

Fluorous Biphasic Chemistry

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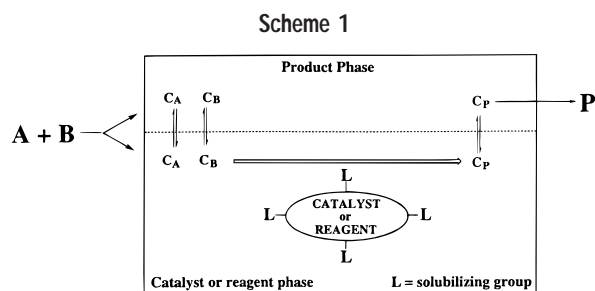
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Introduction

The development of environmentally benign technologies is the most challenging goal of contemporary chemistry and chemical engineering.¹ Environmentally friendly chemical processes should be designed to use environmentally benign feeds and solvents, have high product selectivity at an economical reaction rate (e.g., high product yield), and utilize efficient reagent or catalyst recycling systems. While the use of solid reagents and catalysts with gaseous or liquid feeds and products provides easy separation, the presence of various surface species with different activity and selectivity frequently limits high yields.² In contrast, homogeneous liquid phase reactions are generally characterized by high product yields, but the separation of the products is a major obstacle for practical applications. One of the most vigorously pursued research areas of homogeneous transition metal catalysis has been the development of novel approaches for facile catalyst recycling.³

The use of liquid–liquid biphasic processes, in which a reagent or a catalyst is designed to reside in one of the liquid phases and the product forms the other liquid phase, could be the enabling approach for the commercial applications of many, very selective chemical reactions. Since the formation of a liquid–liquid biphasic system is due to the sufficiently different intermolecular forces of two liquids,⁴ the selection of a reagent or catalyst phase depends primarily on the solvent properties of the product phase at a high conversion level. For example, if the product is apolar, the reagent or catalyst phase should be polar, and vice versa, if the product is polar, the reagent or catalyst phase should be apolar. The success of any biphasic system depends on whether the reagent or catalyst could be designed to dissolve preferentially in the reagent or catalyst phase. Perhaps the most important rule for such design is that the catalyst has to be catalyst

phase like, since it has been known for centuries that “similia similibus solvuntur”, or “like dissolves like”.⁵ Thus, the required solubility can be achieved by attaching appropriate solubilizing groups to reagents or catalysts (Scheme 1).

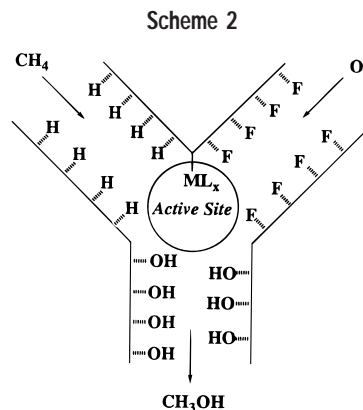


Water soluble reagents and catalysts are known, and they could offer facile reagent or catalyst separation for many reactions.⁶ However, aqueous media cannot be used for chemical systems in which a component of the system undergoes undesired chemical reactions with water. Furthermore, the low solubility of many organic compounds in water could limit the applications of aqueous reagents or catalysts. Nonaqueous biphasic systems could overcome some of these limitations, and alcohols⁷ and ionic liquids⁸ have been used to replace water.

This Account describes the fluorous biphasic concept,⁹ which opened the way to the development of fluorous biphasic chemistry, providing a complementary approach to other known biphasic systems for stoichiometric and catalytic chemical transformations.

The Fluorous Biphasic Concept

The fluorous biphasic concept evolved from the search for a novel approach for the selective oxidation of methane to methanol utilizing molecular oxygen, which could be one of the most important breakthroughs for natural gas utilization.¹⁰ In light of the structure of methane monooxygenase (MMO)¹¹ and the well-known shape selectivity of zeolites,¹² the development of a “molecular Y-tube” consisting of three functional channels and a strategically positioned catalyst was imagined (Scheme 2). While methane would be delivered to the catalyst site



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through a hydrophobic channel, just like in MMO, molecular oxygen would approach the site through a perfluorinated channel. The later assumption was based on the fact that the solubility of oxygen in perfluoroalkanes is extremely high.¹³ Finally, the product methanol would be removed from the active site through a hydrophilic channel. Since the synthesis of such a *molecular reactor* seemed exceedingly difficult, the idea was adapted to solution chemistry. It became apparent that the miscibility of perfluoroalkanes with methanol is low, and they form biphasic systems with methanol at room temperature.¹⁴ Thus, the use of a two-phase system, consisting of a perfluoroalkane phase containing an oxidation catalyst and a product phase being methanol itself, seemed an attractive approach. To avoid the oxidation of the catalyst and to achieve high solubility in the perfluoroalkane phase, perfluoroalkyl chains were to be attached to the ligand core of the catalyst, e.g., L = (CF₂)_nCF₃ (*n* > 5) in Scheme 1. Although this approach has not resulted in a new methane oxidation catalyst so far, it led to the development of a much broader concept.

When it was realized that the miscibility of perfluoroalkanes, perfluorodialkyl ethers, and perfluorotrialkylamines is low even with common organic solvents such as toluene, THF, and acetone,¹⁴ a general concept, the *fluorous biphasic concept*,^{9a} was born which led to the development of *fluorous biphasic chemistry*. The term *fluorous* was introduced, as the analogue to the term *aqueous*, to emphasize the fact that a chemical transformation is primarily controlled by a reagent or a catalyst designed to dissolve preferentially in the fluororous phase. The *fluorous phase* was defined as the perfluoroalkane, perfluorodialkyl ether, or perfluorotrialkylamine rich phase of a biphasic system. Thus, a *fluorous biphasic system*^{9b} consists of a fluororous phase containing a preferentially fluororous soluble reagent or catalyst and a second product phase, which may be any organic or nonorganic solvent with limited solubility in the fluororous phase. Reagents and catalysts can be made fluororous soluble by attaching fluorocarbon moieties to ligands in appropriate size and number. The most effective fluorocarbon moieties are linear or branched perfluoroalkyl chains with high carbon number that may contain other heteroatoms (the “fluorous ponytails”). Because of the well-known electron-withdrawing properties of the fluorine atom, the attachment of fluororous ponytails could change significantly the electronic properties and consequently the reactivity of fluororous reagents and catalysts. Therefore, the insertion of insulating groups before the fluororous ponytail may be necessary to decrease the strong electron-withdrawing effects. For example, theoretical calculations show that the electronic properties of P[(CH₂)_x(CF₂)_yCF₃]₃ (*x* = 0, *y* = 2 or 4 and *x* = 0–5, *y* = 2) can be tuned by varying the number of methylene groups [–(CH₂)_x–] between the phosphorus atom and the perfluoroalkyl moiety (Table 1).¹⁵ The effect of perfluoroethyl-terminated alkyl ponytails, which are sufficient models for longer perfluoroalkyl-terminated alkyl groups, is small for two (*x* = 2) and essentially negligible for three (*x* = 3) methylene units.

Table 1. Electronic and Physical Properties of P[(CH₂)_x(CF₂)_yCF₃]₃ and P[(CH₂)₃CH₃]₃

species	P lone pair level	P Mulliken population (<i>q</i>)	protonation energy (eV)	P–H (Å)	∠HPL (deg)
P[CF ₂ CF ₃] ₃	–11.7	0.83	–6.5	1.189	85.9
P[(CF ₂) ₃ CF ₃] ₃	–11.7	0.83	–6.4	1.192	85.4
P[(CH ₂ CF ₂ CF ₃)] ₃	–10.6	0.62	–7.7	1.205	86.3
P[(CH ₂) ₂ CF ₂ CF ₃] ₃	–9.9	0.48	–8.3	1.218	92.3
P[(CH ₂) ₃ CF ₂ CF ₃] ₃	–9.5	0.40	–8.6	1.225	91.8
P[(CH ₂) ₄ CF ₂ CF ₃] ₃	–9.3	0.38	–8.8	1.226	92.0
P[(CH ₂) ₅ CF ₂ CF ₃] ₃	–9.2	0.36	–8.9	1.228	91.8
P[(CH ₂) ₃ CH ₃] ₃	–8.7	0.33	–9.3	1.230	91.7

However, the differences between the electronic properties of P[(CH₂)_xCF₂CF₃]₃ with more than three methylene groups (*x* > 3) and P[(CH₂)₃CH₃]₃ are small but finite. It should be noted that the possibility of dipole–dipole interactions¹⁶ render *perfluoroaryl*-containing reagents and catalysts more soluble in common organic solvents and therefore less useful as part of fluororous biphasic systems.

Convincing evidence that such systems can be constructed was disclosed more than 40 years ago.¹⁷ Researchers at 3M Company have faced the challenging question of how to develop dye pigments which can be employed for coloring perfluoroalkanes and Teflon, as ordinary oil or water soluble dyes were not compatible with perfluorinated materials. Perfluoroalkylation of a Cu–phthalocyanine yielded a blue dye, which was soluble in perfluorotributylamine and could be used to prepare a Teflon compatible ink. It was recently established that analogous perfluoroalkylated metal–phthalocyanine complexes (Co and Fe) are preferentially soluble in the lower fluororous phase of a fluororous biphasic system consisting of 3 mL of *n*-hexane, 1 mL of toluene, and 3 mL of perfluoromethylcyclohexane (C–C₆F₁₁CF₃) at room temperature (Figure 1).^{9a}

Fluorous biphasic systems are well suited for converting apolar reactants to products of higher polarity, as the partition coefficients of the reactants and products will be higher and lower, respectively, in the fluororous phase. The net results are no or little solubility limitation on the reactants and easy separation of the products. Furthermore, as the conversion level increases, the amount of polar products increases, further enhancing separation. One of the most important advantages of the fluororous biphasic catalyst concept is that many well-established hydrocarbon soluble reagents and catalysts can be converted to fluororous soluble. A fluororous biphasic reaction could proceed either in the fluororous phase or at the interface of the two phases, depending on the solubilities of the reactants in the fluororous phase. When the solubilities of the reactants are very low in the fluororous phase, the chemical reaction may still occur at the interface or appropriate phase transfer agents may be added to facilitate the reaction.

It should be emphasized that some fluororous biphasic systems can become a single phase at increased temperatures.^{14b} For example, the fluororous biphasic system consisting of 3 mL of *n*-hexane, 1 mL of toluene, and 3

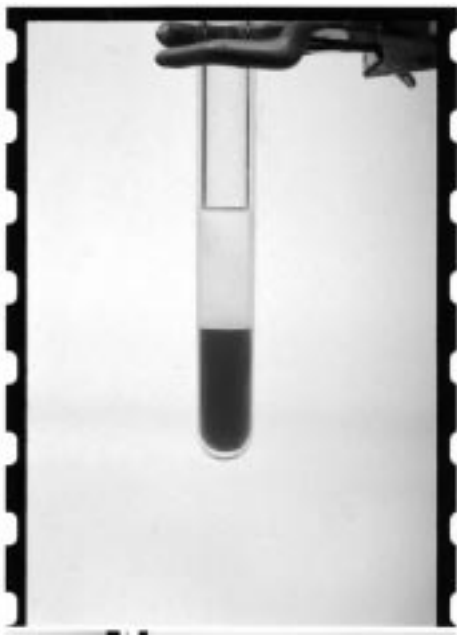


FIGURE 1. Phase separation of a *n*-hexane (3 mL)—toluene (1 mL)—*c*-C₆F₁₁CF₃ (3 mL) fluorous biphasic system at room temperature. The blue color of the fluorous phase is due to a perfluoroalkylated cobalt—phthalocyanine complex. Reprinted with permission from Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72–75. Copyright 1994 American Association for the Advancement of Science.

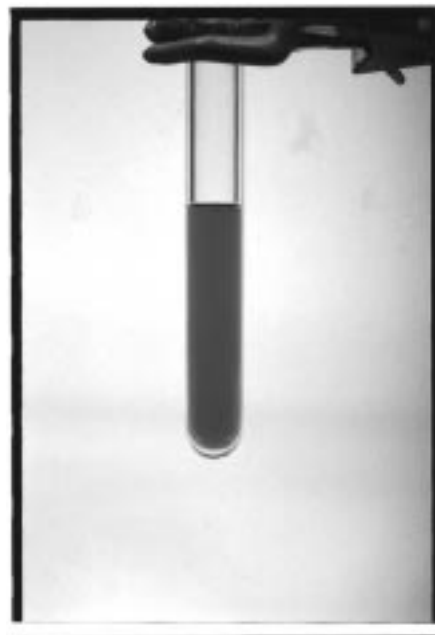


FIGURE 2. Hand-warmed (36.5 °C) *n*-hexane (3 mL)—toluene (1 mL)—*c*-C₆F₁₁CF₃ (3 mL) one-phase solution. The blue color is due to a perfluoroalkylated cobalt—phthalocyanine complex. Reprinted with permission from Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72–75. Copyright 1994 American Association for the Advancement of Science.

mL of *c*-C₆F₁₁CF₃ becomes a one-phase system at 36.5 °C (Figure 2).^{9a} Thus, a fluorous biphasic system could combine the advantages of one-phase reaction with biphasic product separation by running the reaction at higher temperatures and separating the products at lower temperatures.

As frequently happens in science, a new direction is emerging in a given field, and as a consequence the same discovery is made independently in different laboratories practically at the same time. The application of perfluorinated polyalkyl ether soluble transition metal (Co, Ni, and Mn) complexes in catalytic oligomerization of ethylene, oxidation of cyclohexene, and polymerization and telomerization of butadiene was described in the Ph.D. thesis of Vogt.¹⁸

Reactions in Fluorous Media

A liquid fluorocarbon as a solvent was first used in the separation of uranium isotopes in 1940.²⁰ Although the remarkable chemical inertness, thermal stability, and nonflammability of perfluoroalkanes, perfluorodialkyl ethers, and perfluorotrialkylamines make them particularly attractive reaction media,²¹ they have been sparingly used²² in the following half century. The first systematic application of perfluoroalkanes and perfluorotrialkylamines as inert media for organic reactions was published by Zhu in 1993²³ and has been followed by others.²⁴ It should be emphasized that perfluoroalkanes, perfluorodialkyl ethers, and perfluorotrialkylamines are practically *nontoxic*.²⁵ Although their thermal degradation can produce toxic decomposition products, such decomposition

generally begins only at very high temperatures well above the thermal stability limits of most reagents and catalysts.

Fluorous Extraction

One of the first examples for the use of fluorous solvents in chemical reactions was the photodegradation of fluorous extracts of PCBs-contaminated solid- or liquid-phase wastes.^{22c} It has been shown that the fluorous phosphine P[CH₂CH₂(CF₂)₅CF₃]₃ can be used as a reagent for the extraction of Rh(CO)₂(CH₃COCHCOCH₃) from toluene and RhCl₃ from ethanol by the formation of fluorous rhodium phosphine species.^{9b}

Fluorous Biphasic Catalysis

Although most molecular catalysts could be made fluorous soluble by attaching fluorous ponytails to the catalyst core in appropriate size and number,²⁶ only transition metal complexes have been converted to fluorous soluble through ligand modification. Fluorous soluble phosphines,^{9,27} phosphites,⁹ porphyrins,^{9,28} phthalocyanines,^{9,17,29} diketones,^{18,30} tris(pyrazolyl)borates,³¹ bipyridines,³² cyclopentadienes,³³ and 1,4,7-triazacyclononane³⁴ have been prepared. The fluorous analogues of several transition metal complexes have also been synthesized including HRh(CO){P[CH₂CH₂(CF₂)₅CF₃]₃},⁹ the fluorous Wilkinson catalyst, ClRh{P[CH₂CH₂(CF₂)₅CF₃]₃},³⁵ the fluorous Vaska complex, ClIr(CO){P[CH₂CH₂(CF₂)₅CF₃]₂},³⁶ and its rhodium analogue,³⁷ fluorous porphyrins with Co, Fe, and Mn metal centers,²⁸ and fluorous cyclopentadienyl complexes

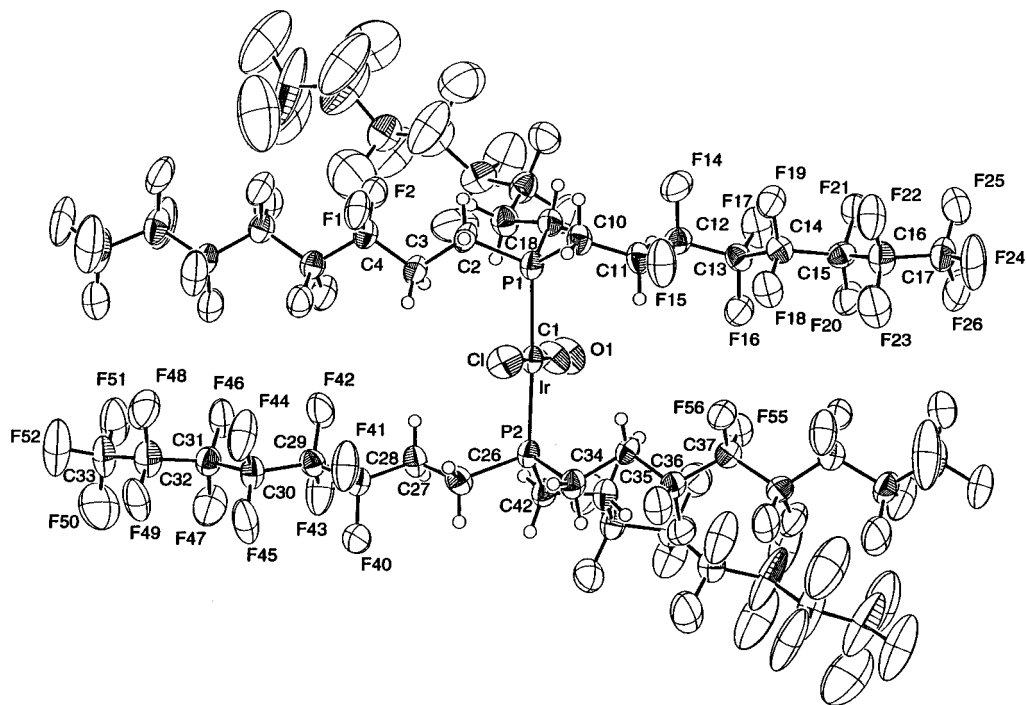


FIGURE 3. Molecular structure of $\text{IrIr}(\text{CO})\{\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}_2$.³⁶

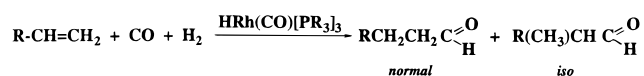
with Mn, Re, Fe, and Co metal centers.³³ The molecular structure of $\text{CIM}(\text{CO})\{\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}_2$ ($\text{M} = \text{Rh}$,³⁷ Ir ³⁶) has recently been established. Both compounds contain six pentafluorohexyl groups which provide a fluororous blanket around the hydrocarbon domain of the molecule (Figure 3). Rhodium K-edge EXAFS studies of $\text{CIRh}(\text{CO})\{\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}_2$ in the solid state and in fluororous solution indicate that it maintains its structure in the fluororous phase.³⁷

The successful application of any fluororous organometallic catalyst depends on whether the catalyst selectively partitions into the fluororous phase. In general, a neutral fluororous compatible organometallic catalyst, $\text{M}_x\{\text{L}[(\text{R})_n(\text{Rf})_m]\}_z$, contains at least one metal center to which at least one fluororous ligand, $\text{L}(\text{R})_n(\text{Rf})_m$, is bonded which includes the hydrocarbon domain, $(\text{R})_n$, and the fluororous domain, $(\text{Rf})_m$. The fluororous partition coefficients ($P_{\text{FBS}} = c_{\text{fluorous phase}}/c_{\text{other phase}}$) of such complexes depend on the type and size of the fluororous and hydrocarbon domains. The simplest fluororous domain consist of linear perfluoroalkyl chains, with the size of the domain depending on the number and length of the chains. For example, it has been shown that the fluororous partition coefficients can be significantly increased by increasing the number of perfluoroalkyl groups attached to the ligands (Table 2).³⁸ While the total fluorine content of fluororous compatible complexes should be above 60%, the number of perfluoroalkyl groups is an important factor controlling their fluororous partition. This is in agreement with the original proposal that appropriate shielding of the hydrocarbon domain, which could have attractive interaction within itself or with the constituents of the nonfluorous phase, leads to higher fluororous solubility and higher fluororous partition coefficients.⁹

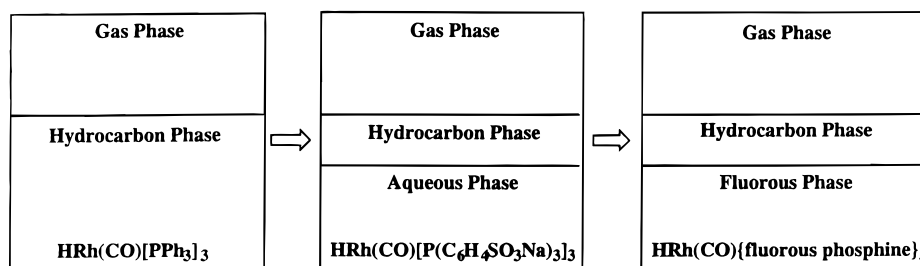
Table 2. Fluororous Partition Coefficients ($P_{\text{FBS}} = c_{\text{fluorous phase}}/c_{\text{other phase}}$) in 50/50 vol % $\text{c-C}_6\text{F}_{11}\text{CF}_3/\text{Toluene}$

Compound	MW	% of F	P_{FBS}	Ref.
$\text{CF}_3(\text{CF}_2)_9(\text{CH}_2)_2$ 	750	53.2	1.8	33
$\text{CF}_3(\text{CF}_2)_9(\text{CH}_2)_2$ 	741	53.8	0.8	38
$\text{CF}_3(\text{CF}_2)_9(\text{CH}_2)_2$ 	1278	65.3	20	33
$\text{CF}_3(\text{CF}_2)_9(\text{CH}_2)_2$ 	1813	62.9	29	38
$[\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_2]_3\text{P}$ 	2274	65.2	83	38
$[\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_2]_3\text{P}$ 	3348	66.4	190	15

The application of hydrocarbon soluble phosphine-modified rhodium catalysts for the hydroformylation of higher olefins such as decene-1 is limited by catalyst degradation during distillation of the aldehyde from the catalysts.³⁹



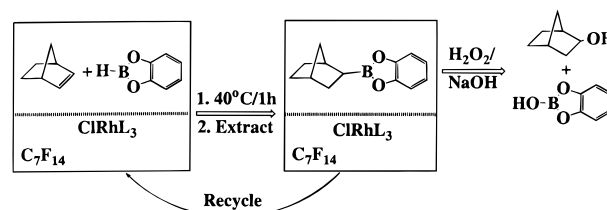
While the use of water soluble catalysts could provide easy separation for heavy aldehydes, the low solubility of the higher olefins in water could limit the application of aqueous catalysts (Scheme 3).⁴⁰ In contrast, a fluororous

Scheme 3. Evolution of the Fluorous Biphase Hydroformylation Catalyst⁹

soluble phosphine-modified rhodium catalyst appeared very attractive for the hydroformylation of high molecular weight olefins as their solubility is high in fluoros media and the catalyst could be separated from the product aldehydes. The facile separation of high molecular weight aldehydes was first demonstrated for the hydroformylation of decene-1 in the presence of the fluoros soluble $P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ -modified rhodium catalyst at 100 °C and 11 bar of CO/H_2 (1:1) in 50/50 vol % toluene/ $\text{C}_6\text{F}_{11}\text{CF}_3$ solvent mixture.⁹ $P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ was selected on the basis of a semiempirical calculation of the electronic properties of $P[(\text{CH}_2)_x(\text{CF}_2)_y\text{CF}_3]_3$ ($x = 0, 2, 4$ and $x = 0-5, y = 2$) (Table 1).¹⁵ It was shown that the solution structure of $\text{HRh}(\text{CO})\{P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}$ in $c\text{-C}_6\text{F}_{11}\text{CF}_3$ is similar to $\text{HRh}(\text{CO})(\text{PPh}_3)_3$ in toluene and $\text{HRh}(\text{CO})\{P(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_3\}$ in water. Kinetic studies established that the reaction is first order in both rhodium and decene-1, the reaction is inhibited by $P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$, and the *n/i* (normal/iso) ratio of the aldehyde increases with increasing phosphine concentration.¹⁵ The catalytic activity of the $\text{Rh}/P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ catalyst is similar to that of the nonfluorous analogue $\text{Rh}/P[(\text{CH}_2)_7\text{CH}_3]_3$ catalyst and is an order of magnitude lower than that of the Rh/PPh_3 catalyst. The *n/i* product selectivity of $\text{Rh}/P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ is closer to the selectivity of the Rh/PPh_3 catalyst than that of the $\text{Rh}/P[(\text{CH}_2)_7\text{CH}_3]_3$ catalyst. The fluoros biphase catalyst recovery was tested in a semicontinuous hydroformylation of decene-1 with the $\text{Rh}/P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ catalyst. During nine consecutive reactions/separations a total turnover of more than 35 000 was achieved with a loss of 1.18 ppm of Rh/mol of undecanals. The $\text{Rh}/P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ catalyst can also be used for the continuous hydroformylation of ethylene using the high boiling fluoros solvent FC-70, which allows the continuous removal of propanal. The long-term (60 days) stability of the $\text{Rh}/P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ catalyst is better than that of the Rh/PPh_3 catalyst.¹⁵ The $\text{Rh}/P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3$ catalyst is the first catalyst system which can be used for the hydroformylation of both low and high molecular weight olefins and provides facile catalyst separation for both low and high molecular weight aldehydes. It was demonstrated for the first time that the separation of low and high boiling products can be achieved by using the same catalyst system in high boiling fluoros solvents.

The fluoros analogue of Wilkinson's catalyst, $\text{ClRh}\{P[\text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3]_3\}$, was used as a catalyst for hydrogenation,⁴¹ hydroboration,³⁵ and hydrosilylation reactions.⁴² For example, the catalytic hydroboration of a

great variety of alkenes and alkynes was achieved using catecholborane.³⁵ Catalyst loadings of 0.01–0.25 mol % were effective (25–40 °C, 1–40 h) and gave turnover numbers as high as 8500! The alkylboranes or alkenylboranes were readily separated from the fluoros catalyst and converted to alcohols by the subsequent addition of $\text{H}_2\text{O}_2/\text{NaOH}$ to the product phase, and the fluoros catalyst solution was reused with minimal activity loss.

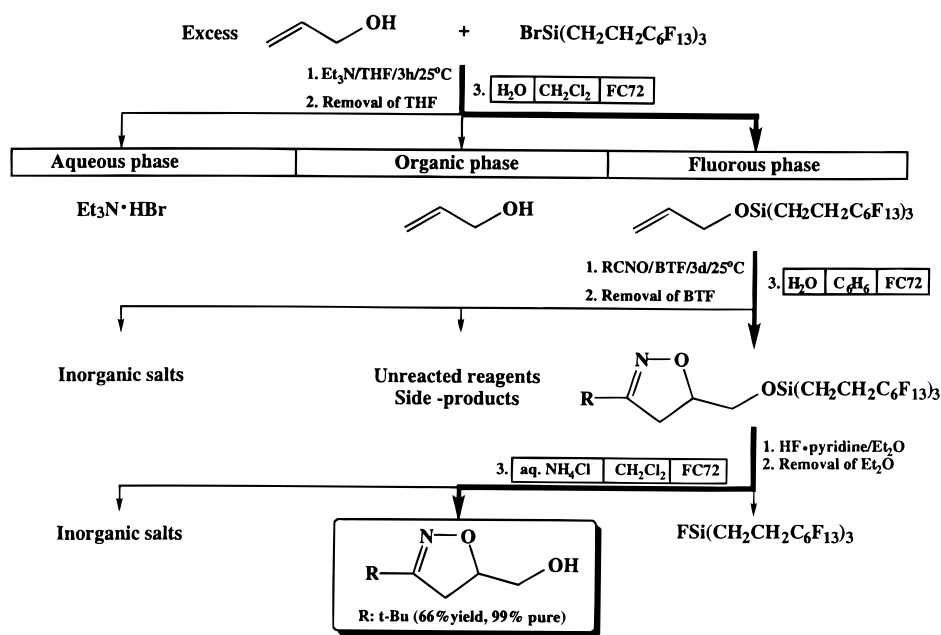


Several fluoros soluble nickel catalysts have been used for the oligomerization of ethylene.¹⁸ For example, an active catalyst was obtained by the reaction of $\text{Ni}(\text{COD})_2$ with $\text{HOCCOCH}_2\text{CO}[\text{CF}(\text{CF}_3)\text{OCF}_2(\text{CF}_3)\text{CF}_3]_3$. Compared to conventional nickel catalysts, an increased formation of *trans*-2-butene was observed for the fluoros catalysts, and the products were readily separated from the catalyst phase.

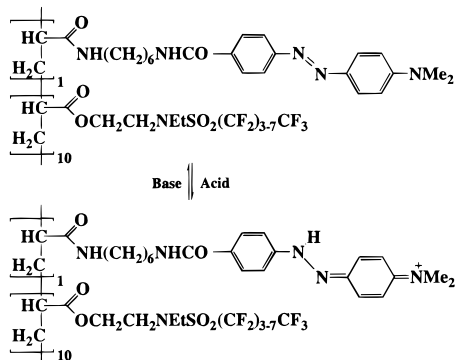
The fluoros medium is especially suitable for oxidation reactions as the solubility of dioxygen is very high in fluoros solvents¹³ and perfluoroalkanes are extremely resistant to oxidation. In addition, most oxidation reactions lead to highly polar products, which are inherently less soluble in fluoros solvents, thus resulting in easy separation. The oxidation of cyclohexene using O_2 in the presence of fluoros soluble cobalt-phthalocyanato^{9b} and cobalt-carboxylato, $\text{Co}\{\text{OCCF}(\text{CF}_3)[\text{OCF}_2(\text{CF}_3)\text{CF}_4\text{F}]\}$,¹⁸ complexes has been investigated. While the cobalt-phthalocyanine complex remained intact during oxidation and could be separated from the products,^{9b} the cobalt-carboxylato complex decomposed under the reaction conditions.¹⁸ It has recently been shown that the addition of 1 equiv of tris-*N*- $[(\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3]_3$ -1,4,7-triazacyclononane to $\text{M}\{\text{OOC}(\text{CH}_2)_2(\text{CF}_2)_7\text{CF}_3\}_2$ ($\text{M} = \text{Mn}$ and Co) provides fluoros soluble catalysts for alkane and alkene oxidation in the presence of *t*-BuOOH and O_2 .³⁴

The epoxidation of olefins in the presence of fluoros cobalt-porphyrins using O_2 and 2-methylpropanal at room temperature proceeds with excellent selectivities at high conversion levels, and the fluoros catalyst can be reused without decreasing either catalytic activity or selectivity.^{28c}

Scheme 5



Bergbreiter and Franchina have designed a fluorous soluble polymer, which can covalently bind reagents and thus render them soluble in the fluorous phase.⁴⁸ A fluorous solution of the Methyl Red derivative of the fluorous soluble polymer undergoes instantaneous color change from yellow to red upon contacting the fluorous phase with aqueous HCl or a THF solution of HCl. Addition of NaOH to the water or NEt₃ to the THF resulted in rapid deprotonation as evidenced by the color change from red to yellow.



Fluorous Synthesis

Curran has recently extended the application of the fluorous biphasic concept for multistep organic synthesis⁴⁹ which also provides a new approach to liquid-phase combinatorial synthesis.^{49b} The fluorous synthesis begins with the attachment of a fluorous phase label to the starting substrate with a fluorous reagent. The fluorous-labeled starting material can then be used in multistep reactions, and each of the fluorous-labeled intermediates can be purified by a three-phase extraction. While the fluorous-labeled intermediates remain in the fluorous phase, excess reagents and other organic side products partition into the organic and water phases. The final

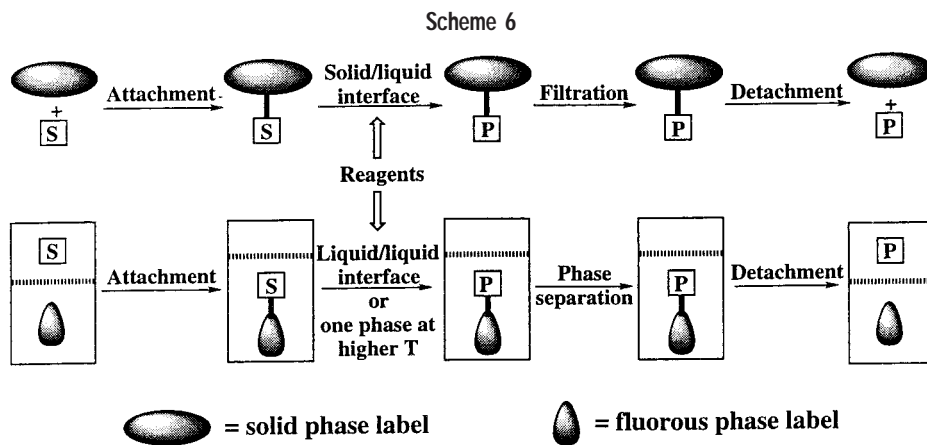
product is obtained by detachment of the fluorous label. The fluorous synthesis has been applied successfully for the preparation of tetrazoles, isoxazoles (Scheme 5), isoxazolines, amino acid amides (Ugi condensation), and dihydropyrimidines (Biginelli condensation).⁴⁹

Fluorous Combinatorial Chemistry

Fluorous synthesis can be used in combinatorial chemistry by replacing the solid-phase label with the fluorous-phase label shown in Scheme 6.^{49a} The fluorous combinatorial synthesis approach combines many of the advantages of solid-phase and organic liquid-phase synthesis: (1) better molecular control by performing all reactions in the liquid phase; (2) the fluorous label influences phase behavior; (c) facile separation of fluorous intermediates from organic solvents and/or water allows the use of excess reagents and the formation of spent reagents and side products.^{49f}

A Fluorous Vision

The most complex and traveled chemical highway important to mankind is the blood vessels of the human body. Chemicals enter the blood stream from various sources by dissolution or suspension and are distributed. While the chemical management is remarkably efficient, occasionally chemicals with adverse health effects are generated or enter the blood stream. There are many natural processes that keep a healthy composition of the components of the blood. However, breakdown of these processes could increase the concentration of unwanted chemicals. A novel approach for the removal of chemicals from the blood stream could be the use of fluorous reagents to extract poisons and other unhealthy molecules or disarm them by chemical transformations by fluorous reagents or catalysts. Fluorocarbons have already been



used successfully as oxygen transport media or “blood substitutes” as well as for diagnosis and drug delivery.⁵⁰

While cholesterol is not soluble in perfluorodecalin at room temperature, after the addition of 10 equiv of 2-perfluorooctylethanol as the fluorous reagent, cholesterol is detectable in the fluorous medium by GC and NMR.⁵¹ The formation of a fluorous shower curtain around the cholesterol through attractive interactions between the hydroxyl groups of 2-perfluorooctylethanol and cholesterol (Scheme 7) could be a plausible explanation for the solubilization of cholesterol. It is interesting

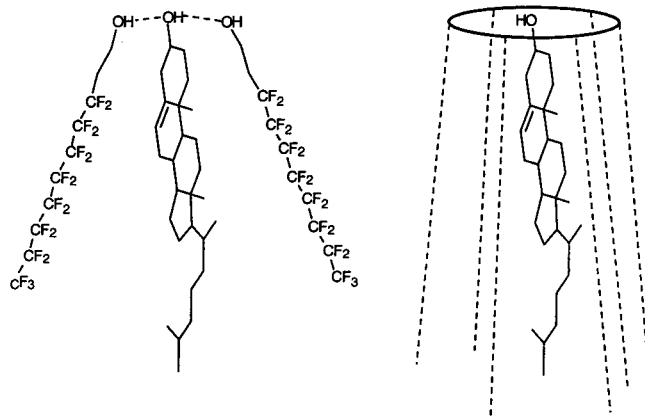
to completely separate a reagent or a catalyst from the products at mild conditions could expand the application of liquid-phase catalysts or reagents in industrial processes. In addition, it could lead to the design and synthesis of novel reagents and catalysts with extremely high selectivity. Although new reagents and catalysts could be designed to adapt to the fluorous environment, many “hydrocarbon-like” reagents or catalysts could be converted to “fluorous-like” ones by the incorporation of fluorous ponytails of appropriate number, size, and shape. The insertion of two or three ($-\text{CH}_2-$) groups before the fluorous ponytail may be necessary to decrease the strong electron-withdrawing effects of the fluorous ponytails, an important consideration if catalyst reactivity is desired to approximate that observed for the unmodified species in traditional single-phase hydrocarbon solvents.

Although it is hard to predict the most attractive applications of the fluorous biphasic concept at such an early stage, fluorous extraction of poisonous metals from water or hydrocarbons or both seems a challenging new direction for environmental chemistry. In particular, the development of fluorous reagents for the extraction of radioactive atoms seems particularly attractive, as perfluoroalkanes were invented as a solvent for the separation of uranium isotopes. The development of fluorous reagents and catalysts for selective functionalization of organic molecules could be another fruitful area. Fluorous combinatorial chemistry could certainly have a major impact on the synthesis of small organic molecules leading to large molecular libraries. Chiral fluorous reagents and catalysts for asymmetric transformations could offer a new avenue in the affordable synthesis of biologically important molecules. Finally, the use of fluorous reagents or catalysts in biological systems seems a logical extension of the research on artificial blood substitutes and drug delivery.

Since each chemical reaction could have its own *perfectly* designed reagent or catalyst (the chemzyme), the possibility to select from biphasic systems ranging from fluorous to aqueous systems provides a powerful portfolio for reagent and catalyst designers.

It is a great pleasure to acknowledge my gratitude to my friend Professor J. Rábai (Eötvös Loránd University, Budapest, Hungary)

Scheme 7



to note that intravenous infusion of *cis,trans*-perfluorodecalin emulsion into monkeys decreased the blood cholesterol level.⁵² It has recently been shown that a water soluble tricyclic cyclophane receptor^{53a} and cyclodextrin dimers^{53b} can selectively form inclusion complexes with cholesterol in water. Attachment of fluorous ponytails to such molecules could lead to a simple extraction process for the removal of cholesterol from the blood stream. Circulating the blood stream into a liquid-liquid extractor could allow the selective removal of chemicals with adverse health effects.

Conclusions

Although fluorous biphasic chemistry is still in its infancy, the results are already indicating that it is a complementary approach to other biphasic chemistries. The ability

who lifted off the fluorous biphasic concept from the drawing board by his creative and aggressive synthetic work during his two-year stay at Corporate Research. The careful technical work of R. A. Cook is gratefully acknowledged. I express my sincere gratitude to Professor J. A. Gladysz (University of Utah) for many helpful discussions during our collaboration jointly supported by the NSF (Grant CHE-9401572) and Exxon Research and Engineering Co. My best thanks are due to Dr. P. Bernatis, J. E. Bond, Dr. P. J. F. de Rege, K. A. Eriksen, P. J. Guzi, Dr. V. Herrera, Professor R. P. Hughes (Dartmouth College), Dr. J. J. Juliette, Dr. G. Kiss, Dr. F. Lopez, E. J. Mozeleski, L. M. Scuzorzo, Dr. P. A. Stevens, and W. Weissman for their fruitful participation in certain parts of our fluorous endeavor. Finally, I am indebted to Drs. R. L. Espino, A. Kaldor, M. G. Matturro, S. C. Mraw, and J. L. Robbins for their continuous support and encouragement.

References

- (1) Ausubel, J. H.; Sladovich, H. E., Eds. *Technology and Environment*; National Academy Press: Washington, DC, 1989.
- (2) Moulijn, J. A., van Leeuwen, P. W. N. M., van Santen, R. A., Eds. *Catalysis*; Elsevier: Amsterdam, 1993.
- (3) Cornils, B., Herrmann, W. A., Eds. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996.
- (4) Hildebrand, J. H.; Prausnitz, J. M.; Scott, R. L. *Regular and Related Solutions*; Van Nostrand Reinhold Co.: New York, 1970.
- (5) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1990.
- (6) (a) Kuntz, E. G. *CHEMTECH* **1987**, *17*, 570–575. (b) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524–1544. (c) Horváth, I. T., Joó, F., Eds. *Aqueous Organometallic Chemistry and Catalysis*; Kluwer: Dordrecht, 1995. (d) Starks, C. M.; Liotta, M.; Halpern. *Phase-Transfer Catalysis*; Chapman & Hall: New York, 1994.
- (7) (a) The first commercial biphasic process, the Shell Higher Olefin Process (SHOP), developed by Keim et al.^{7b} is nonaqueous and uses butanediol as the catalyst phase and a nickel catalyst modified with a diol soluble phosphine, R₂PCH₂COOH. (b) Keim, W. *Chem. Ing. Technol.* **1984**, *56*, 850–853. (c) Bianchini, C.; Frediani, P.; Sernau, V. *Organometallics* **1995**, *14*, 5458–5459.
- (8) Chauvi, Y.; Olivier-Bourbigou, H. *CHEMTECH* **1995**, *25*, 26–30.
- (9) (a) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72–75. (b) US Patent 5,463,082, 1995.
- (10) Curry-Hyde, H. E., Howe, R. F., Eds. *Natural Gas Conversion II*; Elsevier: Amsterdam, 1994.
- (11) (a) Colby, J.; Dalton, H. *Biochem. J.* **1978**, *171*, 461. (b) Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J.; Nordlund, P. *Nature* **1993**, *366*, 537.
- (12) Jansen, J. C.; Stocker, M.; Karge, H. G.; Weitkamp, J., Eds. *Advanced Zeolite Science and Applications*; Elsevier: Amsterdam, 1994.
- (13) (a) Clark, L. C.; Gollan, F. *Science* **1966**, *152*, 1755. (b) Riess, J. G.; Le Blanc, M. *Pure Appl. Chem.* **1982**, *54*, 2383–2406.
- (14) (a) Grosse, A.; Cady, G. H. *Ind. Eng. Chem.* **1947**, *39*, 367–374. (b) Munson, M. S. B. *J. Phys. Chem.* **1964**, *68*, 796.
- (15) Horváth, I. T.; Kiss, G.; Stevens, P. A.; Bond, J. E.; Cook, R. A.; Mozeleski, E. J.; Rábai, J. *J. Am. Chem. Soc.* **1998**, *120*, 3133–3143.
- (16) Filler, R. In *Fluorine Containing Molecules*, Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH: Weinheim, 1988; Chapter 2.
- (17) Minnesota Mining and Manufacturing Co. British Patent 840,725, 1960.
- (18) Vogt, M. Ph.D. Thesis, Rheinisch-Westfälischen Technischen Hochschule, Aachen, Germany, 1991. Despite the tremendous potential of the fluorous biphasic concept in chemistry, neither papers nor patents were published and the thesis cannot be accessed by any literature search methods (except personally searching in the library of RWTH). Cornils, one of the leading authorities on biphasic organometallic catalysis, has recently stated that “German theses which do not lead to publications do not become internationally known”.^{19a} It is interesting to note that after the first public disclosure of the fluorous biphasic concept at the NATO Advanced Research Workshop on Aqueous Organometallic Chemistry and Catalysis,^{6c} Cornils published an overview of the meeting including the fluorous biphasic concept with no mention of Vogt’s thesis, indicating that it was unknown even to the local expert.^{19b}
- (19) (a) Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2057–2059. (b) Cornils, B. *Nachr. Chem. Techn. Lab.* **1994**, *42*, 1136–1138.
- (20) Brice, T. J. In *Fluorine Chemistry*; Simons, J. H., Ed.; Academic Press: New York, 1950; Chapter 13.
- (21) Howe-Grant, M., Ed. *Fluorine Chemistry: A Comprehensive Treatment*; Wiley: New York, 1995.
- (22) (a) Kaufman, M.; Jamison, W. C. L.; Liotta, D. *Fuel* **1986**, *65*, 148–150. (b) Kaufman, M.; Jamison, W. C. L.; Gandhi, S. Liotta, D. *Fuel* **1987**, *66*, 1621–1625. (c) Stevens, R. D. S.; Brown, P. M. US Patent, 4,793,931, 1988. (d) Zuckerman, E. B.; Klabunde, K. J.; Olivier, B. J.; Sorensen, C. M. *Chem. Mater.* **1989**, *1*, 12–14.
- (23) Zhu, D.-W. *Synthesis* **1993**, 953–954.
- (24) (a) Nakamura, T. and Yabe, A. *Chem. Lett.* **1995**, 533–534. (b) Pereira, S. M.; Savage, G. P.; Simpson, G. W. *Synth. Commun.* **1995**, *25*, 1023–1026. (c) Klement, I. and Knochel, P. *Synlett* **1995**, 1113. (d) Zhu, D.-W. *Macromolecules* **1996**, *29*, 2813–2817. (e) Chambers, R. D.; Sandford, G.; Shah, A. *Synth. Commun.* **1996**, *26*, 1861–186x. (f) Pozzi, G.; Montanari, F.; Rispen, M. T. *Synth. Commun.* **1997**, *27*, 447–452.
- (25) Clayton, J. W., Jr. *Fluorine Chem. Rev.* **1967**, *1*, 197–252.
- (26) (a) The fact that perfluoroalkylated biomolecules can be immobilized onto fluorocarbon surfaces^{26b} suggests that the attachment of fluorous ponytails in appropriate size and number to enzymes could provide fluorous solubility. (b) Kobos, R. K.; Eveleigh, J. W.; Arentzen, R. *Trends Biotechnol.* **1989**, *7*, 101–105.
- (27) (a) Kampa, J. J.; Nail, J. W.; Lagow, R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1241. (b) Tamborski, C.; Snyder, C. E., Jr.; Christian, J. B. US Patent 4,454,349, 1984. (c) Benefice-Malouet, S.; Blancou, H.; Commeyras, A. *J. Fluorine Chem.* **1985**, *30*, 171–187.
- (28) (a) Pozzi, G.; Colombani, I.; Miglioli, M.; Montanari, F.; Quici, S. *Tetrahedron* **1996**, *52*, 11879–11888. (b) Pozzi, G.; Montanari, F.; Quici, S. *Chem. Commun.* **1997**, 69–70. (d) DiMagno, S. G.; Williams, R. A.; Therien, M. J. *J. Org. Chem.* **1994**, *59*, 6943–6948.
- (29) Keller, T. M.; Griffith, J. R. *J. Fluorine Chem.* **1978**, *12*, 73–77.
- (30) (a) Klement, I.; Lutjens, H.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1454–1456. (b) Mikami, K.; Terada, M.; Nakai, T. *Chem. Commun.* **1993**, 343–345.

- (31) Dias, H. V. R.; Kim, H. J. *Organometallics* **1996**, *15*, 5374–5379.
- (32) Garelli, N.; Vierling, P. J. *Org. Chem.* **1992**, *57*, 3046–3051.
- (33) Hughes, R. P.; Trujillo, H. A. *Organometallics* **1996**, *15*, 286–294.
- (34) Vincent, J.-M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2346–2349.
- (35) Juliette, J. J. J.; Horváth, I. T.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1610–1612.
- (36) Guillevic, M. A.; Arif, A. M.; Horváth, I. T.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1612–1615.
- (37) Fawcett, J.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Russel, D. R.; Stuart, A. M.; Cole-Hamilton, D. J.; Pane, M. J. *Chem. Commun.* **1997**, 1127–1128.
- (38) Herrera, V.; de Rege, P. J. F.; Horváth, I. T.; Husebo, T. L.; Hughes, R. P. *Inorg. Chem. Commun.* **1998**, *1*, 197–199.
- (39) Jamerson, J. D.; Pruett, R. L.; Billig, E.; Fiato, R. A. *J. Organomet. Chem.* **1980**, *193*, C43.
- (40) Horváth, I. T. *Catal. Lett.* **1990**, *6*, 43–.
- (41) Rutherford, D.; Juliette, J. J. J.; Rocaboy, C.; Horváth, I. T.; Gladysz, J. A. *Catal. Today*, in press.
- (42) Juliette, J. J. J.; Gladysz, J. A.; Horváth, I. T. *10th International Symposium on Homogeneous Catalysis*, Princeton, NJ, 1996; Abstract PP-A59.
- (43) Bergbreiter, D. E. *Chemtracts Org. Chem.* **1995**, *8*, 108–112.
- (44) (a) DesMarteau, D. D.; Donadelli, A.; Montanari, V.; Petrov, V. A.; Resnati, G. *J. Am. Chem. Soc.* **1993**, *115*, 4897–4898. In this paper it is stated that good results could be obtained despite the fact that the reactions became two-phase systems. (b) Petrov, V. A.; Montanari, V.; Resnati, G.; DesMarteau, D. D. *J. Fluorine Chem.* **1991**, *33*, 399–. (c) DesMarteau, D. D.; Petrov, V. A.; Montanari, V.; Pregnolato, M.; Resnati, G. *Tetrahedron Lett.* **1992**, *33*, 7245–. (d) Arnone, A.; Bernardi, R.; Cavicchioli, M.; Resnati, G. *J. Org. Chem.* **1995**, *60*, 2314–2315. (e) DesMarteau, D. D.; Petrov, V. A.; Montanari, V.; Pregnolato, M.; Resnati, G. *J. Org. Chem.* **1994**, *59*, 2762–. (f) Cavicchioli, M.; Montanari, V.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 6329–6330.
- (45) DiMagno, S. G.; Dussault, P. H.; Schultz, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5312–5313.
- (46) (a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531–2532.
- (47) (a) Curran, D. P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480–6481. (b) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583–5587.
- (48) Bergbreiter, D. E.; Franchina, J. G. *Chem. Commun.* **1997**, 1531–1532.
- (49) (a) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S. Y.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826. (b) Curran, D. P. *Chemtracts Org. Chem.* **1996**, *9*, 75–87. (c) (d) Horner, J. H.; Martinez, F. N.; Newcomb, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 2783–2786. (e) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917–2924. (f) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681–6696.
- (50) (a) Weers, J. G. *J. Fluorine Chem.* **1993**, *64*, 73–93. (b) Riess, J. G. *Colloids Surf.* **1994**, *84*, 33–48.
- (51) (a) Horváth, I. T. Unpublished results.
- (52) Clark, L. C.; Wesseler, E. P.; Kaplan, S.; Emory, C.; Moore, R.; Denson, D. *ACS Symp. Ser.* **1976**, *28*, 135–170.
- (53) (a) Peterson, B. E.; Diederich, B. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1625–1628. (b) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1996**, *118*, 8495–8496.

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