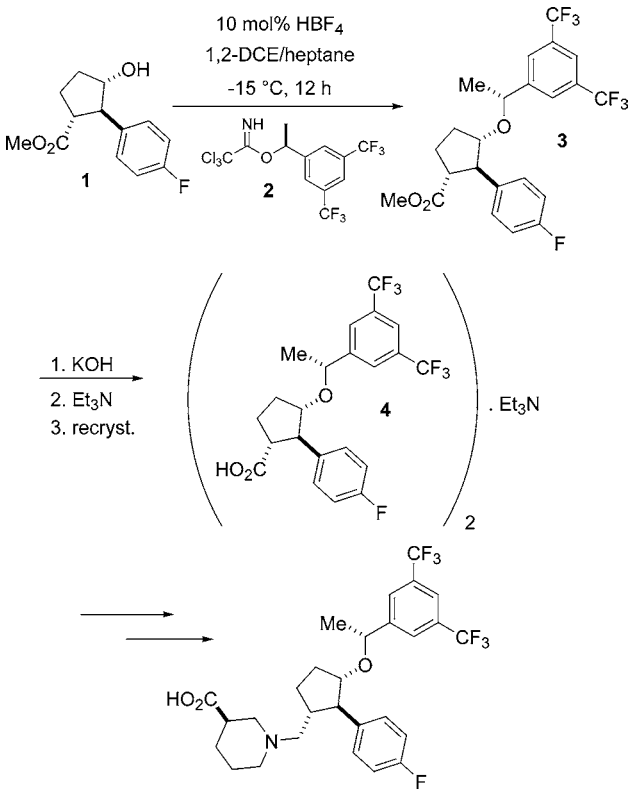
Organic Process Research & Development **2006**, *10,* 1086–1100

Highlights from the Literature

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

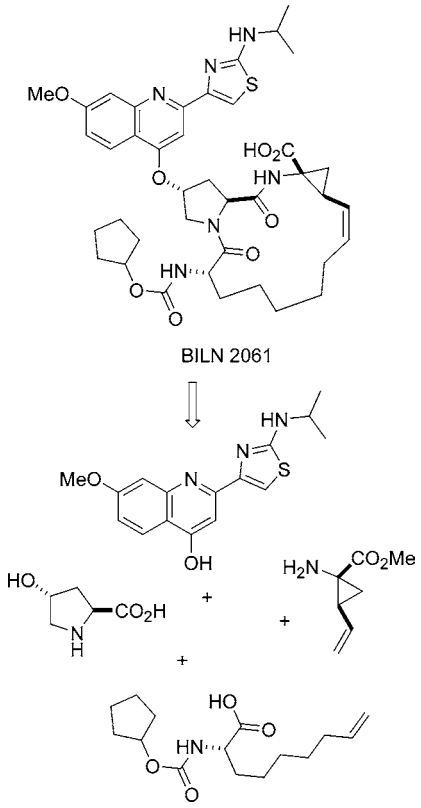
Stereoselective Preparation of a NK1 Receptor Antagonist



A synthesis of a selective NK-1 receptor antagonist is described by Kuethe and co-workers at Merck (*J. Org. Chem.* **2006**, *71*, 7378−7390). The key transformation, which was catalyzed by HBF_4, involved ether formation between cyclopentanol **1** and chiral imidate **2** to initially give ether **3** as a 17:1 mixture of diastereomers and in 75% combined yield. Hydrolysis of the methyl ester and treatment with triethylamine afforded a crystalline solvate **4** and allowed diastereoselectivity upgrade to 109:1 (54% overall isolated yield from **1**). Mechanistic studies confirmed that this etherification proceeds via an S_N2 reaction pathway, as opposed to the S_N1 pathway more typically observed with these reaction conditions.

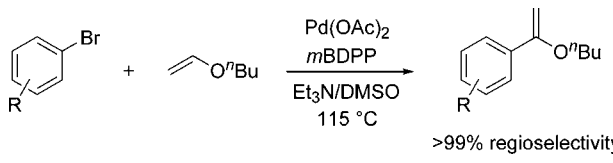
Large-Scale Synthesis of BILN 2061, a Potent HCV Protease Inhibitor

A synthesis of the clinically important hepatitis C virus (HCV) protease inhibitor BILN 2061 (**1**) is described by Yee, Farina, and co-workers (*J. Org. Chem.* **2006**, *71*, 7133−7145). The authors provide an interesting and very detailed account of the numerous challenges faced during scale-up



of a synthetic route featuring a ring-closing metathesis (RCM) reaction. In particular, issues such as catalyst loading, reaction time, high dilution, and oligomerization are discussed. Other highlights include modification of the original synthetic sequence so as to avoid the use of protecting groups and a Mitsonobu inversion of a secondary alcohol. The end result is a convergent synthesis consisting of two amide bond formations, one etherification, and one RCM step, using readily available building blocks **2**−**5**. Eventually, the RCM reaction was scaled up to produce >400 kg of cyclized product.

Pd-Catalyzed Regioselective Internal Arylation of Electron-Rich Olefins

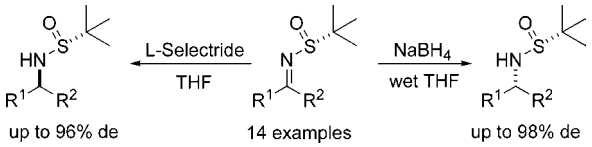


Xiao and co-workers describe novel conditions to effect regioselective Heck arylation of electron-rich olefins (*J. Org. Chem.* **2006**, *71*, 7467−7470). By using *meso*-2,4-bis(diphenylphosphino)pentane (*m*BDPP) as a ligand and DMSO as

Published on Web 11/17/2006
10.1021/op060213u CCC: $33.50

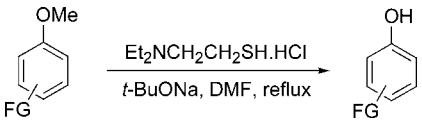
solvent, olefins such as *n*-butyl vinyl ether can be arylated in the α-position with high regioselectivity. Choice of solvent for this reaction was shown to have a dramatic effect on both conversion and regioselectivity, with strongly polar solvents giving the best results. The authors note that this procedure does not require the use of halide scavengers (e.g., silver salts) normally employed to facilitate the so-called "ionic" mechanistic pathway, which favors the α-product. A potential drawback of this procedure is the need for relatively high catalyst loadings (4−8 mol %) and extended reaction times (36 h). In order to address these concerns, an alternative procedure was also developed, where the use of stoichiometric amounts of $Et_3N{\cdot}HBF_4$ as an additive allowed for reduction in catalyst loading to 0.5 mol % with a reaction time of 12 h. The arylated products can easily be hydrolyzed to afford aryl ketones.

Reversal of Diastereofacial Selectivity in Hydride Reductions of *N-tert*-Butanesulfinyl Imines



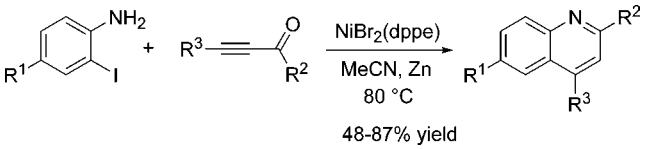
Andersen and co-workers at Amgen report on the reduction of *N-tert*-butanesulfinyl imines (*J. Org. Chem.* **2006**, *71*, 6859−6862). Although Ellman had already shown that reduction using $NaBH_4$ in THF containing 2% water provides the corresponding secondary sulfinamides in high yield and diastereoselectivity, the use of alternative hydride sources was not fully studied. As detailed in this report, changing the reductant to L-Selectride causes a reversal in stereoselectivity and affords the opposite product diastereomer in high yield and selectivity from the same starting material. Although both enantiomers of the sulfonamide auxiliary are commercially available, the authors point out that the (*R*)-enantiomer is approximately 50% more expensive.

New Reagent for the Odorless Deprotection of Aromatic Methyl Ethers



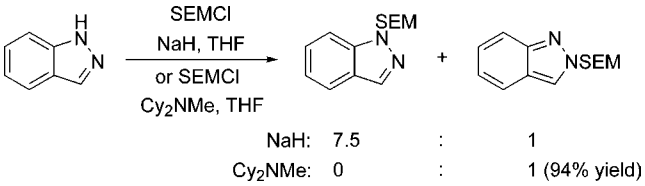
A new reagent for the deprotection of aromatic methyl ethers, 2-(diethylamino)ethanethiol, is reported by Magano and co-workers at Pfizer (*J. Org. Chem.* **2006**, *71*, 7103−7105). This compound, commercially available as its HCl salt, affords the corresponding phenols in good to excellent yields on a wide variety of substrates. A clear advantage of this method over the use of more common thiols, such as ethanethiol, is the easy extraction of both the deprotecting reagent and the byproduct 2-(diethylamino)ethyl methyl sulfide into the aqueous phase by quenching with dilute acid, which allows an essentially odorless workup.

Nickel-Catalyzed Cyclization of 2-Iodoanilines with Aroylalkynes



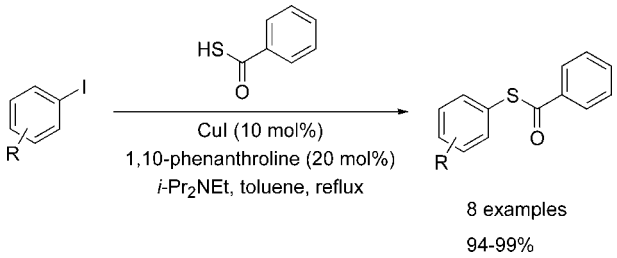
A nickel-catalyzed cyclization of 2-iodoanilines with alkynyl aryl ketones to give 2,4-disubstituted quinolines is reported by Cheng and co-workers (*J. Org. Chem.* **2006**, *71*, 7079−7082). Initial attempts with $R^3 = H$ did not afford quinolines but instead led to 1,4-addition of the amino group to the alkynyl ketone and no further reaction. With a substituent at the alkyne terminus, 1,4-addition is sterically retarded, and the predominating pathway is oxidative addition of Ni(0) to the aryl iodide followed by insertion of the alkyne and then protonolysis. Last, intramolecular condensation of the amino function with the pendant ketone gives the quinoline. Two equivalents of alkyne are necessary for optimum yields, and zinc metal is required as a stoichiometric reductant.

Regioselective Protection at *N*-2 and Derivatization at C-3 of Indazoles



Under certain conditions, indazoles are regioselectively protected at *N*-2 by a 2-(trimethylsilyl)ethoxymethyl (SEM) group, as described in a recent report by Luo and co-workers at Bristol-Myers Squibb (*J. Org. Chem.* **2006**, *71*, 5392−5395). Previous literature conditions for this protection, using NaH as the base in THF, favored the *N*-1 protected product. Following a screen of various bases, the authors observed that weaker non-deprotonating bases provided high selectivity for *N*-2 protection. The SEM group can efficiently direct regioselective *C*-3 lithiation, and the resulting nucleophile can react with a wide range of electrophiles to generate novel indazole derivatives. The SEM group can be removed by treatment with TBAF in THF or aqueous HCl in EtOH.

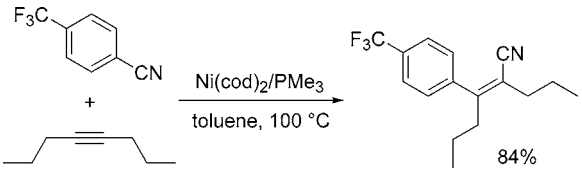
Cu-Catalyzed Coupling of Aryl Iodides and Thiobenzoic Acid



Sawada and co-workers at Banyu Pharmaceuticals report on a copper-catalyzed coupling between aryl iodides and

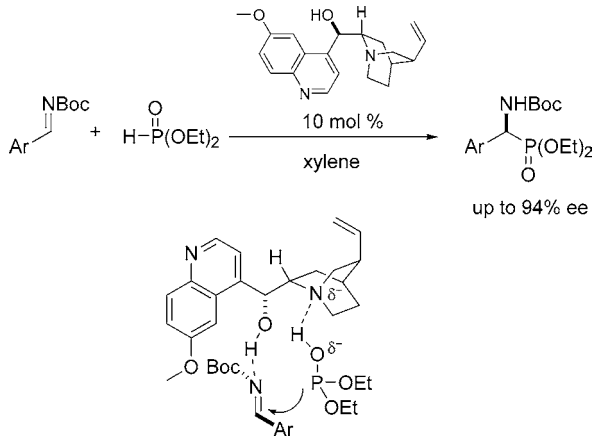
thiobenzoic acid (*Tetrahedron Lett.* **2006**, *47*, 6595−6597). The method uses 10 mol % of copper iodide and 20 mol % of 1,10-phenanthroline in refluxing toluene and is applicable to both electron-deficient and electron-rich aryl iodides. The product *S*-aryl thiobenzoates can be deprotected to thiols with potassium carbonate in methanol. Bromobenzene did not react under the developed conditions.

Ni-Catalyzed Arylcyanation of Alkynes



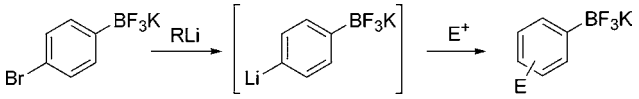
Following up on an earlier communication, Nakao and Hiyama provide further details on an interesting arylcyanation process (*Tetrahedron* **2006**, *62*, 7567−7576). A nickel catalyst prepared from $Ni(cod)_2$ and PMe_3 is capable of oxidative insertion into the C−CN bond of aryl cyanides. Subsequent insertion of an alkyne followed by reductive elimination generates β-arylalkene nitriles. A wide range of functional groups are tolerated, and several heterocyclic nitriles are included. Terminal alkynes do not participate due to competing oligomerization, and when unsymmetrical alkynes are employed, the regioselectivity appears to be sterically controlled, placing the cyano group next to the bulkier substituent. Although the catalyst loading is 10 mol %, the aryl cyanides and alkynes are used in equimolar amounts, leading to an atom-economical process.

Organocatalytic Asymmetric Hydrophosphonylation of Imines



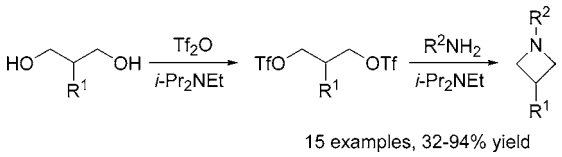
Enantioselective organocatalytic hydrophosphonylation of imines is reported by the Pettersen group (*J. Org. Chem.* **2006**, *71*, 6269−6272). The enantiomerically enriched α-amino phosphonate products are amino acid analogs, potentially useful for incorporation into medicinal agents. By using 10 mol % of quinine as the catalyst in the addition of diethyl phosphite to *N*-Boc protected imines, α-amino phosphonates are obtained in moderate to good yields and with up to 94% ee. The free hydroxyl in the quinine catalyst was critical for reactivity since protected variants gave low conversion. Additionally, the Boc group on the imine was superior to tosyl. The mechanism of activation proposed by the authors is shown.

Metalation of Aryl Bromides Bearing a Potassium Trifluoroborate Moiety



Aryl bromides bearing a potassium trifluoroborate moiety will participate in lithium−halogen exchange at low temperature using a variety of alkyllithium reagents, as reported by Molander (*J. Org. Chem.* **2006**, *71*, 7491−7493). A number of different electrophiles were evaluated in their reactions with the aryllithiums produced therein. Under the optimized conditions, which are fairly dilute (0.1 M), potassium bromophenyl trifluoroborates afforded good yields of the corresponding alcohols (64−94% isolated yield) when aldehydes or ketones were used as the electrophilic partner. Other electrophiles used successfully include TMSCl, I_2, and an isocyanate. Esters were found to be unreactive.

One-Pot Preparation of 1,3-Disubstituted Azetidines

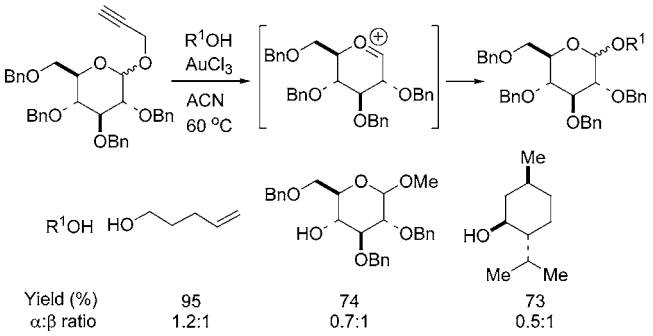


A straightforward synthesis of 1,3-disubstituted azetidines is reported by Hillier and co-workers at Merck (*J. Org. Chem.* **2006**, *71*, 7885−7887). The method involves double activation of 1,3-diol substrates using triflic anhydride and subsequent formation of the azetidine in the same pot by addition of an appropriate amine. The corresponding 1,3-ditosylate substrates proved inferior for azetidine formation. Although elimination of the activated 1,3-diols was previously reported as a competing side reaction, under the conditions developed here this problem was effectively minimized. The scope of this method was investigated using a variety of 2-substituted-1,3-propanediols and amine nucleophiles.

Transition Metal Activation of Propargyl Glycosides

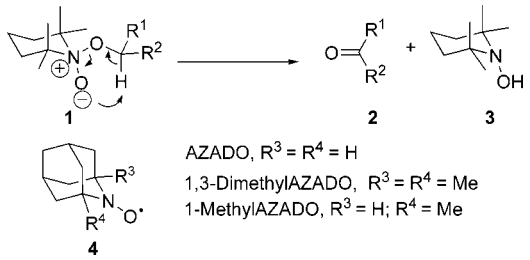
Hotha and Kashyap from the National Chemical Laboratory in Pune (India) reported the use of propargyl glycosides as stable glycosyl donors using $AuCl_3$ as the catalyst (*J. Am. Chem. Soc.* **2006**, *128*, 9620−9621). Anomeric activation occurred presumably due to the high alkynophilicity exhibited by gold catalysts. In the optimized conditions, per-*O*-benzylated propargyl glycosides **1** reacted with aglycone R^1OH (1.2 equiv) in the presence of $AuCl_3$ (3 mol %) in acetonitrile at 60 °C. The transglycosylation product was obtained as an anomeric mixture at C-1 in good to excellent yields. The α:β ratio of the products was independent from

the α:β ratio at C-1 of the glycosyl donor. It is worth noticing that per-*O*-benzoylated or per-*O*-aceylated compounds did not work as donors. Additionally, using other alkyne activators ($PtCl_2$, $Co_2(CO)_8$, and $RuCl_3$) resulted in the isolation of unreacted starting materials or decomposition.



Oxidation of Alcohols Catalyzed by Nitroxyl Radicals

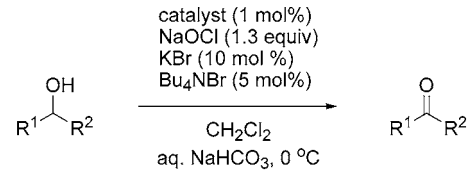
The use of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, **1**) as a proficient catalyst in the oxidation of primary alcohols is widespread among the chemical literature. However, this readily available compound does not perform as well in the oxidation of secondary alcohols to the corresponding ketones. The four methyl groups flanking the nitrogen presumably prevent bulkier substrates from forming intermediate **2**, which in turn generates the desired carbonyl compound and hydroxylamine **3**. Iwabuchi and co-workers reported the catalytic activity of the less hindered 2-azaadamantane *N*-oxyl (AZADO) nitroxyl radicals (**4**) in the oxidation of a variety of alcohols (*J. Am. Chem. Soc.* **2006**, *128*, 8412−8413).

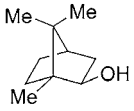
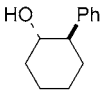
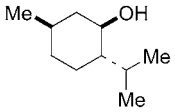
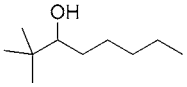


Using the conditions developed by Anelli for the oxidation of primary alcohols [NaOCl (1.3 equiv); KBr (10 mol %, Bu_4NBr (5 mol %)], the reaction takes place using 1/100 of catalyst relative to TEMPO. Additionally, the yields in the oxidation of hindered secondary alcohols (1 mol % catalyst) were boosted from 0 to 16% with TEMPO to 87−99% using the AZADO catalysts.

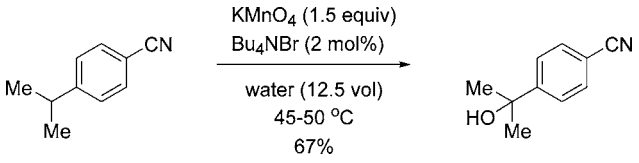
Scalable Benzylic Oxidation

Collaborative work between Pfizer and CarboGen resulted in the development of a novel protocol for the benzylic oxidation of cuminonitrile using aqueous $KMnO_4$ (*Synth. Commun.* **2006**, *36*, 2145−2150). The methodology was developed to access the target compound without using Grignard reagents, as the reaction of MeMgBr with methyl cyanobenzoate or 4-acetyl benzonitrile proved troublesome (addition to the cyano group, self-condensation, etc.).



Substrate	Yields (%) TEMPO	1-Me-AZADO
	0	94
	16	99
	5	95
	15	93

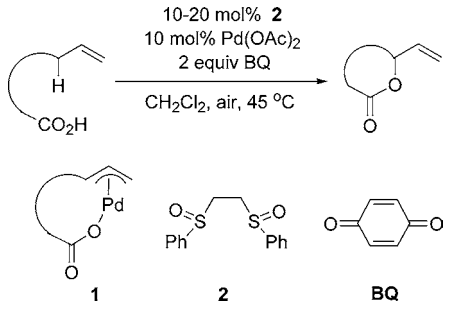
Traditionally, oxidations with $KMnO_4$ require basic conditions, large volumes, and lengthy reaction times. In a first stage, the authors improved the water solubility of the starting material by adding *t*-BuOH, and prevented the hydrolysis of the cyano group by using Na_2CO_3 instead of KOH as the base. The process was further streamlined by preparing a water-soluble permanganate salt in the presence of Bu_4NBr. [Note: Solid Bu_4MnO_4 has been reported to be pyrophoric (Morris, J. A.; Mills, D.C. *Chem. Ind.* **1976**, 446).] The volume-efficiency improved from 65 to 12.5 L/kg, and the product was isolated as a crystalline solid after exchanging EtOAc with heptanes.



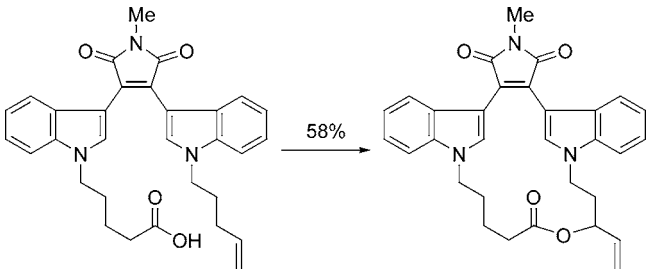
Macrolactonization via Hydrocarbon Oxidation

Following recent reports of Pd-catalyzed allylic oxidations promoted by sulfoxides, the group of Christina White at the University of Illinois described the first macrolactonization that proceeds via allylic oxidation of ω-alkenoics acids (*J. Am. Chem. Soc.* **2006**, *128*, 9032−9033). In addition to mediating the formation of tether **1**, the Pd catalyst also activates the two reacting termini. As a result, the macrolactonizations can be carried out at a concentration of 10 mM, evading the high-dilution conditions generally required for such transformations. A variety of functional groups tolerated the conditions, and 14-to-17-membered macrolides could be obtained in good yields and regioselectivities (>20:1 branched versus lineal). The reactions proceed in the presence of air and adventitious water. Interestingly, no olefin isomerization was detected in the case of vinylic acids.

The mechanism of related $Pd(OAc)_2$/benzoquinone α-olefin allylic oxidations is extensively described in a previous

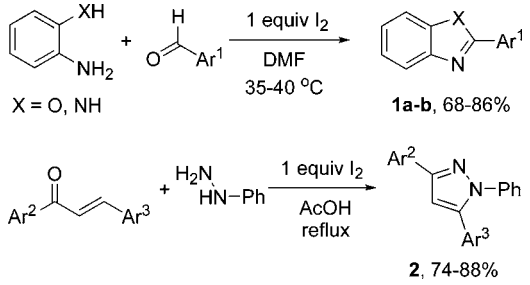


publication from the group (*J. Am. Chem. Soc.* **2005**, *127*, 6970−6971). To emphasize the compatibility of the methodology with a nitrogen-containing substrate, bis(indolyl-)maleneimide macrolide **3** was prepared in 58% yield.



Iodine-Mediated Synthesis of Heterocycles

Oxidative cyclization of Schiff bases is a general method to obtain 2-arylbenzimidazoles and 2-arylbenzoxazoles. 1,3,5-Trisubstituted pyrazoles are synthesized by condensation of chalcones with phenylhydrazine, followed by aromatization. Whereas a number of oxidants successfully promote these transformations, common disadvantages include the generation of copious waste streams, extended reaction times, and formation of impurities. In a recent communication, Ponnala and Sahu from the Central Drug Research Institute in Lucknow (India) reported a single-pot, environmentally benign synthesis of the above compounds using iodine as the oxidation agent (*Synth. Commun*. **2006**, *36*, 2189−2194). Benzaldehydes bearing different substituents and heterocyclic carboxaldehydes (Ar = 2-furyl, 2-thiophenyl) were converted into benzoxazoles **1a**, and benzimidazoles **1b** by reaction with *o*-aminophenol in DMF at 35−40 °C. The formation of pyrazoles **2** from phenylhydrazine and chalcones required more vigorous conditions (AcOH, reflux), but in all examples the products were isolated as solids in good yields.

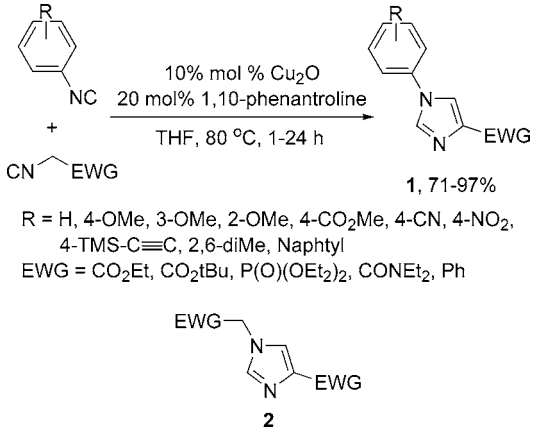


Catalyst Design: The Concept of Site Isolation

A limiting factor for carrying out multiple steps without isolation of intermediates is the incompatibility between the reactive components of different transformations, which can deactivate or quench each other (e.g., Brønsted acids and bases). Prof. Brigitte Voit selected examples from the literature in which multistep reactions are performed in one-pot by employing polymeric reagents (*Angew. Chem., Int. Ed.* **2006**, *45*, 4238−4240). The original concept relies on inactivating the incompatible reagents by attachment to a polymeric support. Two strategies for site isolation of acid and base catalysts are: (1) using of two different layered clays (heterogeneous catalysis) and (2) shielding catalytic sites by star-shaped polymeric architecture (homogeneous catalysis). Ti^{4+}-exchanged montmorillonite (Ti-mont, acid) and Mg−Al hydrotalcite (HT, base) represent heterogeneous catalysts. The acidic and basic sites are accessible to the organic compounds, but HT particles are too large to enter the narrow spaces between the layers of Ti-mont. These reagents proved useful in sequences involving acetal deprotection and Michael addition. For the latter strategy, copolymerization of various monomeric species results in a cross-linked core shielded by many polyestyrene arms (star). The acid active site is prepared by hydrolysis and acidification of phenylsulfonate esters, while the basic consisted of pendant [(methyl(pyridyl)amino]methyl units. The polymers are readily soluble in DMF, and effective in sequences involving acetal deprotection and Baylis−Hillman reactions.

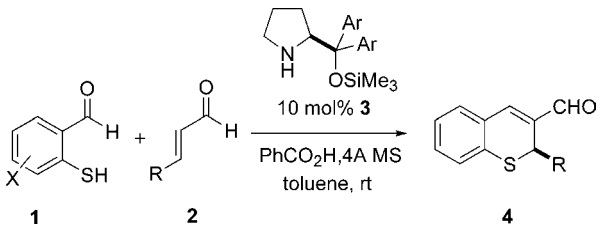
Copper-Catalyzed Formation of Imidazoles

Kanazawa, Kamijo, and Yamamoto described the use of Cu_2O as catalyst for the cycloaddition of two different isocyanates to produce 1,4-disubstituted imidazoles (*J. Am. Chem. Soc.* **2006**, *128*, 10662−10663). After screening a variety of catalysts—including combinations of Ru and Ag salts and a variety of ligands—the Cu_2O/1,10-phenanthroline pair gave the best results. Although the role of the ligand remains unclear, in the absence of 1,10-phenanthroline the reaction gave compound **1** in only moderate yields. The electronic properties of the substituents on the aryl isocyanide were barely relevant to the outcome of the reaction, and disubstituted imidazoles were obtained in excellent yields. Nevertheless, the coupling between ethyl isocyanoacetate and an aliphatic isocyanate (butyl, cyclohexyl) yielded only 10−12% of the desired mixed adducts, giving homocycloadducts **2** as the main products.



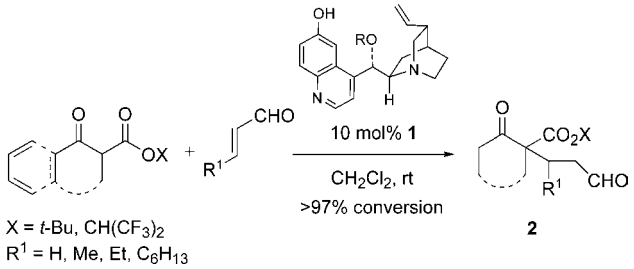
One-Pot Synthesis of Thiochromenes

The interest in thiopyranes has recently escalated, as a wide variety of biological activities has been associated with this scaffold. The group of Wang at the University of New Mexico reported a one-pot organocatalytic synthesis of homochiral thiopyrans (*J. Am. Chem. Soc.* **2006**, *128*, 10354−10355). Reaction of a variety of α,β-unsaturated aldehydes **1** (R = Ph, 2- and 4-MeO-C_6H_4, 4-F-C_6H_4, alkyl) with 2-mercaptobenzaldehydes **2** (X = 5-Cl, 5-MeO, 5-Me, 4,6-$(OMe)_2$) was catalyzed by **3** in the presence of benzoic acid in toluene at room temperature. In general, the transformations proceeded with yields >80% and enantioselectivities ≥85%. Silylated chiral pyrrolidine **3** outperforms other pyrrolidines in the organocatalytic tandem Michael−Aldol reaction.

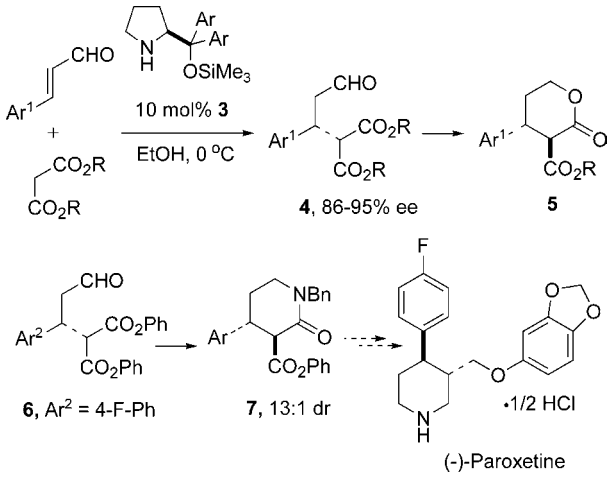


Organocatalysis: Enantioselective Addition to α,β-Unsaturated Aldehydes

Enantioselective addition of carbonyl donors to α,β-unsaturated aldehydes remains elusive. By using cinchona alkaloids derivatives, Deng and co-workers reported the addition of α-substituted β-keto esters to acrolein and related alcohols (*Angew. Chem., Int. Ed.* **2006**, *45*, 4301−4305). Due to the rapid oligomerization of acrolein in the presence of DABCO, quinuclidine, or isocupreidine, this challenging transformation required the design of an effective general base catalyst rather than a nucleophilic catalyst. Mechanistic studies indicated that 6′-OH cinchona alkaloids **1** (R = Bn, R = 5-phenanthrene) act as hydrogen acceptors and donors, and do not induce polymerization. A wide range of α-alkyl-β-ketoesters added to acrolein and related aldehydes to afford 1,4 adducts **2** containing an all-carbon quaternary chiral center in 91−98% ee and virtually quantitative yield. When β-substituted aldehydes were used as substrates, the products containing adjacent quaternary and tertiary stereocenters were isolated with 18−25:1 dr.

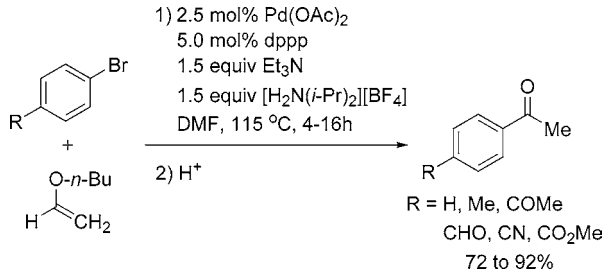


The group of Jørgensen reported a new methodology for the chiral synthesis of lactams and lactones using proline-derived catalysts (*Angew. Chem., Int. Ed.* **2006**, *45*, 4305−4308). Pyrrolidine (*S*)-**3** [Ar = 3,5-$(CF_3)_2$-C_6H_4] catalyzed the reaction of methyl or benzyl malonates with α,β-unsaturated aldehydes to yield addition products **4** in very good ee's. Reduction to the alcohol and cyclization in the presence of Si_2O yielded exclusively *trans*-chiral lactone **5**. By using (*R*)-**3**, and subjecting intermediate **6** to a reductive amination−cyclization sequence, the authors achieved the formation of lactam **7** (13:1 dr), a known precursor of the antidepressant (−)-paroxetine.



Heck Arylation of Electron-Rich Olefins with Ammonium Salts

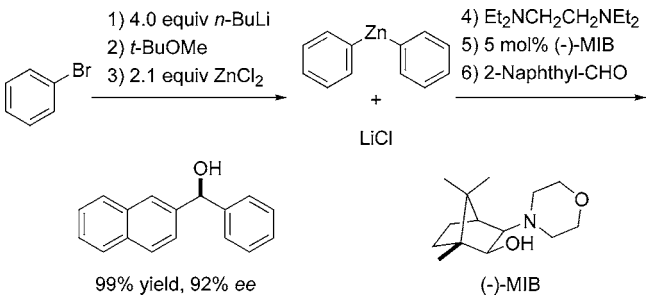
The Heck arylation of electron-rich olefins requires silver or thallium salts as halide scavengers to attain high α/β regioselectivities. Mo and Xiao at the University of Liverpool found that the use of ammonium salts as hydrogen-bond donors constitutes an attractive option to such additives (*Angew. Chem., Int. Ed.* **2006**, *45*, 4152−4157). For example, $[H_2N(i\text{-}Pr)_2]^+$ $[BF_4]^-$ in DMF promotes the olefination of aryl bromides with butyl vinyl ether with excellent yields and selectivities (>99:1). In a mechanistic hypothesis, the authors propose that the ammonium salts act as scavengers themselves by forming hydrogen bonds between the $[HNR_3]^+$ species and the departing halide anion. A typical procedure involves the use of 2.5 mol % Pd catalyst and 1.5 equiv of $[HNR_3]^+$ in DMF at 115 °C. Remarkably, deactivated aryl chlorides could also be coupled with electron-rich olefins under these conditions.



Catalytic Asymmetric Arylation of Aldehydes

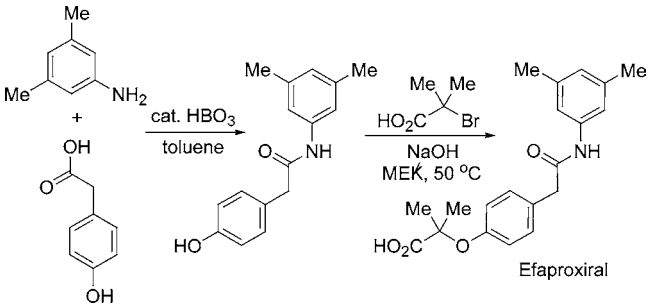
Telescoping operations is a popular assignment in process development. However, the succession of multiple reactions in a single flask is still a daunting task, especially when the reactions involve organometallic transformations that have strong dependencies to mixture composition. Kim and Walsh at University of Pennsylvania telescoped the catalytic asym-

metric addition of aryl zinc reagents generated from aryl bromides, using a sequence that involves lithium−bromide exchange, transmetalation, and 1,2-addition catalyzed by 5 mol % of chiral amino alcohol (−)-MIB in a single pot (*Angew. Chem., Int. Ed.* **2006**, *45*, 4175−4178). The manuscript is a brilliant example of traffic control in a reaction mixture that contains organolithium and organozinc reactants as well as Li and Zn salt byproducts in the presence of ligands that are specific for each metal. Since summarizing such a complex transformation would exceed the purpose of this note, the reader is referred to the original manuscript to enjoy the details. As a token of significance, the addition of Ph_2Zn generated from PhBr and *n*-BuLi to 2-naphthyl carbaldehyde occurs in 90% yield and 92% ee, avoiding the use of costly Ph_2Zn or $PhB(OH)_2$.



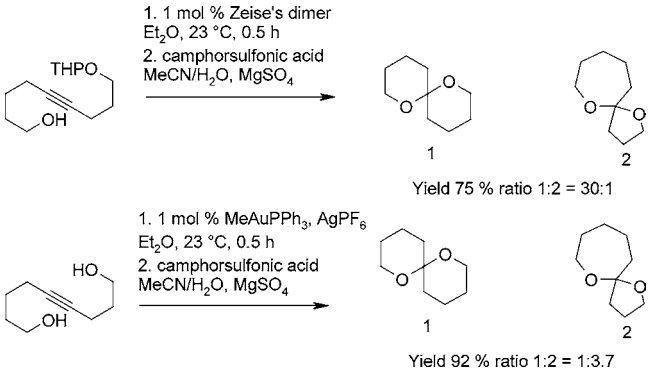
An Improved Preparation of Efaproxiral

The Chemical Development group at GlaxoSmithKline described a highly efficient, two-step synthesis of efaproxiral (*Synth. Commun.* **2006**, *36*, 2129−2133). Efaproxiral is the active pharmaceutical ingredient of Allos Therapeutic's Efaproxyn, currently under Phase III clinical trials for the treatment of brain metastasis originating from breast cancer. A mixture of 3,5-dimethylaniline and 4-hydroxyphenylacetic acid was heated in toluene in the presence of catalytic boric acid under Dean Stark conditions. Anilide **1** was obtained in 86−95% yield after precipitation. The methyl propanoic acid moiety was introduced by alkylation of the phenol with 2-bromo-2-methyl propionic acid using NaOH in 2-butanone (MEK). Formation of polyacrylates, which were not easily detected or cleaned from the reactors, was minimized. The API was obtained as a solid by crystallization from toluene/heptane in 64% yield over two steps from 4-hydroxyphenyl acetic acid.



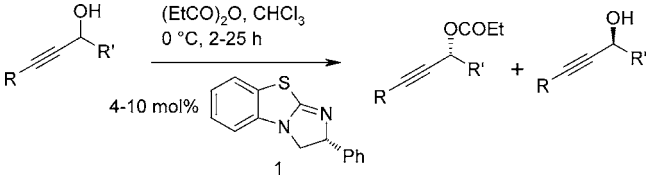
Metal-Catalyzed Regioselective Oxy-Functionalization of Internal Alkynes

The oxy-functionalization of internal alkynes (hydration, hydroalkoxylation represents a potentially attractive strategy for constructing ketone, acetal, or spiroketal substructures found in many natural products. Alkynes are relatively inert toward many reaction conditions that can be leveraged to delay installation of valuable but sensitive δ-hydroxyketone or acetal functionality until later in the synthesis via C−O bond formation. De Brabander et al. (*Org. Lett.* **2006**, *8*, 4707−4910) have reported efficient protocols for the Pt^{II}- and Au^{I}-catalyzed oxy-functionalization of unactivated internal alkynes. Zeise's dimer($[Cl_2Pt(CH_2{=}CH_2)]_2$) was identified as an efficient catalyst for the intramolecular hydroxyalkoxylation of 5-alkynols and 3-alkynols. For the 5-*exo* selective cycloisomerization of 4-alkynols a new catalyst obtained by premixing $MeAuPPh_3$ and $AgPF_6$ was found to be the most efficient.



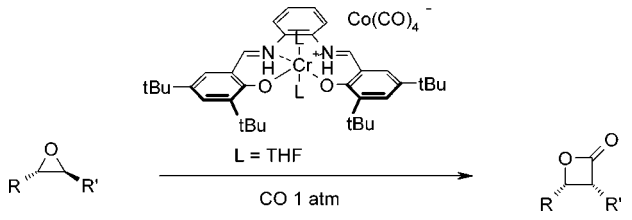
Kinetic Resolution of Propargylic Alcohols Catalyzed by Benzotetramisole

Several of the nonenzymatic asymmetric acylation catalysts developed to date achieve their highest enantioselectivities in kinetic resolution (KR) of benzylic alcohols. Some of them have also been found to be suitable for KR of allylic alcohols. Birman, V. B. et al. (*Org. Lett.* **2006**, *8*, 4859−4861) have found that benzotetramisole **1** promotes the KR of variously substituted secondary propargylic alcohols. The selectivity factor is as high as 32, the highest ever achieved with nonenzymatic catalysts for this class of substrates. Although the authors claim chloroform to be the best solvent for the conversion, *tert*-amyl alcohol is almost as good.



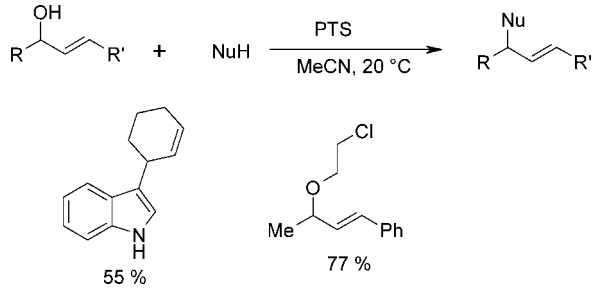
Practical β-Lactone Synthesis: Epoxide Carbonylation at 1 atm

Coates, G. W. et al. (*Org. Lett.* **2006**, *8*, 3709) have found that a readily prepared bimetallic catalyst **1** is capable of effecting epoxide carbonylation to produce β-lactones at substantially lower CO pressures than previously reported catalyst systems. A functionally diverse array of β-lactones is produced in excellent yields at CO pressures as low as 1. This procedure allows for epoxide carbonylation without the requirement of specialized, high-pressure equipment.



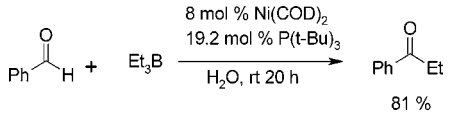
Brønsted Acid-Catalyzed Nucleophilic Substitution of Alcohols

Sanz, R. et al. (*Adv. Synth. Catal*. **2006**, *348*, 1841) have reported that simple Brønsted acids such as *p*-toluene sulfonic acid or a polymeric bound version catalyze the direct nucleophilic substitution of the hydroxyl group of allylic and benzylic alcohols with a variety of carbon- and heteroatom-centered nucleophiles.



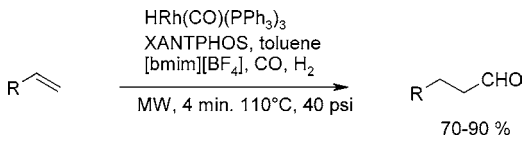
Nickel-Catalyzed Alkylation of Aldehydes with Trialkylboranes in Water

Oshima, K. et al. (*Adv. Synth. Catal*. **2006**, *348*, 1543) have reported that water enables the alkylation of aldehydes with trialkylboranes under nickel catalysis without the addition of base. Trialkylboranes prepared from borane dimethyl sulfide and terminal olefins via hydroboration as well as commercially available trialkylboranes could be employed in the reaction. The corresponding secondary alcohols were obtained in low to good yields.



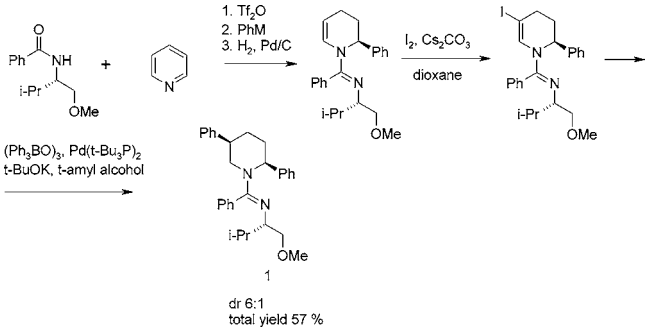
Microwaves Make Hydroformylation a Rapid and Easy Process

Taddei, M. et al. (*Org. Lett*. **2006**, *8*, 3725) have reported that hydroformylation of alkenes can be carried out in a few minutes under microwave activation at relatively low pressure (40 psi) using commercially available catalysts and ligands. A mixture of an alkene, Wilkinson's catalyst, and XANTPHOS was submitted to microwave irradiation under a 40 psi atmosphere of CO and H_2, giving after 4 min high conversion into the corresponding aldehyde without formation of the isomerized alkene.



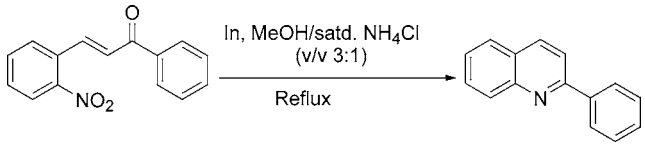
New Methodology Towards Chiral, Non-Racemic 2,5-*cis*-Substituted Piperidines

Piperidine units are found in many natural products and are key pharmacophores in many biologically active compounds. Charette, A. B. et al. (*Org. Lett.* **2006**, *8*, 3955) have reported on their newly developed methodology for the stereoselective synthesis of 2,5-*cis*-disubstituted piperidines. For example, compound **1** was synthesized in five steps from pyridine in 57% overall yield, demonstrating that the halogenation of 1,2,3,4-tetrahydropyridines forms a versatile vinyl iodide intermediate.



Indium-Mediated Reductive Cyclization of 2-Nitrochalcones to Quinolines

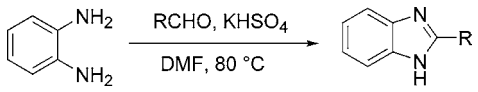
Quinolines are an important class of heterocycles—mainly due to their presence in several biologically active compounds and natural products. There have been a number of reports on their synthesis. Kim (Yanbian Univesity, Jilin, China) and others have described [*Heterocycles 68*, **2006**, 1675] a novel, environmentally friendly, and efficient indium-mediated reductive cyclization of *o*-nitrochalcones to quinolines in good yields. The starting *o*-nitrochalcones are synthesized from the corresponding benzaldehyde and acetophenone derivatives using a modified Claisen−Schmidt reaction. These are subsequently reacted with indium powder in MeOH-saturated aqueous ammonium chloride mixture to afford the products (see below)). The authors have dealt in detail with the various conditions they have tried as well as a possible mechanistic pathway in this paper. The reaction has been demonstrated to work with a number of substrates. The only drawback for a large-scale synthesis is that the final compounds are purified usually by column chromatography.



$KHSO_4$-Promoted Synthesis of 2-Arylbenzimidazoles

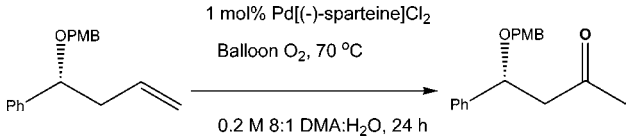
Benzimidazole derivatives exhibit significant biological properties (fungicidal, antitumor, etc.) which make their synthesis of great interest to medicinal and pharmaceutical chemists. As a result, a number of syntheses are known for benzimidazole. Several of these methods suffer disadvantages such as high reaction temperature, prolonged reaction time, etc. Wang (Henan Normal University, Henan, China) and Wang (Shanghai Institute of Organic Chemistry, Chinese Academy of Science, Shanghai, China) have reported

[*Heterocycles* **2006**, *68*, 1669] a mild $KHSO_4$-promoted synthesis of 2-arylbenzimidazole by oxidative condensation of aldehydes with *o*-phenylenediamine in good yields as illustrated below. This reaction, however, does not work with aliphatic aldehydes or arylacids.



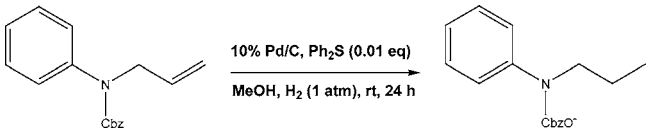
A Practical Wacker Oxidation

Conversion of terminal olefins to methyl ketones using metal catalysts such as Pd, Cu, and oxygen is an industrially and synthetically useful reaction for over half a century in spite of the need to have high mol ratios of metals. Sigman and Cornell (Cornell C. N.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 4117−4120) found highly practical conditions for conducting Wacker reaction. This utilizes catalytic amounts of Pd catalyst and O_2 (1 atm) whose oxidation properties are modulated by amine ligands such as sparteine in dimethyl acetamide and water at room temperature. The reaction is very chemoselective. Esters, acetals, and hydroxyls are tolerated under these conditions. Enantiomerically enriched PMB, TBS-protected allylic alcohols are also oxidized without racemization.



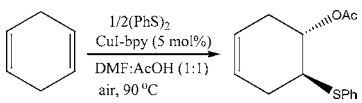
Pd/C-Catalyzed Chemoselective Hydrogenations

Transition metal-catalyzed chemoselective hydrogenations are generally performed by reducing the reactivity of the catalyst (poisoning) with amine bases, and sulfur compounds. Sajiki and co-workers used diphenylsulfide as catalyst poison. This allowed Pd/C-catalyzed chemoselective hydrogenation of olefins and acetylenes in the presence of aromatic carbonyls, halogens, benzyl esters, and *N*-Cbz protective groups. (Mori, A.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Sajiki, H. *Org. Lett*. **2006**, *8*, 3279−3281).



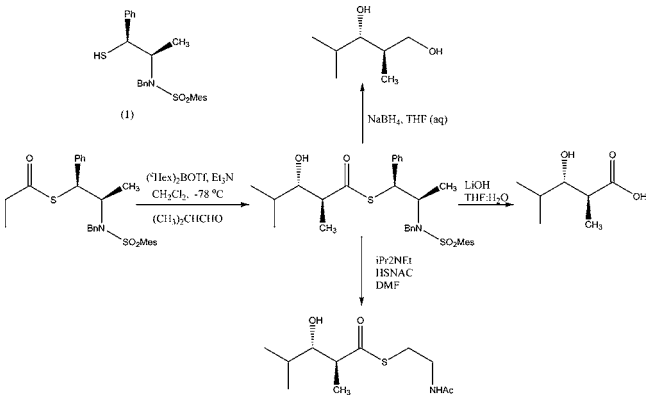
1,2-Hydroxysulfenylation of Alkenes

Usually 1,2-hydroxysulfides are prepared from the regioselective ring opening of the corresponding epoxides with thiols. Taniguchi reports a high-yielding procedure (Taniguchi, N. *J. Org. Chem*. **2006**, *71*, 7874−7876): the reaction of an olefin with a phenyl- or alkyldisulfide and a catalytic amount of copper−pyridine complex with air, acetic acid, and DMF mixture gives hydroxyacetyl sulfides in good yields. The reaction is regiospecific.



A New Chiral Auxiliary for Boron-Mediated Aldol Reactions

Auxiliary controlled stereoselective aldol reactions have a choice of Evans' oxazolidinone or its thiol derivatives and Masamune's norephedrine derivatives. These auxiliary-based strategies are sometimes limited during displacement of auxiliaries with nucleophiles due to competitive retro-aldol or elimination reactions. Hulme and co-workers synthesized a new thiol auxiliary (**1**), and this is shown to give high diastereoselectivity in boron-mediated aldol reactions with a range of aldehydes, and the new auxiliary is directly displaced with nucleophiles such as phosphonate esters, alcohols, acids, thiols (*N*-acetylcysteamine, HNAC) (Fanjul, S.; Hulme, A. N.; White, A. W. *Org. Lett*. **2006**, *8*, 4219−4222). The high yields associated with this reagent, the ease of its synthesis, and its bench stability should make this reagent an attractive alternate to norephedrine or oxazolidinone auxiliaries.

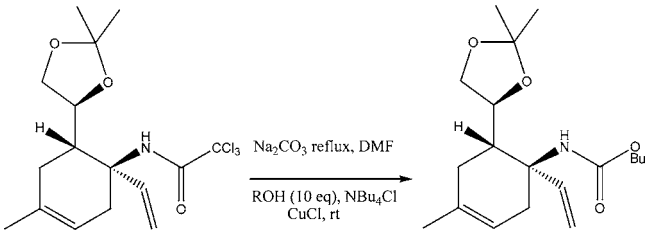


Transformation of Trichloroacetamide into Carbamates

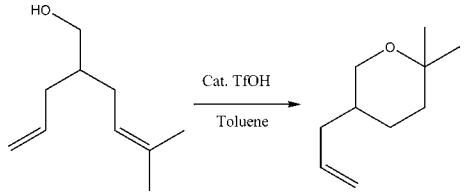
The rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides is a widely used method for transforming readily available allylic alcohols to less available allylic amines (Overman rearrangement). This is a very useful synthetic method for nitrogen heterocycles. However, the deprotection of the trichloroacetamide requires harsh conditions (4 N HCl or NaOH in ethanol) or reductive conditions using boron reagents. Nishikawa and co-workers developed a convenient method to transform trichloroacetamide into carbamates by heating in DMF and a desired alcohol (excess) in the presence of excess tetrabutylammonium chloride and copper (I) chloride and sodium carbonate as base at room temperature (Nishikawa, T.; Urabe, D.; Tomita, M.; Tsujimoto, T.; Iwabuchi, T.; Isobe, M. *Org. Lett.* **2006**, *8*, 3263−3265). The reaction is sensitive to steric factors; thus, *tert*-butyl alcohol gives poor yields. Acetals and silyl ethers are compatible with the conditions. This transformation could be performed in one pot and readily converted into easily removable carbamates.

Hydroalkoxylation of Unactivated Olefins

Usually N,O-nucleophiles are generally added to inactivated olefins using metal oxide catalysts. He and co-workers

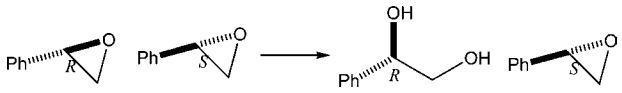


and Hartwig and co-workers simultaneously found that phenols, alcohols, sulfonamides, and benzamides can be added in the presence of 1−2 mol % of triflic acid. Cyclization of an alcohol containing pendant monosubstituted and trisubstituted olefins catalyzed to form products from addition to the more substituted olefin. Functional groups such as methoxy substituents on the aromatic phenols are tolerated at low temperature. This reaction provides one of the simplest olefin addition methods and is an alternative to metal-catalyzed reactions (Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.: Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175−4178; Rosenfeld, D. C.; Shaker, S.; Takemiya, A.; Utsuomiya, M.; Hartwig, J. *Org. Lett.* **2006**, *8*, 4179−4183).

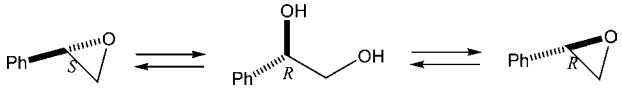


Enzymatic Resolution of Oxiranes

Lin et al. (*J. Ind. Microbiol. Biotechnol.* **2006**, *33*, 274) disclosed their results on the use of an epoxide hydrolase from *Aspergillus niger* SQ-6 in the resolution of *rac*-phenyloxirane. The hydrolase involved in this resolution process was (*R*)-stereospecific. Chiral capillary electrophoresis was used to analyze the reaction products. Conversions over 56% were obtained.



The authors made claims for an unknown racemase as playing a role in this process, since using the (*S*)-epoxide gave minor amounts of (*R*)-epoxide However, it is possible that this or another hydrolase can also attack the most substituted carbon on the (*S*)-epoxide via a S_N2 like mechanism, thus yielding the same reaction products.

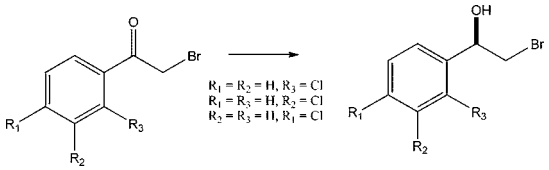


The present process makes use of fed-batch fermentation, and the effects of temperature and pH were investigated. Thus, temperatures of about 35 °C and pH of 7 were proved to be the best in terms of activity.

Yeast Carbonyl Reductase

Kizaki et al. (*Biosci. Biotechnol. Biochem.* **2005**, *69*, 79) described the purification and characterization of a yeast carbonyl reductase capable of reducing phenacyl halides.

Rhodotorula glutinis var. *dairensis* IFO 414 was discovered on a screening of microorganisms, and it is capable of carrying out this transformation in ee's as high as 99% despite *o*-, *m*-, and *p*-chloro substituents in the aromatic ring.



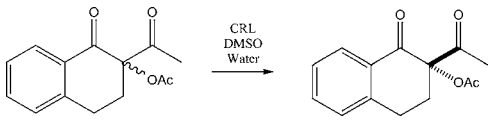
Other substrates were tested, and the relative activity was, in general, lower; however, activities were more than two times lower for ketopantoyl lactone and methyl pyruvate.

Lipases at High Concentrations

Tanyeli and co-workers (*Tetrahedron:Asymmetry* **2006**, *17*, 1125) have described the first resolution of quaternary α-acetoxy-α-substituted cyclic ketones.

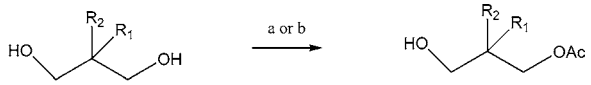
The synthesis of the substrates was carried out via $Pb(OAc)_4$ oxidation of suitable precursors, although the authors emphasized that $Mn(OAc)_3$ should be a suitable oxidant.

Various lipases were tested (PLR, VTL, HLR, and PPL) in very high concentrations using DMSO as cosolvent (best pH was 8). In one example, (*R*)-(+)-2-acetoxy-2-acetyl tetralone, was obtained in 45% isolated yield and 81% ee.



Chiral Recognition of Prochiral Substrates Using Lipases

Ohkata and co-workers (*J. Mol. Catal. B: Enzym.* **2006**, *38*, 1) described the use of a novel lipase (CSL) isolated from *Cryptococcus* spp. S-2 in chiral recognition in comparison with immobilized PPL. The desymmetrization and asymmetrization of 2-substituted-1,3-propanediols was chosen as reaction model.



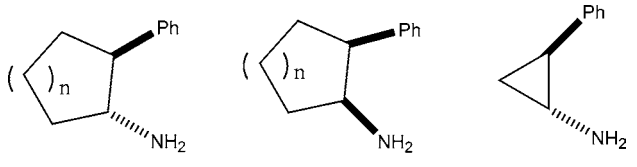
a) 0.2 mmol of the diol; 54 mg of lipase; 2.0 mL organic solvent; 0.037 mL of vinyl acetate
b) 0.2 mmol of the diol; 216 mg of immobilized lipase; 2.0 mL organic solvent; 0.11mL of vinyl acetate

When R^1 = Ph and R^2 = H although high yields of diacetate are formed, monoacetate was produced in 80% ee with CSL and in 91% ee using immobilized PPL, although in opposite configurations. With different 2,2-disubstituted-1,3-propane diols ee's were much lower (up to 50% ee), but considering that few examples with even lower ee's were previously described, these are promising results. Different

solvents have been tested, but there is no simple relationship between ee's and log *P*.

Lipase-Catalyzed Aminolysis of Esters

The aminolysis of esters is a model reaction between a nucleophile and an electrophile. Different reaction mechanisms for this reaction have been proposed thus far, and the enzyme-catalyzed system can be considered a weak, base-catalyzed sequence. In this arena González-Sabín et al. (*Tetrahedron: Asymmetry* **2006**, *17*, 1264) screened several *rac*-amines to study the mechanism of this reaction. However, from the synthetic point of view such study constitutes a new protocol to the resolution of *rac*-amines.



rac-1 n = 1
rac-2 n = 2

rac-3 n = 1
rac-4 n = 2

rac-5

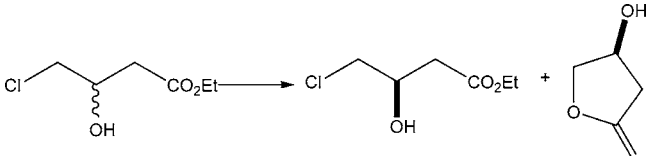
Candida Antarctica lipase B (CAL-B) was chosen for this study. Remarkable enantiomeric ratios, $E > 200$ and $E = 166$, were obtained using, respectively, *rac*-1 and *rac*-3. The fast reacting enantiomer in both cases was the (1*R*,2*S*)-enantiomer.

Asymmetric "Dehydrochlorination"

Nakagawa et al. (*J. Biosci. Bioeng.* **2006**, *101*, 97) has described the use of *Enterobacter* sp. DS-S-75 in the resolution of (*R,S*)-4-chloro-3-hydroxybutyrate into (*S*)-3-hydroxy-γ-butyrolactone.

The enzyme was purified, and the code gene from the strain DS-S-75 was isolated in order to improve the productivity using the transformant.

When a culture broth of *Escherichia coli* DA5α transformed with the isolated gene was used, the reaction time was shortened about 20-fold, and both ethyl (*S*)-3-hydroxy-γ-butyrolactone (HL) and remaining (*R*)-4-chloro-3-hydroxybutyrate (CHB) were obtained with over 99% ee.

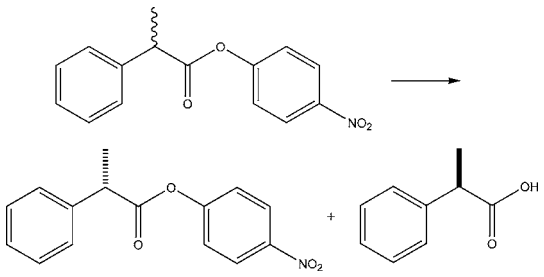


rac-CHB (*R*)-CHB (*S*)-HL

Thermostable Lipases

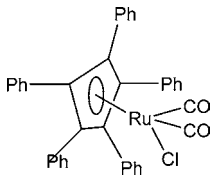
Whole-cell biocatalysis presents several drawbacks when applied to industrial processes. Jung, Kwon, and Pan (*BMC Biotechnol.* **2006**, 6:23; http://dx.doi.org/10.1186/1472-6750-6-23) disclosed their results in immobilizing a thermostable lipase from *Pseudomonas fluorescens* on the cell surface of a solvent-resistant bacterium, *Pseudomonas putida* GM730.

The system was successfully tested in different processes and shown to be useful in the resolution of *p*-nitrophenyl-2-phenylpropionate with an enantiomeric ratio (*E*) of 36.



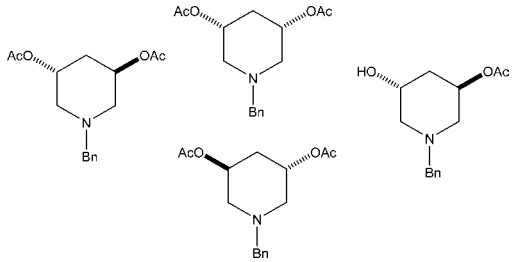
Divergent Asymmetric Synthesis of 3,5-Disubsituted Piperidines

The Bäckvall group (*J. Org. Chem.* **2006**, *71*, 8256) disclosed an efficient chemoenzymatic protocol to generate chiral 3,5-disubstitued piperidines.



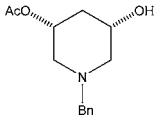
The Ru(II) catalyst plays an important role in epimerizing the hydroxyl groups attached to be piperidine ring while lipase "resolution" proceeds.

Thus, it was possible to study the general transformation of 3,5-dihydroxypiperidines into the respective diastereoisomers.



The so-called dynamic kinetic asymmetric transformation (DYICAT) involves the use of the Ru(II) catalyst combined with different lipases and vinyl acetate.

For example, 3-acetoxy-5-hydroxy-1-benzylpiperidine was obtained in 91% yield and 99% ee.



High Throughput Solubility Measurement with Automated Polarized Light Microscopy Analysis

Several groups from Pfizer-Japan (Sugano, K. et al. *J. Pharm. Sci.*. **2006**, *95*(10), 2115) compare the DMSO-solution precipitation (DMSO-SP) solubility high throughput method used in drug discovery, with the solubility method using solid material (coded by the authors as the PWD method, because of the use of powder material). The latter, also known as the "thermodynamic solubility method", is typically used in the development stages of a drug candidate. In this investigation, the final concentration of the DMSO solvent in samples measured with the DMSO-SP method was

1% (v/v). An important component of this high throughput method was the observation of the precipitant using a polarized light microscope. Two "incubation" times were used: 10 min and 20 h. Twenty-six compounds were evaluated, with results for the PWD method obtained mostly from the literature. To simplify the direct comparison, solubilities of neutral species were used. In all cases the DMSO-SP solubilities were practically equal to, or slightly higher than the PWD solubilities. The values were found to be closer when the incubation time used in the DMS-SP method was 20 h rather than 10 min, especially when the precipitant was crystalline. The few instances of large differences between the two methods were found for cases of noncrystalline materials. The authors suggest that a high throughput DMSO-SP solubility measurement can be very meaningful in drug discovery when the incubation times used are long (20 h) and the crystallinity of the precipitant is evaluated.

Esterification of Acetic Acid with Isopropanol Coupled with Pervaporation. Part II. Study of a Pervaporation Reactor

An academic collaboration from Germany and Spain, (Sanz, M. T. et al. *Chem. Eng. J.* **2006**, *123*, 9) discusses the advantages of carrying on esterification reactions using a pervaporation unit. Pervaporation has been used for several years in the chemical industry to purify chemicals using a membrane prcess (for example, dehydrating chemicals). Water, the "minor" component in an esterification process, permeates the membrane, thus being eliminated from the system. The term "pervaporation" is used for such cases where the feed to the membrane is liquid, and the minor component appears to "e*vaporate*" through the membrane (when in fact, the minor component *per*meates the membrane). In this study a PVA membrane, PERVAP 2201 was used, together with a heterogeneous catalyst, Amberlyst 15. The conversions achieved were 30−100% higher than the corresponding conversions without pervaporation. The influence of several operating parameters on conversion was investigated in a one-factor-at-a-time fashion. Favorable effects on conversion were found at higher temperatures, catalyst amounts, and ratio of membrane area to initial reacting volume. Interestingly, a stoichiometric use of isopropanol leads to a higher conversion than the case of 2-fold molar excess of isopropanol to acetic acid. Models for the reaction rate and for the water flux through the membrane were proposed.

Bubble Sizes in Agitated Solvent/Reactant Mixtures Used in Heterogeneous Catalytic Hydrogenation of 2-Butyne-1,4-diol

An industrial−academic collaboration from the United Kingdom (Hu, B. et al. *Chem. Eng. Sci.* **2006**, *61*, 6765) analyzes bubble size distribution in stirred tanks simulating hydrogenation processes. In catalytic hydrogenation processes, the rate of gas−liquid mass transfer, which depends on bubble size, is often the overall rate-limiting step of the process. The study used a model containing several solvent mixtures based on the water/isopropanol system; air at 1% by volume simulated the hydrogen gas. A baffled, 3-L reactor fitted with a Rushton turbine was used. The mixing was characterized by a turbulent dissipation energy range (ϵ_T) of 20−50 W/kg, under fully turbulent conditions. The presence of the unsaturated organic substrate was simulated using 2-butyne-1,4-diol at 0.2 M concentration. The bubbles were measured using a computerized video microscope. The results reported were obtained at 25 °C and atmospheric pressure.

Interestingly, for the case of pure solvents, in spite of the large difference in surface tension, the bubbles observed were of comparable (irregular) shape, size, and size distribution. In isopropanol−water mixtures, at low isopropanol concentrations, the bubbles were spherical, much smaller, and of narrower size distribution. The addition of the organic substrate did not affect the bubble shape, size, or size distribution. Bubble size d_{32} was found to have a weak dependence on ϵ_T: $d_{32} \sim (\epsilon_T)^{-0.25}$, where ϵ_T is the turbulent dissipation energy.

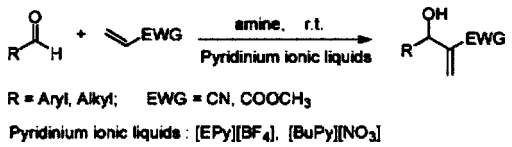
The observations reported are explained using a model based on the polarization of bubble surfaces in solvent mixtures of various polarities. On the basis of this model, further investigations are planned to verify the hypothesis that a solvent system of optimal polarity could be found for achieving the maximum overall hydrogenation reaction rate.

Metallosurfactants

Metallosurfactants are a new class of material in which the polar headgroup of the surfactant molecule contains a metal centre as an integral structural component. The incorporation of d- and f-block metal complexes into amphiphilic structures has attracted some attention because the variable charge, magnetic properties, and potential catalytic activity of transition metal complexes render their incorporation within amphiphilic structures a means of concentrating these features at interfaces. The self-assembly of such surfactants further provides a simple means of preparing well-defined metal complex aggregates of nuclearities equal to the aggregation numbers of the micelles themselves. Such surfactants are rare compared with conventional surfactants, but they have recently found important potential applications in diverse subject areas such as magnetic resonance imaging, the templating of mesoporous materials, thin-film optoelectronics, interfacial photophysics, and homogeneous catalysis. To reduce the lability of the metal, various chelating or macrocyclic ligands may be employed, leading to a family of homologous series of related metallosurfactants with a structural diversity that is arguably broader than is inherently possible with conventional surfactants. A recent review by Griffiths et al. covers the physico−chemical properties of metallosurfactants and highlights their classical as well as non-classical surfactant behaviour, providing an insight into the structure of micelles and films formed from these novel materials (*Adv. Colloid Interface Sci.* **2006**, *122*(1−3), 107−117).

Pyridinium Ionic Liquid-Accelerated Amine-Catalyzed Morita−Baylis−Hillman Reaction

The Morita−Baylis−Hillman reaction is one of the most versatile carbon−carbon bond-forming reactions in modern organic synthesis and has drawn considerable attention in the past decade due to its many advantages in regard to atomic economy, nonmetal catalysis, mild conditions, compatibility with multiple functional groups, and so on. However, there are a number of problems commonly associated with this useful reaction, most notably, its sluggish reaction rates and low-to-moderate yields. Pyridinium ionic liquids *N*-ethylpyridinium tetrafluoroborate ([EPy][BF_4]) and *N*-butylpyridinium nitrate ([BuPy][NO_3]) as reaction media were efficient for the DABCO-catalyzed Morita−Baylis−Hillman reaction. In short reaction time, good yields have been obtained. In addition, in the presence of ionic liquid [EPy][BF_4], the hexamethylenetetramine (HMTA), a cheap tertiary amine, effectively catalyzed the Morita−Baylis−Hillman reaction (*J. Mol. Cat. A: Chem.* **2006**, *258*(1−2), 251−256).



Combustion of Chlorinated Aliphatic Pollutants and Toluene over Ceria-Zirconia

Chlorine-containing organic compounds are among the most polluting VOCs. In Europe the Gothenburg Protocol adopted by the 15 EU member states in 1999 requires a 40% reduction in VOC emissions by 2010. In view of the scale of the problem presented to the chemical and processing industries the major challenge they face is to reduce the emission of polluting VOCs without stifling economic growth. Among the methods applied to remove chlorinated VOCs from effluents (<0.1%) to very low levels (typically high-temperature incineration, hydrodechlorination, biological processes, steam reforming, photocatalytic degradation, etc.), catalytic oxidation to HCl, H_2O, and CO_2 is the most viable and economical approach. Supported noble metals catalysts are known for their high activity for the oxidation of organic compounds including aromatics. Their applicability towards the destruction of chlorinated hydrocarbons, however, is limited due to deactivation of the noble metal in the presence of chlorine. Alternatively, the use of oxides of transition metals (Cr_2O_3, Mn_2O_3, V_2O_5) represent viable alternatives, since they resist deactivation to a larger extent. Among these systems chromium oxide exhibits the highest activity, but the high toxicity of chromium oxychloride causes serious disposal problems with this system. Consequently, there is a strong interest in developing catalysts that are less expensive and more robust than the materials presently in use.

The oxidation of representative VOCs, such as toluene, 1,2-dichloroethane, and trichloroethylene, present in trace amounts in air streams over a series of $Ce_xZr_{1-x}O_2$ oxides (CeO_2, $Ce_{0.8}Zr_{0.2}O_2$, $Ce_{0.68}Zr_{0.32}O_2$, $Ce_{0.5}Zr_{0.5}O_2$, $Ce_{0.15}Zr_{0.85}O_2$, ZrO_2) as catalysts is reported with focus on the difference in catalytic performance in the oxidation of single and chlorinated VOC/toluene mixtures, and on the mixture effects on product selectivity. In general, the efficiency for the single VOC destruction was found to decrease in the following order: toluene >1,2-dichloroethane > trichloroethylene. For chlorinated compounds the best performance was observed for the mixed oxides with 50 and 85 mol % of zirconia content, while ceria exhibited the best behaviour for toluene oxidation. With regard to chlorinated compounds the combination of surface acidity and accessible lattice oxygen appeared to control the catalytic performance of the mixed oxides. On the contrary, the combustion of toluene was essentially controlled by surface oxygen species (*Appl. Cat., A* **2006**, *314*(1), 54−63).

Cinchonidine-Modified Pt Nanoclusters Deposited on Alumina

Catalysts that can induce high enantiomeric excess (ee) under mild reaction conditions are important. In particular, a heterogeneous system capable of inducing high ee under mild conditions without additional external forces (i.e., sonication) would be of interest. A novel preparation of Pt nanoclusters (3 nm) deposited on a nonporous alumina support and modified with cinchonidine was found to be very efficient for hydrogenation of ethyl pyruvate at low pressures. The catalyst demonstrated 80−88% of enantiomeric excess in ethyl pyruvate hydrogenation under mild reaction conditions (2.5−10 bar of hydrogen pressure) in acetic acid. Further, the catalyst was found to be very stable and could be recycled at least four times without an observable decrease of activity or enantioselectivity (*Appl. Cat., A* **2006**, *314*(1), 1−8).

Catalytic Wet Air Oxidation of Phenol with an Fe/Activated Carbon Catalyst

Catalytic wet air oxidation (CWAO) has gained an increasing interest in the last decades. Different catalysts based on noble metals and transition metal oxides over different supports (Al_2O_3, CeO and TiO_2) have been investigated. These catalysts provided satisfactory results with pollutants of different natures (such as phenol and phenolic derivatives, dyes, ammonia, carboxylic acids, alcohols, etc.), but some limitations have also been reported. Deactivation by deposition of carbonaceous material on the catalyst surface, in the case of the noble metal catalysts, and leaching of the active phase, due to the acidity of the reaction media, in the case of metal catalysts based on metal oxides can take place. CWAO of phenol with molecular oxygen using an Fe/activated carbon catalyst at mild operating conditions (100−127 °C; 8 atm) has been studied in a trickle-bed reactor. Aromatics such as hydroquinone, *p*-benzoquinone, and *p*-hydroxybenzoic acid and short-chain organic acids such as maleic, malonic, oxalic, acetic, and formic acids have been identified as intermediate oxidation products. It was found that phenol is oxidized through two different ways. It can be either para-hydroxylated to hydroquinone, which is instantaneously oxidized to *p*-benzoquinone or para-car-

boxylated to *p*-hydroxybenzoic acid. *p*-Benzoquinone is majorly mineralized to CO_2 and H_2O through oxalic acid formation, whereas *p*-hydroxybenzoic acid gives rise to short-chain acids. Only acetic acid appeared to be refractory to CWAO. The catalyst avoids the presence of ring-condensation products in the reactor effluent which were formed in absence of it. This is an additional important feature because of the ecotoxicity of such compounds (*Appl. Cat, B* **2006**, *67*(3−4), 206−216).

Biodiesel Process

The transesterification of vegetable oils to the methyl esters (biodiesel) is characterized by excellent properties as diesel engine fuels and thus can be used in compression−ignition (diesel) engines with little or no modifications. The transesterification reaction of vegetable oils with methanol is commonly carried out in the presence of homogeneous base or acid catalysts. Acid-catalyzed processes often use sulfonic acid and hydrochloric acid as catalysts; however, the reaction time is very long (48−96 h) even at reflux of methanol, and a high molar ratio of methanol to oil is needed (30−150:1, by mol). Potassium hydroxide, sodium hydroxide, their carbonates as well as potassium and sodium alkoxides, such as $NaOCH_3$, are usually used as base catalysts for this reaction. As the catalytic activity of a base is higher than that of an acid and acid catalysts are more corrosive, the base-catalysed process is preferred to the acid-catalyzed one and is thus most often used commercially. However, in the conventional homogeneous manner, removal of these base catalysts is technically difficult, and a large amount of wastewater is produced to separate and clean the catalyst and the product. Therefore, conventional homogeneous catalysts are expected to be replaced in the near future by environmentally friendly heterogeneous catalysts mainly due to environmental constraints and simplifications in the existing processes. The transesterification of soybean oil with methanol to methyl esters was carried out using NaX zeolites loaded with KOH as a solid base catalyst. Best result was obtained with NaX zeolite loaded with 10% KOH, followed by heating at 393 K for 3 h. When the transesterification reaction was carried out at reflux of methanol (338 K) with a 10:1 molar ratio of methanol to soybean oil, a reaction time of 8 h, and a catalyst amount of 3 wt %, the conversion of soybean oil was 85.6% (*Bioresour. Technol.* **2007**, *98* (4), 936−939).

Cyclodehydration of 1,4-Butanediol to Tetrahydrofuran Catalyzed by Supported Silicotungstic Acid

Catalytic synthesis of tetrahydrofuran from maleic anhydride or its derivatives, such as 1,4-butanediol, has attracted a great deal of attention in view of its economical and environmental benign nature. The cyclodehydration of 1,4-butanediol to tetrahydrofuran catalyzed by heteropoly acids (tungstophosphoric acid, silicotungstic acid, and molybdophosphoric acid) supported on alumina, Y-, β-, and ZSM-5 zeolites exhibits high activity and selectivity. The interactions between heteropoly acid and various kinds of supports should result in different catalytic activities. Acid strength, acid density, and the combination ability between silicotungstic acid and support were investigated when supported silicotungstic acid was used as a catalyst for cyclo-dehydration of 1,4-butanediol to tetrahydrofuran. The interaction between heteropoly acid and support influenced the catalytic activity. TiO_2-supported silicotungstic acid catalyst exhibited high activity when compared to the other catalysts supported by kaolin, kieselguhr, and activated charcoal. (*Catal. Commun.* **2006**, *7*(10), 778−782).

Process Design and Energy Requirements for the Capture of Carbon Dioxide from Air

The atmospheric concentration of carbon dioxide, the most critical greenhouse gas, has increased from 280 ppm in the pre-industrial age to more than 370 ppm now and is expected to increase above 500 ppm by the end of this century. Present strategies rely on improving the efficiency in energy use, on reducing fossil fuel consumption, and on using renewable energy sources or nuclear power plants. However, the continuing increase of the world's population together with the concomitant growth in energy consumption and the industrial development in developing countries such as China and India conflicts with the efforts to reduce greenhouse gas emissions. A process to capture carbon dioxide from air to reduce its atmospheric concentration and to mitigate climate change has been studied. It is based on the absorption of carbon dioxide in a sodium hydroxide solution, its precipitation as calcium carbonate, and its release as a pure gas stream through oxy-fuel calcination. The process utilizes existing commercial technologies wherever possible, particularly in the case of the absorber, whose design is carried out in detail. The analysis allows the derivation of material and energy balances for the whole process and determination of energy demands that can be used for a technical, economical, and environmental feasibility evaluation of the technology. In particular, it indicates that the real specific energy demand is larger than the heat released to emit the same amount of CO_2 by the combustion of coal, and smaller than that of methane (*Chem. Eng. Process.* **2006**, *45*(12), 1047−1058).

Green and Efficient Diazotization and Diazo-Coupling Reactions on Clays

Azo dyes contain azo groups linked to methine or aromatic sp^2-hybridized C-atoms. The formation of the diazotizing reagent starts with protonation of nitrous acid under strongly acidic conditions, and azo coupling is carried out at low temperature in the presence of nucleophilic coupling components, the reactivity of a nucleophilic substrate increasing with increasing basicity phenolates and amines. These conventional acid−base-catalysed processes are effective for the near quantitative formation of the desired products. But the main limitation of such synthetic processes is their environmental incompatibility. The acidic and basic effluents from the laboratory and industry produce permanent damage to the environment and disturb the ecological balance. In recent years, clay-based catalysts are reported to be effective for performing many of the acid−base-catalyzed organic reactions in a better, environmentally benign manner.

Diazotization and diazo-coupling reactions of sodium sulfanilate dihydrate and *p*-diazonium benzene sulfonyl azide with aromatic phenols over eco-friendly clay catalysts are described. These inexpensive, noncorrosive, and reusable catalysts were found to exhibit bifunctional catalytic properties for diazotization and diazo-coupling reactions. No considerable decreases in the efficiency of the catalysts were observed after four cycles of operation. The new method totally avoids the use of acids, alkalies, and toxic solvents in diazotization and diazo-coupling reactions. (*Dyes Pigm.* **2007**, *73*(2), 239−244).

Fouling in Membrane Bioreactors Used in Wastewater Treatment

The membrane bioreactor (MBR) technology is a reliable and efficient technology, which has become a legitimate alternative to conventional activated sludge processes and an option of choice for many domestic and industrial applications. However, membrane fouling and its consequences in terms of plant maintenance and operating costs limit the widespread application of MBRs. To provide a better understanding of the complex fouling mechanisms and propensities occurring in MBR processes, a recent review compiles and analyses more than 300 publications. It also proposes updated definitions of key parameters such as critical and sustainable flux, along with standard methods to determine and measure the different fractions of the biomass. Although there is no clear consensus on the exact phenomena occurring on the membrane interface during activated sludge filtration, many publications indicate that the extracellular polymeric substances (EPS) play a major role during fouling formation. More precisely, the carbohydrate fraction from the soluble microbial product (also called soluble EPS or biomass supernatant) has been often cited as the main factor affecting MBR fouling, although the role of the protein compounds in the fouling formation is still to be clarified. Strategies to limit fouling include manipulating bioreactor conditions, adjusting hydrodynamics and flux, and optimizing module design (*J. Membr. Sci.* **2006**, *284*(1−2), 17−53).

Hollow Silica Nanotubes for Immobilization of Penicillin G Acylase Enzyme

Porous, hollow, silica nanotubes (PHSNTs) synthesized via a sol−gel route using nanosized needle-like $CaCO_3$ inorganic templates have been employed as a support for immobilization of penicillin G acylase (PGA) biocatalyst. The produced PHSNTs were characterized by BET and transmission electron microscopy (TEM). The effect of various factors such as loading temperature and ratio of carries to free PGA (g/mL) on the catalytic activity of the immobilized PGA was also investigated by unitary factor testing methods. The results show that under optimized conditions the relative loading amount and the total activity yield of immobilized enzyme (IME) amounts to 97.20% and 88.80%, respectively. Several advantages, i.e. the rapid immobilization of PGA onto PHSNTs, the high tolerability to the pH, the lowered sensitivity to the temperature, and the improved storage stability render PHSNTs potential support materials for enzyme immobilization (*J. Mol. Catal. B: Enzym.* **2006**, *42*(1−2), 14−19).

Mark McLaughlin
Merck & Co. Inc., Rahway, New Jersey 07065, U.S.A.
E-mail: mark_mclaughlin@merck.com

Silvina García Rubio
Sapphire Therapeutics, Inc., Bridgewater, New Jersey 08807, U.S.A.
E-mail: sgarciarubio@sapphirethera.com

Ulf Tilstam
Development Centre S.A., Parc Scientifique de Louvain-la-Neuve, B-1348 Mont-Saint-Guibert, Belgium.
E-mail: tilstam_ulf@lilly.com

Ramaiah Muthyala
Center for Orphan Drug Development, Department of Medicinal Chemistry, University of Minnesota, Minneapolis Minnesota 55455, U.S.A.
E-mail: muthy003@umn.edu

Joseph Swaroop Mathen
Pharmacore Inc., High Point, North Carolina 27265, U.S.A.
E-mail: jsmathen@vsnl.com

Octavio Augusto Ceva Antunes
Departamento de Quimica Inorganica, Instituto de Quimica, UFRJ, Cidade Universitaria, Rio de Janeiro, RJ 21949-900, Brazil.
E-mail: octavio@iq.ufrj.br

Trevor Laird*
Editor

Ganapati D. Yadav
Department of Chemical Engineering, University Institute of Chemical Technology, University of Mumbai, Matunga, Mumbai - 400 019, India.
E-mail: gdyadav@yahoo.com; gdyadav@udct.org

Andrei Zlota
The Zlota Company, Sharon, Massachusetts 02067-2858, U.S.A.
andrei.zlota@thezlotacompany.com

OP060213U