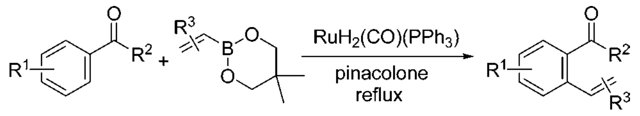
Organic Process Research & Development **2007**, *11,* 652–662

Highlights from the Literature

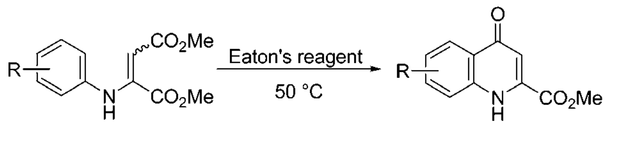
Some Items of Interest to Process R&D Chemists and Engineers

Ru-Catalyzed Alkenylation of Aromatic Ketones



Having previously developed conditions for the Ru-catalyzed arylation of aromatic ketones, the Kakiuchi group has now extended this method to the alkenylation of C−H bonds of aromatic ketones using alkenylboronates (*J. Org. Chem.* **2007**, *72*, 3600−3602). The coupling reaction of pivalophenone with 2-isopropenyl-5,5-dimethyl[1,3,2]dioxaborinane gave the corresponding isopropenylation product in 73% yield. In the case of a sterically congested alkenylboronate, such as 2-methylpropenylboronate, the yield was decreased (37%). When α-styrylboronates were used, the corresponding coupling products were obtained in moderate yields. A single example using acetophenone with an α-styrylboronate afforded the corresponding 1:1 coupling product in 48% yield.

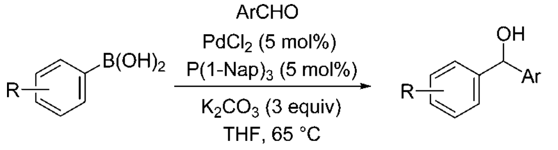
Mild Synthesis of Quinolone Heterocycles



26 examples, 60-98% yield

The cycloacylation of aniline derivatives to 4-quinolones using Eaton's reagent is described by Zewge and co-workers at Merck (*J. Org. Chem.* **2007**, *72*, 4276−4279). The preparation of these quinolones following previously reported procedures typically required the use of extremely high temperatures, $\sim$250 °C, that would render application to large-scale batch processing problematic. It was found that dissolution of the requisite substrates in neat Eaton's reagent (8 wt % P_2O_5 in CF_3SO_3H) and heating to 50 °C gave complete conversion and good yields within 1−3 h. This method was shown to be applicable to a wide variety of functionalized anilines and was used to prepare a host of heterocycles and bis-quinolones. Notably, product isolation from these reactions is straightforward, involving quenching into aqueous base and filtration of the precipitate. Limitations of this method include a lack of regioselectivity when meta-substituted anilines are used and its failure to generate a seven-membered benzoazepine and a five-membered indanone.

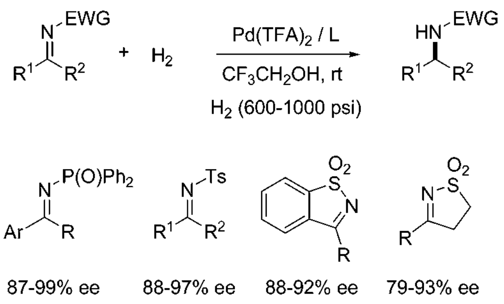
Pd-Catalyzed Addition of Arylboronic Acids to Aldehydes



30 examples, 5-98% yield

More established as a Rh-catalyzed process, the 1,2-addition of arylboronic acids to aldehydes can also be promoted by Pd complexes. Seeking to develop a general catalyst system for this reaction, Wu, Cheng, and co-workers started their investigation with the reaction between phenylboronic acid and piperonal (*J. Org. Chem.* **2007**, *72*, 4102−4107). After a broad screening of phosphine ligands, the authors found that tri(1-naphthyl)phosphine exhibited particular efficiency in this process. The conditions are compatible with numerous functional groups including nitro, cyano, acetamido, acetoxy, acetyl, carboxyl, trifluoromethyl, fluoro, and chloro groups. The authors also suggest that the reaction performs equally well under an air atmosphere. As is frequently the case with this reaction type, it is required to use the boronic acid component in excess (2 equiv).

Pd-Catalyzed Asymmetric Hydrogenation of Activated Imines



Zhou and co-workers report on the homogeneous catalytic asymmetric hydrogenation of activated imines using Pd/bisphosphine complexes (*J. Org. Chem.* **2007**, *72*, 3729−3734). The asymmetric hydrogenation of *N*-diphenylphosphinyl ketimines using 2 mol % $Pd(CF_3CO_2)$/(*S*)-SegPhos gave 87−99% ee, and *N*-tosylimines gave 88−97% ee with $Pd(CF_3CO_2)$/(*S*)-SynPhos as the catalyst. Cyclic *N*-sulfonylimines were hydrogenated to afford chiral sultam derivatives in 79−93% ee. The reaction appears to be highly solvent dependent, proceeding only in trifluoroethanol, and molecular sieves are required to obtain the best yield.

Pd-Catalyzed Reductive Carbonylation

Following up on an earlier communication, the Beller group now provides a full account of a general and efficient

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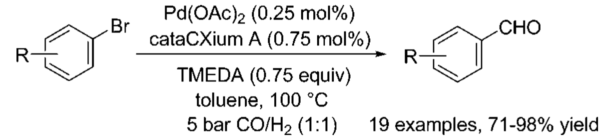
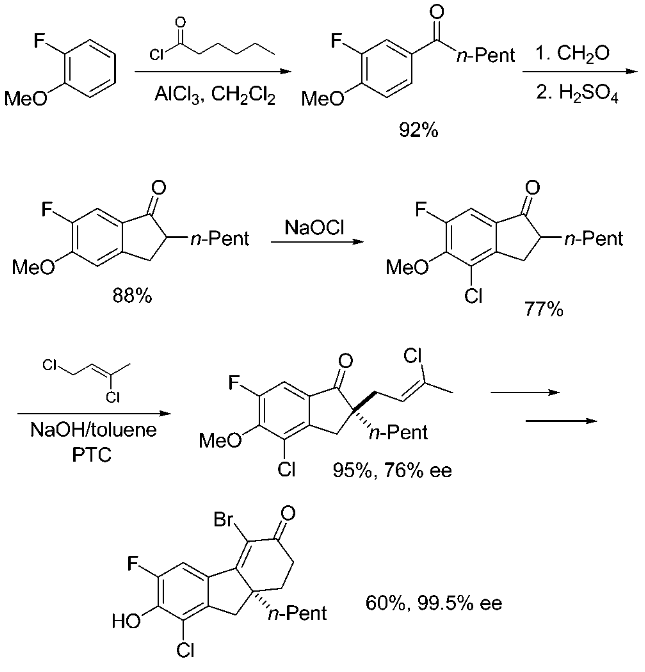


Pd-catalyzed reductive carbonylation with low catalyst loadings (0.5 mol % Pd or less) (*Tetrahedron* **2007**, *63*, 6252−6258). The formylation of aryl and heteroaryl bromides proceeds smoothly in the presence of palladium/di-1-adamantyl-*n*-butylphosphine (cataCXium A) at ambient pressure of synthesis gas to afford the corresponding aromatic aldehydes in good yields and excellent selectivity. A detailed description of the optimization of this process is given, including the effect of ligand, solvent, base, temperature, concentration, and gas pressure. Interestingly, the use of synthesis gas at pressures greater than 5 bar led to significantly lower yields of the desired aldehydes. In addition, vinyl halides (Br and Cl) react under similar conditions to form α,*β*-unsaturated aldehydes in good yield.

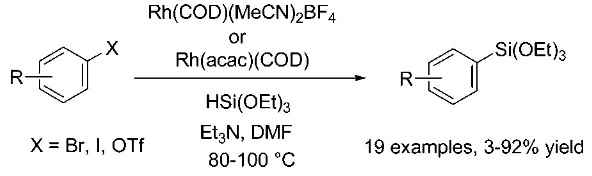
Synthesis of an Estrogen Receptor Modulator Using Asymmetric PTC



estrogen receptor modulator

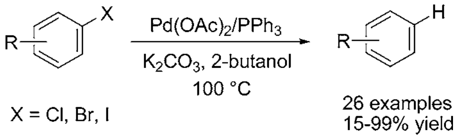
In support of a drug development program, Huffman and co-workers at Merck required an efficient asymmetric synthesis of an estrogen receptor *β*-modulator (*Tetrahedron* **2007**, *63*, 4459−4463). The route used during the drug discovery phase of this project was unsuitable for scale-up due to the inefficiency of the first step, which involved Friedel−Crafts acylation of the electron-deficient 1-chloro-6-fluoroanisole. To circumvent the problems created by this sluggish reaction, the synthetic sequence was altered such that the Friedel−Crafts step was conducted on 2-fluoroanisole, with downstream installment of the necessary chlorine atom. This adjustment resulted in clean, high-yielding reactions and straightforward access to the key indanone intermediate used in an asymmetric phase transfer-catalyzed alkylation. Under cinchona alkaloid catalysis, the indanone was alkylated in high yield (95%) with 1,3-dichlorobut-2-ene to give a product with 76% ee. It was possible to continue the synthesis with this material and perform a downstream ee upgrade by preferentially crystallizing the less soluble racemate from solution, leaving behind the desired enantiomer which could then be crystallized in 99% ee in an overall yield of 61% (three steps) from the indanone. Another highlight from this work was the development of a robust bromination reaction using imidazole as an in situ bromine trap to avoid overreaction. The synthesis proceeds in 34% yield over eight steps from 2-fluoroanisole and provides material with >99.5% ee.

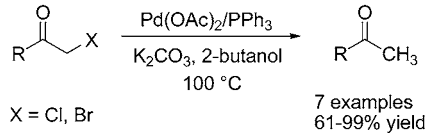
Rh-Catalyzed Silylation of Aryl Halides



Arylsiloxanes and their hypervalent derivatives are versatile reagents for carbon−carbon and carbon−heteroatom bond formation, and provide an alternative to organoboron compounds. The transition metal-catalyzed preparation of arylsiloxanes from aryl halides was known in the literature, although the substrate scope was fairly limited. Now the Murata group describes a general and efficient silylation of aryl halides utilizing triethoxysilane and a rhodium catalyst (*Tetrahedron* **2007**, *63*, 4087−4094). The substrate scope is broad and includes ortho-, meta-, and para-substituted electron-rich and electron-deficient aryl iodides. In addition, the silylation of aryl bromides and fluoroalkanesulfonates proceeds in the presence of tetra-*n*-butylammonium iodide.

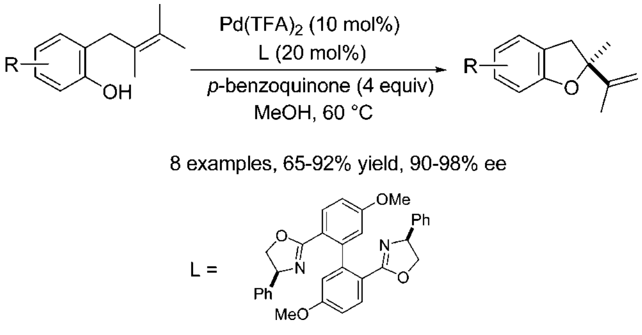
Practical Pd-Catalyzed Dehalogenation of Aryl Halides





Synthetic sequences requiring dehalogenation of an aryl halide would typically be less than optimal for the manufacture of pharmaceuticals although circumstances may dictate the use of this transformation on occasion. In this regard, a practical and high-yielding protocol for the dehalogenation of aromatic halides is described by the Zhang group (*Tetrahedron* **2007**, *63*, 4266−4270). In the presence of palladium acetate (1 mol %), triphenylphosphine (4 mol %), and potassium carbonate (200 mol %) a number of highly functionalized aromatic halides can be cleanly dehalogenated using 2-butanol as the solvent/reductant. Chlorides, bromides, and iodides are reduced, while fluorides survive the developed conditions. Alkenes, benzyl ethers, and various carbonyl functional groups are unaffected by this system. Additionally, α-haloketones can also be dehalogenated in good yield.

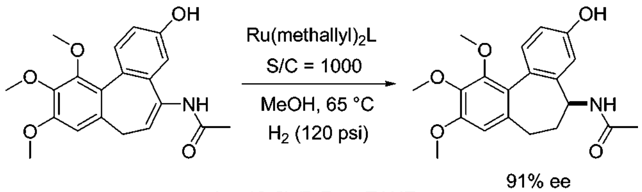
Asymmetric Wacker Reactions



8 examples, 65-92% yield, 90-98% ee

Relative to Pd(0)-catalyzed asymmetric reactions, Pd(II)-mediated asymmetric transformations have received less attention. Zhang and co-workers report on the application of their C2-symmetric “axis unfixed” axially chiral bisoxazoline-based ligand family to the asymmetric Wacker-type cyclization of allylated phenols (*Tetrahedron Lett.* **2007**, *48*, 4179−4182). These ligands have been shown to exist as a mixture of two equilibrating diastereomers in solution. Significantly, upon coordination to Pd(II), the ligands afford only one of the two possible diastereomeric Pd(II) complexes. Following a screen of five ligands the optimal system was identified and shown to give yields of 65−92% with >90% ee across eight cyclization substrates. Catalyst loadings are fairly high at 10 mol % (with 20 mol % ligand), and 4 equiv of *p*-benzoquinone are used as the oxidant.

Asymmetric Enamide Hydrogenation



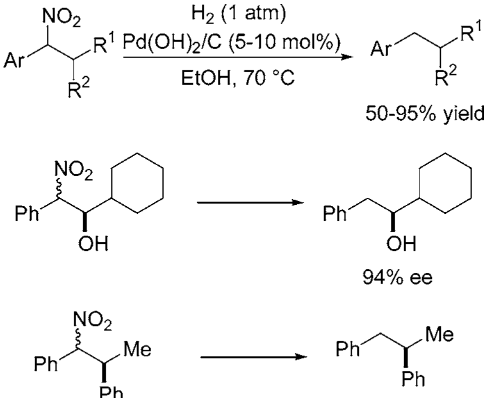
91% ee

L = (*S,S*)-*i*PrFerroTANE

A synthesis of *N*-acetylcolchinol, a key intermediate in the synthesis of ZD6126, was developed by Ramsden and co-workers at both AstraZeneca and Dowpharma (*Tetrahedron Lett.* **2007**, *48*, 4623−4626). The key step in this synthesis was an asymmetric hydrogenation of a seven-membered ring enamide. After screening a range of metal and ligand combinations, it was found that (*S,S*)-*i*Pr−FerroTANE Ru(methallyl)$_2$ and [(*S,S*)-*t*BuFerroTANE Rh(COD)]BF$_4$ both gave comparable enantioselectivity (>90% ee) and yield. The choice of solvent for each of these processes is critical since THF or a toluene/methanol mixture proved optimal for the Rh system, while these solvents gave poor results for the Ru system (MeOH alone was preferred for Ru). The authors note this is indicative of markedly different mechanisms operating for the Rh and Ru systems. This is further emphasized by the fact that the two optimal ligands, (*S,S*)-*t*BuFerroTANE and (*S,S*)-*i*Pr−FerroTANE have the same absolute stereochemistry but give rise to equal and opposite stereoselectivity in the product.

Pd-Catalyzed Cleavage of Benzylic Nitro Bonds

The cleavage of benzylic nitroalkanes when exposed to H$_2$−Pd/C is deemed as an “undesirable” side reaction in the synthesis of *N*-benzylamines. In a clever maneuver, Fessard, Motoyoshi, and Carreira noted that the heterolytic C−N bond reduction allows access to alkanes that are otherwise difficult to prepare (*Angew. Chem., Int. Ed.* **2007**, *46*, 2078−2081). A range of secondary benzylic nitro groups was hydrogenated in the presence of Pearlman’s catalyst [Pd(OH)$_2$/C] in EtOH at 70 °C to cleanly afford the alkane products. Interestingly, benzylic denitration is faster than the cleavage of a benzyl ether. Mechanistic studies identified the solvent (CD$_3$OD) as a proton source, presumably via protonation of the organopalladium intermediate resulting from the displacement of the nitro group by Pd^0. The removal of the nitro group occurs without loss of optical activity at adjacent centers. The authors applied modern synthetic methods to access to the required nitroalkanes.



50-95% yield

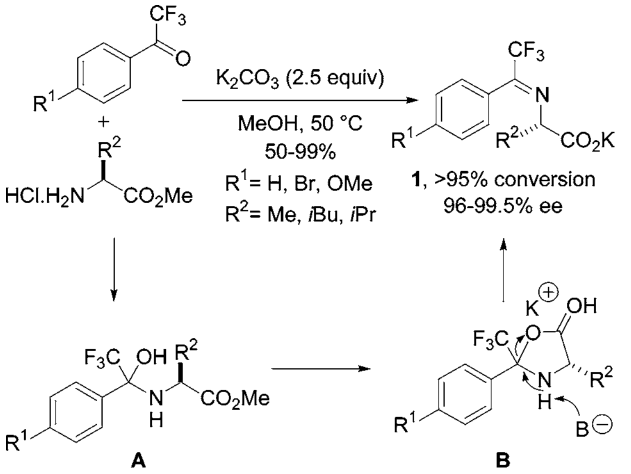
94% ee

95% ee

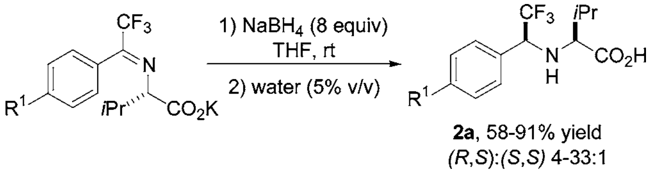
Reductive Amination of Aryl Trifluoromethyl Ketones and α-Amino Esters

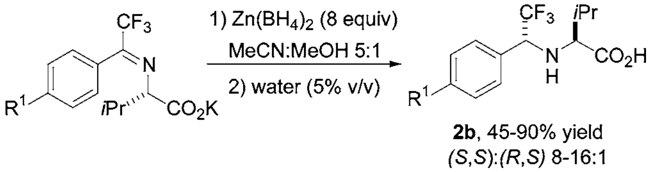
While instinctively simple, the reductive amination of 2,2,2-trifluoroacetophenones and α-amino esters to yield CF$_3$-substituted amino acids presents two key challenges: (1) finding suitable conditions for the formation of the imine between sensitive α-amino esters and ketones and (2) the development of stereoselective conditions for the reduction of the imine. Scientists from the Process Research group at Merck described the formation of a trifluoromethylketimine mediated by K$_2$CO$_3$, followed by complementary reduction protocols for direct access to diastereomers of amino acids **4** (*Angew. Chem., Int. Ed.* **2007**, *46*, 1839−1842). In the presence of a mild base the aminal intermediate can be converted into carboxylate **1**, presumably via an oxazolidinone.

A convenient reduction protocol involved the slow addition of water to the mixture of **1** and NaBH$_4$ in THF over 3 h to yield the *R,S*-diastereomer **2a**. Reduction of **1**



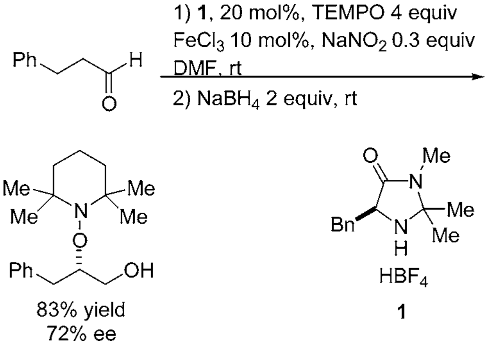
using Zn(BH$_4$)$_2$ in MeCN at lower temperatures selectively provided the *S*,*S*-diastereomer **2b**.





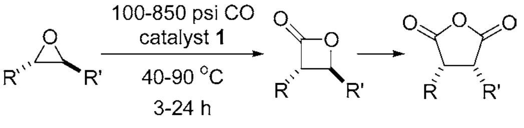
Organocatalysis in Radical Chemistry

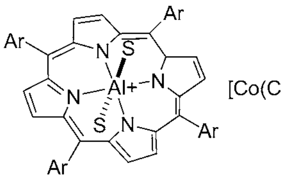
Sibi and Hasegawa (North Dakota State University) discovered an enantioselective α-oxyamination of aldehydes mediated by the combination of a chiral imidazolidinone organocatalyst (**1**) and a single electron transfer (SET) reagent in the presence of TEMPO (*J. Am. Chem. Soc.* **2007**, *129*, 4124−4125). The oxygenation proceeds via an enamine generated from the aldehyde and the chiral amine. Subsequent oxidation by the SET reagent (catalytic FeCl$_3$ in the presence of cooxidant NaNO$_3$) originates an intermediate radical, which is stereoselectively trapped by TEMPO. In order to simplify product analysis, the α-aminoxy aldehydes were reduced to the primary alcohols. Optimization of the reaction conditions—including the solvent—resulted in a general method capable of oxidizing a variety of aldehydes with high selectivities and good yields. The resulting N−O bond can be cleaved using Zn/AcOH to afford the corresponding 1,2-diols.



Double Carbonylation of Epoxides

The bimetallic catalyst **1** containing aluminum and cobalt promotes the conversion of epoxides to succinic anhydrides via a one-pot double carbonylation in high yields on multigram scale. Coates and co-workers at Cornell University report the development and mechanistic studies of this remarkable transformation in *J. Am. Chem. Soc.* **2007**, *129*, 4948−4960. The reaction takes place through two individual steps: (1) epoxide carbonylation to a *β*-lactone and (2) carbonylation of the *β*-lactone to the succinic anhydride. Interestingly, the strength of the solvent (S) for binding the Al$^+$ centre of the catalyst controls the rates of each step, allowing for the selective stop at the *β*-lactone stage by using THF or for carrying on to succinic anhydride using 1,4-dioxane. The complete sequence is compatible with a variety of functionalized epoxides and proceeds with excellent retention of stereochemical purity and inversion of configuration. The accessibility of the epoxides and the future commercial availability of catalyst **1** add to the usefulness of the carbonylation.

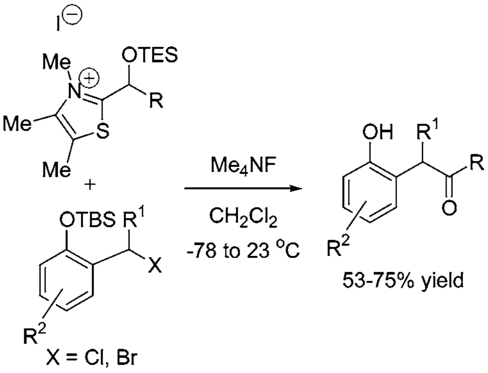




1; Ar = 4-Chlorophenyl
S = THF

Umpolung-Mediated Synthesis of α-Aryl Ketones

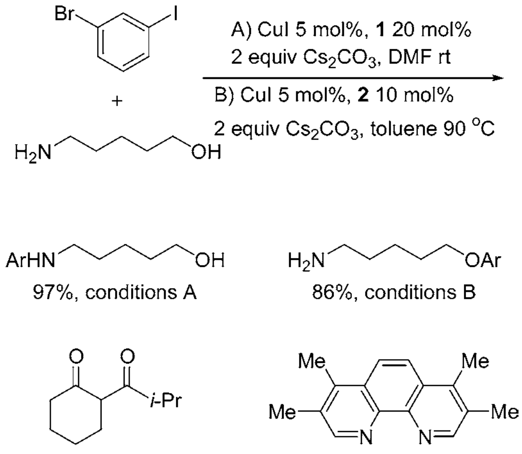
The preparation of α-aryl ketones is a challenging task commonly addressed by coupling enolates and aryl halides using transition metals. Mattson and Scheidt (Northwestern University) investigated a different disconnection based on an umpolung strategy: the addition of a carbonyl anion to an *o*-quinone methide electrophile (*J. Am. Chem. Soc.* **2007**, *129*, 4508−4509). In general, a protected *O*-silyl thiazolium carbinol reacts with an *O*-silylated phenol in the presence of a fluoride source (Me$_4$NF) under mild conditions. *o*-



Quinone methides generated from benzylic bromides gave the highest yields, and a survey of the protected thiazolium carbinols revealed the broad scope of the transformation.

N- versus O-Arylation of Amino Alcohols

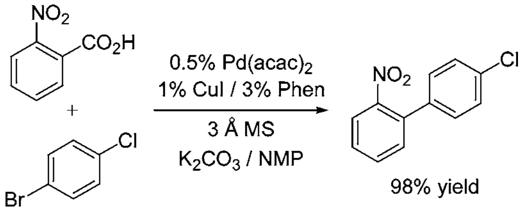
The Ullman-type arylation assisted by modern copper catalysts has become an indispensable tool in organic synthesis. Pushing the limits of this transformation, the group of Buchwald at MIT has reported experimental conditions that enable orthogonal N versus O selectivity in the arylation of amino alcohols (*J. Am. Chem. Soc.* **2007**, *129*, 3490−3491). For example, the coupling of 5-amino-1-pentanol with 3-iodobromobenzene using 5% CuI and 20% diketone ligand **1** affords the N-arylated product (conditions A), whereas the same reaction yields the O-arylated product using 5% CuI and 10% tetramethylphenanthroline ligand **2** (conditions B). The mechanistic hypothesis suggests that deprotonation of the heteroatom and subsequent coordination to the Cu catalyst are responsible for the observed selectivities.



1 **2**

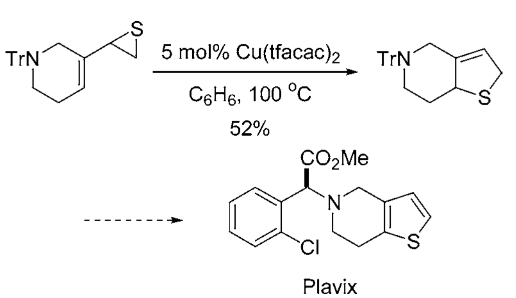
Coupling of Aromatic Carboxylates with Aryl Halides

The search for new cross-couplings that generate biphenyl derivatives has recently resulted in a creative strategy reported by the group of Goossen at the Institut für Organische Chemie in Kaiserslautern (*J. Am. Chem. Soc.* **2007**, *129*, 4824−4833). The protocol involves the Pd-catalyzed coupling of aryl halides with aryl copper derivatives formed by Cu-catalyzed extrusion of CO_2 from aromatic carboxylates. Under optimized conditions, high-yielding couplings can be achieved using 1% CuI, 3% phenanthroline as ligand, and 0.5% $Pd(acac)_2$ at 160 °C in the presence of a weak base such as K_2CO_3. In contrast to biaryl cross-couplings that require the use of stoichiometric amounts of elaborated organometallic reactants (e.g., Suzuki−Miyaura reaction), the decarboxylative methodology generates the aryl nucleophiles from readily available carboxylic acids. The reaction successfully transforms a variety of functionalized halide and carboxylate substrates.



Cu-Catalyzed Ring Expansion of Vinyl Thiiranes

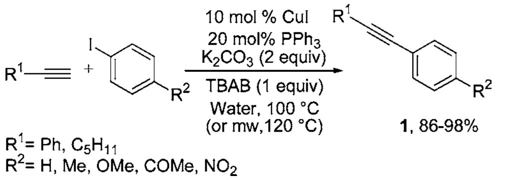
The group of Jón Njarđarson at Cornell University developed a methodology that selectively converts thiiranes to 2,5-dihydrothiophenes in excellent yields using readily available Cu(II) catalysts (*J. Am. Chem. Soc.* **2007**, *129*, 2768−2769). Following a catalyst screening, $Cu(tfacac)_2$ could be identified as the selective species that would overcome two main obstacles, namely the coordination of the thioether to the metal centre and the competing nucleophilic sulfide addition to the metal-activated thiirane. Under typical conditions, 0.1−30 mol % catalyst affords good yields of the rearranged thiophene at temperatures between 80 and 120 °C in a hydrocarbon solvent. The ring expansion tolerates a variety of substitution patterns on the thiirane as well as functional groups. The synthetic utility of this methodology was demonstrated in the synthesis of the heterocyclic core of Plavix, the blood thinner used to reduce the risk of stroke and heart attack.



Plavix

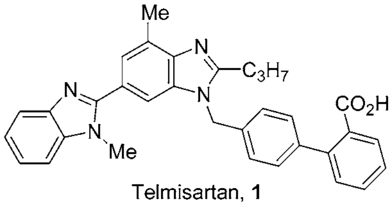
Copper-Catalyzed Coupling of Aryl Iodides and Acetylenes in Water

The Sonogashira cross-coupling of terminal acetylenes with aryl or vinyl halide is a powerful tool for the construction of C−C bonds. Disadvantages of its use in large scale involve the cost of Pd and the use of large amounts of amines as base or cosolvents. Scientists from Sun Yat-Sen University in Guangzhou, China, developed a palladium-free copper-catalyzed coupling of aryl iodides and terminal acetylenes in water (*Synth. Commun.* **2007**, *37*, 1355−1361). The optimized conditions use catalytic CuI/PPh_3, K_2CO_3 (2 equiv) as the base, and 1 equiv of tetrabutyl ammonium bromide (TBAB) to afford the desired coupling product in excellent yields. Reaction times were significantly shorter (20−40 min) when the reaction was carried out under microwave irradiation at 120 °C than when using regular heating at reflux temperature (16−24 h).

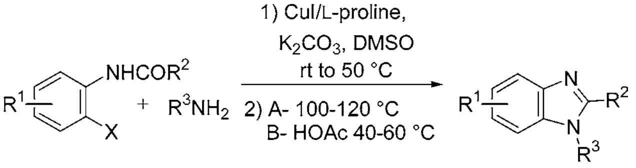


Synthesis of Benzimidazoles and Benzimidazolium Salts

1,2-Disubstituted benzimidazoles and benzimidazolium salts are a common theme in active compounds (i.e., the antihypertension drug telmisartan (**1**)). Methods to access these compounds lag behind those leading to indoles and are limited by the scarce diversity of starting materials (*o*-aminoanilines, *o*-nitroanilines, and 2-substituted benzimidazoles). Ma and co-workers recently reported a novel cascade process for the formation of 1,2-disubstituted benzimidazoles from 2-haloanilides and primary amines (*Angew. Chem., Int. Ed.* **2007**, *46*, 2598−2601). The first step is the CuI/L-proline-catalyzed formation of an *o*-aminoanilide. The *o*-$NHCOCF_3$ or *o*-NHCOMe group of the anilide **2** promotes the amination reaction, which does not occur with iodobenzene under the same conditions. The second step is the cyclization to afford the desired 1,2-disubstituted benzimidazoles, which takes place by heating the coupling reaction mixture at 100 °C or by adding AcOH and heating at 50 °C. Variation at the 1- and 2-positions of the benzimidazole is achieved by using different primary amines and with variation in the amido groups of the 2-haloacetanilides. Moreover, the strategy allows the introduction of substituents on different positions of the benzimidazole phenyl ring.



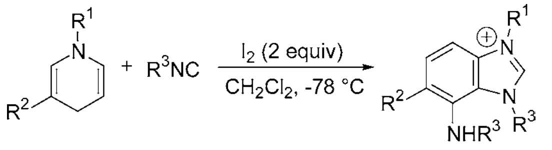
Telmisartan, **1**



2, X = I, Br

3, 61-94%

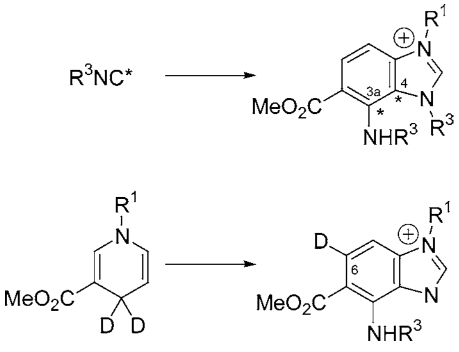
The group of Lavilla at the Barcelona Science Park renewed efforts to functionalize heterocycles using MCRs. Thus, the reaction of electron-rich dihydropyridines (DHPs) with cyclohexyl isocyanide in the presence of iodine led to the clean and unprecedented formation of benzimidazolium salt, **4** (*Angew. Chem., Int. Ed.* **2007**, *46*, 3043−3046). **4** results from the formal double insertion of two isocyanide molecules in the DHP ring followed by rearrangement to the benzimidazole core. Overall, the reaction generates four bonds in a single step.



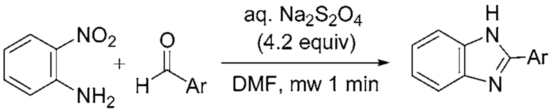
4, 40-85%

R^1 = Me, Et, Bn, phenetyl, *p*-tolyl, *c*C_6H_{11}, α-MeBn
R^2 = CO_2Me, CO_2Et, CO_2Allyl, CN
R^3 = Bn, *c*C_6H_{11}, *p*-$MeOC_6H_4$

Adventitious water is well tolerated by the process, whereas bases slow or prevent the reaction. ^{13}C labeling and NMR studies showed that the insertion of the isocyanate was contiguous (C3a−C4), and deuteration of the DHP on C4 provided a product deuterated on C6, ortho to the CO_2Me group. The authors include a mechanistic proposal that accounts for the facts above.



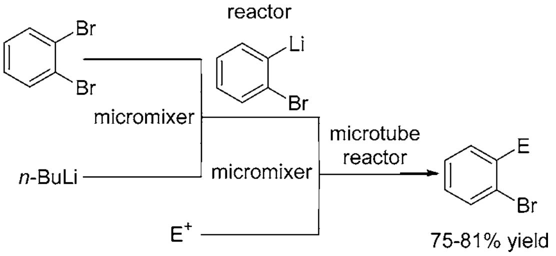
Samant and co-workers from the University Institute of Chemical Technology in Mumbay reported a method for the synthesis of benzimidazoles from *o*-nitroanilines using sodium dithionite ($Na_2S_2O_4$) and microwave irradiation (*Synth. Commun.* **2007**, *37*, 1375−1379). Sodium dithionite has been reported to reduce aryl nitro groups to anilines via a six-electron mechanism. It is inexpensive and efficient and requires reaction conditions that tolerate a number of functional groups. Following reaction completion (1 min), the benzimidazoles **1** were isolated by precipitation with NH_4OH and purified by crystallization from EtOH.



1, 65-92%

Avoiding Benzyne Formation Using a Microreactor

Yoshida and co-workers at Kyoto University reported the taming of highly unstable *o*-bromophenyllithium using microreactor technologies (*J. Am. Chem. Soc.* **2007**, *129*, 3046−3047). Since *o*-bromophenyllithium decomposes to give benzyne in macroscale batch reactors even at −78 °C, it is an ineffective nucleophile for the preparation of bromophenyl derivatives. However, controlling temperature and fine-tuning the residence time in a stainless steel microtube reactor (−78 °C, 0.8 s) enabled the reaction of the unstable intermediate with a variety of electrophiles, including MeOTf, TMSCl, TMSOTf, Bu_3SnCl, aldehydes, and ketones. Furthermore, the authors examined the sequential Br−Li exchange of the remaining bromine substituent to successfully achieve the introduction of two groups on the benzene ring.



Lithium Diisopropyl Amide

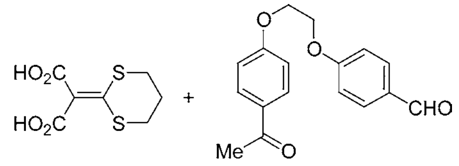
Lithium diisopropyl amide (LDA) is as ubiquitous in organic processes. Collum, McNeil, and Ramirez reviewed the properties and uses of LDA (*Angew. Chem., Int. Ed.* **2007**, *46*, 3002−3017). Rate studies of LDA-mediated reactions are placed in the broader context of organic synthesis. In the first section the authors lure readers by providing a friendly tutorial on solution kinetics, emphasizing the characteristic rate behavior caused by dominant solvation and aggregation effects. The second section summarizes substrate- and solvent-dependent mechanisms that reveal basic principles of solvation and aggregation. The final section indicates how an understanding the mechanism can be combined with empirical methods to optimize yields, rates, and selectivities of organolithium reactions. The practical toolbox in section 4 should be read by the practitioner of organolithium chemistry when considering development of a process using LDA.

Odorless Thioacetalization in Water

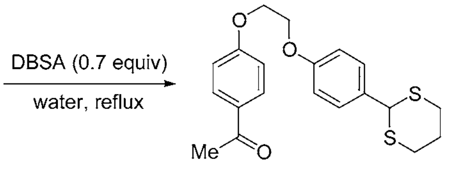
The seminal work by Breslow in 1980 showed that, "*Hydrophobic effects can strongly enhance the rates of organic reactions in water*." This phenomenon is exploited by Dong's group at Northeast Normal University in China, which uses the surfactant agent *p*-dodecylbenzenesulfonic acid (DBSA) as the catalyst for thioacetalization reactions in water (*Synth. Commun.* **2007**, *37*, 993−1000). Using odorless cyclic ketene dithioacetals (e.g., **1**) as 1,3-propanedithiol equivalents, the authors investigated the thioacetalization reaction in selected carbonyl compounds.

Interesting findings include the following: (1) reactions are accelerated as the concentration of DBSA increases, suggesting a critical micelle concentration for thioacetalization; the authors postulate that the reaction takes place inside the micelles and that the by-product water is expelled, accelerating the reaction; and (2) the thioacetalization proceeds faster in water than in organic solvents.

A variety of aldehydes and ketones readily reacted under the optimized conditions (DBSA, water, reflux, 1−2 h). Upon cooling and filtration, the desired thioacetals were obtained as solids in 88−98% yields. On the other hand, the reaction of **1** with aromatic ketones was sluggish. This difference of reactivity lead to a remarkable selectivity which allowed the monoprotection of dicarbonylic compounds such as **2**.

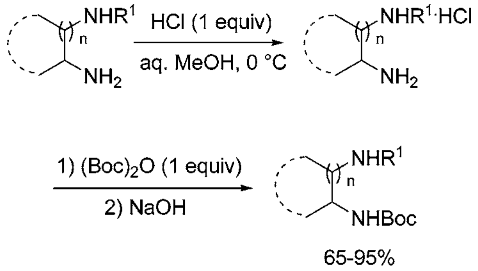


1 **2**



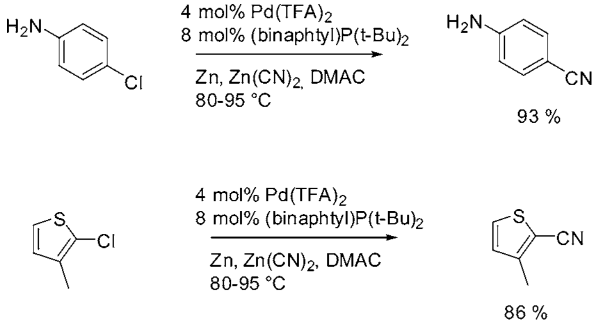
Selective Mono-Boc protection of Diamines

Lee, Ha, and Lee developed a simple protocol for the monoprotection of symmetrical and unsymmetrical diamines by sequential addition of 1 equiv of HCl and 1 equiv of $(Boc)_2O$ followed by neutralization (*Synth. Commun.* **2007**, *37*, 737−742). The two amine groups are differentiated by formation of the monohydrochloride in aqueous MeOH, resulting from the addition of 1 equiv of gaseous hydrogen chloride to the diamine. Subsequent addition of 1 equiv of $(Boc)_2O$ to the solution of the monohydrochloride, neutralization, and aqueous workup yields the mono-Boc-protected amine as the main product. The procedure proved more efficient than conventional methods that require long addition times of Boc_2O and tight control of substrate concentration to avoid the formation of the bis-Boc-product.



Mild and General Methods for the Palladium-Catalyzed Cyanation of Aryl Chlorides

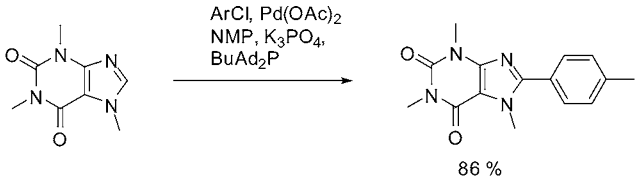
New methods for the palladium-catalyzed cyanation of aryl and heteroaryl chlorides have been developed, featuring sterically demanding electron-rich phosphines (Littke, A. et al., *Org. Lett.* **2007**, *9*, 1711). Highly challenging, electron-rich aryl chlorides, in addition to electron-poor substrates as well as nitrogen, and sulfur-containing heteroaryl chlorides, have been found to undergo a general and mild palladium-catalyzed cyanation reaction. The protocol uses $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$ as catalyst. Functional groups such as anilines, phenols, esters, nitro groups, amides, carboxylic, and boronic acids are well tolerated. Yields are good to excellent for aryl and heteroaryl nitriles.



Palladium-Catalyzed Arylation of Electron-Rich Heterocycles with Aryl Chlorides

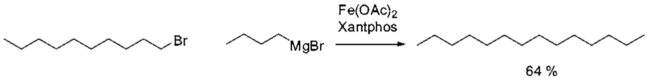
The group of Olaf Daugulis (*Org. Lett.* **2007**, *9*, 1449) has developed a new, efficient, and general, electron-rich, intermolecular, heterocycle arylation process based on C−H activation. This is the first general method for heterocycle arylation with aryl chlorides. The key to the success of this reaction is the use of bulky, electron-rich phosphine ligands.

The mechanism for the reaction is probably electrophilic substitution. The method needs no copper additive. The best source of palladium is $Pd(OAc)_2$, and as base, K_3PO_4 was found to be the best choice.

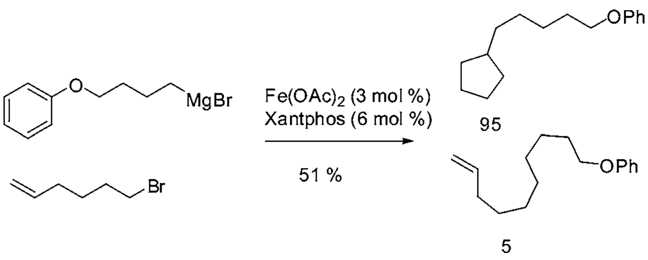


Iron-Catalyzed sp^3–sp^3 Cross-Coupling Reactions of Alkyl Bromides with Alkyl Grignards

Chai, C. L. L.; et al. (*Adv. Synth. Catal.* **2007**, *349*, 1015) have presented a preliminary report on an iron-catalyzed sp^3–sp^3 Kumada coupling with primary and secondary alkyl bromides. The yield from the coupling is highly dependent on the nature of the alkyl bromide, ranging from low to moderate. Steric hindrance around the active center lowers the yield significantly, but the potential of the method after further development is large. Xantphos was found to be the best ligand, and the best iron source was found to be $Fe(OAc)_2$.

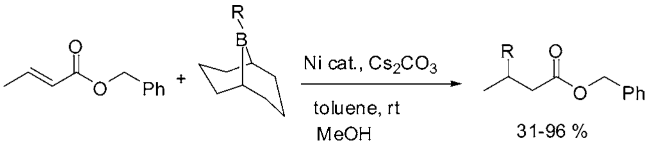


The preliminary investigation suggests the intermediacy of radical intermediates based on the results in the following scheme.



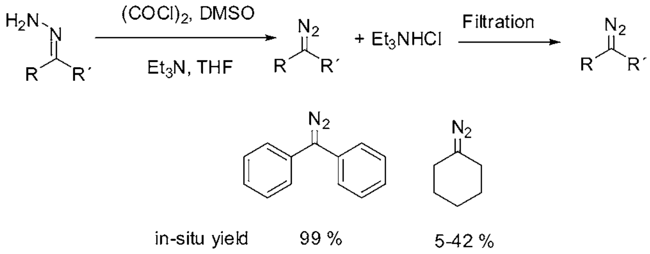
Nickel-Catalyzed 1,4-Addition of Trialkylboranes to α,β-Unsaturated Esters

Oshima, K. et al. (*Org. Lett.* **2007**, *9*, 1541) have developed a new nickel catalyst system for the addition of trialkylboranes to α,β-unsaturated esters. Addition of methanol was found to be essential for the alkylation reaction with 9-alkyl-9-BBNs. Yields from the methanol-promoted process are low to excellent, depending on the structure of the alkene used. The catalyst system is a mixture of $Ni(cod)_2$ and P(*t*-Bu)$_3$.



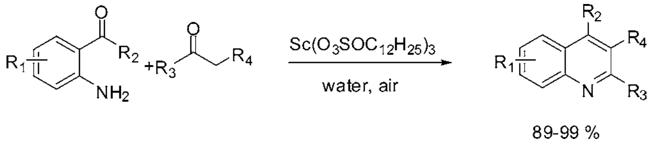
Diazo Preparation via Dehydrogenation of Hydrazones with "Activated" DMSO

Brewer, M.; et al. (*Org. Lett.* **2007**, *9*, 1789) have reported that "activated" dimethyl sulfoxide efficiently dehydrogenates hydrazones to the respective diazo species at −78 °C. Under optimized conditions, triethylamine hydrochloride is removed quantitatively by vacuum filtration to provide solutions of diazo compounds. Stable diazo compounds can be isolated from the procedure in high yield. Alternatively, the direct treatment of these solutions with carboxylic acids provides esters.



Lewis Acid Surfactant Catalytic Friedländer Synthesis of Quinolines in Water

Zhang, L. and Wu, J. (*Adv. Synth. Catal.* **2007**, *349*, 1047) have found that by employing a catalytic amount of a Lewis acid surfactant it is possible to do the Friedländer annulation for the synthesis of various polysubstituted and polycyclic quinolines. The best catalyst for the reaction was found to be scandium tris(dodecyl sulfate) which gave with a loading of 5 mol % excellent yields of quinolines in water under aerobic conditions at 40 °C with 1.5 equiv of the ketone counterpart.



My former colleague and close friend Dr. Hilmar Weinmann has sent me some interesting articles for the highlights showing our business with another eye-view. A close collaboration between medicinal chemistry and process chemistry is for every pharmaceutical company very important. New technological approaches in medicinal chemistry for performing reactions in a more efficient way will necessarily in the long run also be used in process chemistry, so it is important to be aware of the development in medicinal chemistry.

Synthetic Approaches to the 2005 Approved New Drugs.

Li, J. et al. (*Mini-Rev. Med. Chem.* **2007**, *7*, 429) have reviewed the published synthesis of 22 new drugs that have been introduced to the market in 2005. This makes interesting reading as it shows the limited number of reactions that are performed on large scale. In the review are shown just a handful of nonstandard semibatch reaction conditions. I always find it amazing the complexity of structures that can be synthesized on large scale with a very limited variety of reactions. What, if a much larger variety of reactions would be available, would this increase the complexity of the new drugs and or would it only lead to more focused synthesis of the same type of drugs?

Microwave-Assisted Medicinal Chemistry.

Alcazar, J. et al. from J&J pharmaceutical research (*Mini-Rev. Med. Chem.* **2007**, *7*, 345) have reviewed the use of microwave heating for the synthesis of various classes of pharmaceuticals. They have found that although the use of microwave heating has been used to enhance reactions since the mid-1980s its use in medicinal chemistry is not so evident in the literature. The review highlights the use of microwaves as a tool to enhance the structure−activity relationship in several programs related to various therapeutic areas.

Organocatalytic Synthesis of Drugs and Bioactive Natural Products

Catalytic reactions are a key element in the design of sustainable chemical processes. As witnessed in the field of transition metal-catalyzed processes only those reactions that are reliable over a broad substrate range and tolerant toward a multitude of functional groups have found their way into the repertoire of preparative chemists. Natural product synthesis provides a good benchmark for the maturity of a new synthetic method, and in the microreview of de Figueiredo R. M. and Christmann, M. (*Eur. J. Org. Chem.* **2007**, 2575) they discuss the scope and limitations of organocatalytic reactions in the synthesis of biologically important molecules.

Crystallization of Racemic Ketoprofen

Ketoprofen is a nonsteroidal anti-inflamatory agent commercially available as a racemate. Although a number of processes for the production of the *S*-enantiomer have been previously published, there is still a growing interest in this compound, and Wa and co-workers (*Sep. Purif. Technol.* **2007**, *53*, 144) have recently disclosed a protocol for the production of this compound in enantioenriched form.

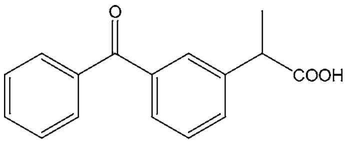
The use of enzymes as chiral mediators (low substrate/enzyme ratio) for enantioseparation through non-biotransformation routes can be a good process alternative. In addition, recycling of the enzyme can be easily done via, for example, ultrafiltration.

In this paper the authors describe the use of ion-paired lipases as chiral mediators. They found that lipases in organic solvents in the presence of sodium bis(2-ethylhexyl)sulfosuccinate (AOT) can mediate enantioselective crystallization of ketoprofen.

The ion pairs were prepared via solubilization of the enzyme in phosphate buffer containing NaCl or $CaCl_2$, mixing with isooctane AOT solution, stirring, and centrifugation. The transparent isooctane layer was then used.

The process is carried out simply by mixing the ion-paired enzyme isooctane solution with an acetone solution of ketoprofen. After controlled evaporation of the solvents, the formed crystal is filtered, and the remaining solution is let to evaporate further.

The ion-paired organic solvent/soluble enzyme is very efficient in this process. The enantiopurity of *S*-ketoprofen in the remaining solution reached as high as 67% in the case of *Candida rugosa* lipase.



Ketoprofen

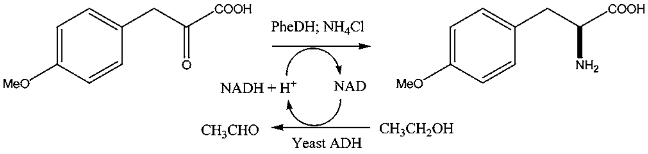
There are two different complexes, enzyme/*R*-substrate and enzyme/*S*-substrate, which have different dissociation constants, thus enriching the medium with one enantiomer. Crystallization of this particular enantiomer then occurs. The enzyme role is to complex the two enantiomers and favor dissociation of one of them. AOT is used to allow the formation of reverse micelles in the hexane (or hydrocarbon) phase, allowing the presence of the enzyme in the organic phase.

Nonnatural L-Amino Acids

Chen and Engel (*Enzyme Microb. Technol.* **2007**, *40*, 1407) described an engineered mutant of phenylalanine dehydrogenase (PheDH), L307V, capable of being used in the production of L-*p*-methoxyphenylalanine and related L-amino acids.

They discovered that leucine 307 in PheDH is implicated in substrate specificity. So, in the mutant L307V, in which a smaller amino acid is present, the longer substrate pocket should accommodate larger substrates than Phe. Therefore, L307V PheDH was predicted to be an efficient catalyst for para-substituted derivatives of Phe. Several nonnatural derivatives were screened (4-F, Cl, Me, OMe, NO_2), and several process conditions were tested.

Due to the good performance of this mutant enzyme, it was used in the production of L-*p*-methoxyphenylalanine.



Conversions of up to 74% were obtained with 100% ee.

An Experimental Verification of Morphology of Ibuprofen Crystals from CAMD-Designed Solvent

Computer-assisted molecular design (CAMD) continues to make progress in many areas, including crystallization solvent selection. As a continuation of a 2006 communication, a team from the University of Connecticut and from the Technical University of Denmark (Karunanithi, A. T.; et al. *Chem. Eng. Sci.* **2007**, *62*, 3276) addresses this topic using ibuprofen as a case study. In the first paper (ibid. **2006**, *61*, 1247), the authors use mixed integer nonlinear programming (MINLP) to design two solvents for (racemic) ibuprofen crystallization: one for a cooling crystallization and the other for the drowning-out crystallization process. Certain goals are set for several objective functions: solubility, potential recovery, flashpoint, toxicity, viscosity, boiling point, melting point, and crystal morphology. Good-quality models are available for all these constraints, except for the practically important crystal morphology. The authors recognize the need for a deeper understanding of solvent impact on crystal morphology. As a suitable compromise, the hydrogen-bonding solubility parameter is used to quantify the impact of solvent on crystal morphology. Using this approach, an optimal solvent was designed for the cooling crystallization process and a binary mixture for the drowning-out crystallization process. Apparently, the optimal solvent designed for the cooling crystallization is not readily commercially available ($CH_3O{-}CH_2{-}O{-}C({=}O){-}CH_2{-}OC_2H_5$). The "next best" structure of an available solvent is that of 2-ethoxy-ethyl acetate (interestingly with one less alkoxy-oxygen atom than the optimal structure). In the second paper, the authors report the experimental verification work. Therein, the ibuprofen crystal morphology obtained from crystallization in *n*-hexane is compared with that obtained when using the designed solvent, 2-ethoxy-ethyl acetate. It is shown that the morphology of the two types of crystals is significantly different, with 2-ethoxy-ethyl acetate producing larger crystals of lower-aspect ratio. The crystallization yield is also higher when using 2-ethoxy-ethyl acetate. It is interesting to see the results of a similar comparison using also alcoholic solvents (with or without additives) as is often used for ibuprofen crystallization.

Fabrication and Handling Safety of Highly Reactive Powders

A contribution from the Atomic Weapons Establishment in the United Kingdom (Towndrow, P. *Powder Technol.* **2007**, *174*, 38) discusses the fabrication and handling of the highly reactive powder, LiH. This organization handles LiH in kilogram amounts. Interestingly, full understanding of the mechanisms of the reactions of LiH with water is still under development. Formation of Li_2O (along with H_2) is observed at very low moisture levels (10 ppm); this is followed by formation (as an outer crust, for bulk material) of LiOH. Small amounts of H_2 can thus be entrapped in the LiH matrix. Most of the handling is executed in glove boxes, at 10−30 ppm H_2O and <100 ppm O_2. The author mentions the importance of safety training for the handling of such reactive materials; this training is offered both to company personnel and to the company Fire Brigade. To give the reader a broad perspective, the author also describes what can happen during "unplanned events". For example, if a LiH disk 50-mm in diameter and 10-mm thick were to be dropped into a beaker of water, the behavior observed would be similar to that of an Alka Seltzer tablet, albeit with the evolution of hydrogen rather than carbon dioxide. Smaller particles pose a much higher risk, of course.

Tools for Efficient High Throughput Synthesis

A short review covering the developments of the last 5 years in high throughput synthesis was published by a team from the University of Edinburgh (Chighine, A. *Drug Discovery Today* **2007**, *6*, 616). Even though the review is intended primarily for medicinal chemists, the paper may be of relevance for process chemists' and engineers' work. Several examples of supported chemistry (including enveloped OsO_4, entangled Pd^0, etc.) and of the use of microwave heating are presented. In addition, and perhaps of more relevance to process R&D work, recent advances in microreactor technology are reviewed. For highly mixing sensitive processes, in particular for homogeneous parallel competitive reactions, selectivity can be improved by using microreactors. Moreover, scale-up ("scale-out") strategies can be more straightforward compared to the scale-up of (semi) batch reactors. In addition to the many well-known organic reactions that were successfully conducted in microreactors, more recent successes include hydrogenations in the H-Cube apparatus; therein, continuous flow, high-pressure, high-temperature catalytic (cartridges) hydrogenations can be executed. This device can be interfaced with HPLC instruments and with robots for reagent handling, making it very effective in high throughput synthesis. Scaling-out microreactors fitted with supported reagents and/or catalysts may be of industrial interest in the future. This review contains 47 references.

Tech Transfer Fails To Translate into Startups

A brief but rather extensive analysis of technology transfer and its economic impact in the last 5 years was recently published (Lawrence, S. *Nat. Biotechnol.* **2007**, *6*, 616). In this context, technology transfer is understood to occur from Universities to Industry. The financial volume of licensing activities is quite impressive: in 2005, in the United States alone, academic licensing brought in approximately $2 billion. Across the world, 628 firms were started in 2005, with one-sixth of them life-science based. Nevertheless, startup activity in the world in 2005 is considered to be poor, as described in the table below. Note that the data are presented as percentage of startups of total companies in the country analyzed.

	2005	2004	2003	2002	2001
Spain	14	n/a	n/a	n/a	n/a
Denmark	3	6	10	13	26
Ireland	n/a	n/a	10	6	6
UK	3	7	9	9	10
Europe	n/a	6	8	8	13
Germany	6	2	6	6	14
Sweden	n/a	5	10	5	13
Switzerland	4	7	8	11	13
France	7	7	5	6	16
USA	5	4	6	7	9
Norway	n/a	8	3	6	14
Finland	2	n/a	4	9	12
Israel	n/a	n/a	n/a	7	14
Belgium	n/a	7	7	17	12
Japan	13	17	14	9	16

New companies as % of total in country.

Source: Critical I, Japan Bioindustry Association, BIO, BioCOM/biotechnology.de.

Key Green Chemistry Research Areas: A Perspective from Pharmaceutical Manufacturers

In 2005 the ACS Green Chemistry Institute (GCI) and several pharma companies developed the ACS GCI Pharmaceutical Roundtable to discuss green chemistry. They have developed a list of key areas in which they wish to encourage research. These include reactions which companies use but for which they would strongly prefer better reagents (e.g., reduction of amides without using hydride reagents) or more aspirational topics which require discovery of new chemistry (e.g., C−H activation of aromatics such as cross-coupling to avoid the preparation of haloaromatics or equivalents).

The full list of ideas is given in the paper (Constable, D. J. C.; et al. *Green Chem*. **2007**, 9, 411−420) which should be required reading, not only for industrial chemists but also for academics. The aim is to encourage academic research in these areas—research which, if successful, should have a speedy commercialisation. Hopefully, funding agencies will be encouraged to fund proposals in these areas.

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