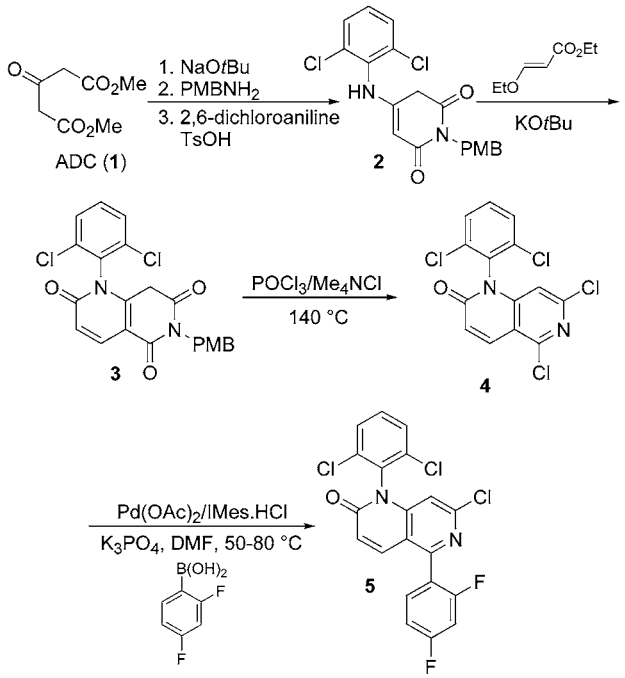
Organic Process Research & Development **2006**, *10,* 168–183

# *Highlights from the Literature*

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

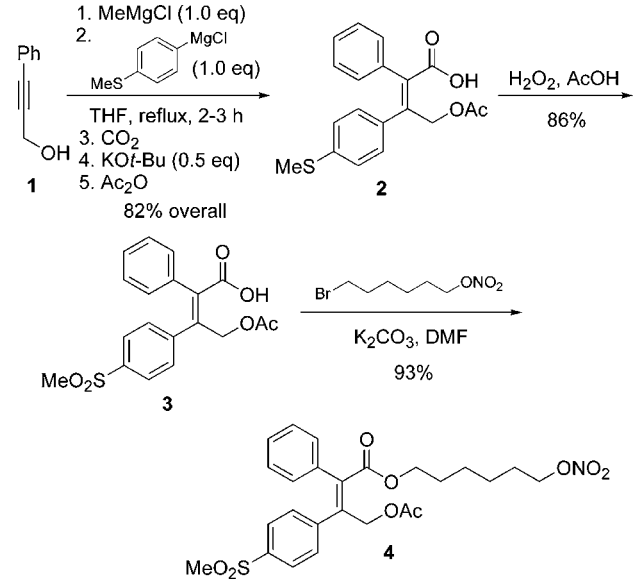
### Efficient Naphthyridone Synthesis




Chung and co-workers at Merck report on an efficient five-step synthesis of a challenging 1,6-naphthyridone **5** (*J. Org. Chem.* **2005**, *70*, 10342−10347). Compound **5** is an intermediate in a synthesis of a p38 mitogen-activated protein (MAP) kinase inhibitor. The synthesis begins with a selective monoamidation of acetonedicarboxylate (ADC) dimethyl ester **1**. The in situ formation of the enolate of **1** served as a convenient means of inhibiting the bis-amidation reaction. Subsequent treatment with 2,6-dichloroaniline under Dean−Stark conditions afforded the enamide imide **2**. Treatment of **2** with KO$^t$Bu and 3-ethoxyacrylate produced lactam **3**, which was converted to tetrachloronaphthyridone **4** via a one-pot PMB deprotection and bischlorination. Initial attempts to form **5** via a Suzuki cross-coupling reaction using Pd(dppf)$Cl_2$/$Cs_2CO_3$ in toluene at 110 °C led to an unselective process. Ultimately, high regioselectivity was obtained using Pd$(OAc)_2$/IMes-catalyzed cross-coupling with $K_3PO_4$ as the base in DMF at the reduced temperature of 50−80 °C.

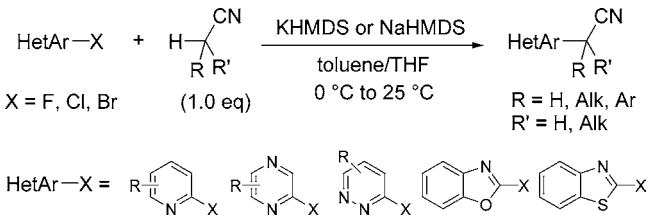
### Tetrasubstituted Alkene via Carbometalation Strategy

Traditionally, tetrasubstituted alkenes with defined stereochemistries represent a challenging synthetic motif in organic chemistry. In a paper detailing the development of a practical synthesis of a NO-releasing prodrug **4** of rofecoxib, Engelhardt and co-workers at Merck demonstrate




a highly efficient four-step one-pot carbometalation reaction that constructs a tetrasubstituted alkene with remarkable stereocontrol (*J. Org. Chem.* **2006**, *71*, 480−491). The Grignard carbometalation reaction transforms a simple propargyl alcohol **1** into (*Z*)-2,3-biaryl-4-acetoxybut-2-enoic acid **2**, the core of prodrug **4**. Previously, this type of transformation was used to prepare butenolides, but the current work shows that the intermediate (*Z*)-4-alkoxybut-2-ene carboxylate can be intercepted with an appropriate acetate trap ($Ac_2O$). The optimization of this four-step process required an intricate understanding of the reaction intermediates which was obtained by using ReactIR. The sequestering of excess carbon dioxide by introducing an alkoxide base (KO$^t$Bu) was instrumental in the success of the subsequent acetate trapping reaction to generate the opened product **2**. Finally, the synthesis of the NO-COXIB drug was completed via two different end-game strategies designed to control impurity and byproduct levels. An overall yield of 64% was achieved for this elegant five-step synthesis.

### Mild and Efficient Arylation of Nitriles




A mild, practical, and transition-metal-free method for the α-arylation of aliphatic nitriles with activated heteroaryl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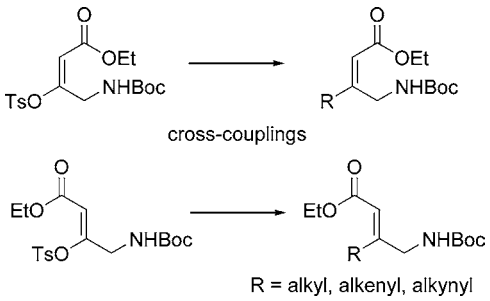
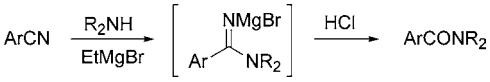
halides using NaHMDS or KHMDS as the base at ambient temperature is described by Klapars, Waldman, and co-workers at Merck (*J. Org. Chem.* **2005**, *70*, 10186−10189). Key to the success of this method is the generation of the nitrile anion in the presence of a heteroaryl halide, whereby any competing decomposition pathways are minimized. The method is applicable to both primary and secondary carbonitriles and a wide range of heteroaryl halides. Selective monoarylation is observed with primary carbonitriles. In most cases, either heteroaryl bromides, chlorides, or fluorides could be used as the arylating agents although the more reactive aryl fluorides provided better results with particularly sensitive substrates. The operational simplicity and the mild reaction conditions add to the value of this method as a practical alternative for the preparation of α-heteroaryl carbonitriles.

### Enol Tosylates as Partners in Cross-Coupling Reactions



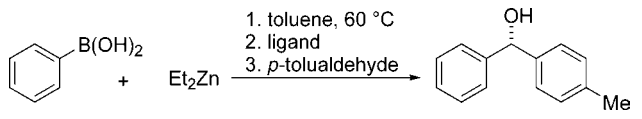

Enol tosylates are emerging as important alternatives to enol triflates and vinyl halides in Pd-catalyzed cross-coupling reactions. Enol tosylates are often more stable than the corresponding enol triflates both in the solid state and in solution. In addition, the preparation of enol tosylates possesses distinct advantages over the preparation of enol triflates. On a large scale, $Ts_2O$ is relatively inexpensive compared to $Tf_2O$, and the fact that it is a stable solid renders it easier to handle than $Tf_2O$. In comparison to vinyl halides, which often require multiple steps to prepare, enol tosylates are easily prepared by enolization of the corresponding ketone followed by treatment with $Ts_2O$. This enolization strategy allows for the selective formation of either (*E*)- or (*Z*)-enol tosylates in high isomeric purity simply by choosing the appropriate reaction parameters. As a direct result of these described advantages, enol tosylates are becoming prominent substrates in cross-coupling reactions. In this report (*J. Org. Chem.* **2005**, *70*, 10124−10127), Steinhuebel and co-workers at Merck describe a variety of cross-coupling reactions using functionalized enol tosylates, which provide stereodefined trisubstituted unsaturated esters.

### Addition of Mg-Amides to Nitriles



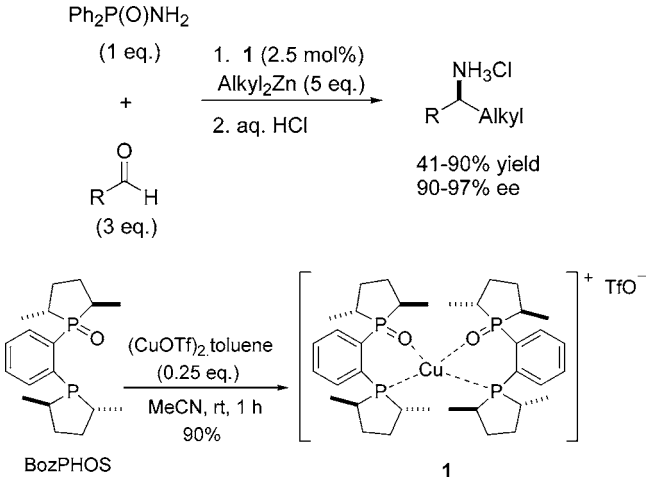

Bhattacharya and co-workers report on the addition of Mg-amides to arylnitriles as a method for the production of carboxamides (*Tetrahedron Lett.* **2006**, *47*, 505−506). The authors speculate that the enhanced reactivity of these magnesium reagents could be due to the combined effects of increased nucleophilicity of the Mg-amide and Mg-related Lewis acid activation of the nitrile. The Mg-amides, generated from the alkylamine and ethylmagnesium bromide in THF, efficiently add to arylnitriles and afford the desired amides in good yields after aqueous workup. Interestingly, the corresponding lithium amides were ineffective, and the presence of a large excess of amine inhibited the reaction. This methodology was successfully utilized to prepare the insect repellant *N*,*N*-diethyl-*m*-toluamide (DEET) in 90% yield.

### Enantioselective Addition of Arylboronic Acids to Aldehydes




Pyrrolidinylmethanols, derived from (*S*)-proline, were applied as ligands in the diethylzinc-mediated asymmetric addition of arylboronic acids to aromatic aldehydes, as described in a report from the group of Braga (*Tetrahedron Lett.* **2005**, *46*, 7827−7830). Following a procedure originally developed by Bolm and later extended by Chan, the reaction is thought to proceed via the in situ formation of an arylzinc species, which undergoes asymmetric addition under the influence of the amino alcohol ligand. The authors comment that their results are similar or even superior to those obtained by Bolm or Chan and suggest that their ligands are more readily available/less expensive than those previously reported. This being said, the demonstrated substrate scope is rather narrow and significant drawbacks are the use of excess amounts (>7 equiv) of pyrophoric $Et_2Zn$ coupled with the requirement for >2 equiv of the arylboronic acid.

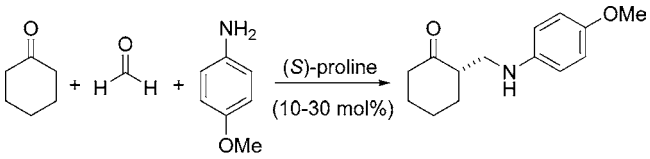
### Multicomponent Chiral Amine Synthesis




The synthesis of chiral amines by a one-pot multicomponent procedure from commercially available starting materials is described in a report from the Charette group (*J. Org. Chem.* **2005**, *70*, 10864−10867). A key feature of

this enantioselective reaction is the Cu-catalyzed asymmetric addition of dialkylzinc reagents to in situ prepared *N*-diphenylphosphinoylimines. The asymmetry is derived from the BozPHOS ligand, which is used as an air-stable precatalyst complex **1** with CuOTf. The chiral amines are prepared in a one-pot procedure from alkyl and aryl aldehydes in good yield (41−90%) and with high enantioselectivity (90−97% ee). However, similar to the preceding Highlight, excess quantities of dialkylzinc reagents and the aldehyde substrates are required, detracting from the utility of the current process with respect to scale-up.

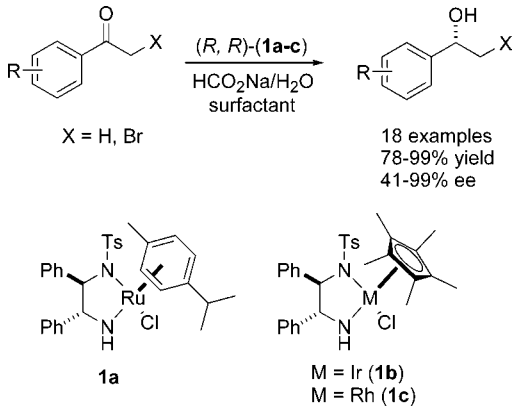
### Organocatalytic Aminomethylation of Ketones




other arylamines and carbonyls 45-92% yield, 70-99% ee

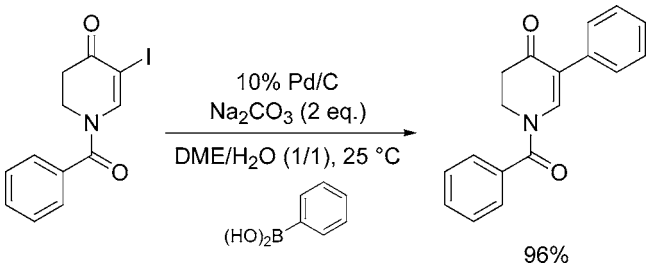
The scope and limitations of an organocatalytic asymmetric α-aminomethylation of ketones are disclosed in report by Cordova and co-workers (*Tetrahedron* **2006**, *62*, 357−364). The proline-catalyzed classical Mannich reactions between unmodified ketones, aqueous formaldehyde, and aromatic amines furnished the desired Mannich bases in high yield with up to 99% ee. Methyl alkyl ketones were also regioselectively α-aminomethylated at the methylene carbon, affording the corresponding Mannich products with up to 99% ee. In addition, the proline-catalyzed one-pot three-component reaction between *p*-anisidine, aqueous formaldehyde, and 4,4-dimethyl-2-cyclohexen-1-one furnished the corresponding bicyclic aza-Diels−Alder adduct with 99% ee.

### Asymmetric Transfer Hydrogenation of Ketones



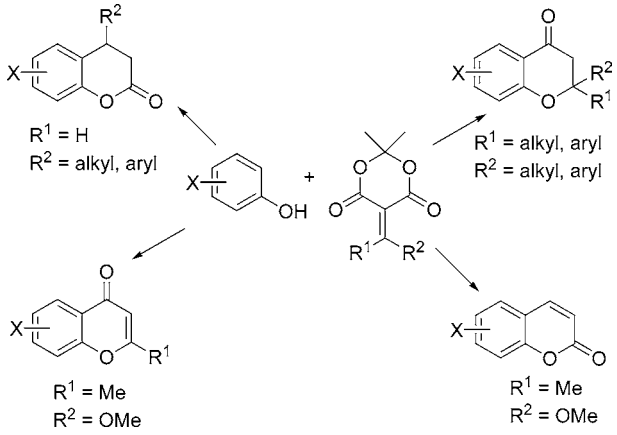

Zhu, Deng, and co-workers report on the asymmetric transfer hydrogenation of ketones, including α-bromomethyl aromatic ketones, catalyzed by unmodified, hydrophobic, transition metal−amido complexes (TsDPEN-M) (*J. Org. Chem.* **2005**, *70*, 9424−9429). The authors noted a significant enhancement in activity, chemoselectivity, and enantioselectivity (up to 99% ee) in aqueous media when surfactants (cetyltrimethylammonium bromide or sodium dodecyl sulfate) were employed. It was demonstrated that the separated aqueous phase (after extractive workup) retained its catalytic activity through six recycles.

### Efficient Suzuki−Miyaura Cross-Coupling of Iodoenones and Arylboronic Acids




The Suzuki−Miyaura cross-coupling of 2-iodocycloenones with arylboronic acids catalyzed by 10% Pd/C, described by Felpin, is an alternative to homogeneous conditions (*J. Org. Chem.* **2005**, *70*, 8575−8578). Most of the substrates reacted under mild conditions at 25 °C under air in aqueous DME. The conditions described tolerate a wide range of iodoenones and boronic acids. Notably, the procedure features inexpensive reagents and solvents with low toxicity. Additionally 10% Pd/C was recovered and reused at least five times without significant alteration of the yields of the cross-coupled product.

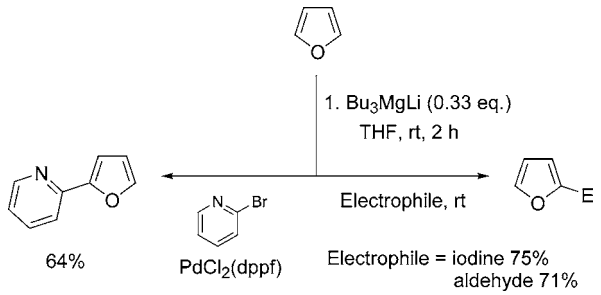
### One-Pot Synthesis Of Chromanones and Coumarins




The group of Fillion reports on $Yb(OTf)_3$-catalyzed annulation reactions of phenols with 5-alkylidene Meldrum's acid derivatives, which provide structurally diverse heterocycles in high isolated yields (*J. Org. Chem.* **2006**, *71*, 409−412). A series of 4-substituted 3,4-dihydrocoumarins, 2,2-disubstituted 4-chromanones, coumarins, and 2-substituted chromones were assembled, including the naturally occurring coumarins citropten, scoparone, and ayapin. Addition of phenols to bis-electrophilic 5-alkylidene Meldrum's acids proceeds through two distinct multibond-forming modes: Friedel−Crafts *C*-alkylation/*O*-acylation and Friedel−Crafts *C*-acylation/*O*-alkylation. The regioselectivity of the catalytic annulation reaction was controlled by the degree of substitution on the alkylidene moiety. The authors also note that

the use of 5 equiv of TFA instead of $Yb(OTf)_3$ in many cases provides similar yields of product.

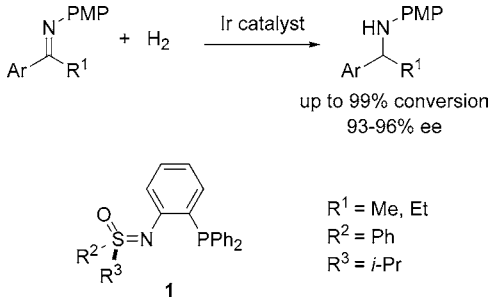
### Deprotonation of Furans Using Lithium Magnesates




The group of Mongin has investigated the deprotonation of furan and benzofuran using lithium magnesates (*Tetrahedron Lett.* **2005**, *46*, 7989−7992). Using 0.33 equiv of $Bu_3MgLi$ in THF, furan can be deprotonated at room temperature. The resulting lithium arylmagnesate was either trapped directly with electrophiles or utilized in a palladium-catalyzed cross-coupling reaction with 2-bromopyridine. The highly coordinated magnesate $Bu_4MgLi_2$ (0.33 equiv) proved to be a better deprotonating agent than $Bu_3MgLi$. $Bu_4MgLi_2$ gave 90% yield for iodine quench vs 85% with $Bu_3MgLi$ and 75% vs 72% for 3,4,5-trimethoxybenzaldehyde quench. The reactions were monitored using NMR spectroscopy, which indicated that the deprotonation of furan using $Bu_4MgLi_2$ at room temperature required 2 h, whereas the subsequent electrophilic trapping was instantaneous. The method was extended to benzofuran, allowing its functionalization at C2 in high yields. The deprotonation of 2-methylfuran and lithium furfurylalkoxide at C5 turned out to be difficult, requiring either long reaction times or higher temperatures. A potential advantage of this method is that in contrast to the corresponding lithio compounds, the furan magnesate complexes have sufficient thermal stability to undergo cross-coupling reactions without the need for conversion to organoboron, organotin, or organozinc derivatives.

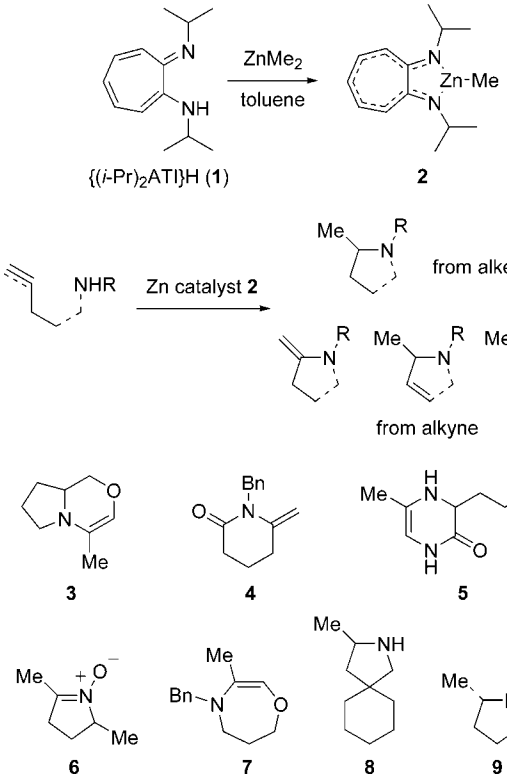
### Ir-Catalyzed Asymmetric Hydrogenations of Imines

The discovery of hydrogenation catalysts that mediate the asymmetric reduction of imines to amines is a challenging task. In addition, to usher the reaction coordinate to an enantioselective pathway, methods for the transformation of acyclic imines must operate on substrates that usually display *E*/*Z* stereoisomerism. Moessner and Bolm reported the use of novel P,N-ligands (e.g., diphenylphosphanylsulfoximine **1**) as mediators of iridium-catalyzed asymmetric hydrogenations of *N*-(*p*-methoxyphenyl)imines (*Angew. Chem., Int. Ed.* **2005**, *44*, 7564−7567). High enantioselectivities (93−96% ee) were attained using a 0.5 mol % catalyst loading and hydrogen (20 bar) in toluene at room temperature during 4−12 h. The active catalyst is generated in situ by mixing $[\{Ir(cod)Cl\}]_2$, the sulfoximine ligand, and iodine in a 1:2:4 ratio, respectively. The choice of *p*-methoxyphenyl imines is not accidental: the *p*-methoxyphenyl (PMP) group offers the best results and can be simply removed by a variety of methods.



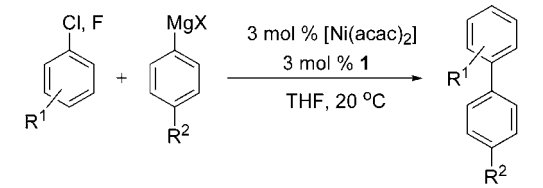

### Zn-Catalyzed Hydroamination of Alkenes and Alkynes

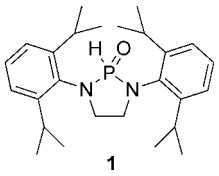
Homogeneous zinc-based catalyst **2** promotes the intramolecular hydroamination of functionalized, nonactivated alkenes and alkynes to give heterocycles of pharmaceutical interest (e.g., **3**−**9**; see Roesky, Blechert et al., *Angew. Chem., Int. Ed.* **2005**, *44*, 7594−7598). Zinc iminate **2** is readily prepared in 83% yield by reacting $\{(i\text{-Pr})_2ATI\}H$ (**1**) and $ZnMe_2$ in toluene. In general, optimal conditions for hydroamination include the use of 1−10% mol of **2**, and an equimolar amount of cocatalyst $[PhNMe_2H][B(C_6F_5)_4]$ relative to **2** in benzene at 120 °C in a sealed tube. Quantitative conversions are obtained at variable reaction times (4−312 h) depending on the structure of the substrate and catalyst loading. Interestingly, catalyst **2** displays high functional group tolerance, including ethers, thioethers, and amides, and is stable towards moisture and air. Although the reaction conditions need some improvement to be transferred to preparative scale, this zinc-catalyzed hydroamination constitutes a promising alternative to rival transition-metal based procedures.



## Hetero Aryl−Aryl Coupling by Activation of C−Cl and C−F Bonds

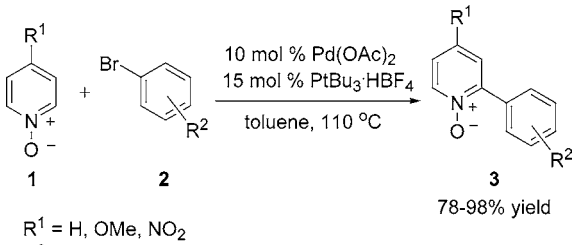
Transition metal-catalyzed cross-coupling reactions of organomagnesium compounds provide access to asymmetrically substituted biaryls. The use of aryl chlorides and particularly aryl fluorides as electrophiles in such reactions lags far behind the use of their bromo and iodo counterparts. In a recent communication, Ackerman and co-workers report the first use of air-stable secondary phosphine oxides for the activation of C−F bonds in aryl fluorides (*Angew. Chem., Int. Ed.* **2005**, *44*, 7216−7219). Following the screening of air-stable dioxo- and diaminophosphine oxides in a Kumada reaction with 4-chloroanisole, the sterically congested phosphine oxide **1** was selected because of the minimal formation of dimeric and reduced byproducts. The catalyst derived from **1** facilitated the efficient conversion at room temperature of a representative set of electron-rich aryl chlorides and fluorides, particularly pyridyl derivatives.




## Catalytic Direct Arylation of Pyridine Oxides

The instability and difficult synthesis of 2-pyridyl organometallics limit their application in the preparation of 2-arylpyridines. Campeau, Rousseaux, and Fagnou at the University of Ottawa report the use of pyridine *N*-oxides as commercially available or readily accessible bench-stable replacements for 2-metallapyridines (*J. Am. Chem. Soc.* **2005**, *127*, 18020−18021). Reactions of pyridine *N*-oxides with a variety of aryl bromides occur in excellent yields with complete selectivity for the 2-position. Development work rendered $Pd(OAc)_2$ (5 mol %), the air-stable $HBF_4$ salt of P*t*$Bu_3$ (15 mol %) and $K_2CO_3$ (2 equiv) as the optimal combination of reagents for the reaction of **1** and **2** in toluene at 110 °C. The 2-aryl *N*-oxides products can be converted to the corresponding aryl pyridines in high yield by catalytic hydrogen transfer using ammonium formate. Although 4 equiv of **1** are used, the unreacted *N*-oxide can be recovered by chromatography. The authors include proper warnings about dangers associated with thermal decomposition of pyridine *N*-oxides at high temperatures ($T_o$ = 208−307 °C).

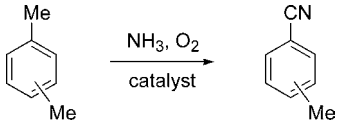



$R^1$ = H, OMe, $NO_2$

$R^2$ = 2-Me, 4-Me, 3,5-diMe, 3-OMe, 4-OMe, 4-$CO_2$Me, 4-$CF_3$

## One-Step Synthesis of Tolunitriles

Aromatic nitriles are commodity chemicals widely used in the fine chemicals industry. Ma and co-workers at Wuhan University have developed a new synthesis of toluene mononitriles by ammoxidation of xylenes over a silica-supported Co/Mn/Mg/Ni catalyst (*Synth. Commun.* **2005**, *35*, 2951−2954). In a typical experiment, oxygen and ammonia (5:1 ratio) were injected at 90 °C into an autoclave previously charged with xylene and the heterogeneous catalyst, and the pressure was controlled at 0.5 MPa. After 5 h, the reaction was terminated by addition of cool water, the catalyst filtered, and the residue distilled. Although the yields are at best modest (14−29%), the selectivity for mononitriles is almost quantitative, the procedure does not require the use of solvents, and it is environmentally benign compared to existing methods.

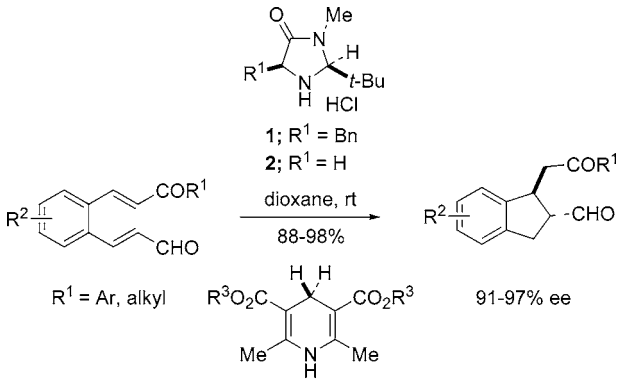


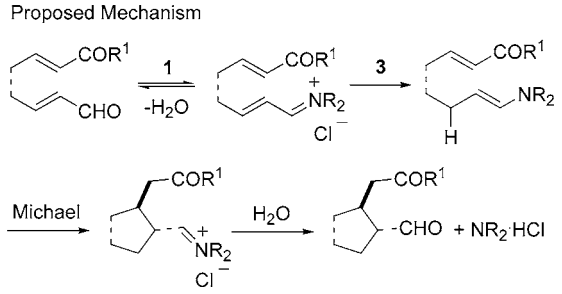

## Iminium−Enamine Organocatalysis

The combination of iminium and enamine catalysis in tandem and cascade reactions constitutes a new breakthrough in the field of organocatalysis. Beyond extending the scope of catalytic chiral amines in synthesis, the groups of List and McMillan have succeeded in emulating multistep transformations reminiscent of enzymatic activity. The "traffic control" achieved in these processes is remarkable.

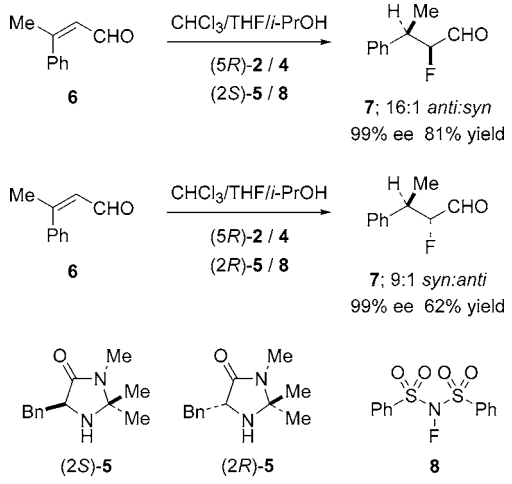
List and co-workers reported a stereoselective reductive Michael cyclization of enal enones (*J. Am. Chem. Soc.* **2005**, *127*, 15036−15037). Imidazolidinone salts (e.g., **1**, 20 mol %) catalyze the reaction initiated by commercially available Hantzsch ester **3** (1.1 equiv) as hydrogen donor. The cyclization is general for different Michael acceptors. Chemo-, regio-, diastereo-, and enantioselectivities are high. A proposed mechanism involves the nonasymmetric conjugate reduction of hydride to an α,*β*-unsaturated iminium followed by intramolecular asymmetric Michael addition of the resulting intermediate enamine.

The group of McMillan has developed a new organocatalytic strategy that mimics biochemical enzymatic cascades. The capability of specific organocatalysts to coexist in the same reaction media without interference is key to the success of this methodology. For example, using a combination of iminium catalyst (5*R*)-**2** and enamine catalyst (2*S*)-**5** the authors achieved the enantioselective hydrofluorination of trisubstituted enal **6** to give *anti*-**7** with 16:1 selectivity and 81% yield. Most importantly, substitution of



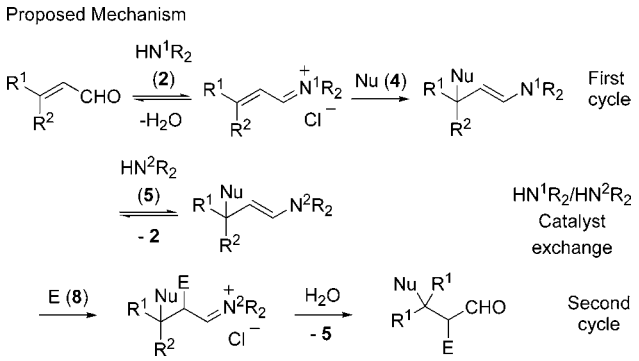




enamine catalyst (2*S*)-**5** with its enantiomer (2*R*)-**5** afforded *syn*-**7** with 9:1 selectivity and 62% yield. The cascade product results from two consecutive cycles: first, an iminium activation that facilitates the nucleophilic conjugated hydride attack mediated by Hantzsch ester **4** and second, an enamine activation that promotes the electrophilic attack. Thus, modular control of stereoinduction was achieved by selection of the catalyst enantiomer involved in each cycle. In addition, the manuscript applies the organo-cascade catalysis scheme to several aromatic nucleophiles and a chlorinating electrophile with remarkable success to generate 3-aryl-2-chloropropanals (*J. Am. Chem.* Soc. **2005**, *127*, 15051−15053).

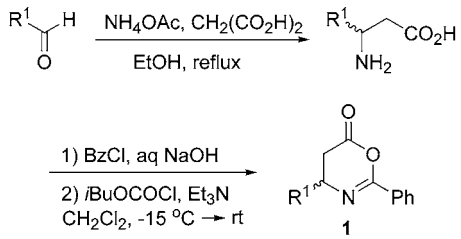



## Enantiomerically Pure β-Amino Acids by Kinetic Resolution of Oxazinones

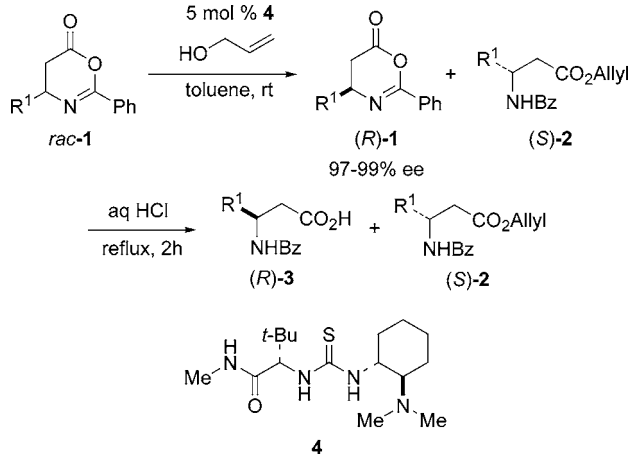
Berkessel and co-workers applied organocatalytic kinetic resolution of oxazinones to the synthesis of β-amino acids (*Angew. Chem., Int. Ed.* **2005**, *44*, 7466−7469). Oxazinones




are configurationally stable compounds accessible via the cyclodehydration of the corresponding *N*-benzoyl β-amino acids synthesized from inexpensive aldehydes (*Tetrahedron* **2002**, *58*, 7449−7461).



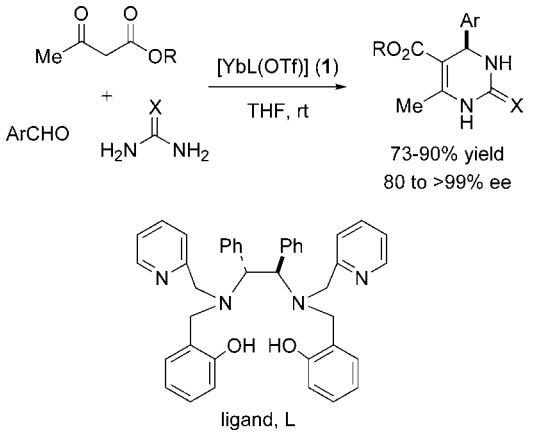

Allyl alcohol (1 equiv) was used as the nucleophile for the ring-opening reaction in the presence of thiourea **4**. At 57% conversion, (*S*)-**1** was completely consumed, and the ee of the product was 86%. By treatment of the reaction mixture with aqueous HCl, the remaining oxazinone was quantitatively hydrolyzed to insoluble amino acid **3**. The allyl ester remained in solution, without detriment of its chiral integrity. The novel resolution method works with substrates bearing aliphatic and a variety of aromatic substituents. It is noteworthy that remaining enantiomerically pure oxazinones are activated amino acid derivatives that can be used in coupling reactions for the synthesis of β-peptides.




## Yb-Catalyzed Enantioselective Biginelli Reaction

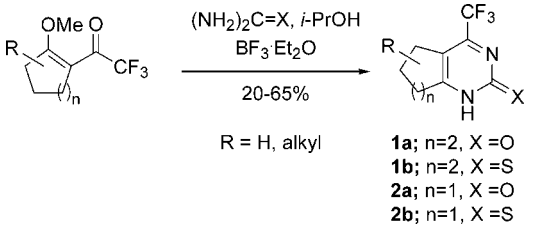
The Biginelli reaction is a classic among multicomponent reactions. In this cyclocondensation, an aldehyde, a 1,3-ketoester, and urea or thiourea come together to generate a polyfunctionalized dihydropyrimidine. These heterocycles are

of enormous interest to the pharmaceutical industry since they exhibit antiviral, antitumor, antibacterial, and antiinflammatory properties, and can be considered privileged structures. Zhu and co-workers explored a catalytic approach to the enantioselective version of the Biginelli cyclocondensation using a Yb catalyst (**1**) containing a hexadentate chiral ligand (*J. Am. Chem. Soc.* **2005**, *127*, 16386−16387). Optimum reaction conditions include the use of 10 mol % catalyst generated in situ by ligand exchange of $Yb(OTf)_3$ with an equimolar amount of **1** at room temperature in THF. The process is very efficient, affords high yields and ee's, and displays an excellent functional group tolerance. The basic catalyst could be recovered by adjusting the solution pH and was reused several times without measurable loss of ee.



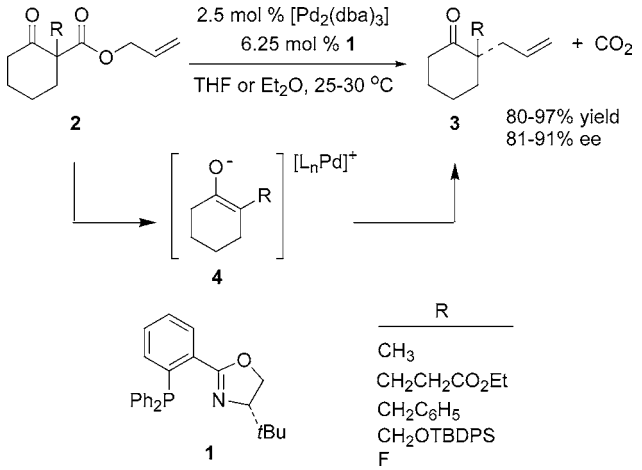

## Synthesis of 2(1*H*)Quinazolinones and 2(1*H*)Pyrimidinones

The synthesis of a series of trifluoromethylated tetrahydro-2(1*H*)quinazolinones (**1a**), cyclopenta-2(1*H*)pyrimidinones (**2a**), and their sulfur analogues (**1b** and **2b**, respectively) was reported by Bonacorso and co-workers (*Synth. Commun.* **2005**, *35*, 3055−3064). In general, compounds bearing these heterocyclic nuclei display a variety of biological activities such as antivirals or calcium antagonists. The targeted adducts were prepared by cyclocondensation of $\beta$-alkoxyvinyl trifluoromethyl ketones with urea or thiourea in a single step using boron trifluoride diethyl etherate as catalyst in 2-propanol. Despite moderate yields, the methodology outperforms conventional procedures that use concentrated hydrochloric acid in methanol.

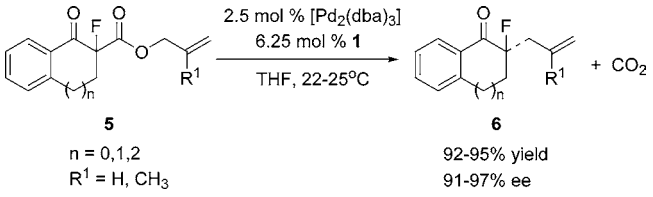



## Chiral Phosphinooxazoline Ligands in Catalytic Asymmetric Decarboxylation

Racemic compounds with chiral quaternary centers are atypical substrates for stereoablative enantioconvergent synthesis because of the difficulty associated with C−C bond cleavage. The group of Stoltz at CalTech developed a method to convert racemic α-substituted 2-carboxyallylcyclohexanones in highly enantioenriched cyclohexanones that bear quaternary stereocenters (*Angew. Chem., Int.* Ed. **2005**, *44*, 6924−6927). The process involves a catalytic asymmetric decarboxylation reaction using a Pd catalyst supported by chiral phosphinooxazoline ligand **1**. The principle of the strategy is that the substrate experiences stereoablation, providing an achiral intermediate that undergoes enantioselective conversion into product. The authors propose the achiral ketone enolate **4** as the intermediate. The catalyst is involved in the stereoablative (C−C bond-breaking) and stereoselective (C−C bond-forming) steps. Application of this methodology to the synthesis of a wide array of chiral cyclic ketones with one or more quaternary stereocenters is possible due to the commercial availability of racemic $\beta$-ketoesters **2**.

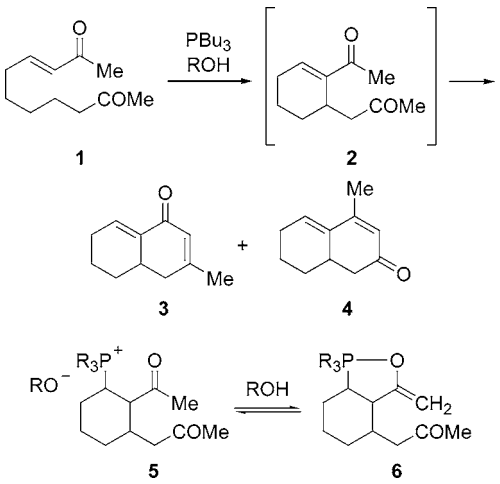



As an alternative to the enantioselective α-fluorination of carbonyl compounds, Nakamura, Nakamura, and co-workers report the conversion of racemic α-fluoroketones **5** into optically active α-fluoroketones **6** by Pd-catalyzed extrusion of carbon dioxide (*Angew. Chem., Int. Ed.* **2005**, *44*, 7248−7251). After screening a variety of chiral phosphinooxazolines, best results were found with the *tert*-butyl substituted ligand **1**. Mechanistic investigations are ongoing.




## Highly Regioselective Synthesis of Cross-Conjugated Dienones

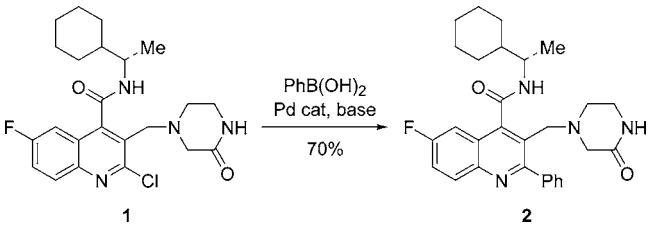
In a recent communication, Thalji and Roush present a complementary method to a traditional aldol process for the regioselective synthesis of cross-conjugated dienones via phosphine-mediated aldol cyclizations of diketones (*J. Am. Chem. Soc.* **2005**, *127*, 16778−16779). Representative starting materials were readily accessible using phosphine-catalyzed intramolecular vinylogous Morita−Baylis−Hillman cyclization of bis-α,$\beta$-unsaturated carbonyl compounds.




The authors found remarkable regioselectivity for the less stable cross-conjugated dienones **3**. In the phosphine−enone Michael adduct **5**, interaction between the phosphonium unit and the adjacent carbonyl increases the acidity of the $\beta$-phosphonium methyl ketone, which is selectively deprotonated by the alkoxide to give **3** as the only product detected by $^1$H NMR. Typical reaction conditions use 1 equiv of $PBu_3$ and $CF_3CH_2OH$ as the solvent at 60 °C. For bidifferentiated substrates containing a sterically hindered $\beta,\beta$-disubstituted enone, optimal conditions involved the use of 5 equiv of $PBu_3$ in *tert*-amyl alcohol at 80 °C. Interestingly, if the reaction is carried out under thermodynamic control ($^i$PrONa, $^i$PrOH, rt), the aldol condensation takes place with opposite selectivity to yield **4** as the main product (**3**:**4**, 18:82).

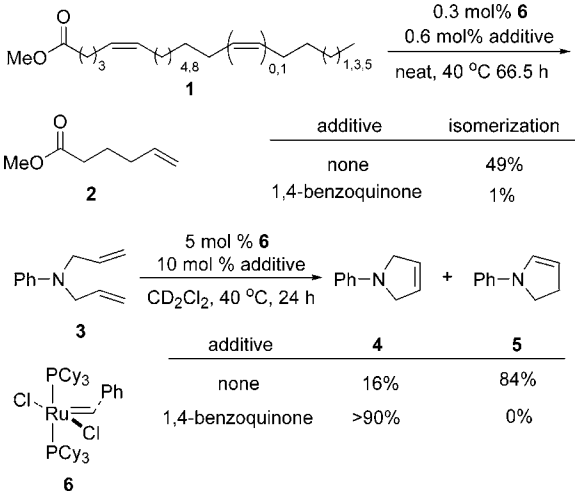
## Synthesis of 2-Phenyl Quinolines

Researchers at GlaxoSmithKline Pharmaceuticals describe the preparation of 2-phenylquinoline **2** from 2-chloroquinoline **1** in *Synth. Commun.* **2005**, *35*, 3105−3112. A priori, 2-chloroquinolines are versatile intermediates that allow the installation of the molecular diversity required for SAR studies. However, the elaborated substrate displays poor reactivity under a variety of standard Suzuki conditions for its cross-coupling with phenylboronic acid in the presence of $Pd(Ph_3)_4$ and $K_2CO_3$. The search for a better catalyst resulted in a remarkable result: pretreatment of a POPd complex with *n*-BuLi improved yields up to 70% probably due to the rapid generation of Pd(0). This observation may be of general interest for the promotion of Suzuki cross-couplings of unreactive hereroaryl chlorides.




## 1,4-Benzoquinones Prevent Isomerization During Olefin Metathesis

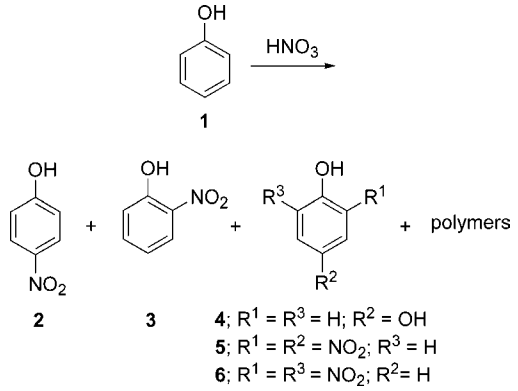
Side-products resulting from olefin migration and isomerization in olefin metathesis alter the product distribution and are difficult to remove using regular purification methods. Nobel Prize laureate Robert Grubbs and co-workers reported a mild and inexpensive method to block olefin isomerization using benzoquinones as additives (*J. Am. Chem. Soc.* **2005**, *127*, 17160−17161). Whereas radical scavengers (BHT, TEMPO) did not prevent isomerization, weak acids (AcOH, 1,4-benzoquinone) inhibited olefin migration without decreasing the catalyst activity. 1,4-Benzoquinone suppressed isomerization in the ethenolysis of seeds oils and their fatty acid esters, an industrial procedure for the synthesis of $\alpha$-olefins. Additionally, isomerization of allylic amine **3** to the corresponding enamines was minimal when the reaction was carried out in the presence of 1,4-benzoquinone. Electron-deficient benzoquinones (2-chloro, 2,6-dichloro, and tetrafluoro) were more effective. Olefin migration can be caused by ruthenium hydride species generated from the decomposition of the ruthenium metathesis catalysts. The inhibition mechanism may involve reduction of the benzoquinone to 1,4-hydroquinone by ruthenium hydrides.




## Controlled Autocatalytic Nitration of Phenol in a Microreactor

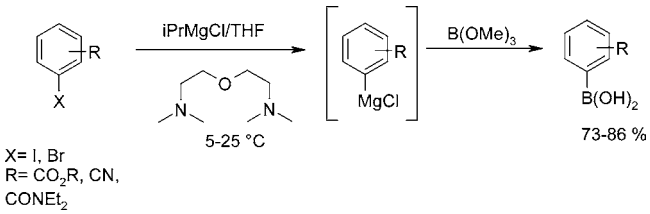
Nitrations are amongst the most hazardous industrial procedures. Their extremely exothermic behavior is critically combined with the explosive potential of many nitro compounds. Ducry and Roberge from Lonza, Ltd. chose the nitration of phenol to assess the use of microreactors in safety-compromised processes (*Angew. Chem., Int. Ed.* **2005**, *44*, 7972−7975). The reaction of phenol is autocatalyzed by nitrous acid ($HNO_2$) generated in the process. When the experiment was carried out in an RC1 calorimeter (2 equiv of $HNO_3$ added to a 23% solution of phenol in AcOH), a strongly exothermic reaction was observed (170 kJ/mol, 115 °C adiabatic temperature rise). Despite efficient cooling, the temperature rose to 55 °C. DSC analysis of the final organic phase showed an exotherm at 104 °C followed by one at 185 °C that corresponds to a thermal runaway scenario. The final mixture contained 32% of polymeric material. When the reaction was carried out in a microreactor, the phenol solution (23%) and the $HNO_3$ solution (65%) were pumped through the mixer at variable ratios with a phenol throughput of 3.7 g/min. The autocatalysis started after 1 min at 45 °C

with 1.5 equiv of $HNO_3$, while at lower temperatures it did not start, was quenched, or took place outside of the reactor. The glass microreactor also allowed the observation of gas release (presumably $N_2O_4$). The reaction produced **2** and **3** with high purity (65−78%) and yields (65−76%) and a reduced amount of polymeric side products (less than 10%). When the same set of experiments was carried out in the absence of AcOH, the batch reaction led mostly to polymeric material and 20−30% of the desired products, as a result of an exotherm that took place at 0, 10, or 20 °C. In the case of the microreactor, the reaction was performed solvent-free, with the exception of the water in the $HNO_3$ and the water required to liquefy the phenol. The autocatalysis started in the mixing zone and was easy to control. The amount of polymeric products decreased, but the formation of impurities **4**−**6** increased to 3−8%. The microreactor provided a confined volume with enhanced heat exchange and good mixing properties. The smaller volumes allowed better control of exothermic reactions, making this technology attractive ofr carrying out autocatalytic reactions on an industrial scale.



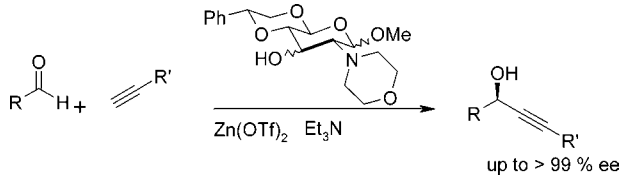

## Noncryogenic I/Br−Mg Exchange of Aromatic Halides Bearing Sensitive Functional Groups Using *i*-PrMgCl−Bis[2-(*N*,*N*-dimethylamino)ethyl] Ether Complexes

Iodo- and bromoaromatics bearing sensitive carboxylic esters and cyano groups underwent a selective halide−magnesium exchange with isopropylmagnesium chloride at ambient temperature in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl] ether to afford the corresponding Grignard reagents (Wang, X. *Org. Lett*. **2006**, *8*, 305). The newly formed reactive Grignard reagents were allowed to react with trimethylborate to afford arylboronic acids in good yields.



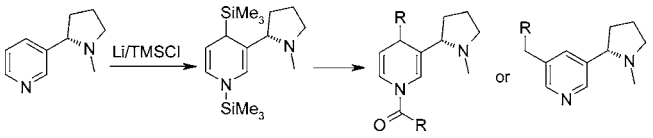

## Carbohydrate-Derived Amino-Alcohol Ligands for Asymmetric Alkynylation of Aldehydes

Conformationally restricted amino alcohols based on carbohydrate scaffolds have been shown to provide a flexible and fine-tuneable library of ligands for the Zn(OTf)2-mediated addition of alkynes to aldehydes (Davis, B. G.; et al. *Org. Lett*. **2006**, *8*, 207). The most successful ligands bearing 2-(4-morpholinyl) moieties gave in some cases very high stereoselectivities.



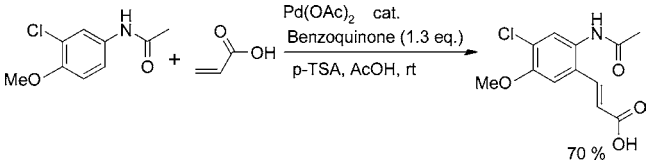

## Synthesis of Nicotine Derivatives via Reductive Disilylation of (*S*)-Nicotine

A variety of novel nicotine derivatives have been prepared via reductive disilylation of (*S*)-nicotine (Comins, D. L.; et al. *Org. Lett*. **2006**, *8*, 179). Treatment of nicotine with lithium powder and chlorotrimethylsilane affords 1,4-bis-(trimethylsilyl)-1,4-dihydronicotine in high yield. Addition of various electrophiles and a catalytic amount of TBAF provides either C-5-substituted nicotines or 1,4-dihydronicotine derivatives, depending on reaction conditions.




## Pd-Catalyzed Ortho-Selective Oxidative Coupling of Halogenated Acetanilides with Acrylates

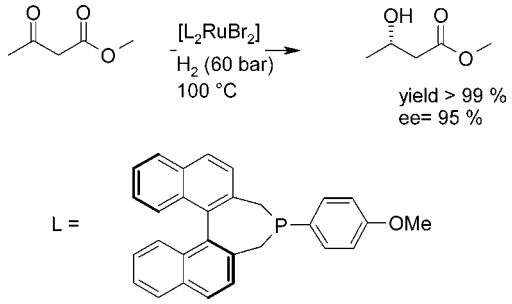
Prasad, K. et al. from the process group at Novartis (*Adv. Synth. Catal*. **2005**, *347*, 1921) have reported coupling of different halogenated acetanilides with acrylates using Pd-catalyzed ortho-selective C−H bond activation. The yields of coupled products are low to high, depending on the substrate; electron-rich arenes give higher yields than electron-poor. The presence of halogen substituents does not interfere with the activation process under the reaction conditions.




## Enantioselective Hydrogenation of $\beta$-Keto Esters using Monodentate Binaphthophosphepine Ligands

Monodentate phosphepine ligands of the general structure 1 have been synthesized and tested in the asymmetric hydrogenation of various $\beta$-keto esters (Beller, M.; et al. *Adv. Synth. Catal*. **2005**, *347*, 1978). By variation of the substituents of the aryl group on the phosphorus atom a fine-tuning of the selectivity of the catalytic system is possible. Quantitative yields and enantioselectivities up to >95% ee have been achieved with different substrates. Best selectivities were obtained with a para methoxy substituents on the phenyl

group at comparably high temperatures (100−120 °C) which reduces reaction times.

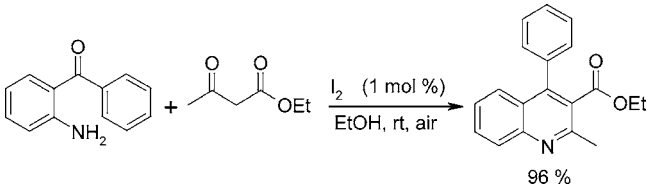



## Industrial-Scale Palladium-Catalyzed Coupling of Aryl Halides and Amines

Buchwald, S. L. et al. (*Adv. Synth. Catal.* **2006**, *348*, 23) have reviewed the palladium-catalyzed amination of aryl halides or aryl alcohol derivatives from an industrial vantage point. The article includes several large-scale applications. The synthesis of ligands, arylpiperazines, arylhydrazines, and diarylamines have been used to show how to handle issues of scale-up and safety during the use of C−N couplings as solutions for industrial-scale synthetic problems.

## Molecular Iodine: A Highly Efficient Catalyst in the Friedländer Annulation

Wu, J. et al. (*Org. Biomol. Chem.* **2006**, *4*, 126) have developed a mild and efficient route for the synthesis of quinolines and polycyclic quinolines by utilizing molecular iodine as a novel catalyst via Friedländer annulation. The method avoids the use of hazardous acids or bases and harsh reaction conditions and has a good substrate generality.




## Use of Ureas and Thioureas as Catalysts in Enantioselective Reactions

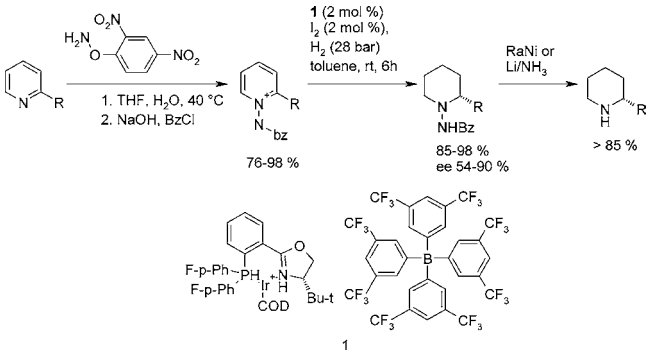
Hydrogen-bonding interaction plays a crucial role in the molecular recognition in various biologically important reactions that are mediated by enzymes. Takemoto, Y. (*Org. Biomol. Chem.* **2005**, *3*, 4299) provides an overview of a rapidly growing field utilizing urea and thiourea derivatives as organocatalysts in enantioselective reactions. These general acid catalysts hold considerable promise as cheap, stable, moisture-insensitive, and easy-to-construct alternatives to well-studied metal-based catalysts.

## Macrolactonizations in the Total Synthesis of Natural Products

Campagne, J.-M. et al. (*Chem. Rev.* **2006**, published online January 25, 2006, http://dx.doi.org/10.1021/cr0301402) have reviewed the use of macrolactonization in total synthesis of natural products. The need for macrolactonizations has inspired many clever solutions by either activation of the alcohol or activation of the acid moiety. Among future challenges will be further developments of enantio-, atrop-, and diastereoselective methods and also truly atom-economic solutions under moderate dilution conditions.

## Asymmetric Hydrogenation of Aromatic Compounds

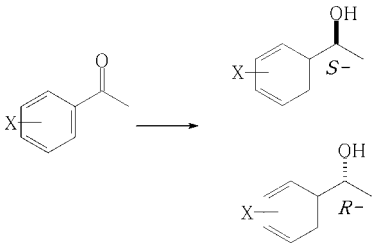
The asymmetric hydrogenation of aromatic and heteroaromatic compounds arguably presents one of the most attractive methods for the synthesis of six-membered cyclic compounds (Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171). In recent years, some promising stereoselective methods for the asymmetric hydrogenation of pyridines and related heterocycles have been reported. The developments are promising and should be stimulating for further research. However, it is especially important to point out that these methods are still rather limited in scope. Understanding of the underlying principles might eventually lead to general asymmetric hydrogenations of aromatic compounds.




## Enzymatic Reduction of Ketones

Hua and co-workers (*Tetrahedron: Asymmetry* **2005**, *16*, 1541) have been working on the enzymatic reduction of ketones. They developed, via protein engineering, a set of recombinant keto reductases and used them for a series of applications.

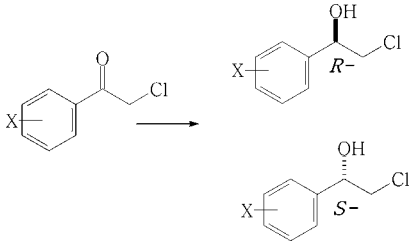
First, a group of aryl ketones was successfully tested.




In general, the *S*-enantiomer was produced in many cases in over 99% ee. Reaction rates were dependent on both enzymes and substrates. Such systems can, of course, be employed in the production of a series of APIs.

So, following these findings, this group (Hua and co-workers *Tetrahedron: Asymmetry* **2005**, *16*, 3275) applied this set of enzymes in the reduction of α-chloromethylaryl ketones. Enzyme activity was, as above, dependent on both enzyme and substrates, but at least two enzymes were shown

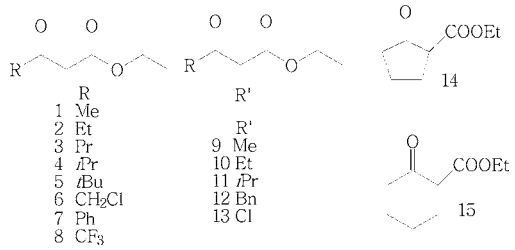
to retain their activities on going from hydrogen to chlorine as α-methyl substituent. In this case, depending of the enzyme either *S*- or *R*-enantiomer can be produced in over 95% ee's.



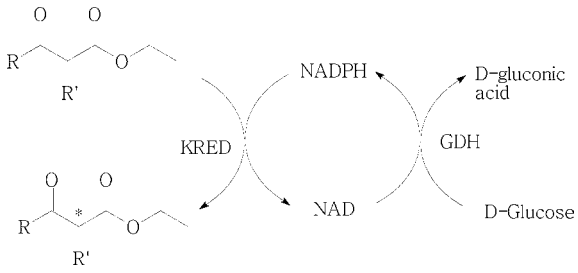

## Recombinant Ketoreductase Tool-Box

Still in this arena, Hua and co-workers (*Tetrahedron* **2006**, *62*, 901) recently published a very interesting paper on the evaluation of different ketoreductases on the reduction of *β*-keto esters.

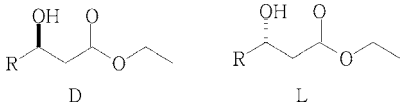
A tool-box comprising 31 recombinant ketoreductase enzymes, so-called KRED 101−131 previously developed, was tested on two sets of substrates, one set (**1**−**8**) having different substituents linked to the *β*-keto moiety and the other set (**9**−**15**) containing substituents at the α-position.




The recycle $NADP^+$ system chosen in this reaction was the oxidation to D-glucose to D-gluconic acid-catalyzed by glucose dehydrogenase (GDH).

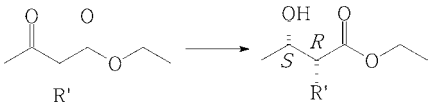



In substrates **1**−**8** either D- or L-isomers can be produced in very high ee, depending on the enzyme used.



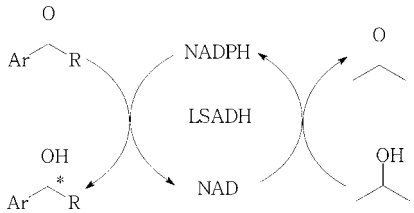

For some enzymes, activity decreased with increasing size of the substituent, while others did not show significant activity change across the series **1**−**5**. What was very interesting was the fact that enantioselectivity can dramatically change from L (96% ee) to D (99% ee) with increasing size of the substituent.

The most significant feature of these enzymes was the fact that most of them are able to lead to a single 2*R*,3*S*-enantiomer whenever α-substituted-*β*-keto esters are used.




## *Leifsonia* Alcohol Dehydrogenase (LSADH)

Inoue, Makino, and Itoh (*Tetrahedron: Asymmetry* **2005**, *16*, 2539) elegantly describe the use of the title enzyme (LSADH) in the asymmetric reduction of ketones. The principle of the use of the enzyme relies in the $NAD^+$ recycle by using 2-propanol as electron source.




Several different substrates with a wide range of structures were successfully tested with, in many cases, ee's over 99% ee. What makes this system so attractive is the fact that as 10% aqueous 2-propanol is used, substrate solubility is increased, therefore, increasing mass transfer. Many examples of related API compounds are described.

## Lipase-Catalyzed Production of (*S*)-Ketoprofen

Ketoprofen is a nonsteroidal anti-inflamatory drug. Only the *S*-enantiomer exhibits the desired activity, while the *R*-enantiomer shows undesired activities. In a recent publication, Lee et al. (*Enzyme Microb. Technol.* **2006**, *38*, 443) reported the resolution of (*R*,*S*)-ketoprofen ethyl ester using a lipase from *Acinetobacter* sp. ES-1 in aqueous or in a dispersible aqueous reaction systems. The enzyme was purified and characterized and shown to be monomeric with a molecular mass of 32 kDa. For the *N*-terminal sequence it was stated that this is a novel lipase that can be distinguishable from other lipases.

Optimum pH found was 7.0 and optimum temperature 40° C. The lipase activity was stimulated by $Ca^{2+}$ and $Mg^{2+}$. Lipase activity was inhibited by most solvents but DMSO. Using 10, 20, and 40% aqueous DMSO solutions, relative activity was 121, 92, and 40%, respectively. In MeOH and acetonitrile activity dropped only to 85 and 68%, respectively. The lower activity in aqueous organic solvents limits the scope of application of this lipase, but not to a very great extent.

This lipase was shown to be very useful in the resolution of (*R*,*S*)-ketoprofen ethyl ester. At 42% conversion 98% ee was attained in an aqueous phase system. Using 10 mM of

immiscible (*R,S*)-ketoprofen ethyl ester, reaction was nearly complete within 36 h.

### (*R,S*)-1-Phenylethanol Resolution

Also concerning the use of aqueous solvent reactions catalyzed by lipases was the work of Chua and Sarmidi (*Enzyme Microb. Technol*. **2006**, *38*, 551).

In general log *P* (the partition coefficient between octanol and water) is used as a good indicator if a given solvent is or is not suitable for biocatalysis (with lipases). In general solvents presenting log $P > 4$ are considered the best. On the other hand the content of water in a given solvent cannot be neglected and, in general, greatly affects enzyme performance.

On the basis of these considerations, the resolution of (*R,S*)-1-phenylethanol, a very good model for a wide range of APIs, was studied with two different commercial immobilized lipases (ChiroCLEC-PC, cross-linked enzyme crystals of *Pseudomonas cepacia* lipase and chirazyme L2, cf. C3, lyo, lyophilized carrier-fixed lipase B from *Candida antartica*) in different solvents. The effect of water content was studied as well.

Lauric acid was chosen as acylating agent. Enzyme activity in general increased with increasing log *P*. Isooctane (log $P = 4.5$) was shown to be the best solvent for both enzymes in terms of initial reaction rate.

Using isooctane and different water concentrations it could be verified that using over 2% (v/v) of initial water content led to a dramatic decrease in initial reaction rate since in over 0.5% water the suspended enzymes tends to aggregate. But, importantly was the fact that maximum activity for these enzymes was observed without the addition of water.

In this esterification reaction it was possible to verify that the use of molecular sieves 3.0 Å increased the performance of both enzymes, and reactions went to higher conversions. In all examples studied the enantiomeric ratio was over 200 ($E > 200$) and the (*R*)-enantiomer was selectively acylated (Suan and Sarmidi *J. Mol. Catal. B: Enzym.* **2004**, *28*, 111).

### Biotechnological Process for the Removal of Hydrogen Sulfide from Gas Streams

Before gas streams such as natural gas, synthesis gas, or biogas can be combusted, hydrogen sulfide has to be removed to prevent environmental problems caused by emission of S-compounds, corrosion of equipment, and for reasons of toxicity. Biotechnological processes can be an interesting option for this task because they generally lack some of the disadvantages of physicochemical processes (e.g., need of special catalysts, high temperature, or pressure) and can therefore be cheaper and safe. Foam formation in aqueous suspensions of biologically produced sulfur has been studied by Kleinjan et al. in a foam generator at 30 °C, with the objective of describing trends and phenomena that govern foam formation in a biotechnological hydrogen sulfide removal process. Air was bubbled through a suspension, and the development of the foam height in time is measured, showing essentially two types of foam, unstable foam of constant foam height and stable foam with a rapidly increasing foam height. The transition between these types of foam can occur when the local sulfur concentration near the surface of the liquid is higher than a critical concentration, so that a stable network structure can be formed. Sulfur particles are transported to the top of the liquid by flotation. Upon foam formation, large aggregates of sulfur fall apart into smaller fractions. Especially the larger fraction of the sulfur particles is present in the foam, indicating that these particles have the right hydrophobicity to form a network structure. Furthermore, polysulfide anions were found to have antifoaming properties in biologically produced sulfur suspensions, either because of the changing of the surface properties of the biologically produced sulfur or because of the antifoaming properties of the hydrophobic elemental sulfur formed upon the chemical oxidation of polysulfide ions. (*Colloids Surf., A* **2006**, *275*, (1−3) 36−44).

### Three-Component Distillation Using Structured Packings

Performance tests for contacting devices used in distillation are usually carried out under total reflux conditions with standard binary test systems. The mass transfer performance of packings is usually expressed as the HETP, i.e. the height equivalent to a theoretical plate or equilibrium stage. These HETP values enlarged by a safety factor are used in conjunction with the number of equilibrium stages (theoretical trays) determined from rigorous calculations as bases for determining the height of packing necessary to achieve the desired separation in practice. In case of binary mixtures there is no difficulty encountered while using this method. However, in case of nonideal three- and more component mixtures it cannot be expected that efficiencies of all components will be equal, and with this, the reliability of the conventional column-sizing approach may be undermined. Indeed, the so-called nonequilibrium modelling approach, which is fully rate-based but not practical, is more fundamental in this respect and preferred by many researches in the field. Mori and collaborators have presented experimental evidence on the performance of a structured packing in distilling three-component systems and addressed the capabilities of nonequilibrium and conventional approaches as predictive models for column performance analysis and design purposes, using the results of pilot-scale distillation experiments for validation purposes. Both two- and three-component systems are considered as well as total reflux and continuous operation. With the binary mixture, the packing performed slightly better than with a three-component mixture. Surprisingly, the continuous operation performance appeared slightly better than in case of the total reflux operation. The Delft University model predictions of the overall mass transfer efficiency appeared to be conservative enough around the operating/design point load of the packing in question. The composition profiles measured with the three-component mixture were used to validate the rate-based (nonequilibrium) model developed at the Nagoya Institute of Technology, which appeared to be highly accurate, but also sensitive to the choice of the predictive

method for the interfacial area. (*Chem. Eng. Sci.* **2006**, *61* (6), 1760−1766).

### Separation and Purification in the Food Industry

Separation and purification technology has been used elegantly in the food industry in search of ever-diversifying consumer markets. Recently, the food industries worldwide including many developing countries have evolved in attempting to seek a better utilisation of the local resources for value addition to their traditional as well as newer products. Society these days has become conscious of the diet and dietary supplements. Nutraceuticals are being introduced into the food industry and are likely to appear in the diets of modern consumers. Nutraceutical product differs from a natural foodstuff since it implies a deliberate attempt to formulate or engineer the product so that its health benefits are enhanced. Nutraceutical product requires the separation and purification of heath-promoting compounds. Many compounds have been identified as contributing to the prevention of diseases (e.g., heart disease, cancer, and osteoporosis) and/or the healthy functioning of the body. Some compounds currently regarded as being the most important are: vitamins, antioxidants, minerals (e.g., calcium and selenium), fibre, probiotics (e.g., bifidis and acidophilus), omega-3 fatty acids, phytochemicals, and proteins with specific functions. The move towards nutraceutical products has been presented as a major trend in the development of the food industry over recent years, ensuring the continued need for research and development in the area of separation and purification technology. This area of technology has played and will continue play a key role in modern society for better well-being. The entire issue of *Separation and Purification Technology* (**2006**, *48* (2), 93−213) is devoted to food processing. From the novel separation of minor but highly valuable compounds from a traditional food source, separations using the common membranes, the methods dealing with fouling and the cleaning of these membranes, separation with low-temperature processes, such as freeze concentration, to fundamental modelling of supercritical fluid extraction and air-drying processes are discussed.

### Photocatalytic Degradation of Organics in $TiO_2$-Coated Optical Fiber Reactor

$TiO_2$ heterogeneous photocatalysis has proved to be one of the most powerful techniques for remediating environmental pollution in both liquid- and gas-phase reactions. The main advantages are (i) a total destruction of organic contaminants, (ii) a complete oxidation of a wide variety of organic pollutants to $CO_2$, achieved at ambient temperature and atmospheric pressure, and (iii) the possibility of using solar energy as the UV source. The wide range of needs for environmental remediation and cleanup requires the introduction of immobilized photocatalytic systems over the heterogeneous slurry reactor design, which needs a filtration step at the end of the process. A large number of reactors using fixed $TiO_2$ have been used which has inherent disadvantages such as: (i) low light utilization due to absorption and scattering of the light by the reaction medium and (ii) mass transport limitations. The photocatalytic degradation of the fungicide fenamidone is studied by Danion and co-workers in a $TiO_2$-coated optical fiber photoreactor. Fenamidone is slowly transformed with a kinetic order of 1 and a degradation rate of 0.02 $h^{-1}$. A proposed degradation pathway of fenamidone is presented, involving mainly hydroxylation and oxidation reactions. Carboxylic acids and sulfate ions resulting from the same reaction in a powder reactor were also identified.(*Appl. Catal., B* **2006,** *62* (3−4), 274−281).

### Adaptations in Bacterial Catabolic Enzyme Activity and Community Structure in Membrane-Coupled Bioreactors

Membrane-coupled bioreactors (MBRs) offer substantial benefits compared to conventional reactor designs for biological wastewater treatment. MBR treatment efficiency, however, has not been optimized because the effects of the MBR on process microbiology are poorly understood. In this study, the structure and function of the microbial communities growing in MBRs fed simple synthetic wastewater were investigated. In four starch-fed MBRs, the bacterial community substantially increased its α-glucosidase affinity (>1000-fold), while the leucine aminopeptidase and heptanoate esterase affinities increased slightly (<40-fold) or remained relatively constant. Concomitant to these physiological adaptations, shifts in the bacterial community structure in two of the starch-fed MBRs were detected by PCR-DGGE. Four of the bacterial populations detected by PCR-DGGE were isolated and exhibited specific growth rates in batch culture ranging from 0.009 to 0.22 $h^{-1}$. The results obtained by LaPara and colleagues suggest that bacterial communities growing under increasingly stringent nutrient limitation adapt their enzyme activities primarily for the nutrients provided but that there is also a more subtle response not linked to the substrates included in the feed medium. It is demonstrated that MBRs can support relatively complex bacterial communities even on simple feed media (*J. Biotechnol.* **2006**, *121* (3), 368−380)

### Advantages of Three-Phase Reactions: Solid−Liquid-Phase Transfer Catalysis with Aqueous Omega Phase

A large number of industrially important reactions involve the use of phase transfer catalysis (PTC) under liquid−liquid conditions. The major disadvantage of L−L PTC is that the catalyst remains distributed between the two liquid phases and it cannot be recovered easily, and due to presence of water it can lead to side reactions such as hydrolysis and oxidation in substituted phenolic compounds. To overcome this problem the conversion of an L−L PTC reaction into a solid−organic liquid reaction proves to be favourable from the perspective of not only suppression of different types of side reactions but also the intensification of rates and selectivity to the desired product. The rates are enhanced

due to the increase in particle surface area by orders of magnitude in comparison to that offered in liquid−liquid dispersion. Furthermore, in a S−L PTC process, addition of a third aqueous phase in trace amounts to form the so-called omega phase ($\omega$) enhances the rates and selectivity to a great extent. The alkylation of vanillin, containing three reactive groups, with benzyl chloride is challenging and can lead to both C- and O-alkylated products, particularly when liquid−liquid (L−L) PTC is used. In the studies by Yadav and Lande, solid−liquid (S−L) PTC has been employed in the reaction of solid sodium salt of vanillin and benzyl chloride in toluene at 90 °C to make 4-benzyloxy vanillin, an ether, which is used as a perfume and also as a starting material for the synthesis of thalifoline, ephedradine as alkaloids and in synthesis of flavonoid compounds. The selectivity towards the desired product under S−L PTC is 100%. The rates of reaction are enhanced greatly by using trace quantities of water (the so-called omega phase ($\omega$)) with 100% selectivity to the ether. Efficacy of various phase transfer agents such as TBAB (tetra-*n*-butylammonium bromide), TBAHS (tetra-*n*-butylammonium hydrogen sulfate), TPAB (tetra-*n*-propylammonium bromide), TEAB (tetraethylammonium bromide), and ETPB (ethyl triphenyl phosphonium bromide) was evaluated under otherwise similar conditions at 90 °C and explained. (*J. Mol. Cat. A: Chem.* **2006**, *244* (1−2) 271−277)

## Quantitation of Polymorphs in Drug Product by Raman Spectroscopy

A Pfizer team (La Plant, F.; et al. *Am. Pharm. Rev.* **2005**, *8* (5), 88) reviews the advantages and challenges of using Raman spectroscopy to quantify polymorphs in drug product. The evaluation of Raman methodology is made in the context of the ICH Q6A guidelines, which recognize the technical difficulties associated with quantification of polymorphic changes in drug products. A brief review of various methods used in the pharmaceutical industry to quantify polymorphs is presented. In addition to calibration challenges, one of the classical difficulties against Raman is discussed: undersampling. The authors also remind us that "Raman is not a fundamental measurement the way XRD is...", and encourage the use of reliable orthogonal techniques. The authors have noticed that, quite surprisingly, multivariate analysis in the Raman context is still significantly lacking. An important advantage of Raman is the relative insensitivity to excipients and physical form of the sample. Even though this review is geared towards drug product, several sections may be very useful for the application of Raman spectroscopy to polymorph quantification in active pharmaceutical ingredients (APIs).

## Application of Attenuated Total Reflectance-Fourier Transformed Infrared (ATR-FTIR) Technique in the Monitoring and Control of Anti-Solvent Crystallization

Attenuated total reflectance-Fourier transformed infrared (ATR-FTIR) and focused-beam reflectance measurement (FBRM) methods have been used quite extensively in the monitoring and control of crystallization processes in the past decade.

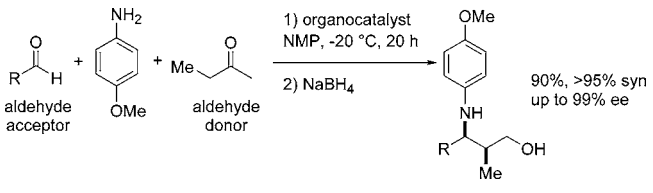
Work from the National University of Singapore and the Institute of Chemical and Engineering Sciences in Singapore (Yu, Z. Q.; et al. *Ind. Eng. Chem. Res.* **2006**, *45*, 438) addresses a specific topic in on-line crystallization monitoring: feedback supersaturation control of anti-solvent crystallization using ATR-FTIR. The case of isothermal paracetamol crystallization from acetone−water was analyzed, investigating both seeded and unseeded protocols, using ATR-FTIR and FBRM. Constant anti-solvent addition rate does not allow for simultaneous optimization of average particle size, particle size distribution coefficient of variation, and batch time. Such optimization was possible using feedback control to maintain constant supersaturation. The paper has an excellent set of 26 references, including a less quoted one, discussing the observation that square-weighted chord length distribution from FBRM may resemble conventional laser diffraction distribution.

## Modeling and Scale-Up of Mixing- and Temperature-Sensitive Chemical Reactions

Prof. Patterson (Patterson, G. *Ind. Eng. Chem. Res.* **2005**, *44*, 5325) provides another review (83 references) discussing the impact of mixing on chemical reactions. An excellent historical account of the progress in the last 40 years on this topic is provided, and numerous classical case studies are reviewed. Important progress with CFD calculations is reported as are some of the challenges of this methodology, such as the modeling of turbulence energies. The author generously allows access to a subroutine developed in his group, PAIRIN, that can be used with FLUENT or adapted to other fluid dynamic simulators. Dr. Patterson concludes, among others, that: "Scale-up will generally continue to be based on intelligent use of both experimental and simulation results".

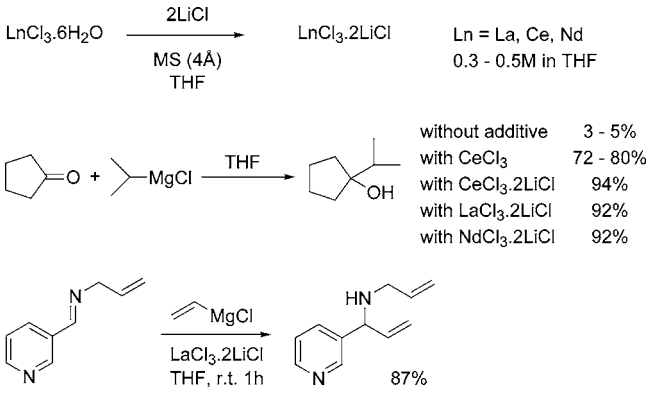
## Enantioselective Cross Mannich Reaction of Aldehydes

A short review of the asymmetric Mannich reaction has appeared (Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45* (9), 348−352). The Mannich reaction is one of the most attractive three-component coupling reactions, and in its most useful form, a free aldehyde, another aldehyde or ketone, and an amine are used. However, for the asymmetric version, sometimes prior formation of an imine is desirable, and often the amine is restricted to *p*-methoxyaniline. This short review covers new catalysts and succinctly describes the achievements over the past few years, including the use of organocatalysts. Mechanistic rationales for the syn selectivity are shown.



## Addition of Organomagnesium Reagents to Carbonyls: Use of Soluble Lanthanide Reagents to Minimise Side Products

Although the addition of Grignard reagents to aldehydes, ketones, and imines is often an excellent synthetic process, occasionally side reactions such a enolisation and reduction (via $\beta$-hydride transfer) can be problematic. The usual remedy is to use lanthanide III salts, but the activation depends on how dry the catalyst is and its solubility. The group of Knochel in Munich now reports that $LnCl_3$·2LiCl can be prepared as a solution in THF (0.3−0.5M) and these are superior promoters for the addition of various Grignard reagents to hindered and enolisable ketones (Krasovskiy, A.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 497−500).




## Direct Oxidation of Benzene to Phenol

Although phenol is one of the most important industrial chemicals (7.2 megatons per year), the three-step production process—the cumene oxidation process—runs at low conversion, and the main byproduct acetone and minor byproduct α-methylstyrene have to be found uses for.

Direct synthesis from benzene would be attractive, but most attempts, using oxidising agents such as $O_2$, $H_2O$, $N_2O$, air/Co and $O_2/H_2O$, have not been sufficiently successful for commercial use. A recent report from a mainly Japanese group (Rajaran, B.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 448−452) uses an interstitial-N/Re cluster/zeolite catalyst and achieves up to 94% selectivity to phenol, though at low conversion, at a temperature of 553 K. The oxidising agent is molecular oxygen in the presence of ammonia.

## Synthetic Approaches to New Drugs

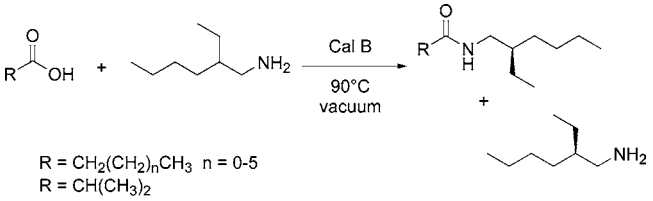
The latest review from the Pfizer group covers the drugs launched in 2004 (Li, J.; et al. *Mini-Rev. Med. Chem.* **2005**, *5*, 1133−1144) and describes the synthesis of all the small-molecule new chemical entities (NCEs). These tend to be more medicinal chemistry syntheses rather than manufacturing processes, but the authors have tried to pick up, via patents, *Org. Process Res. Dev.*, and other sources, any process information they can. In 2004 only 23 NCEs (including biologicals) and two diagnostic agents reached the market, but some were approved too late to be included in the review. The article focuses on 11 NCEs and 1 diagnostic agent and provides very interesting reading.

The drugs covered are:

azacitidine (Vidaza)
belotecan hydrochloride (Camtobell)
canacalcet hydrochloride (Sensipar, Minpara)
duloxetine hydrochloride (Cymbalta, Yentreve, Ariclaim)
erlotinib hydrochloride (Tarceva)
gadoxate disodium (Primovist)
indisetron hydrochloride (Sinseron)
mitiglinide calcium hydrate (Glufast)
pemetrexide disodium (Alimta)
pregbalin (Lyrica)
solfenacin succinate (Vesicare)
ximelagatran (Exanta)

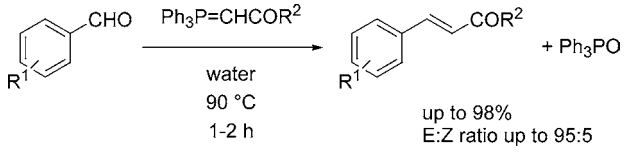
## Biocatalytic Amidation of Carboxylic Acids

An unusual paper reports the reaction of a racemic amine and a carboxylic acid to form an amide in high ee, using an enzyme catalyst but no solvent. The amine, acid, and biocatalyst (CAL-B) were heated to 90°C under vacuum to give the desired product and the unreacted enantiomer of the amine as byproduct. The "green" credentials of the process were spoiled by diluting the product with dichloromethane, filtering off the enzyme, and then using chromatography to isolate the product (Prasad, A. K.; et al. *Tetrahedron Lett.* **2005**, *46*, 4511−4514). Given the list of acids used, the liquid nature of starting materials and products (at 90°C) may be essential for this reaction to occur.




## Wittig Reactions in Water

Water has been shown to be an excellent medium in which to carry out Wittig reactions employing stabilised ylides and aldehydes, and the reactions are accelerated compared to organic solvents such as $CH_2Cl_2$ or $CH_3CN$ (Dambacher, J.; et al. *Tetrahedron Lett.* **2005**, *46*, 4473−4477).



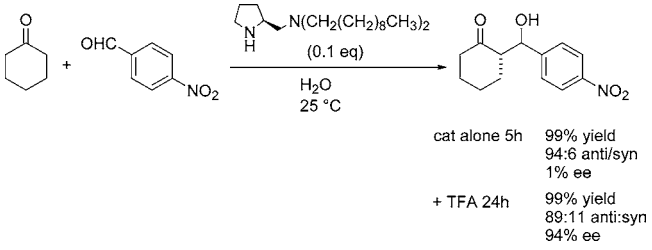
Heteroaromatic aldehydes and aliphatic aldehydes also react readily under these conditions, as do aldehydes and ylides containing protecting groups, which would be expected to reduce water solubility (TBS, troc). When the reaction is conducted in $D_2O$, deuterium is incorporated in the hydrogen attached to the α-carbon atom, adjacent to the carbonyl group.

No experimental data is given, so the difficult question of how to remove the $Ph_3PO$ from the product is not mentioned—presumably conventional techniques are used.

It would be interesting to see whether the phosphonium ylide itself could be prepared in water directly from an alkyl halide and $Ph_3P$, in the presence of base, and then reacted directly with an aldehyde.

## Organocatalysis in Water

Most organocatalytic reactions are performed in organic solvents such as DMF and DMSO. A small quantity of water in these solvents can enhance reactivity and sometimes selectivity, but a large amount of water is usually detrimental. By using organocatalysts with longer alkyl chains, however, a group of Japanese chemists in collaboration with the group of Barbas at Scripps has found that aldol reactions can be carried out in water (Mase, N.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 734−735).

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