

FROM THE ACS MEETING

DESIGNING SOLVENT SOLUTIONS

Novel reaction systems combine best features of homogeneous and heterogeneous catalysis

STEPHEN K. RITTER, C&EN WASHINGTON

ONE DAY, CONTINUOUS HOMOGENEOUS catalytic reactions will be used to produce commodity chemicals with little or no downstream environmental impact and requiring only the bare minimum amount of energy and raw materials. Important to achieving this "perfect solution" will be developing new catalysts. But that's only half of the story. A stable full of great catalysts is no good unless you can let them out to run.

Enter then the second half of the story: developing solvent systems and separation techniques that take advantage of the best properties of both heterogeneous and homogeneous catalysis to aid in maximizing catalyst stability while allowing continuous catalyst operation and easy product separation.

The quest for such novel solutions was the subject of a Division of Inorganic Chemistry symposium held last month at the American Chemical Society national meeting in New York City. The symposium, "Organometallic Catalysis in Alternative Solvent Systems," brought together a group of international all-stars representing universities, industry, and national research centers to discuss the emerging field of facilitated chemical synthesis.

Processes discussed at the symposium fall into two basic classes: catalysts immobilized on soluble or insoluble supports, and biphasic or nonorganic solvent systems. These processes include a host of possible liquid-liquid and liquid-solid systems, including aqueous-organic and fluorous-organic systems, supercritical or liquid water and carbon dioxide, ionic liquids, and any of these possibilities in various combinations. One important property unifying these processes is their potential to reduce the en-

vironmental impact of traditional industrial processes, in part by reducing the loss of catalyst by leaching, reducing the use of conventional organic solvents, and reducing energy consumption.

"The field of 'alternative media' has matured enough to be part of contemporary, everyday chemistry," noted István T. Horváth, a chemistry professor at Eötvös University, in Budapest, Hungary, and a symposium co-organizer. "We can now probably lose the term 'alternative,' or replace it with the term 'designer,' since each of these solvents requires up-front design efforts."

Fluorous biphasic solvent systems, developed by Horváth and his colleagues while he was at Exxon (now ExxonMobil) Research & Engineering in the early 1990s, have emerged during the past decade as one of the more attractive methods. In its original form, the fluorous technique involves dissolving a catalyst with long per-

fluorinated alkyl chains, or "ponytails," in an aliphatic perfluorocarbon solvent. Generally, ethylene or other hydrocarbon spacer groups are used to attach the perfluoroalkyls to the catalyst to insulate against the strong electron-withdrawing properties of fluorine. Reactants are added to an organic solvent that is immiscible with the perfluorocarbon phase at room temperature, forming a second phase.

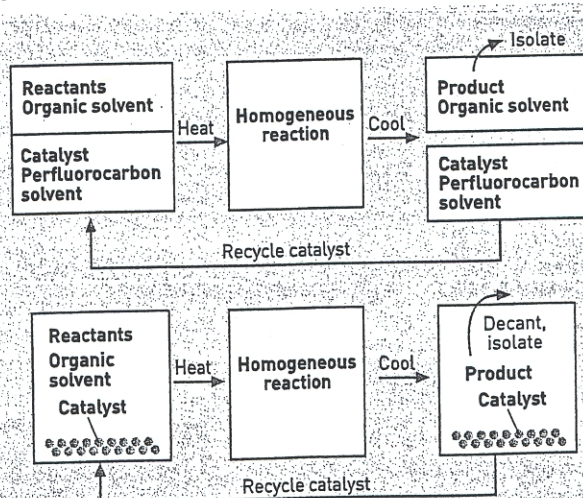
On heating, the two phases become miscible and the reaction occurs; on cooling, the fluorinated and organic layers separate. The organic phase can be removed and the product isolated, while the fluorinated catalyst-solvent phase can be reused.

HOWEVER, the large-scale use of perfluorocarbon solvents has the drawbacks of higher cost and growing concern over their environmental fate (C&EN, June 16, page 24). The heavy compounds typically used in fluorous reactions are stable, nonflammable, not known to be toxic, and not thought to contribute to ozone depletion. Yet the issue of persistence and potential bioaccumulation remains.

"Since fluorous solvents and fluorous ponytail fragments are persistent, we have to be sure that they have no negative health and environmental effects," Horváth told C&EN. "This is, however, true for all new compounds potentially entering our environment. Thus, the design process of fluorous systems must include sustainability measures, including toxicity and bioaccumulation."

The speakers who discussed fluorous systems at the symposium agreed that getting fluorinated solvents out of the picture will be important for using fluorous chemistry on an industrial scale. One of the first groups to demonstrate "fluorous biphasic catalysis without fluorous solvents" is that of chemistry professor John A. Gladysz of the University of Erlangen-Nuremberg, in Germany. Gladysz, an early collaborator with Horváth, focused on designing fluorinated catalysts that themselves have a temperature-dependent miscibility—that is, solubility—in ordinary organic solvents.

Gladysz reviewed the work of graduate student Marc Wende on fluorinated phosphine catalysts such as $P[(CH_2)_2(CF_2)_7CF_3]_3$, and he added some nuances about con-



PHASING IN AND OUT Fluorous techniques take advantage of the temperature-dependent miscibility of organic and perfluorocarbon solvents (top) to give homogeneous reactions with heterogeneous product and catalyst separation. Even simpler systems can operate without the perfluorocarbon solvent (bottom) by using a fluorinated catalyst that has a temperature-dependent solubility in an organic solvent.

trolling the solubility of catalysts by varying the length of the fluorinated ponytails and hydrocarbon spacer groups. The catalysts have been tested by carrying out a series of additions of alcohols to methyl propionate in octane [*J. Am. Chem. Soc.*, 125, 5861 (2003)].

The phosphine catalysts are insoluble in octane at room temperature, but upon heating to 65 °C, they become soluble and the reaction proceeds, Gladysz explained. After cooling, the catalysts precipitate out of the reaction mixture and are recovered by decanting the liquid. The catalysts can be recycled multiple times with yields consistently above 80%, he noted.

In a further refinement, Gladysz and coworkers have shown that the same reactions can be made even greener by not using any solvent. Raising the temperature of a mixture of the neat reactants and solid catalyst above the catalyst's melting point of 47 °C yields the addition product. The catalyst simply precipitates from the liquid product at room temperature and is recyclable. Product yields are consistently above 95%.

"The message is that we can eliminate

the fluoruous solvent but retain the biphasic recoverability of the phosphine catalysts," Gladysz told C&EN. "Homogeneous catalysts that can be recovered by simple precipitation are going to have a big future."

Exploring the potential of fluoruous techniques beyond biphasic systems was the focus of a talk by University of Pittsburgh chemistry professor Dennis P. Curran, one of the pioneers in fluoruous chemistry. In recent years, Curran's group has investigated using fluorinated catalysts in traditional fluoruous biphasic solvent systems as well as in supercritical CO₂ and triphasic solvent systems.

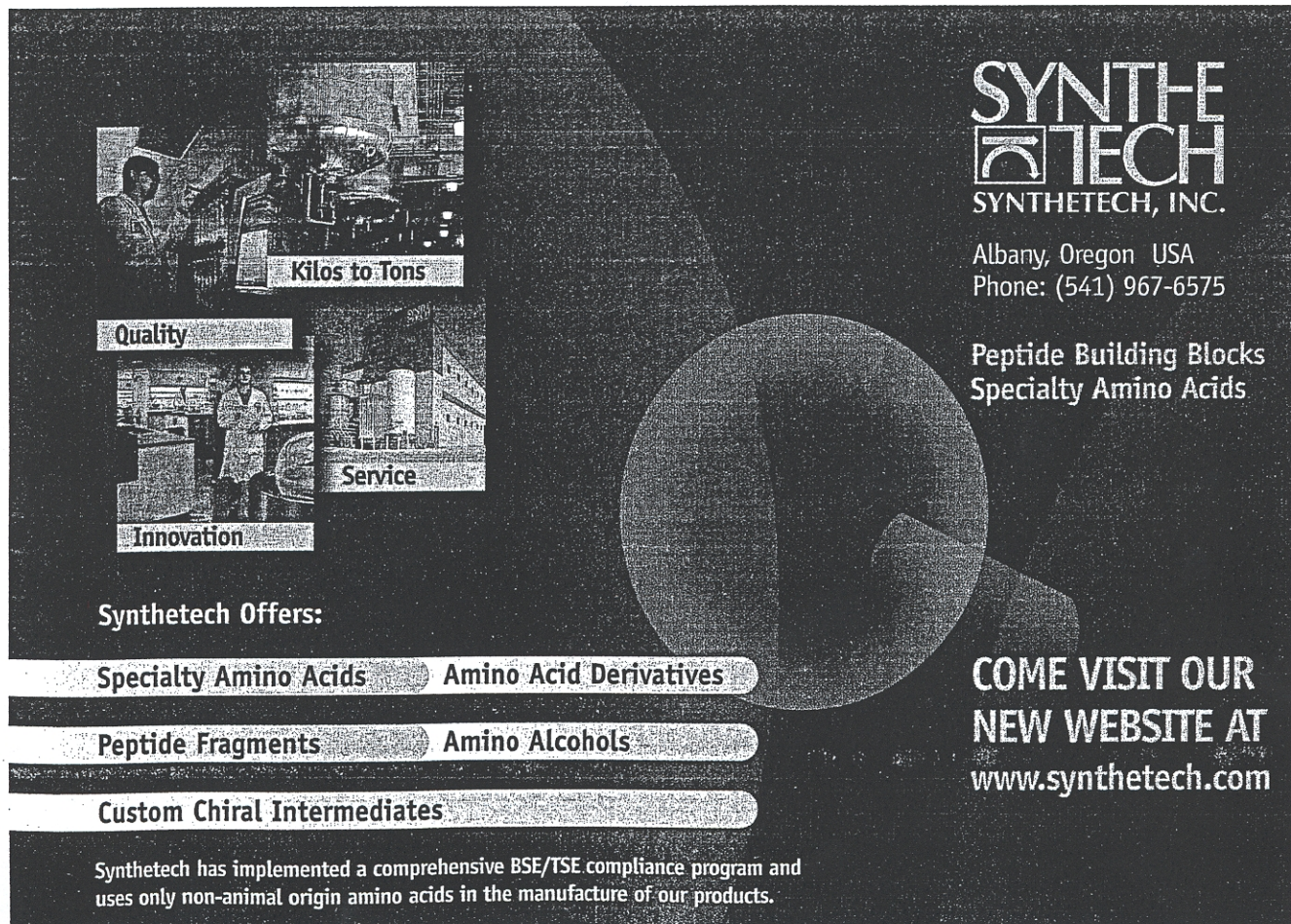
Much of Curran's chemistry relies on avoiding fluoruous solvents by partitioning tagged fluorinated reagents and de-tagged reagents or other nonfluorinated reagents. This strategy has proven useful as a combinatorial chemistry technique that has been commercially developed by Fluorous Technologies, a company Curran started three years ago.

One line of recent research Curran highlighted at the symposium is palladium-catalyzed Heck coupling reactions. In one example, graduate students Karen Fischer

and Gustavo Moura synthesized a palladium catalyst with a cyclic fluorinated ligand that was used to couple iodobenzene with isoprene in tributylamine and dimethylacetamide. The reaction can be carried out conventionally at 140 °C to give the addition product in 95% yield, he noted. With microwave heating, the reaction takes place in 15 minutes, he said.

The product and catalyst were separated by Curran's patented fluoruous solid-phase extraction technique. This process relies on Fluorous Technologies' FluoroFlash chromatography cartridges, which are packed with silica gel bonded with perfluoroalkyl chains, Curran explained. In the case of the Heck reaction, the fluorinated catalyst is retained on the column and the nonfluorinated product is separated when flushed with a fluorophobic 90:10 methanol-water wash. The catalyst is then recovered by washing the column with pure methanol.

"This is an early example of catalyst recycling by solid-phase extraction," Curran said. "Before, the catalyst was only removed, but not recovered intact or was not good enough to be purified and



SYNTECH
TECH
SYNTHETECH, INC.

Albany, Oregon USA
Phone: (541) 967-6575

Peptide Building Blocks
Specialty Amino Acids

**COME VISIT OUR
NEW WEBSITE AT
www.synthetech.com**

Synthetech Offers:

- Specialty Amino Acids
- Amino Acid Derivatives
- Peptide Fragments
- Amino Alcohols
- Custom Chiral Intermediates

Synthetech has implemented a comprehensive BSE/TSE compliance program and uses only non-animal origin amino acids in the manufacture of our products.

reused." The speed of the coupling in the microwave reactions with fluorous solid-phase extraction is "a combination that is prized in discovery settings, such as parallel synthesis," he added.

There are still improvements to be made to biphasic systems. One problem is that, even if operating in a batch-continuous process, some of the catalyst must be removed from the reaction vessel before catalyst separation and recycling can take place. Thus, taking the technique to a fully continuous process would have additional advantages of maintaining a single set of reaction conditions in which the catalyst can be engaged full time.

Chemistry professor David J. Cole-Hamilton of the University of St. Andrews, in Scotland, described one such continuous homogeneous process that uses a biphasic supercritical CO₂-ionic liquid solvent system. Supercritical CO₂ has been known for several years to be miscible with ionic liquids, a property being explored by several research groups. Under CO₂, ionic liquids become more liquid-like, more like a regular organic solvent, he pointed out.

The reaction Cole-Hamilton and his colleagues chose to work on is the rhodium-catalyzed hydroformylation of C₈ and longer alkenes, an important reaction for the production of aldehydes and alcohols that are used to make soaps, detergents, and plasticizers. Rhodium catalysts are typically used in industrial hydroformylations of C₂ to C₅ olefins, he noted. But for longer chain olefins, the catalysts begin to decompose at temperatures below the boiling point of the products, which makes catalyst-product separation difficult.

For propene, an aqueous-organic biphasic system is used commercially with a water-soluble rhodium catalyst, he said, but this process can't be used for the longer olefins because of their limited solubility in water. This means less efficient cobalt catalysts, which require higher temperature and pressures, currently are being used in commercial production of aldehydes and alcohols.

About two years ago, Cole-Hamilton's group developed its continuous process and designed a reactor. The catalyst is first prepared in situ in an ionic liquid in a stirred tank reactor. Then the alkene, CO, and H₂ dissolved in supercritical CO₂ are transported into the reactor. The CO₂ dissolves

in the ionic liquid, forming a homogeneous reaction mixture in which the reactants can come together with the catalyst.

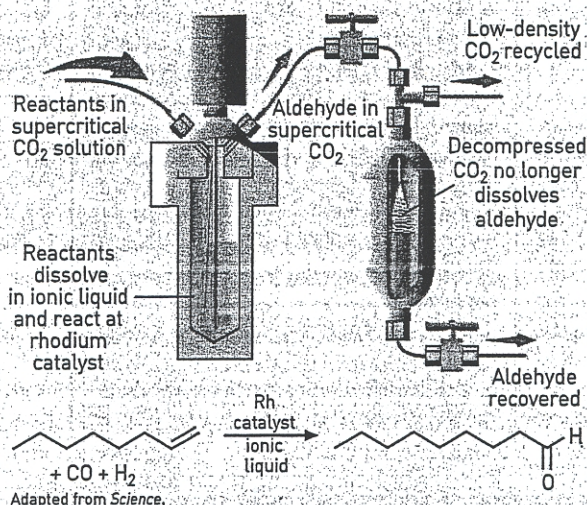
Meanwhile, the newly formed product is captured by the passing supercritical CO₂ and flows out of the reactor. The supercritical CO₂ is then decompressed in a separator adjacent to the reactor to release

The appealing feature of the supercritical fluid-ionic liquid system is that it is essentially an emissionless process with low potential environmental impact, Cole-Hamilton concluded. The process has 100% atom economy—that is, all the atoms of the reactants are present in the product—and the only volatile organic compounds are the alkene and the aldehyde. "Importantly, the catalyst and ionic liquid remain in the reactor at all times," he said, "so that all of the catalyst is in its active state and under optimum conditions all the time."

Ionic liquids have come a long way as alternative solvents and are more popular than ever. Chemist R. Tom Baker of Los Alamos National Laboratory, one of the symposium speakers, pointed out that the New York meeting was the second fall ACS national meeting in a row to have at least 10 sessions on ionic liquids in the Division of Industrial & Engineering Chemistry.

Baker and Christian P. Mehnert, a symposium co-organizer and research chemist at Exxon-Mobil, in Annandale, N.J., each

NONSTOP Supercritical CO₂'s solubility in ionic liquids allows continuous homogeneous catalytic hydroformylation



the product. The catalyst and ionic liquid remain in the reactor, and the recovered CO₂, CO, and H₂ can be reused.

Early on, the research team was unable to achieve both high conversion of the olefin and high aldehyde selectivity at the same time, Cole-Hamilton reported. That led to a series of experiments to refine the ionic liquid, catalyst, and reaction conditions to come up with a system that now provides results approaching those of commercial hydroformylations.

The process has been tested by running hydroformylations of octene, dodecene, and styrene using an ionic rhodium-based catalyst dissolved in the ionic liquid 1-octyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide. The reaction rates achieved with octene are now more than 500 catalyst turnovers per hour and product recovery is better than 95%, according to Cole-Hamilton.

Moreover, the system can operate continuously for more than 80 hours with catalyst loss limited to 12 ppb in the product, he said. And when operating at a lower rate of 270 turnovers per hour with a different modifying ligand, the ratio of linear to branched products reaches 40, significantly more selective than the ratio of about 6 to 10 observed for commercial reactions.

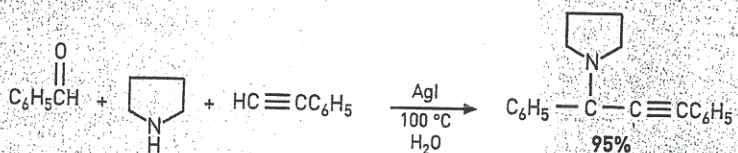
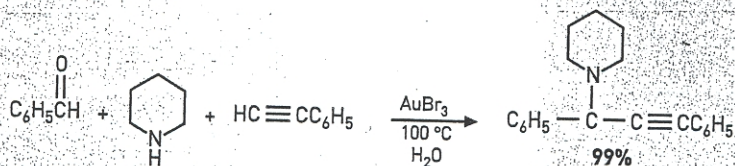
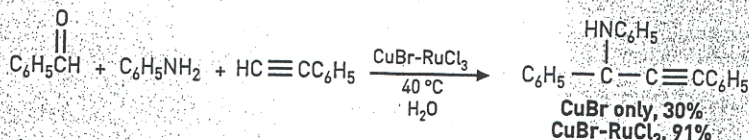
provided an overview of catalysis in functionalized ionic liquids. For example, Mehnert focused on supported ionic liquids used for hydrogenation and hydroformylation reactions [*J. Am. Chem. Soc.*, 124, 12932 (2002)].

IN THESE SYSTEMS, a monolayer of ionic liquid is covalently bound to the surface of a solid support, such as silica. Additional unbound ionic liquid is added, along with the catalyst that dissolves in the ionic liquid. The result is a free-flowing solid that is amenable to heterogeneous fixed-bed technology, which is favored by industry, Mehnert said. Yet when the reactants are added, they dissolve in the ionic liquid layer as well, allowing homogeneous catalysis to occur. The low volume of ionic liquid that is needed, compared with a bulk solution, is additionally useful for a potential industrial process.

Water is a reaction medium that a growing number of chemists and chemical engineers are turning to in order to steer away from organic solvents. Several key transition-metal-catalyzed reactions in water have been industrialized over the years, such as the Wacker oxidation for converting ethene to ethanal and the hydroformylation of propene to butanals.

GREENING UP

Three-component coupling reactions in water use coinage metals to mediate C-H activation, reducing steps and saving time and resources



In New York, chemistry professor Chao-Jun Li of Tulane University, who is in the process of relocating to McGill University, in Montreal, described how his research group has developed an array of

Grignard-type reactions carried out in open air using water as the solvent or no solvent at all. These syntheses are in contrast to typical reactions involving transition-metal catalysts that require an inert at-

mosphere and anhydrous organic solvent to protect the catalyst. Li's group also is collaborating with other groups to extend its catalytic syntheses for use in ionic liquids and in solventless reactions carried out using microwave heating.

One of several reactions Li described was work by graduate student Chunmei Wei to prepare propargyl amines by addition of terminal alkynes to various imines. The amines have important applications in pharmaceuticals and agricultural chemicals, Li said. The imine reactant is first generated in situ from an aldehyde and aniline, followed by addition of phenylacetylene and a CuBr-RuCl₃ cocatalyst. The reactions can be carried out in water or under solventless conditions with yields generally above 85%. The organic products can be isolated by simple phase separation from the water rather than by distillation, and most of the catalyst solutions can be directly reused, he added.

To make the syntheses even more efficient, Li and Wei figured out that they could avoid making the imine first and instead directly couple the aldehyde, alkyne, and amine. The reaction doesn't work well

Challenge Us With Your Complex Synthesis

- Custom Synthesis
- Process Research
- cGMP Synthesis
- Gram to Kilogram Scale

J-STAR
RESEARCH, Inc.

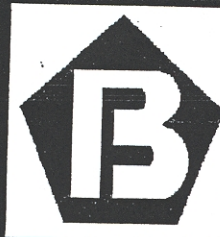
South Plainfield, New Jersey

908-791-9100

info@jstar-research.com

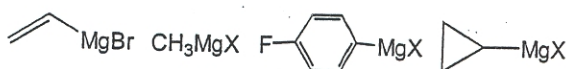
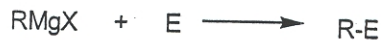
www.jstar-research.com

BOULDER SCIENTIFIC COMPANY



30 Years Experience in the Manufacture and Use of Air Sensitive Organometallics

- The Grignard Reaction -



Increase Your Capacity by Outsourcing Organometallic Compounds & Reactions

Bulk, Kilo, and R&D quantities available

BSC can Supply the Reagent and/or Perform the Reaction

Boulder Scientific Company

Box 548, Mead, Colorado 80542 www.bouldersci.com

Voice 970-535-4494 ♦ Fax 970-535-4584

using CuBr as the catalyst, Li reported, but they discovered that the heavier coinage metals—silver and gold—provide good results.

The researchers found that the three-component coupling of benzaldehyde, phenylacetylene, and piperidine catalyzed by as little as 0.25 mol % of Au(I) or Au(III) halides in water gives quantitative yields of propargyl amines [*J. Am. Chem. Soc.*, **125**, 9584 (2003)]. The synthesis is general, Li said, and can be applied to both aromatic and aliphatic aldehydes and amines. Li and Wei further observed that the reactions run in tetrahydrofuran, toluene, and dimethylformamide result in lower conversions with formation of by-products. A co-catalyst or large ligand is not required, as is the case with the copper-catalyzed reactions, Li added.

Li and Wei next turned to silver as a catalyst. Traditional silver catalysts are commonly considered to have low efficiency, so they generally are passed over for more effective transition metals, Li explained. But since silver is less expensive than gold, it was intriguing to see if silver halides would work just as well, he said. Using the three-

component coupling reaction in water, Li, Wei, and graduate student Zigang Li explored a series of silver salts and found that AgI works best to catalyze the reaction, providing isolated yields of propargyl amines generally above 85%.

"THESE RESULTS open up new opportunities for using coinage metals for catalyzing organic reactions, in particular silver and gold, which have largely been neglected so far," Li said.

Horváth's group also has been pursuing water-based reactions, investigating the potential large-scale conversion of carbohydrates derived from plants into a variety of industrial chemical products. These reactions involve a combination of catalytic dehydration with in situ catalytic hydrogenation of C=C and C=O bonds and the hydrogenolysis of C-O bonds, he explained.

In one example, Horváth described work by his group using water-soluble ruthenium complexes under 80 bar of H₂ at 140 °C to convert sucrose in acidic solution to γ -valerolactone, along with minor products levulinic acid and formic acid.

The organic products can be isolated by extraction with ethyl acetate.

"The use of an aqueous biphasic approach is natural," Horváth pointed out, "as the carbohydrates are water soluble, the side product is water, and the final product—organic alkanes—can be easily separated from the aqueous catalyst phase."

The team also has quantitatively converted levulinic acid to γ -valerolactone under similar conditions. Another result is conversion of neat γ -valerolactone to 1,4-pentanediol. The group is preparing new catalysts to convert sucrose to 1,4-pentanediol in one step and hopefully will move on to pentanols or pentanes, Horváth said.

Horváth commented that the symposium had clearly demonstrated, once again, that chemists can design solvent systems that provide great solutions. "While the application of organometallic catalysts in industrial processes offers high atom economy at lower energy requirements, the development of simple and efficient separation of the generally thermally sensitive organometallic catalysts from their products under mild conditions will be crucial for commercialization." ■



DO YOU RECOGNIZE THIS

When we're not solving tough technical problems in the national interest, Battelle tackles challenges faced by the average person like creating a cut-resistant coating for a major golf ball manufacturer.

As a contract research organization, Battelle offers unmatched value:

- Broad solutions and technology breadth
- Expertise to streamline processes
- Innovative, cost-effective approach
- Protection of intellectual property

Battelle has been a pioneer in technology research and development in nearly every field of science since the late 1930s.

Battelle

The Business of Innovation

Find out what Battelle can do for you.
Come meet our people and tour our labs.
Call Jerry Koll at 1-410-306-8500 or
email results@battelle.org.