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Palladium-catalyzed Heck reaction under thermomorphic mode

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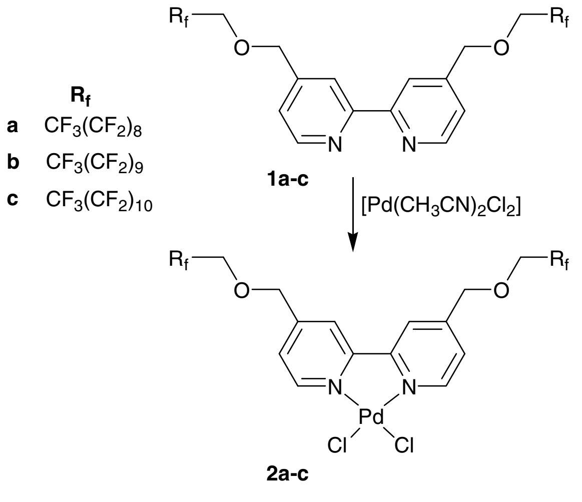
Abstract— Complex $PdCl_2$(4,4′-bis-(n-$C_{10}F_{21}CH_2OCH_2$)-2,2′-bpy) (**2b**) was known to be a good recoverable catalyst under fluorous biphasic system. Complex **2b** and $PdCl_2$(4,4′-bis-(n-$C_{11}F_{23}CH_2OCH_2$)-2,2′-bpy) (**2c**), soluble in polar organic solvents at >120 °C but insoluble at 25 °C, were demonstrated here as catalysts in the Pd-catalyzed Heck reaction under the thermomorphic mode and recovered for reusage, that is, the Heck reaction is homogeneously carried out at ca 140 °C, and after reaction the product mixtures remain in solution with the catalyst heterogeneously separated at room temperature.

Homogeneous catalysis is a powerful tool in highly active and stereoselective organic transformations.[1] However, the majority of catalytic processes in industry are still conducted under heterogeneous conditions, since the separation of the catalysts from the product mixture is easier than under traditional homogeneous conditions. Therefore, besides developing homogeneous catalysts that can be used in very low concentrations (for which the catalyst quantity is at the ppm level, and thus separation is not required), efforts have been made to provide heterogeneous reactions, which need the catalysts to be fixed to a solid supporter.[2,3] In other words, it is important to find a recoverable catalyst that could easily be separated from the product mixture after reaction.[4] One of the new approaches to solve the problems of separation and catalytic efficiency is the thermomorphic catalysis[2,3,5,6] with or without the fluorous solvents. Bergbreiter et al. used a polymer-based thermomorphic system whose polymeric supporter was not totally dissolved at high temperature.[2,3] Yamamoto and co-workers[7,8] and Gladysz and co-workers[5,6] have published the fluorinated compounds to catalyze the addition reaction on unsaturated substrates without the use of expensive fluorous solvents. Fan and co-workers have also reported the use of the thermomorphic system with a non-fluorous catalyst for asymmetric hydrogenation.[9] Recovery and reusage with the non-fluorous catalysts are not as good as those with the fluorous ones. A unique feature in ideal thermomorphic catalysis is that the reaction mixture, when heated during the reaction, is homogeneous and the product mixture, when cooled after the reaction, becomes phase separated. Taking advantages of the thermomorphic property of high fluorine content compounds,[10,11] we report here the Pd-catalyzed Heck reactions using **2b–c** that carry fluorous-ponytails in the structure[12] of 2,2′-bpy and are soluble in polar organic solvents only at elevated temperatures. We demonstrate in this Letter that the use of expensive



Scheme 1. Synthesis of **2a–c**.

Keywords: Fluorous biphasic system; Heck reaction; Thermomorphic mode; Homogeneously; Heterogeneously.

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fluorinated solvents can thus be avoided, the homogeneous catalysis achieved, and the Pd-catalysts recovered and reused.

As shown in Scheme 1, the reaction of $[PdCl_2(CH_3CN)_2]$ with three highly fluorinated bipyridine derivatives, 4,4′-bis($R_fCH_2OCH_2$)-2,2′-bpy **1a–c**, resulted in the Pd complexes, $[PdCl_2$(4,4′-bis-($R_fCH_2OCH_2$)-2,2′-bpy)$]$ **2a–c**, as pale yellow solids, where $R_f = n\text{-}C_9F_{19}$ (**a**), $n\text{-}C_{10}F_{21}$ (**b**), $n\text{-}C_{11}F_{23}$ (**c**), respectively. The solubility of Pd complexes **2a–c** in DMF as a function of temperature is shown in Figure 1. The solubility was measured by the variable temperature NMR spectrometer, where the temperatures were varied from −30 to 90 °C (also see Supplementary data). We recorded the NMR integration of the peak of the C5(5′)-protons in 2,2′-bpy and compared its value to that of the peak integration of ω-proton (from terminal HCF_2 group) of the standard, $HCF_2(CF_2)_3CH_2OH$. It was shown that compound **2a** was slightly soluble in DMF at 25 °C, but **2b** and **2c** were not soluble. The solubility of **2a** in DMF began from virtually zero at or below −10 °C, increased slowly with the temperature from −10 to 60 °C and increased remarkably at >60 °C. The solubility curves of **2b** and **2c**, however, began from virtually zero below 40 °C and increased only at higher temperature, that is, 90 °C, as limited by the NMR spectrometer employed in the variable temperature NMR experiments. Upon changing from 25 °C to 90 °C there was ca sevenfold increase of solubility for **2a** and several orders of magnitude increase of solubility for **2b–c**. Therefore, Pd complex **2a** was not used for the reactions under the thermomorphic mode because it is still slightly soluble at room temperature. The Pd complexes **2b–c** were then selected as good candidates for the subsequent catalytic experiments to examine the temperature dependency of the reactions.

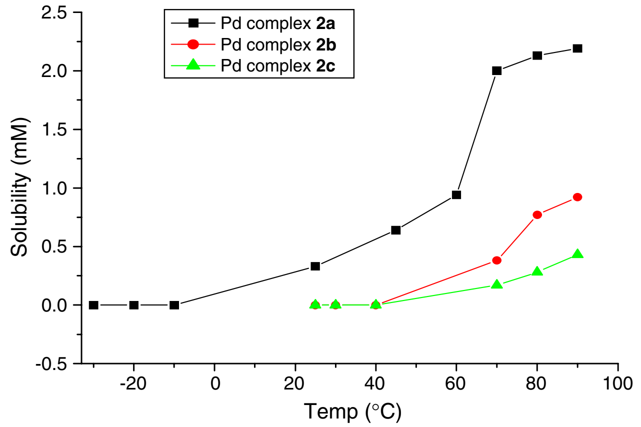


Figure 1. Solubility of Pd complexes **2a–c** as a function of temperature.

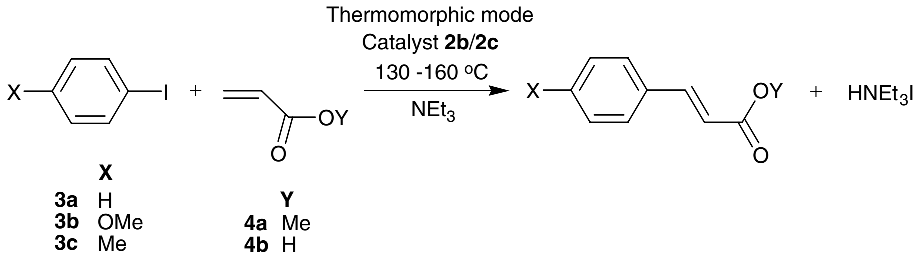
As shown in Scheme 2, the Pd-catalyzed Heck arylation of methyl acrylate/acrylic acid with aryl iodides was selected to demonstrate the feasibility of recycling usage with **2b–c** as the catalyst using DMF as the solvent under thermomorphic mode, at ca 140 °C for 3–7 h varying in each run. At the end of each cycle, the product mixtures were cooled to 25 °C and were centrifuged; then catalysts were recovered by decantation. The recovered **2b–c** was added with DMF, substrates, and base to proceed to the next cycle. The products were quantified with GC analysis by comparison to internal standard (NMP). The results of Heck reaction exhibited a 100% selectivity favoring the trans product. As one example shown in Table 1, the Heck reaction of C_6H_5I (**3a**) with methyl acrylate (**4a**) could be catalyzed by **2b** with good recycling results for a total of eight times. To our knowledge, this is the first example of Pd-catalyzed Heck reaction under the thermomorphic mode.

With electron releasing OMe and Me substitutents on iodobenzene, excellent yields, and recyclabilities could also be achieved for the Heck arylation on **4a** as catalyzed by **2b** under the thermomorphic mode. The results with **2c** as the catalyst were very similar to those with **2b** as the catalyst, although the temperature of reactions was ca 10 °C higher in the case of **2c** as the catalyst.

Table 1. Recycling results of **2b**-catalyzed Heck reaction of **3a** and **4a** under thermomorphic mode

Cycle no.	Time (h)	Temperature (°C)	Yield (%)	TON	TOF
1	3	140	100	1000	333
2	6	140	100	1000	167
3	6	140	100	1000	167
4	6	140	100	1000	167
5	6	140	100	1000	167
6	7	140	100	1000	143
7	7	140	100	1000	143
8	7	140	100	1000	143

Reaction conditions: DMF (3 mL); **3a** (2.5 mmol, 510 mg), **4a** (5.0 mmol, 355 mg), NEt_3 (5.0 mmol, 510 mg), 0.1 mol % **2b** (3.64 mg).



Scheme 2. The Pd-catalyzed Heck reaction under thermomorphic mode.

Table 2. Recycling results of **2b**-catalyzed Heck reaction of **3a** and **4a** under thermomorphic mode using NMP as solvent

Cycle no.	Time (h)	Temperature (°C)	Yield (%)	TON	TOF
1	5	150	100	1000	200
2	6	150	100	1000	167
3	8	150	100	1000	125
4	8	150	100	1000	125
5	8	150	100	1000	125
6	8	160	100	1000	125
7	8	160	100	1000	125
8	8	160	85.3	853	107
9	8	160	>99	>990	>123

Reaction conditions: NMP (3 mL), **3a** (2.5 mmol), **4a** (5.0 mmol), NEt_3 (5.0 mmol), 0.1 mol % **2b**. During the 10th cycle, only 0.02 mol % **2b** was used, and the yield was >80%.

Overall, complexes **2b**–**c** could be easily recovered and reused in the Pd-catalyzed Heck arylations of methyl acrylate under the thermomorphic mode (see Supplementary data).

The polar aprotic NMP was also tested alternatively for the same reactions, and the results in Table 2 exhibited excellent yields and a recycling ability for overall 9 times for the Heck reaction of **3a** with **4a** using **2b** as the catalyst under the thermomorphic mode using NMP as solvent.

In Figure 2 the pictures of the three stages of **2b**-catalyzed Heck reaction of **3a** and **4a** are shown. Before the reaction started, the reactants and the base were soluble in DMF yet complex **2b** was insoluble. During the catalysis, the DMF solution was homogeneous when the temperature was raised to ca 140 °C. At the end of reaction, the catalyst precipitated at room temperature and was readily recovered after centrifugation from the product mixture.

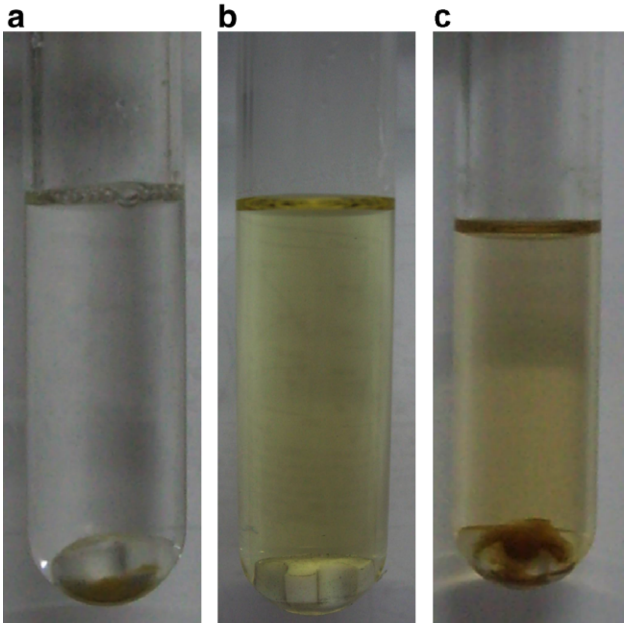


Figure 2. Photographs of **2b**-catalyzed Heck reaction: (a) reactant mixture in DMF and the insoluble Pd-catalyst, (b) homogeneous DMF solution at 140 °C, and (c) product mixture in DMF and the Pd-catalyst after centrifuge at 25 °C.

The Pd complexes **2b**–**c** were also employed as catalyst in the Heck arylation of acrylic acid (**4b**) under thermomorphic mode.[13] As expected, this catalysis was more difficult to carry out, attributed to the acid group of **4b** that was relatively less stable than the methyl ester group of **4a** under the reaction conditions. The Pd-catalyzed Heck reaction of **3a** with **4b** was tested with **2b** as the catalyst under thermomorphic mode, at 130–160 °C during the reaction. The procedures performed for the recovery step by centrifugation and decantation after each run were similar to those performed in the methyl acrylate studies. The products were also quantified with GC analysis by comparison to internal standard (NMP). The results of Heck reaction here again exhibited the 100% trans selectivity, the excellent yields and the recyclability. As one example, Table 3 indicated that **2b** was indeed a recoverable catalyst to catalyze the Heck reaction of **3a** and **4b**, without disturbing the –COOH group after eight cycles.

Table 3. Recycling results of **2b**-catalyzed Heck reaction of **3a** and **4b** under the thermomorphic mode

Cycle no.	Time (h)	Temperature (°C)	Yield (%)	TON	TOF
1	3	140	100	333	111
2	6	140	100	333	55.5
3	6	140	96	320	53.3
4	6	140	100	333	55.5
5	6	140	100	333	55.5
6	6	140	100	333	55.5
7	6	140	100	333	55.5
8	6	140	100	333	55.5

Reaction conditions: DMF (3 mL), **3a** (1.0 mmol, 204 mg), **4b** (1.5 mmol, 106.5 mg), NEt_3 (2.0 mmol, 202.4 mg), 0.3 mol % **2b** (4.37 mg).

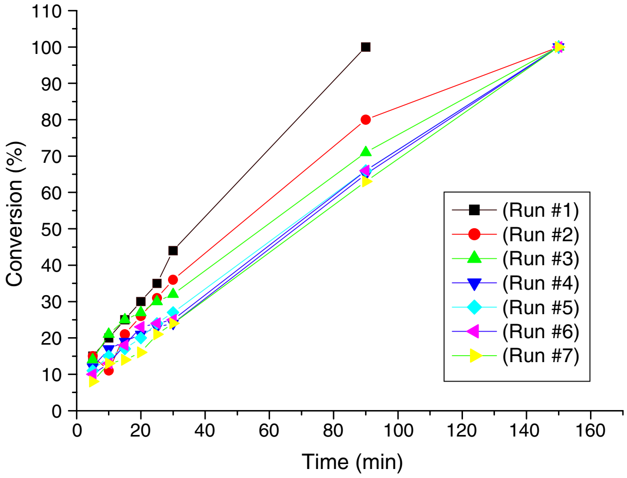


Figure 3. Conversion as a function of time for **2c**-catalyzed Heck reactions.

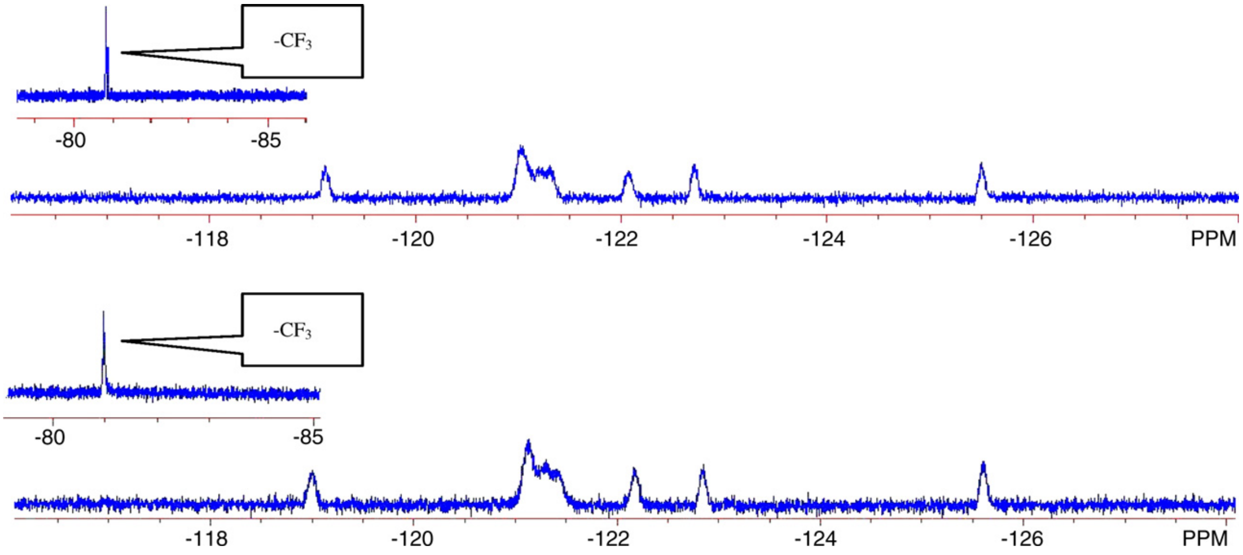


Figure 4. ^{19}F NMR spectra in DMF-*d* at 90 °C; (top) **2b** before the 1st cycle and (bottom) recovered **2b** after the 8th cycle. [The CF_3 peak (ca −81 ppm) was shown as the inset at the upper left of either spectrum.]

To analyze the kinetics, the **2c**-catalyzed Heck reactions of **3a** and **4a** were monitored, by periodically taking out small amounts of the reaction mixture for GC/MS analysis. In Figure 3 the plots of conversion versus time for the seven recycled runs, whose temperatures were maintained at ca 118 ± 2 °C, are shown. It was clear that there was no induction period at all in the initial run nor in any of the recycled runs. The rate of run no. 1 was the fastest, and the rates of other runs were slightly slower. It showed that the rate profiles from run no. 3 to run no. 7 were repeatable. These results indicated that the run no. 3–7 were mainly via the homogeneous catalysis.

The amount of residual Pd-catalyst in the product solution after centrifuge from each run was determined by ICP-MS, the results indicating that the recovery of Pd-catalyst left only less than 0.02% of the Pd-catalyst in solution. Earlier the same reaction (also see Supplementary data; Table 4) was carried out by **2b**[14] under fluorous biphasic system,[15–18] the TOF obtained was only ca 20% of the TOF recorded under the thermomorphic mode in this Letter.

Although the Pd complexes **2a**–**c** are thermally very stable with decomposition temperature >330 °C in fast scan TGA,[12,14] the supernatant solution from the initial cycle, however, after centrifuge and catalyst precipitates removal, was able to catalyze the Heck reaction (though much more slowly), if extra substrates and the base were added to the system and the temperature increased to 140 °C. These observations possibly suggested a second route of catalysis in the Heck reaction. That is, in addition to the pathway of molecular catalysis (and the catalyst recyclable with the fluorous ligands), a minor pathway due to the Pd nanoparticle catalysis likely exists, which resulted in soluble Pd nanoparticles in the above supernatant solutions.[19–21] The contribution of Pd nanoparticle catalysis was only minor, evidenced by the absence of induction period in the rate measurements at 120 °C of the Heck reactions. Another piece of information is shown in Figure 4, the identical ^{19}F NMR spectra of **2b** in DMF-*d* at 90 °C before the 1st cycle and after the 8th cycle, in neither spectrum could signals from free ligand **1b** be observed.

In summary, for the first time the novel catalysts **2b**–**c** were successfully used in the Heck reactions under the thermomorphic mode, which is more efficient than under fluorous biphasic system.[15–18] Under the thermomorphic mode, Pd complexes **2b**–**c** gave excellent yields and very good recyclabilities and offered the advantages of reactions being carried out without the use of fluorous solvents. As a series of fluorous 2,2′-bpy ligands[12] were available, the ones insoluble in polar organic solvents at room temperature were converted to the Pd(2,2′-bpy) complexes with fluorous ponytails, among which Pd complexes **2b**–**c** were close to the ideal recoverable catalysts,[22,23] because in addition to high rates of conversion they could be recovered quantitatively with just centrifuge and decantation at room temperature.

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Supplementary data

The general procedures, analytical data of **2a**–**c**, the data for other Tables (4–9), the solubility measurement of Pd **2a**–**c** and the procedures for kinetic study of **2c**-catalyzed Heck reaction are described. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.034.

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