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# Organic Synthesis in Fluoroalcohol-Water Two-Phase Systems

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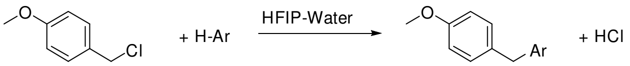
Organic synthesis in aqueous media was largely ignored due to incompatibility with metal catalyst compounds as well as the poor solubility of many reactants until 1980 when Breslow and Rideout reported rate acceleration for Diels Alder reaction when carried out in water.[1] The problem of low aqueous solubility for reactants can be overcome by using surfactants[2-5] or performing the reactions under "on water" conditions. "On water" reactions are carried out by stirring the reactants with water to form an aqueous suspension oftentimes giving higher rates and yields than reactions done in water or under solvent free conditions.[6-8] "On water" conditions have been applied to several types of reactions including Friedel-Crafts benzylations(FCB) [9] although only reactive heteroarenes could be used due to the high nucleophilicity of water, which traps the electrophiles, thus preventing less nucleophilic reactants from reacting in the presence of large amounts of water.

Fluoroalcohols , particularly hexafluoroisopropanol (HFIP), have been shown to be beneficial as solvents or additives for asymmetric homogeneous catalysis of organic reactions often improving yields and reaction times while preserving enantioselectivity.[10,11] The unique properties of fluoroalcohols include strong H-bond donation, low nucleophilicity and high ionizing power, which make them ideal solvents for generating reactive electrophilic species and allowing them to react with the desired nucleophile.[10,12] In particular, electrophilic aromatic substitution reactions including Friedel-Crafts type reactions have been shown to often proceed well in FA solutions[12-14] without the need for any type of acid catalyst due to the strong H-bond donation ability of fluoroalcohols.

Recently, we reported that fluoroalcohols (such as trifluoroethanol (TFE) and HFIP) that are fully miscible with water could induce phase separation and coacervation in aqueous solutions of a wide range of individual and mixed amphiphiles (surfactants, polyelectrolytes, phospholipids)[15]. It was hypothesized that the fluoroalcohols solvate the polar or charged groups on the amphiphiles and dehydrate the hydrophobic tail that leads to formation of a coacervate phase that is rich in amphiphiles and fluoroalcohols and an aqueous-rich phase. Takamuka et al. have also reported that addition of amides to aqueous solutions of HFIP could lead to phase separation even though the amides were individually miscible with both water and HFIP.[16,17] This phase separation was attributed to weakening of the hydrogen bond interaction between water and the carbonyl group of the amide due to the formation of a hydrophobic shell of trifluoromethyl groups from HFIP around the hydrophobic moieties of the amide as the alcohol concentration increases. This preferential solvation by HFIP eventually leads to a hydrophobic environment from which water molecules are excluded leading to phase separation.

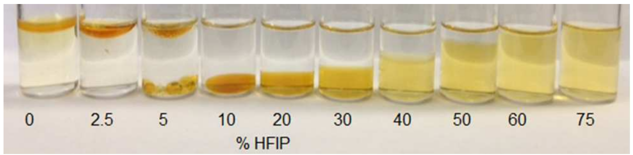
Here we report the first example of organic synthesis in two-phase systems composed of aqueous solutions of HFIP. In the presence of organic reactants, the otherwise miscible HFIP and water are present in separate phases where one phase is enriched with HFIP and organic reactants and the other phase is aqueous-rich. These two-phase systems were used as the reaction media for electrophilic aromatic substitution of arenes and heteroarenes using a benzyl halide to form diaryl alkane products shown in scheme 1.



Scheme 1. Friedel Crafts benzylation reaction in HFIP-Water two phase system.

The ternary mixture of water, HFIP, and organic reactant forms two separate phases. As shown below, one phase is enriched in HFIP and the organic compound and will be referred to as the H-O phase throughout the rest of the paper. The second phase is a largely aqueous phase. Image 1 shows the solutions resulting from the addition of 1-methylpyrrole (1mp) at a 1 M concentration to aqueous solutions of increasing % HFIP. In the absence of and at lower concentrations of HFIP, 1mp floats on top until enough HFIP is present to solvate the 1mp. Due to the higher density of HFIP (1.596 g/mL), the newly formed HFIP-1mp (i.e. H-O) phase sinks to the bottom. As the amount of HFIP is increased the volume of the bottom phase increases until at 75% HFIP, where a single phase solution is formed.

**Image1.** 1-methylpyrrole (1M) in HFIP-Water solutions of increasing HFIP% v/v



The same trend of increasing H-O phase volume with increasing % HFIP of the solution was observed for all nucleophiles (chart 1). Through phase composition analysis it was determined that the increase in volume was due to more HFIP and water being incorporated into the H-O phase in solutions with higher % HFIP shown in charts 2 and 3.

**Chart 1.** % Volume of the H-O phase formed by different nucleophiles in solutions of increasing % HFIP

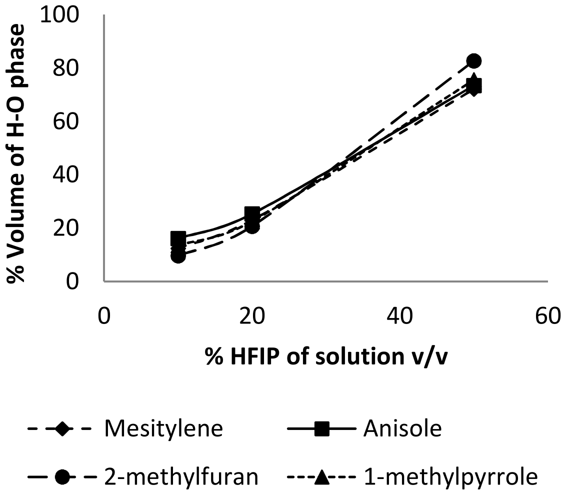


**Chart 2.** % Water in H-O phase formed by different nucleophiles at increasing % HFIP

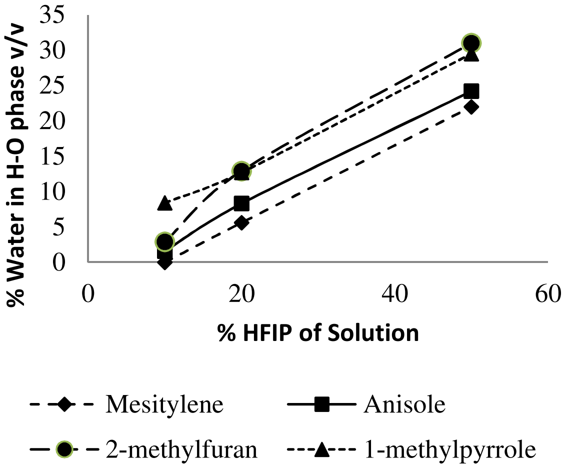
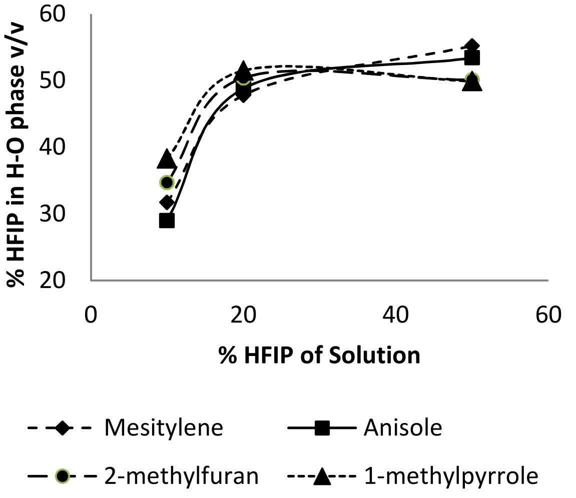


**Chart 3.** % Volume of HFIP in the H-O phase formed by different nucleophiles in solutions of increasing % HFIP



The Friedel Crafts type reactions were carried out with different π-bond nucleophiles and the benzyl halide, 4-methoxybenzyl chloride (4mbc) (Scheme 1). The nucleophiles represented a wide range of nucleophilicity strength according to the nucleophilicity scale (N) reported by Mayr[12] which included: mesitylene (N=-2.6), anisole (-1.18), 2-methylfuran (3.8) and 1-methylpyrrole (5.85). . A higher N value indicates higher nucleophilicity. HFIP is a weak nucleophile with N value of -2.4. The FCB reactions were carried out in the Water / HFIP-Organic two phase systems (scheme 1).

Table 1A shows the results of reaction carried out between the four nucleophiles with 4mbc in both pure water and HFIP as well as HFIP-Water solutions at different HFIP% that resulted in the formation of two-phase systems. As reported by Mayr, 2,6-lutidine was used as a base additive (unless otherwise noted) to trap the HCl generated by the reaction. All yields reported are for single substitution products although smaller amounts of multiple substitution products were observed for certain reactions. Initial reaction yields were obtained using HPLC calibration curves of the desired single substitution product. The HPLC yields are representative of the total amount of product in both phases as isopropanol was used to form a single-phase solution prior to analysis by HPLC.

Surprisingly, the yields in the two-phase systems are significantly higher than those in 100% HFIP for nearly all cases. As expected, the reactions did not proceed to any notable extent in “on-water” condition (i.e. 100% water) with the exception of 1-methylpyrrole; the strongest nucleophile where the yield was 34%. The trend is similar for all four reactants in the two-phase systems as the reaction yield reaches a maximum at 20% HFIP. Note that the initial concentrations of the reactants were 1M nucleophile and 0.2M 4mbc. However, in the two-phase systems, the reactants are concentrated in the H-O phase by a factor of 4-5 due to the inverse relationship with the smaller volume of the H-O phase (20%-25% v/v; Chart 1). The other factor is the presence of a small percentage of water (5%-12%) in the H-O phase. Whether the enrichment effect and/or presence of water in the H-O phase play a role leading to higher yields (as compared to 100% HFIP) is not clear. Mesitylene which has a slightly lower N value than HFIP was also able to react in these systems. This is consistent with the results reported by Mayr's group [12] where similar nucleophiles showed enhanced nucleophilicity in TFE in reacting with 4mbc even though they had lower N values than the solvent. They investigated the possibility that TFE and 4mbc initially formed a trifluoroethyl ether product followed by reaction with the arene and found that not to be the case in the presence of base. Thus they concluded that the nucleophile reacted faster with the 4-methoxybenzyl cation than the solvent, showing enhanced nucleophilicity.

**Table 1A.** Reactions of π-bond nucleophiles with 4mbc with 2,6-lutidine as a base additive

| Entry | Nucleophile | % HFIP | % Yield[a] |
|---|---|---|---|
| **1** | Mesitylene | 0 | 0 |
| **2** | Mesitylene | 10 | 61.2 |
| **3** | Mesitylene | 20 | 81 |
| **4** | Mesitylene | 50 | 77.5 |
| **5** | Mesitylene | 100 | 14.5 |
| **6** | Mesitylene | 100 | 66.2[b] |
| **7** | Anisole | 0 | 0 |
| **8** | Anisole | 10 | 42 |
| **9** | Anisole | 20 | 70.5 |
| **10** | Anisole | 50 | 69.3 |
| **11** | Anisole | 100 | 38.9 |
| **12** | Anisole | 100 | 42.8[b] |
| **13** | 2-methylfuran | 0 | <5 |
| **14** | 2-methylfuran | 10 | 80 |
| **15** | 2-methylfuran | 20 | 85 |
| **16** | 2-methylfuran | 50 | 69 |
| **17** | 2-methylfuran | 100 | <5 |
| **18** | 2-methylfuran | 100 | <5[b] |
| **19** | 1-methylpyrrole | 0 | 34 |
| **20** | 1-methylpyrrole | 10 | 92.5 |
| **21** | 1-methylpyrrole | 20 | 95 |
| **22** | 1-methylpyrrole | 50 | 75 |
| **23** | 1-methylpyrrole | 100 | 69 |
| **24** | 1-methylpyrrole | 100 | 85.6[b] |

[a] Yields determined by HPLC [b] Used $NH_4HCO_3$ as a heterogeneous base additive instead of 2,6-lutidine. Both base additives were present at a 0.4 M; nucleophile was 1 M while 4mbc was 0.2 M.

Interestingly, good yields were observed in the two-phase systems even in the absence of a base additive. Table 1B shows yields obtained from reactions performed without any base additive. It was hypothesized that in the two-phase systems the HCl is removed from the reaction media as it partitions into the aqueous phase; driving the reaction to completion. The pH of the aqueous phase was measured before and after 20H reactions between anisole and 1mp and was observed to decrease significantly from 5.64 and 6.20 to 0.20 and 0.41 respectively. These results support the hypothesis that the HCl is transferred into the aqueous phase. Thus, the aqueous phase can essentially perform the same role as a base additive such as 2,6-lutidine. The only exception was for the reaction between 2-methylfuran and 4mbc in the two-phase systems without a base additive. In 20% HFIP system with 2,6-lutidine, a much better yield of 85% was obtained for the 2-methylfuran - 4mbc reaction while for anisole a slightly higher yield was observed without a base additive indicating that whether or not a base additive is necessary could be dependent on the nucleophile.

**Table 1B.** Reactions of π-bond nucleophiles with 4mbc with no base additive

| **Entry** | **Nucleophile** | **% HFIP** | **% Yield**[a] |
|---|---|---|---|
| **1** | Mesitylene | 10 | 73 |
| **2** | Mesitylene | 20 | 81 |
| **3** | Mesitylene | 100 | 41 |
| **4** | Anisole | 10 | 68 |
| **5** | Anisole | 20 | 79 |
| **6** | Anisole | 100 | 30 |
| **7** | 2-methylfuran | 10 | 66 |
| **8** | 2-methylfuran | 20 | 37 |
| **9** | 2-methylfuran | 100 | no rxn |
| **10** | 1-methylpyrrole | 10 | 93 |
| **11** | 1-methylpyrrole | 20 | 88 |
| **12** | 1-methylpyrrole | 100 | 79 |

Nucleophile was 1 M while 4mbc was 0.2 M, same as the reactions done with base additives. Mesitylene reactions included diethyl ether to aid in phase separation as previously mentioned.
[a] Yields determined by HPLC

Similar experiments were carried out using other solvents. As shown in Table 2 the results in the 20% HFIP two-phase system are significantly better than those in the other solvents. Toluene and dichloromethane are not miscible with water and form a separate phase with the nucleophile from the aqueous phase; similar to the aqueous HFIP two-phase systems. The difference is that these solvents like most other organic solvents do not combine the properties of strong H-bond donation and low nucleophilicity like HFIP. Isopropanol, the aliphatic analog of HFIP with hydrogen bonding properties, is completely miscible with water just like HFIP. Only a modest yield was observed with 1-mp that is the strongest nucleophile. Similar solutions can be formed using TFE as well but due to its higher nucleophilicity when compared to HFIP (N=1.23 and -2.4 respectively) it did not work as well with less nucleophilic reactants; thus HFIP was chosen as the preferred solvent.

**Table 2. Effect of different solvents**

| **Solvent** | **Nucleophile** | **% Yield**[a] |
|---|---|---|
| HFIP | Anisole | 79 |
| | 1-methylpyrrole | 88 |
| 2-propanol | Anisole | 0 |
| | 1-methylpyrrole | 48 |
| Dichloromethane | Anisole | 0 |
| | 1-methylpyrrole | <10 |
| Toluene | Anisole | 0 |
| | 1-methylpyrrole | <10 |

All reactions were done in 20% solutions of the solvent in water. Nucleophile was present at 1 M and 4mbc was 0.2 M. [a] Yields determined by HPLC

In typical reaction procedures, especially those involving aqueous solutions, liquid-liquid extraction using an organic solvent such as diethyl ether or ethyl acetate is used to remove the organic components from the reaction solution for purification and isolation of the product. Due to the two-phase nature of these systems it should be possible to simply remove the bottom HFIP-Organic phase containing the product, followed by isolating the product using chromatography, thus eliminating the liquid-liquid extraction (LLE) step. Isolated yields were obtained for reactions using both LLE and bottom phase removal. In order to perform LLE, water was added to the reaction solutions following the desired reaction time in order to dilute the HFIP, and ethyl acetate was used to extract the product. The second method takes advantage of the two-phase system where the synthesis and extraction into the organic phase occurs concomitantly. Thus, the reaction solution was centrifuged following the desired reaction time in order to completely separate the phases. The bottom phase (i.e. H-O phase) was then removed using a glass pipette and dried with sodium sulfate to remove any water; and then the HFIP was removed by a rotary evaporator leaving behind the product as well as any unreacted starting materials. The results obtained using both methods are shown in table 3. The main takeaway from these results is that LLE and bottom phase removal give similar results because nearly all of the product should be present in the H-O phase. Not having to use LLE is an advantage of these HFIP-water two phase systems from an economical and environmental standpoint and also simplifies the procedure.

**Table 3.** Isolated Yields using two methods

| Nucleophile | With LLE | Without LLE |
|---|---|---|
| Mesitylene | 86 | 81 |
| Anisole | 70 | 75 |
| 2-methyl furan | 73 | 67 |
| 1-methyl pyrrole | N/A[a] | 79[b] |

Reactions were carried out in 20% HFIP-water two-phase systems using 2,6-lutidine. [a] LLE procedure did not result in clear phase separation. [b] Done in 20% HFIP solution without any base additive.

In summary, the Friedel Crafts benzylation of arenes and heteroarenes using benzyl halides was shown to proceed in the aqueous HFIP two-phase system. This system offers a new, largely aqueous medium for organic reactions that will benefit from the properties of HFIP such as Friedel-Crafts and Diels Alder.[18] Equivalent or better yields were obtained in the two-phase systems when compared to pure HFIP for most reactions. The use of the two-phase system also reduces the consumption of HFIP by 80% leading to a significant reduction in cost as well as toxicity of the reaction media. The strong hydrogen bond donation properties can also eliminate the need for Lewis acid catalyst, further simplifying the procedure. Due to the two-phase nature of the system, hydrophilic by-products of reactions can be extracted into the aqueous phase as they are being produced, thus driving the reaction to completion. The two phase nature also allows for recovery of the product by removal of the H-O phase and evaporation of the HFIP without the need for liquid-liquid extraction.

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