Fluorous Biphasic Catalysis: A New Paradigm for the Separation of Homogeneous Catalysts from Their Reaction Substrates and Products

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Abstract: The concept of fluorous biphasic catalysis (FBC) represents a new paradigm for the separation of homogeneous catalysts from their substrates and the products emanating from these reactions. Since its published inception four years ago, FBC has been demonstrated in a variety of catalytic reactions that encompass hydroformylation, hydrogenation, hydroboration, hydride reduction, alkene epoxidation, and alkane and alkene functionalization. The common theme in all these homogeneous catalysis reactions, accomplished under FBC conditions, is the modification of the homogeneous catalyst with long-chain fluoroponytails to render them soluble in the fluorous phase; most hydrophobic substrates, and, to a large extent, hydrophilic products, are relatively insoluble in fluorocarbon solvents. The fact that fluorocarbon solvents are apparently nontoxic provides the FBC concept with a possible entry to the new Green Chemistry regime of being environmentally friendly, and therefore potentially attractive in a wide variety of industrial processes for the catalytic production of important organic chemicals worldwide. Clearly, FBC has caught the imagination of many colleagues all over the world, and thus, the outpouring of new fluorocarbon-soluble catalysts for the aforementioned applications will continue unabated into the next millennium.

Keywords: biphasic catalysis · fluorocarbon solvents · fluoroponytails · homogeneous catalysis · separation

Introduction

Ever since the biphasic solvent approach was first introduced, chemists conducting homogeneous catalysis experiments have asked themselves: how do we better separate the substrates and the products of these reactions from the inorganic or organometallic complexes that facilitate these catalytic transformations? Recently, several groups have created a new concept for this continuing homogeneous catalyst separation problem. In a 1991 PhD thesis that was unfortunately not readily available to the homogeneous catalysis community nor published in the open literature, M. Vogt, under the guidance of his Ph.D. advisor W. Keim, of the Rheinisch-Westfälischen Technischen Hochschule in Aachen, Germany, presented the first conceptual aspects of the fluorous biphasic catalysis (FBC) approach with an emphasis on oligomerization of alkenes, oxidation of alkenes, hydroformylation of olefins, and telomerization of dienes.[1] It was not until 1994, when Horváth and Rábai published the first archival paper on this simple but elegant FBC concept, that the global chemical community took notice of this novel advance in the more general area of biphasic catalysis.[2]

The process of developing a new paradigm for the separation of the homogeneous catalyst from the substrate and the product must start with the solvent system. It is well known that perfluorohydrocarbons have unusual properties such as being extremely hydrophobic and lacking hydrogen-bonding capabilities, which renders them relatively insoluble in their hydrocarbon analogues, and are also able to dissolve various gases such as oxygen, hydrogen, and carbon dioxide.[3] Thus, it is surprising that it took so long for this FBC approach to be discovered, since the above-mentioned parameters would allow a number of critical catalytic reactions to be demonstrated by using perfluorohydrocarbons as one phase in a biphasic solvent mode.

One of the most important aspects of this overall FBC process is the requirement that the homogeneous precatalyst for the designated reaction *be totally soluble in the fluorous phase*. Therefore, long-chain fluoroponytails are appended to the organic ligand that is bound to the catalytic metal-ion center.[1, 2] In addition, another crucial modification of this approach is the introduction of several spacer methylene groups between the heteroatom of the ligand and the first CF_2 group of the fluoroponytail, which mitigates the powerful electron-withdrawing effect of the CF_2 groups that can cause the heteroatom attached to the metal center to be a weak or nonbinding site. Furthermore, metal-ion complexes that have an overall charge and that are to react with a fluorous soluble

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ligand to form the final fluorous soluble precatalyst must themselves be modified, in some cases, to have fluoroponytails to further enhance their fluorocarbon solubility.

Since 1994, FBC has been demonstrated for hydroformylation,[2, 4] hydrogenation,[5] hydride reduction,[6] hydroboration,[7] alkene epoxidation,[8] and alkane and alkene functionalization,[9] while new fluorocarbon-soluble catalysts are being discovered at a rapid pace for these applications and others. Thus, the demonstration of each of the above-mentioned applications of this FBC approach, along with the plausible synthetic strategy mentioned above, will be instructive for the chemist not familiar with this novel biphasic technique and allow those chemists with experience in homogeneous catalysis to generate new ideas to further this burgeoning field.

Discussion

Two reaction scenarios (Figure 1) will be demonstrated and discussed with pertinent examples that show the flexibility of the FBC process with regard to conducting experiments at room temperature in the biphasic mode (scenario 1) or utilizing a solvent(s) such as perfluoromethylcyclohexane toluene along with higher temperatures (scenario 2) to create a single phase for reactivity and a separation of phases at room temperature.[1, 2] I will first discuss the synthetic strategy that can create the fluoroponytailed ligands and the subsequent metal-ion complexes, allowing both FBC scenarios to be implemented.

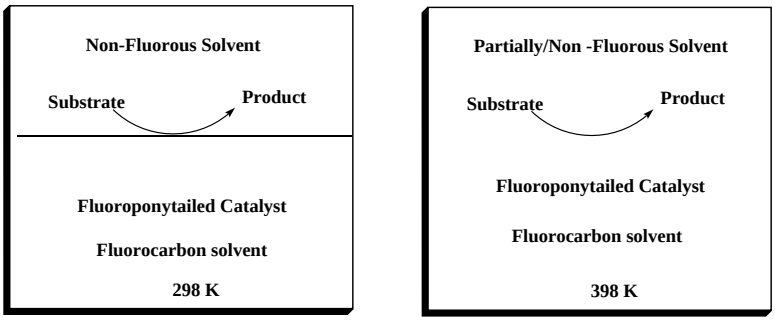
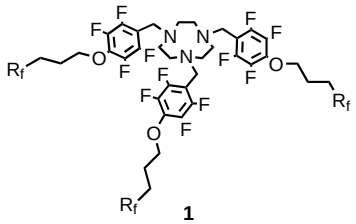


Figure 1. Two FBC reaction techniques.

A. Fluoroponytailed ligands and their metal ion complexes for fluorocarbon solubility: Since many of the fluoroponytailed ligands and their subsequent fluorocarbon-soluble metal-ion complexes were synthesized in research laboratories, owing to the simple fact that they are not readily available commercially, we will provide an overview of the synthesis strategy that could be followed to enhance the success of the FBC approach. To reiterate, it is instructive to understand that a CF_2 group α to a heteroatom that can potentially bind to the metal ion will basically inhibit this binding process. Thus, two or, preferably, three methylene spacer groups are necessary to eliminate this powerful electron-withdrawing effect (typical fluoroponytails with spacer groups are $CF_3(CF_2)_xCH_2CH_2$- and $CF_3(CF_2)_xCH_2CH_2CH_2$-), unless of course the fluoroponytail is attached to an aromatic ring.[8b,d] More importantly, the length and number of the fluoroponytails should provide a $>60\,\%$ fluorine content to further guarantee effective fluorocarbon solubility.[2]

Another caveat of which the FBC researcher must be cognizant is the use of fluoroponytailed, substituted fluoroaromatic ligands; *these ligands are usually not fully fluorocarbon-soluble*. The solubility problem appears to be related to a possible hydrogen-bonding regime between a polarized aromatic C–F bond, for example, a pentafluorophenyl group, which can occur with non-fluorinated substrates/solvents and further inhibit fluorocarbon solubility. An example is given below of a ligand, **1**, synthesized by J.-M. Vincent (unpublished results) during our LBNL FBC studies, which is instructive on this critical point; ligand **1** ($R_f = C_8F_{17}$) is not soluble in cold perfluoroheptane and, in addition, has a fluorine content of $<60\,\%$.



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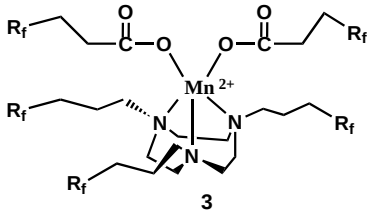
The other aspect of this FBC approach that needs attention, as mentioned, is the metal-ion complexes of these fluoroponytailed ligands, especially if these metal-ion complexes are charged species; hydrophobic fluorocarbons do not readily solubilize charged metal-ion complexes. To overcome this deficiency, fluoroponytailed ligands can be used on the precursor metal-ion complexes,[9] which are then allowed to react with the fluoroponytailed ligands already found to be soluble in fluorocarbon solvents. Thus, as an example, the complex $[(CF_3(CF_2)_7CH_2CH_2COO)_2Mn]$ (**2**) alone is not totally soluble in cold perfluoroheptane, but in the presence of a perfluoroheptane-soluble ligand, such as R_fTACN ($R_f = C_8F_{17}$), it forms a new $[R_fMnR_fTACN]$ complex, **3** (tentative structure) in situ, which is now fully fluorocarbon-soluble.[9a]



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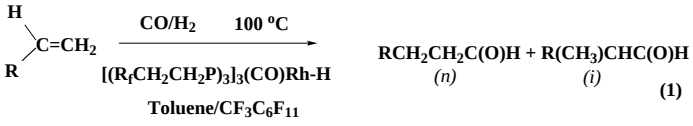
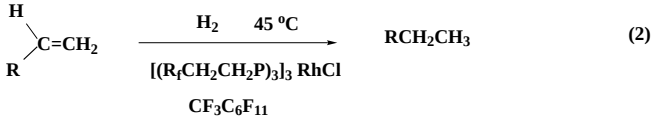
B. Illustrative examples of FBC advancements: Many homogeneous catalysis reactions, where separation of the catalyst from the product and starting substrate is difficult or impossible, can be converted to the FBC paradigm. Therefore, it is my intention to illustrate various single-solvent-phase catalysis reactions that have been made more viable by the simple decantation of the lower fluorous phase containing the synthesized fluorocarbon soluble precatalyst analogue at room temperature for recycling.

1. Hydroformylation: The initial archival publication that showed the tremendous potential of this FBC approach was focused on the hydroformylation of 1-alkenes.[2, 4] This is illustrated by using a hydroformylation solvent system that is homogeneous at 100 °C (Figure 1, scenario 2), but separates into two phases at room temperature (scenario 1). Thus, a hydroformylation reaction in which the 1-alkene substrate is soluble in cold toluene and the catalyst, $[\{(CF_3(CF_2)_5CH_2CH_2P)_3\}_3(CO)RhH]$, is soluble in cold trifluoromethylperfluorocyclohexane ($CF_3C_6F_{11}$) may be conducted at 100 °C in the presence of CO/H_2, under which conditions the reaction mixture is homogeneous, while cooling to room temperature results in separation of the reaction product aldehydes (*n*/*i* ratios are high) from the fluoroponytailed catalyst [$R_f = C_6F_{13}$, Eq. (1)].



(1)

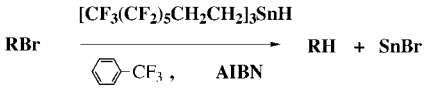
2. Hydrogenation: The hydrogenation of organic compounds with transition metal hydrides is another example of FBC compatibility. An aliphatic version of Wilkinson's catalyst was modified with fluoroponytails, $[\{(CF_3(CF_2)_5CH_2CH_2P)_3\}_3RhCl]$, to render it soluble in $CF_3C_6F_{11}$. The substrate alkene, for example cyclododecene, was dissolved in toluene, while the fluoroponytailed, aliphatic Wilkinson's catalyst is soluble in $CF_3C_6F_{11}$. Hydrogenation at 1 atm of H_2 gas (45 °C) under FBC conditions (Figure 1, scenario 1) provided cyclododecane, 94% yield and 120 TON.[5] Recycling of the lower fluorocarbon phase containing $[\{(CF_3(CF_2)_5CH_2CH_2P)_3\}_3RhCl]$ allowed for continuous catalytic runs [Eq. (2)]. Interestingly, the catalytic dihydride



(2)

complex was also shown by ^{31}P and ^1H NMR to be *meridional* P and *cis* H_2, $[\{(CF_3(CF_2)_5CH_2CH_2P)_3\}_3Rh(H_2)Cl]$, and similar to Wilkinson's catalyst, [tris(triphenylphosphine)$Rh(H_2)Cl$].

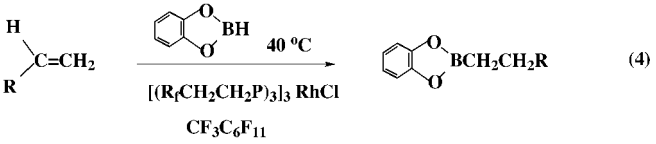
3. Hydride reduction: Another interesting FBC example was reported with a fluoroponytailed organotin hydride, $[\{CF_3(CF_2)_5CH_2CH_2\}_3SnH]$, that could be utilized in various free-radical reduction reactions with functional groups such as halides (Br, I) or NO_2-, with trifluoromethylbenzene as the solvent [Eq. (3)].[6] This process can be made catalytic by the addition of a reducing agent, $NaCNBH_3$, to recycle the SnH



(3)

from SnX, while separation of the $[\{CF_3(CF_2)_5CH_2CH_2\}_3SnX]$ compound from the reduced product for recycling (for example, X = Br) was accomplished by a fluorocarbon extraction procedure.

4. Hydroboration: A unique example of the use of the FBC process for the facile separation of the fluoroponytailed catalyst from products is the classical hydroboration reaction.[7] Again, using the aliphatic Wilkinson's catalyst $[\{(CF_3(CF_2)_5CH_2CH_2P)_3\}_3RhCl]$, in conjunction with catecholborane and an alkene, hydroboration occurs to provide the alkylcatecholboron compound [Eq. (4)], that is oxidized, in a subsequent step, directly by H_2O_2 to alcohol with the fluorous phase containing the catalyst $[\{(CF_3(CF_2)_5CH_2CH_2P)_3\}_3RhCl]$ being recycled.



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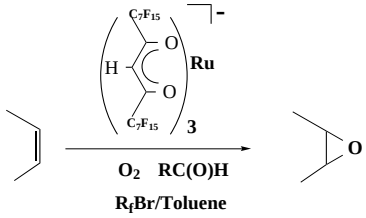
5. Alkene epoxidation: The great advantage of performing classical oxidation reactions, for example, epoxidation[8] or alkane/alkene functionalization,[9] in the FBC mode is the high solubility of the important reactant, oxygen gas, in fluorocarbon solvents.[10] Thus, the epoxidation of olefins has recently been demonstrated in the FBC mode by several groups.[8] The reported oxidation systems utilized an aldehyde and oxygen gas as necessary reactants, presumably to form in situ the corresponding percarboxylic acid that then performs the subsequent epoxidation chemistry. To reiterate, the critical task in these epoxidation reactions, as in all the FBC examples, was the difficult synthesis of the fluoroponytailed catalyst that has fluorocarbon solubility. It appears, in general and in this context, that fluoroponytailed non-porphyrin ligands[8c,d, 9] are more easily synthesized than the fluoroponytailed porphyrin ligands.[8b] An example of a fluoroponytailed non-porphyrin Ru complex is shown in the FBC epoxidation of disubstituted olefins at 50 °C [Eq. (5), Figure 1, scenario 2].[8c]



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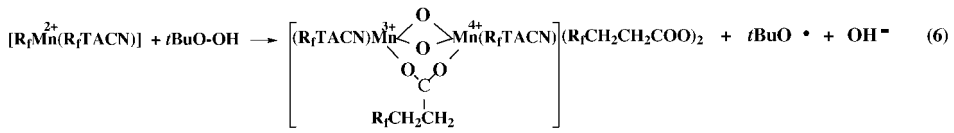
6. Alkane and alkene functionalization: Although the above-mentioned classical reactions to organic compounds are essential for possible new industrial processes using the

FBC paradigm, the functionalization of alkanes and alkenes to alcohols, aldehydes, and ketones under FBC oxidation conditions[9] represents an important advance for the catalytic synthesis of globally important organic chemicals, the ultimate, future alkane functionalization reaction being conversion of CH_4 to CH_3OH. In this regard, our group at LBNL[9a] and the CNR group in Milan[9b] focused on the synthesis of fluoroponytailed substituted nitrogen macrocycles in conjunction with fluoroponytailed metal carboxylates (for example compounds **2** and **3**) for oxidation precatalysts.

The functionalization reaction[9a] (Figure 1, scenario 1) that provides facile allylic oxidation of alkenes and, to a lesser extent, alkane oxidation, using *tert*-butyl hydroperoxide/O_2 as the critical components and **3** generated in situ as the precatalyst, was found to occur by the well-known Haber–Weiss process that generates *t*BuO• radicals with concomitant oxidation of Mn^{2+} to an ESR-identified $[Mn^{3+}(\mu\text{-}O)_2Mn^{4+}]$ dimer [Eq. (6), tentative Mn structures]. Thus, it is the *t*BuO• radicals that initiate the free radical process that generates a



(6)

carbon radical from alkene or alkane, and is followed by O_2 trapping to provide the alkyl/alkenyl hydroperoxides, the precursor to the oxidation products. As usual, recycling the fluorous phase permits a continual oxidation process, but further research is needed to develop any possible industrial scenario for important organic chemical synthesis.

Conclusions

My intention in this Concept article was to enlighten the chemical community concerning a very exciting new method for conducting biphasic homogeneous catalysis, and to inspire chemists to design new FBC systems for their non-fluorous catalytic chemistry. I hope that, in the near future, this FBC paradigm will be added to the nascent list of Green Chemical Processes, as it is environmentally friendly and therefore potentially attractive for a wide variety of industrial processes for the ultimate catalytic production of important organic chemicals worldwide. Finally, I touched upon several classical reaction systems, as examples that have been converted to the FBC mode, but other important FBC approaches not mentioned in this Concept article have been, and will be, invented.[11]

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