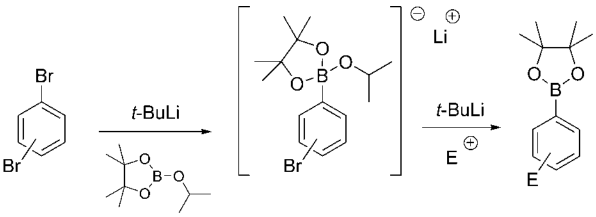
Organic Process Research & Development **2007**, *11*, 928–939

Highlights from the Literature

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

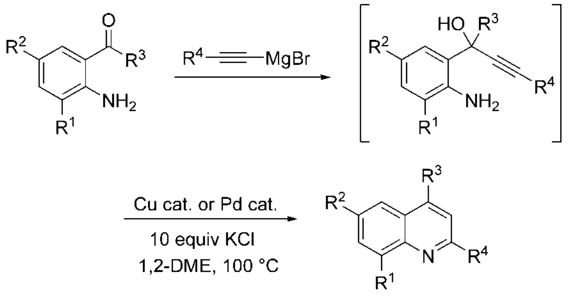
Metal−Halogen Exchange of Halogenated Arylboronates



8 examples, 47-78% yield

Metal−halogen exchange is an important and widely used method for the selective functionalization of aromatic compounds. However, successful metal−halogen exchange of halogenated arylboronic acids (or related boron derivatives) is normally regarded as a challenging transformation. This can be explained by the fact that boronates, being Lewis acids, react with most organometallic reagents used in metal−halogen exchange. Now Zhichkin and co-workers at AMRI describe the in situ protection of arylboronates with lithium isopropoxide (*J. Org. Chem.* **2007**, *72*, 6618–6620). The key to preventing side reactions with the metalating agent is the reversible complexation of the boron atom with isopropoxide to give a stable "ate" species. Inexpensive dibromoarenes can be employed as starting materials for one-pot reaction sequences involving monometalation and boronation/protection, followed by a second metalation and electrophilic quench, ultimately leading to functionalized arylboronates. Eight substrates, including some heterocyclic examples, are provided with yields ranging from 47% to 78%.

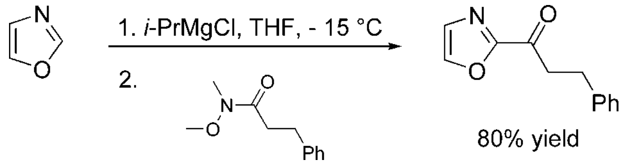
Synthesis of Substituted Quinolines



40 examples, 20-90% yield

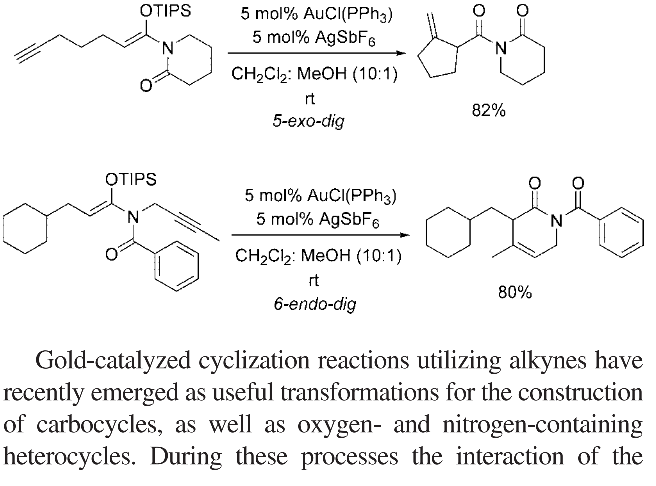
A general and convenient synthesis of substituted quinolines by regioselective Cu- or Pd-catalyzed 6-*endo-dig* cyclization−dehydration of 1-(2-aminoaryl)-2-yn-1-ols is reported by Gabriele and co-workers (*J. Org. Chem.* **2007**, *72*, 6873–6877). The necessary substrates were obtained by Grignard addition reaction between the appropriate alkynylmagnesium bromide and 2-aminoaryl ketones and could be used without further purification for the subsequent cyclization step. Heteroannulation reactions were carried out in MeOH or DME as the solvent at 60 or 100 °C in the presence of $CuCl_2$ or PdX_2 (in conjunction with 10 equiv of KX, X = Cl, I) as the catalyst to afford the quinoline derivatives in good yields.

Efficient Preparation of 2-Acyl Oxazoles



The C2 functionalization of oxazoles via metalation provides a unique challenge within the area of oxazole chemistry. Complications stemming from the "open-chain" structure of the metallated intermediate are often encountered. In particular, attempts to directly acylate lithiated oxazoles using acid chlorides have led to the undesired *O*-acylated compounds as the major products. Pippel and co-workers at Johnson and Johnson now report that treatment of oxazole or 5-aryl oxazoles with *i*-PrMgCl smoothly generates the corresponding 2-magnesiated reagents, which react with Weinreb amides to provide exclusively 2-acyl oxazole products (*J. Org. Chem.* **2007**, *72*, 5828–5831). Initially, a study of the solution structure of a magnesiated oxazole using NMR spectroscopy indicated that the predominant form was the ring-opened enolate. Following this observation, the authors concluded that any subsequent reaction to provide ring-closed products would have to proceed via a dynamic kinetic resolution. Consequently, Weinreb amides were chosen as likely successful electrophiles, owing to their attenuated reactivity and the stability of the resultant tetrahedral intermediates.

Au(I)-Catalyzed Cyclizations



Gold-catalyzed cyclization reactions utilizing alkynes have recently emerged as useful transformations for the construction of carbocycles, as well as oxygen- and nitrogen-containing heterocycles. During these processes the interaction of the

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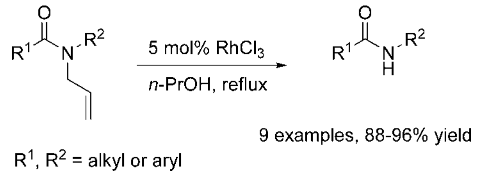
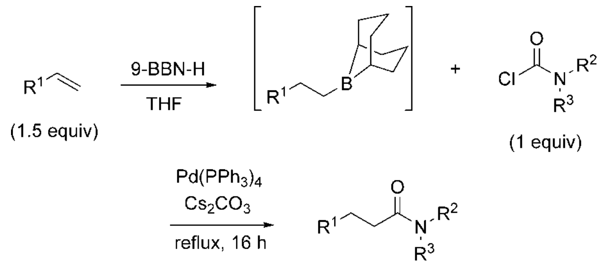
alkyne with a cationic gold catalyst (π-acid) reduces the electron density of the triple bond, thereby rendering it electrophilic. Consequently, a pendent carbon or heteroatom nucleophile may undergo nucleophilic addition followed by subsequent transformations to furnish carbocycles or heterocycles. In a recent Note, Shen and co-workers at Merck describe an extension of chemistry previously reported by the Toste group, where silyl ketene amides and carbamates provide the nucleophilic reactivity in these cyclizations (*J. Org. Chem.* **2007**, *72*, 6287–6289). The mild reaction conditions, convenient procedures, and complete control of regiochemistry are the main advantages associated with this method for the generation of cyclopentane and dehydro-δ-lactam derivatives.

Rh-Catalyzed Deprotection of Acyclic *N*-Allyl Amides



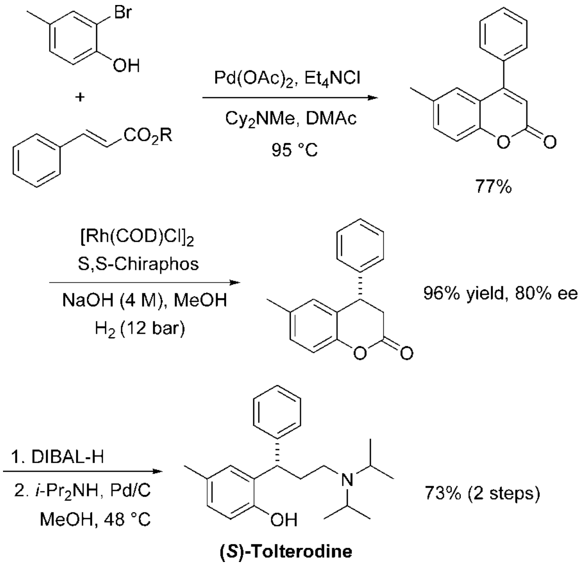
Although the allyl group can afford useful protection for amides, its subsequent removal from the substrate is often a nontrivial task. Reported methods for this deprotection have included both Rh- and Ru-based procedures; however these involve acidic hydrolysis as a separate step after isomerization of the double bond. Now, a convenient one-step $RhCl_3$-catalyzed deprotection of acyclic *N*-allyl amides is described by Zacuto and co-workers at Merck (*J. Org. Chem.* **2007**, *72*, 6298–6300). The developed conditions proved applicable to a range of *N*-allyl amides, including aromatic and aliphatic substrates and also a carbamate. Preliminary mechanistic studies revealed that the key to success is the dual function of $RhCl_3$ in the alcoholic solvents used for this process. Reaction of $RhCl_3$ with *n*-PrOH not only provides an active rhodium hydride species to catalyze isomerization of *N*-allyl amides to corresponding enamides but also generates a crucial catalytic amount of HCl to convert the enamides to deallylated amides through *N*,*O*-acetal exchange.

One-Pot Amidation of Olefins



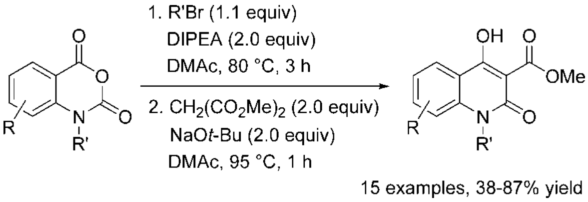
In another paper concerning the amide functional group, Takemoto and co-workers describe a one-pot synthesis of C1-elongated amides starting from olefins and carbamoyl chlorides (*J. Org. Chem.* **2007**, *72*, 5898–5900). To probe the reaction parameters, styrene and *N*,*N*-dibenzylcarbamoyl chloride were chosen as substrates. Hydroboration of styrene with 9-BBN-H in THF was followed by addition of the carbamoyl chloride, palladium catalyst (5 mol %), and an inorganic base and the mixture was heated to reflux. To avoid hydrolysis of carbamoyl chloride, anhydrous basic conditions rather than aqueous conditions were chosen for the coupling. Following some experimentation, $Pd(PPh_3)_4$ and Cs_2CO_3 surfaced as the optimum catalyst and base. Application of the developed conditions across 9 different substrates afforded yields ranging from 62% to 87%.

Enantioselective Syntheses of (*S*)- and (*R*)-Tolterodine



A short enantioselective synthesis of (*S*)- and (*R*)-tolterodine is reported by Ulgheri and co-workers (*J. Org. Chem.* **2007**, *72*, 6056–6059). The synthesis begins with a Heck reaction between methyl cinnamate and 2-bromo-4-methylphenol, which affords the coumarin upon workup. Attempts to conduct a similar Heck coupling between the same aryl bromide and *N*,*N*-diisopropylcinnamide were unsuccessful. Rh-catalyzed asymmetric hydrogenation of the coumarin intermediate was optimized to proceed in 96% yield and 80% ee, although conditions for this step were not varied extensively. Completion of this synthesis involves lactone reduction and reductive amination, followed by ee upgrade via tartrate salt formation.

Practical Preparation of 4-Hydroxyquinolinone Esters

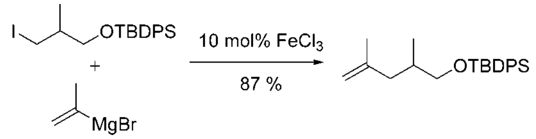


4-Hydroxyquinolinone esters are often found as substructures in pharmaceuticals, and various methods for the preparation of these compounds are available from the literature. A drawback of these methods is the use of sodium hydride as the base, which raises significant safety issues and limits their application to large-scale synthesis. Beutner and co-workers at Merck describe a practical, safe, and general method that employs a combination of diisopropylethylamine and sodium *tert*-butoxide for the preparation of these commonly encountered heterocycles (*J.

Org. Chem. **2007**, *72*, 7058–7061). This allows for the synthesis of 4-hydroxyquinolinone esters and amides in good yields with no requirement for chromatography.

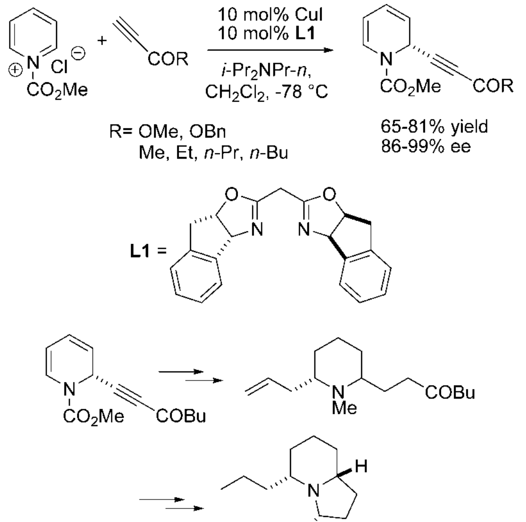
Iron-Catalyzed Cross-Couplings

Fe-catalyzed cross-couplings constitute a more environmentally benign alternative to analogous transformations mediated by Pd, Co, or Ni. Cossy and co-workers at CNRS in Paris have reported the first Fe-catalyzed cross-coupling reactions between alkyl halides and alkenyl Grignard reagents catalyzed by $FeCl_3$ (*Angew. Chem., Int. Ed.* **2007**, *46*, 6521–6524). In a typical experiment, the addition of a solution of Grignard reagent in a mixture of THF and TMEDA to a solution of alkyl halide in THF at 0 °C affords the desired adducts in good yields in the presence of 10 mol % $FeCl_3$. The reaction tolerates a wide scope of functional groups including ethers, acetals, esters, amides, and silyl ethers and does not work with aryl halides. The use of radical clocks to probe the reaction pathways suggests that the oxidative addition of Fe to the alkyl halide proceeds by a single electron transfer mechanism.

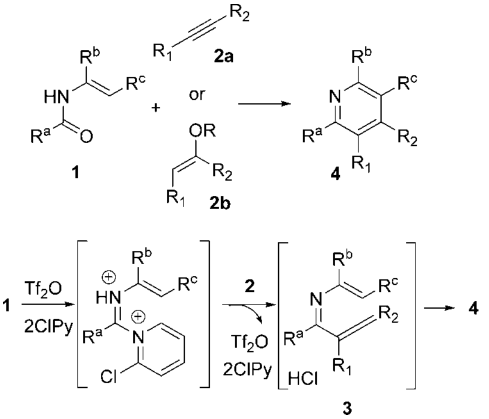


Synthesis of Piperidine and Pyridine Derivatives

The group of Dawei Ma at the Chinese Academy of Sciences in Shanghai developed an asymmetric addition of terminal alkynes to 1-acylpyridinium salts catalyzed by CuI (*J. Am. Chem. Soc.* **2007**, *129*, 9300–9301). Chiral induction was achieved with the bis(oxazoline) ligand **L1**, with best results obtained using a combination of the base *i*-Pr_2NPr-*n* and CH_2Cl_2 as the solvent. It is noteworthy that a 1:5:5:5 ratio of pyridine/ethyl chloroformate/alkyne/base is required for the reaction to occur. Thus, when equimolar amounts of reagents were used, the dihydropyridines were isolated in poor yields, probably due to the incomplete formation of the pyridinium salt. The resulting adducts are useful building blocks for the elaboration of polysubstituted piperidines and indolizidines.

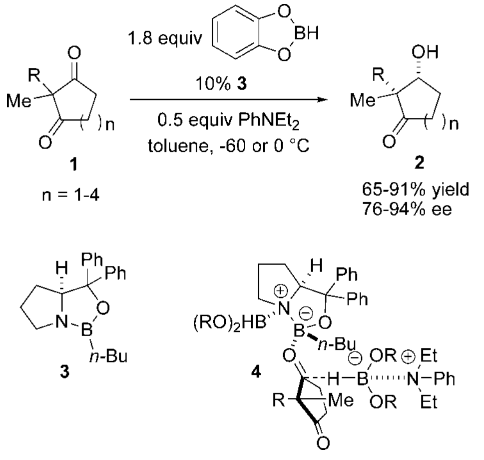


When *N*-vinyl and *N*-aryl amides were activated with triflic acid and 2-chloropyridine, they reacted with alkyloxy or silyloxy acetylenes to yield pyridines or quinazolines in a single-step procedure (Movassaghi, Hill, and Ahmad *J. Am. Chem. Soc.* **2007**, *129*, 10096–10097). Under optimum reaction conditions, these electron-rich π acetylenes added to a variety of electron-rich and electron-deficient *N*-aryl amides. The substitution pattern of the products is determined by the substrates employed. After the addition step, removal of the pyridinium salt (2-ClPyr·TfOH) followed by annulation of the highly reactive intermediate **3** leads to polysubstituted heterocycles **4**. The versatility of this approach is a valuable addendum to the azaheterocyclic synthesis toolbox.



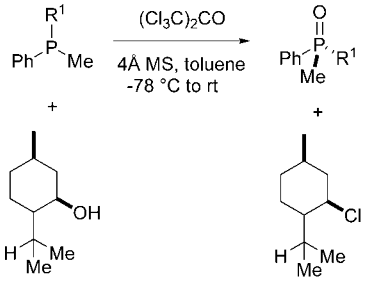
A New Look to Older Strategies (1): Enantioselective Reduction of Cyclic 1,3-Diketones

While developing an enantioselective version of the remarkably short synthesis of estrone reported by Torgov and Anacheko (*Tetrahedron Lett.* **1963**, *4*, 1533–1558), Corey and co-workers at Harvard discovered an enantioselective reduction of cyclic achiral 1,3-diketone using a variation of the Corey−Bakshi−Shibata reduction (*J. Am. Chem. Soc.* **2007**, *129*, 10046–10047). Addition of catechol borane to a solution of diketones **1** and $PhNEt_2$ in the presence of oxaborolidine catalyst **3** (toluene, −60 or 0 °C) afforded alcohol **2** in good yields and ee's. The reaction follows the opposite stereocourse than the standard CBS reduction and can be explained on the basis of the interactions between $PhNEt_2$ and catechol borane in the intermediate assembly **4**. The methodology is an alternative to reduction by enzymatic processes.



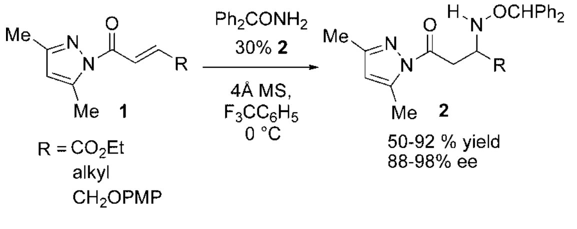
A New look to Older Strategies (2): Appel Conditions for Asymmetric Oxidation of Phosphines

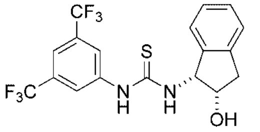
A myriad of chiral nonracemic phosphorus compounds are used as ligands in transition-metal-based chemistry as well as organocatalysis. The vast majority have their chirality located on the carbon backbone (C-stereogenic) instead of on the phosphorous atom (P-stereogenic), as the latter compounds are effective but difficult to synthesize. Collaboration between two research groups in Ireland led to the use of the oxidation/reduction/dehydration system known as the Appel conditions for the asymmetric oxidation of phosphines (*J. Am. Chem. Soc.* **2007**, *129*, 9566–9567). The process is a simple dynamic resolution of P-stereogenic phosphines in P^{III}/P^{V} interconversions. Phosphine oxides were obtained in good ee's (up to 80%) and excellent yields by reaction of phosphines with an excess of inexpensive (−)-menthol (1.2 equiv) and hexachloroacetone (1 equiv) at low temperatures. The cost of stoichiometric quantities of (−)-menthol, which is converted into (+)-*neo*menthyl chloride with high selectivity, compares favorably with the cost of typical loadings of a chiral metal-based catalyst. The enantiomeric excesses obtained are the highest reported for asymmetric phosphine oxidation. The method opens a new route for the synthesis of enantiopure bisphosphine oxides of high utility in asymmetric catalysis.



Thioureas as Organocatalysts in Conjugate Amine Additions

The group of Sibi at North Dakota State University continues pursuing their elegant development of organocatalysts for the synthesis of β-amino acids. They recently reported a highly efficient conjugated addition of hydroxylamine to enoates using a bifunctional catalyst (*J. Am. Chem. Soc.* **2007**, *129*, 8064–8065). Pyrazole crotonate **1** has the properly positioned H acceptors to afford high selectivities upon activation by a chiral thiourea. The urea catalyst is rigid and contains an aminoindanol substituent with *cis*-stereochemistry. Addition of $BnONH_2$ to crotonate **1** under optimized conditions ($CF_3C_6H_5$, 4 Å MS, 0.3 equiv **2**, 0 °C) efficiently afforded hydroxylamine derivatives **3**, which could be readily converted into β-amino acids.





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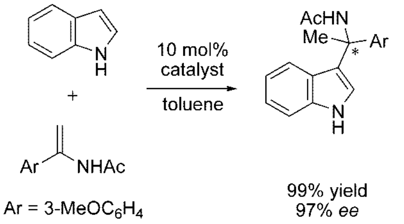
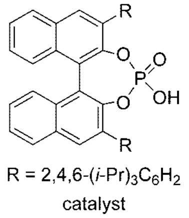
Chiral Brønsted Acid Catalysis

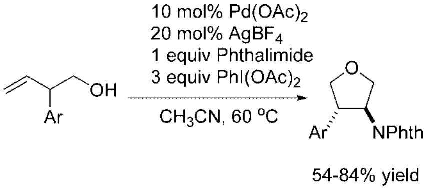
The use of chiral phosphoric derivatives as catalytic Brønsted acids is expanding rapidly. Recently, the group of Zhou at Nankai University (China) developed an asymmetric Friedel–Crafts alkylation of indoles with α-aryl enamides (*Angew. Chem., Int. Ed.* **2007**, *46*, 5565–5567). The reactions mediated by 10 mol % catalyst took place at 0 °C to room temperature in toluene during 6–48 h in the presence of 4 Å molecular sieves. Acetamides bearing quaternary carbons were obtained in excellent yields with high enantiomeric excess. Control experiments suggest that the hydrogens on the N atoms of both the indole and the enamide are crucial for the catalyst to promote the reaction. The authors propose a mechanism involving the dual activation of indole and the enamide—on its ketimine tautomeric form—through two hydrogen bonds with the chiral phosphoric acid.





Aminooxygenation of Alkenes Catalyzed by Pd^{II}/Pd^{IV}

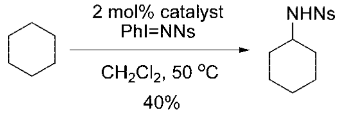
In *Angew. Chem., Int. Ed.* **2007**, *46*, 5737–5740, Desai and Sanford report the aminooxygenation of 3-alken-1-ols in a continuation of the group efforts to develop useful transformations based on Pd^{II}/Pd^{IV} catalytic cycles. Under optimized conditions, treatment of 3 equiv of alkene with 10 mol % $Pd(OAc)_2$, 3 equiv of $PhI(OAc)_2$, 1 equiv of phthalimide, and 20 mol % $AgBF_4$ in acetonitrile yields 3,4-disubstituted tetrahydrofurans resulting from an intramolecular oxygenation. This process is stereoselective, displaying high selectivity for the *trans* diastereoisomers. The communication contains detailed mechanistic studies. In short, *cis*-aminopalladation generates a σ-alkyl Pd species that in turn undergoes intramolecular oxidative functionalization with retention of configuration at the carbon centre.



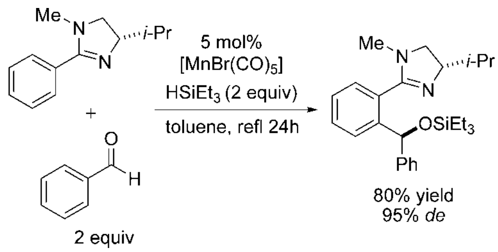
C–H Activations Catalyzed by Metals

The discovery of transition-metal-based catalysts capable of amidating inactivated alkanes in an intermolecular fashion remains a pending subject. He and co-workers at University of Chicago describe a silver-catalyzed amidation that enables the transformation of a C–H into a C–N group (*Angew. Chem., Int. Ed.* **2007**, *46*, 5184–5186).

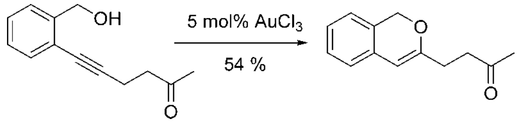
For example, the species generated from AgOTf and 4,7-diphenyl-1,10-phenanthroline amidates cyclohexane in the presence of PhI═NNs (Ns = *p*-nitrosulfonyl) as the source of nitrene. The crystal structure of the catalytic complex reveals a disilver(I) core with two ligands stacked. A series of insightful experiments based on this observation suggest that the dinuclear core is compulsory to achieve the nitrene transfer. In addition, the catalytic system also works in intramolecular amidations and amidations at benzylic positions.



Kuninobu and co-workers achieved the insertion of an aldehyde into an arene C–H bond to give benzyl alcohols using catalytic [$MnBr(CO)_5$] and stoichiometric Et_3SiH (*Angew. Chem., Int. Ed.* **2007**, *46*, 6518–6520). The procedure involves the generation of an aryl nucleophile through oxidative addition of the arene to the Mn, insertion of the aldehyde, and reductive elimination of Mn via silylation of the resulting alkoxy moiety. The latter step yields dihydrogen and contributes to the recycling of the Mn complex. An asymmetric variation of the theme uses a chiral imidazoline, which plays the role of "ortho-directing" group and most probably coordinates the Mn^{III} intermediates.

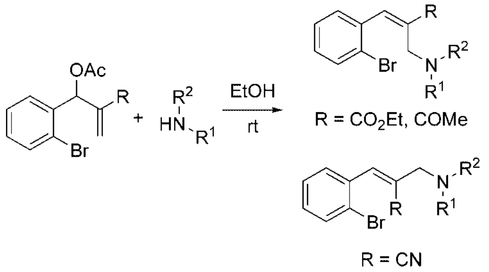


Gold is an active metal in C–H activation. The groups of Hashmi (Sttutgart University, Gemany) and Laguna (Universidad de Zaragoza-CSIC, Spain) describe the transformation of 2-propargyl benzylic alcohols into isochromenes catalyzed by gold under mild conditions (*Angew. Chem., Int. Ed.* **2007**, *46*, 6184–6187). A mechanistic hypothesis supported by experimental data suggests a sequence involving electrophilic C–H activation at the benzylic followed by insertion of the alkyne.



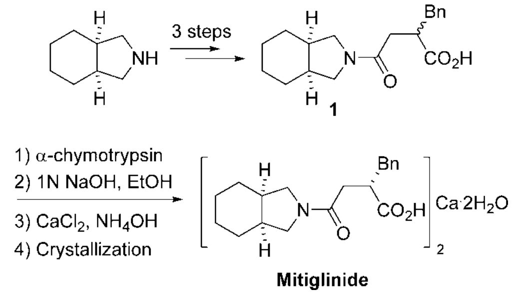
Amination of Baylis−Hillman Acetates in EtOH

While researching a Pd-catalyzed one-pot synthesis of dihydroquinolines by reaction of Baylis−Hillman acetates with *p*-toluidine, Park, Yoon, and co-workers isolated the target product along with the corresponding allylamine (*Synth. Commun.* **2007**, *37*, 2677–2685). Their serendipitous discovery prompted the development of a simple protocol for the reaction of the aforementioned acetates with *p*-toluidine, benzyl amine, and potassium phthalimide. Pd-containing reagents did not play a role in the reaction, which progressed at room temperature in EtOH as the solvent. When R = CO_2Et or COMe, the products obtained featured the *E*-configuration. In contrast, when R = CN, the *Z*-alkenes were obtained (70–95% yields).

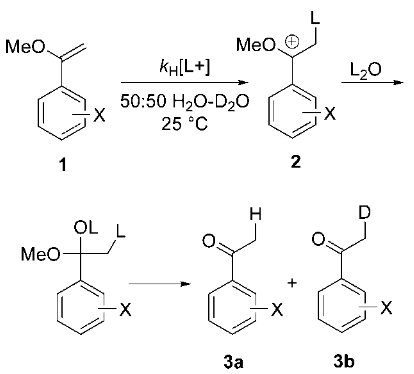


Convenient Synthesis of the Hypoglycemic Agent Mitiglinide

Scientists at the Shanghai Institute of Pharmaceutical Industry reported a short synthesis of the novel title agent aimed as a putative treatment for type-2 diabetes mellitus (Huang and Cen, *Synth. Commun* . **2007**, *37*, 2153–2157). The key step involves the resolution of the racemic ester **1** with α-chymotrypsin. The desired enantiomer is obtained with >99% ee's and an overall yield of 26%, which constitutes a considerable improvement over previous resolution methods that used chiral bases.

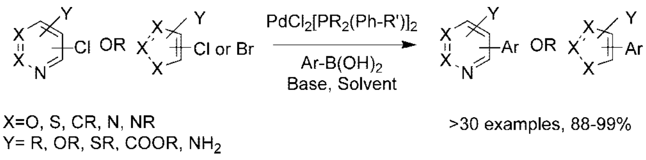


Determination of Kinetic Isotope Effects by ^{1}H NMR



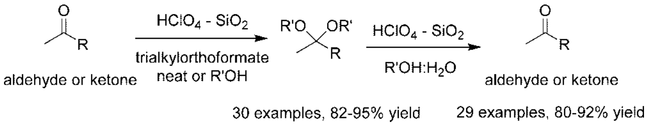
Kinetic isotope effects on proton transfer (KIEs, k_H/k_D) at carbon in hydroxylic solvents can be predicted by theory and determined by experiment. Recent theoretical studies incorporate advances in computer power, but there has been little effort to apply modern analytical techniques to extend classical experimental studies. Tsang and Richard used ^{1}H NMR to determine KIEs in the protonation of ring-substituted α-methoxy styrenes (*J. Am. Chem. Soc.* **2007**, *129*, 10030–10031). The authors determined the product isotope effect (PIE) on the acid-catalyzed protonation of vinyl ethers **1** in 50:50 H_2O/D_2O at 25 °C by analyzing ACH_3 and ACH_2D, the peak areas for the singlet corresponding to the Me group in **3a**, and the triplet corresponding to the CH_2D grouping **3b** ($PIE = [ACH_3]/1.5[CH_2D]$). Since the protonation is the first step in the hydrolysis reactions, KIE measures the fractionation of H and D between L_3O^+ and the transition state **2**. The data provided evidence that the Hydron transfer at **1** proceeds by overcoming the reaction barrier, as opposed to tunneling through it.

New Catalysts for Heteroaromatic Suzuki–Miyaura Couplings



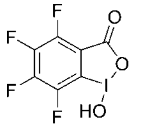
Deactivation of metal catalysts by heteroatoms and labile protons has long plagued cross-coupling reactions. Many reactions still suffer from low yields, high catalyst loadings, or the need for protection/deprotection strategies. A recent advance described by Guram and co-workers is the development of new air-stable palladium catalysts for Suzuki–Miyaura cross-coupling reactions of heteroaryl chlorides with aryl/heteroaryl boronic acids (*J. Org. Chem.* **2007**, 5104–5112). The catalysts, generated in two steps from commercially available starting materials, promote excellent product yields and high catalyst turnover (up to 10,000 TON) on a diverse array of substrates. Deactivation studies showed little effect of chelating substrates on catalyst efficiency. Tolerance of up to 50 mol % of 2-aminopyridine or 4-aminopyrimidine was demonstrated in the reactions of 2-chloro-*m*-xylene and 3-amino-2-chloropyridine with *p*-tolylboronic acid without loss of catalyst activity.

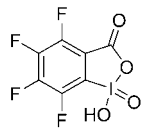
Inexpensive, Efficient, and Reusable Catalyst for Acetal/Ketal Formation and Their Deprotection to Aldehydes/Ketones



An inexpensive and efficient catalyst for both the protection of aldehydes and ketones as acetals and ketals and their deprotection utilizing perchloric acid adsorbed on silica gel ($HClO_4 \cdot SiO_2$) has been reported by Chakraborti and co-workers (*Synthesis* **2007**, *2*, 299–303). Methyl or ethyl acetal formation is effective using 1.1 equiv of trialkylformate and 0.5 mol % $HClO_4 \cdot SiO_2$. The reaction can be performed either neat at room temperature or in anhydrous alcoholic solvents (MeOH or EtOH) and is generally complete in <10 min. High yields and purities were isolated after dilution in EtOAc, separation of the catalyst by filtration, and removal of solvent. The catalyst can be regenerated at 80 °C under reduced pressure. Deprotection to the parent carbonyl compounds was achieved in moderate to high yield utilizing the same reagent (0.5 mol % $HClO_4 \cdot SiO_2$) in aqueous methanol or ethanol.

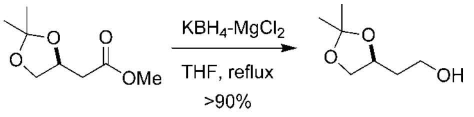
New Hypervalent Iodine Reagents: Tetrafluoro-IBA and -IB


FIBA


FIBX

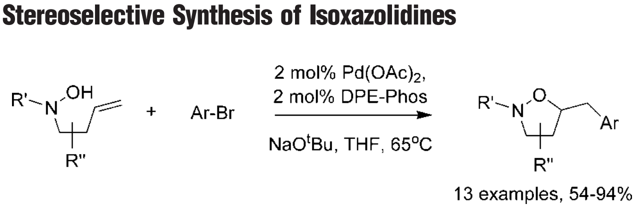
IBA and IBX promote many powerful transformations such as installation of α,*β*-unsaturation to carbonyl compounds, oxidations, and cyclizations by single-electron transfer processes. Their use has been limited due to safety reasons (explosive), the need for elevated temperatures, and low solubility in organic solvents necessitating highly polar aprotic solvents such as DMSO. In order to increase solubility and reactivity, Wirth and co-workers have prepared FIBA and FIBX in two steps from commercially available 2,3,4,5-tetrafluorobenzoic acid (*Angew. Chem., Int. Ed.* **2007**, *46*, 6529–6532). Both promote in all cases faster reactions than their nonfluorinated counterparts and have demonstrated utility in common solvents such as acetonitrile. Another attractive feature of FIBA and FIBX is the ability to directly measure reactivity by ^{19}F NMR spectroscopy without the use of deuterated solvents. The safety profile of these new reagents as yet remains unexplored.

Practical Reductions of Carboxylic Acids and Their Derivatives Using KBH_4–$MgCl_2$



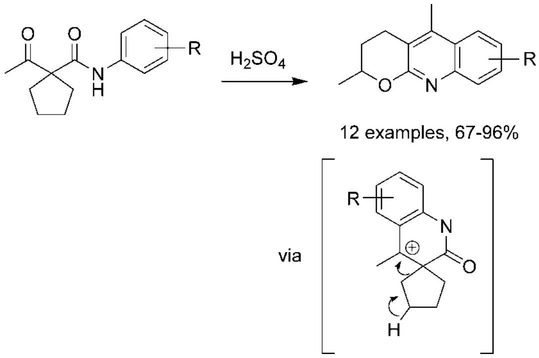
In an effort to develop inexpensive alternatives to lithium aluminum hydride and sodium borohydride reductions to obtain 1,2-*O*-isopropylidine-1,2,4-dihydroxybutanetriol, a practical and efficient method for reductions of carboxylic acids has been shown by Zhang and co-workers (*Tetrahedron Lett.* **2007**, *48*, 7595–7598). With 1 equiv of the potassium borohydride complex with $MgCl_2$, yields greater than 90% were obtained in under 2 h. Notably, reduction of other carboxylic acid derivatives containing halogens, Si-O bonds, and nitro groups were tolerated in moderate to good yields.

Stereoselective Synthesis of Isoxazolidines



A new method of synthesizing isoxazolidines through palladium-catalyzed carboetherification of *N*-butenylhydroxylamines has been described by Wolfe and co-workers (*Angew. Chem., Int. Ed.* **2007**, *46*, 6492–6494). The substrate scope showed tolerance of electron-poor, electron-rich, *ortho*-substituted, and heterocyclic aryl bromides. The reaction can also accommodate substitutions on the tether between the hydroxylamine and the alkene, providing disubstituted isoxazolidines with moderate to excellent stereocontrol (3:1 to 20:1), complementary to that of nitrone cycloadditions.

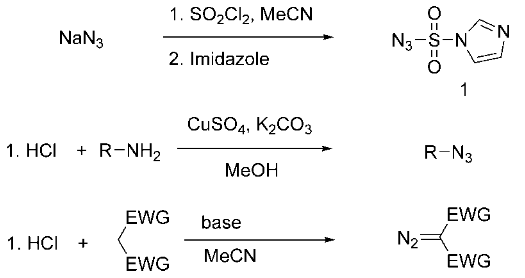
An Efficient Synthesis of Pyranoquinolines



An unusual sulfuric acid mediated domino reaction to produce pyrano[2,3-*b*]quinoline derivatives has been described by Zhang and co-workers (*Org. Lett.* **2007**, *9*, 3651–3653). The starting cyclopentanecarboxamides were generated in high yields through reactions of 1,4-dibromobutane and the corresponding β-ketoamides. The proposed mechanism involves cyclization and loss of water to generate a tertiary carbocation, followed by ring expansion and subsequent cyclization. The presence of electron-withdrawing or electron-donating substituents on the aryl ring did not result in lower product yields.

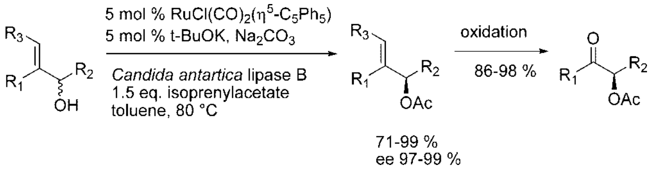
An Efficient and Shelf-Stable Diazotransfer Reagent

The design and synthesis of a new diazotransfer reagent, imidazole-1-sulfonyl azide hydrochloride has been reporteLd (Goddard-Berger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797). This reagent has been proven by the authors to equal triflyl azide in its ability to act as a "diazo donor" in the transfer of primary amines into azides and activated methylene compounds into the corresponding diazo compounds. In the case of the diazo compounds only highly activated compounds such as diethyl malonate seem to give a fairly good yield. Less activated compounds are inert towards the reaction conditions. The authors have prepared the reagent in a one-pot reaction on large scale from inexpensive starting materials. They also state that the reagent is shelf-stable.



Chemoenzymatic Dynamic Resolution of Allylic Alcohols: A Highly Enantioselective Route to Acyloin Acetates

The group from J.-E. Bäckvall at the Arrhenius Laboratories in Stockholm (*Org. Lett.* **2007**, *9*, 3401) has developed various dynamic kinetic resolutions (DKR) based on the principle where the racemic starting material is in an oxidation–reduction equilibrium through a ruthenium-catalyzed process. From the product mixture an enzyme is selectively producing one isomer and subsequently forming the corresponding acetate or some other ester derivative. The group has now reported the DKR of sterically hindered allylic alcohols utilizing *Candida antartica* lipase B and a ruthenium catalyst. The optically pure allylic acetates were subsequently subjected to an oxidative cleavage with ruthenium trichloride and sodium periodate to form the corresponding acyloins without loss of chiral information.

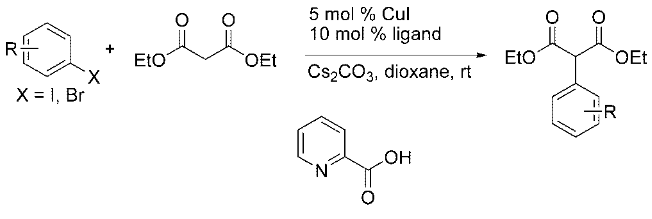


Convenient Synthesis of Palladium Nanoparticles in Water

Sarkar, A. et al. (*Org. Lett.* **2007**, *9*, 3639) have found an efficient synthesis of Pd nanoparticles in water using a Fischer carbine complex as the reductant and PEG as the capping agent. The collodial palladium (1 mol %) was found to efficiently catalyze the Hiyama cross-coupling reaction under aerobic conditions. The authors found that the catalytic activity and the stability of the nanoparticles inversely correlate. The authors present 16 examples of the cross-coupling reactions of arylsiloxanes with aryl bromides to form broad range of products catalyzed by the nanoparticles in water in yields between 88% and 98%.

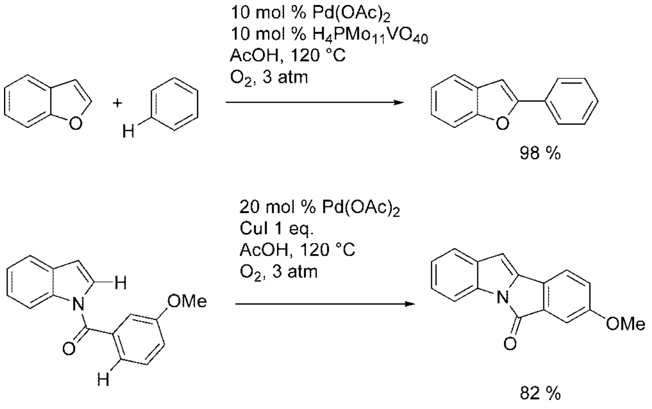
Room-Temperature Copper-Catalyzed α-Arylation of Malonates

Kwong, F. Y. et al. (*Org. Lett.* **2007**, *9*, 3469) have reported an effective method for the α-arylation of malonates. In the presence of a catalytic amount of 2-picolinic acid and CuI, the coupling of aryl iodides with diethylmalonate proceeds smoothly even at room temperature. The reaction has a high level of functional group compatibility. The mild reaction conditions make this an attractive protocol for the access of various arylated malonates. The authors describes 17 examples with yields ranging from 68% to 93% for aromatic and heteroaromatic iodides. They also describe one example for an aromatic bromide (79%) and one example for a heteroaromatic bromide (88%).



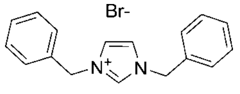
C–C Bond Formation via Double C–H Functionalization: Aerobic Oxidative Coupling as a Method for the Synthesis of Hetero-biaryls

DeBoef, B. et al. (*Org. Lett.* **2007**, *9*, 3137) have described an aerobic oxidative coupling of arenes such as benzofuran and *N*-substituted indoles with benzene and derivatives thereof. The authors have shown that the reaction takes place in both inter- and intramolecular scenarios. The authors found 10 mol % $Pd(OAc)_2$ and 10 mol % $H_4PMo_{11}VO_{40}$ (HPMV) in an oxygen atmosphere to be the most selective system for the oxidative coupling. The authors have eight examples from intermolecular oxidative couplings in low to good yields.



An *N*-Heterocyclic Carbene-Based Nickel Catalyst for C–S Coupling

Ying, J. Y. et al. (*Org. Lett.* **2007**, *9*, 3495) have developed a *N*-heterocyclic carbene (NHC)-based transition metal catalyst for C-S coupling reactions. Ni-NHC catalysts showed good to excellent activities toward various aryl halides in C-S coupling reactions. The catalytic activity is affected by the electronic and steric properties of the ligands. Bidentate ligands were found to be only slightly more active than the monodentate ligand **1**. The authors present 13 examples, two with aryl iodides and 11 with aryl bromides, in yields from 78% to 99%.



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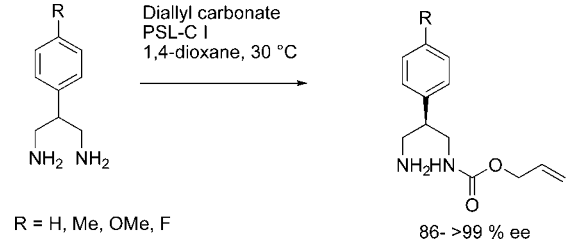
Transfer Hydrogenation with 1,4-Butanediol: An Efficient Reduction of Aldehydes and Ketones

1,4-Butanediol has been used as the hydrogen donor in transfer hydrogenation reactions (Maytum, H. C. et al. *Org. Lett.* **2007**, *9*, 4387). The equilibrium is driven by the formation of γ-butyrolactone, and the diol is therefore not required in excess. $Ru(PPh_3)_3(CO)H_2$ was employed as catalyst for the procedure. Eleven examples for the stoichiometric transfer hydrogenation have been shown where the corresponding primary or secondary alcohol was obtained in good to excellent yields. The authors also compared their method with the enantioselective transfer hydrogenation method from Noyori. In the case of 1 equiv of 1,4-butandiol, the enantioselective transfer hydrogenation is much slower than the Noyori method, which uses 50 equiv of isopropanol. The difference in speed of reaction might be that the 1,4-butanediol is a primary alcohol, which is more difficult to oxidize than isopropanol. Both methods, however, give very high enantioselectivities.

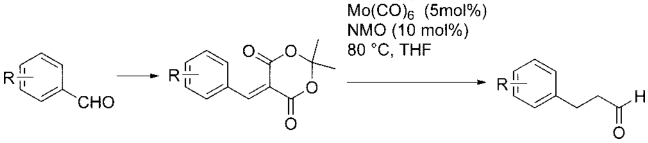
A Desymmetrization Method for 1,3-Propanediamine Derivatives in Organic Solvents

Busto, E. et al. (*Org. Lett.* **2007**, *9*, 4203) have found a method for an enzymatic desymmmetrization of a family of prochiral diamines utilizing lipases in 1,4-dioxane. 2-Aryl-1,3-diamines (4 examples) were obtained in moderate to good yields and good to high enantiopurity in the *Pseudomonas cepacia* lipase-catalyzed reaction.



Tandem Molybdenum-Catalyzed Hydrosilylations: An Expedient Synthesis of β-Aryl Aldehydes

Frost, C. G. and Hartley, B. C. (*Org. Lett.* **2007**, *9*, 4259) have described a synthesis of β-aryl aldehydes from the corresponding benzaldehydes utilizing a tandem molybdenum-catalyzed hydrosilylation. This new functional group interconversion provides an efficient method for the two carbon homologation of benzaldehydes. The authors present 10 examples in moderate to good yields.



Itaconic Acid Production

Itaconic acid, or methylene succinic acid, is extensively used as a substrate in the production of fibers, resins, plastics, rubbers, paints, surfactants, ion-exchange resins, and lubricants. Recently, Okabe and co-workers (*Bioresour. Technol.* **2007**, *98*, 3329) described a biotechnological process for production of this compound based on the use of sago starch hydrolysate as the source of raw material, using *Aspergillus terreus* TN484-M1 as biocatalyst.

Using a 3-L fermentor, it was possible to reach an itaconic acid production rate of 48.2 g/L with a yield of 0.34 g/g of sago starch, which after filtration afforded 37.1 g of itaconic acid with a purity of 97.2%. Considering that sago starch production is 25 tons/ha/year, over 5 times that of corn starch, and that the reported yields were very good, this process is a good industrial alternative for itaconic acid production.

Chitin and Chitosan

Chitin is the second most abundant biopolymer after cellulose. Its derivatives such as chitosan, carboxymethylchitin, and glucosamine, a hydrolysis product, find application in several branches of pharmaceutical and food industries. The commercial method of production of chitin from shrimp shell involves strong acid and alkali treatments, which affect the quality of the final product and, of course, cause waste-related problems. To overcome these problems microorganisms and proteolytic enzymes have been used in the removal of minerals and proteins. In that way Sini, Santhosh, and Mathew (*Carbohydrate Research* **2007**, *342*, 2423) studied *Bacillus subtilis* fermentation to start shrimp shell processing.

It was found that *B. subtilis* produced sufficient quantities of acid to remove the minerals from the shell and to prevent spoilage organisms. The protease enzyme in Bacillus species was responsible for the deprotinisation of the shell. The pH, proteolytic activity, and extent of demineralization and deprotinisation were studied during fermentation. About 84% of the protein and 72% of the minerals were removed from the shrimp shell after fermentation. Mild acid and alkali treatments were given to produce characteristic chitin, and their concentrations were standardized. Chitin was converted to chitosan by N-deacetylation, and the properties of chitin and chitosan were studied. In general this mild protocol can be extended to be used in industrial bases.

Biodiesel Production

Biodiesel production from vegetable oils and alcohols is still a challenge. Although several processes have been described, there is still a need of new improved innovations in this arena. Recently, two new protocols, among many, were described in the literature and disclose new approaches in this area. Suarez and co-workers (*J. Catal.* **2007**, *249*, 154) described the use of 1-*n*-butyl-3-methylimidazolium tetrachloro-indate, bmim·$InCl_4$, as a reaction medium to perform this reaction in the presence of Sn(3-hydroxy-2-methyl-4-pyrone)$_2$(H_2O)$_2$ as catalyst. Although several systems were tested, this one showed the best overall performance. Of great importance in this process is that the free acid content of the oil appears not to interfere in the reaction since they suffer ester formation during the acid-catalyzed transesterification of the triglyceride.

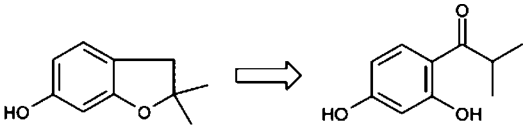
The other related paper, from Yagiz, Kazan, and Akin (*Chem. Eng. J.* **2007**, *134*, 262) was based on the use of lipases immobilized in zeolites and hydrotalcites to produce biodiesel from waste cooking oil. These authors observed that the immobilized lipase was found to be able to catalyse the transesterification of the vegetable oil with methanol to produce the desired methyl esters. The only drawback appears to be decreasing activity after each enzyme recycle.

Asymmetric Synthesis of (*S*)-3,5-Bistrifluoromethylphenyl Ethanol

Pollard and co-workers from Merck Research Laboratories (*Tetrahedron: Asymmetry* **2006**, *17*, 554) reported the asymmetric synthesis of (*S*)-3,5-bistrifluoromethylphenyl ethanol, which involved an enzymatic reduction. The isolated enzyme, an alcohol dehydrogenase from *Rhodococcus erythropolis*, performed the reduction of a poorly water-soluble substrate with excellent ee (>99.9%) and good conversion (>98%). Cofactor was regenerated using formate dehydrogenase in a coupled process. Using glucose dehydrogenase improved the whole process due to the fact that higher temperatures are allowed using this enzyme (which also can be used to recycle either NAD or NADP). The substrate to catalyst molar ratio was as high as 1,000,000:1, and total turnover numbers for NAD were estimated to be over 1000. The process was scaled up to pilot scale using high substrate concentration (390 mM) and a direct isolation process achieving excellent isolation yields (>90%) and effective space time yield (100–110 g/L d). Process improvements, demonstrated at preparative scale, increased the substrate concentration to 580 mM achieving a space time yield of 260 g/L d.

Synthesis of Benzofuran Derivatives using Selective Ring Acylation of Resorcinol

Dihydroxyphenyl ketones are important intermediates for the drugs and perfumery industries. The synthesis of 2,2-dimethyl-2,3-dihydro-benzofuran-6-ol, an important intermediate for benzofuran derivatives having pharmaceutical activity, is based on resorcinol dimethylether, and it uses or produces harmful, corrosive, and dangerous reagents/materials. An eco-friendly route has been developed that achieves 60% preparative yield for the selective direct ring acylation of resorcinol with isobutyryl chloride, using a solvent-free reaction catalysed by solid acids. In contrast to the classical reaction based on Lewis acids such as $AlCl_3$, the chemoselective Friedel–Crafts ring acylation of resorcinol with phenylacetyl chloride was achieved in solvent-free conditions, using acid-treated clays exchanged with transition metal cations (Sn^{2+} and Fe^{3+}), and the method could be scaled up. The synthesis of the precursor **2** of 2,2-dimethyl-2,3-dihydro-benzofuran-6-ol (**1**), another important compound from a pharmacological point of view, is obtained by an environmentally friendly way, from resorcinol and isobutyryl chloride (Békássy et al. *Catal. Lett.* **2007**, *118*, 219–223).



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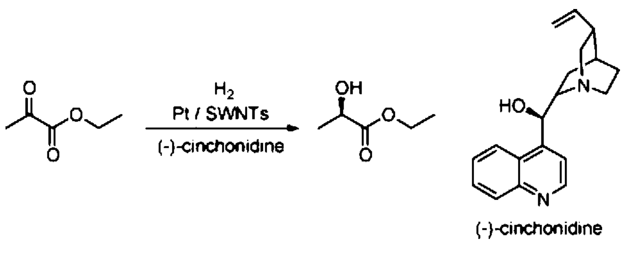
Direct Synthesis of H_2O_2 from H_2 and O_2 and Decomposition/Hydrogenation of H_2O_2 in an Aqueous Acidic Medium over Halide-Modified Pd/Al_2O_3 Catalysts

Hydrogen peroxide is widely used in environmental applications for water purification/wastewater treatments, in bleaching applications for the textile and pulp/paper industry, and also in chemical syntheses. The propylene epoxidation and caprolactam synthesis processes using H_2O_2 as an environment-friendly alternative oxidant has increased the demand for H_2O_2. The current industrial process for manufacturing H_2O_2, based on the sequential hydrogenation and oxidation of an alkyl anthraquinone, is not environmentally clean and has several limitations. A low-cost source of hydrogen peroxide has been sought for many years, and the most effective route has been identified to be the direct synthesis of H_2O_2 from its elements in aqueous reaction medium. Although several palladium-based catalysts have been employed in the direct H_2O_2 synthesis by many inventors, the process safety issues in handling potentially explosive H_2/O_2 mixtures have been a deterrent for commercial exploitation. The other serious problem is low H_2O_2 yield/selectivity because of the simultaneous H_2 combustion to water and the consecutive H_2O_2 decomposition/hydrogenation reactions. Recently, some successful pilot-scale demonstrations for the direct H_2O_2 synthesis have been made by DegussaHeadwaters, a joint venture of Degussa AG, Germany and Headwaters Incorporated, U.S.A. Direct synthesis of H_2O_2 from the gases was carried out in an acidic aqueous reaction medium over halide-modified oxidized and reduced Pd/Al_2O_3 catalysts at 27 °C and atmospheric pressure. The halide ions were introduced into the catalyst by incorporating halide ions into supported Pd/γ-Al_2O_3 catalyst or via depositing halide ions on the support (γ-Al_2O_3) prior to Pd deposition. The halide insertion in the catalyst system prior to or after Pd deposition on the support had a comparable qualitative effect on the H_2O_2 formation. Both the Pd oxidation state and the nature of the halide ions had strong influences on the H_2 conversion (in direct H_2O_2 synthesis process) and H_2O_2 decomposition and/or hydrogenation reaction. Although the effect of Pd oxidation state on the H_2O_2 formation was significant for the catalytic system containing F^- and Cl^- ions, the influence of the Pd oxidation state was found to be less important for the catalyst system containing Br^- ions; the H_2O_2 formation selectivity increased significantly due to the presence of Br^- ions, irrespective of the Pd oxidation state. The nature of the H_2O_2 destruction pathway (i.e., hydrogenation and/or decomposition) in the presence of hydrogen over halide-modified Pd/Al_2O_3 catalysts was found to be strongly dependent upon the nature of the halide ions incorporated in the catalyst during halide-modification of the catalyst. (Samanta and Choudhary *Appl. Catal. A* **2007**, *330*, 23–32).

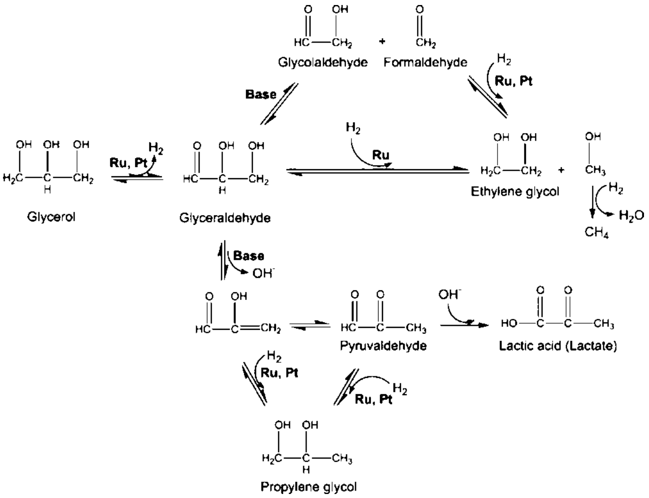
Heterogeneous Asymmetric Hydrogenation of Ethyl Pyruvate

Asymmetric hydrogenation of α-ketoesters catalyzed by cinchona-modified Pt/Al_2O_3 catalyst has been demonstrated to have synthetic potential, and various supports have been studied in the literature. Single-walled carbon nanotubes (SWNTS) have been regarded as one of the most promising nanomaterials for various applications because of their curved aromatic surface, high surface area, and ready electron-transfer capability. With the support of SWNTs, metal catalyst can be dispersed into nanoparticles to exhibit high catalytic activity. The application of SWNTs-supported Pt nanoparticles modified with (−)-cinchonidine (Cd) in asymmetric catalysis are reported for the hydrogenation of α-ketoesters catalyzed by using a series of Pt loadings, such as 5%, 10%, and 20%. After modification with Cd, these Pt/SWNTs catalysts can efficiently hydrogenate ethyl pyruvate in high activities and moderate enantioselectivities. The asymmetric hydrogenation of ethyl pyruvate, providing (*R*)-ethyl lactate in high activity and moderate enantioselectivity. The catalysts are characterized by TEM and XRD (Xing et al. *J. Mol. Catal. A: Chem.* **2007**, *276*, 191–196).



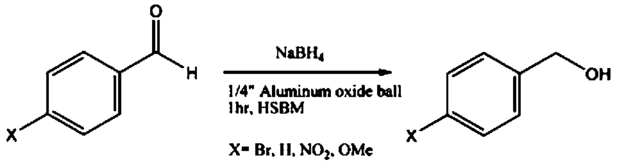
Glycerol Hydrogenolysis on Carbon-Supported PtRu and AuRu Bimetallic Catalysts

Bioglycerol, coming as a coproduct of biodiesel, to the tune of 10% w/w, has been identified as a promising alternative to petroleum and natural gas for the production of commodity chemicals and materials. One route for the conversion of glycerol to oxygenated chemicals involves hydrogenolysis to ethylene glycol, propylene glycol, and lactic acid.



The University of Virginia group of R. A. Davis has evaluated the performance of bimetallic PtRu and AuRu catalysts in aqueous-phase hydrogenolysis of glycerol at 473 K and 40 bar H_2 at neutral and elevated pH. The catalysts were prepared by a surface redox method in which Pt or Au was deposited onto the surface of carbon-supported Ru nanoparticles with an average diameter of 2–3 nm. Although monometallic Pt and Ru exhibited different activities and selectivities to products, the bimetallic PtRu catalyst functioned more like Ru. A similar result was obtained for the AuRu bimetallic catalyst. The PtRu catalyst appeared to be stable under the aqueous-phase reaction conditions, whereas the AuRu catalyst was altered by the harsh conditions. Gold appeared to migrate off the Ru and agglomerate on the carbon during the reaction in liquid water (Maris et al. *J. Catal.* **2007**, *251*, 281–294).

Solvent-Free Reduction of Esters Using Ball Mill



Most of the research conducted in solvent-free conditions has used a mortar and pestle, which has remained a laboratory curiosity. High speed ball milling (HSBM) is an attractive solvent-free method. The high speed attained by the ball-bearing has enough force to make an amorphous mixture of the reagents, which generates tremendous heat and subsequently facilitates a chemical reaction. This method has been studied in metal alloying and for the generation of inorganic salts, including a few organic reactions such as the Baylis−Hillman reaction. The reduction of aldehydes, ketones, and esters by the HSBM approach has been achieved in this work. Using 1 equiv of sodium borohydride and milling for 1 h, aldehydes were able to be successfully reduced in high yields. The reduction was also successful with ketones and esters; however, much longer reaction times were needed in order to achieve comparable yields (Mack et al. *Green Chem.* **2007**, *9*, 1041–1043).

Role of Process Intensification in the Future of Chemical and Process Engineering

Charpentier of CNRS/ENSIC/INPL, Nancy, France has given a critical and detailed analysis of process intensification and its role in future trends in chemical and process engineering, in relation to the changing needs of the chemical process and related industries. He has discussed these issues with reference to the increasing market requirements for specific end-use properties of the product required by the customer, and the social, raw material and energy savings, and environmental constraints of the industrial-scale process. Process intensification deals with the design of novel equipment and new production methods, using either multifunctional separators/reactors, new operating modes, or microengineering and microtechnology for both high throughput and formulation screening and for chemical production. Thus process intensification leads to more or less complex technologies that replace large, expensive, energy-intensive equipment or processes with ones that are smaller, less costly, and more efficient, minimizing environmental impact, increasing safety, and improving remote control and automation or that combine multiple operations into a single apparatus or into fewer devices. With the help of the multidisciplinary and multiscale approach of chemical engineering applied from the scale of the microreaction technology up to the scale of multifunctional macroreactors or equipment, process intensification offers new opportunities for chemical engineering. According to him it is involved in the trend "molecules into money", which is based on the premise that chemical engineering drives today's economic development and is fundamental to wealth creation (Charpentier *Chem. Eng. J.* **2007**, *134*, 84–92).

Advanced Chemical Processing Using Microspace

One of the challenges in widespread acceptance of microreactor technology is the "black box design", hence the need to develop a logical set of design recommendations for microreactors. Not unlike the case of classical reactors, the synergy between experimental and simulation work is expected to be an effective approach to develop microreactor design rules. A group from Kyoto University (Mae, K. *Chem. Eng. Sci. 62*, **2007**, 4842) reviews recent accomplishments in microreactor chemical reaction engineering and microreactor design. Evidence for microreactor technology progress is the development of dimensionless numbers to be used in microreactor design: φ, the ratio of reaction rate to diffusion rate; w, the aspect ratio of the mean diffusion lengths in the two-dimensional directions of the reactor cross section, and a modified Peclet number, the ratio of diffusion rate to circulation rate. Because of effective micromixing and heat transfer, one of the most promising areas for the use of microreactors is exothermic reactions. Examples are provided for homogeneous and heterogeneous organic synthesis and particle production applications. Microreactor technology also benefits from a good chemist/chemical engineer collaboration, because mechanistic information leads to a more powerful design (e.g., leading to enhanced selectivity). This review contains 74 references.

Agglomeration and Adhesion Free Energy of Paracetamol Crystals in Organic Solvents

Because paracetamol crystallization has been extensively studied in the past decade, one can reasonably expect that a first principles approach should be possible for the understanding of the agglomeration behavior of paracetamol. It was previously shown that the degree of agglomeration for paracetamol crystals in organic solvents decreases with the increase of solvent polarity. Because solvent polarity is not a very well-defined property, reliable quantitative models based on this property were not developed. A contribution from the Royal Institute of Technology in Stockholm describes the complexity of a fundamental approach to understanding paracetamol crystal agglomeration (Alander, M. et al. *AIChE J.* **2007**, *53* (10), 2590). This work specifically aimed to establish whether paracetamol crystal agglomeration can be explained and correlated with interfacial properties and the adhesion forces between paracetamol crystals in different solvents. Unfortunately, solid–liquid interfacial energies cannot be easily measured. The approach taken by the authors was to measure the contact angle of various solvents on several faces of large, well-grown crystals. The data is then used within the Lifshitz−van der Waals acid–base theory of van Oss et al. to estimate the surface free energy components, based on which the solid–liquid interfacial energy is calculated. Further complications arise from controversies surrounding the use of the van Oss theory and from experimental challenges in measuring contact angles. As with many other cases of modeling in chemical engineering, the *absolute* values determined for interfacial energies are not as important as is their usefulness in a relative sense and for comparison with the agglomeration results obtained. The authors show evidence in support of their hypothesis that the influence of solvent on the agglomeration of paracetamol crystals is due to differences in crystal–crystal adhesion. Agglomeration was observed during isothermal, seeded crystallization, conducted at constant supersaturation, under turbulent flow. Substantial agglomeration was observed in acetone, and high agglomeration was seen in acetonitrile and MEK, whereas low agglomeration was noted in methanol and ethanol. Of note is the fact that the adhesion forces calculated are much stronger than the forces exerted by the fluid turbulence, but they are comparable to the impact force exerted on particles colliding with the impeller tip. Given the scale-dependence of the impeller tip speed, it will be interesting to measure the degree of agglomeration upon scale-up, for cases where scaling-up was not executed at constant impeller tip speed.

Advanced Geometrical Modeling of Focused Beam Reflectance Measurements (FBRM)

Focused beam reflectance measurements (FBRM) are often employed to monitor crystallization processes; the measured chord length distributions (CLD) can be used semiquantitatively to characterize the behavior of the system analyzed. Several groups have attempted to develop procedures for reliably converting CLD into particle size distributions (PSD) obtained using other methods. Such transformations are important in pharmaceutical industrial practice because particle size specifications are typically based on laser diffraction PSD measurements. Unfortunately, most of the models available rely on rather restrictive assumptions and do not exhibit good predictive power; moreover, the electronic settings of the instrument can introduce undesired bias. A group from Aachen University (Kail, N. et al. *Part. Part. Syst. Charact.* **2007**, *24*, 184) proposes two new models for the analysis of FBRM data: a velocity model and an edge model. The velocity model is useful for data obtained from opaque particles, whereas the edge model is valuable for data obtained from transparent particles. The new models proposed were validated for large particles; for particles in the 1–30 μm range further studies are needed; additional studies are also required in order to analyze particles that are of intermediate transparency and of complex geometry (the particles were considered spherical in the models proposed thus far). We note that for high quality predictions, the FBRM measurements were taken over 1–3 h, an experimental challenge for the case of typical crystallization process monitoring. The predicted CLD using the velocity model depends, as expected, on particle velocities. Understanding this dependence further may be valuable when a monitored crystallization process is scaled-up.

A Revised Program for Operational Discipline

A review of the development and implementation of a next generation approach to improving operational discipline (OD) programs at DuPont, in order to help sustain high levels of process safety management performance, was recently published (Klein, J. A. et al. *Process Saf. Prog.* **2007**, DOI: 10.1002/prs.10216, published online August 27, 2007). Eleven organizational characteristics were used in the past to help evaluate and drive continuous improvement of OD, which have been simplified to four primary characteristics: leadership focus, employee involvement, practice consistent with procedures, and excellent housekeeping. OD was creatively factored in the equation for risk calculation: Risk = (Frequency × Consequence)/OD. This means that for a given process and operating conditions, if OD is estimated to be only 50%, then the risk doubles. A study was conducted to determine what characteristics best defined *individual* OD. Specific targets for these characteristics included that they should be acceptable and meaningful for all employees, simple and logical, and measurable and improvable. An extensive literature search led to the identification of three characteristics required for individuals to work with a high level of OD. They were knowledge, commitment, and awareness ("I anticipate potential problems, and I recognize unusual situations"). In addition to the typical OD metrics (number of incidents, number of injuries, amount of waste, etc.), it was found that the most useful OD evaluation tool is the OD self-assessment (the protocol was based on an Internet survey tool, www.surveymonkey.com). Several useful training tips and 28 references are included in this paper.

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