JOC *Note*

Mizoroki−Heck Arylation of α,*β*-Unsaturated Acids with a Hybrid Fluorous Ether, F-626: Facile Filtrative Separation of Products and Efficient Recycling of a Reaction Medium Containing a Catalyst

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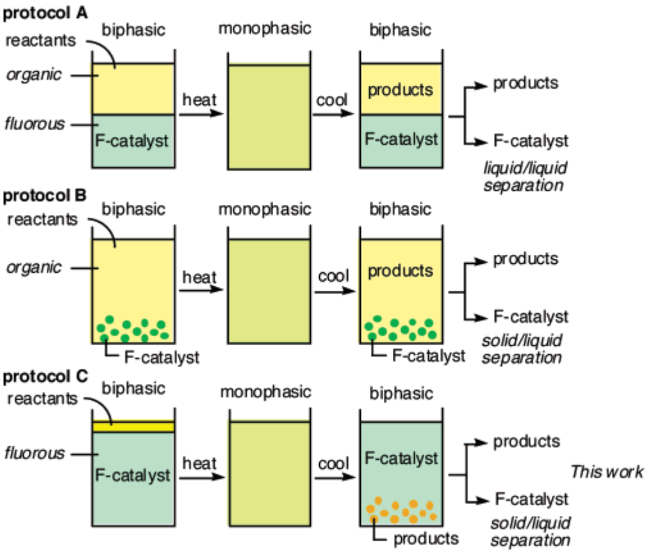
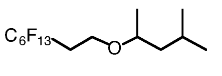
Abstract: The Mizoroki−Heck reaction was carried out using a fluorous ether F-626 as the solvent and a fluorous Pd carbene complex as the catalyst. When carboxylic acids are the products, separation of both the F-626 and the Pd catalyst from the products can be conveniently carried out by simple filtration. The F-626 filtrates containing the Pd catalyst can be recycled.

Fluorous biphasic catalysis (FBC), since the pioneering studies of Vogt and Kaim[1a] as well as the work of Horváth and Rábai were reported,[1c] has provided an elegant solution to a long-standing problem associated with homogeneous metal catalysis, namely the separation of the catalysts from the products and their reuse.[2,3] This protocol, depicted typically as **A** in Scheme 1, exploits the thermomorphic nature of fluorous solvents which form a monophasic solution with an organic solvent when heated. After the reaction, the catalyst, having fluorous ligands, can be separated from the products by means of an organic/fluorous liquid/liquid biphasic workup. A protocol for fluorous catalysis, **B**, has also recently been reported in which ordinary organic solvents are used exclusively as a reaction medium for reactions using fluorous catalysts.[4,5] This protocol **B** exploits the temperature-dependent miscibilities of the fluorous catalyst to the organic solvent, such as octane,[4a,b] xylene,[4c,d] toluene,[4e] and DMF,[5] at higher temperature, but the catalyst precipitates when the solution is cooled and can be recovered by simple solid/liquid separation.

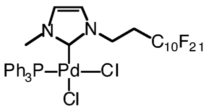
SCHEME 1. Protocols for Separation of Fluorous Catalyst and Solvent in Fluorous Biphasic Catalysis (FBC)



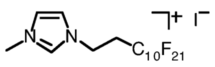
It occurred to us that the use of a fluorous monophasic system[6,7] would be also promising. In such, if the products have a low solubility in the fluorous solvent, they would precipitate during the reaction, which would allow for a homogeneous solution containing fluorous catalysts via simple solid/liquid separation of the products (protocol **C**). In this paper, we report on the successful use of the protocol **C** where a fluorous ether, F-626, 1*H*,1*H*,2*H*,2*H*-perfluorooctyl 1,3-dimethylbutyl ether[7] was used as the sole reaction medium in the Mizoroki−Heck arylation[8] of α,*β*-unsaturated acids. It should be noted that fluorous versions of Mizoroki−Heck arylations have already been reported by other groups. Whereas many of these protocols can be classified as **A**-type,[9,10] Gladysz and Rocaboy recently reported on the **B**-type protocol using a highly effective fluorous palladacycle catalyst, which can be conducted with DMF as the exclusive solvent.[5,11]



F-626



I



II

Fluorous Pd carbene complex **I** was prepared from Pd(OAc)$_2$, fluorous ionic liquid **II**,[12] and PPh$_3$ in the presence of LiCl and was used in an initial test (Scheme 2).[13] Thus, the reaction of iodobenzene (**1a**) with acrylic acid (**2a**) was

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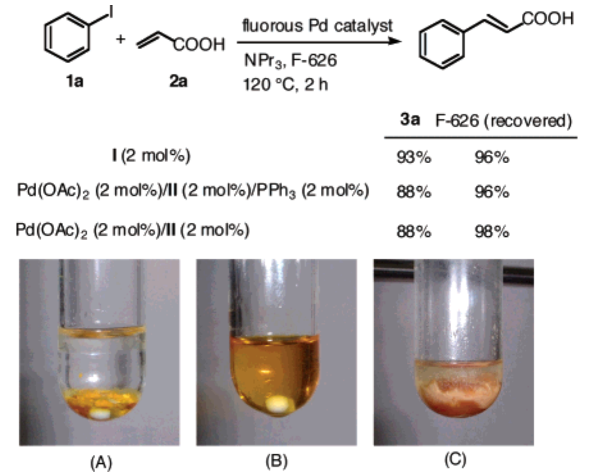
(6) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

(7) Matsubara, H.; Yasuda, S.; Sugiyama, H.; Ryu, I.; Fujii, Y.; Kita, K. *Tetrahedron* **2002**, *58*, 4071.

10.1021/jo049028+ CCC: $27.50

SCHEME 2. Mizoroki−Heck Arylation Catalyzed by a Fluorous Pd−Carbene Complex in F-626 and Photographs of the Reaction Using Pd Catalyst I[a]

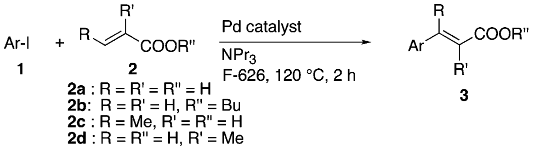


	3a	F-626 (recovered)
I (2 mol%)	93%	96%
Pd(OAc)$_2$ (2 mol%)/II (2 mol%)/PPh$_3$ (2 mol%)	88%	96%
Pd(OAc)$_2$ (2 mol%)/II (2 mol%)	88%	98%

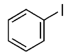
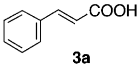
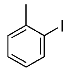
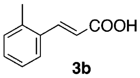
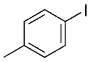
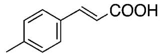
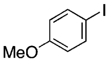
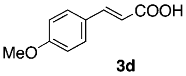
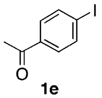
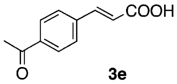
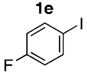
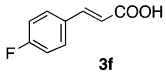
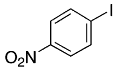
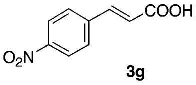
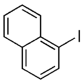
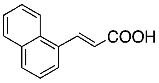
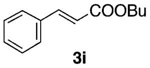
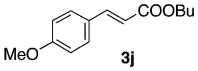
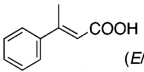
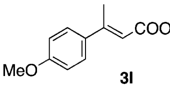
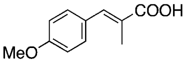
[a] Conditions: (A) before heating, with undissolved **I** and acylic acid (**2a**); (B) homogeneous solution after heating at 120 °C for 5 min; (C) after the reaction, with precipitated cinnamic acid (**3a**) and amine salts.

carried out in the presence of 2 mol % of **I** and tripropylamine (1.5 equiv, bp 155−158 °C) in F-626 (0.5 mL) at 120 °C (bath temperature). Changes in the appearance of the reaction mixture are demonstrated by three photographs (Scheme 2). At room temperature, even after stirring for 10 min, the Pd carbene complex **I** was present on the bottom, and the acrylic acid floated to the top of the F-626, whereas iodobenzene (**1a**) was soluble in F-626 (photograph A). On heating at 120 °C, however, the mixture became a homogeneous solution (photograph B) and the coupling product and amine salts began to precipitate as the reaction progressed. After cooling to room temperature, the coupling product, cinnamic acid, and amine salts precipitated in the bottom of the test

TABLE 1. Mizoroki−Heck Arylation of α,β-Unsaturated Carboxylic Acids and Esters Using F-626 as a Solvent[a]



2a : R = R' = R" = H
2b: R = R' = H, R" = Bu
2c : R = Me, R' = R" = H
2d : R = R" = H, R' = Me

entry	1	2	method	product 3	yield (%)[b]	F-626 (%)[c]
1	 **1a**	**2a**	A	 **3a**	88 (1st) 85 (2nd) 86 (3rd) 85 (4th)	96 94 97 95
2	 **1b**	**2a**	A	 **3b**	91	97
3	 **1c**	**2a**	A	 **3c**	93	94
4	 **1d**	**2a**	A	 **3d**	98	96
5			B		97	97
6	 **1e**	**2a**	A	 **3e**	95	95
7			B		99	94
8	 **1f**	**2a**	A	 **3f**	90	96
9	 **1g**	**2a**	A	 **3g**	80	97
10	 **1h**	**2a**	A	 **3h**	91	95
11	**1a**	**2b**	A	 **3i**	93	95
12[d]	**1a**	**2b**	A		88	97
13	**1d**	**2b**	A	 **3j**	82	97[e]
14	**1a**	**2c**	A	 **3k**	56 (E/Z = 93/7)	97
15[f]	**1d**	**2c**	B	 **3l**	47 (E/Z = 94/6)	98[g]
16	**1d**	**2d**	A	 **3m**	74	95

[a] Method A: **1** (1 mmol), **2** (1.3 mmol), Pd(OAc)$_2$ (2 mol %), PPh$_3$ (2 mol %), **II** (2 mol %) Pr$_3$N (1.5 equiv), F-626 (0.5 mL), 120 °C, 2 h. Method B (without PPh$_3$): **1** (1 mmol), **2** (1.3 mmol), Pd(OAc)$_2$ (2 mol %), **II** (2 mol %) Pr$_3$N (1.5 equiv), F-626 (0.5 mL), 120 °C, 2 h. [b] Yields isolated by flash chromatography on SiO$_2$. Only the *E* isomer was obtained unless otherwise noted. [c] Recovered F-626 contains the Pd catalyst whose weight % is less than 2%. [d] Phosphine ligand having a perfluoro alkyl chain, P(p-(C$_6$H$_4$)-CH$_2$CH$_2$C$_6$F$_{13}$)$_3$, was used instead of PPh$_3$. [e] Recovered F-626 contained 1.7% of the coupling product. [f] Reaction was carried out for 3 h. [g] Recovered F-626 contained 12% p-methoxy-α-methylstyrene, decarboxylation product of **3l**, as a byproduct.

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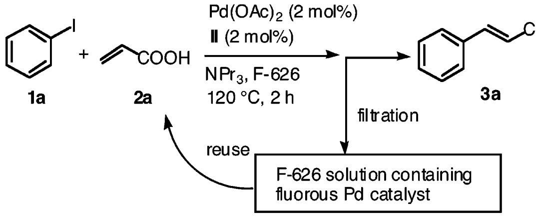
tube (photograph C). The F-626 solution, containing the Pd catalyst,[14] was separated from the precipitates by filtration under argon (96% solvent recovery by weight). The precipitates were subjected to an organic/aqueous biphasic workup to remove the salts, and the organic layer, containing the coupling product, was purified by short silica gel chromatography, to give pure cinnamic acid (**3a**) in 93% yield.[15] The reaction with the Pd carbene complex, prepared in situ from $Pd(OAc)_2$, PPh_3, and **II,** also occurred smoothly to give the coupling product in comparable yield. Later we also found that triphenylphosphine can be omitted without affecting the product yield.[16] The use of pefluorohexanes in place of F-626 was unsuccessful because of the low solubility of substrates.

Scheme 3 shows that the recovered F-626 phase, containing the Pd catalyst, can be successfully reused for further five runs without any detectable loss in catalytic activity. Contamination of the product in the recovered F-626 solution was negligible (less than 0.8% by ^{1}H NMR).

SCHEME 3. Recycling Study of Fluorous Medium and Catalyst



	run 1	run 2	run 3	run 4	run 5	run 6
3a	88%	85%	83%	84%	78%	83%
F-626	98%	97%	93%	96%	95%	94%

As shown in Table 1, using in situ generated Pd catalysts (method A, with PPh_3; method B, without PPh_3), the present filtrative separation of the catalyst and solvent could be applied to the synthesis of a variety of β-arylated α,β-cinnamic acids (entries 1−10). The arylation of crotonic acid (**2c**) and methacrylic acid (**2d**) also proceeded to give the corresponding β-arylated α,β-unsaturated carboxylic acids **3k**, **3l**, and **3m**, although the yields are not uniform (entries 14−16). Unlike the case of the arylation of α,β-unsaturated acids, in the arylation of α,β-unsaturated acid ester products did not precipitate in F-626 (entries 11 and 13). For these cases, a traditional fluorous/organic biphasic workup using ethanol/FC-72 (perfluorohexanes) was carried out to separate the products and fluorous ether F-626 containing the fluorous catalyst. To suppress the partial leaching of Pd catalyst to organic phase, it was necessary to use $P(p\text{-}(C_6H_4)CH_2CH_2C_6F_{13})_3$ as a phosphine ligand in place of PPh_3 (entry 12).

In summary, the Mizoroki−Heck arylation of α,β-unsaturated carboxylic acids and esters proceeds efficiently in a fluorous/organic hybrid solvent, F-626, without the use of an organic cosolvent. The insolubilities of the acid-type coupling products in the F-626 allows for the facile separation of the F-626 and the products, by simple filtration. The recovered F-626 phase, containing the Pd catalyst, can be successfully recycled for further runs.

Experimental Section

Typical Experimental Procedure for Mizoroki−Heck Arylation in F-626 (Method A). F-626 was degassed under reduced pressure at room temperature for 30 min, and then nitrogen gas was introduced. $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), fluorous ionic liquid **II** (16 mg, 0.02 mmol), PPh_3 (5.2 mg, 0.02 mmol), tripropylamine (215 mg, 1.5 mmol), iodobenzene (**1a**) (204 mg, 1 mmol), and acrylic acid (**2a**) (93 mg, 1.3 mmol) were added to F-626 (0.5 mL, 850 mg). The resulting mixture was heated at 120 °C for 2 h under nitrogen. After cooling to room temperature, the precipitate was filtered and washed with FC-72 (perfluorohexanes) (5 × 1 mL) under argon. The filtrate was evaporated under reduced pressure to give F-626 (820 mg, 96%, containing less than 2% of Pd catalyst). The precipitate was dissolved in EtOAc (30 mL) and washed with 2 M HCl aqueous solution (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layer was dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue was purified by short column chromatography on SiO_2 to afford the *trans*-cinnamic acid (**3a**) (130 mg, 88%, mp 133−134 °C (lit.[17] mp 132−135 °C)) as a white solid. The recovered F-626 containing the Pd catalyst was used in the next experiment.

Cinnamic acid (**3a**) was also obtained by washing the precipitates, consisting of cinnamic acid and the amine salt, with 2 M HCl aqueous solution instead of organic/aqueous biphasic workup. After the reaction, F-626 was decanted off and the precipitates were washed with FC-72. HCl (2 M) aqueous solution (3 mL) was added, and the mixture was stirred for 30 min at room temperature. After filtration, the precipitates were washed with water and dried under reduced pressure at 50 °C for 2 h to give cinnamic acid (**3a)** (135 mg, mp 129−132 °C).

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Supporting Information Available: Experimental procedures and characterizations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] To investigate if the Pd nanoparticles[5] are active species in our system, we carried out mercury poisoning experiments by addition of mercury(0) (12.5: 1, Hg/Pd) to the reaction system. The addition of mercury(0) did not suppress the catalysis, which suggests the nanoparticles are not key species in the present system. For recent examples for the Heck reaction promoted by Pd nanoparticles, see: (a) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Hendrickes, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285. (b) Consorti, C.; Zanini, M. L.; Leal, S.; Eberling, G.; Dupont, J. *Org. Lett.* **2003**, *5*, 983. (c) Nowotny, M.; Hanefeld, U.; van Konigsveld, H.; Maschmeyer, T. *Chem. Commun.* **2000**, 1877. See also ref 11.

[15] Cinnamic acid (**3a**) was also obtained by washing the precipitates with 2 M HCl aqueous solution instead of organic/aqueous biphasic workup. See the Experimental Section.

[16] For Mizoroki−Heck reaction using phosphine-free carbene complexes, see: (a) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123. (b) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031. See also ref 13a,b.

[17] Britteri, D. R. *J. Org. Chem.* **1981**, *46*, 2514.