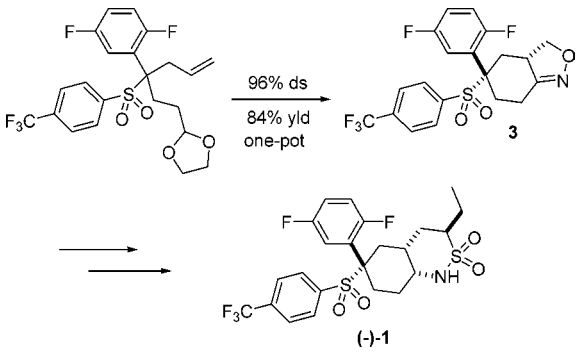
Organic Process Research & Development **2006**, *10,* 687–702

Highlights from the Literature

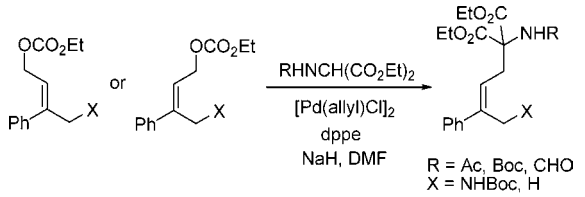
Some Items of Interest to Process R&D Chemists and Engineers

Asymmetric Synthesis of a γ-Secretase Inhibitor



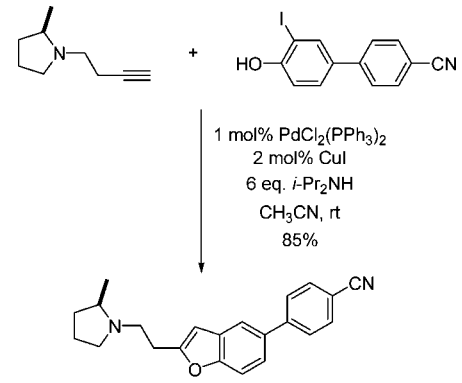
A practical asymmetric synthesis of the γ-secretase inhibitor (−)-**1** is described by Scott, Oliver, and co-workers at Merck (*J. Org. Chem.* **2006**, *71*, 3086−3092). As the key transformation, a highly diastereoselective intramolecular nitrile oxide cycloaddition forms the hexahydrobenzisoxazole core of **3** in four operations. Other aspects of the route include a highly stereoselective reduction of an isoxazole to form a *cis*-γ-amino alcohol, an efficient chemical resolution, a dianion cyclization to construct a sultam ring, and the α-alkylation of a sultam with excellent diastereoselectivity. In each instance, the relative stereochemistry was evolved by way of substrate-based induction with ≥96% ds. Kilogram quantities of the targeted drug candidate (−)-**1** were obtained, without recourse to chromatography, by way of 10 isolated intermediates and in 13% overall yield.

Controlling Olefin Geometry with Pd Catalysis



The palladium-catalyzed formation of *Z*-olefins from allylic carbonates and a variety of protected dialkyl aminomalonates is reported by Steinhuebel and co-workers at Merck (*J. Org. Chem.* **2006**, *71*, 3282−3284). Following a study of various reaction parameters (including Pd source, ligand, and solvent), the combination of $[Pd(allyl)Cl]_2$ with 1,2-bis(diphenylphosphino)ethane and NaH as base proved optimal, affording a 13:1 ratio of *Z*:*E* products in 80% assay yield. Further investigation revealed acetyl, Boc, or formyl to be suitable *N*-protecting groups. The *Z*-olefin product can be formed regardless of whether the *E*- or *Z*-allylic carbonate is used as starting material.

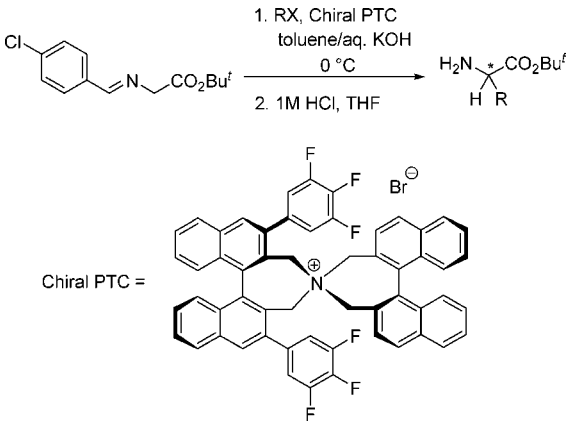
Efficient Synthesis of an H_3 Antagonist



ABT-239

An efficient process for the preparation of a potent and selective H_3 receptor antagonist, ABT-239, is reported by Ku and co-workers at Abbott (*Tetrahedron* **2006**, *62*, 4584−4589). A key step in the synthesis is the tandem Sonogashira alkynylation/cyclization reaction of 1-but-3-ynyl-2-(*R*)-methylpyrrolidine with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile to generate the benzofuran in ABT-239. Conducted as a one-pot process, in the presence of 1% $PdCl_2(PPh_3)_2$ and 6 mol % CuI, this key step proceeds at room temperature in 85% yield. A further interesting aspect of this work is the development of an effective preparation of the requisite chiral amine 2-(*R*)-methylpyrrolidine. Of particular note is the reduction of a primary iodoalkane to a methyl group under simple catalytic hydrogenation conditions. Overall, the chromatography-free process is highlighted by several simple work-up and purification procedures and is amenable to the large-scale preparation of ABT-239.

Enantioselective Monoalkylation of a Glycine Ester under Mild Phase-Transfer Conditions



The selective monoalkylation of the *p*-chlorobenzaldehyde imine of glycine *tert*-butyl ester is reported by Maruoka and

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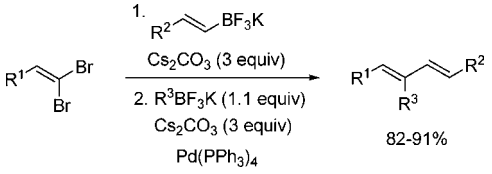
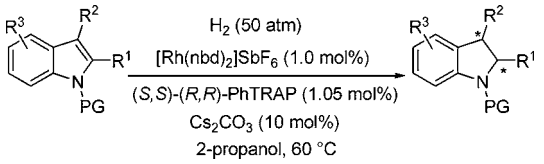
co-workers (*Tetrahedron Asymmetry* **2006**, *17*, 603−606). *p*-Chlorobenzaldehyde is less expensive than the more commonly used benzophenone; however, imines derived from the former normally lead to dialkylated products under typical phase-transfer conditions. In contrast, the binaphthyl-derived chiral quaternary ammonium bromide phase-transfer catalyst, developed in the Maruoka group, gives high chemical yields of monoalkylated products in excellent enantioselectivity under mild liquid−liquid phase-transfer conditions. The *p*-chlorobenzaldehyde can be recovered from the PTC alkylation reaction and reused. The authors comment that this methodology should be useful for the industrial production of various natural and unnatural α-amino acids.

One-Pot Synthesis of Trisubstituted Conjugated Dienes



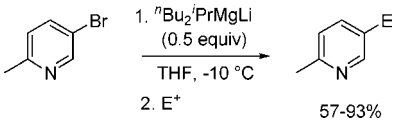
The sequential, stereoselective disubstitution of 1,1-dibromoalkenes using a variety of alkenyltrifluoroborates followed by alkyltrifluoroborates in the presence of $Pd(PPh_3)_4$ is described by Molander and co-workers (*J. Org. Chem.* **2006**, *71*, 2493−2498). This synthetic method proceeds smoothly in one pot under mild reaction conditions to provide the corresponding trisubstituted, conjugated dienes in excellent yield. Moreover, the method is operationally very simple because the organotrifluoroborates are stable in air, and the byproducts are innocuous inorganic salts. A potential drawback of this method is the use of Cs_2CO_3 as the base, although results from a previous study by the same group indicate that significantly lower yields are obtained when this base is replaced with alternative bases, both organic and inorganic.

Catalytic Asymmetric Hydrogenation of Indoles



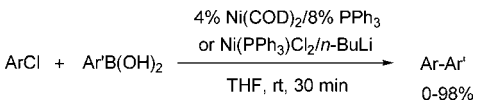
Highly enantioselective hydrogenation of *N*-protected indoles is reported by Kuwano and co-workers (*Tetrahedron: Asymmetry* **2006**, *17*, 521−535). The use of a rhodium catalyst generated in situ from $[Rh(nbd)_2]SbF_6$ and the trans-chelating chiral bisphosphine, PhTRAP, led to the target 2- and 3-substituted indolines in good yield and enantioselectivity. The use of alternative chiral ligands, such as BINAP, Chiraphos, DIOP, and DuPhos, gave very low enantioselectivity. The PhTRAP−rhodium system required catalytic amounts of base (e.g., Cs_2CO_3) to achieve high enantioselectivity. Various 2-substituted *N*-acetylindoles were converted into the corresponding chiral indolines with up to 95% ee. The hydrogenations of 3-substituted *N*-tosylindoles yielded indolines possessing a stereogenic center at the 3-position with high enantiomeric excesses (up to 98% ee). In this work, best results were obtained when the indole nitrogen atom was protected with an acetyl or tosyl group. Further work in the group is directed towards improving conditions to include the synthetically more useful Boc group (see *Org. Lett.* **2006**, *8*, 2653−2655).

Mg−Br Exchange of 5-Bromo-2-picoline under Noncryogenic Conditions



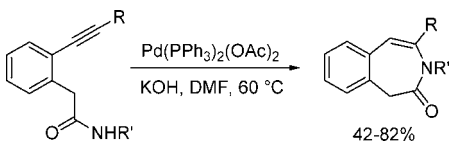
Kii, Akao, and co-workers at Banyu report on a noncryogenic method for the Mg−Br exchange of 5-bromo-2-picoline (*Tetrahedron Lett.* **2006**, *47*, 1877−1879). The organomagnesium complex *n*-Bu_2*i*-PrMgLi, readily prepared from *n*-BuLi and *i*-PrMgCl (2:1), is efficient for the bromine−magnesium exchange of 5-bromo-2-picoline at −10 °C. The prepared picolylmagnesium complex reacts smoothly with various electrophiles. The authors note that attempts to conduct Mg−Br exchange using *n*-BuLi or *i*-PrMgCl or *i*-Pr_2Mg were unsuccessful, owing to side-reactions such as deprotonation of the methyl group. The use of the *i*-PrMgCl·LiCl reagent recently reported by Knochel was apparently not tested in this case.

Ni(0)-Catalyzed Suzuki Cross-Couplings Using Aryl Chlorides



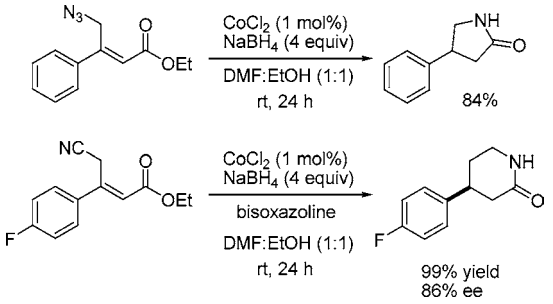
Room-temperature Ni(0)-catalyzed cross-coupling reactions of aryl chlorides with arylboronic acids using triphenylphosphine as a ligand are reported by Hu and co-workers (*J. Org. Chem.* **2006**, *71*, 2167−2169). The ability to conduct Suzuki cross-couplings with aryl chlorides using such simple catalytic systems is noteworthy since typical conditions for this reaction involve more specialized/activated catalysts. In the current study, the scope of arylboronic acids is very limited, most examples using phenylboronic acid. Nonetheless, the biaryl products are obtained in good to excellent yields. Airstable $Ni(PPh_3)_2Cl_2$ was also established as catalyst precursor; the most active nickel catalysts were obtained when the reduction of $Ni(PPh_3)_2Cl_2$ with *n*-BuLi was carried out in the presence of an aryl chloride.

Regioselective Synthesis of Benzazepinones



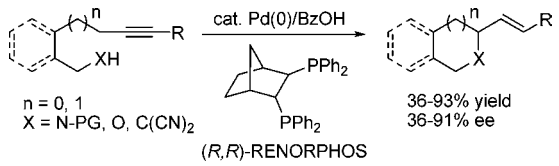
Synthesis of 3-benzazepinones by palladium-catalyzed intramolecular addition of amides to alkynes is reported by Mitchell and co-workers at Lilly (*Tetrahedron Lett.* **2006**, *47*, 3811−3814). Phenyl acetylenes substituted in the ortho position with tethered amide functionality were prepared in a few steps from readily available starting materials. It was found that 5% $Pd(OAc)_2(PPh_3)_2$ and KOH most effectively promoted cyclization. When the tethered group is an acetamide and an alkyl substituent is on the acetylene unit, regioselective 3-benzazepinone synthesis could be achieved in good yields.

Synthesis of Lactams via Reductive Cyclization



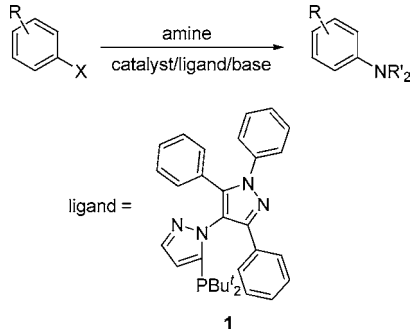
The synthesis of lactams via reductive cyclization is reported by Sudalai and co-workers (*Tetrahedron* **2006**, *62*, 4907−4916). Sodium borohydride in combination with a catalytic amount (1 mol %) of $CoCl_2$ was found to be effective for reductive cyclizations of suitably substituted azido and cyano groups of α,β-unsaturated esters to afford γ- and δ-lactams in high yields. In conjunction with bisoxazoline ligands, the process can be conducted in asymmetric fashion with decent levels of enantiocontrol. The method was demonstrated in enantioselective syntheses of (*R*)-baclofen, (*R*) rolipram, and (*R*)-4-fluorophenylpiperidinone, a key intermediate for (−)-paroxetine.

Pd-Catalyzed Asymmetric Hydroamination



A conceptually novel approach for asymmetric intramolecular hydroamination, hydroalkoxylation, and hydrocarbonation of alkynes using chiral palladium catalysts is reported by Yamamoto and co-workers (*J. Org. Chem.* **2006**, *71*, 4270−4279). The reactions of the aminoalkynes, alkynols, and alkynylmethines in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$/BzOH/RENORPHOS in benzene (or benzene−hexane) at 100 °C gave the corresponding cyclization products (nitrogen heterocycles, oxygen heterocycles, and carbocycles) in good yields with good enantioselectivities. The origins of enantioselectivities in the hydroamination reaction are discussed on the basis of DFT computations.

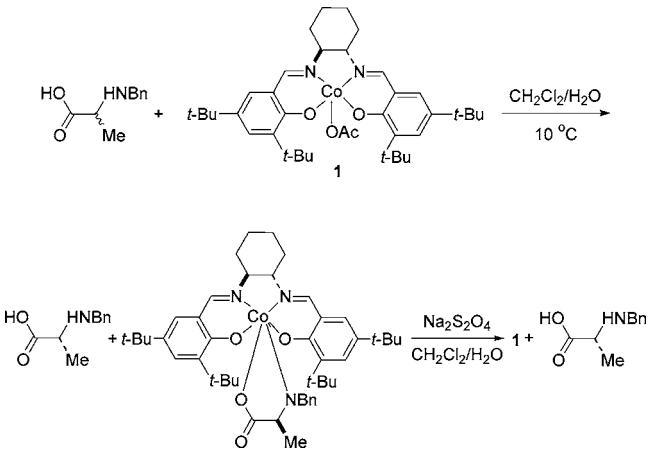
Development of Nonproprietry Phosphine Ligands for Pd-Catalyzed Amination



Over the past decade, a considerable effort has been focused on the development of new ligands for expanding the applications of Pd-catalyzed reactions. In the pharmaceutical industry, we frequently rely upon Pd-catalyzed processes for carrying out key bond formations. A number of research groups in both academia and industry have pursued the development of suitable ligands for the Pd-catalyzed amination reaction. However, the majority of this work has been patented, which often hinders freedom to operate in this area. In this regard, a new family of pyrazole and bipyrazole phosphine ligands are reported by Singer and co-workers at Pfizer (*Tetrahedron Lett.* **2006**, *47*, 3727−3731). Of several ligands prepared and screened, **1** (prepared via a high-yielding four-step route) emerged as the most compatible for amination reactions and is effective for both primary and secondary amines with typical yields of 84−99%. The authors comment that this technology is in the public domain.

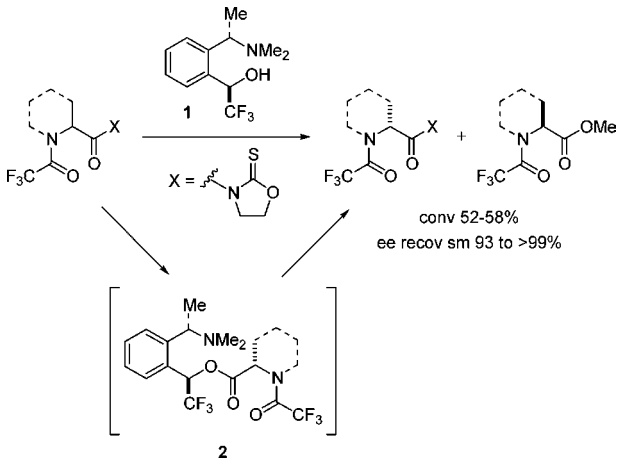
Resolution of α-Amino Acids Using Liquid−Liquid Extraction

Enantiomeric separation of hydrophilic substrates by liquid−liquid extraction involves the extraction of one enantiomer into an organic phase by selective coordination to a hydrophobic selector. Gennari, Piarulli, and co-workers recently reported the resolution of *N*-benzyl-α-amino acids in excellent yields and enantioselectivities by using the liphophilic chiral salen-cobalt (III) complex **1** (*Angew. Chem., Int. Ed.* **2006**, *45*, 2449−2453). A solution of **1** (1 equiv) in CH_2Cl_2 was stirred with an aqueous solution of *N*-benzyl-alanine (2 equiv). The complex **1**-(*R*)-*N*-Bn-Ala was isolated with 99% yield from the organic phase and characterized by ^1H NMR, ESI-MS, and IR, while the ee of the free (*S*)-amino acid was determined by HPLC (93% ee). The bound (*R*)-*N*-Bn-Ala was cleaved from the complex by treatment of the CH_2Cl_2 solution with aqueous sodium dithionite (10 equiv) and was recovered in quantitative yield with an ee that mirrored the ee of the (*S*)-enantiomer. The reduced Co(II) complex resulting from this procedure was isolated by triturating with MeOH and filtration (78% yield). The complex was reused without loss of activity or selectivity following oxidation with air in the presence of AcOH.



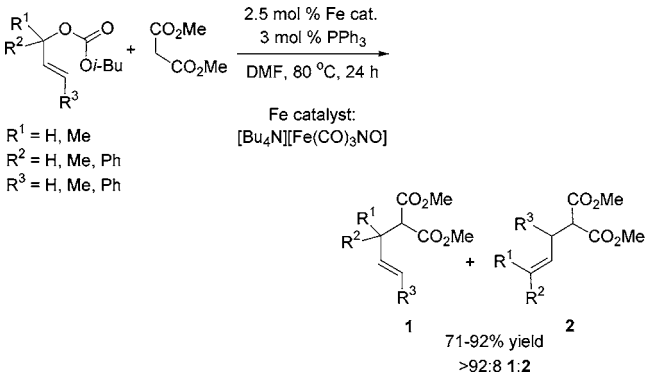
Catalytic Kinetic Resolution of α-Amino Acid Derivatives

Notte and Sammakia described the use of (α-acetoxy)-oxazolidinethione (**1**) as the catalyst for the kinetic resolution of *N*-trifluoroacetyl-protected α-amino acids (*J. Am. Chem. Soc.* **2006**, *128*, 4230−4231). Following the activation of the carboxylic acid as the oxazolidinethione imide, its reaction with 5−10% catalyst and 30 equiv of MeOH in toluene provides the recovered starting material in ee's > 93%. The kinetic resolution affords excellent selectivities for both cyclic and acyclic amino acids, and the preparation of the catalyst is simple. Importantly, the recovered and already activated α-amino acids can be used directly as substrates in peptide-coupling reactions using standard conditions (DIPEA/HOBt). Mechanistic studies support the existence of an acyl-catalyst intermediate (**2**) that undergoes methanolysis in the turnover-limiting step. Most probably, the hydroxy group of the catalyst attacks the activated α-amino acid in a selectivity-determining step, assisted by the benzylic amine.

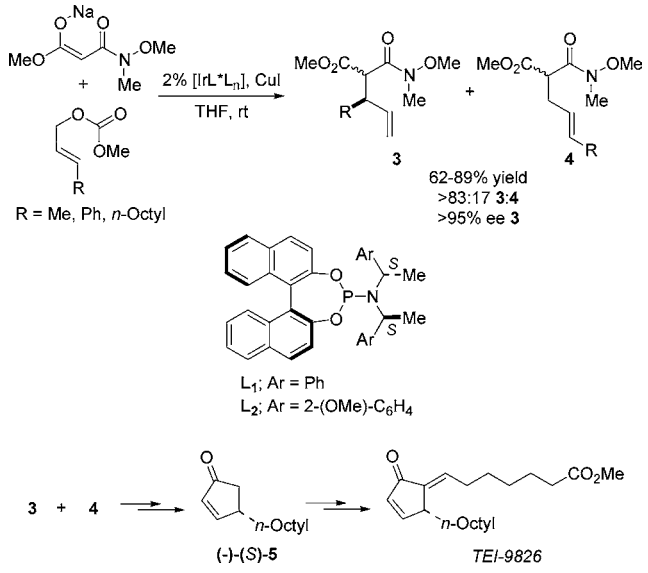


Allylic Alkylation Reactions

Plietker reported the regioselective iron-catalyzed allylation of *β*-diesters and related compounds using allyl carbonates (*Angew. Chem., Int. Ed.* **2006**, *45*, 1469−1473). The need of a toxic CO atmosphere to suppress deactivation of the catalyst was circumvented by using PPh_3 as an additive. In addition, no deprotonation of the nucleophile was required, allowing a salt-free procedure. In the optimized conditions (1 mol/L, DMF 80 °C, 2.5% **2**), reaction of a variety of allyl isobutyl carbonates with the pronucleophile—typically malonic esters, but also *β*-ketoesters or malonitriles—afforded the desired product in 71−92% yield and a ratio favoring branched products **3** (98:2 to 87:13**)**. Substitution on the allyl carbonate led to longer reaction times and lower yields (53−78%) but had no effect on the regioselectivity. The fact that the new C−C bond is formed on the atom bearing the leaving group in the reactants rules out an η^3-allyl intermediate. The author proposes a double S_N2' addition both of the metal and the nucleophile to account for the selectivity observed.

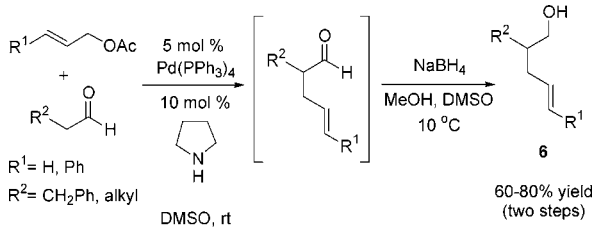


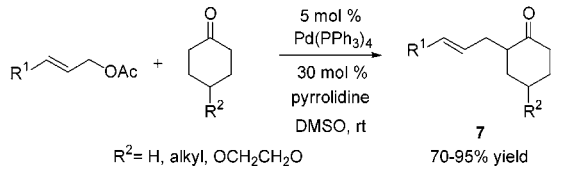
Enolates of malonic esters are common nucleophiles for allylic alkylations catalyzed by transition metals. Recently, Schelwies, Dübon, and Helmchen reported that the enolate of the Weinreb amide **3** gives reactivities and selectivities that are similar to those of the analogous malonates (*Angew. Chem., Int. Ed.* **2006**, *45*, 2466−2469). The catalyst for the allylic alkylation was prepared by reaction of $[\{Ir(Cod)Cl\}_2]$ with the phosphorus amidite ligands introduced by Feringa and Alexakis (*Acc. Chem. Res.* **2000**, *33*, 346−353; *Org. Lett.* **2005**, *7*, 1621−1624). The conversion was complete in a few hours, and the products were obtained as 1:1 mixtures of diastereomers. Using a three-step sequence, the authors converted directly the mixtures of **3** and **4** into 4- and 2,4- substituted cyclopentenones in 50% overall yield.



A prostaglandin analogue active against cisplatin-resistant tumors (TEI-9826) was readily prepared from cyclopentenone (*S*)-**5**.

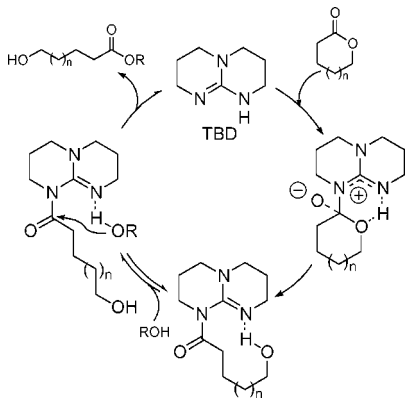
Yet another example of allylic alkylations is presented by Ibrahem and Cordova by merging transition-metal and enamine catalysis (*Angew. Chem., Int. Ed.* **2006**, *45*, 1952−1956). In this case, the reaction substrates were aldehydes or cyclic ketones. The strategy enables simultaneous electrophilic and nucleophilic activation: the catalytic enamine formed in situ by reaction of the carbonyl compound with a secondary amine reacts with the catalytic palladium π-allyl species. Reductive elimination and hydrolysis of the enamine regenerate Pd(0) and amine catalysts, respectively, to yield the α-allyl alkylated products in good yields after purification (70−95%). The aldehydes were reduced with excess $NaBH_4$ to give the corresponding alcohols. General conditions involve the use of pyrrolidine (10−30 mol %) and $Pd(PPh_3)_4$ (5 mol %) in DMSO at room temperature. When substituted acetates (i.e., cinnamates) were used as the alkylating agents, the reaction took place exclusively at the nonsubstituted carbon of the allyl complex.





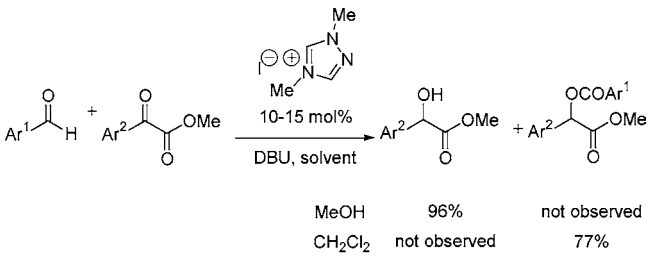
Triazabicyclodecene as an Acyl Transfer Organocatalyst

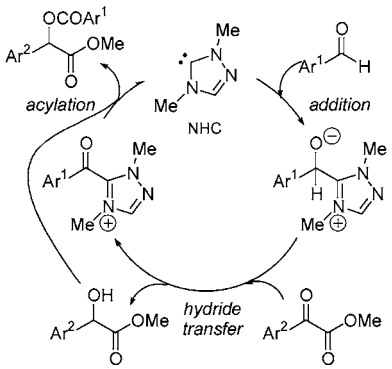
In a collaborative work between industry and academia, groups at IBM and Stanford University investigated the catalytic activity of commercially available guanidine triazabicyclodecene (TBD) in transesterification reactions and ring-opening polymerizations (*J. Am. Chem. Soc.* **2006**, *128*, 4556−4557). TBD catalyzes the ring-opening polymerizations of L-lactide and δ-valerolactone with catalyst loadings of 0.1−0.5% relative to monomer. The desired polymers were obtained in minutes, with conversions >90%, narrow polydispersities, and controllable molecular weights. Studies on the transesterification of vinyl acetate with benzyl alcohol revealed that TBD mediates the acyl transfer by undergoing acylation to give an intermediate *N*-acetyl TBD. Mechanistic considerations suggest that TBD simultaneously activates both the carbonyl of the monomer by nucleophilic attack and the initiator alcohol through hydrogen bonding. As an organocatalyst, TBD challenges the activity of the most active ring-opening polymerization metal catalysts known to date.



Heterocyclic Carbenes as Organocatalysts

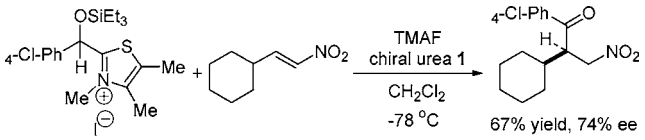
The research program of K. A. Scheidt at Northwestern University is making admirable progress towards the development of new catalytic strategies based on the use of carbonyl anions—*umpolung* species—generated by the interaction of *N*-heterocyclic carbenes (NHCs) with aldehydes. For example, the treatment of an aromatic α-keto ester with 10−15 mol % of a triazolium salt and DBU in the presence of benzaldehyde in MeOH as solvent affords the corresponding hydroxy esters in good yields. Remarkably, the use of dichloromethane as solvent results in acylation of the intermediate hydroxy esters. Overall, this second transformation constitutes a hydroacylation of the activated ketone. Labeling experiments support the mechanism depicted below and indicate that the reduction and acylation steps are independent even though the same NHC catalyst is responsible for the two key transformations. Mechanistic nuances and the scope of the reaction are detailed in the original communication: *J. Am. Chem. Soc.* **2006**, *128*, 4558−4559.

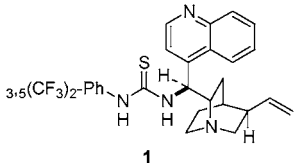




Scheidt and co-workers employed a related thiazolium NHC to promote the nucleophilic acylation of nitroalkenes (*J. Am. Chem. Soc.* **2006**, *128*, 4932−4933). In this case, the carbonyl anion equivalent was generated stoichiomet-

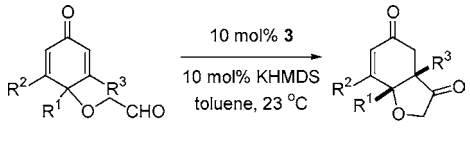
rically by addition of a fluoride source (e.g,. tetramethylammonium fluoride, TMAF) to an aromatic silylated thiazolium carbinol. This species undergoes addition to a variety of nitroalkenes in the presence of commercially available thiocarbanilide, $(PhNH)_2CS$, as an additive. The scope of this transformation is general, and even quaternary centers can be generated by conjugate addition to β,β-disubstituted nitroalkenes. Preliminary investigations indicate that the use of a chiral thiourea derived from quinine (i.e., **1**) can afford β-nitro ketones in a stereoselective fashion and suggest the existence of a crucial interaction between the nitroalkene and the urea during the carbonyl addition.





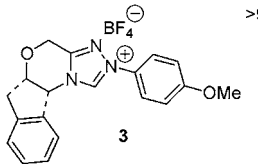
1

Liu and Rovis (Colorado State University) exploit the concept of reactivity umpolung to achieve the asymmetric synthesis of hydrobenzofuranones via desymmetrization of cyclohexadienones using the intramolecular Stetter reaction, the nucleophile-catalyzed addition of an aldehyde to a Michael acceptor (*J. Am. Chem. Soc.* **2006**, *128*, 2552−2553). In a representative experiment, the treatment of a dienone aldehyde (**2**) with 10 mol % of chiral triazolium salt **3** and 10 mol % KHMDS leads to the desired hexahydrobenzofuranones in excellent yields and enantioselectivities. When applied to polysubstituted cyclohexanediones, the conjugate addition generates quaternary and contiguous stereocenters with superb stereoselectivities.



2

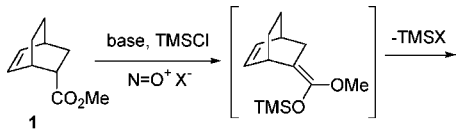
60-94% yield
82-99% ee
>95:5 dr



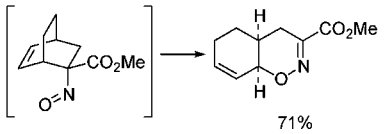
3

Synthesis of Oxazines via a 1,2-Oxaza-Cope Rearrangement

For the synthesis of oxazines, Zakarian and Lu reported a concise method based on a new hetero-Cope rearrangement involving a nitroso group (*J. Am. Chem. Soc.* **2006**, *128*, 5356−5357). Although oxazines are heterocycles present in bioactive natural products and substrates susceptible of further synthetic manipulation, the existing methods for their synthesis are limited. The one-pot sequence starts with the nitrosation of the silyl ketene acetal of a Diels−Alder adduct (e.g., **1**) with $TiCl_4$/isoamyl nitrite in the presence of a substoichiometric amount of base (i.e., 2,6-di-*tert*-butyl-4-methylpyridine) to prevent cleavage of the silyl ketene. This process occurs readily at low temperatures to generate an intermediate nitroso ester that undergoes a [3,3]-sigmatropic rearrangement. Isolated yields range between 50 and 80% for the complete stereoselective transformation.



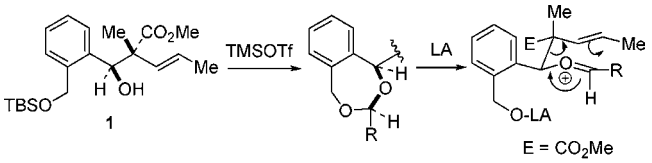
1

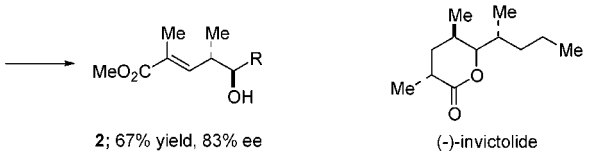


71%

Synthesis of Bispropionates via Oxonia-Cope Rearrangements

Polypropionates (e.g., **2**) are ubiquitous substructures in natural products with interesting biological activities. Chen and McDonald report an ingenious entry to these moieties using a stereospecific 2-oxonia-[3,3]-sigmatropic rearrangement (*J. Am. Chem. Soc.* **2006**, *128*, 4568). Readily available alcohol **1** undergoes stereospecific propionate transfer to a variety of aldehydes in the presence of 10 mol % TMSOTf, 0.6 equiv $SnCl_4$, and 2 equiv Ag_2CO_3. Typically, yields and stereoselectivities are high, and the use of chiral aldehydes affords good diastereoselectivities. The reaction sequence involves the initial formation of a cyclic acetal followed by Lewis acid-promoted allylic rearrangement. The authors illustrate the power of this transformation with a short synthesis of (−)-invictolide, a component of the recognition pheromone of the imported red fire ant queen (*Solenopsis invicta*).

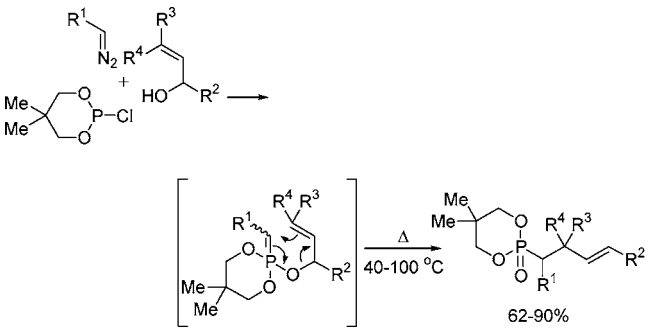




[3,3]-Rearrangements of Phosphonium Ylides

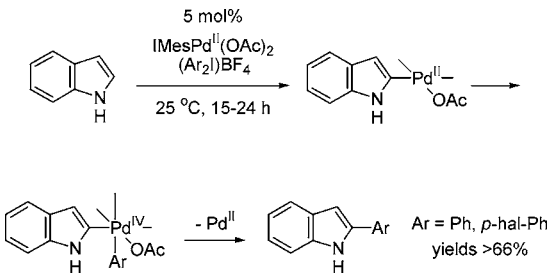
Mapp and co-workers at the University of Michigan explored the synthesis of phosphonates via [3,3]-sigmatropic rearrangements of phosphonium ylides (*J. Am. Chem. Soc.* **2006**, *128*, 4576−4577). The reaction provides phosphonates with a variety of α-and β-substituents through a process that involves the concomitant construction of new C−C and P═O bonds. The ylide intermediates are prepared under mild conditions in a multicomponent sequence. Thus, activated

phosphorus(III) species, phosphines and phosphites, react with a 3-buten-2-ol derivative in the presence of carbenes that are generated by treatment of ethyl diazoacetate with 1 mol % of iron(III) complex ClFeTPP. Using secondary alcohols as reactants (R^2 = alkyl) affords products with only *E* configuration on the olefin. Interestingly, the resulting phosphonates can be transformed into 1,4-dienes by Horner−Wadsworth−Emmons olefination, or can be submitted to amination to provide α-aminophosphonic esters of pharmaceutical interest.



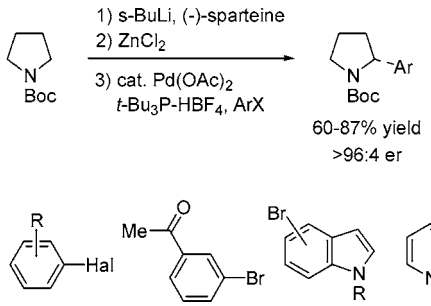
Pd-Catalyzed 2-Arylation of Indoles

The development of a mild methodology for the direct arylation of the 2-position of unprotected indoles has been an elusive task for many years. Typical limitations of the existing methods are the requirement of strong bases, eroded selectivities due to the nucleophilicity at the 3-position, moderate scope, and limited functional group tolerance. The group of Sanford at the University of Michigan reported a new approach based on $Pd^{II/IV}$ catalysis that successfully affords 2-arylindoles in high yields at room temperature (*J. Am. Chem. Soc.* **2006**, *128*, 4972−4973). The use of an electron-deficient Pd^{II} catalyst (e.g., $IMesPd(OAc)_2$, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) is the key to afford a σ-indole Pd^{II} complex that undergoes subsequent oxidative arylation with a I^{III} reagent (e.g., $(Ar-I-Ar)BF_4$) via an intermediate Pd^{IV} species. A variety of arylating reagents can be prepared in situ by reaction of $ArI(OAc)_2$ with commercially available arylboronic acids. The successful extension to the arylation of pyrrole derivatives under analogous conditions demonstrates the wide scope of this transformation.



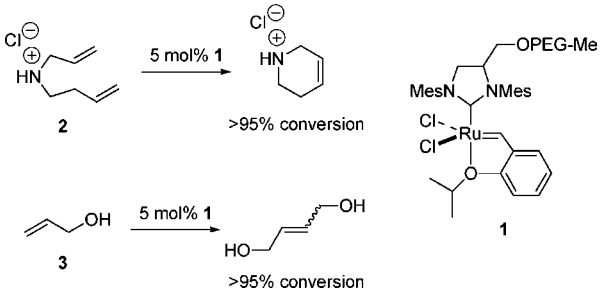
Pd-Catalyzed α-Arylation of *N*-Boc-pyrrolidine

Campos and co-workers in the process research group at Merck Research Laboratories (Rahway, NJ) developed a novel enantioselective arylation of *N*-Boc pyrrolidine. The transformation is of major interest to pharmaceutical chemists since 2-arylpyrrolidines are privileged structures that promote molecular binding to a variety of disparate receptors. 2-Arylpyrrolidines were obtained in high yields and enantiomeric ratios by asymmetric deprotonation of *N*-Boc-pyrrolidine with *s*-BuLi/(−)-sparteine, followed by transmetalation with substoichiometric amounts of $ZnCl_2$ and subsequent Pd-catalyzed Negishi coupling with a variety of aryl bromides (*J. Am. Chem. Soc.* **2006**, *128*, 3538−3539).



Highly Active Water-Soluble Olefin Metathesis Catalyst

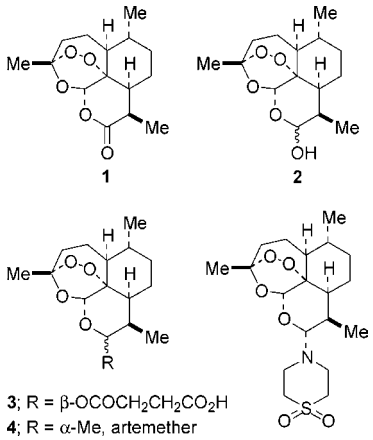
Among the many problems to be solved in the field of aqueous organometallic chemistry, the discovery of water-soluble catalysts that are highly active and stable in water is still prominent. Hong and Grubbs describe the synthesis and applications of a water-soluble metathesis catalyst (**1**) that shows unprecedented activity in ROMP, RCM, and CM in aqueous media (*J. Am. Chem. Soc.* **2006**, *128*, 3508−3509). The strategy for the solubilization of catalyst **1** involves the attachment of poly(ethylene glycol) (PEG) to the nondissociating *N*-heterocyclic carbene portion of the original 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (H_2IMes) ligand. Catalyst **1** is soluble in water, as well as in dichloromethane and toluene. Moreover, structural studies in solution indicate that it may form micelle aggregates in water due to the hydrophilic nature of the PEG chain and the hydrophobic character of the Ru center. Interestingly, **1** shows unprecedented RCM activity with water-soluble α,γ-dienes (i.e., **2**) affording five- and six-membered rings in high yields. Moreover, homogeneous CM of allyl alcohol (**3**) using **1** resulted in excellent yields of homodimerization.



Antimalarial Drugs

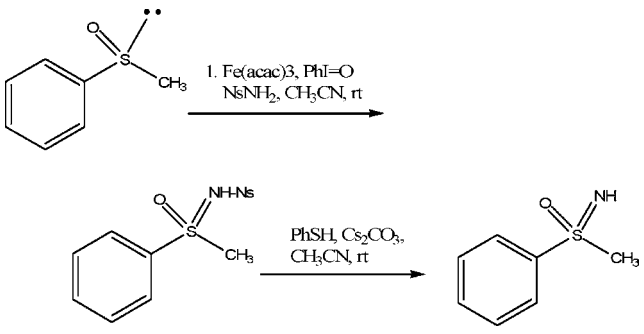
Artemisinin (**1**), the active compound isolated from the herb *Artemisia annua*, is the parent drug of the arteminsins family, the most potent antimalarial drugs. Its ester derivatives **3**−**5** are quickly metabolized in vivo to the less active dihydroartemisin **2**, and large doses of **4** are administered in conjunction with other drugs (i.e., lumifantrine) to increase their half-life. Roughly, 120 tons of **1** are required annually to prepare enough **4** to treat the 120 million patients infected

with the disease. With the objective of finding a more potent derivative with suitable pharmacokinetic properties, Hayneas and co-workers reported the synthesis and evaluation of artemisinin derivatives prepared from **5** (*Angew. Chem., Int. Ed.* **2006**, *45*, 2082−2088). Desirable characteristics for the compound were: (1) slow metabolism and excretion; (2) low lipophilicity, as this property is associated with the neurotoxicity of artemisinines; and (3) production cost comparable to the cost of **2**−**4**, which are prepared in three steps from **5** (60−65% yield). Reactions were carried out in multigram or multikilogram scale, and the products were isolated by crystallization as air-stable, enantiomerically pure, crystalline solids. After a thorough pharmacological evaluation, artemisone (**6**) emerged as the potential clinical candidate. Derivative **6** showed higher activity against *Plasmodium falciparum* than chloroquine and artesunate, and the neurotoxic activity and pharmacokinetic properties were adequate for a drug candidate. In the current synthesis, artemisinone is obtained from artemisinin in three steps. Process chemists should seize the moment to look for ways to make this endoperoxide in a safe manner.



Synthesis of Sulfoximines and Sulfilimines

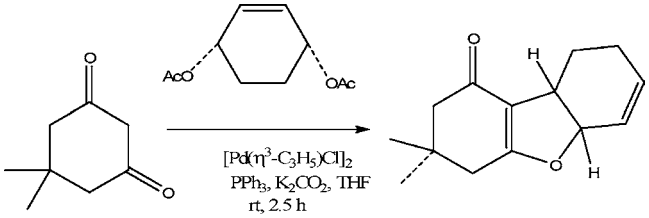
Although sulfoximines and sulfilimines have gained importance in medicinal chemistry, convenient synthetic methods for these compounds have not been well developed. While variety of N-protected sulfoximines and sulfilimines can be prepared, removal of protecting groups on the nitrogen is still a problem. Mancheno and Bolm reported a practical procedure for synthesis of these compounds from sulfoxides and sulfides with the help of iron catalyst, *N*-nosylamide ($NsNH_2$) and an oxidizing agent such as iodosylbenzene (Mancheno, O. G.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349−2352).



The sulfides are more reactive than sulfoxides, giving sulfilimines preferentially. Interestingly sulfoxides retain their stereochemistry in the formation of sulfoximines. Aliphatic and aromatic sulfides and sulfoxides are equally reactive. The *N*-protecting group (nosyl) can easily be removed with the reaction of thiopenol to generate free NH sulfoximines.

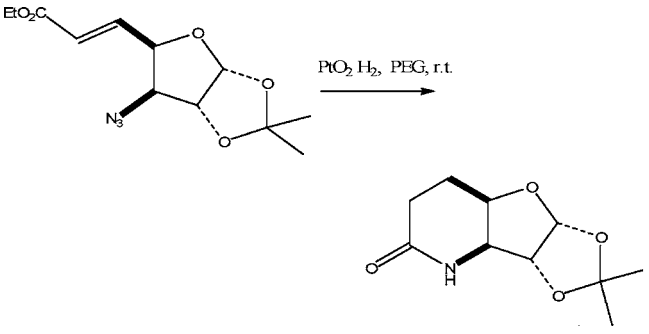
Functionalized Furan Derivatives

In addition to being natural products, furans and fused aryl and hetereroaryl furans are know to have important biological activities. Usually such compounds are synthesized by multistep synthetic schemes. Tanimori et al devised a scheme that utilizes a sequential C−C and C−O bond formation mediated by palladium-phosphine catalyst. (Tanimori, S.; Kato, Y.; Kirihata, M. *Synthesis* **2006**, *5*, 865−869) Interesting mono-, di-, and tri-cyclic furans are prepared in moderate yields. Assembling complex structures is relatively easy by using this method; therefore, it should be useful in medicinal chemistry, for example, to generate compound libraries.



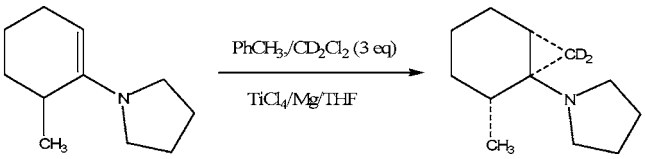
Catalytic Hydrogenations with Platinum Oxides in Polyethylene Glycol 400 (PEG)

PEG has been found to be a superior solvent for a variety of metal-catalyzed reductions and coupling reactions, over traditional solvents as well as not so traditional solvents such as ionic liquids and fluorous solvents. PEG, due to its immiscibility with organic solvents, not only extracts reaction products conveniently but is also recyclable. Chandrasekhar et al (Chandrasekhar, S.; Prakash, S. J.; Rao, C. L. *J. Org. Chem.* **2006**, *77*, 2196−2199) hydrogenated isolated double bonds as well as α,*β* unsaturated -ketones and -esters with PtO_2 with hydrogen in PEG at room temperature at atmospheric pressure. The recyclability of both PEG and catalyst was demonstrated for 10 runs, and no cross contamination was found despite changes in the substrate for four times. Selective reduction can be observed with electron-deficient olefins over that of N−Bz groups. Nitro groups can also be reduced with this system.



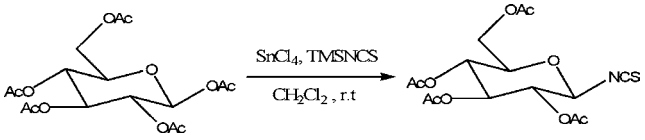
Cyclopropanation of Enamines

Cyclopropanation of olefins with copper or zinc catalysts is a practical process, whereas cyclopropanation of enamines is not. Yan et al (Tsai, C.-C.; Hsieh, I.-L.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2261−2263) accomplished cyclopropanation of enamines with $TiCl_4$−Mg bimetallic complex in CH_2Cl_2. This process appears to proceed via an electrophilic Fischer-type carbene complex. In this reaction 15 mol % of $TiCl_4$ is needed to get the best yield unlike other metals which are required in quantities of one or more equivalents. This reaction exhibits stereo- and chemoselective cyclopropanation with enamines in the presence of isolated double bonds. THF is the preferred solvent. Steric hindrance at the α-position of enamine does not inhibit the reaction and provides a methylene group syn to the α-substitution. This reaction, due to its simplicity and inexpensive nature, should find application in large-scale synthesis.



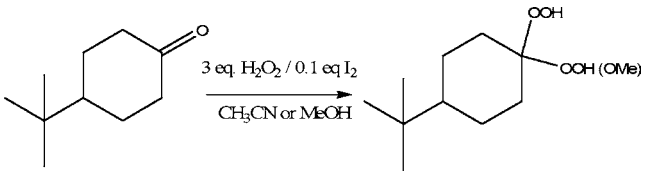
Preparation of Glycosyl Isothiocyanates

Sugar isothiocyanates are very important intermediates for protein ligation and other biochemical reactions. Although isothiocyantes are prepared by a variety of methods, usually they require two or more steps (via bromides). Kune et al. (Kuhne, M.; Guorgydeak, Z.; Lindhorst, T. K. *Synthesis* **2006**, *6*, 949−951) developed a method which utilizes peracetylated sugar derivatives and tin tetrachloride and TMS isothiocyanate at room temperature. Interestingly sugar bromides give opposite (α) anomeric isothiocyanates.



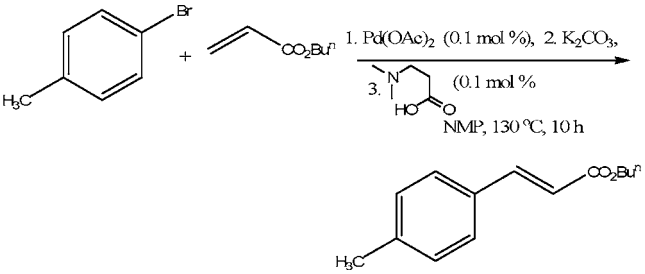
Conversion of Ketones to *gem*-Dihydroperoxides

In recent years, organic peroxides as antimalarial drugs have received particular attention. Most of these compounds are synthesized via dihyroperoxides as intermediates. Current synthetic methods for hydroperoxides involve ozonolysis. Iskra et al (Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett.* **2006**, *8*, 2491−2494) developed selective dihydroperoxidation of ketones with aqueous hydrogen peroxide in the presence of a catalytic amount of iodine. Yields are generally high. Acetonitrile is the preferred solvent. Where solubility problems arise with ketones, the corresponding dimethoxy ketals can be used. Cyclic and acyclic ketones react equally well, giving high yields. Interestingly aromatic aldehydes can also be converted into the corresponding *gem*-dihydroperoxides, but yields are dependent on the electronic nature of the substituents.



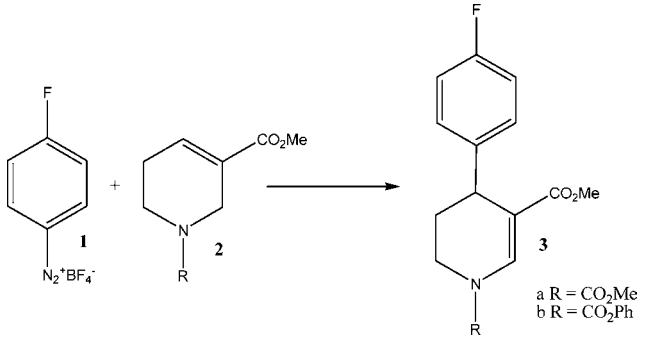
Inexpensive and Efficient Ligands for Heck Reaction

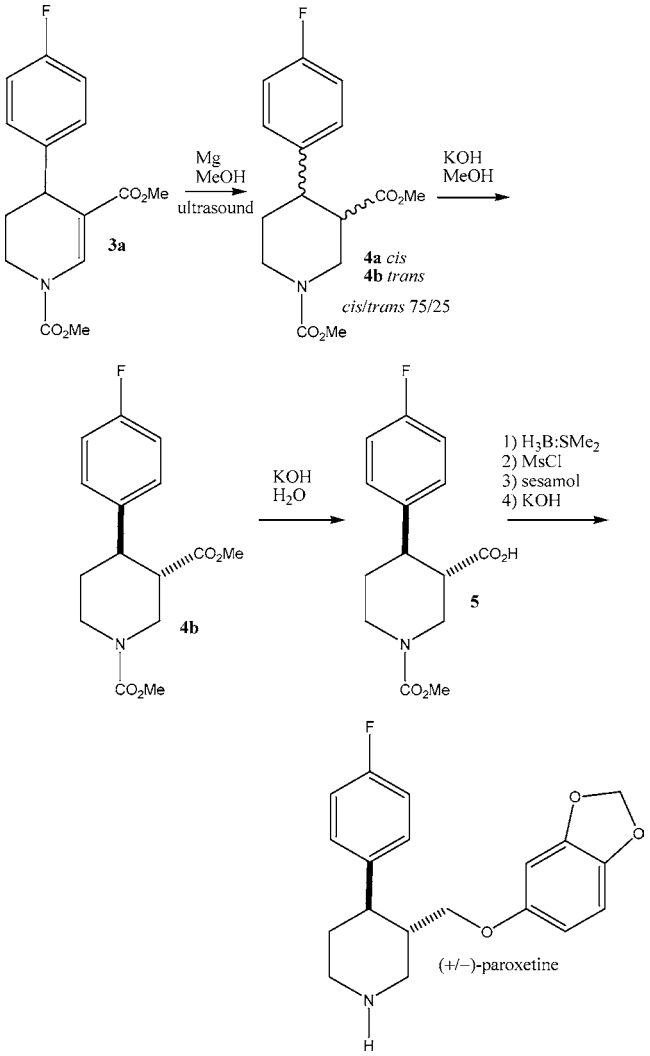
The palladium-catalyzed cross-coupling of olefins with aryl halides normally requires phosphine ligands. This highly useful synthetic process is plagued by contamination of phosphine impurities in finished products. This limits the application of Heck reactions in the pharmaceutical industry. Liu, Guo, and co-workers developed phosphine-free ligands, *N*,*O*-bidentate ligands, e.g., *N*,*N*-dimethyl-*β*-alanine, which provide high turnover of expensive catalyst. (Cui, X.; Li, Z.; Tao, C.-Z.; Xu, Y.; Li, J.; Liu, L.; Guo, Q.-X. *Org. Lett.* **2006**, *8*, 2467−2470). Cross-coupling with a variety of Heck-type olefins required only 0.1 mol % of palladium to give very high yields. In this reaction aryl chlorides are not active unless the aryl groups are activated with electron-withdrawing substituents. Nevertheless, these ligands have potential advantages, such as chemical stability and low cost, to be useful in industrial processes.



(±)-Paroxetine via Heck Reaction

There is a continuous search for cheaper and more efficient processes to produce APIs. In this arena Pastre and Correia (*Org. Lett.* **2006**, *8*, 1657) recently described an elegant protocol to produce (±)-paroxetine involving the Heck reaction between the aryldiazonium salt **1** and piperidine **2**. Final steps involved magnesium reduction, isomerization, reduction, mesylation, and S_N2 displacement with sesamol.

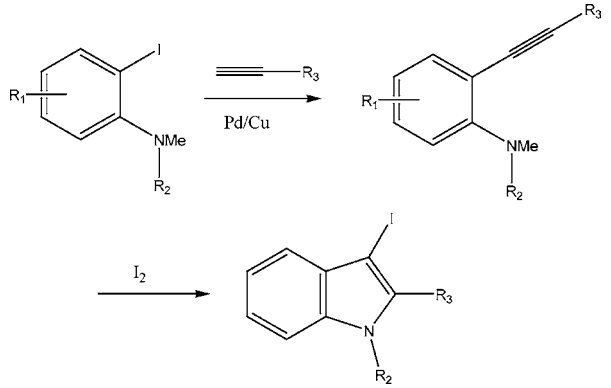




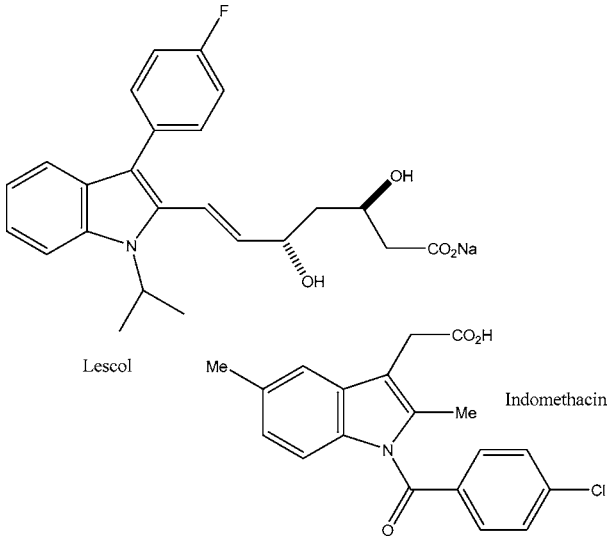
What is very encouraging about the enantioselective process is that the carboxymethyl intermediate (±)-**4b** is suitable to be submitted to resolution with lipases.

Indol Syntheses

Yue, Yao, and Larock (*J. Org. Chem.* **2006**, *71*, 62) developed a straightforward process for the production of (2-substituted)-3-iodoindoles.

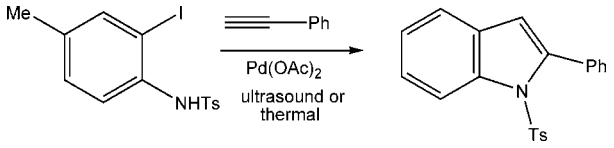


The process involves a Sonogashira coupling of appropriate acetylene followed by iodine-mediated cyclization. These (2-substituted)-3-iodoindoles are useful intermediates for a series of biologically relevant compounds such as lescol and indomethacin.



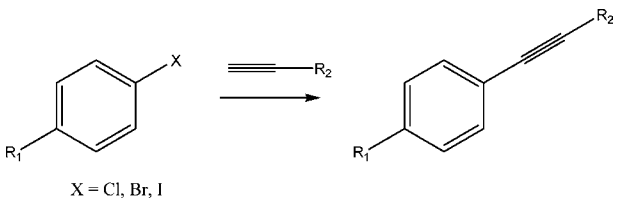
The production of 2-substituted-indoles by a similar protocol was disclosed by Srinivasan's group (*Tetrahedron* **2006**, *62*, 5109).

So a Sonogashira-type coupling followed by a C−N coupling catalyzed by $Pd(OAc)_2$ allows the production of the derived 2-substituted-indoles.



Sonogashira Coupling under Ultrasound

Still in Sonogashira coupling Srinivasan's group have earlier reported encouraging results on a ligand-free Sonogashira reaction catalyzed by Pd(0) nanoparticles under ultrasound irradiation in ionic liquids (or acetone). The noninnocent behavior of ionic liquids was claimed to generate Pd carbene species. Very high reaction yields were obtained in ionic liquids with a very narrow nanoparticle distribution. The very short reaction times (2 h) make this protocol very attractive.

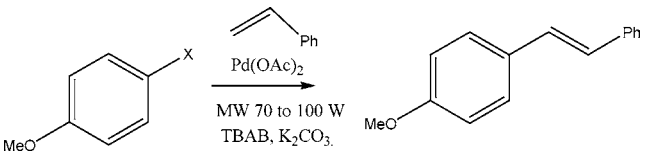


Good yields were obtained with bromo- or iodoarenes, while chloroarenes showed inertness.

Microwave-Promoted Heck Coupling

Arvela and Leadbeater (*J. Org. Chem.* **2005**, *70*, 1786) disclosed a nice protocol to carry out the Heck reaction under MW irradiation. Very low loadings of catalyst were needed (as low as 0.9 mmol %). Reactions proceeded well and gave

rise to very high yields (about 80%). Using styrene as starting materials a series of iodo- and bromoarenes were used as substrates. Very low yields were obtained with chloroarenes.



Ionic Liquids Coupled with Super Critical CO_2 Extraction

Since the first reports on the use of ionic liquids as reaction media, one of the greatest drawbacks for industrial use was product extraction. Very early in this arena the Reetz group (*Chem. Commun.* **2002**, 992) used supercritical CO_2 extraction for lipase-mediated reactions on ionic liquids.

Quite recently, Yoon et al. (*Ind. Eng. Chem. Res.* **2006**, *45*, 4433) reported an application of such a protocol on Heck reactions catalyzed by recyclable $PdCl_2$ in ionic liquids, in which the effects of water levels were studied.

First, it has been observed that there is a dramatic relationship of catalytic activity with water levels (the higher the water level, the lower the activity) that is probably related to HF generation whenever PF_6^- is present.

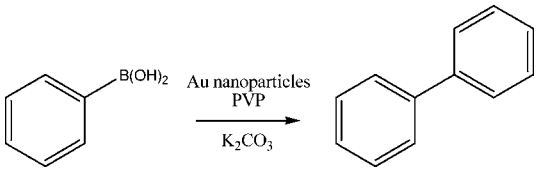
Extraction with $scCO_2$ proceeded well, and in general, extraction was not affected by the water content up to 0.69%, and the $PdCl_2$−ionic liquid system could be recycled.

Colloidal Gold

Colloidal gold nanoparticles showed to be suitable catalysts for C−C homocoupling using phenylboronic acid under aerobic conditions (Tsunoyana et al. *Langmuir* **2004**, *20*, 11293).

A beautiful description of the nanoparticles [stabilized with poly(vinyl pirrolidone) (PVP)] and production and characterization was disclosed as well as the general procedure for C−C homocoupling.

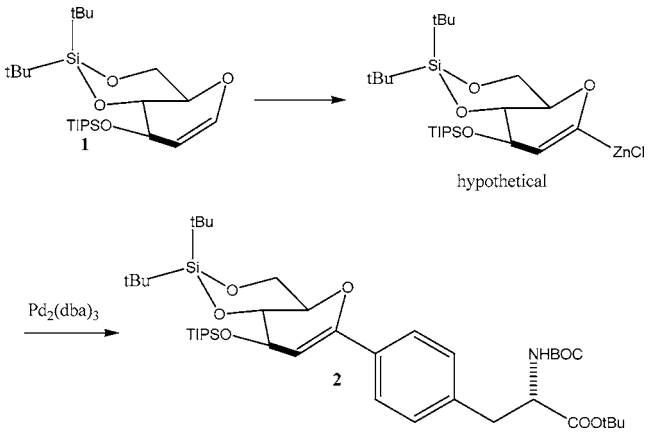
Although yields are not so high, this protocol opens a new access to C−C bond formation.



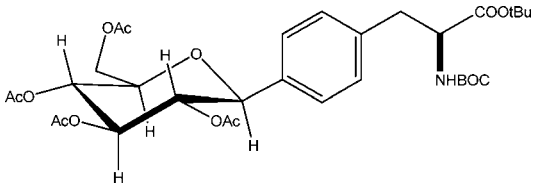
C-Glycosylated Amino Acids

A French group (Ousmer et al., *Eur. J. Chem.* **2006**, 1216) disclosed a gram-scale preparation procedure for *p*-(*C*-glucopyranosyl)-L-phenylalanine derivative via a Negishi cross-coupling reaction.

Protected sugar **1** was metalated with zinc (two steps) and submitted to C−C coupling with 4-iodo-L-phenylalanine producing *C*-glucoside **2**. The right choice of the amino acid derivative (BOC protected) allowed yields as high as 90%.



Transformation of *C*-glucoside **2** into a more suitable derivative *p*-(*C*-glucopyranosyl-L-phenyl alanine was carried out in five steps.

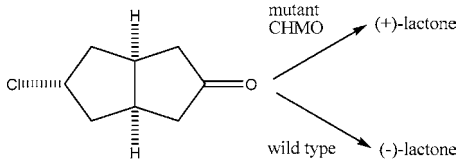


The synthesis of this compound opens a new way to synthesize (stable) glycopeptides.

Directed Evolution

The idea of directed evolution was successfully applied to the microbial Baeyer−Villiger oxidation by Mihovilovic et al. (*Org. Lett.* **2006**, *8*, 1221). Random mutants of cyclohexanone monooxygenase from *Acinetobacter* sp. NCIMB 9871 were screened against a number of different ketones. Consequently, it has been made possible to select different strains carrying the necessary mutations to improve enantioselectivities and conversions.

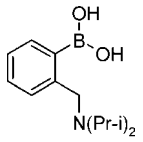
It has been discovered what mutation appears to be more significant to improve general enantioselectivity.



To Catalyze or Not to Catalyze? Direct Amide Bond Formation

Whiting, A. et al. (*Adv. Synth. Catal.* **2006**, *348*, 813) have studied in detail the amide bond formation from amines and free carboxylic acids under thermal and catalyzed conditions. The kinetic study shows that the direct formation of amides from amines and carboxylic acids does occur under relatively low temperature (reflux toluene) but is highly substrate dependent. Boric acid- and boronic acid-based catalysts improve the reaction, especially for less reactive acids, and the bifunctional tertiary amine boronic acid (**1**) was found to have the greatest potential. The catalyst loading was 1 mol % in boiling toluene and 10 mol % in boiling fluorobenzene. In all cases molecular sieves where used to

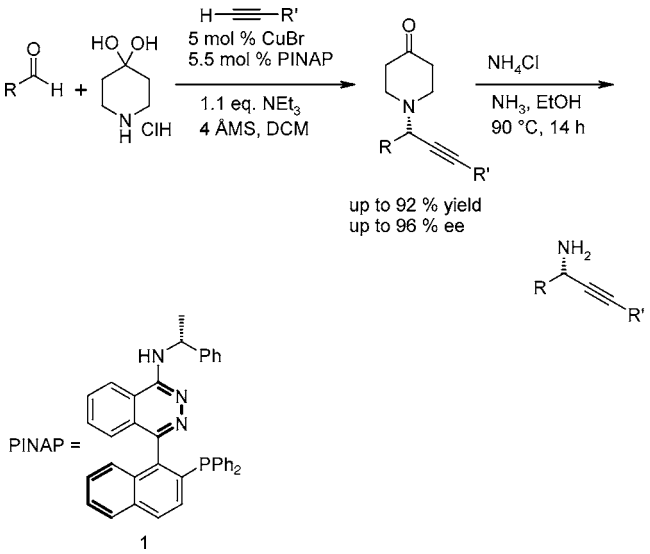
remove water. The catalyst **1** was found to act through a bifunctional mechanism, the exact nature is although not yet clear. However, for more difficult amidations this catalyst is superior to other boronic acid catalysts.



1

Highly Enantioselective Access to Primary Propargylamines: 4-Piperidone as a Convenient Protecting Group for Primary Amines

Carreira, E. et al. (*Org. Lett.* **2006**, *8*, 2437) have developed a highly enantioselective, catalytic three-component coupling of aldehydes, alkynes, and 4-piperidone hydrochloride hydrate using PINAP ligand and CuBr. The desired tertiary propargylamines were isolated in good to high yields and high enantioselectivities. The use of 4-piperidone as the amine component not only provides access to the primary propargylamines, which are useful building blocks, but also eliminates the necessity to use Pd catalysis for the deprotection as with *N*,*N*-dibenzyl or *N*,*N*-diallyl protecting groups. The tertiary amine adducts from the piperidine undergo deprotection when treated with ammonia in ethanol as well as polymer-supported amine scavenger.

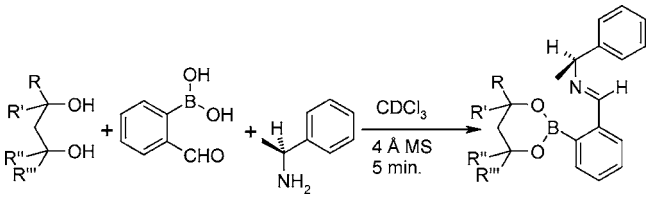


up to 92 % yield
up to 96 % ee

1

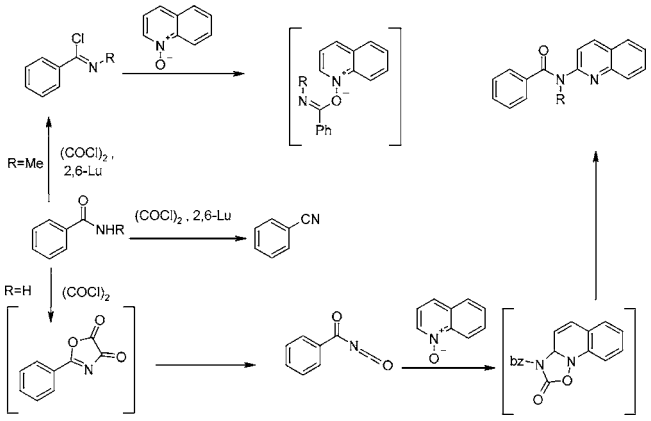
Simple Protocol for NMR Analysis of the Enantiomeric Purity of Diols

A practical simple three-component chiral derivatization protocol for determining the enantiopurity of chiral 1,2-, 1,3-, and 1,4-diols by ^{1}H NMR spectroscopic analysis has been developed by Bull, S. D. et al. (*Org. Lett.* **2006**, *8*, 1971). The method involves treatment with 2-formylphenylboronic acid and enantiopure α-methylbenzylamine to afford a mixture of diastereoisomeric iminoboronate esters whose ratio is an accurate reflection of the enantiopurity of the parent diol.



Mild and Direct Conversion of Quinoline *N*-Oxides to 2-Amidoquinolines

The process group from Pfizer in Groton describes a simple one-pot procedure for the direct conversion of quinoline *N*-oxides to 2-amidoquinolines with primary amides (Couturier, M. et al. *Org. Lett.* **2006**, *8*, 1929). This methodology is complementary to the Abramovich reaction, which is limited to the introduction of secondary amides via imidoyl chlorides. Although reaction conditions are almost the same, omission of the base is key for successful reaction with primary amides. The reaction proceeds through the intermediacy of an acyl isocyanate.



Critical Assessment of Pharmaceutical Processes: A Rationale for Changing the Synthetic Route

Researchers from AstraZeneca in Bristol, GSK in Tonbridge and Pfizer in Sandwich have written a comprehensive review over the criteria for rejecting a synthetic route during scale-up and thus triggering the search for a viable route (*Chem. Rev.*, published online March 8, 2006, http://dx.doi.org/10.1021/cr050982w). Given the current pressures on the pharmaceutical industry, process chemists are facing increasingly tough economic and regulatory hurdles and have less time with which to develop the commercial process for a drug candidate. The review provides a uniform set of criteria (SELECT), which represent the different drivers for changing a synthetic route. The acronym SELECT stands for safety, environmental, legal, economics, control, and throughput.

Boron Reagents in Process Chemistry: Excellent Tools for Selective Reductions

Matos, K.; Burkhardt, E. R. (*Chem. Rev.*, published online March 15, 2006, http://dx.doi.org/10.1021/cr0406918) have reviewed the use of boron reagents for selective reductions. The importance of borane and borohydride reagents in the synthesis of intermediates in the pharmaceutical industry has

been demonstrated in a vast number of examples. The future of these reagents for use in large-scale synthesis is promising due to their excellent selectivity, mild reaction conditions, high yields, and commercial availability. The authors have included many examples were the reagents have been used on multikilogram scale.

Pd/C: an Old Catalyst for New Applications

Felpin, F.-X., et al. (*Eur. J. Org. Chem.* **2006**, 2679) have reviewed the use of Pd/C as a new catalyst for the Suzuki−Miyaura coupling. The Pd/C-catalyzed cross coupling represents a valuable heterogeneous alternative to homogeneous conditions.

Pd/C has many salient advantages: (1) it is an inexpensive source of palladium, (2) it is easily separated from the reaction mixture by filtration, (3) it can sometimes be recycled and good yields maintained, (4) it can be used without ligands, (5) although catalytically less active, it is compatible with a large variety of substrates, including aryl chlorides. For these reasons along with recent discoveries exemplifying the versatility of the catalyst, it will not be surprising to find Pd/C-catalyzed Suzuki−Miyaura couplings as one of the preferred methods in the future.

Emerging Technologies Increasing Impact on Productivity in the Pharmaceutical Industry

Delaney and co-workers (*Chem. Rev.*, published online May 27, 2006, http://dx.doi.org/10.1021/cr040674i) have summed up the increasing impact of emerging technologies within chemical process R&D departments within the pharmaceutical industry. The authors describe the development of automated parallel reaction tools and their usefulness together with design of experiment (DoE) for the fast screening of reactions, workups, and crystallizations. In this area they also point to the large need for software and hardware standardization. Integration of the technologies that make up the workflows is crucial to keep up a fast pace for development.

Another topic which is discussed is the developments in analytical chemistry for impurity profiling and on-line analysis.

The developments of kinetic analysis and reaction modeling are also mentioned.

The final topic in the article is continuous processing/process intensification. Process intensification is a general term used to describe the work done aimed toward dramatically reducing processing, cost, time, waste, equipment size, or land use while maximizing overall efficiency.

As the advantages and limitations of specific reactor and workup technologies become more widely recognized, one could readily predict that specific types of reactions will be designed in an integrated manner with the safest and most economically advantageous physical means to carry them out on-scale.

Choosing an Operating Policy for Seeded Batch Crystallization

A group from Professor Doherty's lab (Ward, J. D. et al. *AIChE J.* **2006**, *52*(6), 2046) proposes an additional perspective and tool for determining the optimal temperature (or supersaturation) profile for a seeded batch crystallization. Even though this topic has been under investigation for more than three decades, several "optimal" cooling protocols were determined. A majority of researchers found that the optimal temperature trajectory is that which leads to an increase in supersaturation near the end of the batch (also termed "late growth"). A significant minority of investigators found the optimal temperature profile in such seeded batch crystallizations is that which exhibits high supersaturation at the beginning of the batch ("early growth"). Last but not least, other crystallization researchers recommend the use of constant supersaturation during crystallization. An interesting review of the results published in the past thirty years by 12 authors is included in this paper. Ward et al. suggest an approach aimed at reconciling the apparently conflicting cooling protocols using the objective functions selected for optimization. The authors point out carefully the great deal of subtleties associated with the definition of such objective functions ("mathematical" vs the word "objectives"). The authors conclude that the constant supersaturation approach remains to be a very reasonable policy (with the occasional practical challenge of monitoring the supersaturation). In addition, the authors indicate that because such cooling profiles are compound dependent, early trial-and-error investigations are used to refine the cooling protocol, and "shift" it, as needed, to "early" or "late" growth modes.

Modeling of Mass Transfer in Combination with a Homogeneously Catalyzed Reaction

A collaboration between DSM Research and the University of Twente (Hoorn, J. A. A. et al. *AIChE J.* **2006**, *52*(7), 2551) addresses the interaction of mass transfer with reaction kinetics in the case of homogeneously catalyzed processes, such as hydrogenations. Despite the frequent occurrence of such processes in industry, the interaction between reaction kinetics and mass transfer, especially for the case of mass-transfer limited processes, has not been extensively addressed in the open literature. The practical small-scale applications are often simplified by avoiding mass-transfer limitations. In plant reactors, because of nonideal mixing conditions, mass-transfer limitations are often encountered. Hence, "typical" kinetic observations may be the result of the overlap of actual reaction kinetics with mass transfer. This paper evaluates the mass-transfer rates for gaseous reactant into a liquid where homogeneously catalyzed reactions take place. The evaluation is executed by obtaining the numerical solution of the diffusion-reaction equations according to Higbie's penetration theory. Simplified versions of the model were also tested. Inclusion of reversible steps in the model complicates the study, as expected. It is fascinating that a catalytic cycle of a reaction network comprising two equilibria and one irreversible reaction can still present challenges for a fundamental understanding of the impact of mass transfer on such processes.

Ketoprofen Nanoparticle Gels Formed by Evaporative Precipitation into Aqueous Solution

An extensive intramural collaboration from the University of Texas at Austin together with Kos Pharmaceutical (Chen, X. et al. *AIChE J*. **2006**, *52*(7), 2428) reports the production of aqueous nanoparticle gels of ketoprofen (a poorly water-soluble drug) by evaporative precipitation into aqueous solution (EPAS). Whereas EPAS was previously reported to produce micrometer-sized crystalline particles, the objective of this work was to produce stable nanosized particles, exhibiting high water solubility. Stable 135-nm amorphous ketoprofen particles were obtained using only 0.1% w/v poloxamer 407 (a poly(ethylene oxide)-*b*-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer. At 5% w/v poloxamer 407, a gel comprising 50-nm particles was obtained. A high dissolution rate was observed for the ketoprofen in the gel nanoparticles: 98% in 2 min. The gel exhibits relatively low viscosity and acceptable one month stability. The process involves using an organic solution of ketoprofen with surfactant, which is atomized through an elliptical conical nozzle into hot water at a flow rate of 1 mL/min and a pressure drop of 23−34 MPa.

Supercritical Fluid Extraction: Phase Separation and Product Recovery

Supercritical fluid extraction processes (SFE), especially using carbon dioxide, have come a long way as methods for obtaining highly valuable products. A lot of scientific effort has been dedicated specially for demonstrating the advantages of SFE with respect to the enhanced nutritional value of the natural extracts obtained. Although thermodynamically consistent, scale-up of such concepts often fails due to a lack of technically and economically feasible solutions. Technical aspects of phase separation and product recovery as a decisive process step in laboratory-, pilot-, and industrial-scale extraction of solids and liquids is critically evaluated by Zacchi and collaborators **(***Chem. Eng. Process*. **2006**, *45*(9) 728−733.). Different methods of liquid level detection are presented as a way of controlling extract separation automatically. The results are discussed in view of guidelines for finding appropriate solutions to the specific separation problem.

Ultrasound Effect on Ice Morphology of Frozen Formulations for Pharmaceutical Proteins Freeze-Drying

Ultrasound has been investigated in several reactions over the years, and its effect in unit operations is commercially exploited. To optimize industrial freeze-drying processes of pharmaceutical proteins in vials, a recent paper discusses an ultrasound system to control the freezing step. During supercooling, nucleation temperatures of the sample could be controlled at selected values below the equilibrium freezing temperature. Because the main freezing elementary phenomena such as nucleation and ice crystal growth are strongly related with ice crystal morphology parameters, the controlled nucleation by ultrasound effectively modified notably the primary drying duration. The primary drying rates during freeze-drying of pharmaceutical formulations (i.e., mannitol, BSA, sucrose) were accelerated due to ice-phase morphological modifications induced by the ultrasound control system. (Nakagawa, et al. *Chem. Eng. Process.* **2006**, *45*(9) 783−791).

Enzyme-Responsive Smart Biomaterials

Enzyme-responsive materials (ERMs) are a new class of smart materials that undergo macroscopic transitions when triggered by selective catalytic actions of enzymes. The use of enzymes as stimuli to trigger mechanical responses in materials opens up a number of possible applications in biology and medicine. Three different classes of ERMs are described, based on supramolecular assemblies, chemically cross-linked gels and (nanoparticle) surfaces. Potential applications in regenerative medicine, diagnostics, and drug delivery are discussed. (Ulijn, R. V. *J. Mater. Chem.* **2006**, *16*, 2217−2225).

Cobalt Ferrite Magnetic Nanoparticles as Catalysts

Cobalt ferrite nanoparticles, $CoFe_2O_4$, are one of the important spinel ferrites due to their high cubic magneto-crystalline anisotropy, high coercivity, and moderate saturation magnetization. $CoFe_2O_4$ nanoparticles have been known to be a photomagnetic material which shows an interesting light-induced coercivity change. Various preparation techniques were used by a group from Egypt to produce cobalt ferrite nanoparticles, namely (i) ball milling of a homogeneous mixture of cobalt(II) acetate and iron(III) acetate (basic) treated by a novel self-flash combustion, (ii) precipitation of cobalt(II) chloride ($CoCl_2 \cdot 6H_2O$) and iron(III) chloride ($FeCl_3$), and (iii) ceramic method by firing of cobalt oxide (CoO) and iron oxide (Fe_2O_3). These techniques help to obtain particle sizes ranging from a few micrometers to about 20 nm. Thermal analysis (TGA and DTA), X-ray diffraction, SEM, TEM, magnetic and surface area measurements have been used for characterization of the prepared samples. The effect of different nanosizes on the total pore volume, adsorption energy, average pore diameter, micropore volume, have been studied. Nanocrystalline $CoFe_2O_4$ showed a catalytic activity towards CO_2 decomposition with the formation of carbon nanotubes. (Khedr, M. H. et al. *Colloids Surf. A: Physicochem. Eng. Aspects* **2006**, *281*(1−3), 8−14)

Hydroxyalkylation of Aniline and Phenol

Bisphenol manufacture is challenging in terms of catalyst activity and selectivity, and there is a continuous search to devise new methods, catalysts, and reactors. Ion-exchange resins and supported heteropolyacids are already well-known as catalysts for this process. Now a process is reported for hydroxalkylation of phenol with acetone to produce bisphenol A. Amorphous aluminosilicates with controlled porosity in the region of micropores (ERS-8, SA) and mesopores (MCM-41, HMS, and MSA) have been compared as catalysts in the hydroxyalkylation of phenol with acetone and of aniline with formaldehyde. The comparison has also included two commercial silica−alumina gels and H-Beta. In the hydroxylakylation of phenol with acetone to bisphenol A (BPA), the catalysts have been compared by batch test in

terms of activity and selectivity. In the hydroxylakylation of aniline with formaldehyde, also the catalyst life has been investigated. As their general behavior, mesoporous aluminosilicates have evidenced better catalytic activity, selectivity, and longer catalyst life than both microporous ones and commercial silica−alumina gels. In the hydroxyalkylation of aniline to methylenedianiline (MDA), mesoporous MSA have shown performances similar to that of H-Beta in terms of MDA yields but demonstrates lower catalyst life. (Perego, C. et al. *Appl. Cat. A: Gen.* **2006**, *307*(1) 128−136).

Microwave-Assisted Synthesis and Crystal Structures of 2-Imidazolines and Imidazoles

A series of 2-imidazolines and imidazoles has been synthesized using green synthetic methodologies. The preparation of 2-imidazolines was performed by cyclization of nitriles with ethylenediamine. The use of microwave irradiation in solvent-free conditions enabled 2-imidazolines to be obtained in high yields within short reaction times. Aromatization of imidazoles was performed under microwave irradiation in toluene and using Magtrieve as the oxidant. The X-ray structures for five of these derivatives are provided. (de la Hoz, A. et al. *Tetrahedron* **2006**, *62*(25), 5868−5874).

Supercritical Antisolvent Process for Sustained Drug Delivery

Supercritical processes for drug-delivery system design have attracted considerable attention recently. The application of a supercritical antisolvent coating process for controlled drug-release design is discussed *(*Wang, Y. et al. *Powder Technol.* **2006**, *164*(2) 94−102). Hydrocortisone as the host drug particles and poly(lactide-*co*-glycolide) (PLGA) as the polymer carrier were selected as the model system for this purpose. In this research the drug particles were suspended in a polymer solution of dichloromethane. The suspension was then sprayed into supercritical CO_2 as an antisolvent. A parallel study of coprecipitation of the drug and polymer using the same supercritical antisolvent process at the same operating conditions was performed for comparison with the coating process. SEM images were used to characterize the drug particles before and after, and the assay analysis was carried out using HPLC. The coated particles and coprecipitated particles were evaluated in terms of encapsulation efficiency and drug-release profiles. The major advantage of this new approach is the ability to physically coat very fine ($<30\ \mu$m) particles without having to dissolve them in an organic solvent. It was found that higher polymer-to-drug ratios produced higher encapsulation efficiencies, and the coated drug particles did show sustained release behavior. The coprecipitation of the drug and polymer (at the same operating conditions), however, did not exhibit any sustained release.

Catalytic Oxidative Elimination of (Chloro)aromatics

A series of two articles has appeared in a systematic investigation of the catalytic activity of 40 different formulations of transition metal oxides-based supported catalysts in the course of the total oxidation of benzene as a model molecule for dioxin. The catalysts consisted of 10 different transition metal oxides (CrO_x, MnO_x, VO_x, SnO_x, WO_x, NbO_x, TaO_x, MoO_x, ZrO_x, and BiO_x) supported on four different supports (two kinds of TiO_2, and Al_2O_3 and SiO_2). A theoretical coverage of 0.75 monolayer of active phase was chosen to minimize the formation of crystallites. XPS and XRD characterizations demonstrated the better spreading as monolayer of the active phases at the surface of titania than at those of Al_2O_3 and SiO_2. The latter induces a poor dispersion of almost all the active phases as crystallites. The variation of spreading of the active phases on the different supports is governed by the difference in surface free energy and is fully explained by the "solid−solid wetting" concept. For almost all active phases, the conversion of benzene progressively improves when the support is changed from SiO_2 to Al_2O_3 and, finally, titanias. The performances of the active phases exhibiting this behavior are clearly dictated by their presence as well-dispersed monolayers at the surface of the support. The screening revealed CrO_x, VO_x, and MnO_x as the most active phases. The first two exhibit their best activity when spread as monolayer at the surface of TiO_2-based supports (classical behavior). At the opposite, MnO_x works best when present in the form of Mn_3O_4 crystallites on the SiO_2 support. The effects of the additions of secondary phases on the activity of VO_x/TiO_2-based catalysts in the course of the total oxidation of benzene and chlorobenzene as model molecules for dioxins were studied systematically. The investigation of the effects of different ratios of WO_x/VO_x and MoO_x/VO_x on the total oxidation of chlorobenzene was performed on binary formulations supported on classical TiO_2 or on sulfated TiO_2. The activation effects brought by WO_x, MoO_x, and sulfated TiO_2 are linked to the increase of the number of Brønsted acid sites as proven by FTIR with adsorbed pyridine. Moreover, the strong Lewis sites present on the sulfated TiO_2 promote the dispersion of the active and secondary phases. The importance of the presence of Brønsted sites for the adsorption of VOCs and Cl−VOCs aromatics is brought out. (Bertinchamps, F. et al. *Appl.Cat. B: Environ.* **2006**, *66*(1−2) 1−9 and 10−22).

Use of Ionic Liquids as Media for the Biocatalytic Preparation of Flavonoid Derivatives with Antioxidant Potency

Reported in this paper is biocatalytic preparation of acylated derivatives of flavonoid glycosides by using various immobilized lipases in two different ionic liquids, namely, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6). The influence of various reaction parameters on the performance and the regioselectivity of the biocatalytic process was pointed out, using as model reaction the acylation of naringin and rutin with vinyl butyrate, catalyzed by immobilized *Candida antarctica* lipase at 60 °C. The biocatalytic modification of flavonoids strongly depended on the ionic liquid used, the molar ratio of substrates, and the acyl donor chain length. The highest conversion yield (about 65% after 96 h of incubation) was obtained with short-chain acyl donors (up to four carbon

atoms), at a relatively high molar ratio (10−15) in both ionic liquids used. The amount of monoacylated flavonoid derivatives produced in a single-step biocatalytic process in [bmim]BF_4 was up to 5.5 g/L for monoacylated rutin and 30 g/L for monoacylated naringin. The regioselectivity of the process was higher in [bmim]BF_4 than in [bmim]PF_6 or organic solvents. Reaction rates observed in ionic liquids were up to 4 times higher than those reported for organic media. The acylation of the sugar moiety of rutin with various acyl donors affected its antioxidant potential towards both isolated LDL and total serum model in vitro. A significant increase of antioxidant activity was observed for rutin-4‴-*O*-oleate (Katsoura, M. H. *J. Biotechnol.* **2006**, *123*(4) 491−503).

Granular Sludge in Full-Scale Anaerobic Bioreactors: Trace Element Content and Deficiencies

The likelihood of the presence of trace elements in methanogenic granular sludge from full-scale anaerobic bioreactors was systematically studied by Dutch workers. Four different anaerobic granular sludges (Nedalco, Eerbeek, Hoogeveen, and Heineken) were screened for their metal content and their response to the addition of a metal cocktail and more specifically to cobalt. Three different methanogenic substrates (methanol, acetate, and H_2/CO_2) were used, and the response to trace metal addition was monitored by on-line measurement of the changes in the specific methanogenic activity (SMA) of the sludge. A significant increase of the SMA due to trace metal addition was observed only with the substrate methanol; addition of only cobalt had an especcially great effect: the SMA with methanol of the Nedalco and Hoogeveen sludge increased from, respectively, 306 and 155 mg of CH_4-COD g VSS^{1-} d^{-1} to 535 and 334 mg CH_4-COD g VSS^{1-} d^{-1} upon the addition of solely 5 μM cobalt. In the Heineken sludge, a limitation for another element was present as well. The cobalt concentrations in the sludges were low compared to those of the other trace elements and could not be directly related to the response of the SMA. With acetate as the substrate and in the presence of cobalt (5 μM) a reduction of the lag-phase was observed for the Nedalco and was more pronounced for the Heineken sludge. This indicates that cobalt is also important for the onset of the activity/growth of the acetotrophic methanogenic population. Screening of the trace metal content of anaerobic granular sludge in combination with the response of the SMA to trace metal addition is therefore a valuable tool to prevent and foresee trace metal limitation in anaerobic bioreactors. (Zandvoort, M. H. et al. *Enzyme Microb. Technol.* **2006**, *39*(2), 337−346).

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