precursors in the Heck reaction with C$_6$F$_5$Br (eq 1). They work in the absence of stabilizing ligands other than halide, the solvent and the reagents.[12]



(1)

Complexes **1** and **2a** catalyze the reaction of C$_6$F$_5$Br and styrene to give *trans*-PhCH═CHPf regioselectively. Since solutions of **1** in the presence of bromide give immediately **2a**, after the first catalytic cycle (where bromide is generated as byproduct) both catalysts are essentially equivalent, and the experiments are discussed for **2a**. A summary of results is given in Table 1.[13] Among the bases examined, CaCO$_3$, KF, and Na$_2$CO$_3$ gave the highest yields. Na$_3$PO$_4$, ^{t}BuOK, Na$_2$CO$_3$/NEt$_3$, and Na$_2$CO$_3$/collidine slowed the reaction rate or led to the reduction product C$_6$F$_5$H. NaOAc or NaOH gave fast reactions, but products of nucleophilic substitution of the para fluorine by acetate or OH were formed. NMP was the best solvent, whereas ^{i}PrCN, dioxane, or xylene gave poor results.

Almost complete conversion of C$_6$F$_5$Br and styrene into pentafluorostilbene was observed with **2a** at 130 °C (entries 1 and 2, Table 1). Decreasing the amount of catalyst lowered yields, but higher TON were obtained (entry 3). Using C$_6$F$_5$I lower conversions and higher reaction times were observed (entry 4). C$_6$F$_5$Cl failed to react with styrene under the same conditions (entry 5). An activated alkene, such as methyl acrylate, gave a faster reaction with catalyst **2a** at 100 °C; in this case, the use of KF as base led to higher conversions (entries 6 and 7). [Pd(PPh$_3$)$_4$] failed to catalyze the reaction of styrene and C$_6$F$_5$Br under the same conditions reported in entry 1. The reaction with styrene was not affected by oxygen or by the addition of galvinoxyl (Pd: galvinoxyl = 1:10). No radical addition products of PfBr to the alkene were obtained.

Table 1. Selected Results for the Heck Reaction in Eq 1[a]

	ArX	olefin	base	Pd (mol %)	time	yield %
1	C$_6$F$_5$Br	styrene	CaCO$_3$	1	1 d	98
2	C$_6$F$_5$Br	styrene	CaCO$_3$	0.1	6 d	97
3	C$_6$F$_5$Br	styrene	CaCO$_3$	0.01	15 d	47
4	C$_6$F$_5$I	styrene	CaCO$_3$	1	1 d	8
5	C$_6$F$_5$Cl	styrene	CaCO$_3$	1	1 d	2
6	C$_6$F$_5$Br	Me-acrylate	KF	1	7 h	80
7	C$_6$F$_5$Br	Me-acrylate	CaCO$_3$	1	10 h	36
8[b]	C$_6$F$_5$Br	α-Me-styrene	CaCO$_3$	2	5 d	79[c]
9	C$_6$F$_5$Br	1-hexene	CaCO$_3$	1	1 d	37[c,d]

[a] The reactions were carried out with 2.29 mmol ArX, 2.52 mmol (3.44 mmol for entries 2 and 3) of alkene, 2.52 mmol base, H$_2$O (0.1 mL) in 4 mL of NMP at 130 °C. [b] C$_6$F$_5$Br:olefin = 1:1.4, NBu$_4$Br (8%) was added. [c] Nonoptimized conditions. [d] Mixture of isomers.

The proposed mechanism for the reaction is represented in Scheme 1. Complex **2a** in CDCl$_3$ gives immediately a 1:1.6 mixture of two isomers corresponding to the cis and trans arrangements of the two C$_6$F$_5$ groups in the dimer. When NMP

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(1) (a) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; Wiley: New York, 1992; Chapter 4. (b) Skupinska, J. *Chem. Rev.* **1991**, *91*, 613−648.

(2) Ittlel, S. D.; Johnson, L. K.; Brookhart, M. *Chem. Rev.* **2000**, *100*, 1169−1203.

(3) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (b) de Meijère, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7. (d) Beletskaya, I.-P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(4) *Organofluorine Chemistry. Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds; Plenum Press: New York, 1994.

(5) (a) Ohff, M.; Ohff, A.; Van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687−11688. (b) Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357−358. (c) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995−1996.

(6) (a) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357−1364. (b) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Riermeier, T. H.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844−1848. (c) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23−41.

(7) (a) Morales-Morales, D.; Redón, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619−1620. (b) Brunel, J. M.; Hirlemann, M.-H.; Heumann, A.; Buono, G. *Chem. Commun.* **2000**, 1869−1870.

(8) (a) Shaw, B. L.; Pereda, S. D. *Chem. Commun.* **1998**, 1863−1864. (b) Shaw, B. L.; Pereda, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361−1362. (c) Van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; Van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1999**, 1073−1076.

(9) Radical addition of fluoroalkyl iodides to alkenes to yield the saturated alkyl iodides, initiated by metals and other reagents, has been reported. Heck-type products are not obtained: Chien, Q.-Y. *Isr. J. Chem.* **1999**, *39*, 179−192.

(10) (a) Albéniz, A. C.; Espinet, P.; Jeannin, Y.; Philoche-Levisalles, M.; Mann, B. M. *J. Am. Chem. Soc.* **1990**, *112*, 6594−6600. (b) Albéniz, A. C.; Espinet, P. *J. Organomet. Chem.* **1993**, *452*, 229−234. (c) Albéniz, A. C.; Espinet, P.; Lin, Y.-S. *Organometallics* **1995**, *14*, 2977−2986.

(11) Albéniz, A. C.; Espinet, P.; Foces-Foces, C.; Cano, F. H. *Organometallics* **1990**, *9*, 1079−1085.

(12) For other examples of Heck catalysis in the absence of good stabilizing ligands, see: (a) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165−168. (b) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449−8452. (c) Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 662−664. (d) Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751−5754. (e) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. *Chem. Eur. J.* **2000**, *6*, 843−848. (f) Beller, M.; Kühlein, K. *Synlett* **1995**, 441−442.

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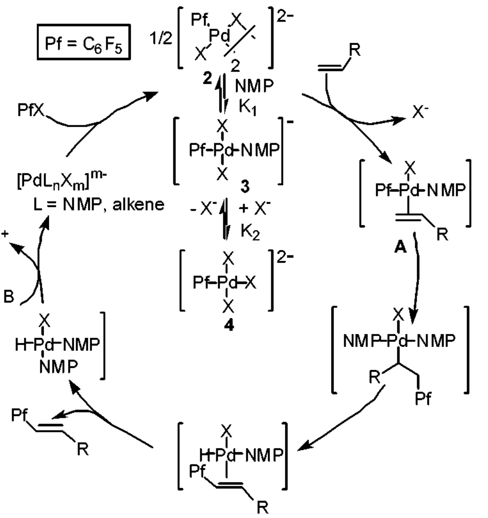
Scheme 1. Cycle for the Heck Reaction of C_6F_5X and Alkenes



is added to this solution, a new signal appears in the ^{19}F NMR spectrum, which we assign to $[PdPfBr_2(NMP)]^-$ (**3a**), that increases when the concentration of NMP increases. If **2a** is dissolved directly in NMP, **3a** is the major species observed at low concentrations and room temperature. Upon addition of Br^- to **3a**, **4a** is also detected.[14] The equilibrium constants between **2**, **3**, and **4** in NMP at room temperature were measured, out of the catalytic cycle by ^{19}F NMR, affording the following values: $K_1 = [\mathbf{3}]/[\mathbf{2}]^{1/2} = 0.603 \pm 0.018$, $K_2 = [\mathbf{4}]/[\mathbf{3}][X^-] = 3.20 \pm 0.13$ for X = Br; $K_1 = 0.180 \pm 0.005$, $K_2 = 3.09 \pm 0.12$ for X = I. At higher temperatures (120 °C) the equilibria in Scheme 1 become fast, and the signals of the three complexes collapse, preventing measurement of the equilibrium constants.

When the reaction of C_6F_5Br and styrene was monitored by ^{19}F NMR at 120 °C under catalytic conditions, only one set of Pf−Pd signals, corresponding to the time-averaged fast equilibrium just described, was observed throughout the catalysis. Similar fast equilibria may affect any other Pd(II) complex represented in Scheme 1 during the catalytic reaction, but only the solvent-ligated species are represented for short. The first process in the catalytic cycle is the coordination and insertion of the alkene. This is likely to be rate-determining, as supported by the observation of the signal of the complexes preceding this step and by the fact that the rate of reaction between C_6F_5Br and styrene catalyzed by **2a** is practically independent of the concentration of aryl bromide but increases when the styrene concentration is increased.[15] We could not detect complex **A** (Scheme 1) either in the catalytic cycle or in stoichiometric experiments; therefore, the coordination and insertion steps could not be studied separately, and we refer to both processes jointly. Independent reactions out of the catalytic cycle show that the insertion of styrene into the $Pd-C_6F_5$ bond of **3a** (synthesized by dissolving **2a** in NMP) is retarded by the addition of NBu_4Br.[16] Monitoring of isolated reactions of **2a** (X = Br) and **2b** (X = I) in NMP with an excess of styrene showed longer reaction times for **2b** (20% PfCH═CHPh for **2a** versus 3% for **2b**, after 17 h at room temperature). Thus, the slow reaction observed for C_6F_5I in the catalytic cycle may be due to a lower rate of substitution of iodide by the alkene in this step. β-hydrogen elimination and reductive elimination of HX follow, giving palladium(0) species stabilized by bromide anions.[17] When the catalytic reaction was carried out using bromide-free conditions (adding Ag_2CO_3 as a base to precipitate the bromide formed), only 3% of the coupling product was obtained after 1 day, and extensive catalyst decomposition was observed. Since the olefin insertion in cationic palladium complexes is feasible and fast,[10b] the absence of bromide must be affecting negatively the oxidative addition step. Besides stabilizing the Pd(0) intermediate, halide anions have been shown to increase the rate of oxidative addition when coordinated to Pd(0) species.[17] Although the reaction rate increases with increasing concentration of styrene, because it favors the coordination−insertion process, a large excess (C_6F_5Br:styrene = 1:20) stops the reaction; on the other hand, addition of NBu_4Br to this reaction mixture reactivates the process. This suggests that these conditions are affecting the ligands coordinating the Pd(0) species. When the bromide ions on Pd(0) are displaced by the alkene at high concentrations of the latter, the oxidative addition is severely slowed, becoming rate-determining, and the cycle is halted.[18] Thus, the success of this catalysis requires finding in each case a compromise between the optimal conditions for the oxidative addition and the coordination−insertion.

Preliminary nonoptimized results show that the system is also efficient for other fluorinated aryls of the type p-C_6F_4XBr (X = CN, CF_3, OMe). Nonactivated terminal alkenes (1-hexene, Table 1, entry 9) or 1,1-disubstituted olefins such as α-methylstyrene (Table 1, entry 8) can also be functionalized, while electron-rich alkenes (butylvinyl ether, 2,3-dihydrofuran) result in low yields and formation of C_6F_5H, presumably as a result of a slow coordination−insertion process.

In conclusion, a new efficient catalytic system for the Heck reaction of fluoroaryls has been developed. The easily stored complexes **1** and **2** provide reaction conditions exempt of ligands other than halide, solvent, and substrates, which seem to be needed for a fast coordination−insertion process. This step can be favored by using excess olefin, but such addition slows down severely the oxidative addition step. Hence a tradeoff between these opposing effects is needed for an efficient catalysis. The reaction works for different fluoroaryls on most olefins, but looks less promising for electron-rich olefins.

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[13] General procedure: A 100 mL Schlenk flask was charged with base, NMP, alkene, ArX, H_2O, and a solution of **2a** in NMP, under N_2 atmosphere. The mixture was stirred and introduced in a preheated oil bath at the reaction temperature. The reaction was monitored by ^{19}F NMR. When it was complete, the mixture was cooled. Addition of water afforded the product for entries 1−8.

[14] ^{19}F NMR (δ, NMP (acetone-d_6 capillary), F_{meta}, F_{para}, F_{ortho}, 282 MHz). **2a**: −166.61 (*cis* + *trans*), −164.50, −164.35 (*cis* + *trans*), −116.79 (*cis* + *trans*). **3a**: −168.18, −166.35, −116.02. **4a**: −168.62 ($F_{para} + F_{meta}$), −114.91. **2b**: −166.53 (*cis* + *trans*), −164.88, 164.66 (*cis* + *trans*), −112.35 (*cis* + *trans*). **3b**: −168.61, −166.71, −112.59. **4b**: −168.75 ($F_{para} + F_{meta}$), −111.67.

[15] % yield of PfCH═CHPh obtained in NMP, **2a** (2% mol Pd), $CaCO_3$, 2.5 h; (a) C_6F_5Br:styrene = 1:1.1: 36%, (b) C_6F_5Br:styrene = 4:1.1: 43%, (c) C_6F_5Br:styrene = 1:4.4: 98%.

[16] In catalytic conditions bromide is formed at each turnover. Provided that the reaction effectively starts, as it happens in our case, this soon makes unimportant the NBu_4Br initially added (if any), which has been reported favorable for other catalysis: Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130.

[17] (a) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321.

[18] A similar conclusion is drawn in a theoretical study: Sundermann, A.; Uzan, O.; Martin, J. M. L. *Chem. Eur. J.* **2001**, *7*, 1703−1711.