Preparation of Fluorous DMF Solvents and Their Use for Some Pd-catalyzed Cross-coupling Reactions

Hiroshi Matsubara,* Louis Maeda, and Ilhyong Ryu*
Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531

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N,*N*-Dimethylformamide derivatives **1a** (Rf_6-DMF) and **1b** (Rf_8-DMF) with a C6 or C8 fluorous ponytail, respectively, have been synthesized and examined for some physical properties. Rf_6-DMF was tested as a solvent for Mizoroki–Heck arylation of butyl acrylate and Sonogashira coupling reaction of iodobenzene with phenylacetylene. Both reactions proceeded as smoothly as in DMF to give the products in high yield. Fluorous DMF derivative **1a** can be recovered easily from the reaction mixture by a fluorous/organic biphasic workup and recycled.

The rapid evolution of fluorous chemistry[1] requires effective amphiphilic solvents that can dissolve both organic and fluorous reagents, and which are easy to recycle via an organic/fluorous biphase workup.[2] We have recently reported that a fluorous ether F-626 (1*H*,1*H*,2*H*,2*H*-perfluorooctyl-1,3-dimethylbutyl ether)[3] (Chart 1) is a useful alternative to high-boiling point organic solvents, yet can be recovered based on its fluorous nature by an organic/fluorous biphasic workup.[4] We also reported that a Pd-carbene complex having a fluorous ponytail can be supported in F-626, which allows for an efficient recycling system of the reaction medium containing a catalyst.[5] While F-626 is an ether derivative, we are interested in some other fluorous amphiphilc solvents having a polar functional group. To that end, we chose as targets for study of DMF derivatives with a fluorous ponytail. Herein, we report preparations and fluorous properties of fluorous DMF-type solvents, *N*-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorononanyl)-*N*-methyl formamide, "Rf_6-DMF," **1a** and *N*-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-*N*-methyl formamide, "Rf_8-DMF," **1b** (Chart 2). We also report that the Mizoroki–Heck and the Sonogashira reactions using "Rf_6-DMF" **1a** as a solvent proceeded smoothly to give the coupling products in good yields. Recycling and reuse of catalyst was achieved by simple organic/fluorous biphasic workup of these reactions; the second runs of the reactions gave the products in almost the same yields as the first.

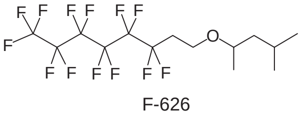
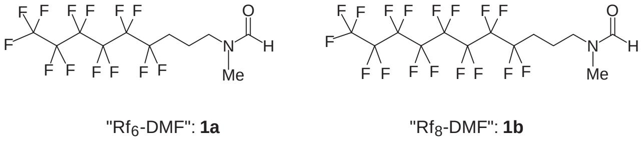
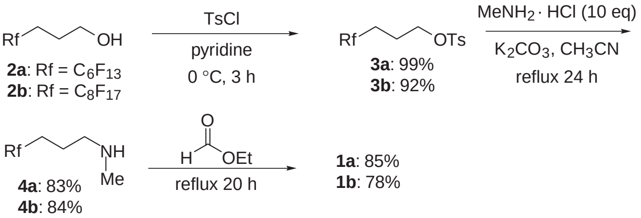


Chart 1.



"Rf_6-DMF": **1a** "Rf_8-DMF": **1b**

Chart 2.



Scheme 1.

Fluorous DMFs **1a** and **1b** were synthesized according to the procedures outlined in Scheme 1. Fluorous alcohol 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorononanol (**2a**) was converted to the corresponding tosylate **3a** in 99% yield, which was treated with ten molar excesses of methylamine hydrochloride in the presence of potassium carbonate in acetonitrile, giving secondary amine **4a** in 83% yield. The amine **4a** was treated with ethyl formate to afford Rf_6-DMF **1a** in 85%. Rf_8-DMF **1b** was prepared by a similar three-step procedure, which started with 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecanol (**2b**).

Rf_6-DMF **1a** is a colorless, clear, and slightly viscous liquid with a boiling point of 110 °C at 0.75 Torr, and a density of 1.544 g/cm^3 (25 °C), whereas Rf_8-DMF **1b** is a colorless semisolid with a melting point of 30 °C. Rf_6-DMF **1a** does not freeze at −35 °C but transforms to a glassy state at −40 °C. Since these fluorous DMFs have a large substituent group at the nitrogen, rotation barriers around the amide (C–N) bond are expected to be higher than those of DMF. In fact, NMR spectra of **1a** reveal that signals assigned to methyl group on the nitrogen do not coalesce even at 120 °C. Fluorous DMFs are miscible with a wide range of organic solvents, such as hexane, benzene, chloroform, ether, acetone, ethyl acetate, and ethanol, however, they are poorly soluble in cyclohexane and water. The approximate partition coefficients associated with biphasic treatment using a 1:1 mixture of organic solvent/FC-72 (perfluorohexanes) were determined for these newcomer solvents. We used a procedure similar to that, which was previously reported by Curran et al.[6] The results

Table 1. Partition coefficient (organic solvent/FC-72) of fluorous DMF and F-626 between FC-72 with organic solvent[a]

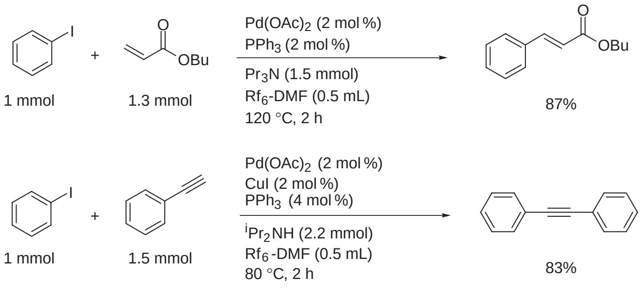
Solvent	1a	1b	F-626[b]
MeCN	1/0.078	—[c]	1/7.3
MeOH	1/0.05	—[c]	1/3.8
C_6H_6	1/1.13	1/0.32	1/1.6
Toluene	1/0.46	—[c]	—[c]
Cyclohexane	1/8.30	1/7.35	1/1.89
Acetone	1/0.10	—[c]	1/1.1
AcOEt	1/0.20	—[c]	1/0.85
$CHCl_3$	1/0.13	—[c]	1/0.85

[a]Determined by gravimetric method at 20 °C. [b]Ref 4. [c]Not determined.

are summarized in Table 1, in which those of F-626 are also given for comparison.

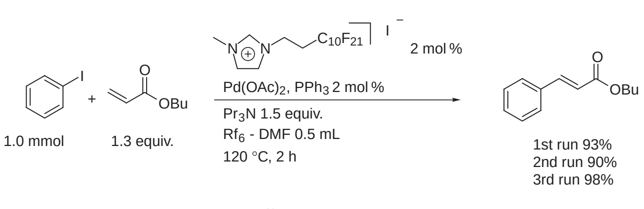
Inspection of the results of Table 1 reveals some interesting trends in partition coefficients of fluorous DMFs. Fluorous DMFs **1a** and **1b** are less fluorous than F-626; however, the majority is distributed in FC-72 phase, when a nonpolar solvent such as cyclohexane is used. This phenomenon can be explained on that while the amide part of the fluorous DMFs should have strong interaction with polar solvents, the fluorous alkyl chain of the DMFs may have a significant role in the case of using nonpolar solvents. Unexpectedly, **1b** with a longer fluorous ponytail shows less fluorous character than **1a**. Poor solubility of **1b** in FC-72 might be the reason for the observed low fluorous character. From the table, it is concluded that using biphasic workup with cyclohexane/FC-72 as the organic/fluorous solvents, fluorous DMFs will be extracted efficiently from the reaction mixture into FC-72 layer.

Needless to say, DMF is a well known polar aprotic solvent widely used for various organic and organometallic reactions.[7] In order to assess whether fluorous DMFs could function as a recyclable alternative to DMF, we decided to test the Mizoroki–Heck arylation[8] and the Sonogashira coupling reaction[9] using Rf$_6$-DMF **1a**. As shown in Scheme 2, both reactions proceeded smoothly in Rf$_6$-DMF as a solvent to give the desired coupling products in good yields.



Scheme 2.

Next, we investigated a recyclable fluorous catalyst/solvent system, which contains a fluorous palladium catalyst dissolved in a fluorous DMF. As shown in Scheme 3, iodobenzene was treated with butyl acrylate and tripropylamine in Rf$_6$-DMF **1a** at 120 °C for 2 h in the presence of 2 mol % of a fluorous palladium carbene complex prepared in situ from palladium acetate, triphenylphosphine, and fluorous imidazolium iodide.[5,10] After the reaction, a biphasic treatment (cyclohexane/FC-72 (perfluorohexanes)) of the reaction mixture was carried out under a nitrogen atmosphere. From the cyclohexane phase, butyl cinnamate was obtained in 93% yield after isolation by flash chromatography, whereas the Rf$_6$-DMF solution containing a fluorous catalyst was recovered from the FC-72 phase by phase separation and subsequent vacuum concentration. The recovered fluorous DMF solution containing a fluorous catalyst was successfully used for two more repeat experiments without reduction in the yields of the product. Sonogashira reaction with the recycled palladium catalyst was also able to achieve in Rf$_6$-DMF, which gave 81% yield of diphenylacetylene.



Scheme 3.

In summary, we have reported on preparation and some physical properties of two types of fluorous DMFs **1a** and **1b**. These have proven to have good potential as an easily recyclable solvent alternative to original DMF for model Pd-catalyzed cross-coupling reactions. Using Rf$_6$-DMF **1a** and an in situ prepared fluorous Pd catalyst, it was demonstrated that a recyclable solvent/catalyst system can be constructed. The development of viable fluorous reaction media, which can replace organic solvents, is actively pursued in this Laboratory.

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