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Highly Active Thermomorphic Fluorous Palladacycle Catalyst Precursors for the Heck Reaction; Evidence for a Palladium Nanoparticle Pathway

Christian Rocaboy and J. A. Gladysz*

*Institut für Organische Chemie, Friedrich-Alexander Universität Erlangen-Nürnberg,
Henkestrasse 42, 91054 Erlangen, Germany*

gladysz@organik.uni-erlangen.de

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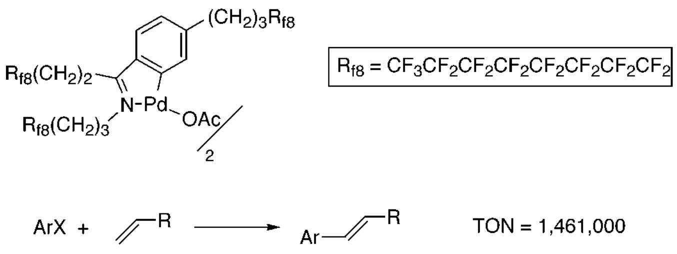
ABSTRACT



The fluorous Schiff base *p*-$R_{f8}(CH_2)_3C_6H_4C({=}N(CH_2)_3R_{f8})(CH_2)_2R_{f8}$ (R_{f8} = *n*-C_8F_{17}) is prepared in six steps from *p*-iodobenzaldehyde and then cyclopalladated ($Pd(OAc)_2$) to give highly effective catalyst precursors for Heck reactions, conducted under homogeneous conditions (DMF, 80–140 °C, turnover numbers $>10^6$) in the absence of fluorous solvents. Rate, recycling, and other data suggest that the palladacycles serve as sources of palladium nanoparticles, which are the dominant active catalysts.

Fluorous biphase catalysis is now a well-established technique for catalyst/product separation and recycling that exploits the temperature-dependent miscibility of organic and fluorous solvents.[1,2] It has yielded impressive results in metal-catalyzed hydroformylations,[3] hydrogenations,[4] hydroborations,[5] hydrosilylations,[6] and oxidations.[7] Surprisingly, there is so far only one report[8] of a fluorous Heck catalyst.[9,10] One contributing factor may be that most Heck catalysts contain benzenoid rings, which typically require three *n*-C_8F_{17} (R_{f8})

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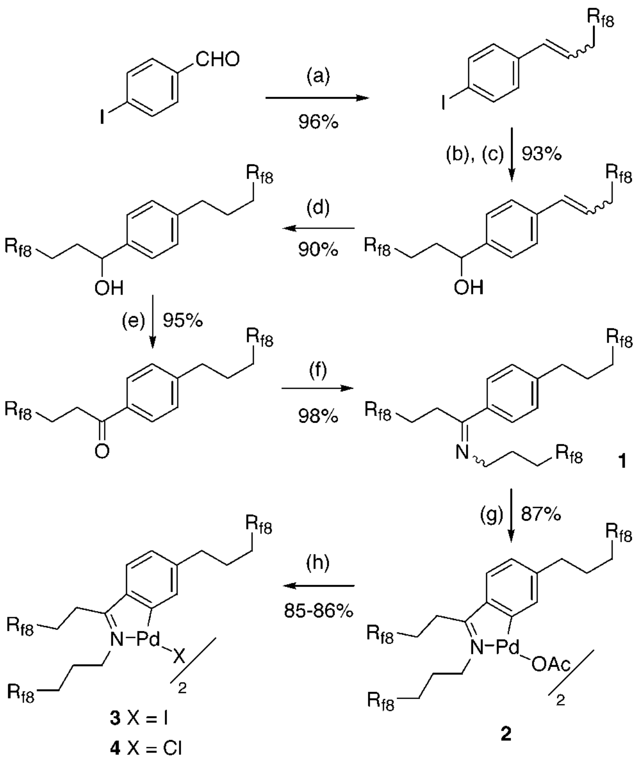
Scheme 1. Synthesis of Fluorous Schiff Base and Palladacycles[a]



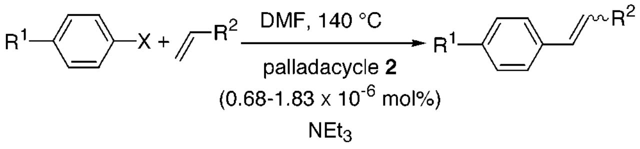
[a] Conditions: (a) $R_{f8}CH_2CH_2PPh_3^{+}I^{-}$, K_2CO_3, *p*-dioxane/H_2O, 95 °C; (b) *i*-PrMgCl, THF; (c) $R_{f8}CH_2CH_2CHO$; (d) $(Ph_3P)_3RhCl$, H_2 (75 psi), EtOH/$CF_3C_6H_5$, 40 °C; (e) Dess−Martin periodinane, $CF_3C_6H_5$; (f) $NH_2CH_2CH_2CH_2R_{f8}$, $SnCl_2(H_2O)_2$, toluene, reflux, Dean-Stark; (g) $Pd(OAc)_2$, AcOH, 95 °C; (h) LiX (X = Cl, I), $CF_3C_6H_5$/MeOH.

"pony tails" for effective immobilization in fluorous solvents.[4b,11] However, we recently showed that the markedly temperature-dependent *solubilities* of many fluorous compounds in organic solvents can also be exploited.[12] Such thermomorphic behavior allows homogeneous reaction conditions at higher temperatures, with catalyst recovery via liquid/solid phase separation at lower temperatures. Since Heck reactions normally require elevated temperatures, we thought they would provide ideal test cases for comparing the new and classical procedures.

Our attention was drawn to a cyclopalladated Schiff base Heck catalyst precursor reported by Milstein, with just one arene per palladium.[13] We prepared a similar fluorous Schiff base containing three pony tails (**1**) from commercial *p*-iodobenzaldehyde as shown in Scheme 1. This sequence features fluorous Wittig methodology[11,14] and fluorous amines[15] described earlier. Although six steps were required, product purifications, often the most important consideration in fluorous syntheses, were easy, and the overall yield was good. Compound **1** showed a high $CF_3C_6F_{11}$/toluene partition coefficient (98.7:1.3, 24 °C) and reacted with $Pd(OAc)_2$ (AcOH, 95 °C) to give the yellow dimeric palladacycle **2** in 87% yield (partition coefficients at 24 °C, 95.5:4.5, $CF_3C_6F_{11}$/toluene; 95.9:4.1, $CF_3C_6F_{11}$/DMF). A crystallized sample melted at 78−80 °C and was thermally stable to 225 °C (DSC/TGA). When DMF or $CF_3C_6H_5$ solutions of **2** were kept at 140 °C (2 h) or 100 °C (16 h), no decomposition was detected visually (e.g., black residues) or by NMR. Reactions with LiX (X = I, Cl) gave the corresponding palladacycle halides **3** and **4**, which were much less soluble than **2**.[16]

We first sought to demonstrate that **2** was a viable catalyst precursor. Accordingly, a solution of an aryl halide in freshly distilled DMF (4−8 mL) was sequentially treated with an alkene, Et_3N, and a standard solution of **2** in $CF_3C_6H_5$ (0.010−0.020 mL; 0.68−1.83 × 10^{-6} mol %), as summarized in Table 1. The apparently homogeneous samples were reacted at 140 °C and then cooled. GC analyses showed Heck coupling products in 49−100% yields, corresponding to turnover numbers (TON) of 266,000 to 1,461,000. This places **2** among the best high-turnover Heck catalyst precursors.[9]

Table 1. Heck Reactions under High Turnover Conditions[a]



X	R¹	R²	**2** (nmol)	*t* (h)	conv (%)	yield (%)	TON
I	H	CO_2Me	3.438	14	100	100[b]	1 461 000
I	H	Ph	3.438	24	94	88[c]	1 286 000
Br	Ac	CO_2Me	9.168	48	77	49[b]	266 000

[a] Conditions: ArX (ca. 5.000 mmol), alkene (ca. 1.25 equiv), NEt_3 (ca 2 equiv), DMF (4−8 mL), 140 °C. [b] *trans* only. [c] *trans*/*cis*, 6.7/1.

Similar reactions were conducted in which **2** was introduced as a solid and at much higher loadings (0.5 mol %). The initially insoluble **2** dissolved as the DMF was warmed. Upon cooling, palladium complexes precipitated. In reactions of phenyl iodide, NMR analyses showed palladacycle iodide **3** to be the dominant species.[17] Other materials remained

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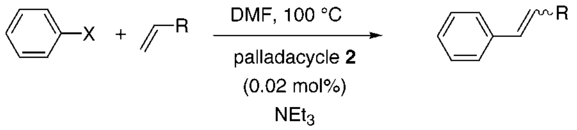
(16) At room temperature, **2** was soluble in fluorinated solvents such as $CF_3C_6F_{11}$, $C_8F_{17}Br$, $CF_3C_6F_5$, and $CF_3C_6H_5$ but poorly soluble in common organic solvents such as CH_2Cl_2, $CHCl_3$, acetone, and THF. Complexes **3** and **4** were completely insoluble in organic solvents and poorly soluble in the preceding fluorinated solvents. However, solubilities in $CF_3C_6F_5$ were much higher above 50 °C, allowing NMR spectra to be recorded.

soluble. Although this posed the possibility of palladium recovery by simple decantation, the quantities involved were impracticably small (an issue that would not exist on industrial scales). Hence, reactions were repeated with 0.02 mol % of **2** as summarized in Table 2. After cooling, the fluorous solvent $C_8F_{17}Br$ was added as a “carrier”, giving a liquid/liquid biphasic sample. Pictures of a reaction sequence are given in Figure 1 (with 0.5 mol % **2** for better visualization). The upper DMF phase was separated, and the $C_8F_{17}Br$ phase was washed with DMF. The $C_8F_{17}Br$ was removed under vacuum, and the residue charged with fresh educts and DMF for a second reaction.

Table 2. Heck Reactions under Recycling Conditions[a]



			run A			run B		
R	cycle	*t* (h)	conv[b] (%)	yield[b] (%)	TON	conv[b] (%)	yield[b] (%)	TON
CO$_2$Me(d)	1	2	100	100	5 250	100	100	5 250
	2	2	100	100	10 500	100	100	10 500
	3	2	77	55	13 370	73	50	13 020
	4	10	100	100	18 620	100	100	18 270
Ph(e)	1	5	92	85	4 490	90	85	4 480
	2	15	88	80	8 670	85	76	8 480
	3	24	86	74	12 570	80	70	12 150
	4	24	74	52	15 320	71	52	14 900

[a] Conditions: **2** (0.0014 g, 0.00043 mmol), PhI (0.250 mL, 2.24 mmol), alkene (ca. 1.25 equiv), NEt_3 (0.625 mL, 4.48 mmol), DMF (4.00 mL), 100 °C. [b] Determined by GC. [c] Cumulative. [d] *trans* only. [e] *trans*/*cis*, 6.7/1.

The results of several cycles are given in Table 2. The data show a gradual loss of activity (turnover frequency) with cycle. With methyl acrylate, conversion and yield drop in the third cycle. Only by extending the duration of the fourth cycle from 2 to 10 h are quantitative yields restored. With styrene, activity loss is evident in the second cycle (15 vs 5 h). These effects, which could have been masked with higher catalyst loadings,[18] are consistent with several scenarios. One explanation would be that the active catalyst is efficiently recycled but is of limited stability, resulting in progressively slower rates. Another would be that catalyst recycling is not as efficient as anticipated.

However, many metallic palladium catalysts for the Heck reaction are known.[9,19−23] These include two distinct varieties of fluorous palladium nanoparticles.[20,21] Also, close relatives of the Milstein catalyst upon which **2** is based decompose to active metallic palladium.[22] Furthermore, colloidal palladium nanoparticles often impart a reddish-orange tint to DMF,[19a] and similar hues are apparent in Figure 1. We therefore considered the possibility that **2** and the palladacycle iodide **3**[17] serve mainly as recyclable sources of soluble colloidal nanoparticle catalysts, with the diminishing activity representing progressively smaller quantities of **2** and **3**. To probe this model, the rate of reaction of phenyl iodide and methyl acrylate was monitored under the conditions summarized in Figure 2.

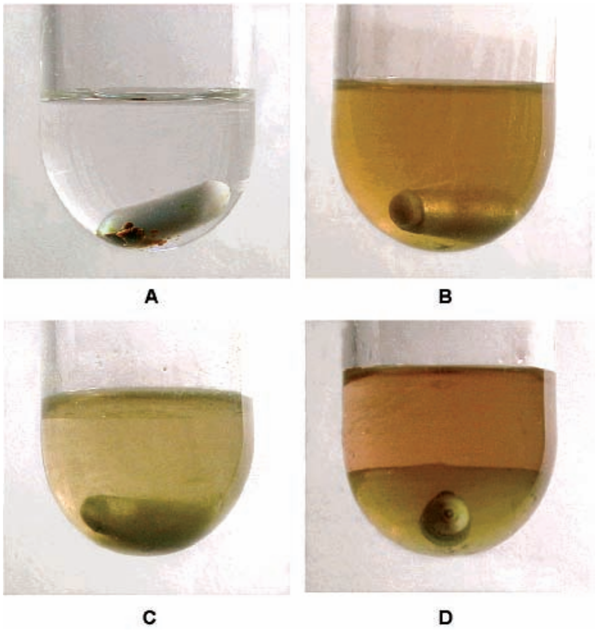


Figure 1. Photographs of a recycling sequence: (A) first entry in Table 2 before heating, with undissolved **2** (0.5 mol %); (B) after 2 h at 100 °C; (C) after cooling to room temperature, with precipitated palladium complexes; (D) after addition of $C_8F_{17}Br$.

Importantly, both the first and second cycles in Table 2 (red and blue traces, Figure 2) appeared to show an induction period, and the second cycle was slightly slower. An induction period for the first cycle could be rationalized under any circumstances, but an induction period for the second cycle suggests that the active catalyst is not being recycled. To improve the time resolution, the experiments were repeated at 80 °C (green and orange traces, Figure 2). The induction periods and rate differences were markedly enhanced. The palladacycle iodide **3** showed identical activity. In all cases, reddish-orange tints became apparent near the end of the induction period. In addition, the DMF was

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(17) Note that regardless of identity of the active catalyst, the iodide ions liberated during the Heck coupling should convert remaining **2** to **3**.

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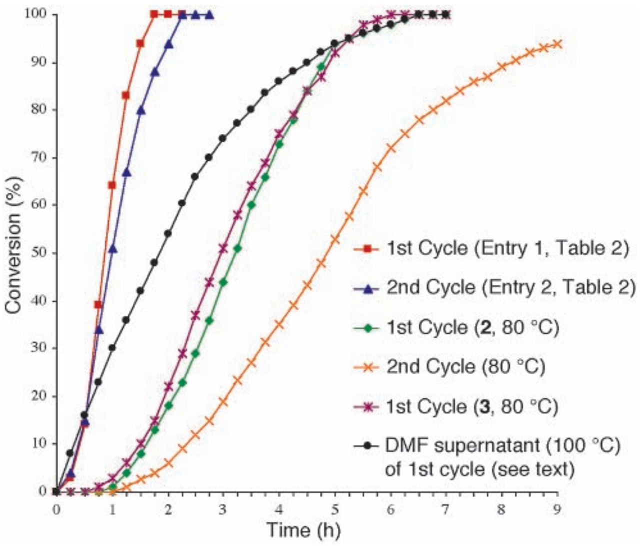

Figure 2. Conversion as a function of time for reactions of phenyl iodide with methyl acrylate.

separated from the DMF/$C_8F_{17}Br$ mixture (see D, Figure 1), combined with a subsequent DMF wash of the $C_8F_{17}Br$ layer (50% of original DMF volume), and charged with additional educts. Reaction now occurred without an induction period, indicating a leached catalyst. Although the activity is somewhat less than for cycles 1 and 2 (100 °C), all concentrations are ca. 67% lower.

Finally, transmission electron microscopy definitely established the presence of palladium nanoparticles, averaging approximately 10 nm in diameter. Given the above data, we believe they are responsible for the bulk of the activity found for catalyst precursors **2** and **3**. However, detailed kinetic studies of other Milstein-type catalysts clearly establish the operation of homogeneous pathways, with rates dependent upon concentrations of dissolved palladium complexes.[24] Interestingly, our nanoparticles have little affinity for C_8F_{17}-Br or presumably other fluorous solvents. This suggests, in accord with much precedent,[19a] that they are stabilized by the byproduct $Et_3NH^+ X^-$. Importantly, nanoparticles that are stabilized by small fluorous molecules have been reported.[21] These catalyze the Heck reaction and can be recycled with fluorous solvents. Thus, minor changes in the ligand **1** or reaction conditions have the potential to dramatically alter the nature of the nanoparticles.

In summary, this study has established a new highly active catalyst system for the Heck reaction that ranks with the best in the literature. The palladacycle catalyst precursors **2** and **3** represent new examples of thermomorphic fluorous compounds, with little or no solubility in organic solvents at room temperature but significant solubility at elevated temperatures, thus enabling homogeneous reactions in the absence of fluorous solvents. However, **2** and **3** act mainly as steady-state sources of extremely reactive, soluble palladium nanoparticles. Such systems are of great current interest,[19−22] and their further exploitation, as well as fluorous analogues of homogeneous Heck catalysts that are expected to show greater stabilities with respect to nanoparticles, will be reported soon.

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Supporting Information Available: Key synthetic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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