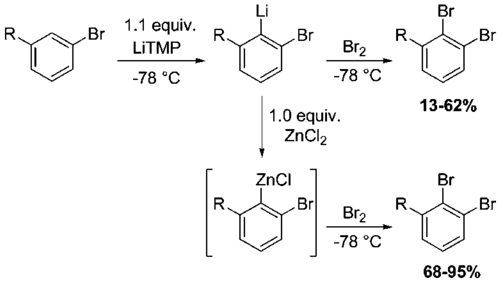
Organic Process Research & Development **2006**, *10,* 364–380

Highlights from the Literature

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

Bromination of Metalated Haloarenes



A facile protocol for the synthesis of 1,2-dibromoarenes is described by Menzel and co-workers at Merck (*J. Org. Chem.* **2006**, *71*, 2188−2191). A standard ortho-lithiation/bromination procedure, when applied to bromoarenes, resulted in poor yields of the corresponding 1,2-dibromoarenes (13−62% yield). However, transmetalation of the aryllithium intermediate to an arylzinc species with ZnCl$_2$, followed by bromination, resulted in dramatically improved yields of the synthetically useful 1,2-dibromoarenes (68−95% yield).

Synthesis of Isoindolin-1-ones

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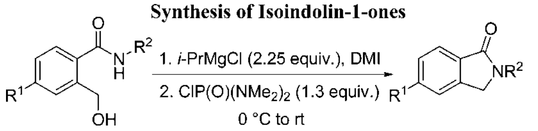
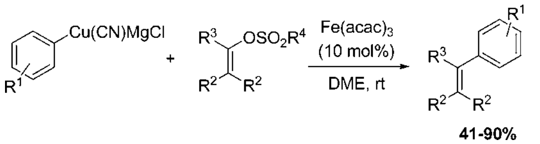


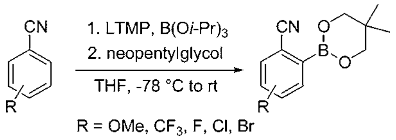
Tsuritani and co-workers at Banyu report on a short and efficient synthesis of isoindolin-1-ones (*Synlett* **2006**, 801−803). Base-induced cyclization of *o*-hydroxymethylbenzamides, prepared from the corresponding lactone and an amine, led predominantly to *N*-alkylation in good yield. The group studied the cyclization in different solvents and also examined the effect of several activating groups on the hydroxyl. Significant differences in yield and *N*/*O*-alkylation selectivity were observed. Optimal conditions involved the use of 1,3-dimethyl-2-imidazolidinone (DMI) as solvent with a phosphoramide leaving group. Diethyl phosphate as a leaving group also gave good results. The reaction proceeded under fairly mild conditions, and bromine and nitrile substituents were tolerated.

Iron-Catalyzed Cross-Coupling between Alkenyl and Dienyl Sulfonates and Functionalized Arylcopper Reagents



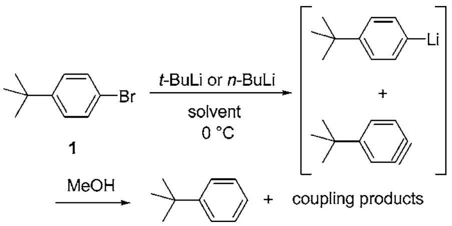
Functionalized arylcopper reagents react readily with alkenyl sulfonates in the presence of catalytic amounts of Fe(acac)$_3$ (10 mol %) providing the expected cross-coupling products in good yields, as described by Knochel (*Synlett* **2006**, 407−410). The conditions are mild (rt), and ester or cyano groups are tolerated. A variety of functionalized arylcopper reagents are available via Knochel's Mg−X exchange chemistry. This cross-coupling can be performed with dienyl sulfonates leading to the corresponding substituted dienes. Needless to say, the use of an iron salt as catalyst offers an alternative to palladium- and nickel-catalyzed cross-coupling reactions, in terms of cost and toxicity. However, the method does require the use of stoichiometric quantities of copper cyanide.

Synthesis of 2-Substituted Cyanoarylboronic Esters



The synthesis of substituted 2-cyanoarylboronic esters via lithiation/in situ trapping is described by the group of Kristensen (*J. Org. Chem.* **2006**, *71*, 2518−2520). The highly hindered LTMP was found to be the optimal base for this process. When LDA was used, addition to the nitrile occurred to varying extent. Reaction workup involved treatment with neopentylglycol to obtain the boronic esters directly. The crude arylboronic esters were obtained in high yields and purities and with good regioselectivities. The authors further demonstrated the utility of these intermediates in a short synthesis of a phenanthridine.

Effect of Solvent on the Lithium−Bromine Exchange of Aryl Bromides



The outcome of reactions of 1-bromo-4-*tert*-butylbenzene (**1**), a representative aryl bromide, with *n*-BuLi or *t*-BuLi at 0 °C in a variety of solvent systems has been investigated by Bailey and co-workers (*J. Org. Chem.* **2006**, *71*, 2825−2828). The products of reactions of **1** with *n*-BuLi vary significantly with changes in solvent composition: **1** does

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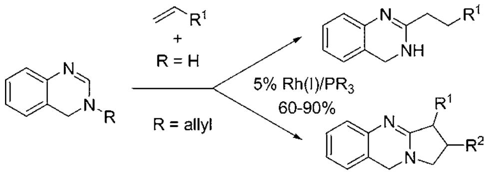
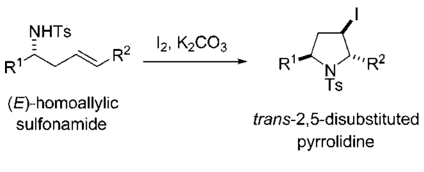
not react with *n*-BuLi in pure heptane; the exchange reaction to give (4-*tert*-butylphenyl)lithium, which is slow in pure diethyl ether, is virtually quantitative in heptane containing a small quantity of THF; and the reaction of **1** with *n*-BuLi in THF leads to considerable coupling. Lithium−bromine exchange is the virtually exclusive outcome of reactions of **1** with *t*-BuLi in every solvent studied except pure heptane: the presence of a small quantity of any of a variety of structurally diverse ethers (Et_2O, THF, THP, MTBE) in the predominantly hydrocarbon medium affords (4-*tert*-butylphenyl)lithium, assayed as *tert*-butylbenzene, in yields exceeding 97%. The only side products observed from reactions of **1** with *t*-BuLi are small amounts of benzyne-derived hydrocarbons.

Rhodium-Catalyzed Direct C−H Addition of 3,4-Dihydroquinazolines to Alkenes



The inter- and intramolecular couplings of unactivated alkenes to 3,4-dihydroquinazolines with a Rh(I) catalyst are reported by Ellman and Bergman (*J. Org. Chem.* **2006**, *71*, 1969−1976). Coupling between olefins and *NH*-3,4-dihydroquinazoline was found to occur consecutively with heterocycle dehydrogenation in the presence of a Rh(I)/PCy_3/HCl catalyst. The reaction was used to develop an effective method for the synthesis of 2-substituted quinazolines through an oxidative workup step. The regiocontrolled synthesis and Rh-catalyzed cyclization of alkene-tethered 3,4-dihydroquinazolines are also described. Applying this method, the second total synthesis of vasicoline was achieved. The key Rh-catalyzed cyclization step was made possible by the use of a rigid bicyclic phosphine ligand. The synthesis further demonstrates a challenging Cu-catalyzed amidation of an ortho-substituted aryl chloride.

Asymmetric Synthesis of *trans*-2,5-Disubstituted Pyrrolidines

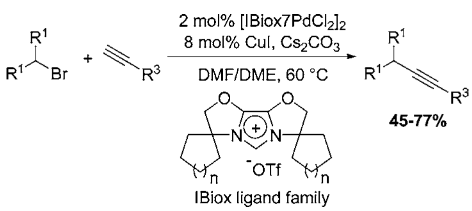


The group of Davis describes an asymmetric synthesis of *trans*-2,5-disubstituted pyrrolidines (*J. Org. Chem.* **2006**, *71*, 2779−2786). Iodocyclization of sulfinimine-derived enantiopure homoallylic sulfonamides affords *trans*-2,5-disubstituted 3-iodopyrrolidines. This paper expands upon prior work from the group in which they developed a route to the requisite enantiopure homoallylic sulfonamides based around asymmetric addition to sulfinimines. It is noted that only the (*E*)-homoallylic sulfonamides undergo the iodocyclization reaction.

Do the Terms "% ee" and "% de" Make Sense?

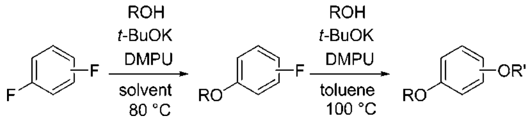
In an interesting paper, Gawley presents a case for the abandonment of the widely used terms ee and de and advocates their replacement with er and dr (*J. Org. Chem.* **2006**, *71*, 2411−2416). Enantiomeric excess (ee) was originally defined as a term to describe enantiomeric composition and was equated with optical purity. More recently, ee and its cousin de (diastereomeric excess) have been used (inappropriately) to quantitate stereoselectivity. The quantity ee has been used in equations describing processes such as kinetic resolutions, but these equations are unnecessarily complex because it is enantiomer ratio, not enantiomeric excess, that directly reflects relative rates. A historical summary of the development of ee as an expression of enantiomer composition and enantioselectivity is presented, along with new equations and figures defining and illustrating the stereoselectivity factor, ***s***, kinetic resolutions versus % conversion, and linear correlations of enantiomer composition of catalysts and products. New figures illustrating nonlinear effects versus enaniomer composition are presented, and Kagan's index of amplification for positive nonlinear effects is discussed and illustrated.

Sonogashira Coupling of Unactivated Secondary Alkyl Bromides



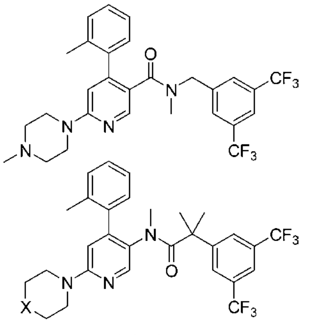
Glorius reports on the first Pd-catalyzed Sonogashira coupling of unactivated secondary alkyl bromides (*Tetrahedron Lett.* **2006**, *47*, 2925−2928). A series of bisoxazoline-derived NHC-type ligands, previously developed in the same group, were successful for this reaction while the use of phosphine ligands led to poor results. Using this method, substrates such as cyclopentyl bromide and cyclohexyl bromide, as well as acyclic secondary bromides, can be coupled with alkynes under relatively mild conditions (60 °C) in moderate yield.

Synthesis of Resorcinols via Nucleophilic Aromatic Substitution



A short, high-yielding synthesis of differentially substituted resorcinol derivatives has been developed by Toczko and co-workers at GSK (*J. Org. Chem.* **2006**, *71*, 2170−2172). The method utilizes 1,3-difluorobenzene as the starting material and employs sequential nucleophilic aromatic substitution (S_NAr) reactions to generate desymmetrized products. The scope and limitations of the second S_NAr reaction on the deactivated 1-alkoxy-3-fluorobenzene intermediates were investigated. The authors note that the use DMPU as an additive was crucial for complete reaction at a reasonable rate (∼3 h), which helped minimize formation of symmetrical bis-substitution products. This method was also employed for the synthesis of desymmetrized catechol derivatives from 1,2-difluorobenzene.

Synthesis of NK1 Receptor Antagonists

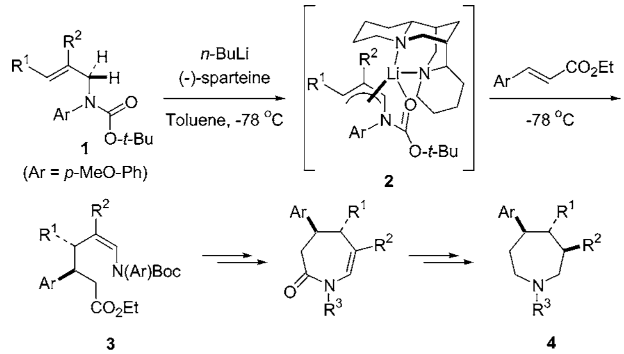


X = O (befetupitant)
X = N (netupitant)

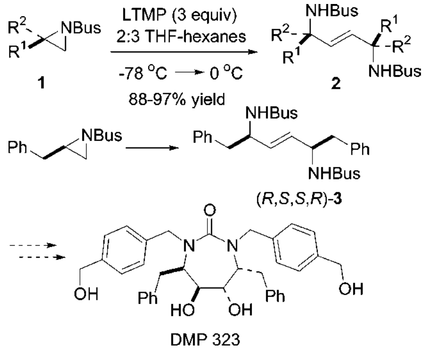
Efficient syntheses of two novel classes of NK1 receptor antagonists, among them befetupitant and netupitant, are described by Hoffmann-Emery and co-workers at Roche (*J. Org. Chem.* **2006**, *71*, 2000−2008). Starting from 6-chloronicotinic acid the introduction of the *o*-tolyl substituent at C(4) of the pyridine ring was achieved by a one-pot selective 1,4-Grignard addition/oxidation sequence to 6-chloronicotinic acid or a derivative of it. The scope of this addition/oxidation sequence was examined. It was also shown that the carboxylic function can be converted to a methyl amino group by a Hofmann rearrangement followed by reduction. Furthermore, a new high-yielding synthesis of 2-(3,5-bis-trifluoromethylphenyl)-2-methyl propionic acid based on the carbonylation of the tertiary alcohol obtained by Grignard addition of 3,5-bis(trifluoromethyl)bromobenzene to acetone was established.

Organolithium-Mediated Reactions

Azepanes, the seven-membered ring homologues of piperidines, are nitrogen heterocycles of pharmacological interest. Lee and Beak communicated the asymmetric synthesis of polysubstituted azepanes by a tandem lithiation-conjugate addition sequence (*J. Am. Chem. Soc.* **2006**, *128*, 2178−2179). The key step in the strategy involves the enantioselective lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)-2,3-substituted allylamines **1** with *n*-BuLi/(−)-sparteine at −78 °C to generate diastereomerically enriched lithiated intermediates **2**. The conjugate addition of these species to *β*-aryl α,*β*-unsaturated esters affords highly diastereo- and enantioenriched enecarbamates **3** in excellent yields with diastereomeric ratios greater than 93:7 and enantiomeric ratios greater than 95:5. Subsequent acid-catalyzed cyclization and functional group transformations originate the corresponding azepanes **4**.

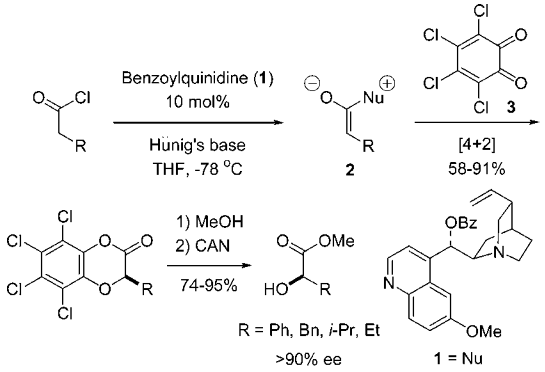


Hodgson and Miles found that lithiated terminal aziridines undergo carbenoid-type reactivity similar to their epoxide counterparts. Dimerization of **1** led to protected 2-ene-1,4 diamines **2** (*Angew. Chem., Int. Ed.* **2006**, *45*, 935−938). The path of the reaction was dependent on the protecting group: Bus (*tert*-butyl sulfonyl) gave the desired product, while Boc or Tos yielded complex mixtures of products with no dimers observed. Enantiopure aziridines (99% ee) with different alkyl substituents ($R^1 = C_{10}H_{21}$, *t*-Bu, or $R^2 =$ Cy, 3-butenyl) dimerized in high efficiency using lithium 2,2,6,6,-tetramethylpiperidide (LTMP) as the base to yield exclusively the compound with *E* configuration. Formation of the *E* isomer is consistent with initial *trans*-lithiation of the aziridine, followed by nucleophilic attack of the lithiated species onto a second unit of **1**, and finally *syn*-elimination. The superior selectivity relative to epoxides (*E*:*Z* ratio is 2:1) may arise from disfavored *anti*-elimination as a result of steric hindrance between the *N*-Bus groups. The methodology was applied in a concise synthesis of diaminodiol (*R*,*S*,*S*,*R*)-**3**, the core unit of a number of HIV protease inhibitors such as the DuPont Merck compound DMP 323.

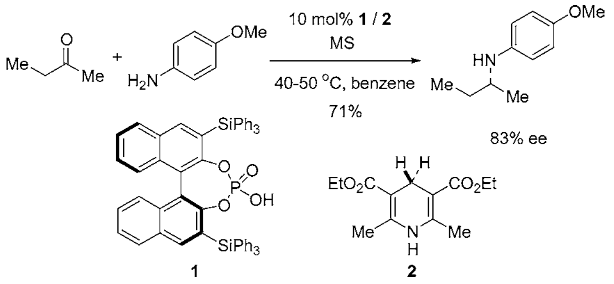


Organocatalytic Reactions

The group of Lectka at Johns Hopkins University has reported an elegant entry to α-hydroxyesters based on [4+2] cycloadditions of chiral ketene enolates and *o*-quinones (*J. Am. Chem. Soc.* **2006**, *128*, 1810−1811). The intermediate chiral ketene enolates **2** were generated from an acid chloride with the assistance of catalytic amounts of nucleophilic benzoylquinidine (**1**, a cinchona alkaloid derivate), and Hünig's base as the stoichiometric dehydrohalogenating agent. The cycloaddition of the ketene enolates with *o*-chloranil (**3**) affords quinone-derived adducts in good yields and excellent enantioselectivities. The latter can be transformed to their corresponding α-hydroxyesters under mild conditions with conservation of optical purity following methanolysis and CAN-mediated oxidation. Whereas benzoylquinidine yields the *R* enantiomers, the use of benzoylquinine affords the *S* antipodes.

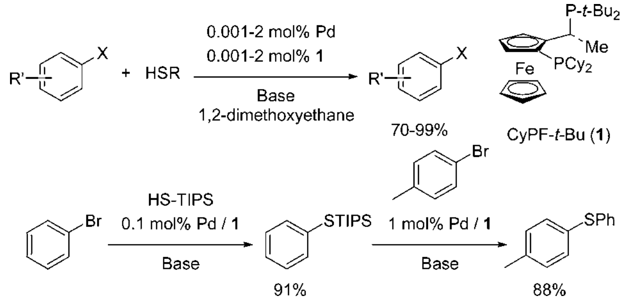


The importance of reductive aminations in organic synthesis cannot be overstated. The group of MacMillan devised an enantioselective organocatalytic strategy that introduces the C−N bonds using chiral BINOL phosphoric acid catalyst **1** and ethyl Hantzsch ester **2** (*J. Am. Chem. Soc.* **2006**, *128*, 84−86). Thus, aryl/alkyl and alkyl/alkyl ketones react with a variety of aryl and heteroaromatic amines in the presence of 10 mol % of the hydrogen-bonding catalyst **1**, NADH analogue **2**, and 5 Å molecular sieves. The latter are critical to the reaction success, since removal of water generated during the imine formation favors both the condensation and the reduction step. A mechanistic hypothesis considering the existence of a chiral intermediate imine-H−OPO_3R_2 complex supports the enantioselective outcome of the amination. Remarkably, the catalytic system discerns between methyl and ethyl substituents: the reductive amination of butanone affords the 2-amino butane product with 83% ee. MacMillan's protocol can be employed in the coupling of complex fragments.



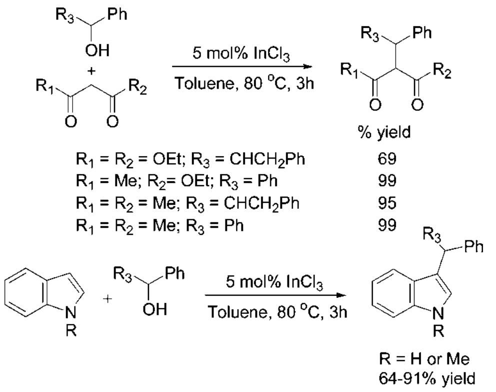
Pd-Catalyzed Coupling of Aryl Halides with Thiols

Methods for the formation of Ar−SR bonds remain the missing instrument in the toolbox of cross-coupling reactions that generate aromatic carbon−heteroatom bonds. In general, the cause lies on the unwanted reactivity of late transition metals towards substrates containing thiol groups: thiolates can displace dative metal ligands from the catalytic species to generate a variety of unproductive complexes. The group of Hartwig at Yale University has come up with a long-lived, general Pd catalyst that contains a strongly binding biphosphine, the Josiphos ligand CyPF-*t*-Bu (**1**), which competes favorably with thiolates generated during the reaction (*J. Am. Chem. Soc.* **2006**, *128*, 2180−2181). In a typical experiment, an equimolar mixture of Pd complex (e.g., $Pd(OAc)_2$, $Pd(dba)_2$), ligand **1** (0.001−2 mol %), and 1.1 equiv of base in 1,2-dimethoxyethane promotes the coupling of ArCl, ArBr, ArI, ArOTf, and ArOTs substrates with alkyl and aryl thiols in excellent yields. Most importantly, the methodology can be extended to the coupling of two aryl bromides with HS-TIPS, a H_2S surrogate, to circumvent the need for aromatic thiols to synthesize bis-aryl sulfides.



$InCl_3$-Catalyzed C−C Bond Formation from Alcohols and Active Methylenes

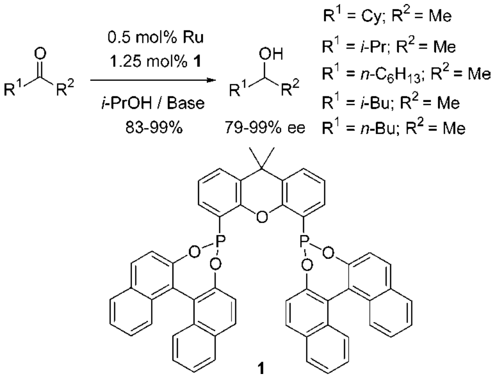
The Tsuji−Trost coupling involves the reaction between allylic acetates and an active methylene species via *π*-allyl intermediates. The group of Baba has broadened its synthetic utility, expanding both classes of substrates by using $InCl_3$ (*Angew. Chem., Int. Ed.* **2006**, *45*, 793−796). The catalyst activates either of the reagents, while possessing low oxophilicity and sensitivity to water. $InCl_3$ successfully activates alcohols, an operation generally hampered by the inefficient leaving group ability of the hydroxyl group. In addition, diesters, which are less active than *β*-diketones or *β*-keto esters, are successfully used as active methylenes. In the optimized conditions, the starting materials and $InCl_3$ were heated in toluene at 80 °C to give the corresponding alkylated product and water as the sole byproduct. The desired compounds were isolated by extraction or distillation. A mechanistic proposal involves dimerization of the alcohol to form an ether, followed by reaction with the $InCl_3$ activated nucleophile. Using indoles as nucleophiles, 3-alkylated products were obtained in high yield (64−91%) and selectivity, with no *N*- or 2-alkylation products obtained.



Ru-Catalyzed Asymmetric Transfer Hydrogenation

The discovery of cheap and general reagents that catalyze the enantioselective hydrogenation of prochiral ketones is still present on the most wanted list. In particular, finding catalytic systems capable of transferring hydrogen to alkyl/

alkyl ketones remains elusive. Recently, Reetz and Li discovered Ru catalysts containing BINOL-derived diphosphonite ligand **1** that effect the reduction of alkyl/alkyl and aryl/alkyl ketones in a general fashion (*J. Am. Chem. Soc.* **2006**, *128*, 1044−1045). The protocol involves the use of *i*-PrOH as the hydrogen donor, a Ru catalyst (0.5 mol %) generated from [RuCl$_2$(*p*-cymene)]$_2$ and 2.5 equiv of ligand **1**, and 0.1 equiv of a base such as NaOH or *t*-BuOK. Interestingly, the method reduces alkyl/alkyl ketones with excellent enantioselectivities (ee = 99%), and the optical purity of the resulting alcohols is insensitive to the extension of reaction times. Moreover, control experiments show that analogous hydrogenations using H$_2$ are less successful. The methodology is of industrial interest since BINOL is a cheap, commercially available chiral auxiliary, and the resulting chiral alcohols are valuable synthetic intermediates.



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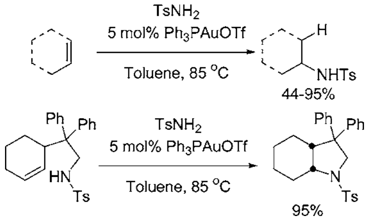
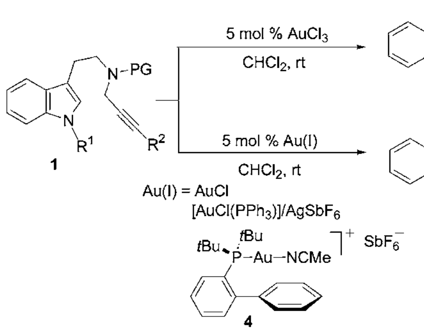
Au-Catalyzed Reactions

He and co-workers at The University of Chicago developed inter- and intramolecular versions of an Au(I)-catalyzed hydroamination of inactivated olefins (*J. Am. Chem. Soc.* **2006**, *128*, 1798−1799). The mixture of equimolar amounts of Ph$_3$PAuCl and AgOTf generates Ph$_3$PAuOTf, the catalytic species that promotes the amination of 4 equiv of olefin with 1 equiv of TsNH$_2$ in toluene at 85 °C. Terminal olefins react regioselectively to afford Markovnikov products, and preliminary results indicate that the reactions can be carried out in the absence of solvent. The choice of gold as Lewis acid is not capricious: Zn(OTf)$_2$, Cu(OTf)$_2$, and Sc(OTf)$_3$ gave none or low yields of the desired amines. Similarly, other nitrogen donors such as amines, anilines, carboxamides, carbamates, alkylsulfonamides, or sulfamates were unreactive. The intramolecular variation of this methodology using tosylated amino olefins allows the preparation of a variety of pyrrolidines with excellent isolated yields.



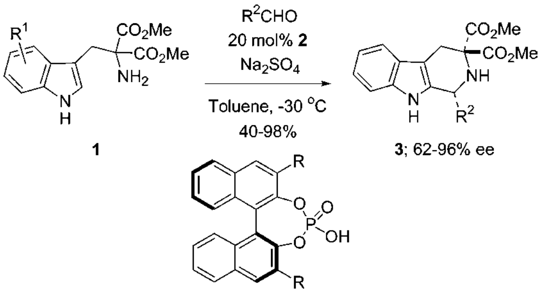
The regiochemistry of the alkenylation of indoles tethered to alkynes by four atoms is controlled by the oxidation state of the gold catalyst. Ferrer and Echavarren found that, whereas substrates **1** cyclize readily with a cationic Au (I) complex to give azepino [4,5-*b*]indole derivatives **3**, the more electrophilic AuCl$_3$ leads to indoloazocines **2** via an 8-*endo*-dig process (*Angew. Chem., Int. Ed.* **2006**, *45*, 1105−1109). When the tether is two or three atoms long, the substrate undergoes 6-*endo*-dig and 6-*exo*-dig cyclizations, respectively, resulting in the formation of 6-membered-ring derivatives. The reaction path in this is case independent of the oxidation state of the Au catalyst. The best catalyst for the formation of seven-membered rings is the air-stable Au (I) complex **4**, but AuCl can also be used. The catalyst made in situ by chloride abstraction from AuCl(PPh$_3$) with AgSbF$_6$ gave mixtures of products **2** and **3**. The communication features a comprehensive table of substrates, detailed information about characterization of byproducts, and a thorough compilation of literature in the field of hydroarylation of alkynes catalyzed by electrophilic transition-metal complexes.



PG = SO$_2$Ph, 2,4-dinitrobenzenesulfonyl

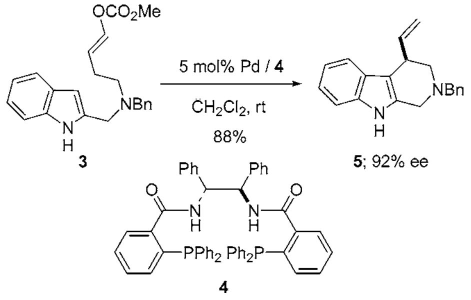
Enantioselective Synthesis of Tetrahydrocarbolines

For almost one century, the Picter-Spengler condensation has owned the franchise to the synthesis of tetrahydrocarbolines. Despite the importance of this reaction, catalytic enantioselective variations for the preparation of tetrahydrocarbolines emerged lately, when Taylor and Jacobsen executed an elegant organocatalytic version (*J. Am. Chem. Soc.* **2004**, *126*, 10558−10559). More recently, the group of List at Max-Planck Institut has developed a catalytic asymmetric Pictet−Spengler condensation promoted by the chiral Brønsted acid **2** (*J. Am. Chem. Soc.* **2006**, *128*, 1086−1087). The process affords enantioenriched tetrahydro-*β*-carbolines (**3**) from geminally diester-substituted tryptamines (**1**) and a variety of aldehydes (R^{2}CHO, R^2 = alkyl or aryl). A typical experiment requires 20 mol % of the chiral phosphoric acid catalyst in the presence of Na$_2$SO$_4$ and toluene as solvent at −30 °C during 3−6 days. The mechanistic rationale for the observed enantioselectivities involves chiral, hydrogen-bond-assisted iminium-phosphate ion pairs.



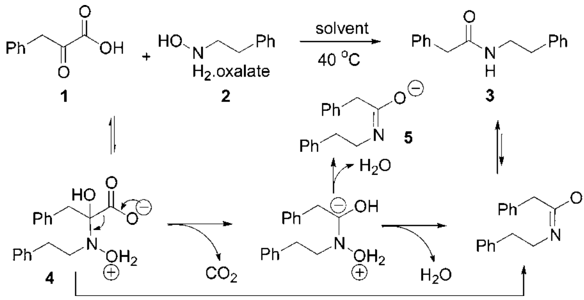
2; R = 2,4,6-(*i*-Pr)$_3$-phenyl

Bandini, Umani-Ronchi, and co-workers at Università di Bologna describe a Friedel−Crafts-type transformation that yields vinyl-substituted tetrahydrocarbolines in excellent yields and enantioselectivities (*J. Am. Chem. Soc.* **2006**, *128*, 1424−1425). The procedure relies on an intramolecular asymmetric allylic alkylation catalyzed by Pd complexes. For example, the reaction of indolyl carbonate **3** with 5 mol % [$Pd_2(dba)_3$], 11 mol % of chiral P/N ligand **4**, and 2 equiv of Li_2CO_3 in CH_2Cl_2 gives (*R*)-4-vinyl-tetrahydro-β-carboline **5** in 88% isolated yield and 92% ee. A variety of functional groups and substitution patterns tolerate these reaction conditions, indicating the generality of the methodology and its potential utility in the synthesis of other types of chiral nonracemic heterocycles.

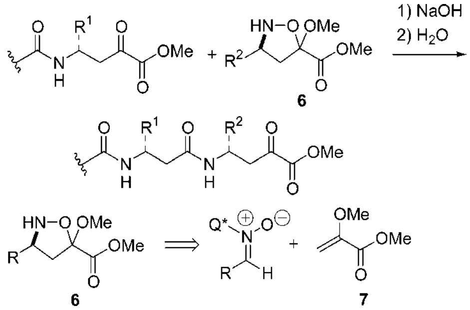


Chemoselective Amide Ligation without Coupling Reagents

The group of Bode at University of California Santa Barbara described an amide coupling that does not require reagents or catalysts, proceeds in the presence of reactive functional groups, and produces only water and CO_2 as byproducts (*Angew. Chem., Int. Ed.* **2006**, *45*, 1248−1252). Reaction of *N*-phenethylhydroxylamine and phenylpyruvic acid worked in a variety of solvents (DMF, MeOH, DMSO, acetate buffer), yielding the desired amide in 70−80% yield. Conveniently, crystalline hydroxylamine oxalates and potassium carboxylates were suitable reactants. More complex peptide ketoacids were prepared by a variant of the Wasserman ylide method (see: *J. Org. Chem.* **1994**, *59*, 4364−4366) and in turn coupled with (*S*)-alanine hydroxylamine oxalate or peptides containing these subunits. The ligation occurred cleanly in aqueous DMF without epimerization of the ketoacid, using both protected and unprotected peptides (58−80% yield). Preliminary mechanistic studies indicate that the conversion most likely takes place trough the decarboxylation of the tetrahedral intermediate **4**.

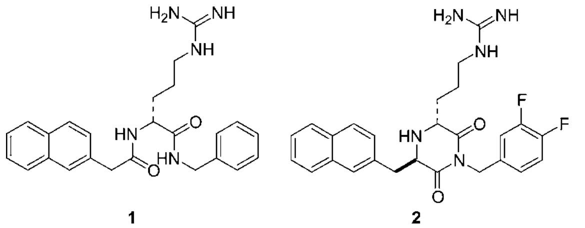


The same group communicated the assembly of poly-β-peptides using a novel synthesis of amide bonds via decarboxylative ketoacid−isoxazolidine ligations (*J. Am. Chem. Soc.* **2006**, *128*, 1452−1453). The β-amino acid building blocks, isoxazolidines **6**, were obtained by diastereoselective cycloaddition of the matching nitrones with methyl 2-methoxyacrylate (**7**) using a carbohydrate-based chiral auxiliary (Q*). The condensation of an isoxazolidine with an α-ketoacid in a 1:1 mixture of *t*-BuOH and water cleanly affords the expected amide. Further extension of the peptide chain can be achieved by reaction with another isoxazolidine, and the resulting ketoesters can be converted to the corresponding acids by oxidative decarboxylation in the presence of basic H_2O_2. The iterative synthesis can be performed without isolation of the intermediate acid. Overall, the strategy overcomes several drawbacks of the classical methodologies, namely the need of deprotection−activation sequences, the use of coupling reagents, typical slow reactions, and the requirement of an excess of the expensive β-amino acids. Moreover, the condensation is chemoselective and completes the amide bond formation in an orthogonal fashion, allowing the presence of unprotected functional groups.



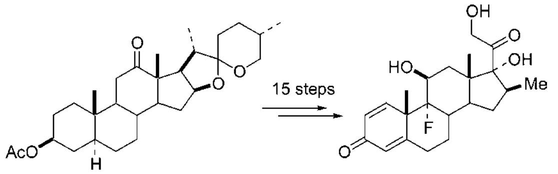
Ketopiperazines as Rigid Peptidomimetics of Arginine Amides

The development of peptidomimetic drugs aims at finding peptide analogues that maintain the conformation of biologically active peptides yet overcome their poor biopharmaceutical properties. Researchers at University of Rochester and Procter & Gamble Pharmaceuticals investigated the conformational space of arginine peptide **1** and designed conformationally constrained ketopiperazine peptidomimetic **2** (*Synth. Commun.* **2006**, *36*, 473−479). Computational modeling revealed that the ketopiperazine substituents retain the spatial orientation found in the unconstrained arginine scaffold **1**. Ketopiperazine **2** was prepared from D-allylglycine in 10 steps (23% overall yield) following a flexible route.



Synthesis of Betamethasone from the Waste of Thai *Agave*

Betamethasone (**1**) and its esters are potent antiinflammatory steroids commonly used in the topical treatment of dermatological diseases. Kongkathip and co-workers at Kasetsart University (Bangkok, Thailand) reported the semi-synthesis of betamethasone from hecogenin acetate (**2**), which in turn is obtained from fermentation of the waste of *Agave sisalana* (*Synth. Commun.* **2006**, *36*, 865−874). Although the transformation requires a sequence of 15 steps, these are high-yielding, and several can be telescoped.

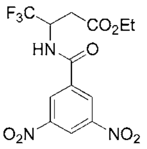


Hecogenin Acetate (**2**) Betamethasone (**1**)

Is Silica Gel Chromatography Safe for the Purification of Optically Active Compounds?

The question is posed in a recent communication by Soloshonok from the University of Oklahoma (*Angew. Chem., Int. Ed.* **2006**, *45*, 766−769). The author revisits the use of internal chirality generated by enantiomer associations to separate non- racemic mixtures using achiral chromatography, and introduces the term “self-deproportionation of enantiomers” to describe the phenomenon.

When a sample of β-amino acid **1** with 66.6% ee was subjected to silica chromatography, the fractions collected showed a large difference of ee values. The first eluted fractions had an 8.1% ee, while the later eluting ones afforded enantiomerically pure material (ee >99.9%). The trifluoromethyl group adjacent to the stereogenic center appears to be responsible for the phenomenon, as the substitution for a methyl group resulted in fractions with the same ee as the original sample. The effect has been observed in a variety of compounds with a trifluoromethyl moiety including alcohols, hydroxy acids, and amino alcohols.



Starting % ee	% ee min	% ee max
95.0	83.3	99.9
31.1	20.9	41.8
61.1	12.6	95.5
66.6	8.1	99.9

Eluent: 5:1 Hexane:EtOAc

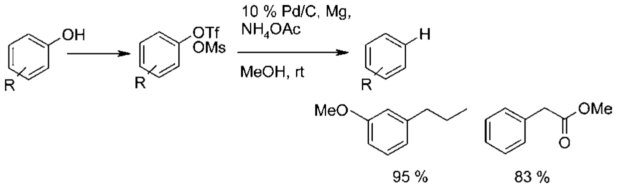
Oxidative Addition of Phenyl Bromide to Pd(BINAP) vs Pd(BINAP)(amine)

Hartwig J. F.; et al. (*Org. Lett.* **2006**, *8*, 851) have investigated the rate of oxidative addition of phenyl bromide to [Pd(BINAP)2] in the presence and absence of added amine to assess a previous hypothesis that the addition to [Pd(BINAP)(amine)] is faster than the addition to [Pd(BINAP)]. From the investigation the authors concluded that the addition to the amine complex is not faster than the addition to [Pd(BINAP)]. Instead the addition to [Pd(BINAP)], even in the presence of amine, is the major pathway for the oxidative addition of phenyl bromide. This investigation shows how valuable it is to study the stoichiometric reactions of isolated complexes when assessing the mechanism of a catalytic process.

Pd/C-Catalyzed Deoxygenation of Phenol Derivatives Using Mg Metal and Methanol

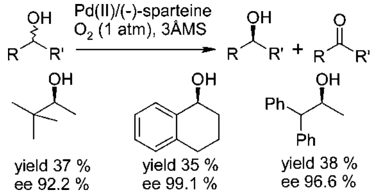
Sajiki, H.; et al. (*Org. Lett.* **2006**, *8*, 987) have developed a Pd/C-catalyzed deoxygenation method of phenolic compounds via aryl triflates or mesylates using Mg metal in methanol at room temperature. The addition of ammonium acetate dramatically affects the reactivity and reaction rate. The best substrates are the triflates. When mesylates are used as substrates, they need more Mg metal and longer reaction times to go to completion.

The use of this method would open the field for the use of a phenolic group as a directing group for the formation of uncommon substitution patterns.



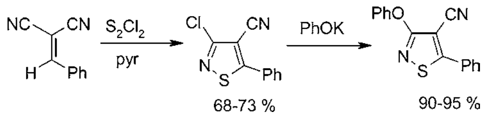
Ligand-Modulated Palladium-Catalyzed Aerobic Alcohol Oxidations

Sigman, M. S.; Jensen, D. R. (*Acc. Chem Res.* **2006**, *39*, 221) have summarized the discovery and investigation of ligand-modulated Pd-catalyzed aerobic alcohol oxidations. The work has evolved from a simple empirical discovery that (−)-sparteine, in combination with Pd^{II} salts, facilitates the aerobic oxidative kinetic resolution of secondary alcohols. The project later evolved into an in-depth physical organic investigation that has provided key insights into how new, more efficient catalysts can be designed.



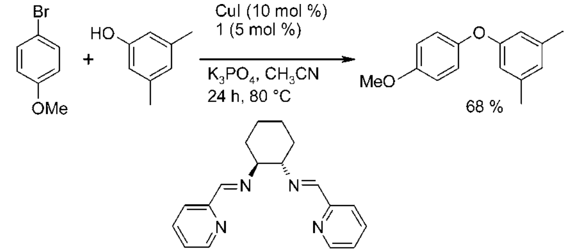
Heterocyclic Chemistry of Sulfur Chlorides: Fast Ways to Complex Heterocycles

Torroba, T.; et al. (*Eur. J. Org. Chem.* **2006**, 849) have highlighted the most important advances in the synthetic applications of sulfur dichloride and disulfur dichloride for the preparation of heterocycles. Sulfur chlorides are some of the best sulfur-transfer reagents in heterocyclic chemistry. Their high reactivity towards nucleophiles such as alkenes, alkynes, amines, nitriles, oximes, and their both chlorinating and sulfurating character explain their extensive use.



Mild Conditions for Copper-Catalyzed Ullman Coupling

Taillefer, M.; et al.(*Adv. Synth. Catal.* **2006**, *348*, 499) have found that coupling of phenols and aryl bromides or iodides can be efficiently performed by means of a catalytic amount of copper iodide (10 mol %) and the ligand **1** (5 mol %). The reaction is applicable to a wide range of substrates and proceeds at 60−80 °C in acetonitrile. K_3PO_4 is used as base. Yields are in the range of 60−97%.



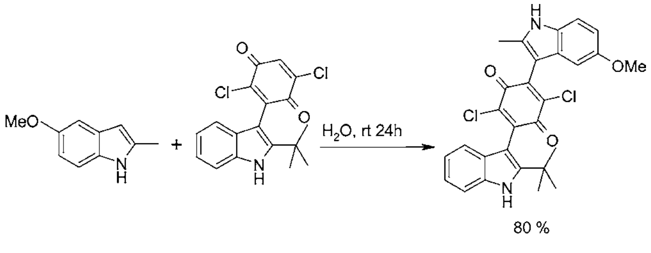
1

Ruthenium-Catalyzed Asymmetric Epoxidation of Olefins Using Hydrogen Peroxide Catalytic Activities and Mechanism

Beller, M.; et al. (*Chem. Eur. J.* **2006**, *12*, 1875) have studied the asymmetric epoxidation of olefins with 30% hydrogen peroxide in the presence of [Ru(pybox)pydic)] and [Ru(pyboxazine)pydic)] (pybox= pyridine-2,6-bisoxazoline, pyboxazine = pyridine-2,6-bisoxazine, pydic = 2,6-pyridinedicarboxylate). Mono-, 1,1-di, *cis*- and *trans*-1,2-di-, tri-, and tetra-substituted aromatic olefins with versatile functional groups can be epoxidized with this type of catalytic system in good to excellent yields and with low to good enantioselectivities. It has been shown that the presence of weak organic acids or an electron-withdrawing group on the catalyst increases the reactivity. The authors also propose new insights in reaction intermediates and reaction pathways.

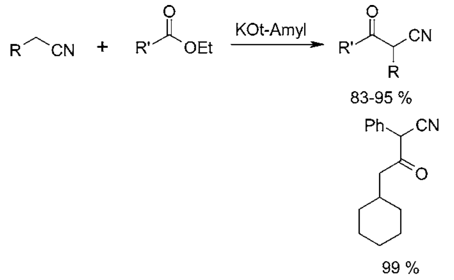
"On-Water"-Promoted Direct Coupling of Indoles with 1,4-Benzoquinones

Li, C.-J.; et al. (*Eur. J. Org. Chem.* **2006**, 869) have found that indole compounds couple highly efficiently with 1,4-benzoquinones in the absence of catalyst, organic solvents, or additives in a mixture with water. The "on-water" conditions provided the best yields of the corresponding products and the only system to produce bis-coupling products. Moderate to good yields were obtained from mono- and bis-coupling products.



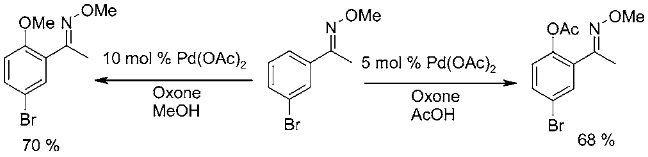
A High-Yielding Preparation of β-Ketonitriles

β-Ketonitriles are important precursors for a wide variety of heterocycles. Ji, Y.; et al. (*Org. Lett.* **2006**, *8*, 1161) have developed a facile procedure for the acylation of nitrile anions with unactivated esters for the synthesis of β-ketonitriles. Deprotonation of the nitrile is done with potassium *tert*-amylate in THF at room temperature. The reaction provides β-ketonitriles in good to excellent yields.



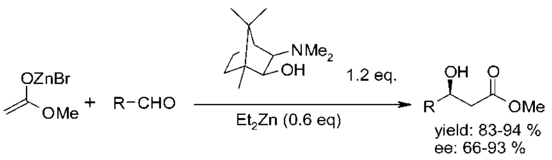
Oxone as an Inexpensive and Safe Oxidant for C−H Bond Oxygenation

Sanford, M. S.; et al. (*Org. Lett.* **2006**, *8*, 1141) have described the application of peroxide-based oxidants in the $Pd(OAc)_2$-catalyzed acetoxylation and etherification of arene and alkane C−H bonds. Oxone in acetic acid and/or methanol proved particularly effective. Moderate to good yields were obtained from a variety of different products.



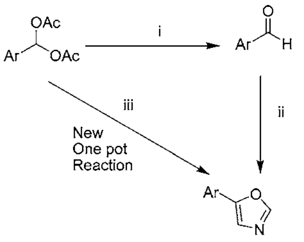
An Improved Asymmetric Reformatsky Reaction

Knochel, P.; et al. (*Org. Lett.* **2006**, *8*, 1125) have found that (−)-*N*,*N*-dimethylamino-isoborneol is an excellent ligand for the enantioselective addition of Reformatsky reagents to aromatic and aliphatic aldehydes. Enantioselectivities up to 93% ee were obtained with sulfur-containing aldehydes. In the case of benzaldehyde it was possible to obtain a higher yield and enantioselectivity when thiophene or tetrahydrothiophene was added to the reaction.



Efficient Synthesis of 5-Aryloxazoles from Arylidine Diacetates Using TosMIC

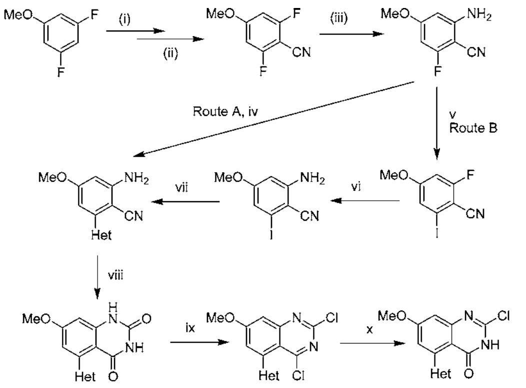
p-Tosylmethylisocyanide (TosMIC) has been found to be a very useful reagent in the construction of a number of heterocycles such as oxazoles, imidazoles, thiazoles, etc. Chen and co-workers at Bristol-Myers Squibb have reported (*Heterocycles* **2006**, *68*, 167−173) the synthesis of 5-aryloxazoles from arylidine diacetates. They have also shown the synthetic utility of this methodology in the preparation of BMS-337197, a novel IMPDH inhibitor. Usually this reaction is done in two steps—acid hydrolysis followed by treatment of the aldehyde with TosMIC in the presence of potassium carbonate. The authors have demonstrated that direct treatment of the diacetate with three equivalents of potassium carbonate gave the aryloxazoles in excellent yields (90−94%). It may be noted that the authors have used a similar strategy in the synthesis of 1-arylimidazole-5-carboxylates also. The reaction seems to be very general for heteroaryl and aryl substrates and can also be done on a large scale. The reaction conditions are mild (methanol, 55 °C), and the workup is very simple (a simple water wash and filtration) which makes this reaction very interesting from a process viewpoint.



Ar = 2-OMe-4-NO_2-C_6H_3, 4-$NO_2C_6H_4$, 2-NO_2-C_6H_4, C_6H_5, 2-Thienyl
Reagents and Conditions: (i) conc. HCl/dioxane, 89 % (ii) TosMIC, K_2CO_3, MeOH, 68 % (iii) TosMIC, K_2CO_3, MeOH, 90- 94 %

Synthesis of 5-Heterocyclic Substituted Quinazolin-4-ones via 2-Aminobenzonitrile Derivatives

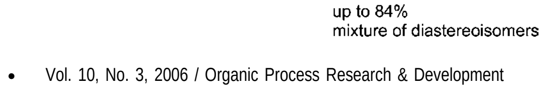
Variously substituted quinazolin-4-ones are very important and interesting building blocks in heterocyclic chemistry. Fray and co-workers at Pfizer have reported (*Heterocycles* **2006**, *67*, 489−494) the two routes synthesis of 5-heterocyclic substituted quinazolin-4-one and dichloroquinazolines via the intermediacy of 2-aminobenzonitrile. The paper describes a number of heterocycle-substituted systems, which were synthesized in moderate to good yields.



Reagents and conditions: (i) n-BuLi, THF, -78 ° C, then $CO_{2(S)}$), 86 %; (iia) $(COCl)_2$, CH_2Cl_2, 20 ° C then NH_3, THF, 71 % (iib) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 0- 20 ° C, 87 %; (iii) NH_3(g), DMSO, 90 ° C, 16 h, 88 % (iv) Het-H, (1.3 eq.), NaH, NMP, 80 ° C, 16 h; (v) $NaNO_2$, con. HCl, -10 ° C, 1 h then KI, -10 ° C to 20 ° C, 16 h, 88 %; (vi) NH_3(g), DMSO, 120 ° C, 16 h, 92 % (vii) either 1-methyl-5-tributylstannyl-1H-pyrazole, 5 mol % $Pd_2(dba)_3$, tri(2-furyl)phosphine, dioxane, reflux, 2 h, 47 % or 1-ethoxymethyl-1*H*-pyrazole, n-BuLi, THF then $ZnCl_2$, then 5 mol % $Pd_2(dba)_3$, tri(2-furyl)phosphine, THF, reflux, 20 h, 47 % or 2-thiazolylzinc bromide, 5 mol % $Pd_2(dba)_3$, tri(2-furyl)phosphine, THF reflux, 20 h, 57 % (viii) CO_2 (40 bar), DBU (3 eq.), DMF, 120 ° C, 18 h; (ix) $POCl_3$ (25 eq.), iPr_2NEt (2.4 eq.), reflux, 3 h; (x) 2M aq. NaOH (5 eq.), dioxane, 20 °C, 2 h

Reaction of α,α-Dichloroketones with Carbonyl Compounds

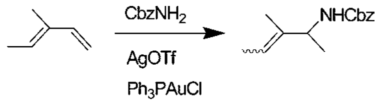
Indium bromide promotes the reductive coupling of dichloroketones with carbonyl compounds to produce highly functionalised molecules which may be useful in synthesis (Peppe, C.; et al. *Syn Lett.* **2006**, 605−609). The reaction is closely related to the Darzens reaction which is promoted by strong bases, but leads to epoxide products without isolation of intermediates. In the indium-catalysed reaction the indium appears to stabilise the intermediate and prevent epoxide formation.



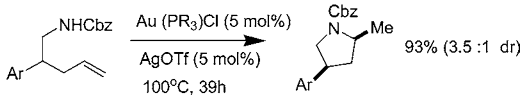
Gold-Catalysed Hydroamination of 1,3-Dienes

Although the nickel-catalysed addition of amines to conjugated dienes was known in 1971 and many other catalysts have been reported since, the reaction is often unselective, giving mixtures of 1,2- and 1,4-products.

It has now been reported that gold catalysts are ideal for the selective addition of carbonates to dienes, producing allylic amines in high yield at room temperature (Brouwer, C.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744−1747). The disadvantages, from an industrial viewpoint, are that a silver triflate cocatalyst is required to generate the "true" catalyst $Ph_3PAuOTf$ and that the best solvents seem to be dichloroethane and chloroform.

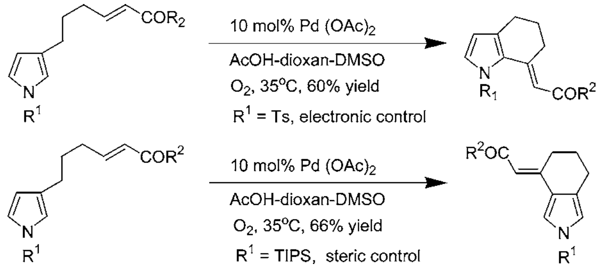


In the following paper a different group report the gold-catalysed intramolecular hydroamination of olefins by carbamates using a similar catalyst. In this case dioxan seemed to be the best solvent in a limited study. Although most reactions were designed to give five-membered ring heterocycles, six-membered rings could also be produced (Han, X.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747−1749).



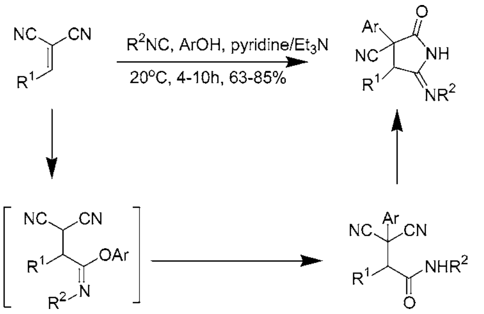
Regioselective (Pd(II)-Catalysed Alkenation of Pyrroles

Depending on the protection group on the nitrogen atom of pyrrole, palladium-catalysed oxidative alkenylation can occur either in the 2- or the 3-position in the presence of air or oxygen. Boc protection leads to C2 alkenylation, whereas TIPS protection leads to 3-alkenylation in moderate to good yields (Beck, E. M.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 2528−2529). The reaction can be used to control annelation of rings onto pyrrole. From an industrial viewpoint, it would be interesting to see if alkenylation of indoles can be similarly controlled.



A New Multicomponent Reaction

Multicomponent reactions offer advantages for organic synthesis, both on small and large scale. A new paper describes the reaction of gem-diactivated olefins with isocyanides and nitrophenols (or heterocyclic hydroxy compounds) in a sequence of reactions shown below (Mironor, M. A.; et al. *Synlett* **2006**, 615−617).

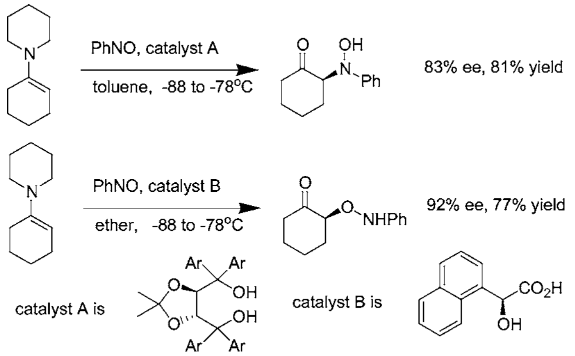


Asymmetric Catalysis by Chiral Hydrogen-Bond Donors

This excellent review, from the group of Jacobsen at Harvard, examines the role that hydrogen bonding can play in all forms of catalysis, and not only as a structural determinant for enhanced selectivity. Hydrogen bonding to an electrophile serves to decrease the electron density, resulting in activation, and this is used by enzymes for the acceleration of chemical processes.

Organic chemists have recently realised the tremendous potential offered by hydrogen bonding for activation of electrophiles in organocatalytic systems. The review examines recent advances from a structural and mechanistic viewpoint (Taylor, M. S.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543). In their conclusion, the authors point out that, to realise the full potential of organocatalysis using H-bond donors, a more detailed mechanistic understanding of the chemistry is required. Mechanistic studies will help to point the way to new catalysts and, hopefully, new transformations. As always—and particularly in process chemistry, “understanding leads to control”.

One example discussed in the review is shown below.



Microreactors: Solving the Clogging Problem

Over the years, we have highlighted many papers using microreactors where reactions are performed in microfluidic devices by flowing reactants through channels that generally range in size from 10 to 500 μm. The surface-to-volume ratio of these devices can be much higher than even round-bottom flasks and up to 3000 times larger than a 1 m^3 vessel. The resultant improved heat and mass transfer may result in increased selectivity and faster, efficient, continuous processing.

Microreactors do have disadvantages, however, the main one being that precipitates that form during reactions may clog the channels. Since in industry a large number of processes produce solids in the reaction, it would be advantageous if a microreactor system capable of handling precipitates could be devised.

The group of McQuade at Cornell has shown that performing reactions in droplets that travel through the microreactor channels inside a carrier phase may alleviate the clogging problem (Poe, S. L.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 1544−1548). The dispersed-phase droplets act as individual reactors, and the solid precipitate is confined to the droplet. The solid is kept away from the reactor walls, and clogging is prevented. (For a description of the system, see an earlier paper from the same group, Quevedo, E.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 10498−10499.)

Several reactions resulting in precipitation were described, including the synthesis of indigo by reaction of acetone with 2-nitrobenzaldehyde. Mineral oil was used as the droplets, and the production of the highly coloured dyestuff can be seen in the droplets.

In some cases, when product recovery would be difficult because of product solubility in mineral oil, a carrier phase such as hexane can be used. Highly exothermic reactions (for example, reaction of an acid chloride with an amine) could be handled safely, and increased yields were obtained. As expected, space-time yields are far superior to the corresponding batch processes.

Microreactors: Optimising Reactions on Submicrogram Scale

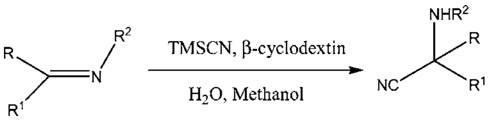
The group of Ismagilor at the University of Chicago has published widely on the topic of microfluidics to screen and optimise reactions. The latest paper from the group reports a screening method that consumes substrates on the scale of less than 1 μg per reaction, using discrete droplets (plugs) as microreactors, separated by a continuous phase of fluorinated carrier liquid (Hatekeyama, T.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 2518). The simple system comprises three components: a preformed cartridge which contains reagents (in plugs) to be screened, a T piece, and receiving tubing. After the substrate is pumped through the system using the fluorinated carrier, the products from each separate reaction, with the use of a different reagent, appear as plugs in the receiving tubing and can be subsequently analysed by MALDI-MS.

The reaction was used to control selectivity in the deacetylation of a hexaacetate of a complex, steroidal natural product, ouabain. Whereas previously the desired triacetate could only be obtained in 22% yield, in the microfluidic system, conditions were optimised to 85% yield using various basic catalysts in methanol and water or DMF.

The system is particularly useful for optimising reactions on precious substrates.

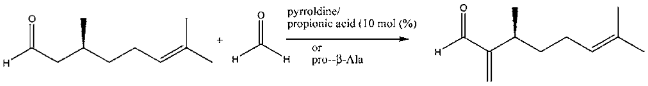
Strecker Reaction in Water

Addition of cyanide ion to imines derived from aldehydes and ketones is accomplished in water using cyclodextrin and trimethylsilyl cyanide. This method does not need an acid catalyst, and simple workup allows the reuse of the cyclodextrin. The reaction times are 1−3 h, and the yields are consistently almost quantitative (Surendra, K.; Krishnaveni, N. S.; Mahesh, A.; RamaRao, K. *J. Org. Chem.* **2006**, *71*, 2532−2534).



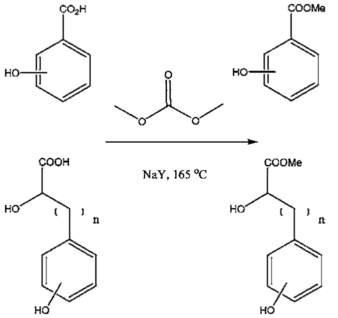
Improved Synthesis of α,*β*-Unsaturated Aldehydes from Formaldehyde and Aliphatic Aldehydes

Although α-substituted acrolein systems are produced industrially from formaldehyde using secondary amines and an acid catalyst, these conditions generally are not applicable for functionalized aldehydes. Erkkila and Pihko developed a practical method applicable to variety of aldehydes including hindered aldehydes and aldehydes containing protected alcohols and amines (Erkkila, A.; Pihko, P. M. *J. Org. Chem*. **2006**, *71*, 2538−2541). The useful catalytic systems are pyrrolidine/propionic acid or L-prol-*β*-Ala in water with small amount of 2-propanol. No isomerization of double bonds or epimerization of chiral centers adjacent to aldehydes occurs. Because of the mildness and good yields and tolerance of functional groups, this method should find practical use in multistep synthesis.



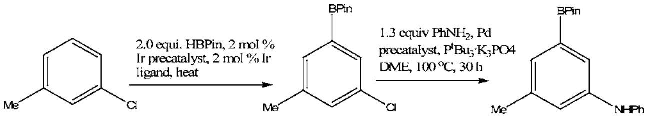
Zeolite-Catalyzed Chemoselective Methylation of Acids with Dimethyl Carbonate

Dimethyl carbonate (DMC) is a nontoxic, inexpensive solvent and reagent for a number of industrially important reactions. DMC can introduce CO_2, CH_3OH, or $-CH_3$ under appropriate reaction conditions. In the presence of commercially available NaY Faujasite, DMC selectively N-methylates substituted anilines containing $-OH$, $-COOH$, $-CH_2OH$, $-NH_2$ groups at 90−120 °C in a stainless steel autoclave (Selva, M.; Tundo, P. *J. Org. Chem*. **2006**, *71*, 1464−1470). Such selectivities can also be observed with thiophenols. In the absence of aromatic amine or aromatic thiols, aromatic carboxylic acids are selectively methylated. Such selectivities are not generally observed with K_2CO_3. The reaction conditions reported for the esterification may limit its use for molecules with heat-sensitive functional groups, but with the physical nature of the catalyst, inexpensive and readily available DMC, this reaction should find use in large-scale synthesis of industrially important molecules.



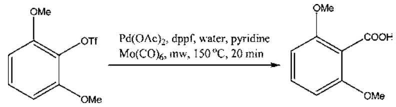
Synthesis of Borylated Aromatic Amines in One Pot

Aromatic boronates and chlorides are substrates for the preparation of aromatic amines in metal (Pd)-catalyzed reactions. Boronates are often prepared from halides including chlorides which are usually less reactive. Recently Smith et al. (Holmes, D.; Chotana, G. A.; Maleczka, R. E., Jr.; Smith, M. R., III. *Org. Lett.* **2006**, *8*, 1407−1410) demonstrated that aryl boronates can be prepared by activating a C−H bond in the presence of a C−Cl aromatic bond with an iridium catalyst. These authors have now developed a one-pot reaction for the synthesis of borylated amines from 1,3- and 1,4-substituted aryl halides. This two-step sequence produces moderate to good yields of the products. Although arylamines replace aromatic chloride, aliphatic amines produce lower yields of the corresponding products. Nevertheless, it should find uses for compounds of medicinal importance.



Hydroxycarbonylation of Aryl and Vinyl Triflates

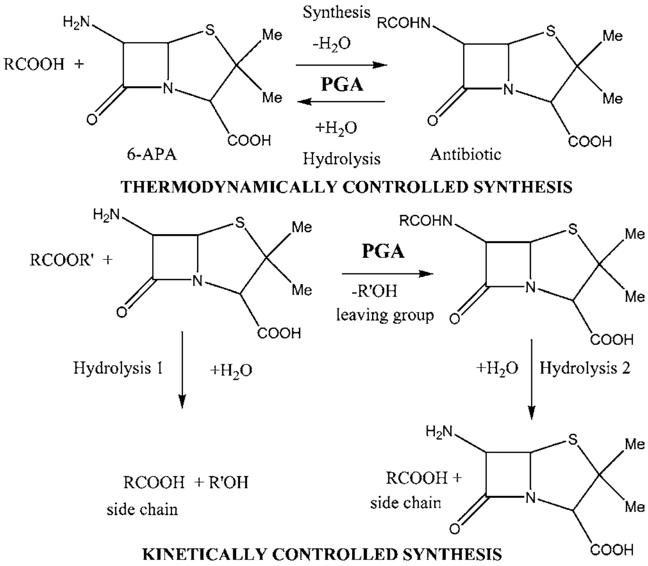
Aryl and vinyl triflates are useful starting materials for the formation of C−C, C−O, C−N, C−S bonds, when reacted with corresponding nucleophiles in the presence of palladium complexes. Silvani; et al. (Lesma, G.; Sacchetti, A.; Silvani, A. *Synthesis* **2006**, *4*, 594−596) developed a simple procedure for the preparation of aromatic carboxylic acids with solid $Mo(CO)_6$ as carbon monoxide source in water under microwave conditions. Although this method provides certain advantages over gaseous CO, molybdenum metal effluents would create problems, and use of 0.1 mol $Pd(OAc)_2$ contributes to the cost. Nevertheless the method ahould be useful for the synthesis of small, specialized aromatic carboxylic acids.



Penicillin G Acylase

In a recent paper, Giordano et al. (*Biotechnol. Adv.* **2006**, *24*, 27) reviewed literature from the viewpoint of the industrial enzymatic reactor optimization. The kinetically controlled process of production of *β*-lactam antibiotics, using immobilized penicillin G acylase (PGA) in aqueous media with simultaneous crystallization of the reaction product appears to be the best process alternative.

Different groups have tried to exploit the thermodynamically controlled process. However, few substrates have the desired charge (in the pH enzyme active range, 6−8), solubility and basic (or nucleophilic) requirements. On the other hand, although the kinetically controlled process is subject to many drawbacks (for instance, competitive hydrolytic pathways), it is much easier to overcome them, and in this case optimization of reactor's operational conditions plays a fundamental role. The mainstream configuration of the industrial reactor, a fed-batch system with immobilized PGA, in aqueous medium, with product crystallization, is appropriate for the application of model-based



dynamic optimization, optimal control, among other engineering techniques.

L-Ascorbyl Linoleate Production

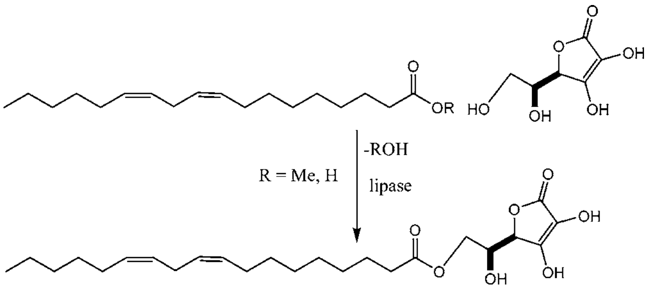
L-Ascorbyl fatty acid derivatives, such as palmitic acid derivatives, are important in the food industry, e.g. to preserve oil- and emulsified-carotene-based food colors and as crumb-softening agents in bread, but they can also be used to protect human umbilical vein endothelial cells treated with H_2O_2.

Therefore, a number of lipase-mediated processes to produce L-ascorbyl saturated fatty acid derivatives have been published in the literature. Recently, Song et al. (*Bioprocess Biosyst. Eng.* **2006**, *28*, 211) studied the lipase-catalyzed production of L-ascorbyl linoleate, the first unsaturated fatty acid derivative, in organic solvents.

Novozyme 435 from *Candida antarctica* was used as catalyst. In addition to linoleic acid, other fatty acids were studied as well, using 2-methyl-2-butanol as solvent.

The experimental results indicated that the reaction yield for unsaturated C18 fatty acid was higher than for saturated C18 fatty acid. In general, conversion decreased with increasing fatty acid concentration (86% at 6 mM and 16% at 400 mM).

Product yield in a transesterification reaction (33.5%), using methyl linoleate, was higher than in a direct esterification (21.8%) at a high substrate concentration. Removal of water and/or methanol shifted the reaction equilibrium towards the production of L-ascorbyl linoleate.



Fatty Acid Esters Production in SC CO_2

Sugar fatty acid esters are nonionic surfactants with a variety of applications, especially as emulsifiers in food products such as ice creams and mayonnaises.

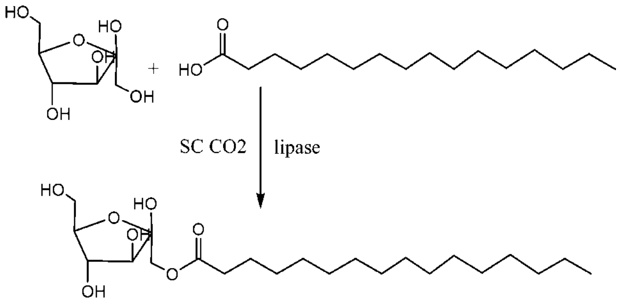
The best method to produce these compounds, direct esterification, however, presents a number of drawbacks, including the need of using toxic reagents and unfriendly solvents in chemical synthesis, and the water formation problem.

Enzymatic synthesis of fatty acid sugar esters led to the production of pure products due to the specificity of the enzyme with no need of using toxic reagents. However, even in this case water formation is a problem, and unfriendly solvents have to be avoided.

Supercritical carbon dioxide (SC CO_2) has several advantages as an alternative solvent for that kind of reaction. It is nontoxic, nonflammable, and presents friendly supercritical requirements ($T = 304$ K, $P = 7.3$ MPa). In this way, Sabeder et al. studied the esterification of fructose, catalyzed by a lipase, with palmitic acid in organic solvents and in SC CO_2 in a batch reactor (*Ind. Eng. Chem. Res.* **2005**, *44*, 9631).

Novozyme 435 from *Candida antarctica* was used as catalyst.

The highest ester concentration was obtained at an enzyme concentration of 10% after 72 h reaction (75% conversion). It was verified that molecular sieves (necessary with ordinary solvents) are not required in SC CO_2 in the absence of cosolvents.



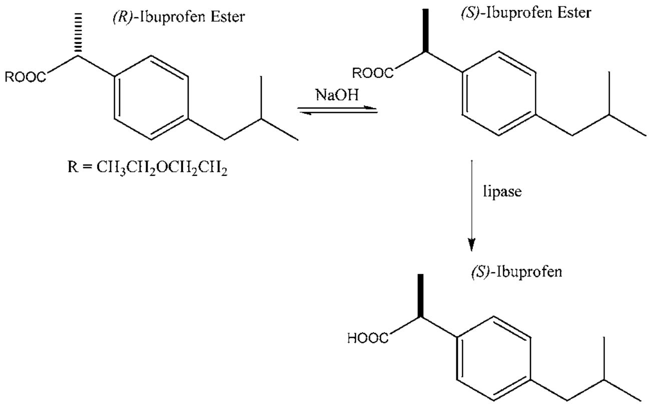
(*S*)-Ibuprofen via Dynamic Kinetic Resolution

A lipase-catalyzed enantioselective hydrolysis process with in situ racemization of the remaining (*R*)-ibuprofen was developed for the production of (*S*)-ibuprofen from (*R*,*S*)-ibuprofen ethoxyethyl esters in isooctane (Fazlena et al. *Bioprocess Biosyst. Eng.* **2006**, *28*, 227).

Lipase from *Candida rugosa*, XAD 7, was used as catalyst and immobilized in Amberlite.

Dynamic kinetic resolution using the addition of NaOH into the reaction medium enhanced the formation of (*S*)-ibuprofen, (27.7 mM at 69.3% conversion, 950% improvement compared to conventional kinetic resolution). Optimum temperature proved to be around 45 °C (79% conversion), leading to a product showing 98.6% ee (for a discussion on the use of the term ee, see: Gawley *J. Org. Chem.* **2006**, *71*, 2411) The best performance was using 0.5

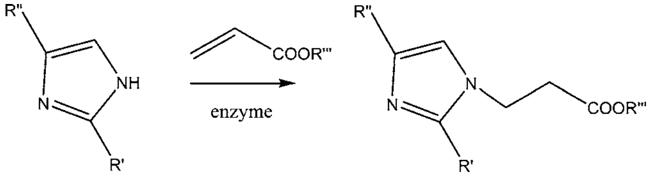
M NaOH, 45 °C and addition of DMSO as cosolvent at 20% (v/v).



Hydrolase-Catalyzed Michael Additions

Wu et al. (*J. Biotechnol.* **2006**, *121*, 330) described a hydrolase-catalyzed Michael action of imidazoles to acrylic monomers in organic media. A variety of enzymes have been tested. The enzyme previously investigated, the alkaline protease of *Bacillus subtilis*, was chosen as the reaction model. In general, good yields were obtained in 3−4 days, using pyridine or chloroform as solvents.

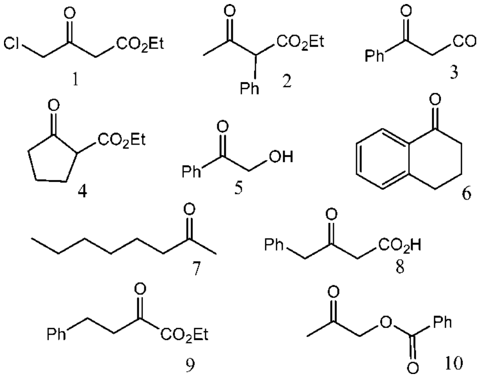
Other enzymes, such as lipases and proteases, were also able to catalyze this reaction. In general, conversion was dependent on log *P*. Higher conversions were attained with solvents with highest log *P*, a behavior found previously with lipases.



Ketoreductases in a Tool-Box

Kaluzna et al. (*Tetrahedron: Asymmetry* **2005**, *16*, 3682) reported the results of a reduction of a variety of ketones using 31 commercially available ketoredutases.

The enzymes accept a wide substrate range (1−10), with good specific activities as measured in spectrometric assays by loss of absorbance at 340 nm resulting from decrease of NADPH concentration in enzyme−substrate mixtures.



Twelve enzymes showed activity on almost every ketone tested, while the other 19 enzymes were active in four or more ketones. High activities were observed (10−59 U/mg), and more importantly, for every ketone tested there was at least one enzyme identified as active.

In general *S*-enantioselectivity was found. However, two enzymes showed the reverse selectivity.

Good isolated yields were achieved, and the enzymes supported well the addition of DMSO.

Process Simulation in the Pharmaceutical Industry: A Review of Some Basic Physical Models

Kremer and Hancock from Pfizer published an interesting review (Kremer, D. M.; et al. *J. Pharm. Sci.* **2005**, *95* (3), 517) of process modeling efforts employed to elucidate certain fundamental physical processes associated with the manufacture and delivery of pharmaceutical dosage forms. Because the use of process models has dramatically increased in the pharmaceutical industry in recent years, this review is a welcome update. The authors briefly discuss model verification and model validation: verification implies that the process model is solving the model's mathematical equations correctly, while validation implies the model is solving the correct equations. We are reminded that, to gain insight into new, or poorly understood physical phenomena, we should use a combined approach of numerical and experimental efforts. Two classes of models are reviewed: continuum and discrete. In the continuum models category solid mechanics, heat and mass transfer, fluid dynamics, inhalation modeling, spray drying, agitated vessels, and flow of granular material are reviewed. Discrete models using the hard sphere or soft sphere approaches are discussed. The growth of computational fluid dynamics (CFD) methods is commented upon, with several physical processes benefiting from CFD calculations. Examples of processes relevant to the pharmaceutical industry that can benefit from CFD simulations are: mass transfer, chemical reactions, multiphase flow, aerosols, mixing, etc. Advanced CFD models are probably being developed for multiphase flow within the human lung, flow of granular materials, etc. The authors conclude that... "fueled by science-centered regulatory initiatives cost and quality concerns, the utilization of process modeling technologies will afford significant opportunities for optimization and quality enhancement in the future".

A Stereochemical Approach that Demonstrates the Efect of Solvent on the Growth of Polar Crystals: A Perspective

Lahav and Leiserowitz from the Weizmann Institute provide their perspective for the topic of the influence of solvent on the kinetics of growth of different crystalline faces (Lahav, M.; et al. *Cryst. Growth Des.* **2005**, *6* (3), 619). This fundamental topic, of interest to crystallization practitioners, has been discussed in the literature extensively, in particular in a recent paper by Srinivasan and Sherwood, explicitly addressed by Lahav and Leiserowitz (ref 12 therein). In that study, Srinivasan et al. observed crystal growth of α-resorcinol in both vapor and aqueous solution. Lahav and coauthors present evidence that the extent of the anisotropic growth observed with certain polar crystals, such as α-resorcinol, may depend on the type of solvent used. Such growth can be rationalized in terms of solvent binding to the pertinent crystal faces; the growth is often slowed by strong solvent binding. In an accompanying article, Lahav et al. use molecular modeling to support an alternative explanation for the crystal growth of polar crystals, that of "self-poisoning". Other groups investigating the growth of α-resorcinol in aqueous solutions, and using a stereochemical approach, were able to control crystal growth by executing the crystallization in the presence of tailor-made auxiliaries.

Monitoring a Crystallization Induced by Compressed CO_2 with Raman Spectroscopy

A group from the Université Paris (Vega-Gonzales, A.; et al. *AIChE J*. **2006**, *52* (4), 1308) reports the use of Raman spectroscopy for detecting and monitoring a CO_2 antisolvent crystallization process of griseofulvin in acetone. One of the challenges for monitoring such processes is the pressure in the vessel; this issue was addressed by placing a Raman probe head, working in backscattered mode, directly in front of a sapphire window of the vessel. Another challenge in online quantitative monitoring is the calibration protocol; the authors used six binary solutions of griseofulvine in acetone. Two griseofulvin Raman peaks were selected for quantification, and because of overlap with acetone, solvent subtraction was executed. To account for incidental changes over time of Raman parameters which could negatively impact accurate quantification, the griseofulvin peak intensity was ratioed to the acetone peak intensity. An excellent calibration model was developed. The authors showed that Raman spectroscopy can be used to measure solute concentration over time and to interpret events observed during crystallization. Such methods could be expanded to process control capabilities, specifically of average particle size and width of particle size distribution, by controlling residence time within and without the metastable zone.

Separation of Organic Acids by Polysulfone Microcapsules Containing Trioctylamine

Separation of organic acids is commercially very attractive, and conventional techniques such as distillation, fractional crystallization, and dissociative extraction have been reported. In this regard, polysulfone (PS) microcapsules containing trioctylamine (TOA) were successfully prepared with a phase inversion method, and the influence factors on the microcapsules have been investigated. The extraction performance of the microcapsules has also been carried out with oxalic acid, propionic acid, and citric acid as solutes, and the stability of the microcapsules was tested. The results show that proper ethanol content in solidification solution, an optimal distance from pinhead to the surface of solidification solution, and an appropriate emulsion composition are in favor of forming regularly spherical microcapsules. The prepared microcapsules have uniform outside surfaces and there is no apparent deficiency. The microcapsules have hollow structures and digital structures in the walls. Parts of TOA are immobilized in the wall with small particle form. The mass-transfer rate and the uptakes to the organic acids are high enough. After seven times of repeated extraction and stripping, the microcapsules kept almost the same extraction ability, indicating that the microcapsules have very good stability in the extraction process (*Sep. Purif. Technol.* **2006**, *48* (3), 235−243).

Direct Propylene Epoxidation over Modified $Ag/CaCO_3$ Catalysts

Direct oxidation of propylene to propylene oxide is not analogous to that of ethylene to ethylene oxide, and the industry is looking for a real breakthrough. In a collaborative work of Japanese and U.S. laboratories, a series of supported Ag catalysts was studied for propylene epoxidation with molecular oxygen as the oxidant. It was found that α-Al_2O_3 and $CaCO_3$ were suitable supports for propylene epoxidation and that, on the latter, Ag particles between 400 and 700 nm gave the highest selectivity to propylene oxide (PO). Ball-milling treatment of the $CaCO_3$ catalyst and promotion with NaCl resulted in improved catalytic performance. The highest PO selectivity (45%) was obtained on a ball-milled catalyst with a silver loading of 56 wt % supported on $CaCO_3$ and promoted with 1 wt % NaCl (Ag(56)−NaCl(1)/$CaCO_3$). The catalysts were tested with reactant flow rates of C_3H_6:O_2:He = 5:10:15 $cm^3\ min^{-1}$, a gas hourly space velocity (GHSV) of 1800 h^{-1}, a reaction pressure of 0.3 MPa, and a reaction temperature of 533 K (260 °C). Addition of 500 ppm of ethyl chloride (EtCl) to the reactant gases enhanced the stability of the Ag(56)−NaCl(1)/$CaCO_3$ catalyst. X-ray diffraction (XRD) of the Ag(56)−NaCl(1)/$CaCO_3$ catalyst detected the existence of AgCl in the catalyst, and ultraviolet−visible (UV−vis) diffuse reflectance spectroscopy confirmed the presence of surface Ag^+ species. SEM showed a roughening of the Ag particles by the ball-milling treatment as well as by the addition of NaCl. The effect of NaCl on the enhancement of the catalytic performance was probably due to both physical and electronic changes in the properties of the catalyst. The NaCl not only helped increase the dispersion of the silver on the $CaCO_3$ support but also probably increased the quantity of electrophilic oxygen species favorable for epoxidation. In situ UV−vis spectra suggested that the rapid reduction of Ag^+ species on the surface of the Ag(56)−NaCl(1)/$CaCO_3$ catalyst could be the cause of a decline in PO selectivity observed during reaction (*Appl. Catal., A* **2006**, *302* (2), 283−295).

Granular Material Flow

The field of granular flow with attention both to the history and the underlying physics that govern the field has been critically reviewed including basic transport mechanisms in a granular flow and contact mechanics—the way that individual particles see each other mechanically. The limiting regimes of granular flow, the Quasi-static and the Rapid-Flow regimes are discussed, leading to a review of the Elastic picture of granular flow, which both unifies the Quasi-static and Rapid regimes and fills in the intervening space. The rheological behavior of granular systems changes with system-scale constraints, and in particular, the materials behave differently under controlled-stress and controlled-concentration conditions. The Elastic model allows one to place boundaries on where the Quasi-static and Rapid-Flow cannot be applied to common granular flows (*Powder Technol.* **2006**, *162* (3), 208−229).

Implementation of Industrial Health and Safety in Chemical Engineering Laboratories

How much safety do we practice in our labs in academia? Or do we just wrap the issue under the carpet? Here is an article for Chemical Engineering educators. Theoretical classes in technical university teaching provide background information, whereas laboratory practices show practical ways of proceeding in real situations. Consequently, the experimental practices are targeted at educating students in solving problems in industry or research studies. It attempts to apply industrial health and safety criteria to the design and start-up of a laboratory for chemical engineering teaching. First, the design and location of the laboratory facilities are fully described. This design is then developed according to the course program priorities, university availability, and affordable budget. Careful attention should be paid to complying with health and safety regulations in laboratories. Second, as far as education is concerned, students should be trained in specific safety regulations for chemical engineering laboratories, in addition to the basic safety information they receive in the preliminary university courses (*J. Chem. Health Safety* **2006**, *13* (2), 19−23).

Al_2O_3-Promoted Sulfated Zirconia for *n*-Butane Isomerization

This paper reports on an investigation using steady-state isotopic transient kinetic analysis (SSITKA) of Al_2O_3-promotion of sulfated zirconia (SZ) for *n*-butane isomerization. SZ promoted with Al_2O_3 showed an approximately 30% increase in *n*-butane isomerization activity at 250 °C. The average surface residence times of the reaction intermediates on unpromoted and Al_2O_3-promoted SZ measured by SSITKA suggest that the active sites on both catalysts were identical. There was, however, a significant increase in the concentration of surface intermediates upon Al_2O_3 promotion, leading to the increased activity. Al_2O_3 promotion also appeared to improve catalyst site stability, resulting in a slower rate of deactivation (*Catal. Commun.* **2006**, *7* (4), 209−213).

Mesostructured Barium Sulfate as Catalyst in Methane Activation

Barium sulfate with lamellar and tubular microstructure is developed by Chinese workers through a surfactant templating route under different synthesis conditions. Lamellar barium sulfate was synthesized through direct combination of Ba^{2+} and $SO_4{}^{2-}$ in an aqueous solution containing sodium dodecyl benzene sulfonate (SDBS). Agglomerate barium sulfate nanotubes are obtained by the reaction of Ba^{2+} and $CaSO_4$ in the SDBS aqueous solution. Preparation of regular single barium sulfate nanotubes is achieved by the controlled hydrolysis of dimethyl sulfate in an aqueous solution containing Ba^{2+} and SDBS. TEM studies indicate the tube wall thickness was 7−8 nm, and the inner diameter was about 6 nm. When such mesostructured barium sulfate was loaded with $VOSO_4$ and sulfuric acid (100%), it performed excellently in catalyzing oxidative conversion of methane to methanol using molecular oxygen. The conversion proceeded at a relatively lower temperature (under 250 °C) than over general solid catalysts, and the selectivity to methanol remained high when methane conversion increased to an acceptable level. When the reaction proceeded stably, the one-pass conversion of methane was about 30%, and the selectivity to methanol could reach 50% (*J. Catal.* **2006**, *239* (2), 282−289).

Removal of Benzene from Aqueous Solutions by Carbon Molecular Sieve-Filled Poly(dimethylsiloxane) Pervaporation Membranes

The preferential permeation of benzene over water has a great commercial relevance, and it has been studied by a large number of workers. Recently, such a study has been conducted by Chinese researchers with carbon molecular sieve (CMS)-filled poly(dimethylsiloxane) (PDMS) pervaporation membranes. The membranes were characterized by SEM and mechanical strength measurement. The effects of CMS content, benzene concentration in feed solution, operating temperature, and feed Reynolds number on the pervaporation properties of the CMS-filled PDMS membranes have been studied. Their results showed that the addition of CMS could enhance the mechanical stress of PDMS membranes. With CMS content increasing, permeation flux decreased slightly, but separation factor increased to some extent. With the increase of benzene concentration in the feed solution and of Reynolds number of the feed, permeation flux and separation factor both improved significantly. With operating temperature increasing, permeation flux increased, but separation factor decreased (*Sep. Purif. Technol.* **2006**, *48* (3), 229−234).

Enzymatic Recovery and Purification of Polyhydroxybutyrate Produced by *Ralstonia eutropha*

Polyhydroxybutyrate (PHB) is the most studied among a wide variety of polyhydroxyalkanoates, bacterial biodegradable polymers known as potential substitutes for conventional plastics. Evaluation of the use of enzymes to recover and purify the PHB produced by *Ralstonia eutropha* DSM545 is recently reported. Screening experiments allowed the selection from six enzymes of trypsin, bromelain, and lysozyme on the basis of their efficiency in lysing cells of a non-PHB-producing *R. eutropha* strain. Then, process conditions for high efficiency in PHB purification from the DSM545 cells were searched for the enzymes previously selected. The best result was achieved with 2.0% of bromelain (enzyme mass per biomass), equivalent to 14.1 U mL^{-1}, at 50 °C and pH 9.0, resulting in 88.8% PHB purity. Aiming at improving the process efficiency and reducing the enzyme cost, experiments were carried out with pancreatin, leading to 90.0% polymer purity and an enzyme cost 3 times lower than the one obtained with bromelain. The molecular mass analysis of PHB showed no polymer degradation. Therefore, this work demonstrates the potential of using enzymes to recover and purify PHB and bacterial biopolymers in general (*J. Biotechnol.* **2006**, *122* (4), 453−462).

Photochemical Treatment of Aqueous Linear Alkylbenzene Sulfonate

A pilot plant for the photochemical degradation of linear alkylbenzene sulfonates (LABS) is tested. LABS are a major aqueous pollutant and need to be treated effectively. A solution of LABS with the initial concentration of 100 mg/L was degraded in the presence of ultraviolet light alone with the wavelength of 254 nm and the combination of ultraviolet light with the wavelength of 254 nm along with hydrogen peroxide (UV-254/H_2O_2). The photochemical degradation of LAS by UV-254 was effectively enhanced by the addition of 720 mg/L H_2O_2 (optimum loading) to the system. In addition, it was shown that the pilot-plant photochemical reactor is not mass-transfer limited and it was appropriate to degrade large amounts of aqueous pollutants by UV-254/H_2O_2 processes (*Sep. Purif. Technol.* **2006**, *49* (2), 115−121).

Direct Synthesis of Hydrogen Peroxide on Zirconia-Supported Catalysts

Palladium catalysts supported on SO_4^{-2}-, Cl^--, F^--, and Br^--doped zirconia were tested for the direct synthesis of hydrogen peroxide under very mild (1 bar and 20 °C) and nonexplosive conditions. The catalysts were characterized by thermogravimetric/differential scanning calorimetry analysis, N_2 physisorption, and temperature-programmed reduction before and after catalytic tests to investigate the oxidation state of the metal. The catalytic tests were carried out in different solvents, and the effect of the Pd oxidation state was ascertained. The best catalytic results were observed in methanol, using H_2/O_2 mixtures containing a large excess of oxygen and using the sulfate-doped zirconia catalyst. Surface-oxidized Pd^0 catalysts showed high catalytic activity and the highest selectivity (Melada, S.; et al. *J. Catal.* **2006**, *239* (2), 422−430).

A Membrane Reactor Intensifying Micromixing

The micromixing efficiency in a membrane reactor was studied by employing competing parallel reactions. In the membrane reactor, one liquid is added gradually into another one through the nanoscaled micropores of ultrafiltration membranes. The effects of molecular weight cutoff (MWCO) of membranes, permeation fluxes, Reynolds number, and reactants concentrations on the segregation index were investigated. The results show that the decreasing MWCO of the membranes and the increasing Reynolds number favour the enhancement of micromixing efficiency. Compared with the other reactors (e.g., stirring tank, ultrasound, static mixer, Coutte flow reactor), the membrane reactor exhibits excellently intensified micromixing (*J. Membr. Sci.* **2006**, *276* (1−2), 295−300).

Chiral Selective Membranes for Electrodialytic Separation of Racemates

Chiral selective cation-exchange membrane (CSCM) and chiral selective anion-exchange membrane (CSAM) were prepared by blending poly(vinyl alcohol) (PVA) as basic material, β-cyclodextrin (β-CD) as chiral selector, and ion-exchange materials. Chiral selective capacities of these membranes were evaluated by electrodialysis resolution experiments. Electrodialysis separation of DL-4-hydroxyphenylglycine (HPG) racemic mixture showed that the chiral selective membranes had resolution effect. In acid medium, D-HPG^+ took the precedence over L-HPG^+ in passing through the CSCM, and the selectivity $\alpha_{D/L}$ of two kinds of CSCM were 1.21 and 1.34, respectively. In base medium, L-HPG^- took the precedence over D-HPG^- in passing through the CSAM, and the selectivity $\alpha_{D/L}$ was 0.84 (*J. Membr. Sci.* **2006**, *276* (1−2), 193−198).

Static Mixers with a Gas Continuous Phase

A group of French researchers have critically reviewed the hydrodynamics and mass-transfer characteristics of gas−liquid contactors containing static mixers (SMs) (*Chem. Eng. Sci.* **2006**, *61* (11), 3429−3434). These mixers are used with a gas continuous phase. Two types of SM were implemented in concurrent flows, Statiflo and Lightnin. The pressure drop ΔP, the volumetric interfacial area a, and the volumetric mass-transfer coefficient k_La were measured in several configurations: horizontal flow, vertical up-flow, and vertical down-flow. The influences of position and flow rates were studied to understand the behaviour of these contactors and to optimise the operating conditions. As expected, the pressure drop was found to increase mainly with gas velocity but also with liquid velocity and to reach 3300 Pa in the range of velocities studied (the gas-flow rate varied between 4 and 30 m^3/h and the liquid flow rate between 0 and 100 L/h), far less than Sülzer SM. The volumetric interfacial area and the volumetric mass transfer coefficient showed the same changes, a varying between 100 and 1000 m^2/m^3 and k_La reaching 0.07 L/s. This is interesting compared with other classical absorption processes: indeed, even if packed towers can provide the same range of values, the operating conditions are more drastic, or the dimensions of the apparatuses are far larger than SM ones. The position was also found to have an influence on the hydrodynamic and mass-transfer parameters (ΔP, a, and k_La).

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OP060084H