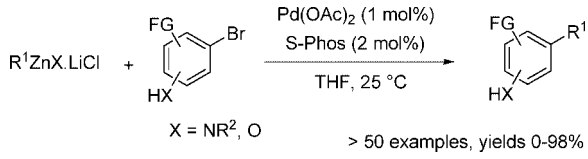
Highlights from the Literature

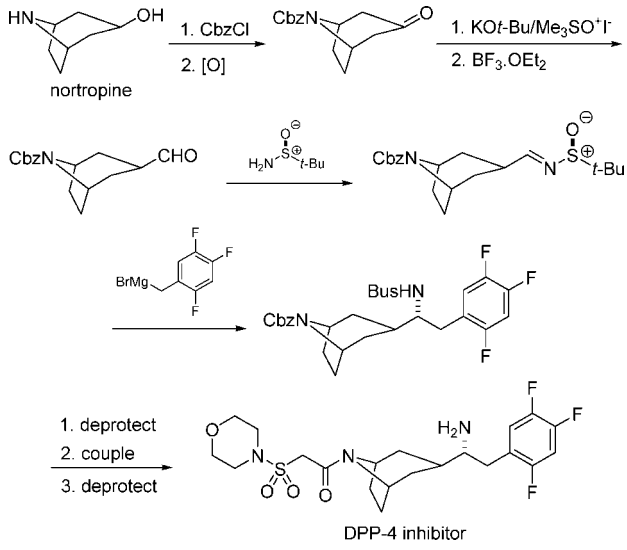
Some Items of Interest to Process R&D Chemists and Engineers

Negishi-Type Cross-Coupling of Substrates Bearing Relatively Acidic Protons



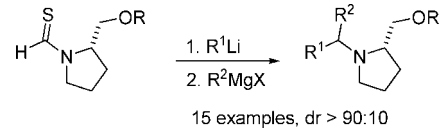
Following up on an earlier communication, the Knochel group now provides a full account of their recent work on Negishi-type cross-couplings (*J. Org. Chem.* **2008**, *73*, 842−8436). A wide range of polyfunctional aryl, heteroaryl, alkyl, and benzylic zinc reagents were coupled at 25 °C with aryl halides bearing an acidic NH or OH proton, using $Pd(OAc)_2$ (1 mol %) and S-Phos (2 mol %) as catalyst without the need for protecting groups. Even bromophenols were found to participate in this process. A similar Ni-catalyzed reaction is described. The relative kinetic basicity of organozinc compounds as well as their stability toward acidic protons is also described. As noted by the authors, potential advantages relative to the widely used Suzuki cross-coupling are the very mild conditions and no requirement for additional base to promote the reaction.

Practical Synthesis of a Novel DPP-4 Inhibitor



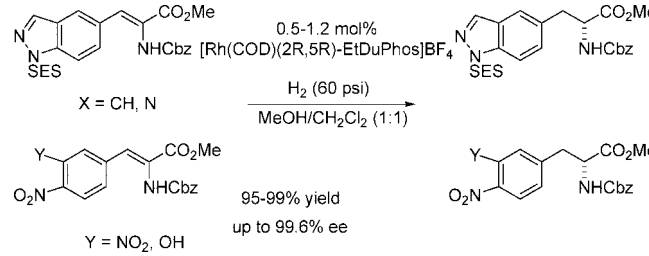
A practical synthetic strategy to a chiral azabicyclooctanyl derivative, a potent DPP-4 inhibitor, starting from a commercially available nortropine is described by Shieh, Prasad, and co-workers at Novartis (*J. Org. Chem.* **2008**, *73*, 9016−9021). Protection and oxidation of nortropine afforded the nortropinone derivative, and then epoxidation and Lewis acid-mediated rearrangement gave the homologated aldehyde. The stereogenic center was established by employing a modified protocol of Ellman's diastereoselective addition of a benzylic nucleophile to the appropriate *tert*-butanesulfinimine. Removal of the Cbz-group using neat MSA (leaving the sulfinamide intact) allowed for amide bond formation followed by final deprotection of the sulfinamide using HCl in MeOH.

Sequential Diastereoselective Organolithium Additions to *N*-Thioformyl 2-Alkoxymethylpyrrolidines



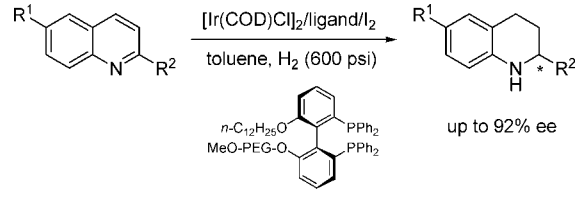
Highly efficient sequential addition reactions of organolithium and organomagnesium reagents to *N*-thioformyl 2-methoxymethylpyrrolidine have been described by Murai and co-workers (*J. Org. Chem.* **2008**, *73*, 9518−9521). By changing the sequence of addition, it is possible to generate alternative diastereomers. The reaction was extended to *N*-thioformyl 2-siloxymethypyrrolidine and 2-methoxymethylpiperidine, and these showed similar efficiencies and selectivities.

Catalytic Asymmetric Syntheses of Tyrosine Surrogates



Amino acid esters that are tyrosine mimics have been synthesized in excellent enantioselectivity (up to 99.6% ee) and in good overall chemical yields, as described by Han and co-workers at BMS (*J. Org. Chem.* **2008**, *73*, 8502−8510). The key step in the sequence was the Burk's [Rh(COD)(2*R*,5*R*)-Et-DuPhos]BF_4-catalyzed asymmetric hydrogenation of enamides in the presence of a variety of reactive functional groups.

Asymmetric Hydrogenation of Quinolines



Zhou and co-workers report on the synthesis of a series of tunable axial chiral bisphosphine ligands (*J. Org. Chem.*

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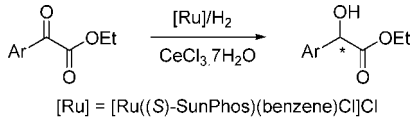
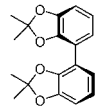
2008, *73*, 5640−5642). Starting from (*S*)-MeO-Biphep, bis-demethylation followed by sequential alkylations led to 17 different ligands, including a PEG-supported version. The Ir complex of the MeO-PEG-supported ligand was successfully applied in the asymmetric hydrogenation of quinolines with up to 92% ee. The catalyst system is air stable and recyclable via precipitation from hexanes.

Ru-Catalyzed Enantioselective Hydrogenation of Aromatic α-Ketoesters



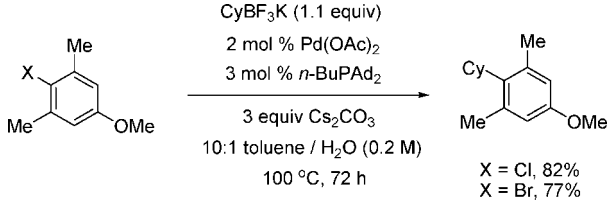


(*S*)-SunPhos

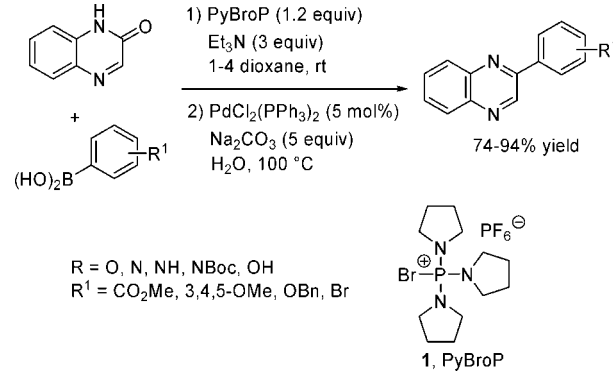
In the presence of catalytic amounts of $CeCl_3 \cdot 7H_2O$, [RuCl(benzene)(*S*)-SunPhos]Cl is a highly effective catalyst for the asymmetric hydrogenation of aromatic α-ketoesters, as described in a report from Zhang and co-workers (*J. Org. Chem.* **2008**, *73*, 3842−3847). A variety of ethyl α-hydroxy-α-arylacetates have been prepared in up to 98.3% ee with a TON up to 10 000. Challenging aromatic α-ketoesters with ortho substituents are also hydrogenated with high enantioselectivities. The addition of $CeCl_3 \cdot 7H_2O$ not only improves the enantioselectivity but also enhances the stability of the catalyst. The ratio of $CeCl_3 \cdot 7H_2O$ to [RuCl(benzene)(*S*)-SunPhos]Cl plays an important role in the hydrogenation reaction with a large substrate/catalyst ratio.

Unusual Partners for Pd-Catalyzed Cross-Coupling Reactions

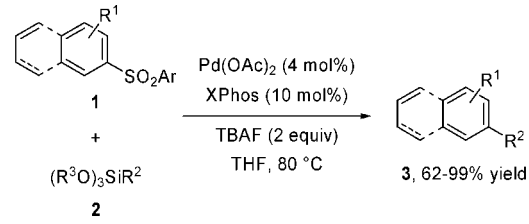
Dreher (Merck and Co. Inc.) and Molander (University of Pennsylvania) reported the results of an industry−academia collaboration intended to discover Pd-based catalysts capable of promoting Suzuki−Miyaura couplings between secondary organotrifluoroborates (RBF_3K) and aryl halides (*J. Am. Chem. Soc.* **2008**, *130*, 9257−9259). The cross-coupling of secondary organometallics is a challenging transformation due to difficult transmetalations and the detrimental competition of β-hydride elimination with the reductive elimination step. The researchers used parallel microscale experimentation to screen a large number of ligand, solvent, and substrate combinations. In short, *n*-butyldiadamantylphosphine (*n*-BuPAd$_2$) with Cs_2CO_3 in toluene at 100 °C afforded the best results (51 to 94% isolated yields) for the arylation of cyclopentyl-, cyclohexyl-, and *i*-PrBF_3K with a series of electronically demanding aryl chlorides and bromides. Different carbo- and heterocyclic substrates afforded good yields with the exception of halobenzonitriles, which were recovered unchanged.



Kang, Siu, and Murray from Johnson and Johnson Pharmaceutical R & D (Exton, PA) reported the first Pd-catalyzed direct arylation of tautomerizable heterocycles (*J. Am. Chem. Soc.* **2008**, *130*, 11300−11302). Treatment of the amide-bearing heterocycle with a phosphonium salt of the kind used as activation agents for the coupling of acids and amines generated a heterocycle-phosphonium salt. This species behaved as preactivated cross-coupling partners (e.g., sulfonate, phosphate) under Suzuki−Miyaura cross-coupling conditions (Pd catalyst and aryl boronic acid counterpart) to furnish the target biaryl product. Optimized experimental conditions included the use of bromide salt PyBroP (**1**), catalyst $PdCl_2(PPh_3)_2$, Et_3N, Na_2CO_3, and water in dioxane. Complete conversion and good to excellent isolated yields (74−94%) were observed for all the heterocycles tested. The utility of the direct arylation via C−OH bond activation is showcased in the one-pot cross-coupling of the naked purine ribonucleoside inosine with aryl boronic acids to synthesize 6-arylpurine ribonucleosides—a process that generally takes four steps including protection and activation.



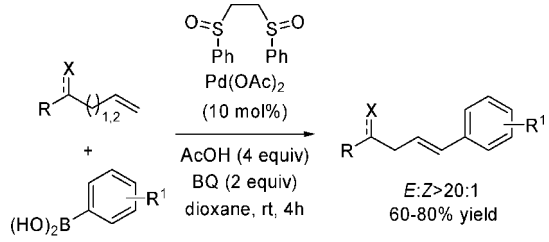
Zhang and Wu, from Fudan University and the Chinese Academy of Sciences, respectively, reported the novel use of arenesulfonates as electrophiles in the Hiyama cross-coupling with organosilicon compounds (*J. Am. Chem. Soc.* **2008**, *130*, 12250−12251). The scope of the reaction was investigated using $Pd(OAc)_2$ (4 mol %), XPhos (10 mol %), and TBAF (1 M in THF, 2 equiv) in THF at 80 °C. The transformation generates the biaryl products in high yields and tolerates both electron-donating and electron-withdrawing groups on the aromatic rings of the arylarenesulfonates and the arenylsilanes (see R^1 and R^2, scheme below). Moreover, tosylates and benzenesulfonates undergo coupling with triethoxy- and trimethoxy(phenyl)silanes. Not surprisingly, the reaction yields are lower for ortho-substituted coupling partners.



R^1 = 4-*t*Bu, 4-Ph, 4-EtO_2C, 4-CN, 2-, 3,- or 4-Me, 4-CF_3, 3-Morpholin, 3-OMe
R^2 = C_6H_5, 4-MeOC_6H_4, 4-$CF_3C_6H_4$, CO_2Me, 3,4,5-OMe, OBn, Br
R^3= Me, Et

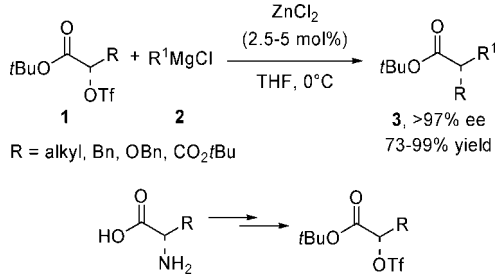
Chelate-Controlled Intermolecular Oxidative Heck Reaction

The intermolecular Heck reaction has enjoyed limited application in complex synthesis due to the restricted scope of the olefin to α-β unsaturated carbonyls, styrenes and enol ethers. Such requirements are needed for high reactivity, regioselective insertion (internal vs terminal) and β-hydride elimination (styrenyl vs allylic). Delcamp, Brucks, and White (University of Illinois-Urbana) reported the use of their signature Pd(II)-sulfoxide catalyst for a chelation-controlled, oxidative intramolecular Heck reaction with a wide range of olefins (*J. Am. Chem. Soc.* **2008**, *130*, 11270−11271). Olefin substituents that could produce 5- or 6-membered Pd(II) chelates (homoallylic carbonyls, bis-homoallylic alcohols, and thiols) gave the desired products with outstanding selectivities. The catalyst is very general, the reaction conditions mild, and *E*-olefin products are exclusively obtained. It is noteworthy that thioethers, often incompatible with Pd(II)-mediated reactions, serve as excellent directing groups. In addition, unprotected alcohols react without oxidation or erosion of their optical purity.



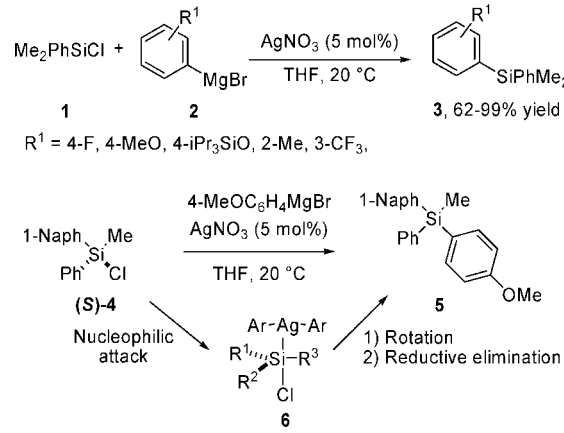
Zn-Catalyzed Cross-Coupling of Grignard Reagents and α-Hydroxy Ester Triflates

In *Angew. Chem., Int. Ed.* **2008**, *47*, 5451−5455, the group of Breit at Albert-Ludwigs-Universität Freiburg University (Germany) reported the development of a Zn-catalyzed cross-coupling of Grignard reagents with α-hydroxy ester triflates as stereogenic secondary electrophiles. Reaction of triflates **1** with chloromagnesium reagents **2** (1.4 equiv) and $ZnCl_2$ (2.5−5 mol %) at 0 °C yielded the alkylated products **3** in quantitative yields and >97% ee's with complete inversion of configuration. Not only primary (R^1 = Et, *n*Bu, *n*Oct) but also secondary acyclic (R^1 = *i*Pr, *s*Bu), secondary cyclic (R^1 = Cy), and functionalized [R^1 = Ph, $(CH_2)_3OMe$] Grignard reagents were suitable substrates, quantitatively yielding the corresponding products. In the case of MeMgCl, an excess of the less-reactive Grignard reagent had to be used to minimize competing side reactions (reduction, dimerization). As an added bonus, enantiopure α-hydroxy ester triflates can be easily obtained from inexpensive α-amino acids via diazotization, followed by functional group manipulation.



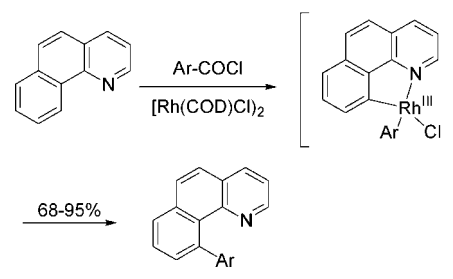
Tetraorganosilanes from Chlorosilanes and Grignard Reagents

Silver salts can catalyze the reactions of chlorotriorganosilanes with organomagnesium reagents to efficiently yield a variety of tetraorganosilanes (*Angew. Chem., Int. Ed.* **2008**, *47*, 5833−5835). Treatment of chlorodimethylphenylsilane **1** with various Grignard reagents **2** in the presence of $AgNO_3$ (5 mol %) in THF at 20 °C provided the corresponding tetraorganosilanes **3**. Other silver salts accelerated the silicon−carbon bond formation, but the product was obtained in only 13% yield in the absence of a catalyst. Whereas uncatalyzed nucleophilic substitution reactions of chlorosilanes generally proceed with either retention or inversion of configuration, the silver-catalyzed reaction of (*S*)-**4** provides the corresponding racemic product **5**. On the basis of this result, the authors propose that scrambling occurs after the nucleophilic attack of the diaryl argentate ($Ar_2AgMgCl$) to the chlorosilane. The intermediate silicate **6** can undergo pseudorotation to yield the racemic product after reductive elimination (−ArAg).



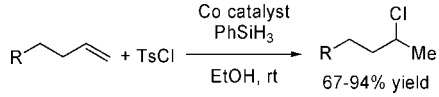
Rh-Catalyzed C−H Functionalization

Zhao and Yu (Shangai Institute of Organic Chemistry) describe a Rh-catalyzed C−H arylation using aroyl chlorides as the coupling partners under phosphine-free conditions in *J. Am. Chem. Soc.* **2008**, *130*, 8136−8137. Optimized conditions involve the use of 1.5 equiv of acid chloride, 5 mol % $[Rh(COD)Cl]_2$, 2 equiv of Na_2CO_3, and molecular sieves in xylene as the solvent. The arylation works with a wide scope of *N*-heteroaromatic substrates including pyridine substructures and a variety of aroyl chlorides. A mechanistic proposal begins with the oxidative addition of the aroyl chloride to the Rh(I)Cl catalyst to generate an aroyl-chlorometal species [RCORh(III)Cl_2] that decarbonylates to give an aryl-chlorometal intermediate RRh(III)Cl_2. This species reacts with the arene substrate in the presence of Na_2CO_3 to form a chelated intermediate that undergoes reductive elimination to afford the desired product.



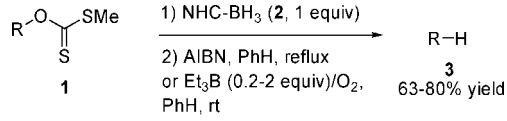
Chlorination of Unactivated Olefins with *p*-Toluenesulfonyl Chloride

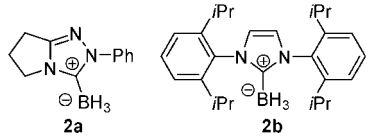
Although the addition of hydrogen chloride to olefins is one of the first reactions taught in organic chemistry courses, it only occurs at acceptable rates in alkenes that render stabilized carbocation intermediates. Yet, this highly interesting transformation grants access to a variety of versatile organic chlorides. The group of Prof. Carreira at ETH Zurich describes the cocatalyzed hydrochlorination of olefins using TsCl as the Cl source (*Angew. Chem., Int. Ed.* **2008**, *47*, 5758−5760). Products obtained from terminal olefins showed excellent Markovnikov selectivity, with no linear chlorides observed. A wide range of functional groups tolerates the mild reaction conditions (EtOH, rt), and all the components are commercially available or can be easily prepared. The authors propose that the reaction mechanism involves olefin hydrocobaltation followed by interception of the organocobalt or derived radical by TsCl. This proposal is analogous to the one considered for cocatalyzed hydrohydrazination and hydroazidation reactions (see *J. Am. Chem. Soc.* **2006**, *47*, 11693−11712).



A New Class of Radical Hydrogen Atom Donor

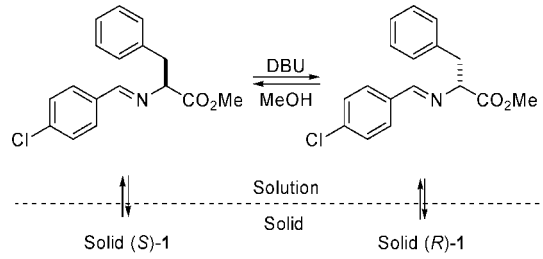
The toxicity of trialkyltin hydrides limits their use as radical hydrogen donors in chemical processes. Scientists from the University of Pittsburgh and the UMR CNRS-Paris found that complexes of nitrogen−heterocyclic carbenes (NHC) and boranes have B−H bonds with dissociation energies (BDE) within the range of Bu_3Sn−H (74 kcal/mol), making them competent radical hydrogen donors (*J. Am. Chem. Soc.* **2008**, *130*, 10082−10083). The NHC−borane complexes are air-stable, solid crystalline compounds, easily assembled from reaction of BH_3−THF and the corresponding carbene. The complexes were tested in a series of Barton−McCombie deoxygenations using AIBN or BH_3−O_2 as radical initiators. In typical experimental conditions, xanthates **1** were reacted with NHC boranes **2** and a radical initiator in benzene to yield the corresponding deoxygenated products **3** (63−84% yield) after workup and purification.





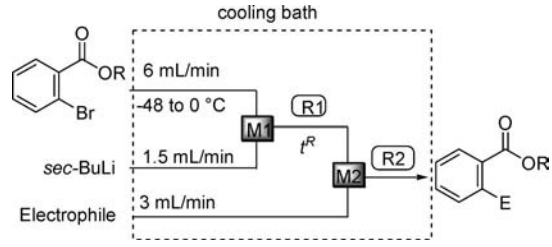
Direct Resolution: Attrition-Enhanced Deracemization

Total enantiomeric transformation can be attained by the combinations of direct resolution with racemization in solution. The abrasive grinding of the solid phase of nearly racemic amino acid derivatives with glass beads in contact with a saturated solution—in which racemization takes place—allows it to evolve to a single chiral end state. Using Monte Carlo simulations, scientists from Radboud University, Nijmegen, and DSM Pharmaceutical Products in The Netherlands showed that two processes are responsible for the deracemization, namely continuous attrition of crystals and Ostwald ripening—i.e., the dissolution of smaller crystals in favor of large ones (*Angew. Chem., Int. Ed.* **2008**, *47*, 5451−5455). In a subsequent paper, the authors successfully apply the methodology to the direct resolution of *N*-(4-chlorobenzylidene)phenylalanine methyl ester **1** (*Angew. Chem., Int. Ed.* **2008**, *47*, 7726−7729). This process was plagued by challenges; the compound crystallizes as conglomerates, and the crystal shows mutual epitaxial growth since a monocrystalline film of one enantiomer is deposited on a monocrystalline film of the opposite enantiomer, making enantiomeric seeding useless. Experimental details are deceptively simple: nearly racemic mixtures of **1** [0.35% ee (*R*)-**1**] were suspended in MeOH and ground by magnetic stirring in the presence of glass beads at room temperature. Once the equilibrium between the solution and solid states had been reached (∼24 h), racemization in solution was initiated by the addition of DBU (10 mol %). After 4−5 days, the solid phase quantitatively converted to (*R*)-**1**, with ee's >99% as measured by HPLC.

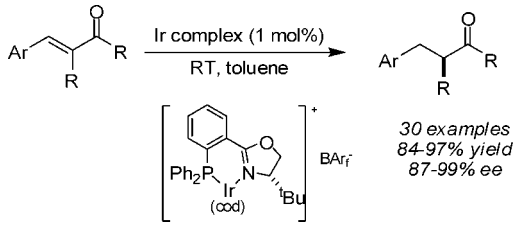


Microreactors: Generation and Reaction of Highly Reactive Aryllithiums

Yoshida and co-workers report the generation of highly reactive aryllithium compounds and their subsequent reaction with electrophiles by using microflow systems (*Angew. Chem., Int. Ed.* **2008** *47*, 7833−7836). Aryllithiums bearing alkoxycarbonyl groups are traditionally difficult to prepare in batch operations because they react with the alkyllithium reagent during the Br/Li exchange. The Br/Li exchange of alkyl *o*-bromobenzoates (R = *t*Bu, *i*Pr, Et, Me) was examined in a microflow system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) at different temperatures and residence times in R1 (t_R = 0.01−10 s). The resulting contour map provided optimized conditions for the Br/Li exchange of each of the alkyl *o*-bromobenzoates, which reacted with different electrophiles (MeI, Me_3SiCl, PhCHO, and ROH) to yield the addition products in acceptable yields (62−96%).



Highly Enantioselective Synthesis of Optically Active Ketones by Iridium-Catalyzed Asymmetric Hydrogenation

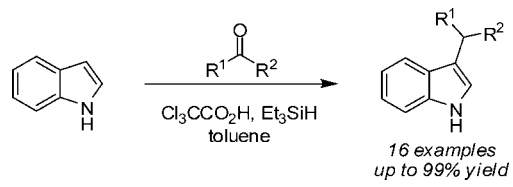


An attractive method for the enantioselective synthesis of α-substituted ketones is the asymmetric hydrogenation of α-substituted enones. Until recently, hydrogenations of this type have been limited to cyclic substrates. In the pursuit of a more general catalyst, Lu and Bolm at Aachen University have described an iridium−phosphinooxazoline (phbox) catalyst that is applicable to hydrogenations of both cyclic and acyclic substrates with aryl monosubstitution at the β-position (*Angew. Chem., Int. Ed.* **2008**, *47*, 8920−8923). With acyclic enones, the catalyst performs admirably in toluene at room temperature with 2 bar (29 psi) hydrogen to afford products in good yields with excellent enantioselectivities. Various electron-donating or electron-withdrawing substituents on the aryl group as well as varying substitution pattern on the ketonic moiety had little effect on either yield or enantioselectivity. In the case of cyclic substrates, exocyclic enones with aryl substitution at the β-position were reduced cleanly regardless of ring size or substituents on the aryl group. Unfortunately, the catalyst is not as selective when alkyl groups are introduced at the β-position of the enone on either the cyclic or acyclic substrates (87%−91% ee).

A Convenient Method for the Preparation of Heterocyclic *N*-Oxides Using Urea-Hydrogen Peroxide

A new method for the synthesis of heterocyclic *N*-oxides using a stable, solid oxidant has been disclosed by Wheelhouse and co-workers (*Tetrahedron Lett.* **2008**, *49*, 6933−6935). In situ generation of trifluoroperacetic acid is accomplished by the combination of trifluoroacetic anhydride and urea-hydrogen peroxide (an odorless, white solid containing 35% H_2O_2), circumventing the need to handle concentrated aqueous hydrogen peroxide. High yields of various substrates were obtained. The byproducts of the reaction can be removed by simple aqueous workup.

An Expedient Synthesis of 3-Substituted Indoles via Reduction Alkylation with Ketones



Procedures utilizing trifluoroacetic acid and triethylsilane in DCM at low temperatures are well-known for the reductive alkylation of indoles with aldehydes (see *Tetrahedron Lett.* **1993**, *34*, 1529−1532 and *Tetrahedron Lett.* **2003**, *44*, 4589−4591). However, when applied to ketones, these conditions produce little of the desired product. This issue has been addressed by Zhang and co-workers (*Tetrahedron Lett.* **2008**, *49*, 6749−6751) through the use of trichloroacetic acid and triethylsilane to produce 3-substituted indoles in one step without the need for protecting groups. The authors found that addition of a premixed solution of ketone and indole to a heated solution of trichloroacetic acid and triethylsilane in toluene produced desired products in high yields. Both aliphatic and aromatic ketones were tolerated, although yields were lower as the steric hindrance of the ketones increased. The chemistry failed when 4-bromo or 4-nitroindole were employed, attributed to both steric and electronic reasons. This protocol has been demonstrated on multikilogram scale.

(Cu−Ni/C): A Bimetallic, Heterogeneous Catalyst for Cross-Couplings

Transition-metal-based heterogeneous catalysis offers attractive opportunities in "green" chemistry. Aside from features commonly highlighted in this regard, including simplicity of workup, recyclability, and minimization of metallic waste, solid supports have the potential to house more than one metal and, hence, catalyze multiple types of bond constructions.

A new heterogeneous catalyst composed of copper and nickel oxide particles supported within charcoal has been developed by Lipschutz, B. H. et al. (*Org. Lett.*, **2008**, *10*, 4279). It catalyzes cross-couplings that traditionally use palladium, nickel, or copper including Suzuki−Miyaura reactions, Buchwald−Hartwig aminations, vinylalane alkylations, etherifications of aryl halides, aryl halide reductions, asymmetric conjugate reductions of activated olefins (three examples, 90−99%), and azide-alkyne "click" reactions (four examples 89−99%).

Cu−Ni/C catalyzes Suzuki−Miyaura couplings of aryl bromides and chlorides with aryl boronic acids in good yields (five examples, 78−92%). Anilines and diarylamines can be formed from aryl halides and primary or secondary alkyl- or arylamines using Cu−Ni/C ligated with DPPF (diphenylphosphinoferrocene; 1−2 equiv relative to Ni; eight examples, 79−96%). Heterogeneous reductions (dehalogenation) of aromatic chlorides can be smoothly accomplished with Cu−Ni/C ligated with PPh_3, along with commercially available $Me_2NH\cdot BH_3$ as a stoichiometric and mild hydride source (three examples, 92−100%).

Etherification of both activated and deactivated aryl bromides can be achieved using Cu−Ni/C, in this case best achieved with a loading of 5% of each metal. 1,10-Phenanthroline was used as a ligand for copper and Cs_2CO_3 as base (five examples, 78−95%). Reactions were heated to 200 °C with microwave irradiation.

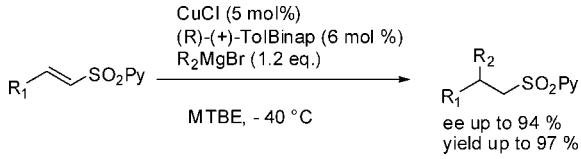
For a review of this area by Lipshutz see: *Aldrichim. Acta* **2008**, *41* (3), 59−72.

Catalytic Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Sulfones

The conjugate addition of organometallic reagents to α,β-unsaturated compounds is one of the most versatile methods for the formation of C−C bonds.

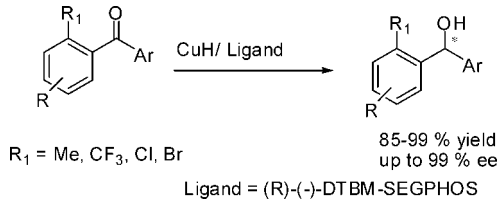
A highly efficient method is reported for the asymmetric conjugate addition of Grignard reagents to α,β- unsaturated 2-pyridylsulfones, Feringa, B. L. et al. (*Org. Lett.* **2008**, *10*, 4219). Using a Cu/TolBinap complex, excellent enantioselectivities and high yields are obtained for a wide variety of aliphatic substrates. This procedure has a broad scope for

aliphatic substrates and provides β-substituted 2-pyridyl sulfones in both excellent yields (88−97%) and enantioselectivities (88−94%). These enantioenriched sulfones are versatile intermediates in the preparation of a wide variety of functionalized chiral building blocks.

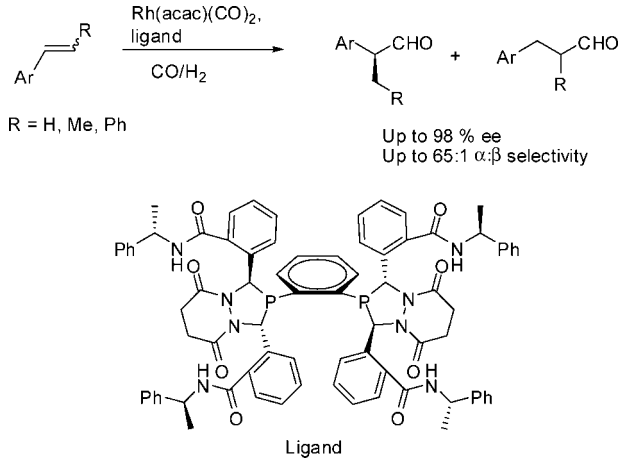


Nonracemic Diarylmethanols from CuH-Catalyzed Hydrosilylation of Diaryl Ketones

An efficient method for the synthesis of asymmetric diarylmethanols has been developed by Lipschutz, B. H. et al. (*Org. Lett.* **2008**, *10*, 4187). The use of (*R*)-(−)-(DTBM-SEGPHOS)CuH effects highly enantioselective 1,2-hydrosilylation of prochiral diaryl ketones. This technology offers an attractive alternative to traditional carbon-based organometallic nucleophiles (zinc/boron reagents) and hydrogenations, as well as to the recently reported enzymatic reductions that do not rely on ortho-substitution on one of the aromatic rings. CuH-catalyzed additions involve very mild conditions, atmospheric pressures, and an economically appealing transition metal.



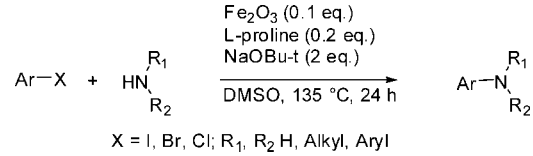
Highly Enantioselective Hydroformylation of Aryl Alkenes with Diazaphospholane Ligands



Asymmetric, rhodium-catalyzed hydroformylation of terminal and internal aryl alkenes with diazaphospholane ligands is reported by Landis, C. R. et al. (*Org. Lett.* **2008**, *10*, 4553). Under partially optimized reaction conditions, high enantioselectivity (>90% ee) and regioselectivities (up to 65:1 α:β) are obtained for most substrates. For terminal alkenes, both enantioselectivity and regioselectivity are proportional to the carbon monoxide partial pressure, but independent of hydrogen pressure. Hydroformylation of para-substituted styrene derivatives gives the highest regioselectivity for substrates bearing electron-withdrawing substituents.

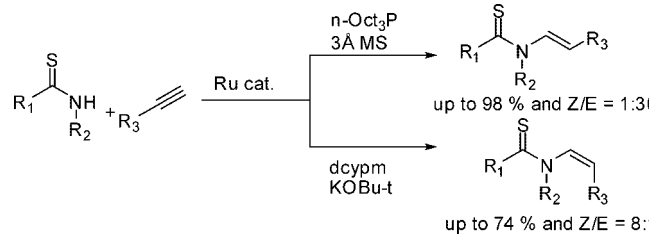
Efficient Iron-Catalyzed N-Arylation of Aryl Halides with Amines

A practical and promising protocol was developed by Guo, D. et al. (*Org. Lett.* **2008**, *10*, 4513) for N-arylations of various amines with differently substituted aryl halides. The processes are efficiently promoted by the catalyst system involving the environmentally benign Fe_2O_3 and the universal ligand L-proline. The versatility, convenient operation, low cost, and environmental friendliness, in combination with the high yields, render this method viable for use in both laboratory research and larger industrial scales.



Ruthenium-Catalyzed Stereoselective Anti-Markovnikov Addition of Thioamides to Alkynes

A catalyst system generated *in situ* from bis(2-methallyl-)cycloocta-1,5-diene-ruthenium(II) (Ru cat.) and a phosphine was found by Goossen, L. J. et al. (*Org. Lett.* **2008**, *10*, 4497) to efficiently catalyze the addition of thioamides to terminal alkynes with exclusive formation of the anti-Markovnikov thioenamide products. The stereoselectivity of the addition is usually high and controlled by the choice of the phosphine ligand; whereas the (*E*)-isomers are predominantly formed in the presence of tri(*n*-octyl)phosphine, the use of bis(dicyclohexylphosphino)methane preferentially leads to the formation of the (*Z*)-configured thioenamides. Various thioenamides can thus be obtained in high regio- and stereoselectivities, among them substrates attractive for further derivatization, for example, trimethylsilyl-thioenamides for cross-couplings and thiodienamides for hetero-Diels−Alder reactions.



Novel Syntheses of Azetidines and Azetidinones

Four-membered monocyclic aza-heterocycles, despite their indisputable importance as bioactive compounds and pharmaceutical tools, have received by the chemical community little interest compared to the interest for the higher homologous counterparts. The greatest interest was obviously gathered by azetidine-2-ones (β-lactams) for their key role in antibacterial activity, but still the main object of study was the synthesis of bicyclic fused compounds for their relationship with natural antibacterial agents. The lower general interest in azetidines is probably due to their strained nature and the difficulty of formation

of the four-membered ring, thereof. Brandi, A. et al. (*Chem. Rev.* **2008**, *108*, 3988) have reviewed the most recent methods for the synthesis of these four-membered ring systems, focusing on the stereoselective methods. The impressive summary of new research described in the review regarding four-membered aza-heterocyclic compounds attests to the importance they assume in the chemistry of organic compounds. The recent syntheses of these ring systems have much profited from the most modern synthetic methods derived from other fields of organic synthesis. In this sense, the biggest impact has been offered by the explosion, in recent years, of transition metal catalysis. Nevertheless, the challenge enforced by the four-membered ring formation has encouraged the researchers to modify or render more efficient synthetic methodologies, with a consecutive feedback to other synthetic tasks. The main challenge for the future remains still the design of general methods for obtaining enantiopure compounds and, in particular, the extension of the most efficient recent methods described to asymmetric synthesis, with special attention to transition-metal-catalyzed reactions.

Update 1 of: Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions

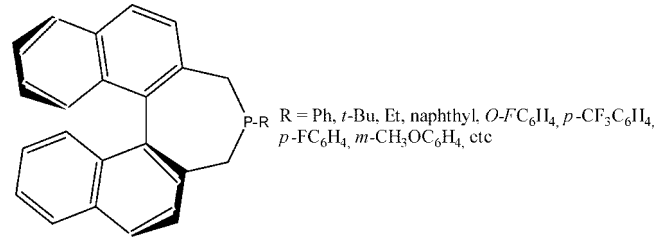
Very few fields in chemistry have held such a considerable interest as fluoroorganic chemistry. Fluorine is perhaps the element that has experienced the greatest recent interest as pointed out by the exceptionally high number of publications and the high percentage of fluorinated new molecules over recent decades. Today, the significant expansion in the use of fluorinated chemicals has attracted the attention of organic, agricultural, medicinal, and material chemists. Outstanding progress has been recently made in the development of reagents and methodologies in asymmetric fluorination, trifluoromethylation, and perfluoroalkylation as reviewed by Ma, J.-A. and Cahard, D. (*Chem. Rev.* **2008**, *108*, PR1−PR43). High levels of diastereoselectivity are frequently observed in nucleophilic and electrophilic fluorination as well as in nucleophilic perfluoroalkylations (CF3 and Rf), whereas diastereoselective electrophilic perfluoroalkylations clearly require more investigations to elevate these reactions to the high standard of diastereoselective synthesis.

Hydroamination: Direct Addition of Amines to Alkenes and Alkynes

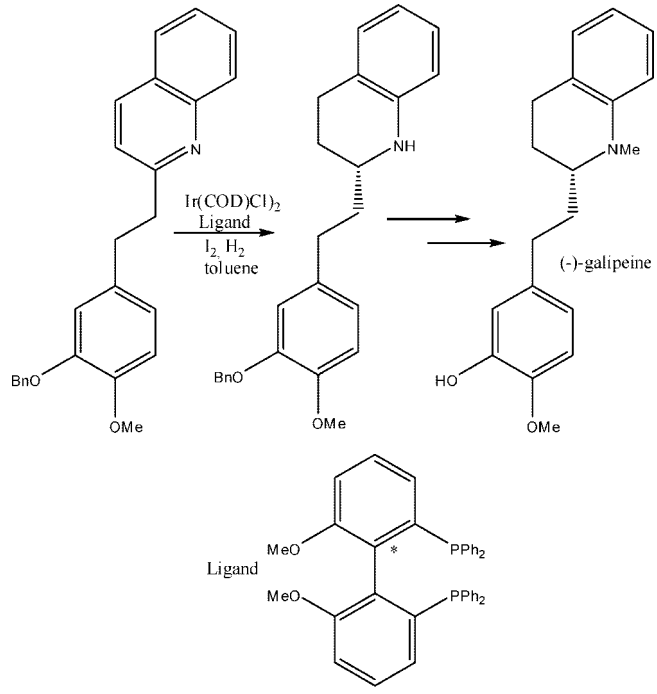
Nitrogen-containing compounds, such as amines, enamines, and imines, are valuable and commercially important bulk chemicals, specialty chemicals, and pharmaceuticals. Among various synthesis routes, hydroamination, the direct formation of a new C−N bond by addition of an amine to an unsaturated CC bond, is of particular significance (Müller, T. E. et al. *Chem. Rev.* **2008**, *108*, 3795). The reaction offers an atom-efficient pathway starting from readily accessible alkenes and alkynes. The hydroamination of alkenes is more difficult compared with that of alkynes because of the lower reactivity and electron density of C═C bonds. A particular challenge is the reversal of the regiochemistry to obtain the anti-Markovnikov product. During recent years, hydroamination became a widely explored operation in the synthesis of nitrogen heterocycles and complex molecules. The Markovnikov addition of protected amines to alkynes is now an established synthesis strategy. With the development of a new generation of catalysts, the addition of protected amines to alkenes will quickly become a routine reaction. More challenging and, thus, demanding further development time is the conversion of strongly basic amines, such as ammonia, as well as achieving adequate control of the regioselectivity in anti-Markovnikov fashion.

Chiral Catalysis

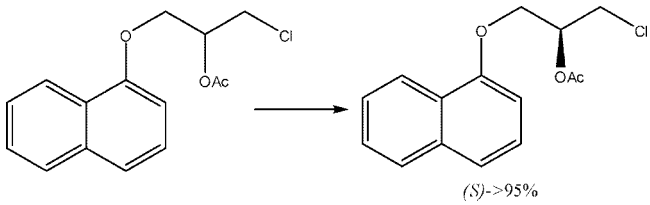
A special number of *Coordination Chemistry Reviews* was devoted to chiral catalysis. The first review (Beller and co-workers, *Coord. Chem. Rev.* **2008**, *252*, 471) covered the synthesis and the application of chiral monodentate phosphines in asymmetric hydrogenation. Several chiral phosphines (phosphanes) with industrial applications were reported, including the very important 4,5-dihydro-3*H*-dinaphtho-[2,1-*c*;1,2-*e*]phosphepines.



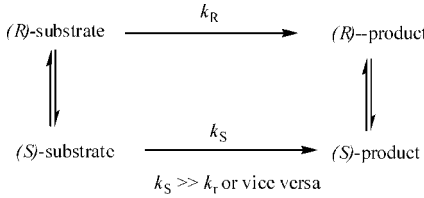
Following this, Church and Andersson (*Coord. Chem. Rev.* **2008**, *252*, 513) described the use of iridium catalysts in the reduction of olefins carrying nontraditional substituents. Of pharmaceutical importance, for example, asymmetric reduction of quinolines, pyridines, and pyridinium salts was described to proceed with excellent ee's and ed's, as exemplified for (−)-galipeine.



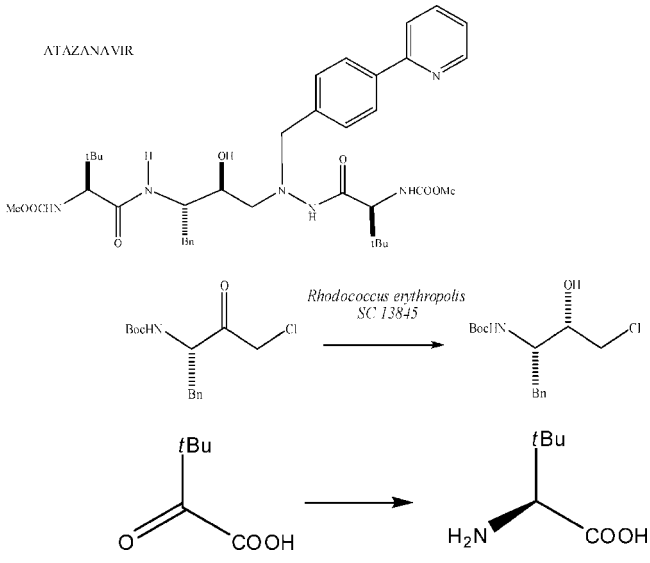
Kamal and co-workers listed a series of applications of enzyme kinetic resolutions (*Coord. Chem. Rev.* **2008**, *252*, 569) applied, for example, in the production of an (*S*)-propanolol intermediate and many other compounds of industrial importance.



Related to this field was listed a series of (transition metal) catalysts to be used in racemization (Ahn et al. *Coord. Chem. Rev.* **2008**, *252*, 647).



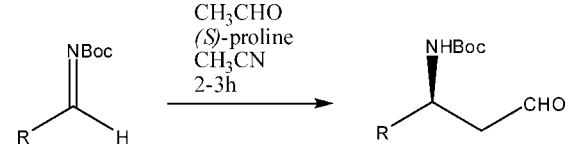
Patel (*Coord. Chem. Rev.* **2008**, *252*, 659) covered biocatalysis as applied to the production of pharmaceuticals including intermediates to anti-HIV drugs, such as atazanavir among others. For example, microbial reduction to the key intermediate and *tert*-leucine production that involved recycle of NAD.



In the same arena, Servi, Tessaro, and Pedrocchi-Fantoni (*Coord. Chem. Rev.* **2008**, *252*, 715) listed a series of protocols to obtain non-natural amino acids by chemo-enzymatic deracemization, including the use of hydantoinase which can be applied to phenylglycine (or *tert*-leucine) building blocks for antibiotics (or antivirals). Pan and Wang (*Coord. Chem. Rev.* **2008**, *252*, 736) covered C−C bond formation in aqueous media, including organic catalytic protocols.

Organic Catalysis

List's group (*Nature* **2008**, *252*, 736) reported a series of reactions of acetaldehyde catalyzed by (*S*)-proline. Ee's were excellent, and this methodology has an enormous importance to those dealing with process development. γ-Ethanolamines, β-amino acids, and many other important key intermediates can be built using this technology.



An Alternate Crystal Form of Gabapentin: A Cocrystal with Oxalic Acid

In addition to polymorphs, salts and solvates, cocrystals became recently an alternative for API form development, both for physical properties improvement (solubility), as well for intellectual properties considerations. Because of the novelty of the field, cocrystal design continues to exhibit certain challenges. More importantly perhaps from a practical perspective, experimental and classification challenges also exist. In a communication from Bernstein's group (Wenger, M. et al. *Cryst. Growth Design* **2008**, *8*, (5), 1595) the formation of a gabapentin cocrystal is reported. This cocrystal was obtained using a traditional crystallization method based on slow evaporation at room temperature. Just as with other crystal forms, using different methods, in this case two different gabapentin forms were prepared under different experimental conditions. For example, judging by the measured XRPD, the cocrystal obtained in a high-throughput series of experiments was different from the cocrystal produced by a traditional crystallization method. The latter was also obtained as a single crystal, whose crystal structure was determined. The asymmetric unit in the *cocrystal* contains one gabapentin *protonated* molecule, and half a molecule of *doubly ionized* oxalic acid, thus exhibiting an overall stoichiometry of 2:1 (gabapentin/oxalic acid). Interestingly, the authors conclude that the "cocrystallization reported here results formally in the formation of a salt". A possible explanation is offered, the authors indicating that "the element of design should be taken into account in determining whether a product should be considered a cocrystal or not..."

Polymorphic Perversity: Crystal Structures with Many Symmetry-Independent Molecules in the Unit Cell

If cocrystals have the justification of novelty regarding nomenclature issues, what can we say about the better-known polymorphs? A distinguished group of academic experts in the field offer their opinion, perhaps not as encouraging as one would like it to be (Bernstein, J., Dunitz, J. D., and Gavezotti, A. *Cryst. Growth Design* **2008**, *8*, (6), 2011). Even though, for a suitable challenge, the authors focused on the case where $Z' > 2$ (Z' = the number of symmetry-independent molecules in the asymmetric unit), their conclusions are also of more general interest. For a useful overview of crystalline systems with $Z' > 1$, a Web site from Professor's Steed's group at Durham University (http://www.dur.ac.uk/zprime/) is quoted. Because "we are almost totally ignorant of the nucleation process", we disagree with the description of high Z'-structures as "snapshot pictures of early stages in crystallization".

Using suitable search criteria, the authors focused on 138 such crystalline systems found in the Cambridge Structural

Database. One general recommendation for crystal structure comparisons is to use, in addition to the traditional experimental and simulated XRPD data (associated with some subjectivity), also distance/energy (*R*/*E*) plot calculations describing the molecular coordination sphere in an organic crystal. The authors encourage caution in handling crystallographic data and emphasize that "...what used to be merely a minor imprecision may turn today into a major nuisance, because the drive to discover new polymorphs...may sometimes be propelled by imagination rather than based on fact." The authors believe that when polymorphs with different *Z*′'s exist, the more stable polymorph is likely to be that of higher *Z*′. A longer-term goal remains the identification and control of the physical factors that promote the formation of multimolecular asymmetric units in organic crystals.

Benchtop-NMR and MRI: A New Analytical Tool in Drug Delivery Research

Even though the use of NMR and MRI in drug delivery research has been reported in the past decade, because of high installation and running costs these technologies have been of limited application. In contrast, lower cost, commercially available benchtop (BT) NMR systems, using a permanent rather than a superconducting magnet, have been successfully used in the chemical and food industries. Due to their low resolution, such instruments were not used for spectral or image acquisition, but rather for process monitoring and the measurement of total amounts of different materials. A recent short review (Metz, H. et al. *Int. J. Pharm.* **2008**, *364*, 170) focuses on BT-NMR and BT-MRI applications in drug delivery research. Rather convincing images are shown for the monitoring of the hydration and swelling of a hydroxy-propyl-methyl-cellulose (HPMC) tablet. Even more impressive are images produced using the BT-MRI technique for the investigation of double-layer tablets, comparing a successful with an unsuccessful formula. It will be interesting to observe the spread of the BT-NMR and MRI methods for PAT/QbD applications.

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