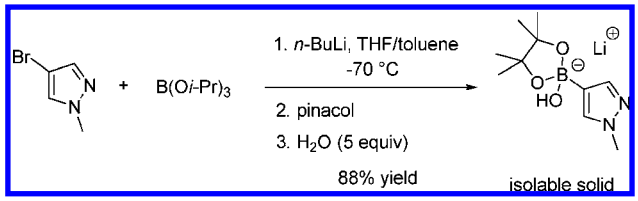
# *Highlights from the Literature*

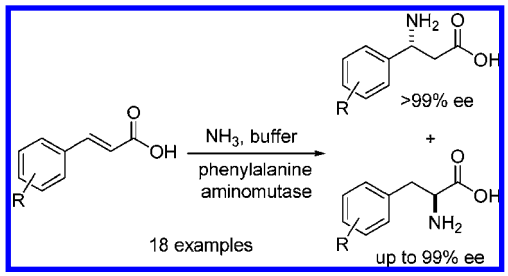
## Some Items of Interest to Process R&D Chemists and Engineers

### Practical Pyrazole–Boron Reagent for Suzuki Cross-Coupling



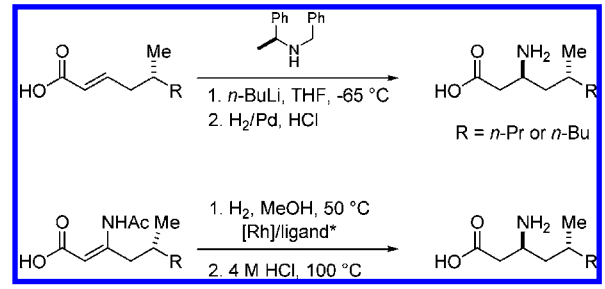

The pyrazole ring system features frequently in modern pharmaceuticals, and consequently, efficient methods for introduction of this heterocycle are useful to process chemists. The Suzuki cross-coupling can be used to elaborate the pyrazole ring however access to suitable boron-bearing pyrazole reagents is often nontrivial. Now an improved synthesis of 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester via isolation of the corresponding lithium hydroxy ate complex is described by Mullens at Merck (*Tetrahedron Lett.* **2009**, *50*, 6783−6786). The hydroxy ate complex is available in one pot from 4-bromo-1-methyl-1H-pyrazole and triisopropyl borate, and is isolated by filtration in high yield. Furthermore, the resulting lithium hydroxy ate complex has long-term bench stability and can be employed directly in Suzuki couplings without the need for added base. A total of eight examples of cross-couplings with aryl chlorides are provided.

### Biocatalytic Route to Enantiopure α- and β-Amino Acids




An approach for the synthesis of aromatic α- and β-amino acids that uses phenylalanine aminomutase (PAM) to catalyze a highly enantioselective addition of ammonia to substituted cinnamic acids is described by Feringa and Janssen at the University of Groningen and DSM Pharmaceuticals, respectively (*J. Org. Chem.* **2009**, *74*, 9152−9157). The reaction has a broad scope and yields substituted α- and β-phenylalanines with excellent enantiomeric excess. For all β-amino acids that were produced, the ee values exceeded 99%, and for most of the α-isomers the enantioselectivity of the enzymatic reaction is also excellent (ee >99%). The regioselectivity of the conversion is determined by substituents present at the aromatic ring. In most of the reactions both α- and β-isomers are formed. For the synthesis of β-amino acids, the best results were obtained with cinnamic acid derivatives with electron-donating (alkyl and alkoxy) groups at the para position, as in these cases the desired isomers are formed in excess (>90%) with excellent enantioselectivity (>99%). A box model for the enzyme active site is proposed, derived from the influence of the hydrophobicity of substituents on the enzyme affinity toward various substrates. The authors also present data correlating the Hammett constants for different aromatic substituents with the initial rate of formation of the β-isomers. An attempt to run this chemistry on 30 mg scale using cinnamic acid itself afforded 60% conversion after 5 days reaction time. Presumably this result could be improved via further optimization and directed evolution of the enzyme.

### Practical Syntheses of α2δ Ligands




α2δ-Ligands are compounds that selectively displace 3H-gabapentin from brain membranes, indicating a high affinity interaction with the α2δ subunit of voltage-gated calcium channels. This type of compound can potentially be used to treat a number of conditions including generalized anxiety disorder (GAD) and insomnia. Two consecutive papers from Magano and co-workers at Pfizer describe alternative approaches for the multikilogram-scale preparation of two compounds required for clinical evaluation. In the first approach the amine-bearing stereocenter is introduced via a diastereoselective aza-Michael addition reaction using a chiral amine nucleophile (*Tetrahedron Lett.* **2009**, *50*, 6325−6328). In the second approach, the amine-bearing stereocenter is controlled via catalytic asymmetric hydrogenation of a protected enamide precursor (*Tetrahedron Lett.* **2009**, *50*, 6329−6331).

### Pd-Catalyzed Synthesis of Primary Anilines

Hornberger and co-workers at GSK report on two methods for the Pd-catalyzed synthesis of primary anilines. In their initial communication the GSK chemists describe the optimization and scope of the reaction between benzophenone imine and various aryl bromide substrates (*Tetrahedron Lett.* **2009**, *50*, 1582−1585). The developed procedure allows the use of mild conditions (30 °C) and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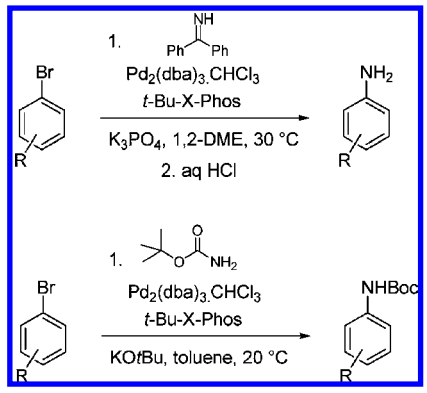
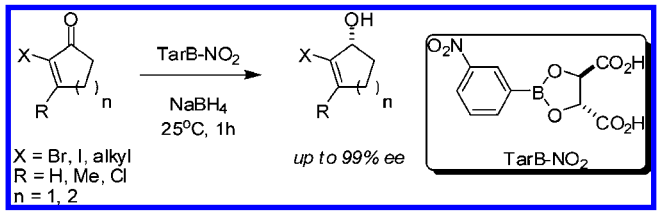


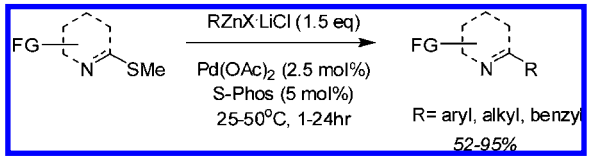

a weak inorganic base (potassium phosphate). A total of 12 aryl bromide examples are provided with yields ranging from 52−83%. Deprotection under standard hydrolytic conditions affords the primary anilines. Following on from this work, the same researchers examined the scope of Pd-catalyzed synthesis of *N*-Boc-protected anilines from aryl bromides and commercially available *tert*-butyl carbamate (*J. Org. Chem.* **2009**, *74*, 4634−4637). This process can be conducted at room temperature (17−22 °C) using a combination of $Pd_2dba_3 \cdot CHCl_3$ and a monodentate ligand, *tert*-butyl X-Phos. Use of sodium *tert*-butoxide is crucial to the success of the reaction, which proceeds in 43−83% yield across 14 examples.

### Highly Enantioselective and Regioselective Carbonyl Reduction of Cyclic α,β-Unsaturated Ketones Using TarB-$NO_2$ and Sodium Borohydride



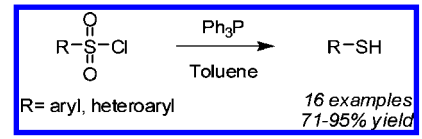

A new asymmetric 1,2-reduction of cyclic α,β-unsaturated ketones has been developed by Singaram and co-workers (*Org. Lett.* **2009**, *11*, 4358−4361) at the University of California, Santa Cruz, utilizing the chiral boronic ester TarB-$NO_2$ and sodium borohydride at room temperature in tetrahydrofuran. Moderate yields and good enantioselectivities are observed when substrates are cyclic α-substituted α,β-unsaturated ketones. Access to the opposite alcohol enantiomer can be realized by simply using the other isomer of tartaric acid in the preparation of TarB-$NO_2$. The boronic acid used to make the catalyst can be easily recycled by a simple acidic extraction. Unfortunately, the enantioselectivity erodes precipitously in the absence of a bulky group in the α-position.

### Pd-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles



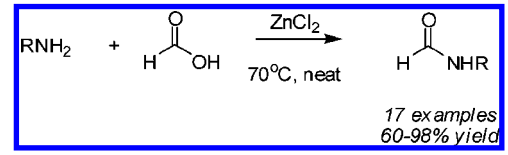

An efficient Pd catalyzed cross-coupling reaction of aryl, benzylic, and alkylzinc reagents with thiomethyl-substituted *N*-heterocycles has been described by Knochel and co-workers (*Org. Lett.* **2009**, *11*, 4228−4231). The scope of the reaction is quite impressive: pyridines, pyrimidines, pyrazines, pyridazines, tirazines, benzothiazoles, benzoxazoles, pyrazoles, benzidazoles and quinazolines are shown to react mostly at room temperature with various organozinc reagents (alkyl-, aryl-, heteroaryl, and benzylic) using a $Pd(OAc)_2$/S-Phos catalytic system. A remarkable advantage of the described system is the tolerability of functional groups (esters, cyanides, and heteroaryl groups) that can be employed in the preparation of zinc reagents.

### A Simple Method for the Preparation of Arylthiols



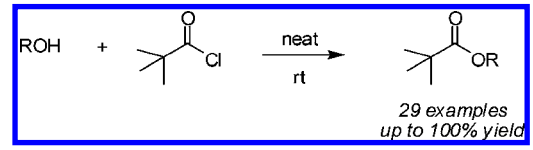

An alternate method for the reduction of arylsulfonyl chlorides to arylthiols using triphenylphosphine has been described by Akamanchi and co-workers at the Institute of Chemical Technology in Mumbai (*Synthesis* **2009**, *19*, 3211−3213). The reaction completes in less than 15 min and can be carried out in a variety of solvents including toluene, dichloromethane, xylene and chloroform. A pH-controlled extraction to effect the removal of the triphenylphosphine byproducts allows the thiols to be isolated in high purities without the need for further purification.

### Facile N-Formylation of Amines Using $ZnCl_2$




A convenient method for the N-formylation of both aliphatic and aryl amines using neat $ZnCl_2$ has been disclosed by Rao and co-workers at the Indian Insitutue for Chemical Technology in Hyderabad (*Tetrahedron Lett.* **2009**, *50*, 7099−7101). Formylation of aliphatic, arylamines, and heteroaryl amines proceeds in moderate to high yields. As expected, the electron nature of the amine has a significant effect on the reaction rates. Reactions of electron-rich arylamines proceed in less than 90 min while electron-poor arylamines with electron-withdrawing groups required up to 12 h for completion.

### A Simple Protocol for Pivaloylation of Alcohols Under Solvent- and Catalyst-Free Conditions




An efficient protocol for the pivaloylation of alcohols employing neat pivaloyl chloride has been reported by Venkateswarlu and co-workers at the Indian Institute for Chemical

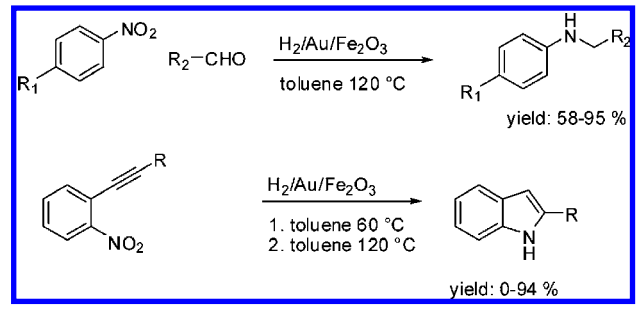
Technology in Hyderabad (*J. Org. Chem.* **2009**, *74*, 8856−8858). When compared to a traditional protection in various organic solvents, the reaction proceeds much faster and is remarkably more efficient. In a model system, 2-phenylethanol was reacted with neat pivaloyl chloride, and the product was obtained in 100% yield in 5 min. When the reaction was carried out in dichloromethane, acetonitrile, and ether under similar reaction conditions, the phenethyl pivalate was obtained only in 89%, 72%, and 83% yield, respectively. The reaction tolerates many primary, secondary, benzylic, and aromatic alcohols; however, attempts to pivaloylate phenols were not successful.

### Synthesis of Heterocycles Mediated by Benzotriazole. 1. Monocyclic Systems

Throughout the years since the first papers from Katritzky, A. R. et al. in the 1980s on the application of benzotriazole derivatives in organic synthesis there has been tremendous progress achieved in the field of benzotriazole chemistry. Benzotriazole intermediates are now commonly used for introduction of a variety of functional groups into molecules. Many aspects of the application of benzotriazole methodology in organic synthesis have been reviewed; however, there is only one outdated review of a limited scope that is specifically devoted to the synthesis of heterocyclic molecules. Now Katritzky, A. R. and Rachwal, S. have reviewed the synthesis of heterocyclic compounds with benzotriazole methodology (Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2009**, 10.1021/cr900204u). The aim of the review is to provide practical guidance for synthetic chemists. Bearing in mind that the major interest in heterocycles is the synthesis of biologically active compounds, they have arranged the material systematically according to the size and shape of the molecules. The nature of the heteroatoms and their number and positions in the molecule are used as secondary discriminators. This way, any chemist searching for bioisosteres of a heterocyclic scaffold or a heterocyclic substituent will find a whole range of useful structures.

### One-Pot Synthesis of Indoles and Aniline Derivatives from Nitroarenes under Hydrogenation Condition with Supported Gold Nanoparticles

One of the major pathways of the transformation of nitroarenes is reduction including hydrogenation into anilines, and then further transformation is carried out by alkylation, reductive alkylation, hydroamination, etc. to obtain their derivatives including heterocyclic compounds. However, when the other unsaturated functional group is located on the aromatic rings or on the substituent with the nitro group, selective reduction of the nitro group by hydrogenation is somewhat difficult. Now Tokunaga, M. et al. (*Org. Lett.* **2009**, *11*, 5162) have developed a one-pot sequences of hydrogenation/hydroamination to form indoles from (2-nitroaryl)alkynes and hydrogenation/reductive amination to form aniline derivatives from nitroarenes and aldehydes were catalyzed by Au nanoparticles supported on $Fe_2O_3$. Nitro group selective hydrogenations and successive reactions were efficiently catalyzed under the conditions.

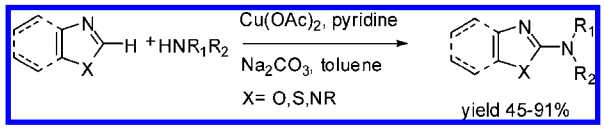



### Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis

The rise of green chemistry has drawn attention to bond construction strategies that promote atom economy and avoid mutagenic reagents. For example, both goals are achieved by replacing highly reactive reagents such as RBr or ROTs with less reactive RH or ROH. Such strategies almost always include a C−H activation component. In the reactions discussed in the review ( Dobereiner, R. H.; Crabtree, G. E. *Chem. Rev.* **2009**, 10.1021/cr900202j), the substrate is activated by catalytic dehydrogenative oxidation. This activation is followed by a bond construction step. These steps proceed under 'one-pot' conditions with a single catalyst or at most two catalysts acting together. Alkane and alcohol substrates are the two best-established reactants. In the first case, alkanes are dehydrogenated to alkenes, which then react further to give the final products. In the second case, alcohol dehydrogenation leads to aldehydes or ketones that then react further with nucleophiles. Amines also have also figured in dehydrogenative activation. The review covers three areas of homogeneous C−H activation: the dehydrogenative oxidation of alkanes, alcohols, and amines. The last section contains specific information on the proposed reaction mechanisms involved. Although much of the earliest work on such activations used heterogeneous catalysts, the emphasis of the review is homogeneous catalysis.

### Copper-Mediated Amidation of Heterocyclic and Aromatic C−H Bonds

The methylation marks on chromatin established by histone methyltransferases (HMTs) are key elements of heritable cell states and can lead to disease when disregulated. Thus, it was of interest that a compound containing a 2-amidobenzimidazole skeleton was reported to inhibit several HMTs. Methods to synthesize this skeleton require multiple-step sequences that do not easily lend themselves to syntheses of many structural analogues. Schreiber, S. L. and Wang, Q. (*Org. Lett.* **2009**, *11*, 5178) have found that a copper-mediated aerobic coupling reaction enables direct amidation of heterocycles or aromatics having weakly acidic C−H bonds with a variety of nitrogen nucleophiles. These reactions provide efficient access to many biologically important skeletons, including ones with the potential to serve as inhibitors of HMTs.




### Transition Metal-Catalyzed Alkene and Alkyne Hydroacylation

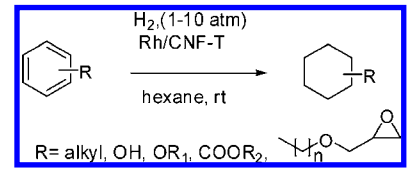
The catalytic activation and subsequent functionalization of C−H bonds is an attractive goal for synthetic chemists (Willis, M. C. **2009**, 10.1021/cr900096x) with reactions that employ low catalyst loadings and result in the formation of C−C bonds being of particular interest. The hydroacylation of alkenes and alkynes are transformations that fulfill these requirements; in addition these processes are inherently atom-economic and can be catalyzed by a variety of transition metals. Hydroacylation formally involves the addition of an acyl unit and a hydrogen atom across a C−C multiple bond; intra- and intermolecular variants of the reactions are known.

The main limitation of hydroacylation as a synthetically useful reaction stems from the general propensity of acyl metal species to undergo reductive decarbonylation. This produces reduced substrates and poorly active carbonylated catalysts. This type of decarbonylation is such a facile process that a number of synthetically useful methods based on this reaction are known.

The most significant advances in hydroacylation chemistry have involved developing strategies, or methods, to limit this undesired decarbonylation pathway.

### Rhodium Nanoparticles Supported on Carbon Nanofibers as an Arene Hydrogenation Catalyst Highly Tolerant to a Coexisting Epoxy Group

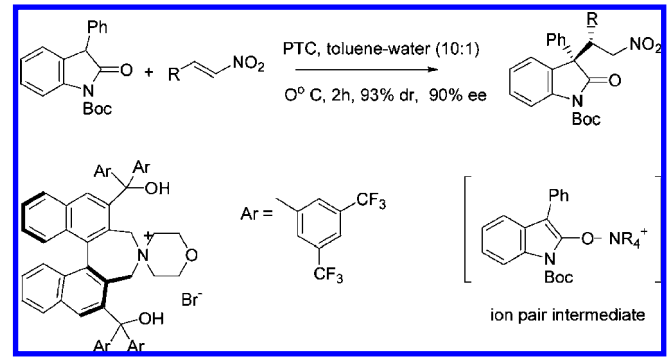
Arene hydrogenation over heterogeneous catalysts has taken part in the facile production of substituted cyclohexane derivatives on both laboratory and industrial scales. Among various transition metal catalysts, rhodium supported on activated carbons (Rh/C) generally shows higher catalytic activity for arene hydrogenation than heterogeneous catalysts containing other transition metals. However, one drawback to the use of expensive rhodium is that the catalyst is often quickly deactivated due to facile sintering of the metal particles and leaching of metallic species from the support. Carbon materials that promote arene hydrogenation under mild conditions with high turnover frequency and are robust enough to be reusable may provide a more suitable support for the rhodium catalysts. In this context, carbon nanofibers (CNFs) having controlled nanostructures consisting of stacked graphene sheets are attractive supports for metal particles. Rhodium nanoparticles supported on a carbon nanofiber (Rh/CNF-T), easily prepared from $Rh_4(CO)_{12}$ and CNFs, show high catalytic activity toward arene hydrogenation under mild conditions in high turnover numbers without leaching the Rh species (Motoyama, Y.; et al. *Org. Lett.* **2009**, *11*, 5042). The reaction is highly tolerant to epoxy groups, which often undergo ring-opening hydrogenation with conventional catalysts. The catalytic activity is not decreased in repeated experiments.




### Enantioselective Base-Free Phase Transfer Reaction

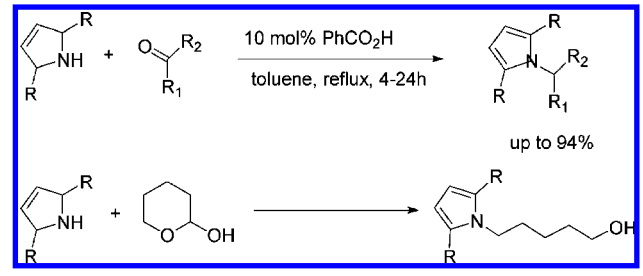
The reaction of nitro-olefins with oxindoles has been a popular reaction for those studying organocatalysis and has been reported to proceed under phase-transfer catalysis (PTC) in the presence of mild bases. Now, surprisingly, it has been shown by the group of Maruoka in Kyoto that the reaction will proceed in the absence of base if the appropriate asymmetric PTC is used (He, R.; et al. *J Am Chem Soc*. **2009**, *131*, 16620). The resultant products can be transformed to interesting heterocyclics under mild conditions.

The reaction, which proceeds in toluene, but only when water is present, is suggested to proceed via an ion pair, and evidence for this was obtained from deuteration studies. Only PT catalysts which have free hydroxyl groups work under these conditions.




### A Simple Synthesis of N-Alkyl Pyrroles

The reaction of a pyrroline with aldehydes and ketones, although previously known, has been improved by the study of a range of catalysts. Benzoic acid proved to be the best catalyst, and it allows a facile synthesis of alkylpyrroles simply by refluxing the components together in toluene (Pahadi, N. K.; et al. *J Am Chem Soc*. **2009**, *131*, 16626). Aliphatic and aromatic aldehydes and ketones can all be used, and there was one example of an unsaturated aldehyde being tried successfully.

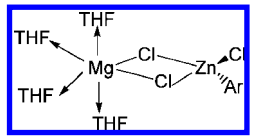



### Aryl Zinc Reagents: Method of Making Determines Reactivity

Organozinc reagents are widely used in cross coupling reactions, and several are now commercially available in bulk. The reagents are easily prepared in situ from the exchange of Grignard reagents or organolithiums with zinc halides, and it is usually assumed that both methods give the same species

RZnX, although clearly the magnesium and lithium halide byproducts are different and may affect reactivity of the organozinc reagent. It has sometimes been found beneficial to remove these byproducts by precipitation/filtration before undertaking further reactions. Now, more detailed studies have revealed that the species generated in the syntheses from Grignards and organolithiums are different in nature (Jin, L.; et al. *J Am Chem Soc.* **2009**, *131*, 16656). First indications of the difference came when the nickel-catalysed homocoupling of arylzincs to biaryls in THF was studied. Whereas the arylzinc made from Grignard chemistry proceeded in a zero-order reaction with complete conversion after 4 min at −20 °C, the arylzinc from aryllithium and zinc chloride reacted sluggishly with only 13% conversion after 50 min at the same temperature. It was shown that in the latter system the transmetalation (Zn to Ni) was rate-limiting, whereas in the former reaction it was very fast, and reductive elimination was the rate-determining step.

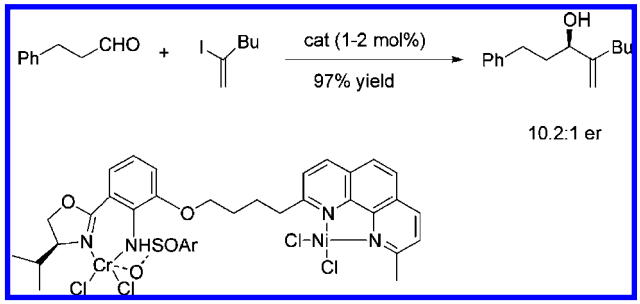
NMR evidence shows the differences in solution in THF, with the byproduct magnesium chloride complexing to the zinc reagent; this was confirmed by isolation of the complex and single-crystal X-ray determination of its structure. Addition of magnesium chloride to the arylzinc prepared from aryllithium restored its reactivity.




## Improved Conditions for the Takai Reaction

The chromium chloride-catalysed addition of an alkenyl halide to an aldehyde, the Takai reaction, is not widely used on scale because of the high catalyst loading, despite its importance particularly in enantioselective synthesis. The reaction is initiated by the presence of a small amount of nickel halide, with the ratio of Ni to Cr being important; asymmetric couplings typically use 10−20 mol % Cr and 1−5 mol % Ni. Since under these conditions the alkenyl halide is used in 1.5 or larger excess to drive the reaction to completion, homocoupling byproducts can also accumulate.

A recent report from the group of Kishi at Harvard appears to have solved many of these problems, and this may make the reaction more suitable for large-scale work if the catalyst becomes more readily available (Liu, X.; et al. *J Am Chem Soc.* **2009**, *131*, 16678). The new catalyst, which binds to both nickel and chromium bringing the metals in close proximity, seems to solve many of the earlier problems and allows the reaction to proceed with 1−2 mol % catalyst with less than 3% homocoupling byproducts.




## Formation of Tubular Crystals of Pharmaceutical Compounds

Crystal morphology control with the aim of producing tubular crystals with relatively large pores (mm) was reported recently from the Jones' group at the University of Cambridge (Eddelston, M. D.; et al. *Cryst. Growth Des.* **2009**, 10.1021/cg900969n). Nano- and microtubular materials are expected to be used in new drug-delivery systems, in optical devices, and for hydrogen storage, etc. Novel, rod-shaped, hollow crystals of caffeine, carbamazepine, carbamazepine dehydrate, theophylline hydrate, and aspirin were prepared by evaporative crystallization from systematically selected solvents. Such crystallization processes occur at high supersaturation; a mechanism for tubule formation is proposed. Apparently, only one active pharmaceutical ingredient (API) exhibiting tubular morphology was reported (dexamethasone acetate sesquihydrate). The novelty of the tubular crystals of well-known compounds is explained, among others, by the lack of stirring during the evaporative crystallization. Interestingly, the authors indicate that the proposed crystallization protocol is compound independent. Future work will perhaps also address scale-up challenges in the preparation of such tubular crystals.

## Fine Dosage of Antisolvent in the Crystallization of L-Histidine: Effect on Polymorphism

Antisolvent membrane crystallization is a relatively new technology available to crystal engineers. An interesting polymorph control application of this approach was reported by several research groups in Italy (Di Profio, G.; et al. *Cryst. Growth Des.* **2009**, 10.1021/cg901038g). L-Histidine exhibits two polymorphs: form A, thermodynamically stable, and form B, metastable (at RT). Crystallization from water, or water−ethanol mixtures at low ethanol levels leads to mixtures of the two polymorphs. At high levels of ethanol in water, only the metastable form B is isolated. In an antisolvent membrane crystallization, supersaturation can be produced by gradual, controlled, antisolvent dosing in the vapor phase through a porous membrane. The authors demonstrated the applicability of this technology for the production of the metastable form of L-histidine, form B. The proposed crystallization mechanism invokes as the first nucleation stage the formation of form A crystals, in an "anti-Ostwald" sense.

## Performance Comparison of Micromixers

Micromixers have been used in chemical research for over a decade, and therefore, their theory has been developed accordingly. In spite of this, the design of effective micromixers can pose challenges. Because of mixing complexity, just as with their bigger counterparts (stirred tanks), microreactor mixing can be meaningfully characterized experimentally. Running test reactions in microreactors can conveniently "fingerprint" them. A group from CNRS (France) reported the use of the Villermeaux−Dushman reaction to characterize the mixing efficiency of certain micromixers (Falk, L., et al., *Chem.*

*Eng. Sci.* **2010**, *65*, 405). In the Villermeaux−Dushman test reaction, a neutralization and a redox reaction can occur. Because the neutralization reaction is much faster, under ideal mixing conditions this would be the only reaction observed. In reality, both reactions can occur, and the chemical selectivity can be used to quantify the mixing performance. Even though the energetic mixing efficiency of micromixers tends to be low, their mixing performance can surpass that of classical reactors. The authors found that the parameter in determining micromixer mixing efficiency is energy dissipation, and not the internal geometry of the micromixer.

### A Novel Compact Reactor for Three-Phase Hydrogenations

Process intensification for hydrogenations was demonstrated in a new, compact reactor by a team from EPF-Lausanne (Graseman, M.; et al. *Chem. Eng. Sci.* **2010**, *65*, 364). This reactor includes a highly effective heat exchanger, integrated with a staged bubble column reactor. The catalytic layers were made of Pd/ZnO deposited on sintered metal fibers (FeCrAl alloy). The (solvent-free) hydrogenation process investigated was that of 2-methyl-3-butyn-2-ol to the corresponding alkene. Computational fluid dynamics (CFD) was used to characterize the fluid dynamics in the reactor, and statistical design of experiments (DoE) was used to determine the optimal operating conditions. In spite of the relatively low catalytic performance compared to the kinetic regime, the novel reactor exhibits a productivity of almost 2 orders of magnitude higher than that of its slurry reactor counterpart.

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