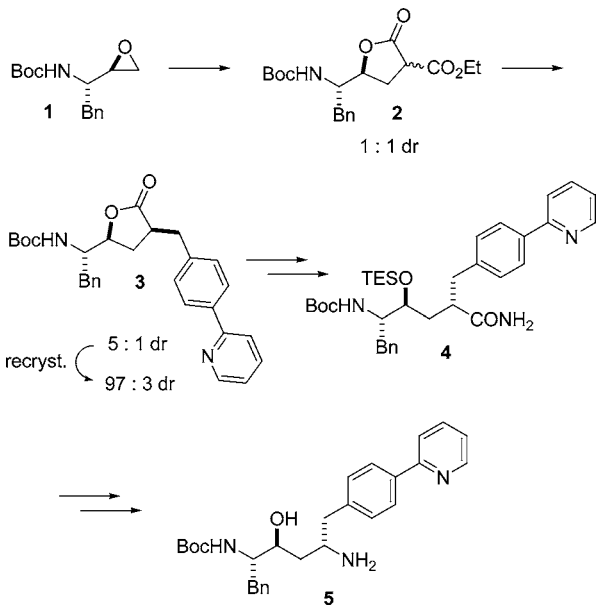
Organic Process Research & Development **2006**, *10,* 853–865

Highlights from the Literature

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

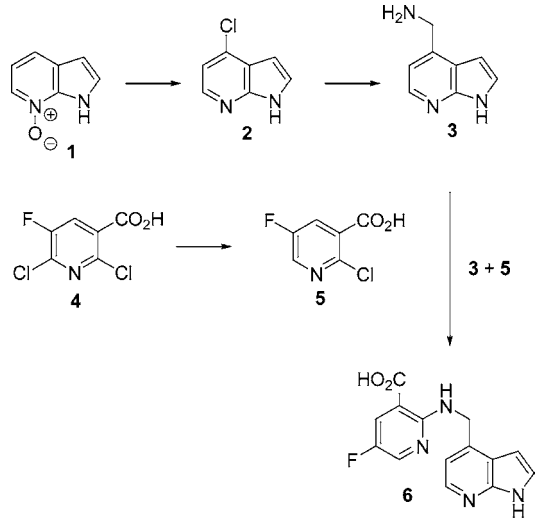
Efficient Synthesis of HIV Protease Inhibitor A-792611



A stereoselective synthesis of the hydroxyethylene dipeptide isostere **5** is described by Wagaw and co-workers at Abbott (*J. Org. Chem.* **2006**, *71*, 5369−5372). Starting from phenylalanine-derived epoxide **1**, reaction with diethyl malonate affords lactone **2** in a 1:1 ratio of diastereomers. Alkylation of **2** is followed by decarboxylation, in which substrate controlled kinetic protonation of the intermediate enol affords 5:1 diastereoselectivity. Recrystallization provides an upgrade to 97:3 with 95% recovery of the desired isomer **3**. Attempts to access amino alcohol **5** via basic hydrolysis of lactone **3** followed by a diphenylphosporyl azide mediated Curtius rearrangement were thwarted by epimerization adjacent to the ester. Instead, lactone **3** was opened using neat ammonia, which preserved the stereocenter, and TES-protection afforded Curtius substrate **4**. Last, a novel procedure for utilizing *N*,*N*-dibromo-5,5-dimethylhydantoin in the Hofmann rearrangement of **4** to **5** is described. This route was used to prepare amino alcohol **5**, the core portion of the HIV protease inhibitor A-792611, in 46% yield from phenylalanine-derived epoxide **1**.

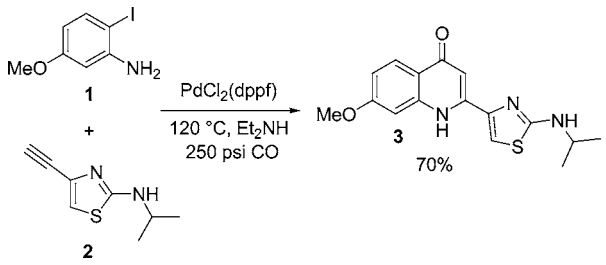
Practical Synthesis of 2-((1*H*-Pyrrolo[2,3-*b*]pyridine-4-yl)-methylamino)-5-fluoronicotinic Acid

A practical synthesis of a key pharmaceutical intermediate, 2-[(1*H*-pyrrolo[2,3-*b*]pyridine-4-yl)methylamino]-5-fluoronicotinic acid **6**, is reported by Wang, Zhi, and co-workers at Amgen (*J. Org. Chem.* **2006**, *71*, 4021−4023). To introduce the aminomethyl moiety of **3** via a palladium-catalyzed cyanation/reduction sequence, a regioselective chlorination



of 7-azaindole via the *N*-oxide **1** was developed. A highly selective monodechlorination of 2,6-dichloro-5-fluoronicotinic acid **4** using $Pd(OAc)_2/Et_3N/HCO_2H$ was developed to afford the nicotinic acid **5**. The two building blocks **3** and **5** were then coupled in 70% yield by heating at 130 °C in 1-pentanol, completing the preparation of **6**.

Convergent Synthesis of the Quinolone Substructure of BILN 2061 via Carbonylative Sonogashira Coupling/Cyclization

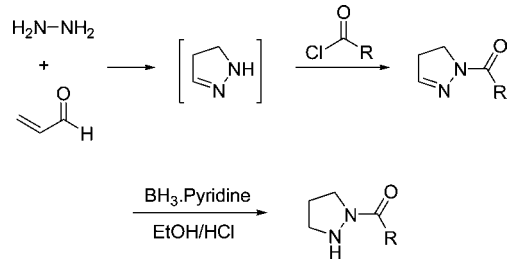


Haddad and co-workers at Boehringer Ingelheim report on a convergent synthesis of quinolone **3**, a key substructure of the protease inhibitor BILN 2061 (*J. Org. Chem.* **2006**, *71*, 5031−5034). Central to the approach was a palladium-catalyzed carbonylative Sonogashira coupling/cyclization of 2-iodo-5-methoxyaniline with a thiazolylacetylene. The iodoaniline was derived from a nitro-precursor via hydrazine mediated reduction, while the ethynylthiazole was obtained through one of two routes. In the first route, 2-isopropylaminothiazoline-4-one was elaborated into an iodothiazole, via an intermediate thiazolyl phosphate, and then alkynylated under Sonogashira conditions using TMS-acetylene. Alternatively, coupling of lithiated TMS-acetylene with *N*-methoxy-*N*-methylchloroacetamide followed by treatment

10.1021/op060169i CCC: $33.50
Published on Web 09/15/2006

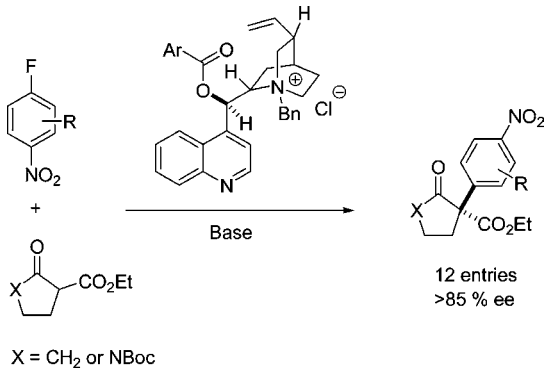
with isopropylthiourea and then basic cleavage of the TMS-group furnished the ethynylthiazole. For the key step, using Et_2NH as solvent and $PdCl_2$(dppf) as the catalyst was found to afford the best yield of the desired quinolone. When $Pd(OAc)_2$ was used the diethyl amide side-product formed by amination of the initial carbonylation intermediate predominated.

Facile Reduction of *N*-Acylated Dihydropyrazoles



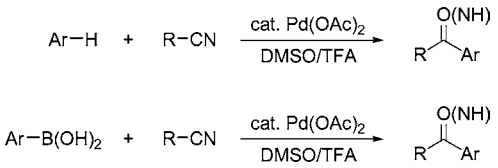
The reduction of a variety of highly functionalized *N*-acylated dihydropyrazoles (**1**) with BH_3·pyridine is reported by Curtis and co-workers at Proctor and Gamble (*J. Org. Chem.* **2006**, *71*, 5035−5038). A facile atom efficient route to the *N*-acylated dihydropyrazole reduction precursors was developed, and multi-kilogram scale experimental details are provided. For the reduction of the dihydropyrazoles, a variety of hydride reagents were screened along with metal-catalyzed hydrogenation conditions. It was determined that the BH_3·pyridine complex with a strong acid additive (HCl) in the polar solvent DMF gave the best results. Attempts to apply the developed conditions to substrates bearing chiral centers adjacent to the acyl carbonyl group led to partial epimerization. Nonetheless, this route provides direct access to potential aza-proline surrogates for peptidomimetic applications.

Organocatalyzed Asymmetric S_NAr Reactions of 1,3-Dicarbonyl Compounds



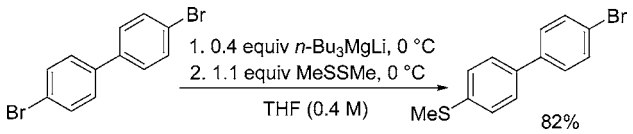
A report from the group of Jorgensen describes the scope and limitation of asymmetric nucleophilic aromatic substitution reactions of α-substituted 1,3-dicarbonyl compounds with activated aromatic systems catalyzed by *N*-benzyl-*O*-benzoylcinchoninium or cinchonidinium salts (*J. Org. Chem.* **2006**, *71*, 4980−4987). Several novel *O*-benzoylcinchona alkaloid derived salts were prepared and evaluated as catalysts in this reaction, which can proceed with enantioselectivities up to 96% ee. Various 1,3-dicarbonyl compounds and activated aromatic systems were evaluated, and it was found that the yield and enantioselectivity are highly dependent on the substrate and reagent. In consequence, this technique is not generally applicable at present. It was also noted that hydrolysis of the benzoylated cinchona catalyst and subsequent arylation by the electron-deficient aromatic produced a new species that also catalyzed the S_NAr reaction but with lower ee. Elaboration of the products to various structures is also discussed, including formation of a spirooxoindole, a ring-opening reaction of 1,3 α,α-disubstituted dicarbonyl compounds with several nucleophiles, and the diastereoselective reduction of the keto functionality in the optically active S_NAr product.

Pd-Catalyzed Arene C−H Addition to Nitriles



Following up on an earlier communication, the Larock group now provides a full account of their work on palladium-catalyzed C−H addition of arenes to nitriles (*J. Org. Chem.* **2006**, *71*, 3551−3558). This chemistry provides moderate to good yields of aryl ketones or the corresponding hindered imines; however drawbacks are the use of 2 equiv of arene and 10 mol % of palladium catalyst. To generate highly active cationic Pd-species, the reactions were run in TFA (no product was observed in AcOH). The addition of a small amount of DMSO increased the yields dramatically. Both intermolecular and intramolecular reactions are successful, although interestingly the intramolecular reactions tend to be more sluggish. The authors postulate that the mechanism for this chemistry involves palladium-catalyzed C−H activation of the arene by electrophilic aromatic substitution, followed by the unusual carbopalladation of a nitrile. Arguments against Lewis acid activation of the nitrile followed by nucleophilic attack by the arene (Houben−Hoesch type mechanism) are discussed. Similar reactions have been successfully developed employing arylboronic acids and nitriles. A concise route to xanthones from cheap starting materials was also developed.

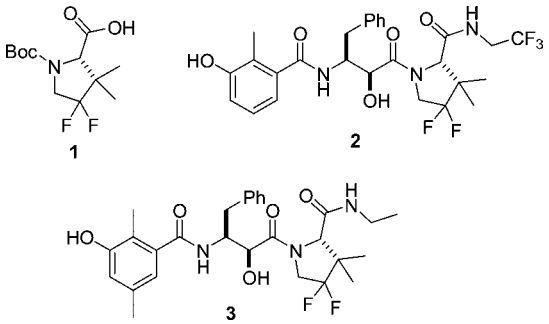
Selective Metal−Halogen Exchange of 4,4′-Dibromobiphenyl Mediated by Lithium Tributylmagnesiate



A selective metal−halogen exchange/electrophilic quench protocol on 4,4′-dibromobiphenyl that proceeds under non-cryogenic conditions is reported by Dolman and co-workers at Merck (*Tetrahedron* **2006**, *62*, 5092−5098). The selectivity of a variety of metal−halogen exchange reagents was studied, and the ratio of mono-, di-, and nonbrominated products was monitored. From this work, lithium tributyl-

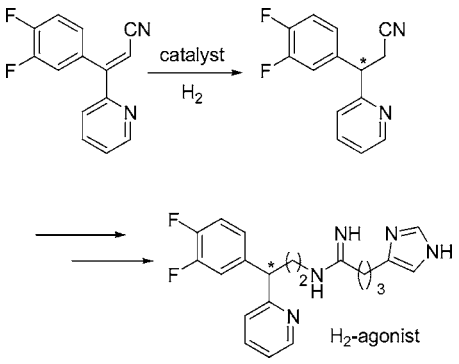
magnesiate emerged as the optimal reagent, with 0.4 equiv affording 94% conversion and high selectivity for the desired monometalated species. The utility of this selective metal−halogen exchange was demonstrated by quenching with various electrophiles. The method provides an economic alternative to transition-metal-catalyzed cross-coupling chemistry to prepare various 4,4′-disubstituted biaryls and was used for the kilogram-scale preparation of a biphenyl ketone that is a key intermediate in the synthesis of a potent cathepsin K inhibitor.

Fluorination-Free Synthesis of a 4,4-Difluoro-3,3-dimethylproline Derivative



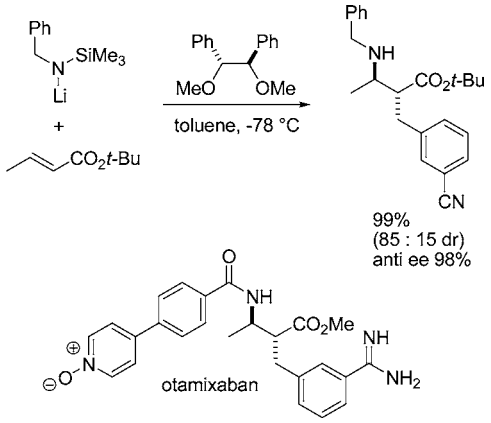
HIV protease inhibitors **2** and **3** are synthesized using difluoroproline **1** as a key intermediate. First generation syntheses of **1** relied upon ketone fluorination using relatively expensive reagents such as DAST or Deoxo-Fluor. Additionally, the yield for this fluorination step was less than 50%. To facilitate large-scale production an alternative synthesis of **1** was sought. Chen and co-workers at Pfizer report on a Claisen rearrangement/iodolactamization sequence starting from commercially available trifluoroacetaldehyde methyl hemiacetal, followed by a classical chemical resolution, which provides enantiomerically pure 4,4-difluoro-3,3-dimethylproline **1** (*J. Org. Chem.* **2006**, *71*, 5468−5473). No hazardous fluorination reagents were used, and the overall yield over 12 steps was greater than 28%.

Enantioselective Hydrogenation of Diaryl-Substituted α,β-Unsaturated Nitriles



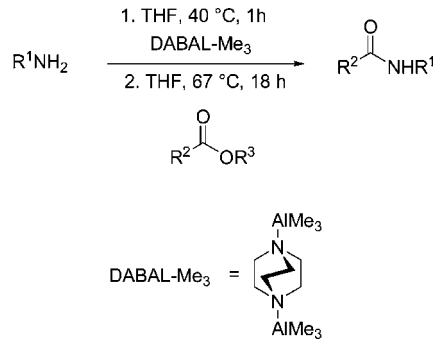
Reiser, Benincori, and co-workers report that α,β-unsaturated nitriles can be hydrogenated with enantioselectivities up to 88% ee using chiral rutheniumdiphenylphosphino bisaryl and bisheteroaryl complexes such as ruthenium(II)-BINAP and ruthenium(II)-BINP (*Tetrahedron Lett.* **2006**, *47*, 3733−3736). Mechanistic investigations indicate that conversion is accelerated by electron-rich ligands and that an additional coordinative group needs be present in order to promote conversion. The chiral products are useful building blocks for the synthesis of histamine H_2 agonists of the arpromidine type.

Asymmetric Synthesis of Intermediates for Otamixaban and Premafloxacin by the Chiral Ligand-Controlled Asymmetric Conjugate Addition of a Lithium Amide



The Tomioka group reports on a chiral ligand-controlled conjugate addition reaction of lithium benzyl(trimethylsilyl)amide to *tert*-butyl enoates (*J. Org. Chem.* **2006**, *71*, 4706−4709). The resulting lithium enolates were treated with electrophiles, giving predominantly *anti*-alkylation products with high ee (up to 98%). The method was demonstrated in the preparation of key intermediates from syntheses of otamixaban and premafloxacin. Interfering functionality in these intermediates precluded the use of hydrogenolysis as the means of removing the *N*-benzyl group, necessitating employment of alternative tactics. *N*-Chlorination of the benzylamines followed by DBU induced elimination afforded benzylimines, which were transoxaminated with hydroxylamine to unmask the free β-amino ester.

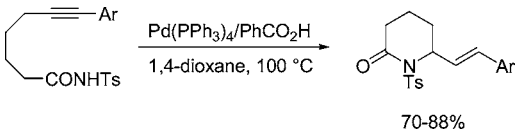
Amide Bond Formation Using an Air-Stable Source of $AlMe_3$



The Woodward group reports on the synthesis of amides directly from esters using a novel reagent (*Tetrahedron Lett.* **2006**, *47*, 5767−5769). The so-called DABAL-Me_3 complex formed from 2 equiv of trimethylaluminum and DABCO is air-stable and effectively mediates the formation of amides

from esters. A range of primary amines were converted to amides in moderate to excellent yields (69−99%), and reactions were run without exclusion of atmospheric oxygen in commercial grade solvents.

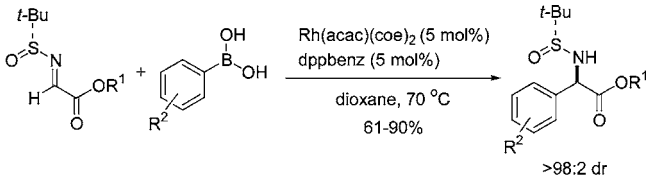
Lactam Synthesis via Pd-Catalyzed Intramolecular Hydroamidation of Alkynes



Following up on earlier work on the Pd-catalyzed hydroamination of alkynes, the Yamomoto group now reports on a hydroamidation reaction (*J. Org. Chem.* **2006**, *71*, 3612−3614). In the presence of 10 mol % of $Pd(PPh_3)_4$ and 20 mol % $PhCO_2H$, the cyclization of toluenesulfonylamidoalkynes in 1,4-dioxane at 100 °C proceeds smoothly to give the corresponding lactams in good yields. The reaction was not applicable to carboxamides or to the synthesis of five-membered lactams. Attempts to conduct intermolecular reactions were also unsuccessful.

Asymmetric Synthesis of Amino Carbonyls

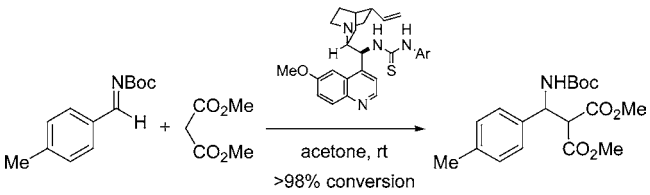
Ellman and co-workers at UC Berkeley reported the Rh-catalyzed asymmetric addition of arylboronic acids to *N-tert*-butanesulfinyl imino esters as a convenient tool to synthesize a variety of protected arylglycines (*J. Am. Chem. Soc.* **2006**, *128*, 6304−6305). Optimal reaction conditions employ a rhodium 1,2-bis(diphenylphosphinyl)benzene complex as the catalyst in dioxane at 70 °C to afford arylglycine derivatives in high yields and diastereoselectivities. The resulting *N*-sulfinyl-α-amino esters are versatile intermediates for the preparation of α-amino esters, α-amino acids, and α-amino alcohols via functional group transformations that are selective and high yielding. These reactions can be accomplished without loss in stereochemical purity.



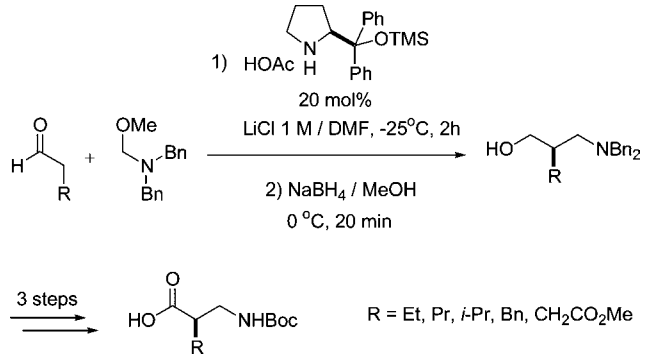
R^1 = Me, Et, *t*-Bu, Bn

R^2 = H, *p*-MeO, *p*-Me, *o*-Me, 3-Ac, 4-Cl, 4-CF_3, 3-NO_2

The Deng group at Brandeis University developed the enantioselective Mannich addition of 1,3-dicarbonyls—malonates or β-ketoesters—to *N*-Boc aryl imines catalyzed by derivatives of cinchona alkaloids (*J. Am. Chem. Soc.* **2006**, *128*, 6048−6049). The chiral catalysts bear a thiourea functionality and presumably act as a bifunctional activator for both the dicarbonyl compound and the imine. In a representative example, 10 mol % catalyst in acetone at room temperature during 16 h promotes the reaction of dimethyl malonate with *p*-methylbenzaldehyde *N*-Boc imine to afford the product of addition in >98% conversion and 77% ee. Interestingly, this methodology has a broad scope offering a simple solution to a long-standing challenge and opportunity for novel transformations.

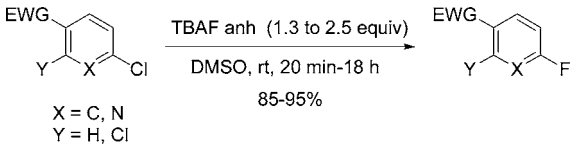


Chi and Gellman (University of Wisconsin) reported an enantioselective organocatalytic method for the aminomethylation of aldehydes, which leads to a new and efficient synthesis of β-amino acids (*J. Am. Chem. Soc.* **2006**, *128*, 6804−6805). Mannich reactions of a variety of aldehydes with methylene iminium precursor Bn_2NH_2OMe were catalyzed by 20 mol % of a silylated chiral pyrrolidine in the presence of 20 mol % of AcOH in DMF containing 1 M LiCl. In general, the transformations proceeded with yields >80% and enantioselectivities ≥90%. The Mannich β-amino aldehyde adducts were immediately reduced to the corresponding γ-amino alcohols to avoid epimerization. In turn, these amino alcohols could be simply converted to the desired β-amino acids following a protocol that involves recrystallization, debenzylation, *N*-Boc protection, and Jones oxidation (in general, >50% overall yield).

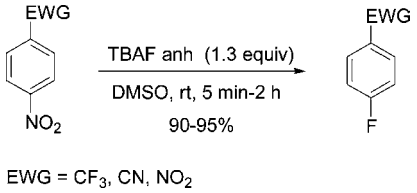


Nucleophilic Aromatic Fluorination at Room Temperature

Organofluorine compounds have been recently the object of the cover article in *Chemical & Engineering News* ("*Fabulous Fluorine*" **2006**, *84*, 15−24). Incorporation of fluorine in bioactive compounds dramatically changes their bioavailability. In particular, the electron-withdrawing nature of fluorine makes aromatic compounds less susceptible to cytochrome P450 catalyzed hydroxylation. Sun and DiMagno recently reported the use of anhydrous tetrabutylammonium fluoride (TBAF) as the source of fluorine in nucleophilic aromatic substitution (*Angew. Chem., Int. Ed.* **2006**, *45*, 2570−2575; for preparation, see *J. Am. Chem. Soc*. **2005**, *127*, 2050−2051). The transformation takes place under surprisingly mild conditions: a variety of chloroaromatic compounds undergo selective halogen exchange at room temperature upon exposure to anhydrous TBAF in DMSO at room temperature. Electron-withdrawing groups are required to activate the substrates. Contrasting with typical halogen exchange fluorinations that require heating at 150 °C, 2,6-dichloropyridine is exhaustively fluorinated in 90 min using the reported method.

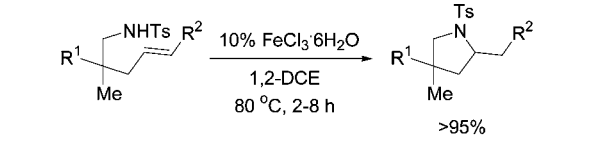


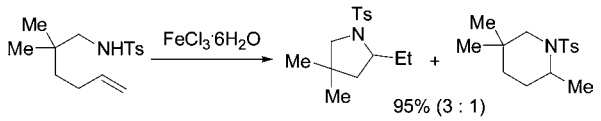
The authors applied this methodology to nitroaromatic compounds. Whereas gas-phase fluorodenitration reactions are thermodynamically favored and fast, computational studies suggest that preferential solvation of the fluoride leads to the large activation barriers for the solution-phase reactions.

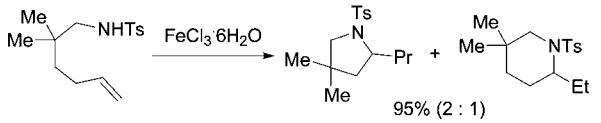


Iron-Catalyzed Intramolecular Hydroamination of Unactivated Olefins

Komeyama, Morimoto, and Takaki described the use of $FeCl_3 \cdot 6H_2O$ as the catalyst for the intramolecular hydroamination of alkenes (*Angew. Chem., Int. Ed.* **2006**, *45*, 2938−2941). The reaction was carried out in aerobic conditions without excluding adventitious water. The outcome depended greatly on the choice of solvent, with the best yields obtained in DCE at 80 °C. β-Mono- and disubstituted amines were smoothly converted in the corresponding pyrrolidines with excellent yields. Under these conditions, even unreactive 1,2-disubstituted olefins afford the desired cyclic products, albeit with low diastereoselectivity (3.8:1). A variety of functional groups are tolerated; in particular, iodinated substrates do not undergo elimination; this is rarely observed using late transition metal catalysis. Attempts to extend this methodology to the synthesis of piperidines gave pyrrolidines as major components along with minor amounts of the desired piperidines in a 3:1 ratio. Since the five-to-six-membered ring distribution does not change after submitting the isolated products to identical reaction conditions, origins of these results may stem from isomerization of the starting material.

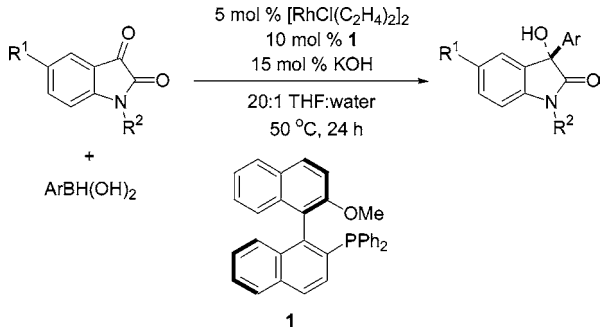






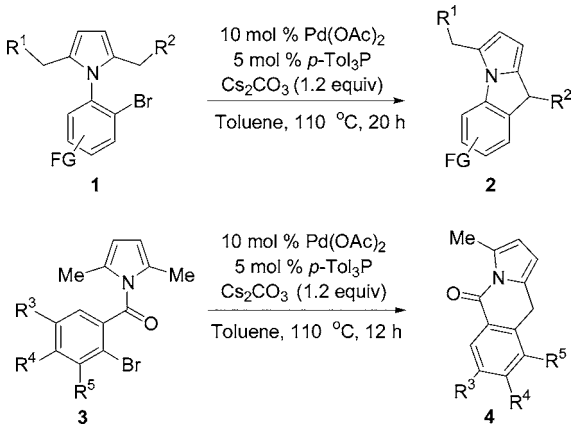
Synthesis of 3,3-Disubstituted Oxindoles

3,3-Disubstituted oxindoles are a common structural motif among drug candidates. Recently, Shintane, Inoue, and Hayashi reported a straightforward method to access these molecules via the asymmetric arylation of isatines with aryl boronic acids (*Angew. Chem., Int. Ed.* **2006**, *45*, 3353−3356). The use of a Rh catalyst in conjunction with monophosphine ligand (*R*)-MeO−Mop (**1**) gave the alkylated products with the (*S*)-configuration in high yields (90−98%) and enantioselectivities (82−91% ee). The strategy works well with substrates bearing different substituents on the nitrogen (R^2 = H, PMB, Me, Bn) and aryl boronic acids substituted on the 4-position.



Preparation of Condensed *N*-Heterocycles

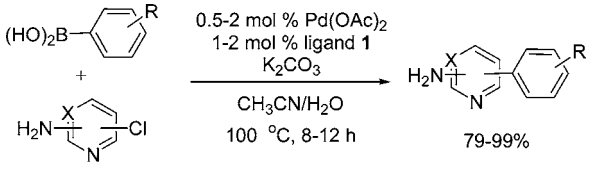
Ren and Knochel described the conversion of a variety of *N*-pyrrole derivatives into condensed *N*-heterocycles by activation of the 2-methyl substituent of pyrroles (*Angew. Chem., Int. Ed.* **2006**, *45*, 3462−3465). The combination of substrates **1** with $Pd(OAc)_2$ and the appropriate ligand [$(p\text{-Tol})_3P$] and base (Cs_2CO_3) in toluene at 100 °C provided 9*H*-pyrrolo[1,2-*a*]indoles of type **2**. The starting materials are readily obtained from the condensation of commercially available bromoanilines with 1,3-diketones in the presence of catalytic *p*-TsOH. The methodology was applied to convert 2,5-dimethyl acyl pyrroles as **3** into [1,2-*b*]isoquinolines **4**. The authors propose a mechanism that involves the formation of a palladacycle intermediate followed by reductive elimination.

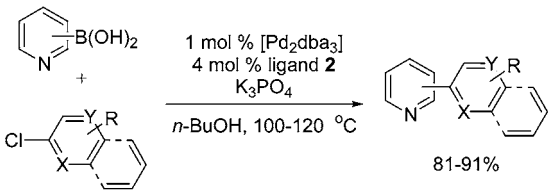


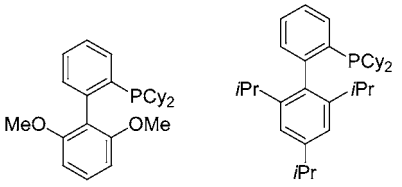
Highly Active Catalysts for Suzuki−Miyaura Coupling on Heteroaryl Compounds

One of the limitations of the powerful Suzuki−Miyaura strategy in biaryl coupling is its low efficacy when one of the partners (the boronic acid/ester or the halide) is a nitrogen

heterocycle or contains a free NH_2 group. Traditionally, free amines are protected before the coupling, which introduces two extra steps in the synthetic sequence. Buchwald and co-workers reported that the use of $Pd(OAc)_2$ and ligand **1** display unprecedented reactivity with a broad spectra of substrates containing amino groups (*Angew. Chem., Int. Ed.* **2006**, *45*, 3484−3488). A wide range of chloroaminopyridines and chloroaminopyrimidines reacted with aryl boronic acids, including sterically demanding and electron-deficient ones. A catalyst system based upon [Pd_2dba_3] and the hindered ligand **2** was best suited for the cross-coupling of pyridine boronic acids with aryl and heteroaryl chlorides. The article also describes an easy route to access coveted pyrrole boronate esters as well as their coupling with aryl chlorides or bromides using ligands **1** or **2**.



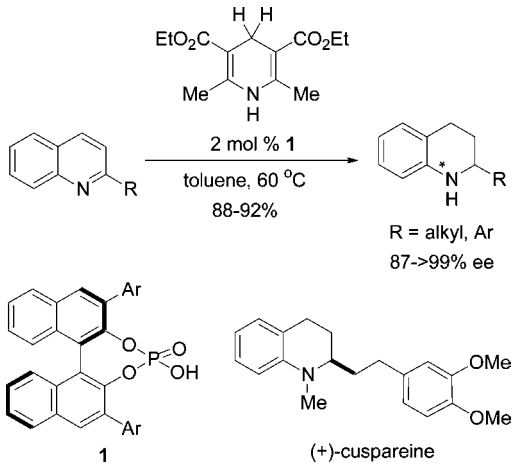




1 **2**

Brønsted Acid Catalysis: Enantioselective Hydrogenation of Quinolines

The group of Rueping in Frankfurt reported the first example of a metal-free reduction of heteroaromatic compounds as a straightforward route to tetrahydroquinoline derivatives (*Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686). The reaction involves a transfer hydrogenation catalyzed by a Brønsted acid that uses dihydropyridine **1** as the source of hydride. After surveying conditions, the sterically congested acid **2** (Ar = 1-naphthyl) emerged as the best catalyst. The treatment of quinolines bearing a variety of aliphatic, aromatic, and heteroaromatic substituents in the 2-poition with 2 mol % of **1** and 2.4 equiv of **2** afforded the corresponding tetrahydroquinolines in good yields and enantiomeric excesses. The procedure is compatible with halogenated aromatic and aliphatic residues. Whereas most of the experiments were conducted in benzene at 60 °C, the reaction works in chlorinated solvents and toluene. The methodology was successfully applied to the synthesis of the alkaloids (+)-cuspareine, (+)-galipinine, and (−)-angustureine.



1 (+)-cuspareine

Silica Sulfate, a Versatile Catalyst for the Protection of Alcohols

Silica sulfate is an environmentally friendly acid containing sulfuric acid moieties. It is easily prepared by reacting silica (SiO_2−OH) with chlorosulfonic acid in dichloromethane. Tong-Shou Jin and co-workers from Hebei University in China reported two different uses of silica sulfate as a catalyst in the protection of alcohols (*Synth. Commun.* **2006**, *36*, 1221−1227 and 1823−1828). Treatment of alcohols with HMDS in the presence of silica sulfate in dichloromethane or chloroform at room temperature or reflux (except for those in absence of solvent) gave the corresponding trimethylsilyl ethers within 1 h. A wide range of alcohols including cholesterol and the triterpenoids betulin and lupeol were protected in good to excellent yields. Tertiary alcohols as triphenylmethanol required longer reaction times or higher temperatures. Silica sulfate also catalyzed the acetylation of alcohols, phenols, and resorcinols with Ac_2O. The catalyst was filtered from the reaction mixture, regenerated, and reused for up to five (acetylation) or six (TMS ethers) reactions without significant loss of activity.

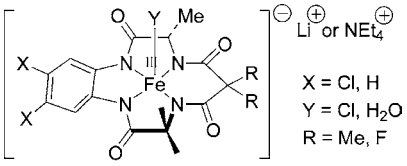
Miscellaneous Uses for *N*-Bromosuccinimide

A transition-metal-free oxidation of benzylic and secondary alcohols to the corresponding carbonyl compounds was reported by Jain and Sain from the Indian Institute of Petroleum (*Synth. Commun.* **2006**, *36*, 1459−1462). Benzylic and secondary alcohols were oxidized using *N*-bromosuccinimide (NBS) and ammonium chloride in aqueous acetonitrile at 80 °C. In the absence of ammonium chloride, the oxidation of cyclohexanol to cyclohexanone did not take place. Other ammonium salts such as ammonium acetate were not effective. The proposed mechanism involves the formation of hypobromite intermediates, which yield the carbonyl compounds following abstraction of hydrogen. Bandgar and Makone from Swami Ramanand Teerth Marathwada University (India) used NBS in conjunction with aqueous ammonia at 0 °C for the one-pot conversion of aldehydes into nitriles (*Synth. Commun.* **2006**, *36*, 1347−1352). The method is particularly useful for the transformation of water-soluble aldehydes such as carbohydrates.

Sustainable Catalytic Oxidation Methods

Sustainability must be a factor to be considered when choosing a method for a synthetic transformation. Dieter

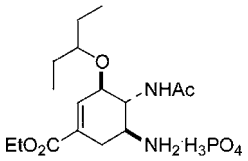
Lenoir compared a variety of oxidation reactions in terms of cost, ecotoxicity, and the environmental factor (E) that is the amount of waste produced in a reaction versus the amount of desired product (*Angew. Chem., Int. Ed.* **2006**, *45*, 3206−3210). An extensive table compiles oxidation methods with special attention given to reactions that employ O_2 and H_2O_2 as oxidants in conjunction with free radicals (TEMPO) or transition metals. The author also describes recent advances to induce the mineralization of contaminants. Particularly promising is the development of Fe-TAML (TAML = macrocyclic tetraamido ligand), which catalyzes the oxidation of persistent organic pollutants such as 2,4,6-trichlorophenol and pentachlorophenol with hydrogen peroxide. In addition to CO_2 and CO, six readily biodegradable organic acids are formed in the process.



Fe-TAML

Synthesis of Tamiflu

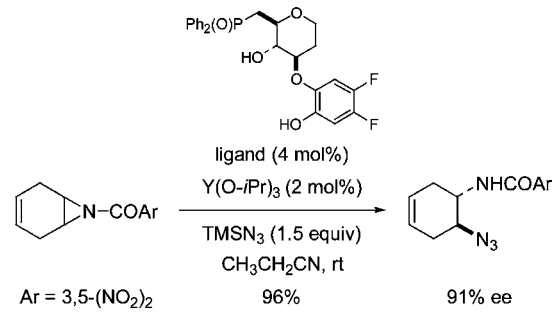
Driven by the need of alternative, more accessible routes for the commercial preparation of the antiviral drug Tamiflu, several research groups scouted new syntheses based on original methodologies.



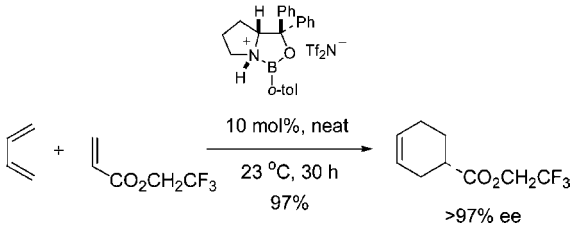
Tamiflu

Kanai, Shibasaki, and co-workers at the University of Tokyo reported the synthesis of Tamiflu using a catalytic desymmetrization of *meso*-nitrobenzoylaziridines. Conditions for a general enantioselective ring opening involve catalytic amounts of the complex of a rare earth metal with a fluorinated chiral ligand, along with an excess of nucleophile $TMSN_3$. Screening of several metals indicated the superiority of yttrium, giving the desired products from a variety of nitrobenzoylaziridines in yields >90% with typical ee's >90%. A proposed mechanism involves the generation of a reactive yttrium azide from $TMSN_3$ via transmetalation followed by intramolecular transfer of the azide to the aziridine activated by a Lewis acidic yttrium within the same catalyst. Products were converted to optically active C_2 symmetric 1,2-diamines in excellent yield. The authors completed the synthesis of Tamiflu starting from the mono-3,5-dinitrobenzoylaziridine of 1,4-cyclohexadiene (*J. Am. Chem. Soc.* **2006**, *128*, 6312−6313).

Corey and co-workers accomplished a total synthesis of Tamiflu that would appear to have advantages over existing processes and the potential to increase the rate of production. The first step of the synthesis implements the Diels−Alder reaction of butadiene with trifluoroethyl acrylate in the presence of a boron (*S*)-proline-derived catalyst previously



developed in the Corey group. This reaction is easily carried out at room temperature on a multigram scale in excellent yield and enantioselectivity. Moreover, the recovery of the chiral ligand is simple and efficient. The full synthesis is disclosed in *J. Am. Chem.* Soc. **2006**, *128*, 6310−6311.

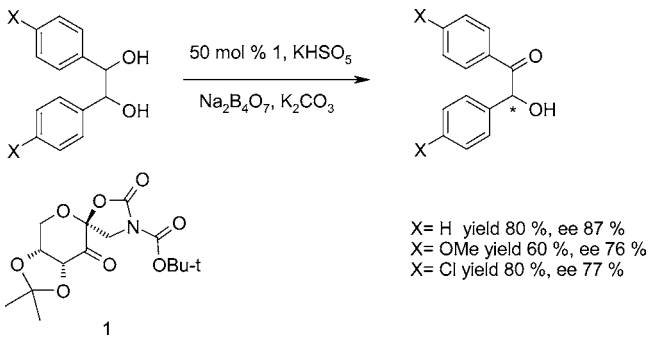


Enhancement of Reaction Rates by Segmented Flow in Microreactors

Wirth T. et al. (*Adv. Synth. Catal*. **2006**, *348*, 1043) have shown that the application of various reaction conditions in microreactors using segmented flow can dramatically increase the reaction rate. The hydrolysis of *p*-nitrophenyl acetate with aqueous sodium hydroxide is used as an example for a heterogeneous reaction, and a tandem diazotation/Heck reaction serves as an example for the enhancement even for homogeneous reactions. The heterogeneous hydrolysis was found to be much faster than when under conventional conditions, in particular when the technologies of segmented flow microreactor and microwave irradiation were used. Also with the Heck protocol compared to standard protocols much higher reaction rates were observed.

Highly Enantioselective in CH Oxidation of *vic*-Diols

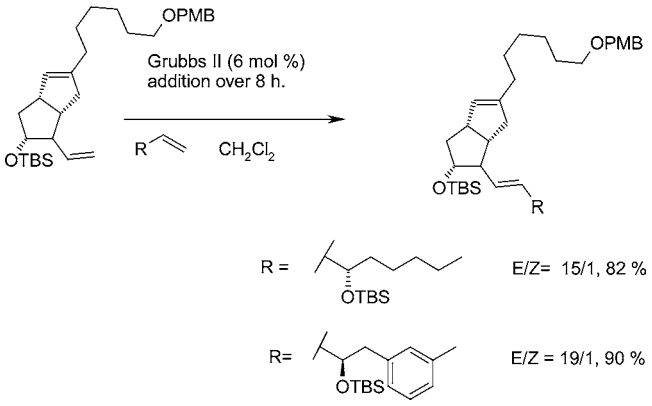
Very good enantioselectivity (up to 92% ee) may be obtained for both desymmetrization of meso *vic*-diols and kinetic resolution of racemic *vic*-diols with a dioxirane mediated catalytic oxidation (Jakka, K., et al. *Org. Lett.*, **2006**, *8*, 3013−3015). The method utilizes Shi's oxazolidinone ketone derivatives and oxone as the stoichiometric oxidant. The method gives



low to high yields depending on the substrate, and although the results need to be improved, it demonstrates the potential for enantioselective oxidation of *vic*-diols.

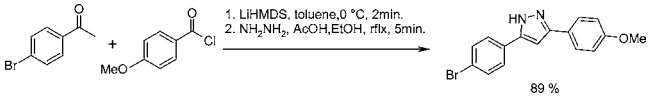
Cross Metathesis as a General Strategy for the Synthesis of Prostacyclin and Prostaglandin Analogues

A cross metathesis (CM) approach has been successfully applied to introduce fully functionalized ω-side chain appendages of various prostacyclin and prostaglandin analogues, resulting in high (E)-selectivities for the C13−C14 double bond and leading to the total syntheses of different derivatives with biological activity (Mulzer, J., et al. *Org. Lett*., **2006**, *8*, 3101−3104).



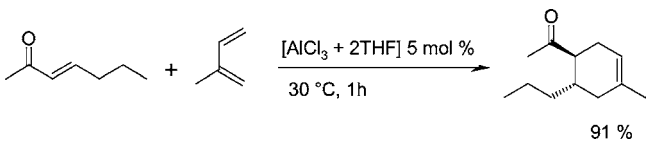
1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One-Pot Synthesis of Pyrazoles

Heller, S. T., et al. (*Org. Lett*., **2006**, *8*, 2675−2678) from the Medicinal Chemistry Dept. at Merck have found that 1,3-diketones can be synthesized directly from ketones and acid chlorides and directly in situ converted into pyrazoles by the addition of hydrazine. The method is extremely fast, general, and chemoselective, allowing for the synthesis of previously inaccessible pyrazoles and synthetically demanding pyrazole-containing fused rings. Most functional groups are tolerated, and the products were obtained in low to high yields.



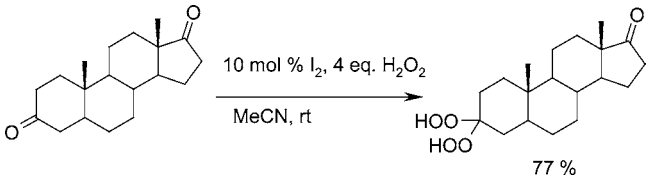
[$AlCl_3$ + 2 THF]: A New and Efficient Catalytic System for Diels−Alder Reactions under Solvent-Free Conditions

[$AlCl_3$ + 2 THF] is a new catalytic system for the Diels−Alder cycloaddition under solvent-free conditions. By using equimolar amounts of reactants, this catalyst prevents the polymerization of the diene and allows the corresponding adducts to be isolated with high regio- and stereocontrol. The products from the reaction were obtained in high to excellent yields (Fringuelli, F., et al. *Org. Lett*., **2006**, *8*, 2487−2489).



Iodine as an Efficient Catalyst for the Conversion of Ketones to gem-Dihydroperoxides by Aqueous Hydrogen Peroxide

Iodine has been found to be an efficient catalyst for the selective dihydroperoxidation of ketones with aqueous hydrogen peroxide (Iskra, J., et al. *Org. Lett*., **2006**, *8*, 2491−2494). The ketones were directly converted to the corresponding gem-dihydroperoxides with 10 mol % iodine and 4 equiv of 30% H_2O_2 in acetonitrile at room temperature. The reaction afforded the corresponding products in good to excellent yields. The corresponding benzaldehydes give either no reaction or up to a high yield dependent on the electron density of the aromatic ring. The neutral conditions of this reaction seem to be important to block further rearangement to the Baeyer−Villiger product.



Chemical Reviews: Process Chemistry

Chemical Reviews has dedicated Volume 106, Issue No. 7 to process chemistry with Michael Lipton and Anthony Barrett as guest editors. This thematic issue brings together a series of articles with a focus on reactions that are highly efficient on a large scale. They represent not only structural motifs and synthetically useful reagents, reactions, and process important to the field but also the modern spirit and philosophy of process development. Throughout the past three decades the importance of good process chemistry has been increasingly recognized. However, since no formal training at the university level yet exists, the editors and we hope that academic researchers and students will gain both an appreciation and interest in process chemistry as a result of this issue of *Chemical Reviews*.

In the Highlights from the Literature of the last issue (*Org. Process Res. Dev*. 2006, *10*, issue 4) we have highlighted three articles from this issue as *Chemical Reviews* ASAP articles: *Emerging Technologies Supporting Chemical Process R&D and Their Increasing Impact on Productivity in the Pharmaceutical Industry*, *Boron Reagents in Process Chemistry: Excellent Tools for Selective Reductions*, and *Critical Assessment of Pharmaceutical Processes-A Rationale for Changing the Synthetic Route*.

Below we have highlighted just a few extra articles from the many interesting ones in this issue:

Process Chemistry: The Science, Business, Logic, and Logistics

Zhang, T. (*Chem. Rev*. **2006**, *106*, 2583) provides an outline of the underlying principles of process research with a focus on safety, cost, environmental issues, and robustness of synthesis. The importance of mass throughput, the correct ordering of steps, factors that control the costs of starting materials, the design of experiments, and the relative merits of linear and convergent syntheses are described.

Organolithium Reagents in Pharmaceutical Asymmetric Processes

Wu, G. and Huang, M. (*Chem. Rev.* **2006**, *106*, 2596) describe the use of stoichiometric organolithium reagents in large scale synthesis, providing excellent examples of the scalability of enantioselective alkylations, aminoalkylations, aldol reactions, and Michael addition reactions.

Selected Patented Cross-Coupling Reaction Technologies

Corbet, J.-P. and Mignani, G. (*Chem. Rev.* **2006**, *106*, 2651) provide an overview of the use of palladium-, nickel-, copper-, and iron-catalyzed coupling reactions in discovery chemistry as well as on a large scale. Many significant products, commercialized or in the development phase, possess aromatic carbon−carbon and aromatic carbon−nitrogen bonds which can be assembled by organometallic catalyzed cross-coupling reactions. So, the scale-up of any new and general technology for the formation of these bonds can be of great industrial significance.

Crystallization-Induced Diastereomer Transformations

Few chemists in discovery laboratories or in academia really understand and acknowledge the usefulness of crystallizations. It is, however, of vital importance in scale-up synthesis and in the separation of enantiomers. Brands, K. M. J. and Davies, A. J. (*Chem. Rev.* **2006**, *106*, 2711) have summarized the crystallization methodology for the resolution of racemic compounds by the formation of salts or other derivatives, which for many classes of compounds is far more effective on scale-up than alternative processes such as enantioselective synthesis.

Asymmetric Synthesis of Active Pharmaceutical Ingredients

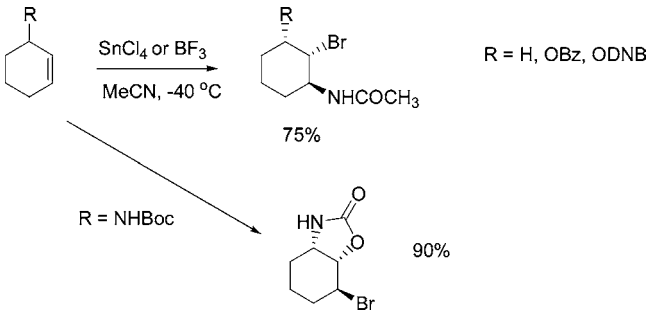
The important trend toward single-enantiomer drugs is what has brought asymmetric synthesis to the forefront as a theme in drug discovery and development. There are now 10 new chemical entities registered per year which need to be produced as a single enantiomers. With the standard attrition rate and the average development time, one can estimate that there are currently 500−1000 single-enantiomer compounds being developed within the industry somewhere between preclinical development and registration. These numbers are large enough to warrant reviewing the field, with special attention to asymmetric synthetic methodologies that have been used on a large scale (Farina, V., et al. *Chem. Rev.* **2006**, *106*, 2734).

Large-Scale Oxidations in the Pharmaceutical Industry

Ripin, D. et al. (*Chem. Rev.* **2006**, *106*, 2989) have compiled the currently acceptable methods for large-scale oxidations of alkenes, arenes, alkylarenes, alcohols, amines, sulfides, and other substrates. The review covers oxidations that have been run in 1980 or later, on a scale of around 100 g or larger, or clearly developed by a process group to be run on a large scale.

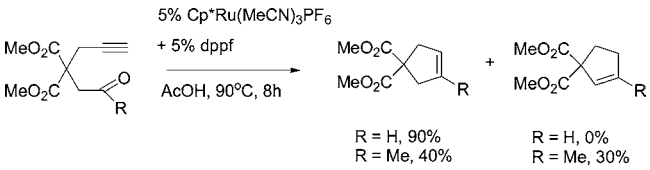
Haloamidation of Olefins

A recent paper from E. J. Corey's group at Harvard had described a new way of synthesising oseltamivir (Tamiflu), and this is described earlier in these highlights (*J. Am. Chem. Soc.* **2006**, *128*, 6310−6311). A key step in that synthesis was haloamidation of an olefin, and in a more recent paper, the scope and mechanism of this very useful reaction are explored (*J. Am. Chem. Soc.* **2006**, *128*, 9644−9645). The reaction occurs typically with N-halosuccinimides in acetonitrile as solvent but also works with iodine and other nitriles. A Lewis acid catalyst is required, and tin(IV) halides or boron trifluoride give the best yields. An additional requirement is to have 1−1.2 mol of water present in the solvent. The results shown in the scheme imply a mechanism via a bromonium ion



New Ruthenium Catalyzed Cyclization Method

The group of Saa at Santiago de Compostela, Spain has reported on the cyclization of terminal alkynes which also have a carbonyl group present, under the influence of ruthenium catalysts. The resultant five- and six-membered carbocyclic and heterocyclic rings are formed in moderate to high yields, and this method provides an alternative method to olefin metathesis for this type of compound (Varela, J. A., et al. *J. Am. Chem. Soc.* **2006**, *128*, 9576−9577). The ratio of products is very dependent on the chosen catalyst and the temperature, as well as the substrate.



Organocatalytic Mitsunobu Reactions

The group of Toy at the University of Hong Kong has described a procedure for carrying out the Mitsunobu reaction which is catalytic in the azodicarboxylate oxidizing reagent, using iodobenzenediacetate as the stoichiometric oxidant. Although the recipe still contains triphenylphosphine, which is oxidized to the oxide, the authors claim that product recovery is much easier in their process, because the hydrazine byproducts are in substoichiometric amounts. However 1 equiv of triphenylphosphine oxide is still generated so there may still be workup issues with this procedure. Enantioselectivity is the same as that for the conventional stoichiometric process, i.e., very high. (But, T. Y. S., et al. *J. Am. Chem. Soc.* **2006**, *128*, 9636−9637).

Hazards of Norbornadiene Dibromides and Related Compounds

We are grateful to Elke Fritz-Langhals of Wacker AG, Germany for pointing out the hazards associated with the

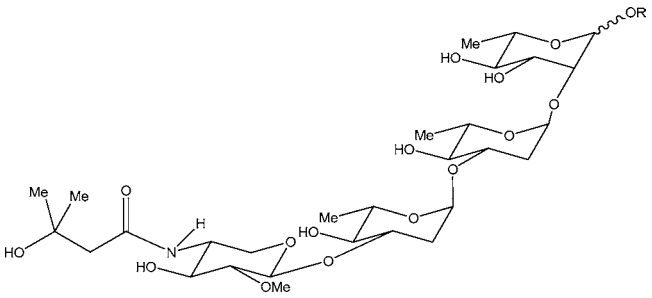
products arising from bromination of norbornadiene. Many chemists are unaware of the severe hazards, and the following paragraph, quoted verbatim from a communication from Winstein in 1961 (Winstein S., *J. Am. Chem. Soc.* **1961**, *83*, 1516−1517), makes chilling reading.

"There is no *a priori* reason to believe these particular compounds are more dangerous to man than several related substances widely used as industrial chemicals; **however, of the three laboratory workers who have used the dibromides and bromohydrin VII, two later developed similar pulmonary disorders which contributed to their subsequent deaths.** The third has exhibited minor skin sensitivity reactions."

You have been warned!!!!

Vaccine for Anthrax

Adamo, Saksena, and Kovac (*Helv. Chim. Acta* **2006**, *89*, 1075) described the synthesis of the tetrasaccharide side chain of the *Bacillus anthracis* exosporium. This multistep synthesis provides fragments of this tetrasaccharide that can be used in the development of a vaccine. The synthesis of the corresponding glycoside was based on the production of L-rhamnose derived fragments that are connected to anthrose (= 4,6-dideoxy-4-[(3-hydroxy-3-methyl-1-oxobutyl)amino]-2-*O*-methyl-D-glucopyranose) which is the upstream terminal residue of the tetrasaccharide.

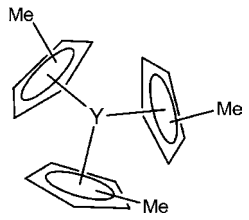


β–Ant(1➤3)-α–L–Rhap-(1➤3)-α–L–Rhap(1➤2)-α–L–Rhap

The Tetrasaccharide Side Chain (R = H)
The Target (R = β-$OCH_2CH_2CH_2CH_2COOH$)

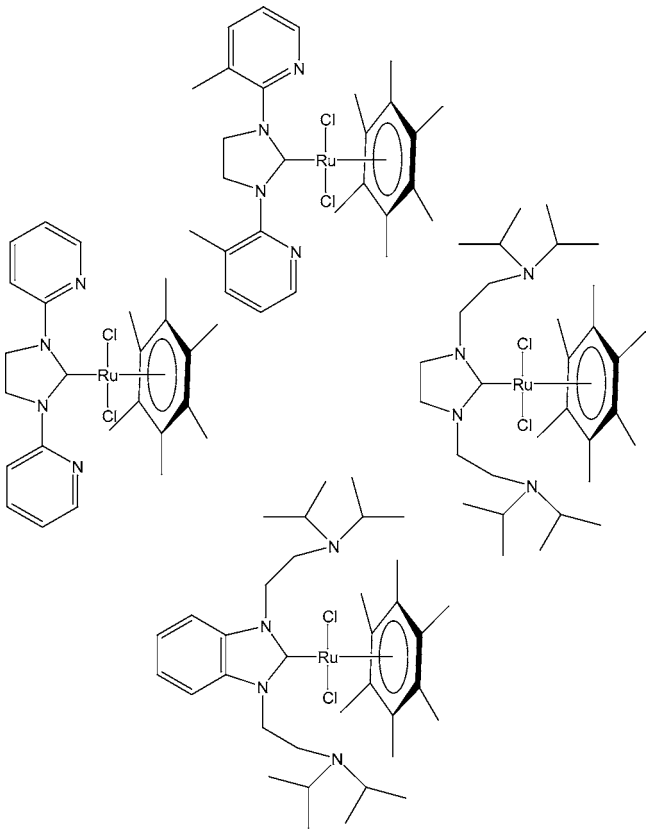
Polymerization of ϵ-caprolactone

Sun et al. (*Appl. Organomet. Chem.* **2006**, *20*, 310) described the synthesis and full characterization of a family of homoleptic lanthanide metallocenes that have been found to be good initiators for the ring-opening polymerization (ROP) of ϵ-caprolactone. Cp'_3Ln [Cp′ = methyl cyclopentadienyl; Ln = Y, Er, Sm] were used as catalysts. Cp'_3Y showed to be the best initiator for the ROP of ϵ-caprolactone.

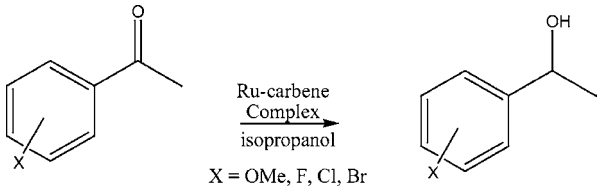


Catalytic Transfer Hydrogenation of Ketones

Connected with the use of carbene complexes, Yigit et al. (*Appl. Organomet. Chem.* **2006**, *20*, 322) described an elegant procedure for the synthesis of ruthenium−carbene complexes and the use of these compounds as catalysts for the hydrogenation of ketones.



The reaction involved a hydrogen transfer from 2-propanol to acetophenone derivatives so producing 1-phenylethanol derivatives in reasonable to high yields.



X = OMe, F, Cl, Br

Metathesis

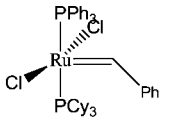
Chauvin (*Angew. Chem., Int. Ed.* **2006**, *45*, 3741), Schrock (*Angew. Chem., Int. Ed.* **2006**, *45*, 3748), and Grubbs (*Angew. Chem., Int. Ed.* **2006**, *45*, 3760), Nobel Prize winners in 2005, reviewed the olefin metathesis processes. These processes have great industrial interests.

Chauvin elegantly described the origins of the so-called metathesis process. So, based on the dimerization of olefins by nickel complexes (Wilke and Boydanovic, I&EC Product Research and Development *apud* Chauvin *op. cit.*), the polymerization of cyclopentene (Natta, *Angew. Chem. Int., Ed. Engl.* **1964**, *3*, 723), and the existence of a (new) metal−carbon bond (Fischer, *Angew. Chem.* **1964**, *76*, 645), he envisaged the very existence of metal−carbenes and their uses.

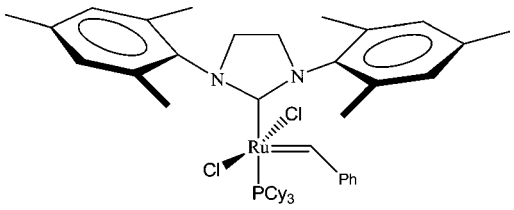
Schrock reported that his inspiration came from the Fischer carbene complexes. He also described his earlier experiments with tantalum complexes that evolved to molybdenum and tungsten complexes. The spectacular

production of a *cis, isotactic* polymer using a molybdenum carbene complex is described emphasizing the influence of the substituents in the ligand. Very nice applications of ring-closing metathesis (RCM) based on molybdenum catalysts were also reported.

Grubbs reported that his inspiration was based on his mentor's (Jim Collman) experience from a trip to Phillips Petroleum where propylene was converted into ethylene and 2-butene. Rationalizing the knowledge, Grubbs prepared a catalyst with a well-defined ruthenium carbene catalyst. This catalyst evolved to the first- and second-generation ruthenium carbene catalysts.



First Generation
Commercial Catalysts



Second Generation
Commercial Catalysts

These catalysts have been used in several organic synthetic applications as well as in ring-opening metathesis polymerization (ROMP) and dicyclopentadiene polymerization.

Adipic Acid

Simonato's group disclosed a "single-step" production of adipic acid from cyclohexane (*Green Chem*. **2006**, *8*, 556). The process design included the use of a lipophilic catalyst which would be recycled. As expected an improved conversion of cyclohexane was attained using various lipophilic carboxylic acids. A mechanically stirred titanium autoclave was used. $Co(OAc)_2$ and $Mn(OAc)_2$ were combined and used as a catalyst, following the Partenheimer recipe (*Catalysis Today* **1995**, *23*, 69), and 4-*tert*-butylbenzoic acid was found to afford the best conversions.

Oxidation of cyclohexane was extensively reviewed by Schuchardt (*Appl. Catal., A* **2001**, *211*, 1), and other systems in which very good conversions were claimed were described elsewhere (for example, U.S. Patent 6,392,093 B1).

Microchannel Reactors

Kobayashi, Mori, and Kobayashi (*Chem. Asian J*. **2006**, *1*, 22) reviewed the development of multiphase organic reactions in microchannel reactors. In gas−liquid reactions, direct fluorination of different substrates was carried out using molecular fluorine diluted in dinitrogen. The gas/liquid microreactor used consisted of a falling film microreactor and microbubble column made of stainless steel. Carbonylative coupling reactions of secondary amines, carbon monoxide, and arylhalides were also undertaken.

In gas−solid reactions, selective hydrogenation of *cis, trans,trans*-1,5,9-cyclododecatriene to afford cyclododecene was also demonstrated. In this case an anodically oxidized microstructured wafer coated with the convenient Pd catalyst precursor was used.

Several examples of liquid−liquid reactions were shown, including aldol reactions, alkylation, and isomerization of allylic alcohols. Very useful devices were carefully disclosed.

In liquid−solid reactors a pressure driven microchannel reactor was used in the Kumada−Corriu reaction using an immobilized nickel catalyst. A Suzuki−Miyaura coupling was also described, as well as esterification and oxidation reactions, among others.

Beautifully described three-phase reactions included gas−liquid−liquid (hydrogenation) reactors and gas−liquid−solid (hydrogenation) reactors. In addition, a schematic representation of a chemical reaction circuit in the production of 2-deoxy-2-fluoro-D-glycose via multistep synthesis was disclosed.

Dielectrically Controlled Enantiomeric Resolution (DCR) of (*R*)- and (*S*)-2-Methylpyrolidine by (*R,R*)-Tartaric Acid

A university−industry collaboration from Japan (Sakurai, R., et al. *Cryst. Growth Des*. **2006**, *6* (7), 1606) investigated the chiral resolution via diastereomeric salt formation by controlling the dielectric constant (ϵ) of the solvent system used. Prior work evaluated this approach for compounds containing aromatic rings, whereas this report discusses DCR with compounds without aromatic rings. The diasteromerically pure salt between (*R*)-2-methylpyrrolidine and (*R,R*)-tartaric acid was obtained in EtOH/water mixtures with the dielectric constant $24 \leq \epsilon < 29$. Similarly, the diasteromerically pure salt between (*S*)-2-methylpyrrolidine and (*R,R*)-tartaric acid was obtained in EtOH/water mixtures with the dielectric constant $30 \leq \epsilon < 36$; this latter crystallized as a hydrate. A molecular mechanism invoking molecular recognition is called upon to explain these observations. (*R,R*)-Tartaric acid forms chains by very strong, negative-charge-assisted hydrogen bonds, and the chains build layers. It is postulated that a chiral space is built between such layers, and the shape and size of the chiral space are dependent on the dielectric constant of the solvent system used in the resolution process.

α-Methylstyrene Hydrogenation in a Flow-Through Membrane Reactor

An industry−academia collaboration from Germany (Purnama, H., et al. *AIChE J*. **2006**, *52* (8), 2805) discusses the advantages of carrying heterogeneous hydrogenation processes in flow-through membrane reactors. The hydrogenation of α-methylstyrene (AMS) to cumene over a Pd catalyst supported on an α-Al_2O_3 membrane was chosen to model the impact of mass transfer on the reaction rate. This three-phase (solid−gas−liquid) reaction has been studied before, exhibiting a number of experimental advantages such as mild exothermicity, nonvolatile reactant and product, etc. Known challenges of this process include the low solubility of hydrogen in the liquid phase and mass transfer limitations. The advantages of using membrane reactors include enhanced mass transfer and the absence of hot spots. This study

used for a catalyst support a hollow, microporous alumina tube with a pore diameter of 1.9 μm. The palladium metal was loaded on the membrane by a wet impregnation method in the range of 0.03−0.08%. The AMS substrate in heptane solvent (typically at 18% concentration) was saturated with hydrogen and recirculated through the membrane. The operating conditions were the following: 45−50 °C and a pressure of up to 40 bar. The performance of the membrane reactor was compared with that of a slurry reactor and other reactors discussed in the literature. The productivity of the membrane reactor exceeds that of slurry, trickle-bed, bubble column, and diffuser membrane reactors. This productivity was defined as the conversion of AMS per time and per mass of palladium. The productivity enhancement is explained by an increased contact area between the liquid and the solid and by a higher dispersion of palladium particles on the membrane. A critical process parameter was identified to be the flow rate through the membrane. Future work will include investigation of selective hydrogenation of substrates containing multiple unsaturated sites.

Analytical Techniques for Quantification of Amorphous/Crystalline Phases in Pharmaceutical Solids

A review from the National Institute of Pharmaceutical Education and Research in Punjab, India (Shah, B., et al. *J. Pharm. Sci.* **2006**, *95* (8), 1641) discusses 16 methods for quantification of amorphous material in pharmaceutical solids. Theoretical and practical aspects are presented, providing criteria for method selection. A brief introduction reviews definitions, differences between crystalline and amorphous material, and reasons for increased interest in quantification of amorphous phase. Of several analytical approaches to quantifying the amorphous phase, the degree of crystallinity is more frequently used than other approaches such as the disruption index or the entropy of processing. Of the 16, 7 methods are tabulated with key characteristics as well as potential advantages and disadvantages; these methods are as follows: PXRD, DSC, IMC (isothermal microcalorimetry), SC (solution calorimetry), IR, FT-Raman, and solid-state NMR. Other methods discussed include the following: Dynamic Vapor Sorption (DVS), Near Infra-Red Spectroscopy (NIRS), Terahertz Pulsed Spectroscopy (TPS), Thermally Stimulated Current Spectroscopy (TSC), Density Measurement, Dynamic Mechanical Analysis, Inverse Gas Chromatography (IGC), and Dissolution Measurements. The review includes 143 references.

Effect of Ultrasonic, Thermal, and Ozone Pretreatments on Waste Activated Sludge Solubilization and Anaerobic Biodegradability

Sludge production is increasing in many countries, and efficient treatment is therefore necessary. Disposal routes are subject to more legal and social constraints: land disposal is now restricted in some countries, incineration is quite expensive, and land application (or agricultural use) is highly debated. This causes a large problem to communities and wastewater treatment plant operators. It is thus necessary to reduce sludge production at the source, in the wastewater treatment plant. This is possible with anaerobic digestion. This treatment, which allows a reduction of sludge quantity of about 40−50%, has become one common method of sludge stabilization, due to the production of biogas that makes the process profitable. In wastewater treatment plants, anaerobic digestion is generally applied to a mixture of primary and secondary (waste activated) sludge. But waste activated sludge (WAS) are known to be more difficult to digest than primary sludge. The anaerobic digestion process is achieved through several stages: hydrolysis, acidogenesis, and methanogenesis. To enhance the efficiency of anaerobic digestion, workers from France (*Chem. Eng. Process.* **2006**, *45*, 711−718) have studied the effects of ultrasound, ozonation, and thermal pretreatment on waste activated sludge. All treatments led to chemical oxygen demand and matter solubilization and had little influence on mineral matter. In terms of solubilization thermal pretreatment was better than sonication or ozonation. But, in terms of batch anaerobic biodegradability, the best results were obtained with ultrasound with an energy of 6250 or 9350 kJ/kg of total solids and a thermal treatment at 170 or 190 °C. Moreover, treatments had effects on physicochemical characteristics of sludge samples: apparent viscosity decreased after all treatments, but the reduction was more significant with thermal treatment. The median diameters of sludge flocs were reduced after sonication, increased after thermal treatment, and did not change after ozonation. Finally, capillary suction time (CST) increased after ozonation, increased significantly after sonication, and was reduced after thermal treatment.

Novel Manufacturing Process of Hollow Polymer Microspheres

Gas-filled, hollow microspheres have been used for a long time. There are various commercial and research-based uses for hollow microspheres. Spheres with an inorganic shell are used, for example, as a filler for cement and latex dispersions or for insulating purposes. Manufacturing processes for these areas of use have been developed extensively. Hollow microspheres with an organic shell have also been synthesized and are used as mentioned above, but there are several other uses, such as in the field of life science and pharmaceutics. These are used as an ultrasound contrast agent in medical diagnostics, where they are administered intravenously. Commercially available ultrasound devices are very sensitive to such particles and can detect them easily; even the detection of a single particle is possible. A prerequisite for using microspheres as an ultrasound contrast agent is that they are biodegradable and that the largest particles do not exceed 10 μm, to avoid capillary blockage. A novel manufacturing process of gas-filled, hollow poly-butyl-2-cyanoacrylate (PBCA) microspheres in an aqueous phase was developed recently. The two-step process enables the control of the particle-wall size as well as the particle size. Depending upon the process conditions, the particle size ranges from 1 to 5 μm. The microparticles are formed by using surfactant-stabilized microbubbles, which act as a template. At the interfacial area of these templates, PBCA nanoparticles create deposits that form the particle wall, as a result of a partial filming process. The density of the particles has been calculated as ranging from 100 up to 300 kg/m^3, and the volume fraction of the entrapped gas can be

5% or more. The developed process is claimed to operate on a scale of several kilograms (*Chem. Eng. Sci.* **2006**, *61*, 4973−4981).

ϵ-Caprolactone Synthesis in Airlift Loop Sonochemical Reactor

Baeyer−Villiger oxidation is frequently employed for oxidative cleavage of a carbon−carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. The oxidation of cyclohexanone to ϵ-caprolactone is commercially important since the product is extensively used in the synthesis of poly-caprolactone (PCL), used as foaming materials, polyesterpolyols, biodegradable plastics, etc. This oxidation is carried out using peracids, such as peracetic acid and *m*-chloroperbenzoic acid, which are industrially impractical for safety and cost reasons. Molecular oxygen, on the other hand, is an ideal oxidant regarding economy and environment. Several procedures for preparation of ϵ-caprolactone from cyclohexanone using molecular oxygen and aldehyde catalyzed by transition metal salts or complexes have been patented. However, the selectivity of ϵ-caprolactone described in most of these patents is not satisfactory (70−80% selectivity), and the conversions of cyclohexanone were generally low (3−30%). A facile oxidation conversion of cyclohexanone to ϵ-caprolactone using molecular oxygen in an airlift loop sonochemical reactor was studied. The influences of ultrasound intensity, reaction temperature, molar ratio of benzaldehyde to cyclohexanone, and oxygen gas flow rate on the conversion and selectivity of cyclohexanone were investigated and discussed. An optimized set of operating conditions was found, and an ϵ-caprolactone production yield of ∼88% was achieved. The reactor plays a synergistic effect of sonochemistry and higher mass transfer. Possible reaction mechanism steps are outlined, and the reasons of ultrasound promoting the reaction are analyzed (*Chem. Eng. J.* **2006,** *121* (2−3), 59−63).

Ionic Liquid Mediated Reactions

Regulating the preference of a reversible multistep reaction by adjusting the substituents of ionic liquids has been successfully demonstrated by researchers in China (*Org. Biomol. Chem.* **2006**, *4*, 2772−2776) with several tetraammonium-based ionic liquids as the medium for the enzymatic glycerolysis. The simultaneous existence of long chain hydrophobic substituents and hydrophilic ethoxyl or hydroxyl moieties was essential for the solubility of triglycerides, driving the reaction away from equilibrium. The reactions in ionic liquids with cations consisting of long chain and free hydroxyl groups led to markedly higher conversions of triglycerides and a better preference to monoglyceride formation. The theoretical predictions from COSMO-RS (a quantum chemical model programme) were in good agreement with the experimental data.

Mesoporous Silicas Functionalized with a High Density of Carboxylate Groups as Efficient Absorbents for the Removal of Basic Dyestuffs

A novel silane bearing a reactive anhydride group was synthesized. Due to its special structure, the direct co-condensation of this synthesized functional silane with TEOS in the presence of different surfactant templates led to ordered mesoporous silicas with different pore sizes and a high density of carboxylic acid groups, which were used as adsorbents for the removal of three basic dyestuffs (methylene blue, phenosafranine, and night blue) from wastewater. The performed measurements showed that, probably due to their high surface area, good affinity to carboxylic groups, and large number of binding sites, the obtained mesoporous materials exhibit a high adsorption capacity and an extremely rapid adsorption rate. Furthermore, these carboxylic-functionalized adsorbents can be regenerated by simply washing with acid solution to recover both the adsorbents and the adsorbed dyes. The experimental data for the adsorption of all three basic dyes were analyzed using Langmuir and Redlich−Peterson isotherm models. It is found that the Langmuir equation provides an accurate description of these adsorption data, suggesting that monolayer adsorption occurred in all cases of the performed sorption processes. In this work, the influences of the pH values of the treated solutions and the pore sizes of the prepared adsorbents on the adsorption behavior were also discussed (*J. Mater. Chem.* **2006**, *16*, 2347−2353).

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OP060169I