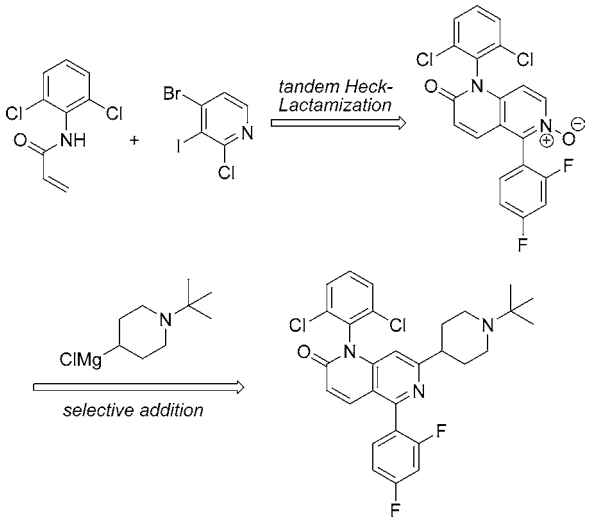
Organic Process Research & Development **2007**, *11*, 2–12

Highlights from the Literature

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

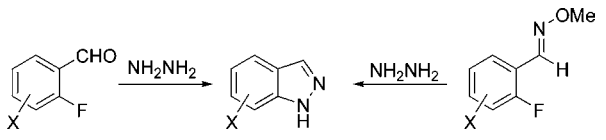
Synthesis of a Naphthyridone p38 MAP Kinase Inhibitor



p38 Map kinase inhibitor

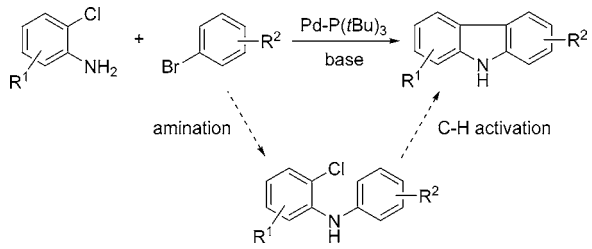
Chung, Cvetovich and co-workers at Merck describe their efforts towards the kilogram-scale synthesis of a p38 MAP kinase inhibitor, potentially useful for the treatment of rheumatoid arthritis and psoriasis (*J. Org. Chem.* **2006**, *71*, 8602−8609). A six-step synthesis suitable for large-scale preparation was developed. Key steps included a tandem Heck-lactamization, *N*-oxidation, and a selective Grignard addition to a naphthyridone *N*-oxide. The essentially complete chemoselectivity observed during addition of the Grignard reagent to the *N*-oxide was attributed to precomplexation of negatively charged oxygen to the magnesium. Under alternative reaction conditions, competing 1,4-addition to the enelactam functionality was observed. The dihydropyridyl adduct obtained directly after Grignard addition was aromatized in situ by reaction with isobutylchloroformate followed by thermal fragmentation in pyridine. Syntheses of Grignard precursor, *N*-*tert*-butyl-4-chloro-piperidine, were accomplished via transamination with a quaternary ammonium piperidone or via addition of methylmagnesium chloride to an iminium ion. Multikilogram-scale experimental procedures are provided.

Practical Synthesis of Indazoles From *O*-Methyloximes



Lukin and co-workers at Abbott report on a practical synthesis of indazoles via reaction of *o*-fluorobenzaldehydes and/or their *O*-methyloximes with excess hydrazine (*J. Org. Chem.* **2006**, *71*, 8166−8172). High yields of indazoles (70−85%) were obtained in the condensations of aldehydes with various substitution patterns with the exception of those possessing electron-donating groups in the 5-position and the unsubtituted *o*-fluorobenzaldehyde. The yields of indazoles prepared from the nonoptimal aldehydes were lower due to competitive Wolf−Kishner reduction. This side reaction was effectively suppressed via utilization of *O*-methyloxime derivatives of the aldehydes for the condensation with hydrazine. All studied aldehydes (with the exception of the poorly reactive 5-methoxy compound) were efficiently converted into the corresponding indazoles using the methyloxime method. A side reaction, resulting in the formation of 3-aminoindazoles, was observed in the experiments with oximes possessing relatively high levels of *Z*-isomers. The aminoindazole side products were formed from *Z*-isomers of these oximes, via the corresponding nitrile intermediates under the reaction conditions.

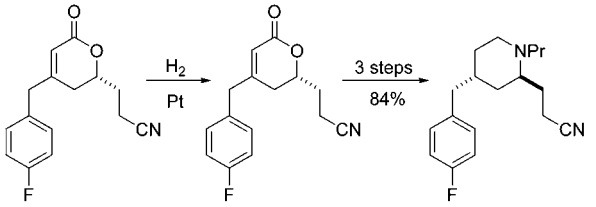
N-H Carbazole Synthesis from 2-Chloroanilines



N-H carbazoles can be produced from 2-chloroanilines and aryl bromides via consecutive catalytic amination and C−H activation, as reported by Bedford (*J. Org. Chem.* **2006**, *71*, 9403−9410). In certain cases, this can be done in a tandem manner in one pot, although microwave promotion was usually necessary. Interestingly, in the system used for the optimization studies (R^1 = H, R^2 = 4-OMe), both the amination and C−H activation reactions were successful under identical conditions when the reactions were conducted separately but failed when a one-pot process was attempted. The use of microwave heating apparently facilitated the one-pot reaction in this case. The methods developed can be used in the synthesis of a range of carbazoles, including the natural products Clausine P and glycozolidine and a precursor in the synthesis of Clausines H, K, O, and 7-methoxy-*O*-methylmukonal, and can be extended to the synthesis of indoles.

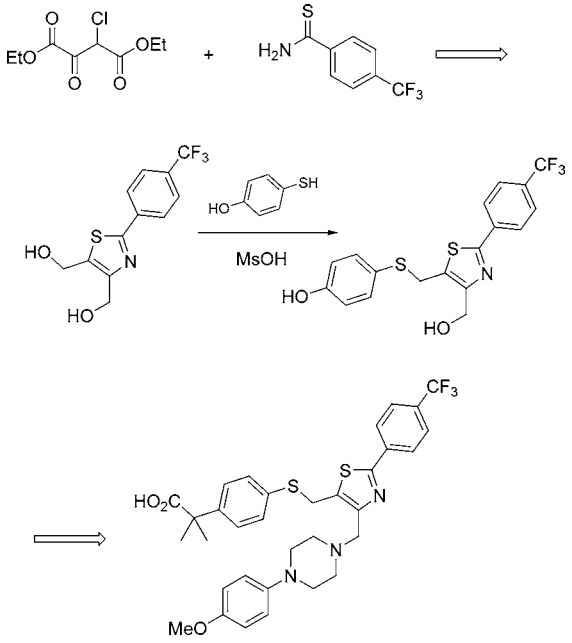
Published on Web 01/19/2007
10.1021/op600268a CCC: $37.00

Enantioselective Synthesis of *trans*-2,4-Disubstituted Piperidines



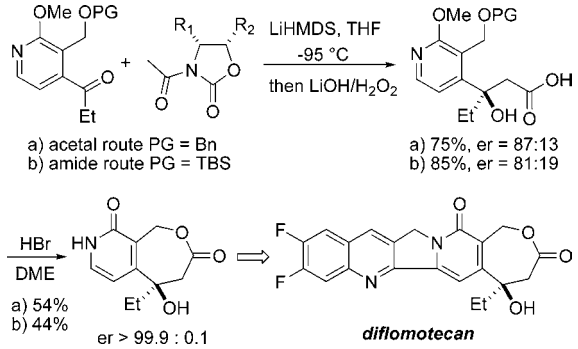
A strategy for the enantioselective synthesis of *trans*-2,4-disubstituted piperidines is reported by Nugent and co-workers at Bristol-Myers Squibb (*J. Org. Chem.* **2006**, *71*, 8975−8977). The C2 stereocenter is derived from commercial (*R*)-epichlorohydrin, whereas the C4 stereocenter is installed via diastereoselective hydrogenation of an unsaturated lactone intermediate, which proceeds with >95:5 cis:trans stereoselectivity. Recrystallization from 2-propanol affords upgrade to >99% de and ee. Inversion of the original stereocenter via an efficient intramolecular S_N2 amination affords the piperidine core of IS811, a potent CCR3 antagonist. An improved procedure for the lithiation of ethyl propiolate is also reported.

An Efficient Synthesis of a Potent PPARpan Agonist



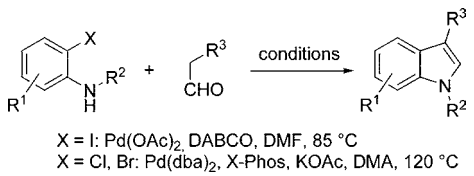
An efficient synthesis of a potent PPARpan agonist, is described by Guo and co-workers at GlaxoSmithKline (*J. Org. Chem.* **2006**, *71*, 8302−8305). The seven-step synthesis, which affords the API in 30% overall yield, includes a highly regioselective carbon−sulfur bond formation via coupling of a bis-hydroxymethylthiazole with 4-hydroxythiophenol. Consideration of the two possible carbocations produced by acid treatment of the diol led the authors to propose that the desired regiochemistry should be favored on grounds of increased stability of the cation formed from the C5 hydroxymethyl group. In the event, 13:1 regioselectivity was observed. Completion of the synthesis involved displacement of the remaining alcohol through a three-step, telescoped sequence featuring an efficient cleavage of an aryl mesylate, and a practical method for introduction of the isobutyric acid fragment.

Synthesis of Homocamptothecin Derivatives



Two asymmetric routes to the DE ring fragment of diflomotecan, a key building block in the synthesis of this homocamptothecin derivative, are described by Peters and co-workers at Hoffmann-La Roche (*J. Org. Chem.* **2006**, *71*, 7583−7595). The "acetal route" starts from 2-chloro-4-cyanopyridine, **8**, and represents an enantioselective and optimized modification of the original racemic discovery chemistry synthesis. An inefficient optical resolution procedure was replaced by an asymmetric acetate aldol addition (dr 87:13) to a ketone substrate as the key step, generating the (*R*)-configured quaternary stereocenter with high stereoselectivity. The targeted bicyclic intermediate was finally obtained in 8.9% overall yield (er 99.95:0.05) over nine steps, avoiding chromatographic purifications and comparing favorably with the initial procedure. In the related "amide route" starting from 2-chloroisonicotinic acid, **41**, a secondary amide directing group was used to facilitate the ortho lithiation of the pyridine 3-position. The key step of this protocol again involves an asymmetric acetate aldol addition (dr 87:13). The DE ring building block was thus obtained in 11.1% overall yield (er >99.95:0.05) over nine steps requiring only one chromatographic purification. In both routes, the asymmetric aldol steps required extremely low temperatures (−95 °C) for optimum results.

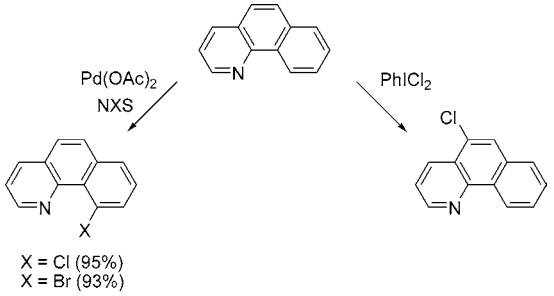
Modular Synthesis of Highly Functionalized Indoles and Tryptophans



A one-pot synthesis of indoles by a palladium-catalyzed annulation of ortho haloanilines and aldehydes is reported by the group of Zhu (*J. Org. Chem.* **2006**, *71*, 7826−7834). Although this type of reaction has been reported previously, the present work serves to expand the overall substrate scope for this process. Coupling of *o*-iodoanilines with aldehydes

can be achieved under relatively mild, phosphine-free conditions ($Pd(OAc)_2$, DABCO, DMF, 85 °C). On the other hand, Buchwald's X-Phos was found to be the ligand of choice for coupling reactions involving *o*-chloroanilines/*o*-bromoanilines and aldehydes. A variety of *o*-haloanilines with different electronic properties are suitable substrates, and aldehydes (including chiral aldehydes) participated in this reaction. Coupling of (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentanoate, derived from L-glutamic acid, with *o*-haloanilines provides a rapid access to the ring-A-substituted tryptophans in good to excellent yields.

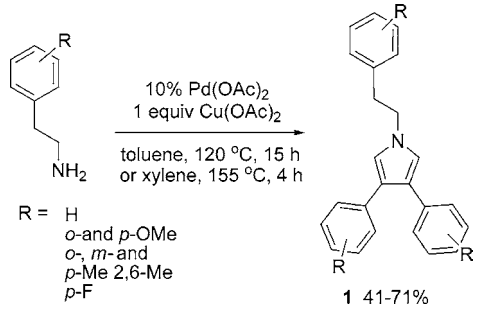
Scope and Selectivity in Pd-Catalyzed Directed C−H Bond Halogenation Reactions



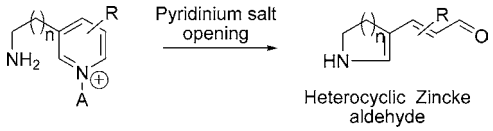
Sanford and co-workers provide a full account of their exploration of the palladium-catalyzed chelate-directed chlorination, bromination, and iodination of arenes using *N*-halosuccinimides as terminal oxidants (*Tetrahedron* **2006**, *62*, 11483−11498). In addition, preliminary results demonstrating that the halogenation of alkene and benzylic sp3 C−H bonds can also be achieved using this method. The reactions are generally tolerant toward a variety of functional groups and show wide scope with respect to directing groups. Furthermore, the dependence of reactivity of the various compounds upon the substitution pattern/electronics of the substrate as well as the ligand abilities of the directing group are delineated. In general, the products obtained from these Pd-catalyzed reactions are complementary to those obtained via traditional methods, such as electrophilic aromatic substitution and benzylic halogenation. The broad scope and often orthogonal nature of these Pd-catalyzed halogenation reactions should make them a valuable synthetic tool for accessing a more diverse array of halogenated organic molecules.

Various Syntheses of Nitrogen Heterocycles

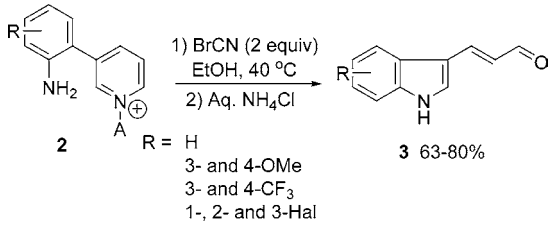
Li and co-workers from Beijing University performed the simultaneous activation of the two sp^3 C−H bonds of phenethylamines to synthesize arylpyrroles (*J. Am. Chem. Soc.* **2006**, *128*, 12046−12047). A combination of $Cu(OAc)_2$ and $Pd(OAc)_2$ is used as the catalyst. While conducting studies on deamination of commercially available phenethylamines, the scientists found that the intermediate imine can react further to yield aryl-substituted pyrroles **1** in good yields. The combination of Pd(II) and $Cu(OAc)_2$ is key for the success of the reaction. Electron-withdrawing groups (F, CF_3) decreased the efficiency of the transformation, which has as byproducts benzonitrile and phenethyl *N*-acetamide. The formation of the pyrrole involves the cleavage of 12 C−C bonds and the formation of five C−C bonds: two C−N bonds, two C═C, and a C−C one.



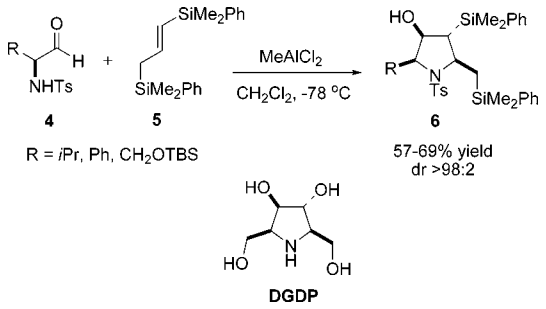
Another synthesis of nitrogen heterocycles was presented by Kearny and Vanderwal (*Angew. Chem., Int. Ed.* **2006**, *45*, 7803−7806). The authors modified a century-old transformation (the Zincke reaction) and prepared indoles by opening pyridinium salts with tethered amines. Those interested in the original chemistry can consult the seminal work by Zincke (*Justus Liebigs Ann. Chem.* **1903**, *330*, 361−374).



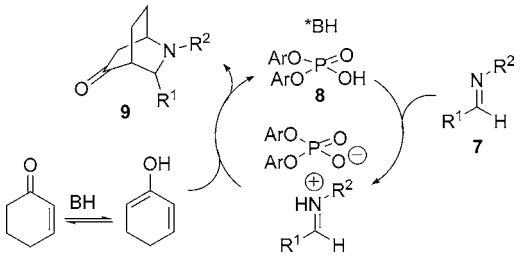
Precursor pyridyl anilines **2** were prepared by Suzuki coupling. Treatment of compounds **2** with BrCN in EtOH at 40 °C followed by aqueous NH_4Cl afforded indoles **3** in 63−80 yields. The products bear a propenal substituent at C-3, which can be used for a myriad of chemical fates (i.e., cycloadditions). The methodology was successfully applied to the synthesis of 7-azaindoles from 2-aminopyridyl pyridines.



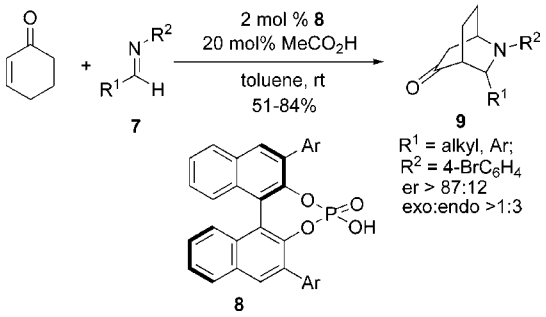
Somfai and co-workers reported the stereoselective construction of densely substituted pyrrolidines by [3 + 2] annulation of silanes and *N*-Ts-α-aminoaldehydes (*J. Am. Chem. Soc.* **2006**, *128*, 12646−12647). Bis-(1,-3-silyl)-propene **5** acts as a 1,2-dipolar synthon that adds to aldehyde **4** to afford an intermediate which is readily cyclized to yield pyrrolidine **6** with good yields and excellent diastereoselectivities. No desilylation or silyl-migration byproducts were detected. Upon evaluation of differently substituted silanes, it was found that $SiMe_2Ph$ reacted with *N*-Ts-valinal using aluminum-based Lewis acids. Since $SiMe_2Ph$ derivatives can be oxidized following a Tamao−Fleming protocol, this method provides straightforward access to polyhydroxylated pyrrolidines. To showcase the utility of the transformation, the authors prepared the glucosidase inhibitor DGDP in three steps from **6** (R = CH_2OTBS).



Isoquinuclidines are structural elements of numerous alkaloids and can be prepared from the reaction of imines with cyclohexenone. Rueping and Azap reported a new, double Brønsted acid-catalyzed reaction for the enantioselective synthesis of isoquinuclidines (*Angew. Chem., Int. Ed.* **2006**, *45*, 7832−7835). The authors used binol phosphate (10 mol %) as the chiral Brønsted acid (*BH) for the activation of the imine and acetic acid (20 mol %) as the non-chiral proton source (BH) for the shift of the keto−enol equilibrium. The cooperative Brønsted acid cycle is shown below.

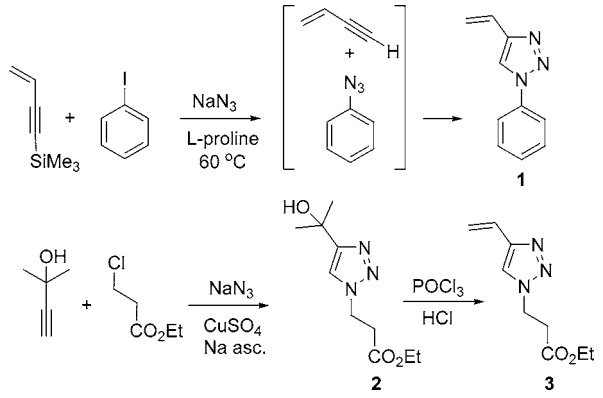


Optimized conditions used toluene as the solvent at room temperature. The reaction afforded aromatic as well as heteroaromatic substituted isoquinuclidines with different stereoelectronic patterns in good yields and selectivities.

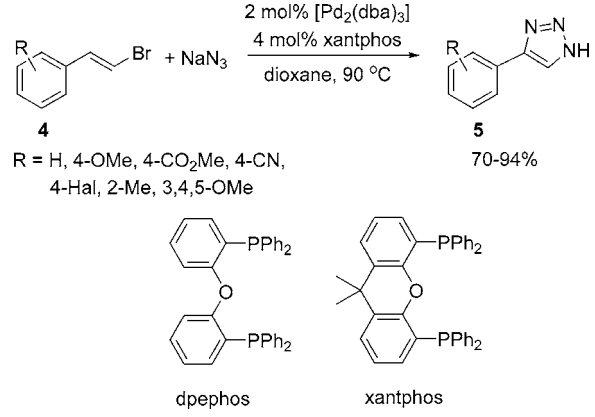


Novel Syntheses of Triazoles

The development of novel materials continuously demands vinyl monomers that are synthetically accessible and easy to derivatize. The basic monomeric unit should possess chemical and thermal stability and, upon polymerization, provide a product with unique properties. Two groups from the University of California at Berkeley and at Santa Barbara collaborated in the design of a library of functionalized 4-vinyl-1,2,3-triazoles (*J. Am. Chem. Soc.* **2006**, *128*, 12084−12085). The compounds were synthesized in high yields by two complementary methods. For the synthesis of 1-phenyl triazoles (**1**) the authors employed a one-pot transformation ("click" chemistry), using iodobenzene, 1-trimethylsilyl-2-vinylacetylene and sodium azide as the starting materials; formation of the azidobenzene intermediate is catalyzed by L-proline and Cu (I). The two-step synthesis starts from inexpensive butynol derivatives and chloropropionic esters, and involves the formation of an intermediate aliphatic azide. Hydroxytriazole intermediate **2** is readily dehydrated to afford the target vinyl triazole unit **3**. A wide range of aryl/acyl chlorides and mesylates can be used as precursors, and the combination of the two routes granted access to triazole monomers with different substituents in the *N*-1 position.

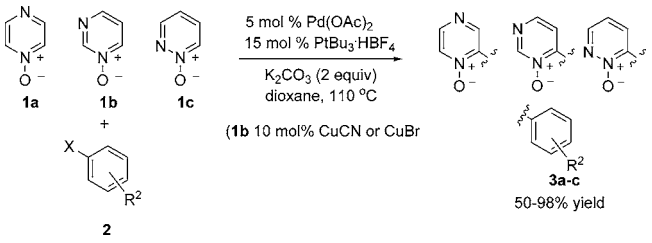


The group of Barluenga developed a new strategy for the synthesis of 1*H*-1,2,3-triazoles using Pd catalysis (*Angew. Chem., Int. Ed.* **2006**, *45*, 6893−6896). While investigating Pd-catalyzed cross-coupling reactions between alkenyl halides and azides to yield vinyl azides, 1*H*-1,2,3-triazoles were obtained as the main product. Reaction of bromostyrene **4** with sodium azide in dioxane at 90 °C afforded 1*H*-triazoles **5** in good yields. The ligand specificity of the reaction is remarkable: only the chelating diphosphines xantphos and dpephos, in which the bite angle is large, promoted the reaction. Systems substituted with electron-withdrawing or electron-donating groups provided similar results. The reaction tolerates sensitive moieties (methyl esters or nitriles), ortho substitution, and heterocycles (i.e., 2-furan). The chemoselectivity of the reaction is noteworthy, as the presence of a halide (bromide or chloride) on the aromatic ring furnishes the triazole **5** as the sole reaction product. Experimentation and computational studies allowed the authors to conclude that the reaction proceeds through a novel mechanistic pathway in which the triazole is formed by a [3 + 2]cycloaddition (either concerted or stepwise) of the azide anion with a vinylpalladium complex.



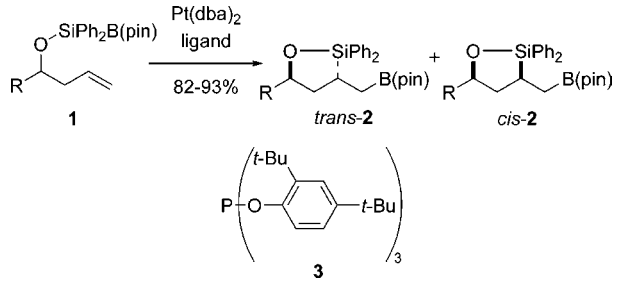
Catalytic Direct Arylation of Diazine Oxides

The deficiencies of 2-pyridyl organometallics as partners for Pd-coupling reactions and the circumvention of this problem by using stable pyridine *N*-oxides have been previously highlighted. The group of Fagnou at the University of Ottawa continues to make strides in this arena and has incorporated diazines *N*-oxides to the battery of readily available, stable reagents that be used in Pd-catalyzed biaryl couplings (*Angew. Chem., Int. Ed.* **2006**, *45*, 7781−7786). Diazine *N*-oxides present additional challenges: they are more π-electron deficient and less nucleophilic than their pyridine counterparts, and the extra nitrogen can poison the catalyst. Reaction of pyrazine (**1a**), pyrimidine (**1b**), and pyridazine (**1c**) *N*-oxides with a variety of aryl bromides, chlorides, and iodides occur in good yields. The combination of reagents and conditions previously found was used for the reaction [$Pd(OAc)_2$ (5 mol %), the air-stable HBF_4 salt of P^tBu_3 (15 mol %) and K_2CO_3 (2 equiv)], but the solvent was switched from toluene to dioxane due to limited solubility of the starting materials. In the case of aryl iodides, Ag_2CO_3 has to be added for the reaction to work, and Cu (I) salts are needed for the coupling of **1b**. *N*-oxides **3** can be deoxygenated by catalytic hydrogen transfer using ammonium formate or (**3c**) hydrogenation using PtO_2. The report includes the first examples of *N*-oxide arylation with equimolar ratios of the two coupling partners.



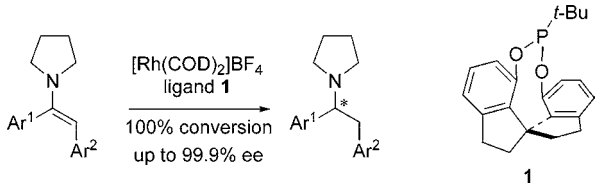
Intramolecular Stereoselective Silaboration of Alkenes

Ohmura, Furukawa, and Suginome at Kyoto University reported a Pt-catalyzed silaboration of homoallyl alcohols based on a silicon tether strategy (*J. Am. Chem. Soc.* **2006**, *128*, 13366−13367). In general, the intramolecular silaboration of borylsilanyl homoallyl ethers **1** mediated by phosphorous/Pt catalysts affords cyclic silyl ethers **2** in good yields. A typical procedure involves the use of 5 mol % Pt and 11 mol % ligand in toluene at 110 °C. Interestingly, the reaction's cis/trans stereoselectivity depends on the nature of the ligand; whereas $PCyPh_2$ affords the highest trans selectivity, the opposite selectivity is obtained in the presence of phosphite **3**. The authors correlate the reversal of selectivity with the steric hindrance of the ligands. This silaboration allows the regioselective introduction of a boryl substituent on the terminal carbon of the alkene along with the stereoselective formation of an oxasilacycle. The resulting silaboranes can be transformed in the corresponding triols under Tamao oxidation of both the C−B and C−Si bonds.



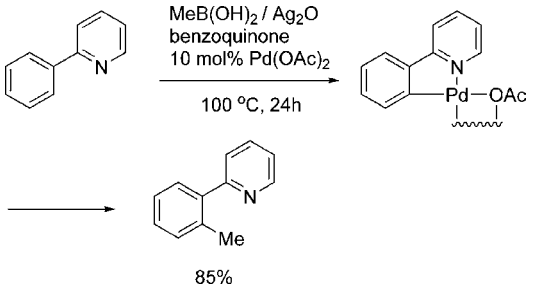
Asymmetric Hydrogenation of Enamines

The group of Professor Zhou at Nankai University (Tianjin, China) communicated a Rh(I)-catalyzed enantioselective hydrogenation of *N*,*N*-dialkylenamines using monodentate spiro phosphonite ligand **1** (*J. Am. Chem. Soc.* **2006**, *128*, 11774−11775). Laborious optimization of the reaction conditions led to the best possible combination of components $[Rh(COD)_2]BF_4$/1igand/I_2/HOAc/substrate in 1:2:2:2:20:100 ratios, where the concentration of substrate is 0.125 M in THF, and the use of 10 atm H_2 at room temperature. The Rh(I) catalyst affords full conversion with up to 99.9% ee's. The addition of I_2 significantly improved the enantioselectivities, whereas the presence of HOAc remarkably increased reaction rates. The methodology opens a window to the synthesis of chiral tertiary amines starting from readily available enamines.



Pd(II)-Catalyzed Alkylation of C−H Bonds

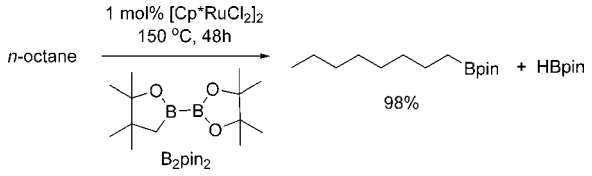
The field of C−H bond activation promoted by transition metal catalysts continues its unstoppable growth. In a recent communication, the group of Jin-Qua Yu at Brandeis University described the development of a C(sp^2)−H bond activation/-alkylation of sp^3 centres with readily available nontoxic methylboroxyne and alkylboronic acids (*J. Am. Chem. Soc.* **2006**, *128*, 12635−12636). The screening of a wide range of bases, oxidants, and solvents found that the best reaction conditions require Ag(I) salts, benzoquinone, and *tert*-amyl alcohol, respectively. Measurement of kinetic isotope effects indicated that the rate-limiting step of these reactions is the C(sp^2)−H bond cleavage. The resulting palladacycle, which contains the pyridine directing group, undergoes subsequent transmetalation to give the desired C(sp^2)−C(sp^3) bond coupling.



Ru(III)-Catalyzed Borylation of Methyl C−H Bonds

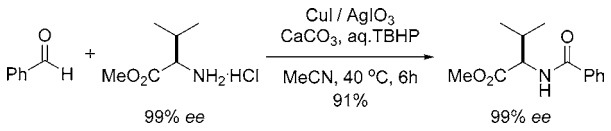
Hartwig and co-workers discovered a family of Ru complexes that serve as precatalysts for the regiospecific terminal borylation of alkanes (*J. Am. Chem. Soc.* **2006**, *128*, 13684−13685). For example, the reaction of B_2pin_2 with

octane catalyzed by 2 mol % of the Ru(III) dichloride dimer $(Cp^*RuCl_2)_2$ gives HBpin and 1-octylBpin in quantitative yield after 48 h at 150 °C. Remarkably, the C−H activation occurs preferentially with alkanes rather than with arenes, and the process tolerates the presence of heteroatoms on the substrate (i.e., ethers, fluoroalkanes, amines). The borylations occur selectively at the least hindered methyl group. In view of the low cost of Ru and its widespread use in organic synthesis, this novel transformation represents a valuable alternative to Rh catalysts for alkane functionalization.



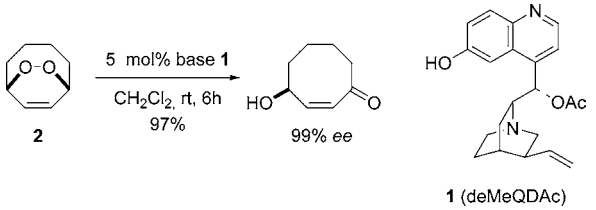
Cu(I)-Catalyzed Amidation of Aldehydes

The importance of the amide bond in science cannot be overstated. Yoo and Li (McGill University, Montreal) communicated the successful oxidative amidation of aldehydes with amine hydrochloride salts and Cu(I)/Ag(I) catalysts (*J. Am. Chem. Soc.* **2006**, *128*, 13064−13065). In general, the amidation provides the desired amides in high yields using the insoluble base $CaCO_3$, TBHP as an oxidant, and a mixture of CuI and $AgIO_3$ (1 mol %). The most plausible mechanism for the amidation involves the nucleophilic addition of the free amine to the aldehyde to generate a carbinolamine intermediate, which in turn is oxidized by the Cu(I)/TBHP system to yield the desired amides. The methodology parallels the effective oxidative esterification of aldehydes with β-dicarbonyl compounds previously described by the same authors (*J. Org. Chem.* **2006**, *71*, 6266).



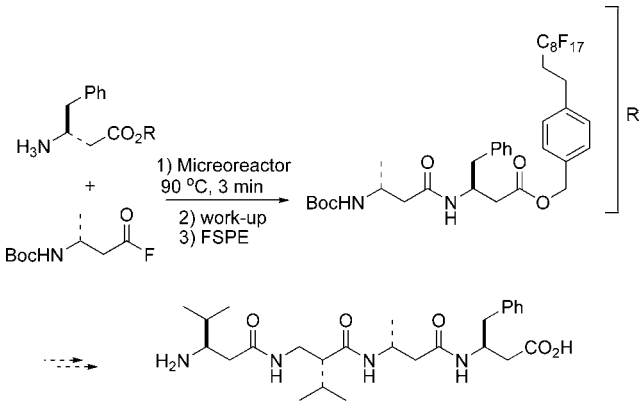
Enantioselective Synthesis of 4-Hydroxyenones

The desymmetrization of *meso*-endoperoxides might constitute a straightforward method for the enantioselective synthesis of 4-hydroxyenones. Staben, Linghu, and Toste at University of California, Berkeley, made this possibility real with the use of a chiral base-catalyzed Kornblum DeLaMare rearrangement (*J. Am. Chem. Soc.* **2006**, *128*, 12658−12659). For example, under the most favorable reaction conditions, 5 mol % of bifunctional cinchona alkaloid **1** (deMeQDAc) catalyzed the rearrangement of endoperoxide **2** to the corresponding 4-hydroxyenone in 97% yield and 99% ee. The transformation has a wide scope and is amenable to a variety of functionalized substrates. The authors propose an *E*2 elimination mechanism in which the cinchona alkaloid acts as a chiral base in consistency with measured isotope effects.



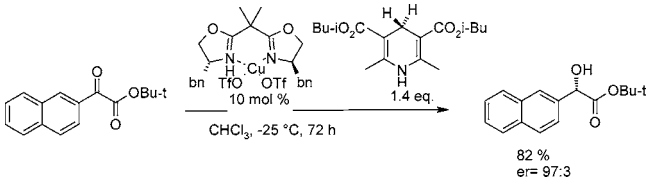
Synthesis of β-Peptides in Microreactors

Seeberger and co-workers at ETH describe the first application of a silicon continuous-flow microreactor to the assembly of synthetically useful amounts of β-peptides (*Angew. Chem., Int. Ed.* **2006**, *45*, 7000−7003). The continuous-flow microreactor used is compatible with various organic solvents and can be operated over a broad temperature range (−80 °C to +150 °C) in a simple laboratory setting. The reaction volume (78.3 μL) allows microscale reaction scanning, the execution of proof of principle, and the production of several grams of target compound. The authors use β_2- and β_3-homoamino acid fluorides for β-peptide couplings with (Boc)- and (Fmoc)-protected amino acids in 1−5 min at temperatures as high as 120 °C. In addition, they introduced a fluorosubstituted benzylic ester ($CH_2C_6H_4$-$CH_2CH_2C_8F_{17}$) as a protecting group in solution-phase peptide synthesis to facilitate the purification of intermediates by fluorous-solid-phase extraction (FSPE). Tetrapeptide **1** was obtained in 67% overall yield; using conventional glassware, poor solubility of intermediates caused mixtures difficult to stir and tedious manipulations, whereas in solid-phase synthesis the overall yield was considerably lower.



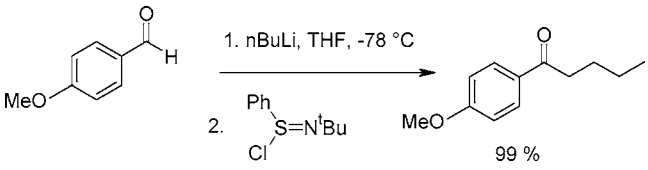
Catalytic Asymmetric Transfer Hydrogenation of α-Ketoesters with Hantzsch Esters

List, B. and Yang, J.-W. (*Org. Lett*. **2006**, *8*, 5653) have found that C_2-symmetric chiral copper(II)-bisoxazolines function as alcohol dehydrogenase mimics and catalyze highly enantioselective transfer hydrogenations of α-ketoesters with Hantzsch esters as a synthetic NADH analogue to give α-hydroxy esters in good to excellent yields and enantioselectivities. Various Hantzsch esters were evaluated, and it was found that the diisobutyl ester showed the highest reaction rate without significantly lowering the enantioselectivity.



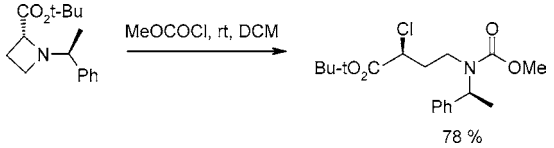
Direct and Efficient One-Pot Preparation of Ketones from Aldehydes

Kerr, W. J. et al. (*Org. Lett.* **2006**, *8*, 5073) have developed a new general one-pot process to prepare ketones from aldehydes using *N-tert*-butylphenylsulfinimidoyl chloride. By employing the developed protocol, a range of unsymmetrical ketones has been prepared in good yields from aldehydes. The process has been shown to be applicable to a variety of both aldehydes and organometallic reagents.



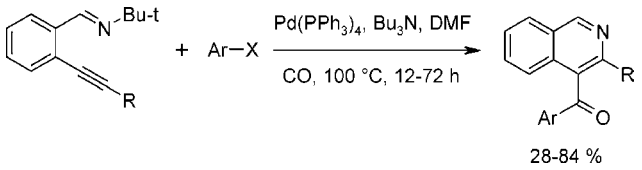
Reaction of Azetidines with Chloroformates

The reaction of tertiary amines with chloroformates, a variant of the Braun reaction developed in the 1970s by Olofson, has become a powerful tool in organic synthesis. In most cases, this procedure is especially effective for selective N-demethylation or N-debenzylation reactions which have been reported in many cases to give high yields under mild conditions. The reaction of an azetidine with chloroformate can give either the dealkylated heterocycle or the ring-opened product. Evano, G. et al. (*Org. Lett.* **2006**, *8*, 5501) have found that azetidines can undergo smooth nucleophilic ring-opening to highly functionalized γ-chloroamines in the presence of a variety of alkyl chloroformates under mild reaction conditions.



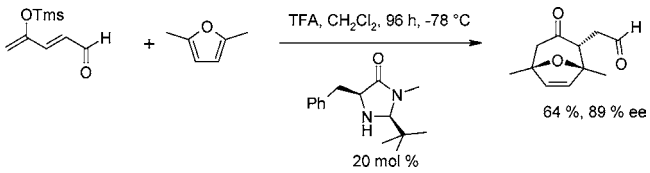
Synthesis of Heterocycles via Palladium-Catalyzed Oxidative Addition.

Zeni, G. and Larock, R. C. (*Chem. Rev.* **2006**, *106*, 4644) have in their review of the synthesis of different heterocycles presented many useful examples of palladium-catalyzed processes involving oxidation addition/reduction elimination chemistry. The chemistry has been developed to prepare heterocycles, with the emphasis on fundamental processes used to generate the ring systems themselves.



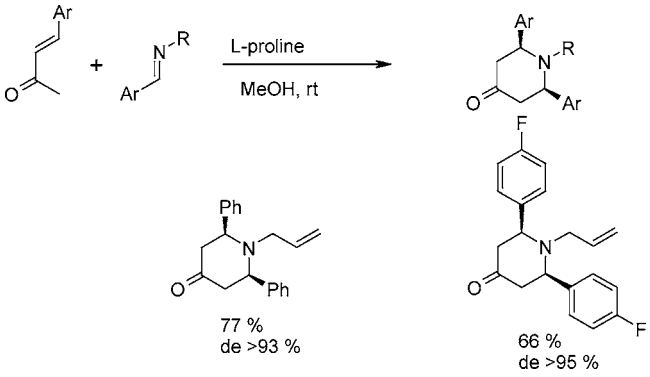
Asymmetric Catalytic [4 + 3] Cycloaddition Reactions

Harmata, M. (*Adv. Synth. Catal.* **2006**, *348*, 2297) has summarized some of the advances made in the area of absolute stereocontrol in [4 + 3] cycloaddition reactions. Although the [4 + 3] cycloaddition reaction has been investigated a lot over the past 10−15 years, only a few studies have been dedicated to the development of a catalytic, asymmetric process.



Proline-Catalyzed Imino-Diels−Alder Reactions.

Aznar, F. et al. (*Adv. Synth. Catal.* **2006**, *348*, 2443) have developed a new synthesis of *meso*-2,6-diaryl-4-piperidones by an L-proline-catalyzed imino-Diels−Alder reaction between acyclic α,β-unsaturated ketones and aldimines. The protocol uses 20 mol% of L-proline and an excess of the unsaturated ketone.

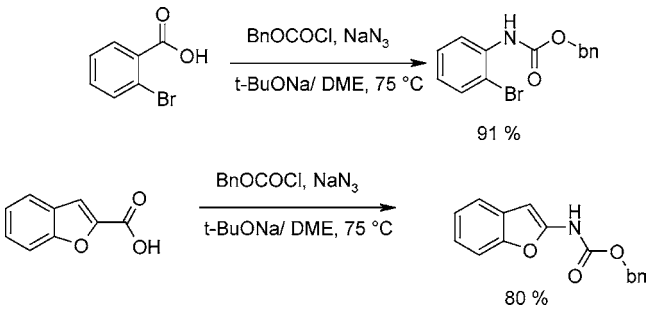


Diazonium Salts as Substrates in Palladium-Catalyzed Cross-Coupling Reactions.

Roglans, A. et al. (*Chem Rev.* **2006**, *106*, 4622) have reviewed the use of diazonium salts as substrates in cross-coupling reactions. The authors have shown that diazonium salts are attractive substrates for Heck couplings, in particular. This field has been extensively developed especially for the synthesis of natural products or other complex molecules. In the use of diazonium salts as electrophiles in the Suzuki−Miyaura coupling there are fewer reported examples, which also goes for Stille and carbon−heteroatom couplings.

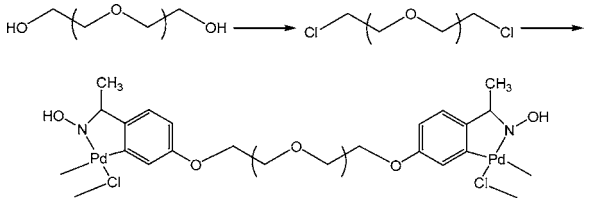
Curtius Rearrangement of Aromatic Carboxylic Acids.

Lebel, H. and Leogane, O. (*Org. Lett.* **2006**, *8*, 5717) have developed an efficient process for the Curtius rearrangement that allows the direct conversion of aromatic carboxylic acids into carbamates and ureas. The process is based on the use of commercial chloroformates and sodium azide for the in situ generation of azidoformate. The formate activates the carboxylic acid and functions as a source of nucleophilic alkoxide.

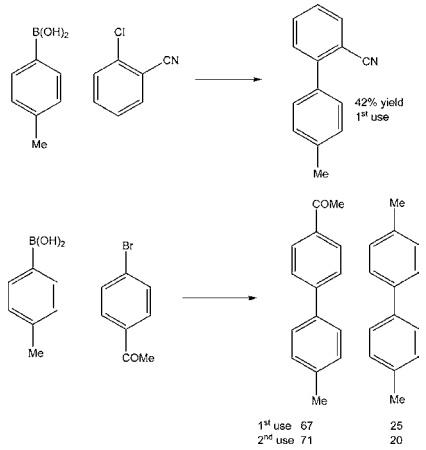


Poly(ethylene glycol)−Pd reusable systems for C−C coupling

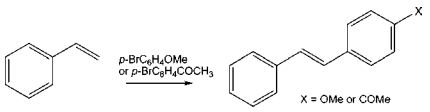
An oximecarbapalladacycle was anchored on a soluble poly(ethylene glycol) (PEG 6000 Da) scaffold (Corma, Garcia, and Leyva *J. Catal.* **2006**, *240*, 87). The system was used for different C−C cross-coupling reactions and could be successfully recycled.



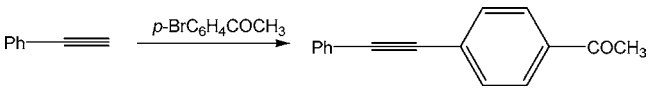
The model Suzuki system was constituted of *p*-tolylboronic acid and 2-chlorobenzonitrile or 4-bromoacetophenone. Yields were good in general but are strongly dependent on reaction media.



Heck coupling (*p*-bromoacetophenone or *p*-bromoanisole and styrene) under Cs_2CO_3 reaches 76% yield.



Sonogashira coupling was also carried out and was successful in the reaction between *p*-bromoacetophenone and phenyacetylene (yields up to 99%) while other substrates were not so successful.

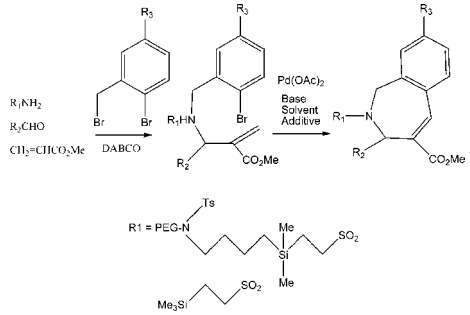


The authors explain the deactivation of the catalyst using TEM images. In their view, the formation of Pd-nanoparticles is evidence that supports the loss in catalyst activity in recycling the system. However, different groups recently described that nanoparticles can work as a catalyst reservoir; thus, a better explanation is needed.

Aza-Baylis−Hillman followed by Heck coupling

Ribière et al. (*Tetrahedron* **2006**, *62*, 10456) reported the synthesis of novel benzazepines using PEG 3400 as a soluble polymeric support.

The reaction cascade beautifully envisaged involved an aza-Baylis−Hillman reaction followed by an intramolecular Heck coupling.

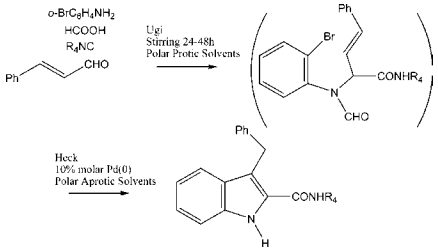


Ugi/Heck Reaction

Multicomponent reactions have been widely studied because very high atom economy is achieved in the synthesis of complex molecules.

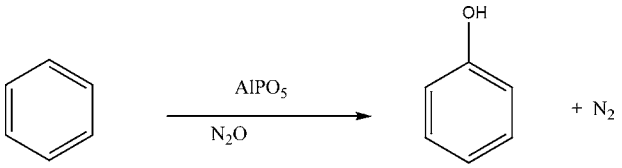
Kalinski and co-workers (*Tetrahedron Lett.* **2006**, *47*, 4683; *Tetrahedron Lett.* **2006**, *47*, 2391) have described the use of a four-component Ugi reaction combined with a Heck reaction in a one-pot protocol.

Production of indole derivatives was achieved using substituted anilines, cinnamaldehydes, carboxylic acids, and isonitriles. Under the Heck conditions the N−CHO bond is cleaved, and isomerization leads to 1H-indoles in moderate to good yields.



Selective Oxidation of Benzene to Phenol over FeAlPO Catalysts Using Nitrous Oxide as Oxidant

Direct oxidation of benzene to phenol, in contrast with the Hock reaction (oxidation of cumene), has the merit of not only utilising nitrous oxide as an oxidising agent but also the absence of acetone as a coproduct and simpler separation processes. Further hydrogenation of phenol leads to cyclohexanol very cleanly.

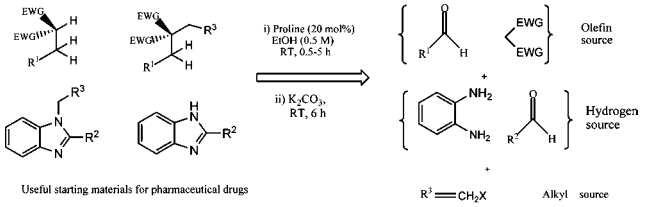


Tetrahedrally coordinated iron in framework-substituted microporous AlPO-5 catalysts are shown to be active and selective for the hydroxylation of benzene to phenol, using nitrous oxide as the oxidant. (*Chem. Commun.* **2006**, 4955−4957).

Crystallization from Ionic Liquids

A large number of papers appear every year on ionic liquids (ILs), but there is still a dearth of information on their use in crystallization. Reichert et al. have addressed this problem to suggest possible strategies for utilization of the mundane and the unique aspects of ILs for novel crystallization including high- and low-melting solids using thermal shifts, "solvothermal" techniques, slow diffusion, electrocrystallization, and use of a cosolvent. These complex, but fascinating, results and the promise of much more intimate control over crystallization processes will drive a growing interest in using ILs as crystallization solvents. (*Chem. Commun.* **2006**, 4767−4779).

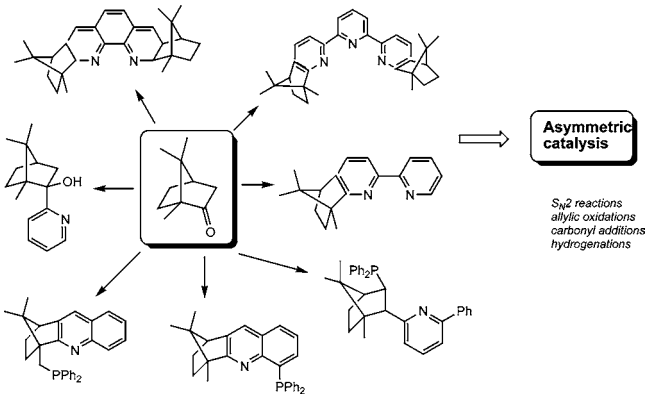
Development of Pharmaceutical Ingredients by Using Direct Organocatalytic Biomimetic Reductions



Advantages over classical reductions include (i) simple mixing of reactants in open vials, in-situ generation of both olefin and hydride, (iii) >93% chemo-selectivity, and no aqueous work-up, (iv) simple filtration for purifications, (v) very good yields

Economic and environmentally friendly biomimetic, one-pot, three- and four-component Knoevenagel−hydrogenation (K-H), five-component Knoevenagel−hydrogenation−alkylation (K-H-A) and six-component Knoevenagel−hydrogenation−alkylation−Huisgen cycloaddition (K-H-A-HC) reactions of aldehydes, CH-acids, *o*-phenylenediamine, alkyl halides, and azides using proline, proline−metal carbonate and proline−metal carbonate−Cu^{I}catalysis, respectively, have been developed. Many of K-H and K-H-A compounds have direct application in the pharmaceutical chemistry. (*Org. Biomol. Chem.* **2006**, *4*, 4463−4468).

Synthesis and Application in Asymmetric Catalysis of Camphor-Based Pyridine Ligands



The synthesis and application in asymmetric catalysis of camphor-based pyridine ligands has been reviewed by Chelucci. These ligands can be roughly divided into two groups: those in which the camphor is annulated in the 2,3-positions to the β-face of the pyridine ring and those in which the pyridine is contained as a pendent on the C2 or C3 of the camphor framework. Camphor-based pyridine ligands can also contain other donor centers located on the pyridine ring or camphor skeleton. Some of these ligands have provided interesting enantioselectivities in several asymmetric reactions, such as S_N2' reactions, allylic oxidations, carbonyl additions with organozinc reagents, and hydrogenations. This review contains a lot of chemistry on ligand synthesis, and readers will find it of value and also perhaps an inspiration for the development of more active and improved versions. **(***Chem. Soc. Rev.* **2006**, *35*, 1230−1243).

Improved Pd-on-Au Bimetallic Nanoparticle Catalysts for Aqueous-Phase Trichloroethene Hydrodechlorination

Groundwater remediation through the catalytic breakdown of the undesired contaminants is a more effective and desirable approach than the conventional physical displacement methods of air-stripping and carbon adsorption. Palladium-on-gold nanoparticles (Pd/Au NPs) have recently been shown to catalyze the hydrodechlorination of trichloroethene in water, at room temperature, and in the presence of hydrogen, with the most active Pd/Au material found to be >70 times more active than Pd supported on alumina on a per-Pd atom basis. The potential of this catalyst as a groundwater remediation technology could be improved by synthesizing Pd/Au NPs with smaller diameters and immobilizing them on a solid support. Pd/Au NPs were synthesized with a core diameter of 4 nm and with different Pd loadings and were studied in colloidal form for aqueous-phase trichloroethene hydrodechlorination. The most active catalysts were considerably more active (>1900 $L/g_{Pd}/min$) than Pd NPs (55 $L/g_{Pd}/min$) and conventionally synthesized Pd/Al_2O_3 (47 $L/g_{Pd}/min$). Accounting for a gas−liquid mass transfer effect and converting the Pd loading to Pd surface coverage using a magic cluster model for the Pd/Au NPs, the reaction rates in terms of initial turnover frequencies were >1.4, 4.35×10^{-2}, and 3.76×10^{-2} s^{-1}, respectively. These materials exhibited volcano-like catalytic activity, in which hydrodechlorination rate was maximum near 70% Pd surface coverage. Au appeared to promote catalysis through geometric and electronic effects. Immobilization of the NPs on alumina, magnesia, and silica supports yielded active oxide-supported catalysts. (*Appl. Catal., B* **2006**, *69*, 115−125).

Membrane-Assisted Fluidized Bed Reactors

The integration of membranes in a catalytic reactor allows either dosing one of the reactants in a controlled manner in order to achieve optimal axial concentration profiles with corresponding higher product yields (higher product selectivity at higher conversion) and simultaneously achieve improved temperature control and safety or, alternatively,-selectively removing one of the products, typically used to circumvent thermodynamic equilibrium. For partial oxidation reactions a membrane reactor especially offers improved reactor safety and controllability, reduced separation costs in case of oxygen perm-selective membranes, and a wider operating range, resulting in higher productivity. Recent

advances in the development of more stable membranes with increased permeance have significantly enhanced the possibilities for integrating membranes into catalytic reactors in order to achieve a major increase in reactor performance by process integration and process intensification. Several reviews and even special issues of catalysis-related journals illustrate the significant progress in the field of inorganic membrane reactors within the last two decades. Chemical engineers and material scientists have joined forces and addressed this topic from various viewpoints. In spite of their considerable efforts in these directions, the application of the membrane reactors, especially packed-bed membrane reactors, in commercial processes has been very limited because of technical as well as economical drawbacks. The most recent trend in membrane reactor technology has been in the direction of incorporating inorganic membranes into fluidized beds to combine the perm-selective and controlled dosing capabilities of membranes with the excellent gas−solid contact and heat-transfer capabilities of fluidized beds, thereby overcoming the limitations often prevailing in packed-bed membrane reactors. The opportunities for this novel, fluidized-bed membrane reactor compared to conventional reactors and packed-bed membrane reactors have been systematically reviewed, and these include new developments in the area of membrane-assisted fluidized-bed reactors, with special emphasis on possible applications, integration of different membranes in the fluidized beds, reactor modeling studies, experimental demonstration of various reactor concepts, and future prospects and hurdles for commercialization. Finally, an assessment of the state of the art has been given, and directions for future research are indicated (*Chem. Eng. Sci.* **2007**, *62*(1−2), 416−436).

Can Pharmaceutical Process Development Become High Tech?

A team from Bristol-Myers Squibb Co. (McKenzie, P. et al. *AIChE J.* **2006**, *52*(12), 3990) proposes an approach for the implementation of Process Analytical Technologies (PAT) and Quality by Design (QbD) concepts in pharmaceutical manufacturing based on ISA (Instrument, Systems and Automation Society) S.88 standards. This perspective note addresses the frequently quoted 2003 *Wall Street Journal* article suggesting that the pharmaceutical industry lags behind potato chip and laundry detergent makers regarding the use of modern manufacturing systems. An important part of this proposal is the inclusion of key PAT/QbD elements and S.88 standards early in process development, attempting to harmonize interactions between R&D and manufacturing. The use of statistical design of experiments, multivariate data analysis, risk analysis, lab automation and of physical organic chemistry and kinetics are emphasized. In addition, modeling tools and parallel experimentation is recommended. The challenges of integrating molecular, process, and system modeling in the pharmaceutical industry are briefly discussed. This perspective communication has 20 references.

In-Line Measurement of a Drug Substance via Near-Infrared Spectroscopy to Ensure a Robust Crystallization Process

A group from Merck reports on the successful use of near-infrared spectroscopy (NIRS) (Zhou, G. X. et. al *J. Pharm. Sci.* **2006**, *95*(11), 2337) for controlling etoricoxib (a COX-2 inhibitor) polymorph formation during crystallization. A crystallization process producing the desired etoricoxib was designed, using seeding at moderate supersaturation. Apparently the etoricoxib concentration in the process is a critical process parameter, and thus must be controlled very carefully. The classical HPLC method for determining this concentration is challenged by the handling of supersaturated solutions at room temperature. A more robust method was developed to measure etoricoxib concentration using NIRS. Feasibility for the method was demonstrated at small scale, followed by demonstration in six batches in the pilot plant (220-gal reactor, two different crystallizers). In the plant reactor the probe was placed in a recirculation loop fitted with a sight glass, and the electronic components were enclosed in an explosion-proof box. Data analysis was performed using both the instrument software package (Vision by Foss NIRSystems) and an independent chemometrics tool (The Unscrambler from Camo, Inc.). Spectral pretreatment was needed, in particular in order to eliminate errors due to the presence of bubbles. Spectral data analysis was used to establish that the supersaturated solution was clear, prior to the addition of the seeds, and to confirm that the solute concentration was indeed in the desired range of operation. The accuracy of the models developed was very good: approximately 0.1% by weight in the concentration (approximately 5−10% by weight) and temperature ranges of interest.

Influence of Particle Wall Adhesion on Particle Electrification in Mixers

Three academic groups in Singapore (Zhu, K. et al. *Int. J. Pharm.* **2007**, *328*, 22) investigated the complex phenomenon of particle electrification during mixing. Three powders were used: adipic acid, microcrystalline cellulose (MCC), and glycine. Adipic acid acquired positive electrostatic charges, whereas MCC and glycine acquired negative charges. Two types of mixers were used: a Turbula and a horizontally oscillating one. In spite of many advancements in powder technology, the mechanism for particle contact electrification is not well understood, especially for insulating compounds. The understanding of particle electrification is very important in powder mixing as well as in drug delivery using inhalation devices. In this study, the authors evaluated the impact of type of particle, particle size, type of mixer, rotational speed, and relative humidity (RH) on particle electrification. A Faraday cage was used to measure electrostatic charges carried by powders through a charge induction method. For the Turbula mixer, in the range of 34−72 rpm, rotational speed was not found to have a strong effect on particle electrification. A possible explanation for this may be the wall coating with some 10% of the particles, especially fines. Particle size effects on electrification were found to be different for larger vs smaller particles: for

relatively larger particles, the specific charge increased with increasing particle size. Relative humidity (RH) impacted the powders differently: adipic acid electrification was not influenced by RH, whereas for MCC a higher charge was found at lower RH. A theoretical model for powder electrification was developed and compared with the experimental data, showing good agreement in several cases.

The Promise of the East: India and China as R&D Options

An international team from the Boston Consulting Group (BCG) (Goodall, S. et al. *Nat. Biotechnol.* **2006**, *24*(9), 1061) briefly reviewed the R&D outsourcing process to India and China. A concise practical analysis of the IP developments and of the biotech markets in the two countries is provided, and certain recommendations are made. This communication is based on a comprehensive, 32-page report produced by BCG in August 2006: "Looking Eastward: Tapping China and India to Reinvigorate the Global Biopharmaceutical Industry". This report is available on the BCG web site: www.bcg.com.

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