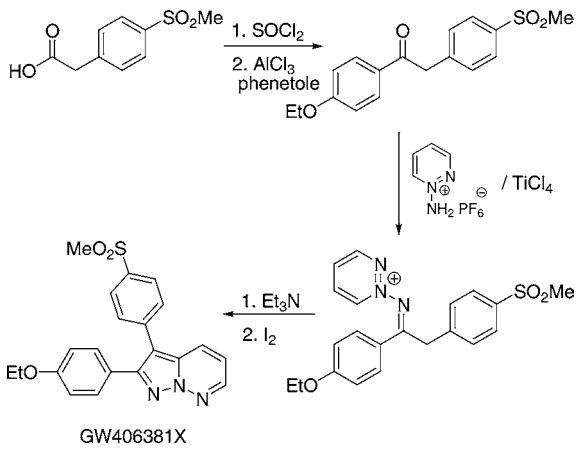
Organic Process Research & Development **2007**, *11*, 299–310

Highlights from the Literature

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

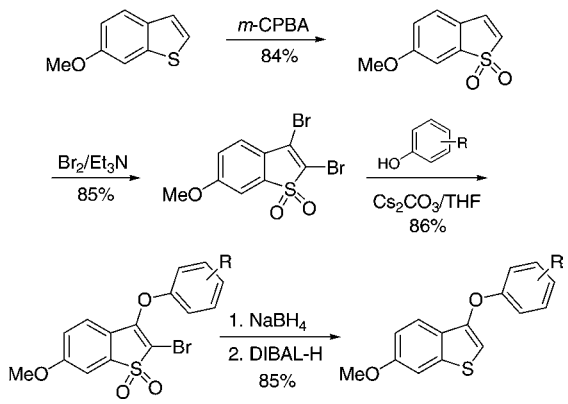
Efficient Synthesis of a Selective COX-2 Inhibitor



GW406381X

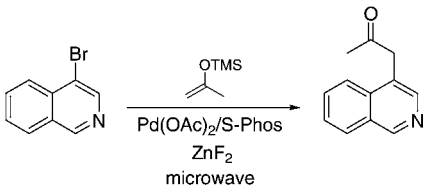
An improved synthesis of the potent and highly selective COX-2 inhibitor, GW406381X, is described by Whitehead and co-workers at GlaxoSmithKline (*Tetrahedron Lett.* **2007**, *48*, 911−913). A number of factors rendered the medicinal chemistry approach unsuitable as a long-term supply route capable of delivering the quantities required for development activities. Two steps that caused particular concern were a Corey−Fuchs dibromo-olefination step and a low-yielding [3+2] cycloaddition, which required an excess of one reaction partner and produced undesired insoluble residues. In a revised approach, it was proposed that a dihydropyrazolopyridazine intermediate (later oxidized to the target heterocycle) could be made by an intramolecular aza-Mannich type reaction. In turn the enamine required for this reaction could be derived from an imine which itself could result from the condensation of a ketone with an *N*-aminopyridazinium salt. Ultimately, the proposed synthesis was reduced to practice, and this chemistry was used to prepare significant quantities of GW406381X.

Efficient Synthesis of 3-Oxygenated Benzothiophenes



In a recent communication, Zhang and co-workers at Lilly delineate a method for the preparation of functionalized benzothiophenes (*Tetrahedron Lett.* **2007**, *48*, 2349−2352). When attempted bromination of 6-methoxybenzothiophene afforded only 5% yield of the desired product, the researchers turned their attention towards investigating the reactivity of the related benzothiophenedioxide. Oxidation of 6-methoxybenzothiophene using *m*-CPBA gave the sulfone, which was brominated in good yield using bromine. Selective nucleophilic displacement of the bromine atom in the 3-position with various phenols was demonstrated to occur smoothly using cesium carbonate as the base in THF. It was also shown that treatment with $NaBH_4$ removed the remaining bromine atom, and further treatment with DIBAL-H returned the reduced benzothiophene. The authors note that the developed process is amenable to multikilogram preparative scale.

Pd-Catalyzed α-Arylation of Acetone



12 examples, 25-88% yield

Metal-mediated α-arylation of carbonyl-containing substrates has been developed into a useful synthetic method in recent times. Seeking to develop a tin-free method for the heteroarylation of acetone, Chobanian and co-workers in the Merck medicinal chemistry group investigated the use of 2-trimethylsilyloxypropene as a potential acetone surrogate (*Tetrahedron Lett.* **2007**, *48*, 1213−1216). 2-Trimethylsilyloxypropene is commercially available and was shown to react with various aryl and heteroaryl bromides, chlorides, or triflates under microwave-assisted conditions, with tris(dibenzylidene acetone)dipalladium ($Pd_2(dba)_3$) or palladium acetate ($Pd(OAc)_2$) and 2-(2′,6′-dimethoxybiphenyl)dicyclohexylphosphine (S-Phos) as the catalyst system and ZnF_2 as a fluoride source. In an isolated example, the use of standard thermal conditions (150 °C in DMF) ultimately gave the same yield as that obtained under microwave promotion, but required a reaction time of 10 h instead of 15 min. A total of 12 examples is presented with yields ranging from 25 to 88%.

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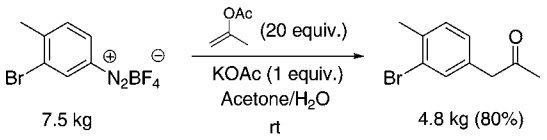
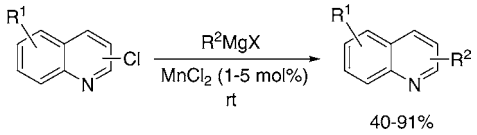
Metal-Free Meerwein Arylation of Acetone



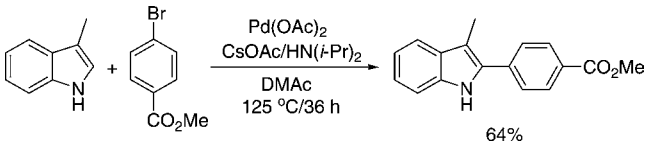
As an alternative to the approach described in the previous Highlight, Molinaro and co-workers at Merck Process report on a simple, scalable, transition-metal-free method for the synthesis of α-aryl methyl ketones (*J. Org. Chem.* **2007**, *72*, 1856−1858). Although the literature contains scattered examples of Meerwein arylation of activated alkenes using diazonium salts, the preparation of α-aryl alkyl ketones using this reaction had not been reported. The current research investigated the use of isopropenyl acetate as a cheaply available acetone source and ultimately led to the development of a practical procedure in which KOAc is used to promote the arylation reaction under mild conditions. This method uses easily accessible and nontoxic starting materials and was applied to the multikilogram-scale preparation of 1-(3-bromo-4-methylphenyl)propan-2-one.

Mn-Catalyzed Cross-Coupling



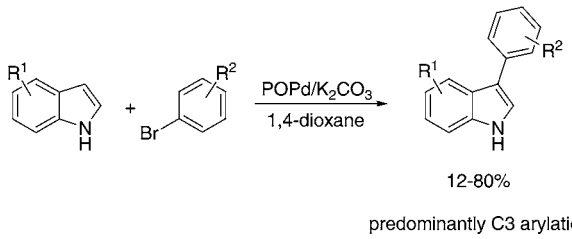
Metal-catalyzed carbon−carbon bond-forming reactions are a highly important class of reactions for the preparation of polyfunctional heterocycles. Typically, these cross-coupling reactions are mediated by Ni- or Pd-complexes, although recent examples using Fe- or Co-based catalysts have been documented. Now, a manganese-catalyzed cross-coupling reaction of heterocyclic chlorides with aryl- as well as alkylmagnesium halides has been developed by the Rueping group (*Synlett* **2007**, *2*, 247−250). The reaction provides a variety of heterocyclic compounds under mild (0−20 °C) and practical reaction conditions using relatively low loadings (1−5 mol %) of inexpensive $MnCl_2$ as the catalyst. In total, 25 examples are reported including quinolines, isoquinolines, quinazolines, benzothiazoles, and pyridines, with yields ranging from 40 to 91%.

Pd-Catalyzed C−H Bond Arylation of Free (NH)-Nitrogen Heterocycles



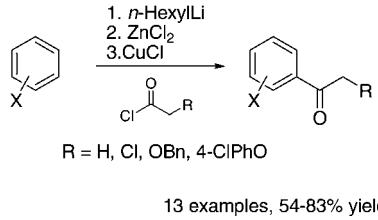
Many natural products and pharmaceuticals contain *C*-arylated azole core structures. Although standard Pd-catalyzed cross-coupling reactions provide an efficient entry to these compounds, such methods require the preparation of functionalized heteroarenes such as boronates and halides. Recently, considerable effort has been focused on the development of direct C−H bond functionalizations of the parent heteroarenes. Despite significant progress in this area, *C*-arylation of free (NH)-indoles and pyrroles with haloarene donors remains an unsolved problem. In a recent Note, the Sames group describes a phosphine-free Pd-catalyzed method for direct *C*-arylation of free (NH)-indoles and pyrroles with iodo- and bromoarene donors (*J. Org. Chem.* **2007**, *72*, 1476−1479). Employing commercially available materials, this procedure provides a rapid entry into a wide range of *C*-arylated (NH)-indoles including derivatives of tryptamine. In the course of this study, a profound halide effect was observed, affecting both the efficiency and regioselectivity of indole arylation.

Direct Pd-Catalyzed C-3 Arylation of Indoles



In another report on the direct C−H bond functionalization of indole substrates Zhang, He, and co-workers describe a catalytic system affording a complementary regiochemical outcome to that observed in the previous Highlight (*Tetrahedron Lett.* **2007**, *48*, 2415−2419). Using the Combi-Phos family of Pd-phosphinous acid complexes in conjunction with K_2CO_3 in toluene or 1,4-dioxane as solvent, the C-3 arylated product predominates when free (NH) indoles are reacted with aryl bromides. Yields are moderate to good when electron-neutral or electron-rich indoles are arylated, while arylation of electron-poor indoles failed. In the previous Highlight, the reactivity of electron-poor indole substrates was not studied.

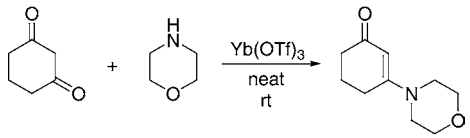
One-Step Synthesis of α-Chloro Acetophenones



Fluorine-bearing aromatic rings are ubiquitous in modern pharmaceuticals, and in consequence, methods for the elaboration of simple fluorinated starting materials to more complex intermediates are of great significance. As part of a drug development program, Rosen and co-workers at Merck required access to 2-chloro-1-(2,3-difluorophenyl)-ethanone (*Org. Lett.* **2007**, *9*, 667−669). The availability and low-cost of 1,2-difluorobenzene made it the preferred choice among potential starting materials; however, traditional Friedel−Crafts acylation chemistry would not provide the desired regiochemistry. To address this issue, the researchers developed a direct and efficient method involving ortholithiation and transmetallation to the thermally stable arylzinc

species, which reacted smoothly with α-chloroacetyl chloride under copper catalysis. The generality of the method was demonstrated against a variety of fluorinated arenes, 1,3-dichlorobenzene, and benzofuran, all yielding stable organozinc intermediates amenable to Cu-catalyzed acylation with acid chlorides. A total of 13 examples is presented with yields ranging from 54 to 83%.

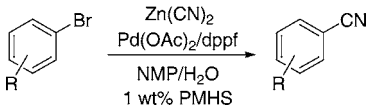
$Yb(OTf)_3$-Catalyzed Synthesis of β-Enaminones



12 examples, 93-99% yield

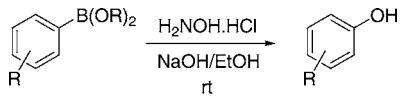
β-Enaminones have been extensively used as key intermediates in organic synthesis, with applications in heterocycle synthesis and as substrates for asymmetric reduction processes. The Epifano group describe the use of $Yb(OTf)_3$ as a catalyst for this well-established condensation process (*Tetrahedron Lett.* **2007**, *48*, 2717−2720). Although numerous reaction conditions are available for this reaction, the authors cite various problems with existing procedures, such as high temperatures, low product yields, or tedious workups. For the 12 examples featured, the isolated yields range from 93 to 99% after 12 h reaction time at room temperature using 0.5 mol % of Lewis acid catalyst under solvent-free conditions. Addition of 1 N aqueous NaOH at the end of reaction precipitates $Yb(OH)_3$, which the authors indicate can be filtered and recycled.

Open Air Pd-Catalyzed Cyanation Using PMHS



Faced with the problem of a capricious Pd-catalyzed cyanation reaction, Martin and co-workers at GlaxoSmithKline developed a simple and highly effective solution (*Tetrahedron Lett.* **2007**, *48*, 2555−2557). Polymethylhydrosiloxane (PMHS) used in catalytic amounts (1 wt % or 0.06 equiv) was shown to prevent catalyst poisoning by oxygen contamination during Pd-catalyzed cyanation reactions. This robust cyanation procedure was demonstrated against a wide range of substrates and is so effective that these reactions can be run fully open to the atmosphere. A control experiment run open to the atmosphere without the PMHS additive stalled at 57% conversion. A possible explanation could involve a silyl hydride reduction of the oxidized palladium back to palladium(0). However, in reactions that were purposfully stalled by exposure to airprior to addition of the PMHS, the addition of PMHS failed to restart the catalytic cycle. In these stalled reactions the addition of either fresh $Pd_2(dba)_3$ or DPPF alone also failed to restart the reactions, suggesting that both the catalyst and ligand were irreversibly inactivated. The addition of both fresh catalyst and ligand did restart the reaction as expected. These observations demonstrate that, although PMHS is capable of maintaining the palladium in a catalytically active state via protection from oxidative inactivation, it is not capable of actually reactivating catalyst that has been deactivated.

Conversion of Arylboronic Acids to Phenols Using Hydroxylamine

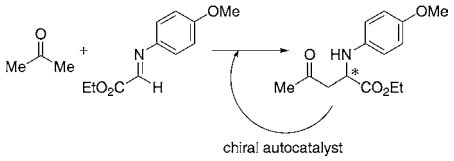


21 examples, 0-94%

The group of Kianmehr has introduced hydroxylamine as an alternative oxidant for the conversion of arylboronic acids to phenols (*Tetrahedron Lett.* **2007**, *48*, 2713−2715). The authors comment that the alkaline hydrogen peroxide conditions commonly used for this transformation are likely to be problematic for certain substrates and proposed that hydroxylamine would be a milder reagent. The described procedure employs hydroxylamine hydrochloride in conjunction with NaOH and EtOH as the solvent at room temperature. Pinacol boronate esters as well as arylboronic acids are converted into phenols using this method. Yields are generally moderate to good for the 21 examples presented, with electron-deficient arylboronic acids affording the lowest yields. Comparative experiments to assess the yields with the same substrates using hydrogen peroxide as oxidant are not discussed.

Autocatalysis in Organocatalytic Reactions

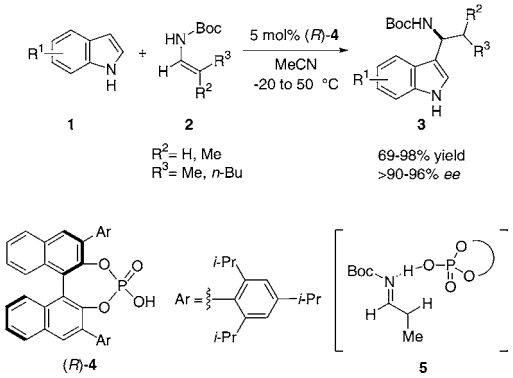
Asymmetric autocatalysis is the process of automultiplication of a chiral compound in which the chiral product acts as a chiral catalyst for its own formation (Mauksch, Tsogoeva, et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 393−396). The implications of this phenomenon in stereoselective transformations captivated the interest of the researchers at Göttingen University, which investigated the possibility that product alone could be a chirality inductor in an asymmetric reversible Mannich reaction. Thus, addition of enantiopure β-amino ketone product to the reaction that generates the same β-amino ketone reveals that the product is formed with nearly the same enantiomeric purity as that of the β-amino ketone product (autocatalyst) at 15 mol %. Longer reaction times result in racemization due to the reversibility of the reaction or to the enantiomerization of the product. To explain the chiral induction, the authors propose a catalytic cycle involving hydrogen-bonded complexes between substrate and product that would react with the acetone enol. The intricate traffic control between the proposed equilibria and productive pathways is investigated using density functional theory computations.



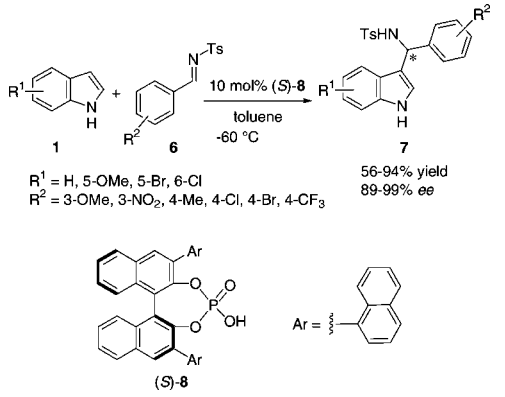
Enantioselective Friedel−Crafts Reaction of Indoles with Imines

The Friedel−Crafts (F−C) reaction is a method for the formation of C−C bonds widely utilized in industrial processes. Two independent communications describe the enantioselective variation of this reaction using chiral phosphoric acids as organocatalysts.

Terada and Sorimachi described the reaction of indoles with enecarbamates (*J. Am. Chem. Soc.* **2007**, *129*, 292−293) to access enantioenriched 1-indolyl-1-alkylamines of pharmaceutical and biological importance. The BINOL-derived monophosphoric acid **4** efficiently catalyzed the reaction of various indole derivatives irrespective of their substitution patterns (R^1 = 5-MeO, 5-Me, 5-Br, 6-Br, 5-CO_2Me), yielding the F−C products in good yields and enantioselectivities. Since (*E*)-**2** and (*Z*)-**2** diastereoisomers (R^2 = H, R^3 = Me) give the same product, the authors suggest that the reaction proceeds through a common intermediate (e.g., aliphatic imine **5**) resulting from the protonation of enecarbamate **2**.

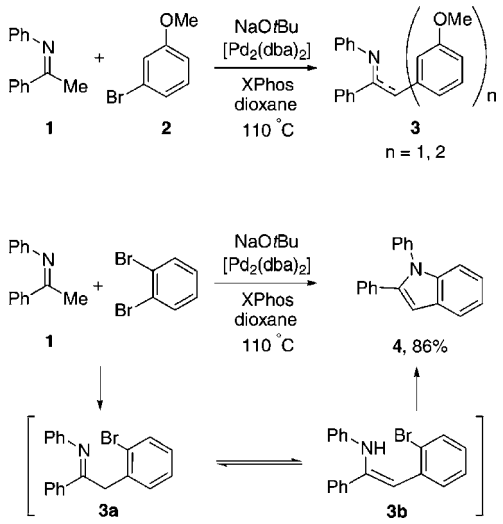


You and co-workers investigated the addition of tosyl imines to indoles (*J. Am. Chem. Soc.* **2006**, *129*, 1484−1485). Several substituted indoles were tested under the optimized conditions (5% catalyst, toluene, −60 °C) to afford the desire F−C adducts in high yields and enantioselectivities. The outcome strongly depends on the imine substituents: whereas the reaction worked well with electron-donating groups, a drop in enantioselectivities was observed upon introduction of electron-withdrawing substituents.

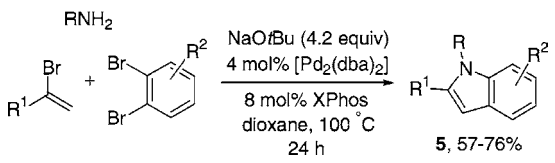


Pd-Catalyzed Synthesis of Indoles using the Azaallylic Anion Synthon

In the search of new strategies for the synthesis of heterocycles through Pd-catalyzed processes, the group of Barluenga focused on azaallylic anions, a regular three-atom synthon in classic heterocyclic chemistry (*Angew. Chem., Int. Ed.* **2007**, *46*, 1529−1532). Screening of conditions included different bases, Pd-ligands, solvents, and reaction conditions and led to several relevant results: (1) imines **1** undergo exclusively C-arylation in the presence of Pd catalysts; (2) whereas diarylated imines (n = 2) can be obtained in quantitative yield using 2 equiv of ArBr, selective monoarylation was elusive; (3) arylation of imines with *o*-bromobenzene yielded indoles **4** through intramolecular amination of enamine **3b**. The latter result indicated that the same Pd catalyst promotes the intermolecular C-arylation as well as the intramolecular N-arylation.



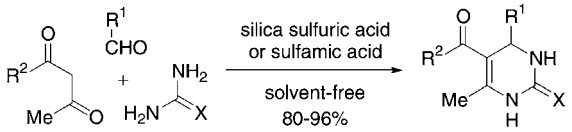
The methodology proved general for a wide set of structurally diverse imines, and can be used for the preparation of 2- and 2,3-substituted indoles with aliphatic or aromatic substituents in the 1, 2, and 3-positions. With a twist of synthetic elegance, the authors applied their recent Pd-catalyzed synthesis of imines from haloalkenes and primary amines (*Chem. Commun.* **2004**, 1400−1401) to obtain indoles in a three-component reaction. The different cross-couplings occur with exquisite chemoselectivity: the higher reactivity of bromoalkenes before haloarenes in the oxidative addition to Pd leads to the formation of the imine instead of the aryl amine. The resulting dihaloarene is incorporated in the sequence when the allenyl halide has been consumed. The same Pd catalyst promotes three independent reactions: (1) formation of the imine by alkenyl amination, (2) α-arylation of the imine, and (3) intermolecular N-arylation.



Biginelli Reactions under Solvent-Free Conditions

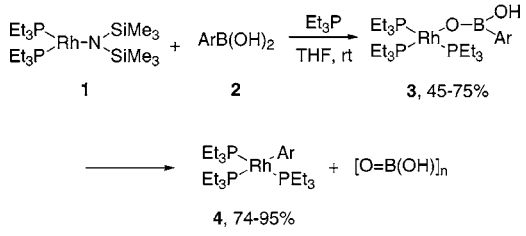
The prevalence of 3,4-dihydropyrimidin-2(1H)-ones in the structure of bioactive products has rejuvenated the Biginelli reaction, a multicomponent process involving the condensa-

tion of an aldehyde and a 1,3-dicarbonyl compound with urea that was reported for the first time in the late 19th century. Researchers at Suzhou University and JiangShan Pharmaceutical Corporation in China describe (*Synth. Commun.* **2007**, *37*, 47−52) an efficient Biginelli reaction catalyzed by sulfamic acid or silica sulfuric acid under solvent-free conditions. The methodology is environmentally benign and operationally simple, and employs cheap chemicals to furnish a wide variety of dihydropyrimidinones and thioderivatives in excellent yields. For example, the reaction of benzaldehyde, ethyl acetoacetate, and urea affords the desired dihydropyrimidinone in 90% yield using 30 mol % silica sulfuric after 10 min at 120 °C. The catalyst can be recovered by simple filtration and can be recycled with comparable activity.

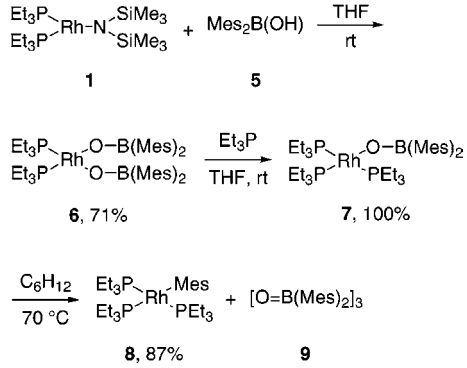


Boron-to-Rhodium Transmetalation by β-Aryl Elimination

Zhao, Incavito, and Hartwig shed light on the mechanism of the catalytic transmetalation from organoboron compounds to rhodium complexes (*J. Am. Chem. Soc.* **2007**, *129*, 1876−1877). The authors reported the isolation of a series of rhodium arylboronate and diarylboronate complexes that undergo intramolecular transfer of the aryl group from boron to rhodium by a β-aryl elimination pathway. The complexes were prepared by reacting Rh(I) silylamido precursor **1** with aryl boronic acids **2** and PEt_3 at room temperature. The para substituted aryl derivatives (Ar = *p*-tolyl, *p*-anisyl, 4-$CF_3C_6H_4$) were obtained as crystalline solids and characterized by X-ray diffraction. The *o*-anisyl derivative was unstable at room temperature but formed quantitatively at lower temperatures and was characterized by NMR spectroscopy. Complexes **3** underwent β-aryl elimination in the absence of added ligand at room temperature to afford the corresponding rhodium−aryl complexes **4**. The insoluble boron product was tentatively identified as a boroxine oligomer.

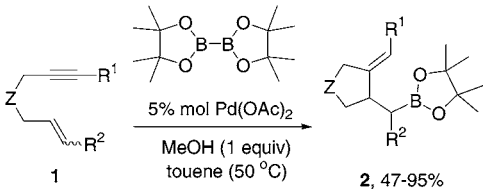


Precursor **1** reacted with diarylborinic acid **5** to afford the bis(phosphine) Rh(I) borinate complex **6**. These species are unstable and react with PEt_3 (1 equiv) to yield the more stable tris(phosphine) complex **7**. Heating **7** in cyclohexane at 70 °C led to β-aryl elimination in 4 h, with the concomitant formation of cyclic boroxine **8**. The results of kinetic studies were consistent with the β-aryl elimination from 14-electron boronate and borinate intermediates. The mechanism is a presumable pathway for the transmetalation from boron to other late transition metals.



Pd-Catalyzed Synthesis of Homoallylic Alkyl Boronates

Alkyl boronates are elaborated synthetic intermediates that combine the advantages of low toxicity, high functional group compatibility, and selective transformation of the C−B bond. The synthesis of alkyl boronates is usually performed by hydroboration of alkenes or by reaction of organometallic species with borate esters. Cardenas and co-workers at the Universidad Autonoma de Madrid described a Pd-catalyzed cyclization of 1,6-enynes in the presence of bis(pinacolato)-diboron as an alternative route to access alkylboronates (*J. Am. Chem. Soc.* **2007**, *129*, 1876−1877). The formation of boronate **2** implies a formal 1,7-hydroboration of enyne **1** with concomitant carbocyclization. One equivalent of MeOH acts as the proton source. To the author's delight, the reaction proved stereoselective. Whereas substrates containing hydrogen atoms susceptible of elimination and non-coordinating substituents (R_1 = Me; R^2 = H) afforded the expected boronates, internal alkynes gave higher yields.

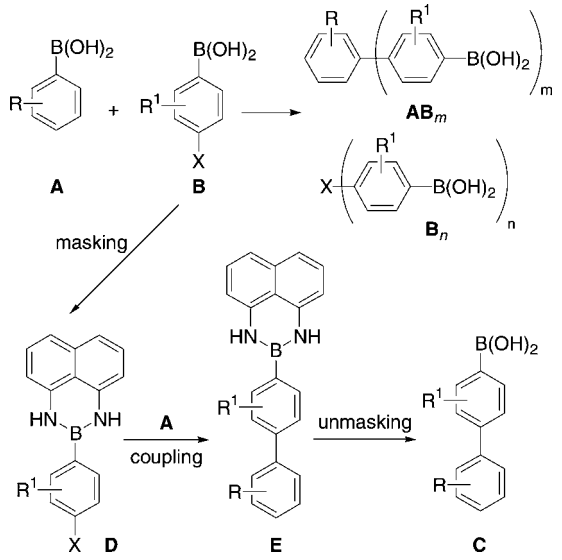


Z = $C(CO_2Et)_2$, $C(CO_2Me)_2$, $C(SO_2Ph)_2$, NTs
R^1 = H, Me, Ph, $SiMe_3$
R^2 = (*Z*)-CH_2OCOMe, (*Z*)-CH_2OCOPh, (*Z*)-CH_2OCOBn, H

Boron-Masking Strategy Using 1,8-Diaminonaphthalene

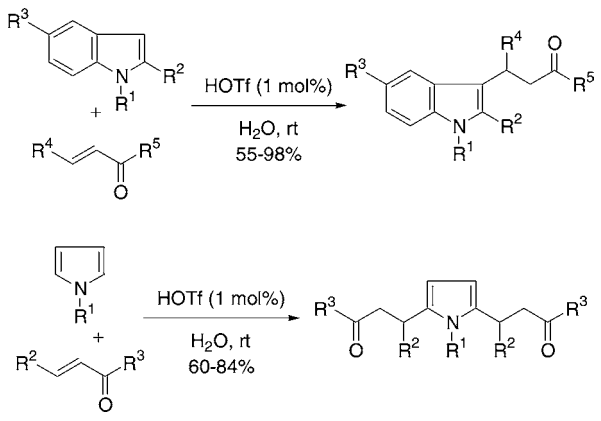
The Suzuki−Miyaura coupling (SMC) is a reliable method for C−C bond formation. The procedure combines high efficiency, stability of the organoboron compounds, and high functional group compatibility. Noguchi, Hojo, and Suginome from Kyoto University describe a masking strategy that renders the boronyl group inactive during the iterative synthesis of oligoarenes using SMC (*J. Am. Chem. Soc.* **2007**, *129*, 758−759). The reaction of arylboronic acid **A** with haloarylboronic acid **B** would not provide the coupling product **C** but a mixture if oligoarenes **A**−$\mathbf{B}_m$ and $\mathbf{B}_n$. Reaction of **A** species with 1,8-diaminonaphthalene provided diamido derivatives **D** as stable compounds in high yields. The masked haloboronamides reacted with **A** in standard conditions ($Pd[P(tBu)_3]_2$, CsF, dioxane/H_2O or THF) to

afford the desired biaryl compounds **E** featuring intact masked boronyl groups. No oligomerization was detected. The protecting group was cleaved by treatment with diluted H_2SO_4 or HCl at room temperature. Coupling the resulting boronic acid **D** with **B** proceeded as efficiently as the subsequent cross-coupling iterations did to give up to quinquearylboronic acid derivatives. The reactivity of the terminal boronyl group can be exploited to afford a variety of products.



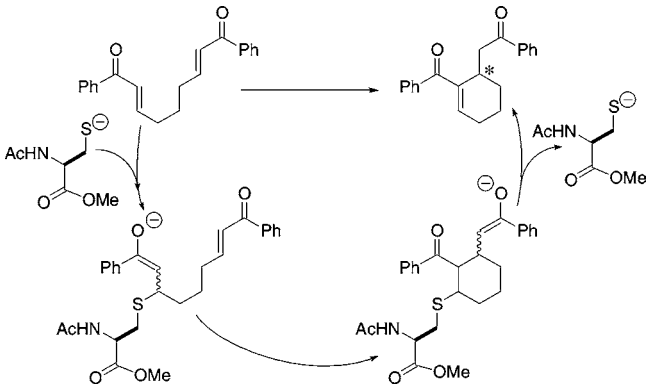
Acid-Catalyzed Michael Reactions of Indoles and Pyrroles

A group of researchers at the Institute of Chemistry of Chinese Academy of Sciences, (Beijing) have recently reported the Michael addition of indole and pyrrole compounds to α,β-unsaturated ketones catalyzed by triflic acid (HOTf, <1 mol %) in water at room temperature (*Synth. Commun.* **2007**, *37*, 173−181). The procedure provides 3-alkylindoles and 2,5-dialkylsubstituted pyrroles in good yields. Even though some substrate combinations afford byproducts resulting from 1,2-addition and the reaction of pyrroles cannot be stopped in the monoalkylation step, the process is highly interesting since the reaction conditions are mild and environmentally friendly. Following the workup, the aqueous phase containing HOTf can be reused several times as an aqueous solution of the catalyst.



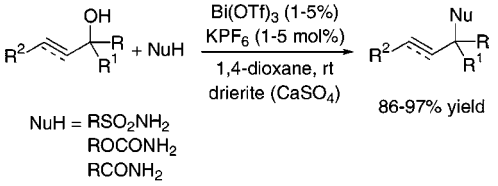
Enantioselective Rauhut−Currier Reactions

Aroyan and Miller disclosed an enantioselective version of the Rauhut−Curier reaction catalyzed by cysteine thiolates (*J. Am. Chem. Soc.* **2007**, *129*, 256−257). For example, treatment of the keto enone represented below with 0.2 equiv of AcCysOMe and 6 equiv of *t*-BuOK in a mixture of MeCN and water during 24 h at −40 °C mediates its cycloisomerization to afford the desired cyclohexenone in 75% yield and 92% ee. A mechanistic interpretation involves the 1,4-addition of the cysteine thiolate to generate an enolate intermediate, which in turn undergoes cyclization via Michael addition followed by proton transfer and elimination. The reversible C−C bond ring-forming step is followed by an irreversible elimination of Cys that may be the stereochemistry-determining step. The authors suggest that K ion chelation between the N-acetyl group of Cys and an intermediate enolate originates the stereoselective outcome.



Direct Substitution of Alcohols Catalyzed by Bismuth

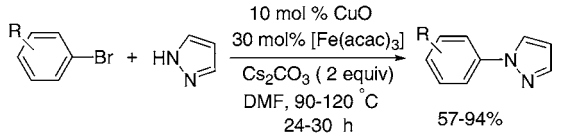
Matsunaga, Shibasaki, and co-workers reported the utility of bismuth catalysis in the direct substitution of allylic, propargylic, and benzylic alcohols with sulfonamides, carbamates, and carboxamides (*Angew. Chem., Int. Ed.* **2007**, *46*, 409−413). A combination of commercially available $Bi(OTf)_3$ and KPF_6 (1−5 mol %) in the presence of drierite ($CaSO_4$) promoted the aminations at room temperature to give the products in up to 99% yield. Whereas sulfonamides and carbamates reacted within 1.5 h, reaction of alcohols with carboxamides took up to 16 h. The methodology circumvents the activation of alcohols by stoichiometric (halides, carbonates) or catalytic (transition metals) methods and therefore reduces the amount of waste.



Iron/Copper-Cocatalyzed Arylation of Nitrogen Nucleophiles

The group of Taillefer at Montpellier revisited the N−C bond formation by the Ullman method using cheap and environmentally friendly iron complexes (*Angew. Chem., Int. Ed.* **2007**, *46*, 934−936). The novel system constitutes a rare

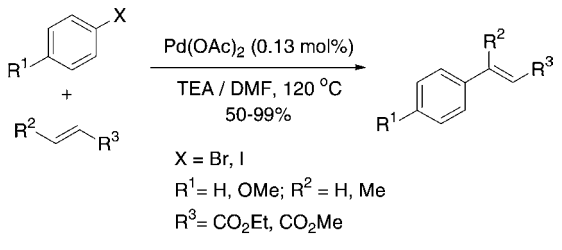
example of bimetallic catalysis and the first involving both iron and copper in a N−C bond formation. Neither catalytic isolated iron nor copper complexes promoted the reaction. The precomplexation of the acetylacetonate (acac) ligand with iron is crucial for an efficient cocatalysis. Excellent yields were obtained in the cross-coupling of iodobenzene and different azoles (pyrazole, imidazole, pyrrole, triazole, indole). The reaction was applied to the arylation of pyrazole with aryl bromides with a variety of substituents to afford the desired products in good yield. The simple experimental procedure (catalyst and salts are filtered off after the reaction) as well as the availability and low price of the catalysts makes this protocol adaptable to industrial scale.

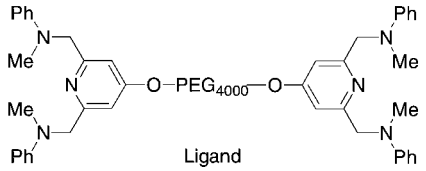


R = H, 4-COMe, 4-CN, 4-Ph, 4-Me, 4-OMe, 3-OMe, 4-NO_2

A PEG-Supported Ligand for the Heck Reaction

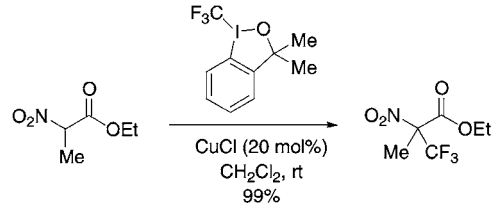
A tridentate ligand immobilized on PEG provides an efficient catalytic system for the Heck reaction mediated by $Pd(OAc)_2$ as reported by Zhang and co-workers at Zhejiang University, China (*Synth. Commun.* **2007**, *37*, 191−197). The immobilization of Pd catalysts offers the opportunity to recycle the expensive metal and minimize the amounts of residual Pd in the product that might pose safety and environmental concerns. The PEG-supported NNN ligand was prepared in four steps with good yields from 4-allyloxy-2,6-pyridinedimethyl ditosylate. The catalytic system promotes Heck reactions (>95% yield) in an air atmosphere at 120 °C during 8 h without generating Pd black during the reaction. Ligand and catalyst could be reused several times without showing significant activity decay.

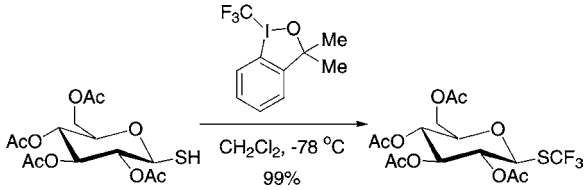




Mild Trifluoromethylation of Nucleophiles

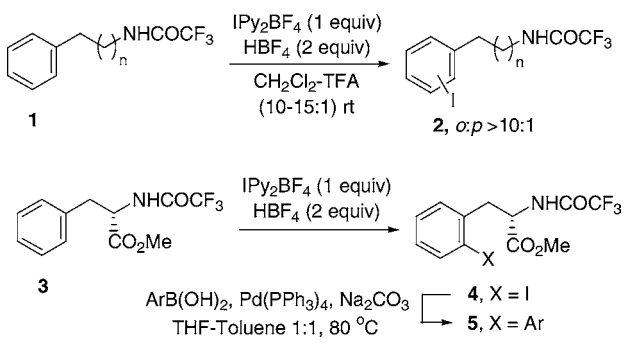
Despite the ubiquity of the trifluoromethyl group in medicinal chemistry, the organic synthesis toolbox has only a few reagents to effectively introduce electrophilic CF_3 in a mild and selective way. The group of Prof. A. Togni at ETH recently prepared a hypervalent iodine compound that promotes the trifluoromethylation of carbon- and sulfur-centered nucleophiles (*Angew. Chem., Int. Ed.* **2007**, *46*, 754−757). The reagent is readily accessible in an overall four-step procedure and reacts with a variety of β-keto esters and α-nitro esters to give the corresponding α-trifluoromethylated derivatives in high yields under very mild conditions as determined by ^1H and ^{19}F NMR spectroscopies. Likewise, aromatic and aliphatic thiols undergo S-trifluoromethylation to afford the trifluoromethylsulfenyl derivatives in 58−99% yields without competitive formation of undesired disulfides. Previous procedures for the installation of SCF_3 groups required complicated functional group transformations.





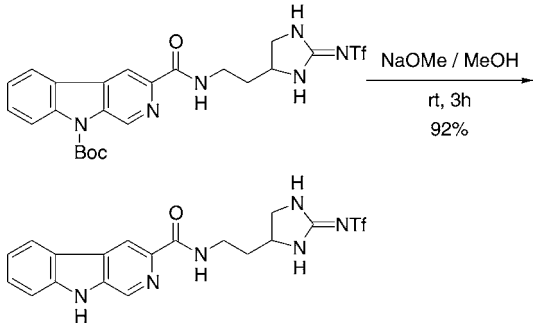
Direct Electrophilic Ortho-Iodination of β- and γ-Arylamines

Barluenga and co-workers reported the selective electrophilic ortho-iodination of trifluoroacetyl β- and γ-arylamines and applied the methodology to the synthesis of phenethylamine and phenylalanine derivatives (*Angew. Chem., Int. Ed.* **2007**, *46*, 1281−1283). The transformation is an alternative to the use of transition metals or strong bases to prepare ortho-halogenated derivatives. Both the solvent selection (CH_2Cl_2/TFA, 15:1) and the addition of HBF_4 were pivotal in achieving ortho selectivity. The length of the tether between the trifluoroacetamide moiety and the arene drastically affected the outcome: compounds with tethers $n = 0$ or 4 afforded 1:1 mixtures of ortho- and para-iodinated products. Selectivity may arise from the interaction of the iodonium species and the trifluoroamide moiety. This interaction would precede the intramolecular delivery of the iodonium to the ortho position. Iodinated phenylalanine derivatives **4** were elaborated into constrained biaryl scaffolds **5** by Pd-catalyzed-coupling reactions. The two-step sequence offers a convenient strategy for the facile preparation of phenyl derivatives of phenylalanine.



Simple Deprotection of the N-Boc Group in Heterocycles

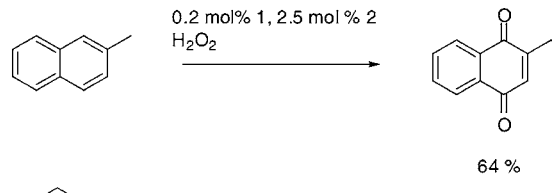
The *tert*-butoxy carbonyl group is widely used to protect primary and secondary amines due to its simple installation, removal, and robustness. Whereas the moiety is designed to be removed under acidic conditions, a recent report by Ravinder et al. (Indian Institute of Chemical Technology, Hyderabad) has expanded its versatility (*Synth. Commun.* **2007**, *37*, 281−287). N-Boc indoles, pyrroles, indazoles, and carbolines can be efficiently deprotected using a catalytic amount of NaOMe as a base (20 mmol %) in dry MeOH at room temperature during 0.5−3 h. The deprotection is orthogonal relative to $(RNH)_2C$ = NTf, RCONHBoc, RNHBoc, R_2NBoc, and ketal groups, and its unoptimized yields fall within the range 86−98%.

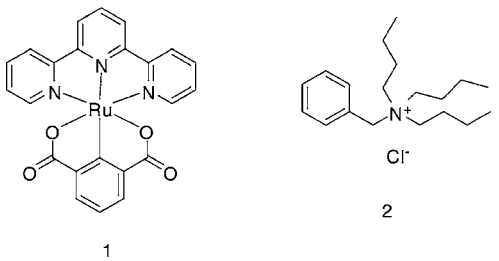


A Convenient Process for the Selective Oxidation of Naphthalenes with Hydrogen Peroxide

Beller, M. et al. (*Adv. Synth. Catal.* **2007**, *349*, 303) have developed a practical ruthenium phase-transfer catalyst system for the oxidation of naphthalene derivatives. Substituted 1,4-naphthoquinone derivatives are obtained in good selectivity and yield in water without addition of cosolvents or acids. The process needs only small amounts of catalyst (0.2 mol %), 7 equiv of 30% hydrogen peroxide and 1−2.5 mol % of a phase-transfer catalyst.

Under the optimized conditions it is possible to obtain menadione (vitamin K3) from 2-methylnaphthalene in 64% yield.

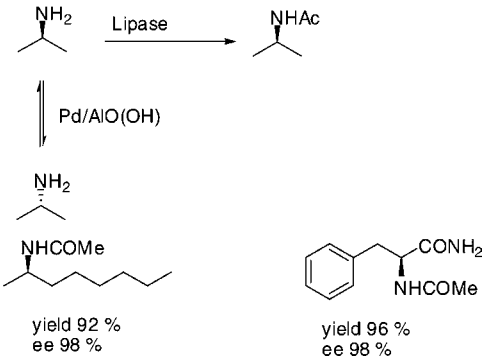




1 2

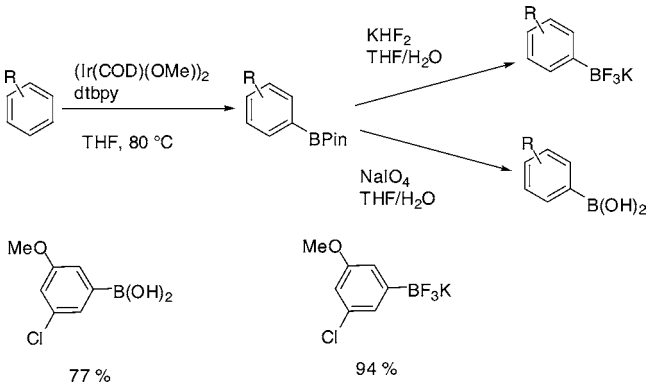
Dynamic Kinetic Resolution of Primary Amines with Pd-Nanocatalyst for Racemization

Park, J. et al. (*Org. Lett.* **2007**, *9*, 1157) have developed a practical procedure for dynamic kinetic resolution (DKR) of primary amines. This procedure employs for the first time a heterogeneous palladium nanoparticle as the racemisation catalyst, a commercial lipase (Novozym-435) as the resolution catalyst, and ethyl acetate or methoxyacetate as the acyl donor. In all tested examples from primary amines and one amino acid derivative were good to high yields and high enantiomeric excesses obtained.



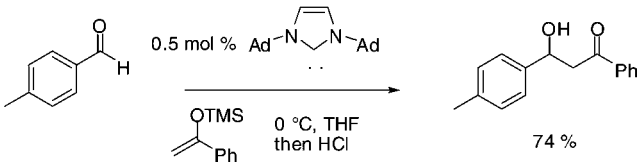
One-Pot Synthesis of Arylboronic acids and Aryl Trifluoroborates by Ir-Catalyzed Borylation of Arenes

Hartwig, J. F. et al. (*Org. Lett.* **2007**, *9*, 757) have reported a one-pot procedure for the synthesis of arylboronic acids and aryl trifluoroborates by Ir-catalyzed borylation of arenes. To prepare the arylboronic acids, the Ir-catalzed borylation is followed by oxidative cleavage of the boronic ester with NaIO4. The aryltrifluoroborates are obtained by displacement of pinacol with KHF_2. This process generates boronic acids with substitution patterns that complement the types of patterns that can be generated from haloarenes.



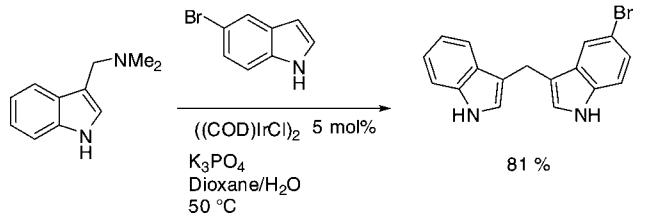
N-Heterocyclic Carbene-Catalyzed Mukaiyama Aldol Reactions

Song, J. J. et al. (*Org. Lett.* **2007**, *9*, 1013) have shown that N-heterocyclic carbenes can be highly efficient catalysts to promote Mukaiyama aldol reactions. In the presence of 0.5 mol % of the carbene, various aldehydes and 2,2,2-trifluoroacetophenone underwent the aldol reactions in THF with trimethylketene acetal at 23 °C and trimethylsilyl enol ether at 0 °C to afford aldol products in good yields. These conditions are mild and tolerate various functional groups.



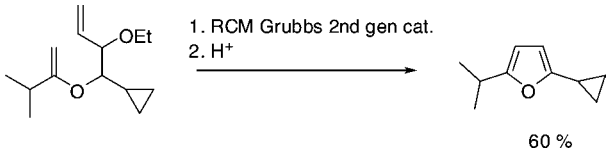
Benzylic Substitution of Gramines with Boronic Acids Using Rhodium or Iridium Catalysts

De la Herrán, G. et al. (*Org. Lett.* **2007**, *9*, 961) have found that gramine-MeI salts are useful starting materials for the synthesis of 3-benzyl- and 3-allylindoles by a 1,4-addition of boronic acids under Rh(I) catalysis. On the other hand, under Ir(I) catalysis, the reaction of gramines with indoles affords nonsymmetrical diindolylmethanes.



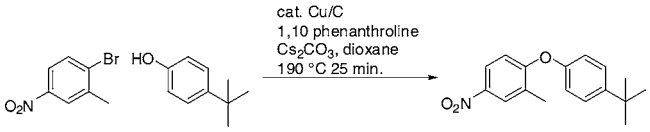
A Metathesis-Based Approach to the Synthesis of Furans

The ring-closing metathesis reaction of enol ether-olefin substrates has been employed to generate 2,3-dihydrofurans that contains a leaving group in the 4-position (Donohoe, T. J. et al. *Org. Lett.* **2007**, *9*, 953). These substrates are at the correct oxidation state to undergo acid-catalyzed aromatization, and this strategy has been utilized to provide a mild route for the synthesis of 2,5-disubstituted furans.



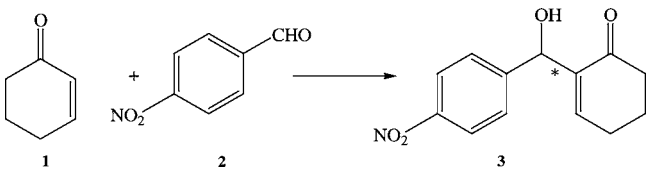
Copper-in-Charcoal-Promoted Diaryl Ether Formation

Copper-impregnated charcoal has been found by Lipschutz, B. H. et al. (*Org. Lett.* **2007**, *9*, 1089) to efficiently catalyze the Ullman ether coupling between aryl bromides and phenols under microwave heating. The authors found that the best base for the reaction is Cs_2CO_3, and that although the precatalyst is heterogeneous it was found that 1,10-phenanthroline promotes the reaction and discourages the competitive aryl bromide reduction.

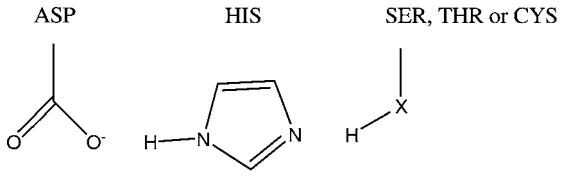


Enzyme Promiscuity

Reetz, Mondiere, and Carballeivre (*Tetrahedron Lett.* **2007**, *48*, 1679) have described the first protein-catalyzed Morita−Baylis−Hillman (MBH) reaction. They chose as a model system the reaction between cyclohexenone (**1**) and *p*-nitrobenzaldehyde (**2**) with formation of the adduct **3**, a standard MBH reaction.



Since in this reaction basic conditions are needed, as for example the use of DABCO, it was speculated that several types of nucleophilic moieties in the side chain of amino acids, for example lysine or histidine, could catalyze the reaction. The latter amino acid is particularly interesting since it is a common part of catalytic triads as in lipases.



Catalytic Triad of Lipases (X = O) and Proteases (X = O, S)

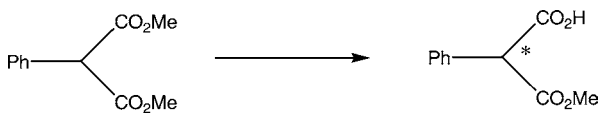
Several proteins were tested. Rabbit serum albumin (30 °C) and a commercial sample of bovine serum albumin, BSA (40 °C), showed conversions of 23 and 35% respectively, in 1 and in 9% ee's. Another sample of BSA showed an ee of 19% in lower conversion. These are very promising results since serum albumins are carrier proteins that do not show any catalytic activity in vivo.

It is important to emphasize that MBH adducts are important intermediates for the synthesis of APIs, for example chloramphenicol, fluoramphenicol, and thiamphenicol (Mateus and Coelho *J. Braz. Chem. Soc.* **2005**, *16*, 386).

Immobilized Penicillin G Acylase in the Asymmetric Hydrolysis of Dimethyl Phenylmalonate

Chiral monoesters of conveniently substituted malonic acids are important intermediates for the synthesis of tamine and christine (Pinnen et al. *J. Chem. Soc., Perkin Trans. 1* **1993**, 819); therefore, any effort in the production of related compounds can have an impact in process chemistry. In this arena, Guisán and co-workers (*Enzyme Microb. Technol.* **2007**, *40*, 997) described the use of immobilized penicillin G acylase (PGA) from *Escherichia coli* in the asymmetric hydrolysis of dimethyl phenylmalonate. Enzymatic desymmetrization is not an easy task, and to carry out a really useful reaction the diester must be highly preferred by the enzyme against the monoester, and the enzyme must exhibit a very high enantiomeric ratio to a particular isomer. Although the enzyme activity towards this particular compound was much lower than that towards the "natural" substrate, penicillin G, it was shown that this enzyme can achieve 100% conversion in 5 h (at 10 mM substrate concentration).

The fact that an immobilized enzyme (in a low loading to the support) was used can make this process useful in the preparation of chiral monoesters of substituted malonic acids, since greater loadings and recycle are possible. It is important to emphasize that ee's of 98% were claimed in this process.



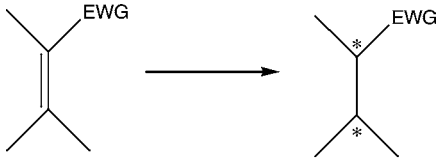
Lipases

Ghanem (*Tetrahedron* **2007**, *63*, 1721) reviewed the use of lipases in the asymmetric access to enantiomerically pure/

enriched compounds. In this review the use of lipases in organic solvents, ionic liquids, hydrofluorocarbon solvents, and supercritical CO_2 is covered. In addition, the kinetic resolution of primary, secondary, and tertiary alcohols is exemplified as well as (domino) dynamic kinetic resolution.

Bioreduction of Activated C−C Bonds

A joint paper from BASF and the University of Graz (Stuener et al. *Curr. Opin. Chem. Biol.* **2007**, *11*, 203) described the state of art on the use of microbial whole cells as catalysts in these processes to avoid (when using isolated enzymes or enzyme preparations) the recycle of cofactors. Coexpression of enoate reductases with the corresponding redox enzymes for NAD(P)H recycle in a suitable host enabled them to overcome the most common drawbacks of using whole cells, for example, low conversions, low stereoselectivities, and side reactions. As the reaction resembles an asymmetric Michael reaction, unactivated C−C bonds are unreactive. Thus, α,β-unsaturated carbonyl compounds, carboxylic acid derivatives, and nitro compounds are good substrates for flavin-dependent enoate-reductases with the creation of up to two chiral centers.



EWG = electron withdrawing groups

Methylated SiO_2 for Molecular Separation

Methylated microporous silica with high thermal stability and tuneable hydrophobicity appears to be an interesting material for separations. It was synthesized by acid-catalysed sol−gel hydrolysis and condensation of mixtures of tetraethylorthosilicate (TEOS) and methyltriethoxysilane (MTES). The gels exhibited a trend towards smaller ultramicropores with increasing methyl content, while in addition some supermicropores were formed with sizes of around 2 nm. For low MTES concentration, dilution prior to gelation and aging resulted in materials with clearly smaller ultramicropores, whereas only a minor effect of dilution on structure was found at high MTES concentration. The small ultramicropore size in "diluted" materials can be associated with a higher extent of condensation of mainly TEOS monomers. Stable structures formed from MTES in an early stage of synthesis may explain the particular micropore structure of MTES-rich gels. With increasing methyl content and with dilution of the sol, the affinity of the surface to water was strongly decreased. The applicability of microporous silica in wet atmospheres may thus be improved by methylation, and their pore structure modified by adaptation of the recipe, which would be highly relevant for industrial gas and liquid separation by inorganic membranes (*J. Mater. Chem.* **2007**, *17*, 1509−1517).

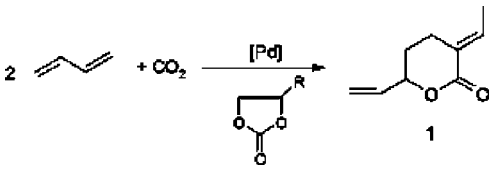
Supported Ionic Liquid-Phase Catalysis with Supercritical Flow

Rapid hydroformylation of 1-octene (rates up to 800 h^{-1}) with the catalyst remaining stable for at least 40 h and with very low rhodium leaching levels (0.5 ppm) is demonstrated when using a system involving flowing the substrate, reacting gases, and products dissolved in supercritical CO_2 ($scCO_2$) over a fixed-bed-supported ionic liquid-phase catalyst (*Chem. Commun.* **2007**, 1462−1464).

Oxidation of Propylene to Propylene Oxide (PO)

Catalytic oxidation of organic substances using molecular oxygen has problems of selectivity due to consecutive overoxidation. The use of mild oxidants, such as nitrous oxide (N_2O), offers a promising solution to the environmental problems associated with this gas. Recently, epoxidation of propylene with N_2O has been discussed in literature since the current PO manufacturing process based on chlorohydrin faces environmental pollution problems due to quantitative $CaCl_2$ production, whereas the hydroperoxide process is shaky due to its dependence on the market price of the alcohol byproduct. Propylene epoxidation with N_2O may provide an environmentally benign PO production route as no byproducts, other than nitrogen, are formed. The catalytic activity of alkaline and earth alkaline-modified silica-supported metal oxide is reported in the epoxidation of propylene with nitrous oxide. Iron oxide gave the best results, and surprisingly, chromium oxide also produced PO. An unmodified iron oxide catalyst showed low oxidation activity and produced propanal (57% selectivity) in concert with small amounts of acrolein, allyl alcohol, and acetone. After modification, the oxidation rate increased significantly, with PO the principal product. PO selectivities up to 85−90% and space−time yields of 0.25−0.53 mmol PO g^{-1} h^{-1} were obtained over supported iron oxide modified with Rb_2SO_4. A high throughput composition study revealed that other alkali and earth alkali salts were less effective modifiers. Isopropanol decomposition demonstrated that Rb_2SO_4 severely reduced the acidity of the catalyst. As a result of the neutralization, PO isomerization was drastically reduced. Accordingly, when feeding PO instead of propylene with N_2O over the catalyst, a similar reduction of consecutive PO reactions was observed on Rb_2SO_4 modification. Despite the excellent epoxidation results, a catalytic process remains unfeasible due to the restricted service time of the catalyst (*J. Catal.* **2007**, *247*, 86−100).

Telomerisation of Butadiene with Carbon Dioxide



The chemical use of carbon dioxide as a C_1-building block and supercritical solvent has attracted wide attention of researchers. The application and the influence on the selectivity of linear carbonates (dimethyl and diethyl carbonate), cyclic carbonates (ethylene carbonate, propylene carbonate, and butylene carbonate) and glycerol carbonate esters were examined in the telomerisation of butadiene with carbon dioxide In the reaction of carbon dioxide with 1,3-butadiene

it is possible to synthesize the very interesting δ-lactone 2-ethylidene-6-heptene-5-olide (**1**) under very mild reaction conditions. The synthesis of the δ-lactone (**1**) from the reactants 1,3-butadiene and carbon dioxide in carbonate solvents is achieved. Palladium bis(acetylacetonate) in combination with the ligand triphenylphosphine is used as homogeneous catalyst. At a reaction temperature of 60−100 °C yields of the δ-lactone up to 50% can be achieved in a reaction time of 4 h. By the substitution of the formerly used acetonitrile with cyclic carbonates the process is now free of hazardous solvents (*J. Mol. Catal. A:Chem.* **2007**, *267*, 149−156).

Thermal Isomerization of α-Pinene in Supercritical Ethanol

Among supercritical solvents/fluids, water, CO_2, alcohols, and some saturated and unsaturated hydrocarbons are most suitable as media for chemical transformations. Supercritical water and CO_2 are regarded as most promising in terms of environmental safety. Ethanol is also a common solvent widely used to conduct organic reactions under supercritical conditions. In combination with high solvation ability and respectively mild critical conditions, ethanol finds an increasingly wide use as a supercritical fluid (critical temperature = 516.2 K, critical pressure = 63 bar). A recent study showed that supercritical ethanol is an effective reaction medium for thermal isomerization of α-pinene. The rate of the reaction in supercritical solvent is by several orders of magnitude greater than the rate observed under normal conditions, with selectivity to the target reaction products being retained. A kinetic model of α-pinene isomerization in supercritical ethanol is developed, and it takes into account temperature and pressure effect on the reaction rate and selectivity (*Chem. Eng. Sci.* **2007**, *62*, 2414−2421).

Partial Oxidation of Aromatic Compounds to Useful Products in Heterogeneous Photocatalysis

Photocatalysis for degradation of pollutants is well studied. Applications of photocatalysis in synthesis have also been tested, but they are not very common because photocatalytic reactions have always been considered as highly unselective processes. Nevertheless, synthesis of methanol from methane and conversion of carbon dioxide to useful chemicals and production of hydrogen from water have attracted attention, due to the prominent growth of chemical and energetic unconventional routes. A group of Italian researchers has investigated the photocatalytic oxidation of different benzene derivatives by using TiO_2 aqueous suspensions at natural pH, irradiated by near-UV light. The organic molecules used as substrate contained an electron-withdrawing group (EWG) (nitrobenzene, cyanobenzene, benzoic acid, 1-phenylethanone), an electron-donating group (EDG) (phenol, phenylamine, *N*-phenylacetamide), or both an EWG and an EDG (4-chlorophenol). The primary photocatalytic oxidation of aromatic compounds containing an EDG leads mainly to ortho and para monohydroxy derivatives, whereas in the presence of an EWG all the monohydroxy derivatives are obtained. This finding can open a new green route for the synthesis of hydroxylated aromatic compounds. Moreover, in the presence of both an ED and an EW group, as in the case of 4-chlorophenol and hydroxycyanobenzenes, the attack of the hydroxyl radical takes place only in the positions activated by −OH. A competing reaction pathway to total oxidation was also observed from the start of irradiation; this pathway was more important for compounds containing an EWG (*Catal. Today* **2007**, *122*, 118−127).

Inline Analysis in Microreaction Technology: A Suitable Tool for Process Screening and Optimization

An important contribution of chemical engineering to modern process research and development is microreaction technology, especially for fast parameter screening. Because microreaction processing is executed in continuous mode, this technology is also an excellent fit for process analytical technology of high level (including process control). A group from the Fraunhofer Institute (Ferstl, W. et al. *Chem. Eng. Technol.* **2007**, *30*(3), 370) compares several inline analytical methods, with the objective of identifying the technique with the highest calibration precision for the quantification of the main product in two test reactions. The analytical methods investigated were Raman, near-infrared, and visible spectroscopy. The test reactions were both toluene nitrations, with monitoring of the formation of 4-nitrotoluene. The analytical probes were interfaced with flow-through cells placed after the microreactor and the residence time unit (see Figure 1 below, from the Ferstl article).

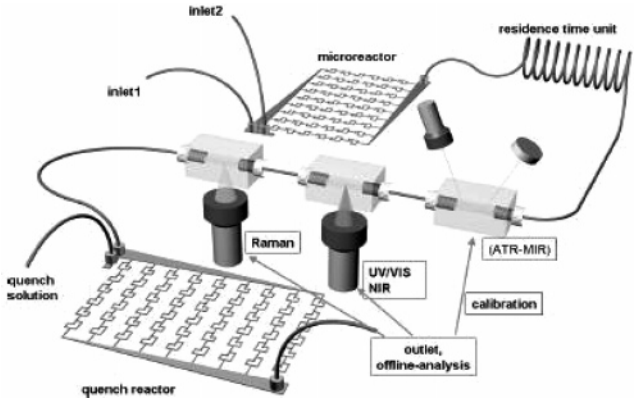


Figure 1. Microreactor setup for benchmarking different inline spectroscopic methods (reprinted from Ferstl, W. et al. *Chem. Eng. Technol.* **2007**, *30*(3), 370 with permission).

In order to be able to analyze also off-line the "reaction snapshot", the reaction mixture was quenched immediately after the inline analysis. In one case the reaction media was homogeneous, and in the other heterogeneous (liquid−liquid). For the development of the calibration model, using a DoE approach, several process parameters were investigated: temperature, stoichiometry, and total volumetric flow. For the homogeneous reaction Raman spectroscopy allowed for the highest calibration precision model (Raman spectroscopy was also the richest in chemical information). As expected, data analysis of the liquid−liquid system was more challenging than that of the homogeneous reaction. For the heterogeneous process all three analytical methods gave calibration models of comparable quality; the number of principal components required by the model is higher in the heterogeneous system

than in the homogeneous one. The heterogeneous system was also analyzed with a near-infrared spectrometer built in-house, operating as an acousto−optic tunable filter (AOTF).

Effective Use of Differential Scanning Calorimtery in Reactive Chemicals Hazard Evaluation

Differential scanning calorimetry (DSC) is a common screening technique used for reactive chemicals hazard evaluation, especially for thermal stability assessment. Whereas a relatively large number of expert publications discussing this topic are available, only a few reviews can be found for the benefit of process research and development scientists. Such a review was published (Frurip, D. et al. *Proc. Saf. Progr.* **2007**, *26*, 1, 51) summarizing the experience accumulated at the Dow Chemical Company over the past 20 years. In addition to the "triage" value, the authors discuss the semiquantitative and quantitative information that can be derived from DSC tests, as well as the situations where DSC should not be used as a safety screening tool. A hypothetical example, with two cases including the reaction of a nitro compound, are used in order to explain DSC testing strategies. A suitable approach to safety screening not only allows for a safe processing environment but also contributes to process research and development speed increase and cost decrease. The authors refer the readers to the appropriate ASTM references for experimental details and discuss some of them briefly; for example, they indicate that in some cases for oxidative stability assessments, DSC tests are performed both in the absence as well as in the presence of oxygen (this latter in an ampule rather than in a capillary tube).

Because kinetics more than thermodynamics determines whether a reaction runway will actually occur, kinetic modeling using DSC data is also presented. The complex case of autocatalytic reactions is discussed, because undesired autocatalytic reactions are encountered in industrial practice.

Biocatalysis for Pharmaceutical Intermediates: The Future Is Now

Because of increasing requests for regio- and stereoselective synthesis in the pharmaceutical industry, use of biocatalysts as isolated enzymes or whole cell systems continues to gain momentum. A review (collaboration between Merck and University College London, Pollard, D. J. et al. *TRENDS Biotechnol.* **2007**, *25*(2), 66) discusses various aspects of chemical processing using biocatalysts. The requirements for biocatalysts to be effectively used in chemical processing are summarized: throughput, catalyst cost, position in the synthesis, enantiomeric purity, and speed of development. Some of those requirements may be organization dependent; for example, with respect to speed of development the authors indicate that identification of a catalyst should occur in about 1 day, whereas the development of a preliminary process for the preparation of the initial gram should be accomplished in about 3 days.

The authors underline that successful process development requires "early integration of chemistry, molecular biology, enzymology, microbiology and bioprocess engineering". It appears that "many companies are now moving to this model, although discipline-specific thinking is difficult to avoid but must be removed for successful application". The contributions of miniaturization and mathematical modeling to the acceleration of process development are outlined. The authors believe that, even though many new, expensive chemocatalysts become more and more available, biocatalysts may have certain advantages, including smaller "environmental footprints". This review has 91 references.

To Triplicate or Not To Triplicate?

Many of us, in various fields, are used to the concept of "triplication"; it makes technical intuitive sense, and it is part of the "tradition" too. We typically execute analytical measurements in triplicate ("three-peats"), sometimes in duplicate, sometimes at higher level of multiplication, also called *m*-plication. But what about the cases when triplication can be expensive, or slows down development processes? A nontrivial answer can be found in a recent report by two teams of statisticians from Brazil (Singer, J. M. et al. *Chemom. Intell. Lab. Syst.* **2007**, *86*, 82). The complicating part may arise when it comes to the calculation of the intraclass correlation coefficient. This calculation requires a preliminary pilot study to evaluate the contribution of the intraclass (intracluster) variability to the total variability. High intraclass correlation coefficients indicate that the measurements are consistent, and therefore triplication may not be needed, especially if development cost and time may be negatively affected. At very low intraclass correlation coefficients "*m*-plication" can be justified, and the size of *m* could be determined on a case-by-case basis.

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