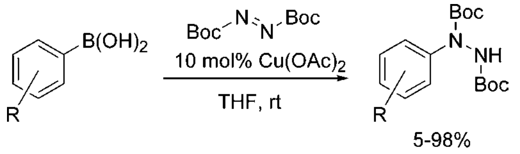
Organic Process Research & Development **2006**, *10,* 2–18

Highlights from the Literature

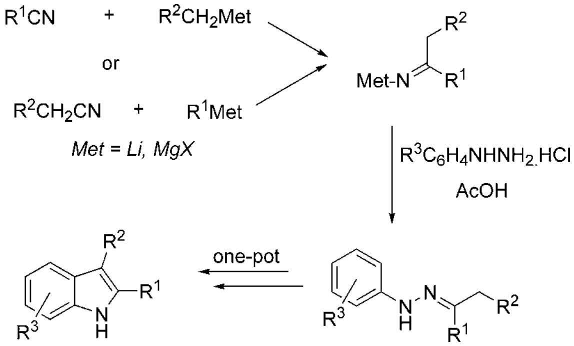
Some Items of Interest to Process R&D Chemists and Engineers

Copper Salt-Catalyzed Addition of Arylboronic Acids to Azodicarboxylates



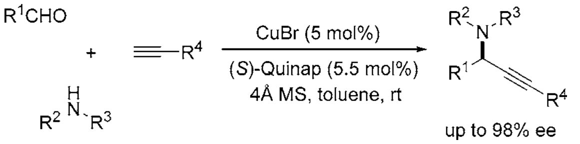
The group of Chatani in Japan report on the addition of arylboronic acids to azodicarboxylates in the presence of a catalytic amount (10 mol %) of a copper salt (*J. Org. Chem.* **2005**, *70*, 8631−8634). The reaction is tolerant of a wide variety of functional groups and takes place under mild conditions to give aryl-substituted hydrazines in high yields. However, the developed conditions employ two equivalents of the arylboronic acid, and the authors do not comment on the fate of the excess material. Although the reaction is generally tolerant of both electron-rich and electron-poor arylboronic acids, the use of *p*-fluoro- or *p*-trifluoromethyl-substituted arylboronic acids leads to lower yields.

Multicomponent Fisher Indole Synthesis



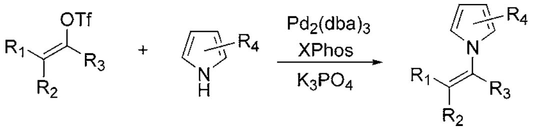
Multiple-component condensation (MCC) reactions, defined as processes ‘in which three or more reactants come together in a single reaction to form a new product that contains portions of all the components”, can provide a useful means of rapidly obtaining complex molecular structures. Seeking to enhance already known reactions of this type, the group of Ganem has investigated new three-component variations of the Fischer indole synthesis (*Tetrahedron* **2005**, *61*, 11374−11379). The idea is based on the reaction of organometallic reagents with nitriles or carboxylic acids, followed by in situ conversion of the metalated imine products into hydrazones and subsequent Fisher cyclization. Although the reported yields are generally moderate, fairly elaborate structures can be quickly accessed by this method. These new variations expand the scope and synthetic utility of this traditional method for the synthesis of indoles.

Enantioselective Three-Component Synthesis of Propargylamines



In another paper relating to multicomponent reactions, Knochel and co-workers report on a general preparation of functionalized primary chiral amines and amides (*Tetrahedron* **2005**, *61*, 11418−11426). The chirality is established by an enantioselective three-component reaction of an aldehyde, a terminal alkyne, and a secondary amine in the presence of copper(I) bromide/Quinap, leading to chiral propargylamines in high yields and enantioselectivities. The use of dibenzylamine/trimethylsilylacetylene leads to excellent yields/enantioselectivities with a variety of aliphatic aldehydes and provides handles for subsequent reactions. As a follow-up to an earlier communication, this full report details the functionalization/reduction of the derived products, leading to a variety of primary amines and amides.

Palladium-Catalyzed Synthesis of *N*-Vinyl Pyrroles and Indoles

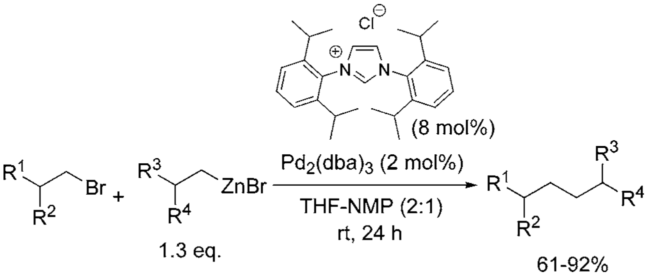


A stereospecific palladium-catalyzed N-vinylation of azaheterocycles with vinyl triflates is described by the Movassaghi group (*J. Org. Chem.* **2005**, *70*, 8638−8641). Configurationally defined vinyl triflates, readily available from 1,3-dicarbonyl compounds, are found to couple with various poorly nucleophilic heterocycles under the influence of the $Pd_2(dba)_3$/X-Phos system. Both cyclic and acyclic vinyl triflates participate along with pyrrole and indole derivatives. The choice of anhydrous potassium phosphate tribasic is found to be crucial for success. Alternative bases tested lead to nonproductive hydrolysis or elimination of the vinyl triflate species.

Room Temperature Pd-Catalyzed Alkyl−Alkyl Negishi Coupling Reaction

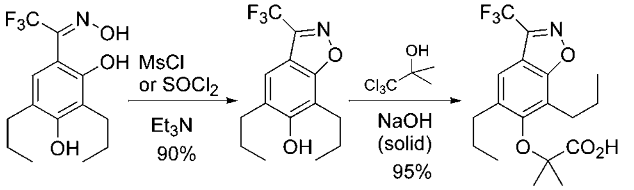
A high-yielding cross-coupling reaction of unactivated alkyl bromides possessing β-hydrogens with alkylzinc halides utilizing a Pd/N-heterocyclic carbene (NHC) catalyst at room temperature has been reported by Organ and co-workers (*J. Org. Chem.* **2005**, *70*, 8503−8507). A variety of Pd sources

10.1021/op0502405 CCC: $33.50



with the commercially available ligand precursor 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr•HCl) successfully couples 1-bromo-3-phenylpropane with *n*-butylzinc bromide in THF/NMP. An investigation of different NHC precursors shows that the bulky 2,6-diisopropylphenyl moiety is necessary to achieve high coupling yields. The corresponding ethyl analogue is poorly active. Under optimal conditions, a number of alkyl bromides and alkylzinc halides possessing common functional groups (amide, nitrile, ester, acetal, and alkyne) are effectively coupled. It is noteworthy that α-substituted alkyl bromides and alkylzinc halides successfully undergo cross-coupling. Also, under these conditions alkyl chlorides are unaffected.

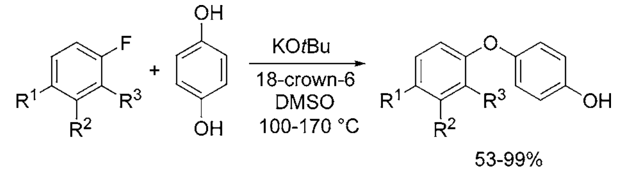
Formation of a Sterically Congested α-Aryloxyisobutyric Acid via a Bargellini Reaction



Chung, Cvetovich, and co-workers at Merck reported on a practical synthesis of a PPAR agonist (*J. Org. Chem.* **2005**, *70*, 8560−8563). Highlights included the efficient formation of a benzisoxazole by treatment of an oxime with methanesulfonyl chloride/base. Alternatively, the same transformation could be achieved using thionyl chloride/base, proceeding via an unusual cyclic sulfite intermediate. The direct formation of the hindered α-aryloxyisobutyric acid using methyl 2-bromo-2-methylpropionate proved ineffective (<50%), necessitating a multistage process involving phenol alkylation with methyl 2-bromopropionate, then methyl iodide, then ester hydrolysis. To circumvent this problem, the Bargellini reaction using 1,1,1-trichloro-2-methyl- 2-propanol (chloretone), was investigated. A highly reactive, short-lived intermediate derived from chloretone, presumed to be dimethyl dichloro epoxide, was detected by ReacIR and its half-life determined to be ~5 min. The use of powdered NaOH as the base was vital to suppress aldol side-reactions of acetone solvent. Thus, the highly hindered α-aryloxyisobutyric acid was made in a single step in high yield. All the steps in this synthesis were demonstrated on a kilogram scale, and the Bargellini reaction produced consistent 92−95% isolated yields.

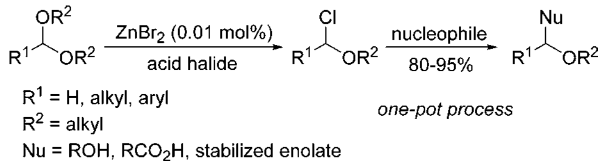
Selective Displacement of Aryl Fluorides with Hydroquinone: Synthesis of 4-Phenoxyphenols

Marcune and co-workers at Merck reported on the selective displacement of a variety of aryl fluorides with



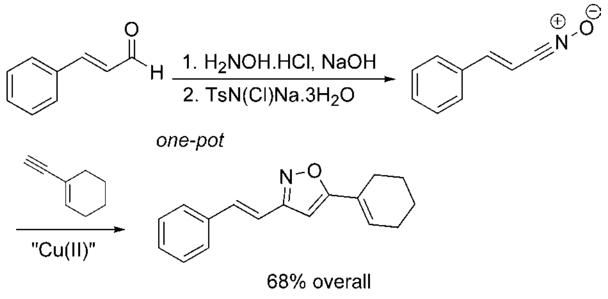
hydroquinone to give substituted 4-phenoxyphenols (*Tetrahedron Lett.* **2005**, *46*, 7823−7826). Following a study of bases, solvents, temperature, and additives, the use of potassium *tert*-butoxide in DMSO was found to optimal. These conditions were shown to minimize trimer formation. In some cases, the addition of 18-crown-6 resulted in a significant rate enhancement, allowing the reactions to proceed at lower temperature (100 °C). One of the products (4-(4-chlorophenoxy)-phenol) was further elaborated in three steps to provide a key intermediate in the synthesis of a PPAR agonist compound.

Simple, Rapid Procedure for the Synthesis of Chloromethyl Methyl Ether and Other Chloro Alkyl Ethers



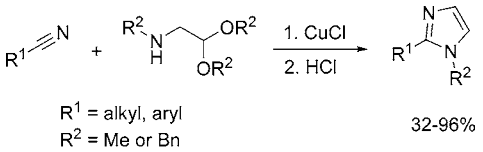
Berliner and co-workers at Pfizer have developed a practical zinc(II)-catalyzed formation of haloalkyl ethers from acetals and acid halides (*J. Org. Chem.* **2005**, *70*, 9618−9621). The simple chloromethyl methyl ether (MOMCl) is a useful reagent for alcohol protection and also for other carbon−carbon bond-forming reactions. However, MOMCl chloride is known to be carcinogenic, and owing to the method of preparation (formaldehyde/MeOH/HCl), commercial material is often contaminated with the even more toxic bis(chloromethyl)ether. Consequently, the described method for simple in situ preparation of haloalkyl ethers from readily available acetals should be very useful. Reactions from millimole to mole scale are typically complete in 1−4 h with low catalyst loadings (ZnBr$_2$, 0.01 mol %) and using inexpensive acetyl chloride. The solutions of haloalkyl ethers thus obtained can be utilized directly in reactions in which the presence of the ester byproduct does not interfere. Excess haloalkyl ether is destroyed on workup, thereby minimizing exposure to this class of carcinogenic compounds.

One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles



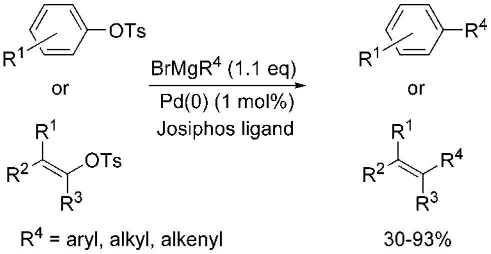
Fokin and co-workers continue to study variations on the "click-chemistry" theme and now describe the preparation of 3,5-disubstituted isoxazoles by a convenient one-pot, three-step procedure (*J. Org. Chem.* **2005**, *70*, 7761−7764). Although the uncatalyzed 1,3-dipolar cycloaddition of nitrile oxides to acetylenes is known, applications to the synthesis of isoxazoles are scarce, and the yields are often quite low; side reactions result in impurities, and both regioisomers are often obtained. Under copper(I) catalysis the cycloaddition reaction is regioselective and high yielding. Importantly, the requisite nitrile oxides can be generated in situ via chlorination/elimination of an intermediate oxime using inexpensive chloramine T trihydrate. Most functional groups do not interfere with the reaction, which can be performed in aqueous solvents without protection from oxygen. A wide range of substituents is tolerated on both the aldehyde/nitrile oxide and alkyne components.

Expedient Synthesis of Substituted Imidazoles from Nitriles



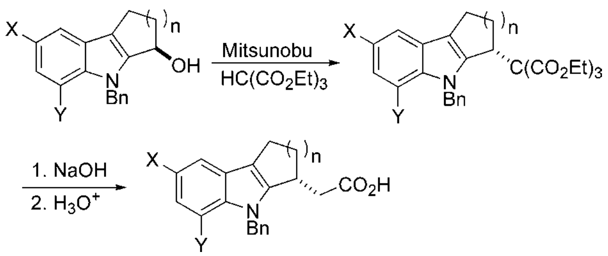
Frutos and co-workers at Boehringer Ingelheim report on a new method for the synthesis of substituted imidazoles (*Tetrahedron Lett.* **2005**, *46*, 8369−8372). The procedure involves Cu(I)-promoted addition of amines to nitriles followed by acid-promoted cyclization of the intermediate amidines. Moderate to good yields of various 2-substituted, 1,2-disubstituted, and 1,2,4-trisubstituted imidazoles are obtained using this one-pot method. A drawback is the use of stoichiometric quantities of a copper salt.

Kumada Coupling of Aryl and Vinyl Tosylates under Mild Conditions



Hartwig and co-workers expand upon their previous work on Kumada couplings of aryl/vinyl tosylates (*J. Org. Chem.* **2005**, *70*, 9364−9370). Aryl and alkenyl tosylates are easily prepared, inexpensive, and thus, attractive for transition metal-catalyzed couplings, but their reactivity is low. In this report, it is shown that catalysts containing strongly electron-donating and sterically hindered bisphosphines of the Josiphos class allow for Kumada couplings to be conducted with aryl and vinyl tosylates, in many cases at room temperature. The resulting biaryls, vinylarenes, and alkylarenes are isolated in good to excellent yield. Significantly, the developed conditions require only a small excess of the Grignard reagent, which would be important if this partner were valuable. The Kumada coupling has advantages and disadvantages, relative to other types of couplings. The Kumada coupling is potentially more direct than equivalent Suzuki or Stille coupling since no synthesis of boronic acids or organotin reagents is required. However, functional group tolerance is usually lower than Suzuki or Stille processes, owing to the more aggressive nature of the Grignard reagent.

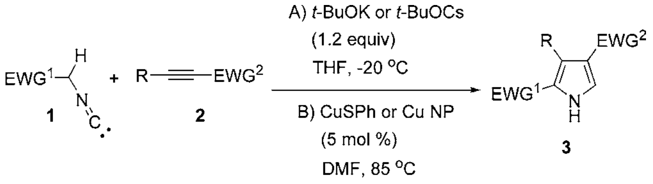
Stereoselective Formation of Carbon−Carbon Bonds via S_N2-Displacement: Synthesis of Substituted Cycloalkyl[*b*]indoles



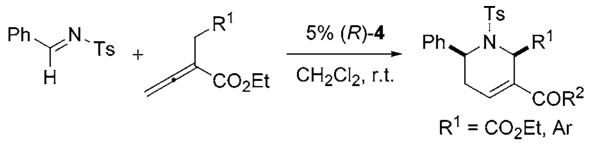
Hillier and co-workers at Merck describe a general asymmetric synthesis of substituted cycloalkyl[*b*]indoles (*J. Org. Chem.* **2005**, *70*, 8385−8394). The key features of this approach are (1) the utilization of a Japp−Klingemann condensation/Fischer cyclization to prepare cycloalkyl[*b*]indolones, (2) the asymmetric borane reduction of these heterocyclic ketones with (*S*)-OAB to obtain enantiomerically pure alcohols, and (3) the stereoselective S_N2-displacement of these indole alcohol substrates with a carbon nucleophile under Mitsunobu conditions to set the C1 or C3 tertiary carbon stereocenter. The use of trimethylphosphine (PMe_3) and bis(2,2,2-trichloroethyl) azodicarboxylate (TCEAD) was found to have an effect on the Mitsunobu dehydrative alkylation. Alternative phosphines significantly reduced both the yield and enatiomeric excess of this step.

Novel Syntheses of Heterocycles: Pyrroles, Piperidines, Carboxyindazoles, Furanes

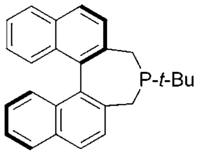
Polyfunctional pyrroles are basic constituents of numerous natural products and pharmaceuticals. Larionov and de Mejiere envisaged a high-yielding synthesis of 2,3,4-pyrroles via the formal cycloaddition of a α-metalated isocyanide derived from **1** and an activated triple bond (*Angew. Chem., Int. Ed.* **2005**, *44*, 5664−5667). The bases that worked best were potassium or cesium *tert*-butoxide. Moreover, the assay of Cu catalysts revealed Cu (I) benzenethiolate and preactivated nanosize metallic copper to be the most efficient species. A variety of 2,3,4-substituted pyrroles bearing sulfonyl, dialkoxyphosphoryl, trifluoromethyl, cyano, and morpholino groups was obtained in one step from readily available acetylenes and commercial methyl isocyanides. Of particular interest are the cyclopropyl-substituted heterocycles, which are present in compounds with a variety of biological activities.



Wurz and Fu reported the enantioselective [4+2] annulation of nonenolizable imines with allenylcarboxylates to afford functionalized piperidines (*J. Am. Chem. Soc.* **2005**, *127*, 12234−12235). Curiously enough, the transformation is mediated by chiral phosphine nucleophiles (e.g., **4**) that are usual ligands for transition metals. Whereas a variety of substituted imines and allenes can be used successfully, the reaction is extremely sensitive to the nature of the catalyst: closely related phosphines and bisphosphines display disparate yields and enantioselectivities. The air-stable salt of catalyst **4** obtained by treatment with HBF_4 promotes the reaction in the presence of K_2CO_3 with results analogous to those obtained with free catalyst **4** and prevents phosphine oxidation. Dichloromethane and 1,2-dichloroethane are solvents of choice for the annulation since nonhalogenated solvents such as toluene, acetone, and THF reduce reaction rates. Typically, high cis:trans selectivities complement excellent enantioselectivities and yields. Arrow push enthusiasts will appreciate that the annulation is favored by allenes bearing an R^1 group that can stabilize an anion. A mechanistic hypothesis can be found in the manuscript that describes the original transformation using PBu_3 as catalyst (Kwon and co-workers, *J. Am. Chem. Soc.* **2003**, *125*, 4716−4717).

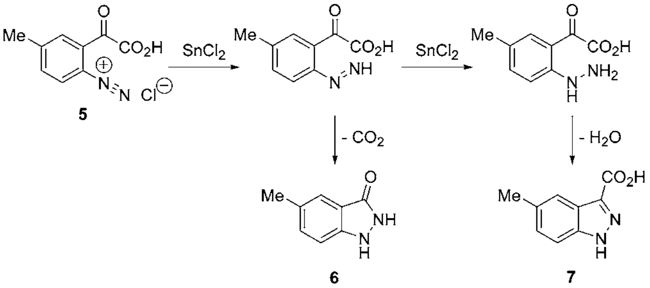


80-99% yield, >90:10 cis:trans, >90% ee

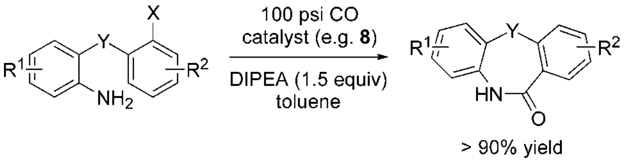


(*R*)-**4**

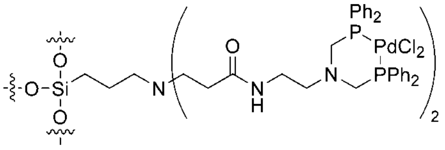
A recent communication by Johnson and Rodgers highlights the correlation between mechanistic considerations and the order of addition of reactants (*Synth. Commun.* **2005**, *35*, 2681−2684). The need for a dependable synthesis of carboxyindazole **7**, a key intermediate in the preparation of a group of HIV protease inhibitors, prompted the study of the reductive cyclization of diazonium salt **5**. This one-pot reaction was first reported in 1893. Subsequent reviews of the procedure described erratic yields, arduous isolations, and the adamant presence of 3-indazolone byproducts (e.g., **6**). The authors surmised that the formation of undesired 3-indazolone **6** results from the incomplete reduction of an intermediate diazo derivative. Following this mechanistic hypothesis, slow reductions resulting from the traditional addition of $SnCl_2$ to a solution of the diazonium **5** would promote contamination with **6**. Accordingly, the inverse addition of diazonium solutions to $SnCl_2$ mixtures maintained a high concentration of $SnCl_2$ and suppressed the formation of **6** to afford high yields (80−90%) of carboxyindazole **7**.



Dendrimer−Pd complexes on silica (e.g., **8**) are efficient catalysts for intramolecular carbonylations in the synthesis of seven- and eight-membered ring fused heterocycles containing oxygen, nitrogen, or sulfur (Lu and Alper, *J. Am. Chem. Soc.* **2005**, *127*, 14776−14784). The catalysts can be recovered by simple filtration and recycled for up to eight reactions with little loss of activity. The carbonylations afford high isolated yields, regardless of the nature of the substituents on the aromatic rings (R^1 and R^2). General conditions involve the use of 15 mg of dendritic catalyst per mmol of aniline and 1.5 mmol of DIPEA in an autoclave pressurized to 100 psi with carbon monoxide. Typical reaction temperatures are 80 °C for iodides and 120 °C for bromides.



Y = O, S, NMe, OCH_2, SCH_2
X = I, Br



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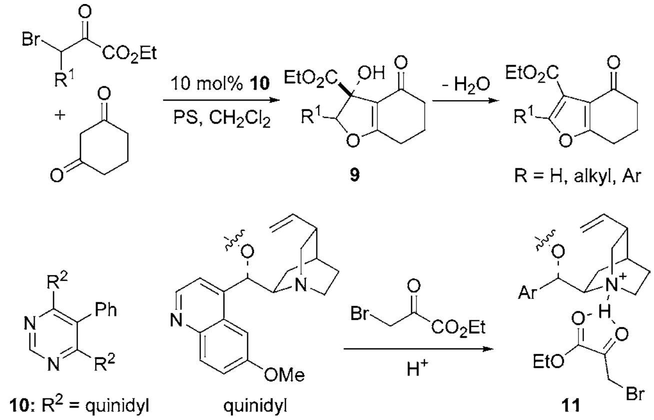
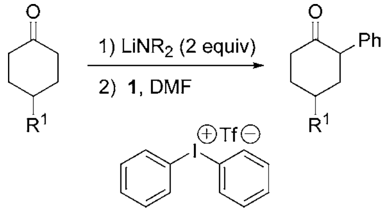
The Feist−Bénary synthesis of furans involves the condensation of a *β*-dicarbonyl compound with a α-haloketone. If the process is interrupted in the stage of the intermediate chiral hydroxydihydrofuran (i.e., **9**), the opportunity to mediate an asymmetric transformation using a chiral catalyst arises. The group of Calter has reported an ingenious catalytic asymmetric variant of the Feist−Bénary synthesis (*J. Am. Chem. Soc.* **2005**, *127*, 14566−14567). Using the condensation between ethyl bromopyruvate and cyclohexanedione as the model reaction, a screening of conditions identified diphenylpyrimidinyl derivatives of *Cinchona* alkaloids **10** as effective catalysts in the presence of 1.1 equiv of Proton Sponge (PS). The latter prevents dehydration and hence formation of undesired furan. Yields and selectivities are good, and even the transformation of racemic secondary α-bromoketones affords excellent diastereo- and enantioselectivities. A mechanistic proposal involves activation of the β-dicarbonyl by the protonated chiral *Cinchona* catalyst (e.g., **11**) followed by attack of the nucleophile on the less hindered face.



α-Arylation and α-Alkylation of Carbonyl Compounds

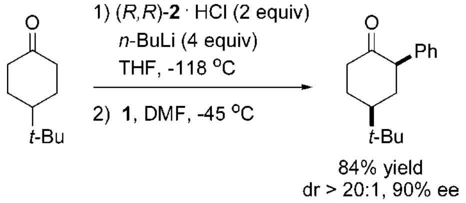
Aggarwal and Olofsson described the direct asymmetric arylation of 4-substituted cyclohexanones with diaryl iodonium (III) salts (*Angew. Chem., Int. Ed.* **2005**, *44*, 5516−5519). This transformation was previously achieved on nonepimerizable tetrasubstituted ketones or via multistep protocols.

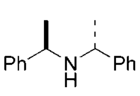


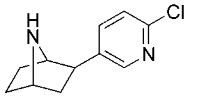
1

R^1	Base	cis:trans
H	LiHMDS	---
t-Bu	LDA	>20:1
$NBoc_2$	LiHMDS	>20:1
NBoc	LDA	10:1

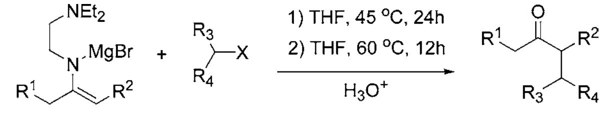
The enantioselective version of this methodology was developed by employing Simpkin's base (*R*,*R*)-**2**. Thus, deprotonation of 4-*tert*-butylcyclohexanone followed by reaction with diphenyl iodonium triflate gave the arylated product (2*R*,4*S*) in 84% yield and 90% ee. The strategy was applied to the synthesis of alkaloid (−)-epibatidine, an analgesic 400 times more potent than morphine.




(*R*,*R*)-**2**


(-)-epibatidine

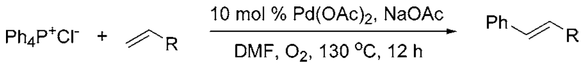
A drawback of the alkylation of metal enolates and enamides is the limitation of alkylating reagents to highly reactive alkyl iodides and bromides, and benzylic and allylic halides. The group of Nakamura reported that magnesium enamides with a nitrogen-coordinating site allow the use of alkyl fluorides and chlorides as electrophiles (*J. Am. Chem. Soc.* **2005**, *127*, 14192−14193). Imines of the types **3** and **4** were deprotonated with MesMgBr. Alkylation of the resulting metalloenamides with primary fluorides or primary or secondary chlorides followed by aqueous workup yielded the desired α-substituted ketones. In the case of unsymmetrical enamides **4**, the alkylation took place preferentially on the least substituted carbon atom (9:1 ratio). It is worth mentioning that the reaction conditions were tolerated by functional groups such as amines and silyl ethers. The secondary alkylating agent 2-chlorocycloheptane gave limited amounts of cycloheptene (3−17%). Moreover, the substitution takes place with inversion of configuration as shown by using (*S*)-1-chloroethylbenzene.



3: $R^1 = R^2$ = Me, Et X = F, Cl
4: R^1 = *i*-Pr; R^2 = Me

Metal-Promoted Transformations

Among the most powerful tools for the formation of C−C bonds are the transition metal-catalyzed olefination and cross-coupling reactions. Chang and co-workers describe the use of tetraarylphosphonium halides as arylating reagents in Heck and cross-coupling reactions, and provide mechanistic details of the activation process (*Angew. Chem., Int. Ed.* **2005**, *44*, 6166−6169). Tetraphenylphosphonium chloride (**1**) was treated with *n*-butyl acrylate (3.0 equiv) in the presence of $Pd(OAc)_2$ (10 mol %) and NaOAc (3.0 equiv), to yield the corresponding *trans*-cinnamate in 85% yield.



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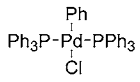
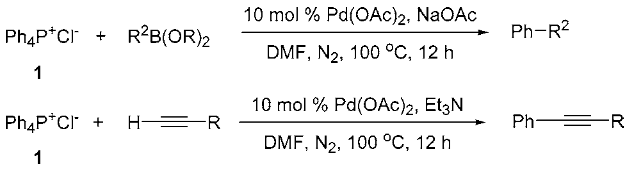

2

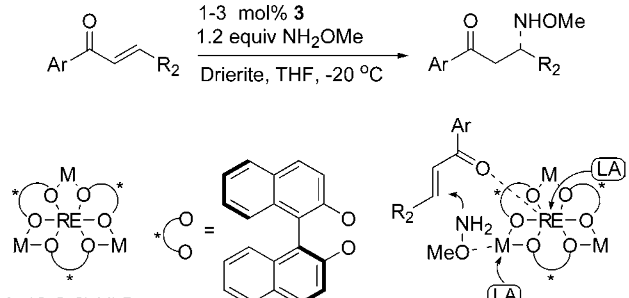
R	yield (%)
CO_2Bu	85
CO_2NMe_2	98
SO_2Ph	74
$PO(OEt)_2$	76
$CH_2CHCOCH_3$	70

Pd-mediated cleavage of the P−C bond of tetraarylphosphonium ions was evidenced by the isolation of oxidatively inserted palladium species. When **1** was treated with 0.5 equiv of $Pd_2(dba)_3$ in the presence of PPh_3, **2** was isolated as a transparent solid that readily reacted with *n*-butyl acrylate at 80 °C. The reaction was faster when carried under an oxygen atmosphere and NaOAc was the most effective of the bases examined. Among the phosphoniun halides, chlorides provided the highest yields. No selective aryl transfer took place when differently substituted phosphonium halides (Ph_3PAr) were used. Instead, 3-to-4:1 mixtures of unsubstituted (major) and substituted cinnamates (minor) were obtained as a result of statistical aryl transfer.

The use of phosphonium species in the Suzuki−Miyaura reaction was next investigated. A variety of functional groups on the organoboron compounds were tolerated under the reaction conditions. Similarly, the reaction of **1** with a variety of alkynes (Sonogashira-type reaction) was not affected by substituents in the alkyne.

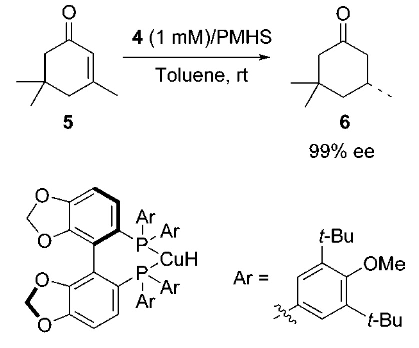


Matsunaga, Shibasaki, and co-workers demonstrate the effectiveness of Lewis acid−Lewis acid cooperative catalysis in an aza-Michael reaction with methoxylamine (*J. Am. Chem. Soc.* **2005**, *127*, 13419−13427). The proposed active catalyst (*S*,*S*,*S*)-YLB **3** (0.3−10 mol %) consists of one rare earth metal (RE), three 1,1′-binaphthoxide units, and three alkali metals (M). The oxygen atom of the methoxylamine coordinates to the alkali metal of the heterobimetallic complex without decreasing the nucleophilicity of the nitrogen. The Lewis acidic part of the catalyst controls the orientation of both the enone and the nucleophile. Overall, the catalyst promotes the addition of methoxylamine to enones in excellent yields (80−97%) and ee's (82−95%). The scope of the methodology was further broadened to α,*β*-unsaturated acylpyrroles that were transformed into chiral aziridines or *β*-amino esters.



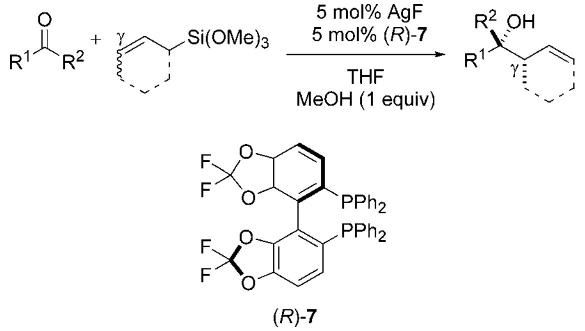
3: (*S*,*S*,*S*)-YLB

Lipshutz and Frieman developed a stable complex of copper hydride with Takasago's reagent (DBTM-segphos) that mediates asymmetric hydrosilylations (*Angew. Chem., Int. Ed.* **2005**, *44*, 6345−6348). Following a survey of copper salts, $Cu(OAc)_2{\cdot}H_2O$ was chosen as the precursor of **4** in the presence of excess polymethylhydrosiloxane (PMHS). Using a solution of **4** (1 mM in toluene) and PHMS that had been stored for 5 weeks at room temperature in a Sure/Seal container, isophorone **5** was successfully reduced to ketone **6** with a substrate/copper ratio of 1000:1. Using microwaves, reaction times were reduced to 10 min without erosion of enantioselectivity.



4:[(DTBM-segphos)CuH]

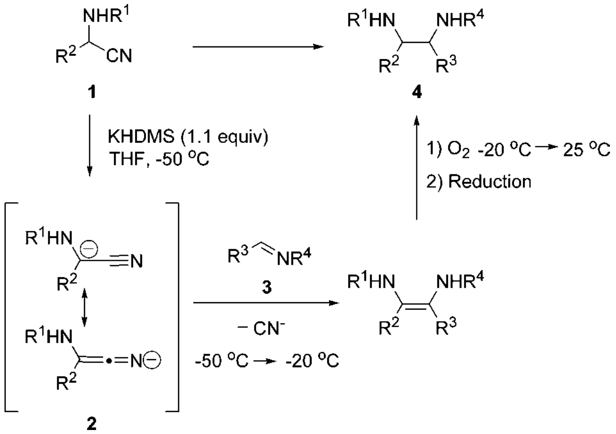
Chiral allylsilver complexes generated from allyltrimethoxysilanes and catalytic amounts of AgF and (*R*)-DIFLUORPHOS (**7**) add to ketones to give tertiary homoallylic alcohols in good yields and enantioselectivities. This variant of the Sakurai−Hosomi allylation was discovered by Wadamoto and Yamamoto at The University of Chicago (*J. Am. Chem. Soc.* **2005**, *127*, 14556−14557). Typical reaction conditions involve the use of an excess (2−3 equiv) of allylsilane and 1 equiv of MeOH in THF to dissolve the AgF−bisphosphine complex. MeOH also promotes the fast protonation of the intermediate silver homoallyl alkoxide at temperatures between −78 and −40 °C. The use of *γ*-substituted allylsilanes unvaryingly provides optically active syn isomers (>90:10 syn:anti). High diastereo- and enantioselectivities are independent of the configuration of the starting allylsilane, indicating that the intermediate diastereomeric allylsilver complexes experience fast interconversion relative to the 1,2-addition time scales.



(*R*)-**7**

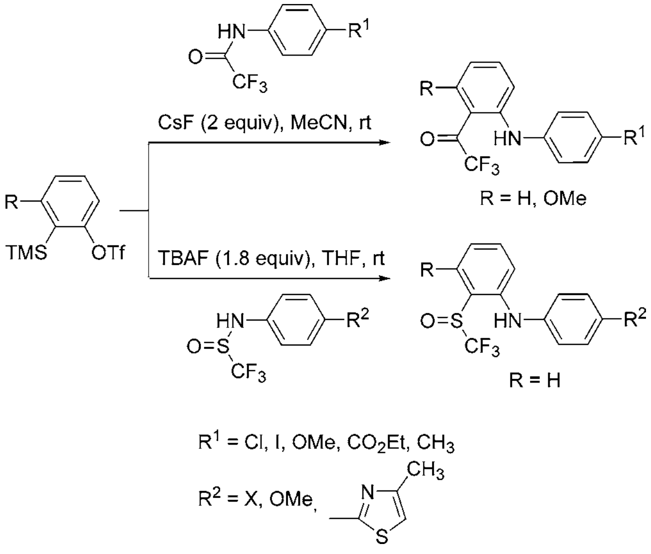
Diastereoselective Synthesis of Unsymmetrical 1,2-Diamines

The group of Opatz reported a one-pot method for the synthesis of 1,2-diamines via ketene iminates that result from the deprotonation of Strecker adducts **1** with KHMDS (*Angew. Chem., Int. Ed.* **2005**, *44*, 5662−5664). Ketene iminates **2** add onto imines **3**, and the intermediate amides spontaneously eliminate cyanide upon warming. Bubbling the reaction mixture with air provides diimines that are reduced in situ by the addition of $BH_3{\cdot}THF$. Thus, the target diamines **4** are obtained in good yields after purification (55−69%). The anti:syn ratio is defined by the additive employed in the reduction step. When $NaBH_4$ is used, the reduction selectively furnishes the *syn*-diamines (dr up to 20:1). The *anti*-diamines are obtained when the reduction is performed in the presence of phthalic acid (dr up to 27:1). This method allows the synthesis of highly substituted unsymmetrical diamines without the use of protecting groups.



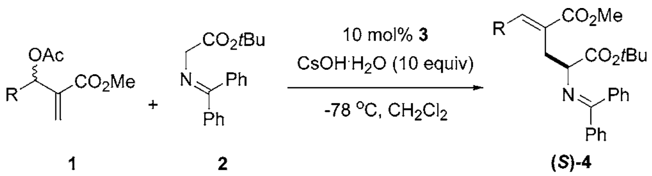
C−N Addition of Amides and S−N Addition of Sulfinamides to Arynes

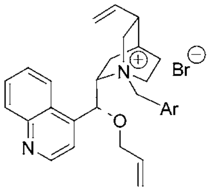
During work on the arylation of amines and sulfonamides, Liu and Larock found that a variety of substituted *N*-aryltrifluoroacetamides undergo C−N addition to the benzyne precursor 2-trimethylsilyl triflate in good yields (*J. Am. Chem. Soc.* **2005**, *127*, 13112−13113). Trifluoroacetamides with electron-donating or electron-withdrawing groups provided the desired addition products upon treatment with CsF in MeCN. In the case of a 3-methoxy-substituted silylaryl triflate, a single regioisomer was obtained. Extrapolation of the methodology to trifluoromethanesulfinamides required optimization of the reaction conditions (TBAF in THF) to afford the products of addition in good isolated yields (75−91%). Since the transformation does not involve a transition metal, halides are readily tolerated.



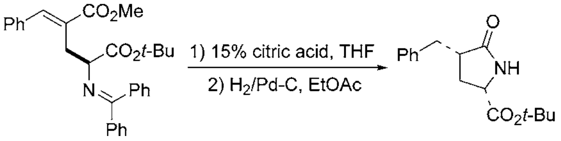
Catalytic Enantioselective Synthesis of Glutamic Acid Derivatives: Chiral PTC

A tandem conjugate addition−elimination under phase-transfer catalysis (PTC) was communicated by Ramachandran and co-workers for the enantioselective preparation of amino acids (*J. Am. Chem. Soc.* **2005**, *127*, 13450−13451). The reaction of allylic acetates **1** with the imine of glycine *tert*-butyl ester **2** occurs in the presence of catalytic amounts of derivatives of *Cinchona* alkaloids such as bromide **3**. Using the optimized conditions, a number of optically active alkylidene glutamates **4** were prepared in good to excellent yields and high ee's. Allylic acetates bearing a variety of aromatic and alkyl substituents were used as starting materials. The scope of the process was demonstrated by transforming **4** (R = Ph) into 4-substituted glutamic acid derivatives.



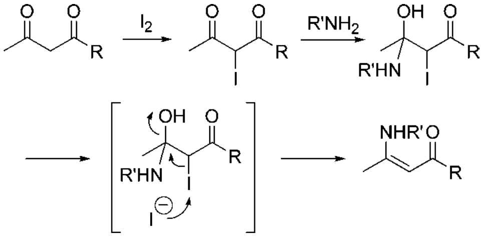


3: Ar = 9-anthracenyl



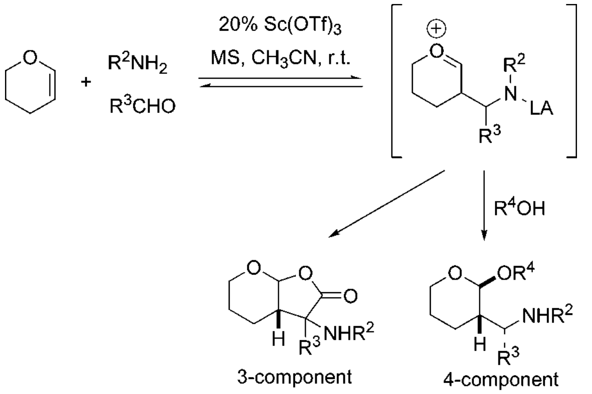
Iodine-Catalyzed Formation of β-Enaminones

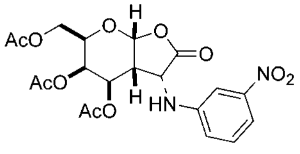
The condensation of amines with β-dicarbonyl compounds is a general strategy for the preparation of β-enaminones. Current methodologies employed for this transformation involve the azeotropic removal of water, a variety of Lewis acids, and the use of microwaves or ultrasound. Barua et al. describe the use of substoichiometric amounts of iodine (20 mol %) for the condensation of a variety of primary amines with β-ketoesters or 1,3-diketones at room temperature under solvent-free conditions (*Synth. Commun.* **2005**, *35*, 2811−2818). The resulting β-enaminones are obtained in excellent yields within minutes as the only isolable compounds. The authors propose a mechanism based on the formation of a reactive α-iododicarbonyl intermediate.



Multicomponent Reactions

Multicomponent reactions (MCRs) allow access to molecular complexity from simple starting materials. The group of Lavilla at the Universitat de Barcelona reported MCRs leading to diversely functionalized oxacycles (*Angew. Chem., Int. Ed.* **2005**, *44*, 6679−6683). During the Lewis acid-catalyzed reaction of an amine, an aldehyde, and an enol ether, the oxocarbonium intermediate is trapped by an external nucleophile (e.g., R^4OH). The process is general to alkylamines and anilines with electron-donating or electron-withdrawing groups. The diastereoselectivity of the MCR ranges from 2.3:1 with anilines to 4:1 with bulkier amines (Ph_2CHNH_2). The carbonyl compounds investigated include glyoxylic acid and ethyl glyoxylate as well as aromatic aldehydes and isatin. Among external nucleophiles, primary alcohols (MeOH, EtOH, and *n*-BuOH) gave the best yields (80%). Remarkably, glycals bearing a substituent at position 4 displayed excellent facial stereoselectivity. For example, adduct **1** was obtained in 71% yield from tri-*O*-acetyl-D-galactal using microwave irradiation.





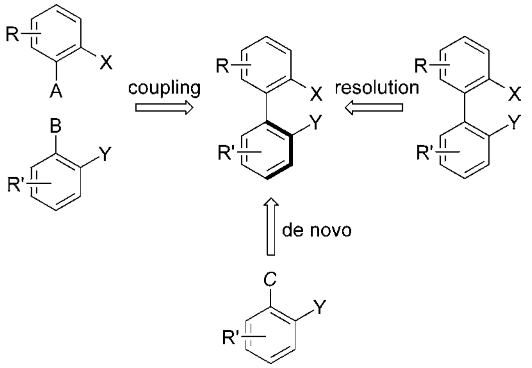
1 (71% yield, dr 99:1)

Atroposelective Synthesis of Axially Chiral Biaryl Compounds

Axial chirality is the basis for common reagents and catalysts in asymmetric synthesis (e.g., diphosphine BINAP), and in several cases governs the pharmacological properties of bioactive compounds such as vancomycin. Bringmann, Breuning, and co-workers compiled a comprehensive review that summarizes the advances in the asymmetric synthesis of axially chiral biaryl compounds (*Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427).

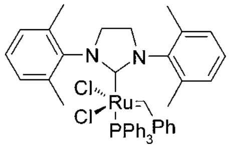
Mechanisms of atropoisomerization, as well as conditions for the rotational stability of the aryl−aryl single bond that is fundamental for the phenomenon of axial chirality, are discussed. Moreover, the authors enumerate prerequisites for the existence of axial chirality along with a thorough collection of brain-teasing examples.

The strategies to synthesize chiral biaryl systems are grouped in three categories. The classic approach entails an atroposelective coupling step in which the construction of the axis and the asymmetric induction take place simultaneously. A less-exploited method involves the resolution of stereochemically not yet defined biaryls. Finally, a new strategy transforms a single aryl carbon bond into the biaryl axis upon de novo construction of the second aryl moiety.

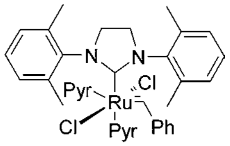


Lewis-Acid-Assisted Cross Metathesis of Acrylonitrile with Functionalized Olefins Catalyzed by Phosphine-Free Ruthenium Carbene Complex

The exchange of the PPh_3 ligand in the metathesis catalyst **1** for a pyridine ligand at room temperature leads to the formation of the stable ruthenium complex **2** (He, R. *Org. Biomol. Chem.*, **2005**, *3*, 4139). This complex exhibits catalytic activity for the cross metathesis (CM) also for the CM of acrylonitrile with various functionalized olefins under mild conditions, and its activity can be further improved by the addition of a Lewis acid such as $Ti(O^iPr)_4$. Products were obtained in moderate to high yields in predominately the *Z*-configuration. The reaction of acrylonitrile is faster with olefins substituted with hydroxyl or aldehyde functions than with carboxylic acids or esters.



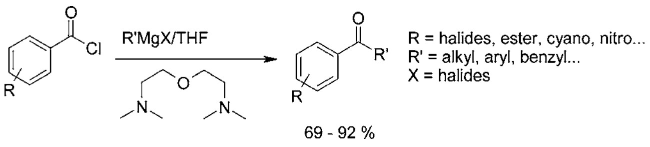
1



2

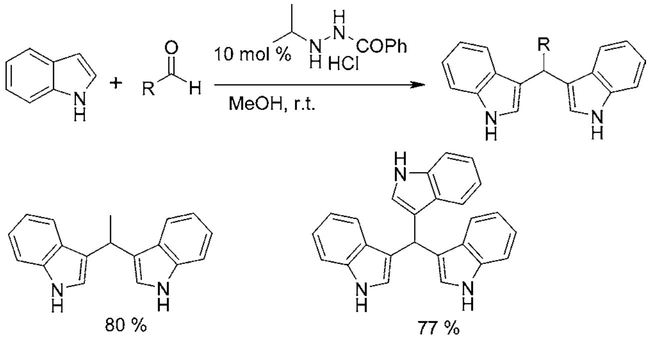
Addition of Grignard Reagents to Aryl Acid Chlorides: An Efficient Synthesis of Aryl KetonesAddition of Grignard Reagents to Aryl Acid Chlorides: An Efficient Synthesis of Aryl Ketones

Direct addition of Grignard reagents to acid chlorides in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl]ether proceeds selectively to provide aryl ketones in high yields (Wang, X. et al. *Org. Lett.* **2005**, *7*, 5593). A possible interaction between the ligand and the Grignard reagent moderates the reactivity, preventing the newly formed ketones from further reaction.



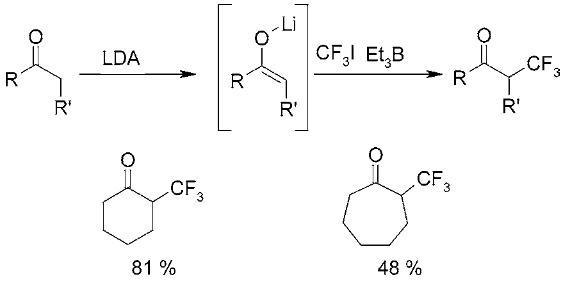
Amino Catalytic Preparation of Bisindolylalkanes

Tomkinson, N. C. O. et al (*Org. Biomol. Chem.* **2005**, *3*, 4043) have developed a novel amino catalytic method for the synthesis of bisindolylalkanes. The benzoic hydrazide-derived catalyst **1** can used with a loading as low as 1 mol %. Bisindolylalkanes are obtained in good to high yields from the corresponding aldehydes and ketones at room temperature. The reaction is believed to proceed via an iminium ion intermediate. If indole-3-carboxaldehyde is used, trisindolyl methane is obtained in a very good yield (77 %).



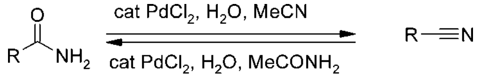
Facile Radical Trifluoromethylation of Lithium Enolates.

Mikami, K. et al. (*Org. Lett.* **2005**, *7*, 4883) have found that lithium enolates are applicable to radical trifluoro methylation. The reaction is very fast and gives α-trifluoromethylated cyclic ketones in moderate to good yields. If the reaction is left for several hours, the yield drops due to dehydrofluorination of the product. Triethylboron is needed as radical initiator, and the source of the trifluoromethyl group is trifluoromethyl iodide.



Mild and Reversible Dehydration of Primary Amides with $PdCl_2$ in Aqueous Acetonitrile

A new, mild and reversible method to convert primary amides to nitriles in good yields using $PdCl_2$ in aqueous acetonitrile has been developed by Maffioli, S. I. et al. (*Org. Lett.* **2005**, *7*, 5237). This is the reversal of the known hydrolysis of nitriles to primary amides. Not only is the catalyst important for the reaction, but acetonitrile and water are also essential for the conversion. The reversal reaction was found to be easily done with a mixture of acetamide and water also at room temperature.

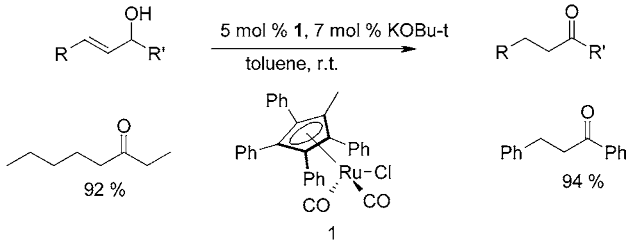


Stereoselective Construction of Quaternary Stereocenters

Christoffers, J. and Baro, A. (*Adv. Synth. Catal.* **2005**, *347*, 1473) have reviewed the stereoselective construction of quaternary stereocenters from the recent literature. With a central view on this particularly challenging structural issue, selected examples from the recent literature have been highlighted.

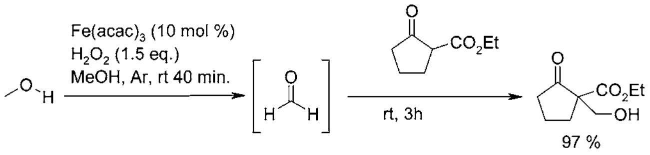
Efficient Redox Isomerization of Allylic Alcohols at Ambient Temperature Catalyzed by Novel Ruthenium–Cyclopentadienyl Complexes

A range of ruthenium cyclopentadienyl (Cp) complexes has been prepared and used for isomerization of allylic alcohols to the corresponding saturated carbonyl compounds in excellent yields (Bäckvall, J.-E. et al. *Chem. Eur. J.* **2005**, *11*, 5832). Complexes bearing CO ligands show higher activity than those with phosphine ligands. The isomerization rate is also highly affected by the substituents on the Cp ring. Tetra(phenyl)methyl-substituted catalysts rapidly isomerize allylic alcohols at ambient temperature.



Iron(III)-Catalyzed Tandem Sequential Methanol Oxidation/Aldol Coupling

An iron(III)-catalyzed methanol oxidation has been developed using aqueous hydrogen peroxide as oxidant (Bolm, C. and Lecomte, V. *Adv. Synth. Catal.* **2005**, *347*, 1666). The formaldehyde formed in situ reacts subsequently with an activated ketone present in the reaction mixture to give α-hydroxy-methylated carbonyl compounds in moderate to good yields. As a side reaction iron-catalyzed α-hydroxylation of the carbonyl compounds has been observed. If the oxidation is performed prior to addition of the carbonyl compound the process becomes more selective.

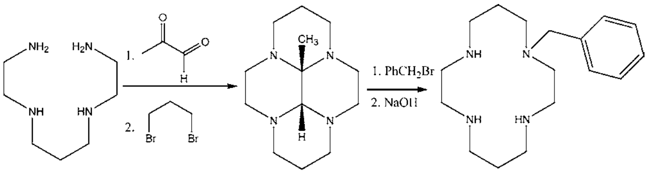


Biosynthetic and Biomimetic Electrocyclizations

Trauner, D. et al. (*Chem. Rev.* **2005**, Articles ASAP) have highlighted electrocyclic reactions that have been found or suspected in the biosynthesis of natural products. The authors have shown that electrocyclic reactions occur regularly in the biosynthesis of natural products and are not confined to a few isolated examples. Most of the reactions reported occurs spontaneously and do not require catalysis, which provides interesting opportunities for biomimetic construction of structurally highly complex molecules.

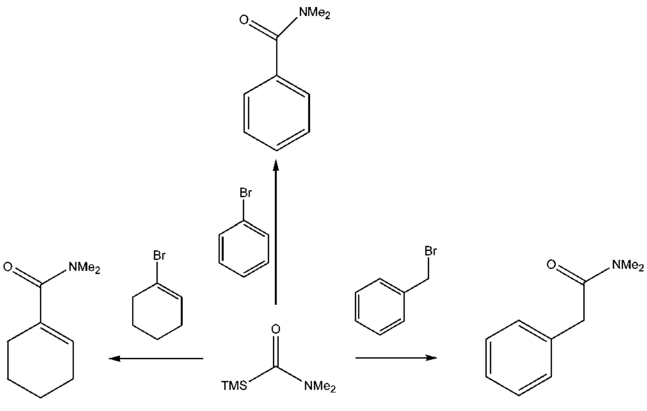
Selective Functionalization of Tetraazacycloalkanes

Synthesis of bifunctional macrocyclic amines for metal coordinating as well as immobilization of monoclonal antibodies generally is not easy. Selective mono alkylation or other types of reactions which introduces N-substitution involves multistep reactions and results in oval all low yields. Guilard et al. (F. Boschetti, F. Denat, E. Espinosa, A. Tabard, Y. Dory, and R. Guilard, *J. Org. Chem.* **2005**, *70*, 7042−7053) found that bis-aminal type compounds, obtained by condensation of pyruvic aldehydes with a suitable open chain tetramine followed by cyclization with either dibromoethane or dibromopropane, can be regioselectively quarternized by a wide range of alkylating agents and the removal of the bisaminal bridge yields the monosubstituted tetra-azamacrocyclic or/and bis-macrocycles in good yields.



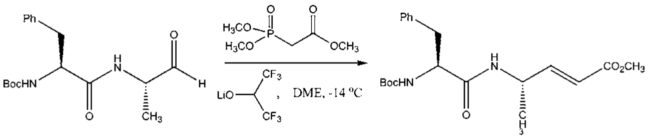
Preparation of Tertiary Amides by *N*,*N*-Dimethylcarbamoyl(trimethyl)silane

Aminocarbonylation with reagent **1** is a safe and economic alternative to carbon monoxide and amine as was demonstrated by Cunico and Pandey (R. F. Cunico and R. K. Pandey, *J. Org. Chem.* ASAP article, jo512406) for the preparation of *N*,*N*-disubstituted carboxamides. The reagent can easily be prepared from DMF and TMS chloride in the presence of LDA at low temperature. Reagent **1** reacts with benzyl- and allylic halids, aryl halides, and alkenyl halides in the presence of catalytic amount of Pd.


(1)

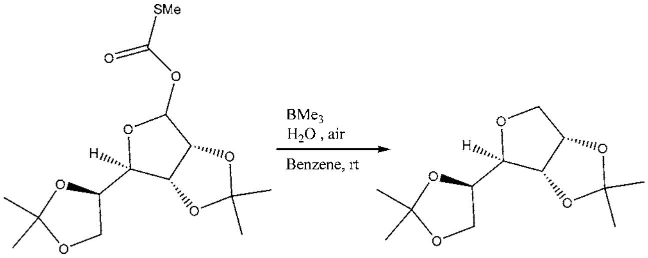
Horner−Wadsworth−Emmons (HWE) Olefination

Although variations in the olefin formation with HWE reactions are available without appreciable epimerization at α position of aldehydes and with high *E* selectivity Meyers and Blasdel (L. K. Blasdel and A. G. Meyers, *Org. Lett.* **2005**, *7*, 4281−4283) report a new base, lithium hexafluorisopropoxide, for this reaction. This reagent gives high yields, high *E* selectivity and little or no epimerization. Lithium as counterion and DME as preferred solvent at −14 °C are ideal conditions. The reagent is prepared in situ from hexafluoro-2-propanol and *n*-butyllithium. The reaction works equally well with inter- and intramolecular condensation.



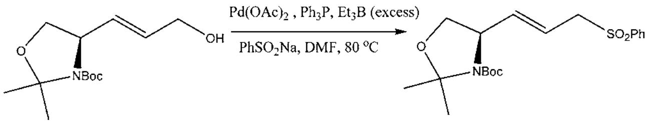
Deoxygenation of Alcohols with Water as Hydrogen Atom Source

A potentially alternate to tin mediated deoxygenation of xanthate esters (Barton-McCombe reaction) is described by Wood et al. (D. A. Spiegel, K. B. Wiberg, L. NSchacherer, M. R. Medeiros, and J. L. Wood, *J. Am. Chem. Soc.* **2005**, *127*, 12513−5) using trimethylborane and water in the presence of oxygen. Simple work up by evaporation of reaction mixture gives desired deoxygenated product in very high yield.



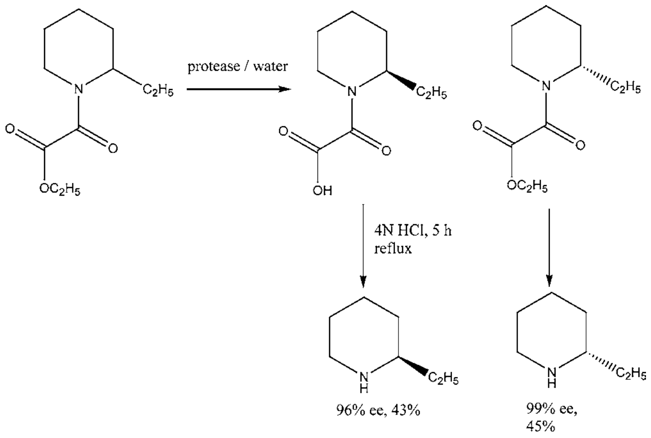
Allyl Phenyl Sulfones from Allyl Alcohols

Although a considerable number of methods are present for the conversion of allylic alcohols to the corresponding sulfones, these methods usually require prior activation which involves several steps. Chandrasekhar et al. devised a one pot conversion of allyl alcohols with sodium phenyl sulfinate in the presence of triethylborane and palladium (0) in very high yields. (S. Chandrasekhar, V. Jagadeshwar, B. Saritha, and C. Narasihmulu, J. *Org. Chem.* **2005**, *70*, 6506−6507) Functional groups such as aryl halogens, conjugated dienes, are tolerated. Allyl sulfones are highly useful for variety of functional group transformation; therefore this method should find use in organic synthesis.



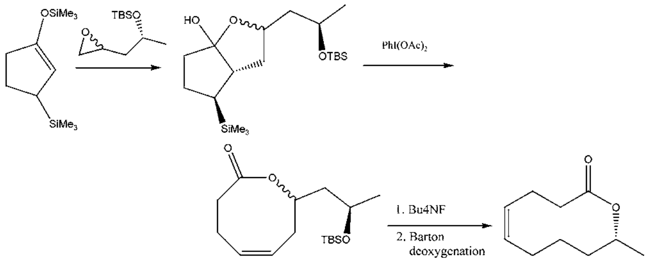
Synthesis of Optically Active Secondary Amines

The synthesis of chiral secondary amines, via enzymatic hydrolysis of secondary amides, is a possibility but may not feasible due to steric hindrance in the enzyme catalytic site. Hu et al. described enzymatic preparation of chiral aryl-or alkyl secondary amines via oxalamic esters with *Aspergillus species* as shown in the scheme below (S. Hu, D. Tat, C. A. Martinez, D. R. Yazbach, and J. Tao, *Org. Lett.* **2005**, ASAP article, olo51392n). Although hydrolysis of the ester bond is three bonds away from the chiral center, high enantiomeric excesses are generally obtained when the reactions are stopped at a conversion of about 50%. This protocol is also useful to prepare chiral amines where substituents are remote from the amino group, e.g. 3-substituted piperidine. This method would allow the preparation of both enantiomers from one racemic amine.



Sequential Ring Expansion of 2-Cycloalkenones into Medium-Sized Lactones

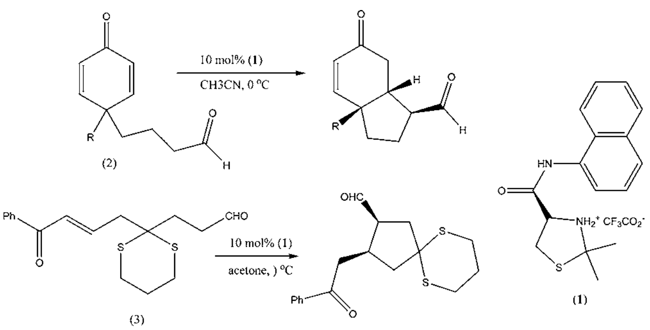
Although large membered lactones with functional groups may be constructed via intramolecular lactonization, Posner et al. (G. H. Posner, M. A. Hatcher, and W. A. Maio, *Org. Lett.* **2005**, *7*, 4301–4303) reports very interesting ring expansion methods as shown below. Using these three steps, they synthesized (−)phoracantholide-J (**1**) a component of defense secretion of insects.



(1)

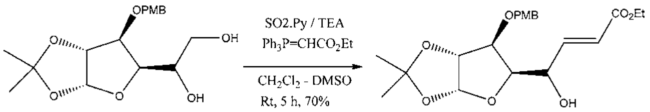
Highly Enantioselective Intramolecular Michael Reaction

Organocatalyst **1** derived from cysteine causes two different types of asymmetric intramolecular Michael reactions—in one it discriminates between two enantiotopic π bonds in cyclic enones **2** giving a bicyclo[4.3.0]-nonene, and in another it discriminates between enantiofaces of an α,β-enone **3** giving *cis* disubstituted cyclopentane skeletons. These compounds, having three and two contiguous chiral centers, are formed in good yields and high diastereo- and excellent enantioselectivities [Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui, and M. Shoji, *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029].



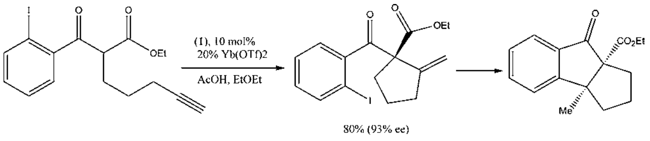
Chemoselective One-Pot Homologation of Glycols

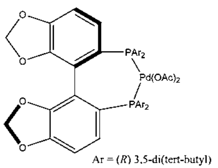
Although oxidation of primary alcohols followed by Wittig reaction with stabilized ylides has been accomplished with a variety of oxidizing agents, pyridine•SO_3 complex appears to be selective for primary—in the presence of unprotected secondary—alcohols as described by Martin et al. (F. R. P. Crisostomo, R. Carillo, T. Martin, F. Garcia-Tellado, and V. S. Martin, *J. Org. Chem.* **2005**, *70*, 10099–10101.) This protocol seems to be mild, inexpensive and the reagent can be safely handled. Varieties of functional groups are tolerated. In general high *E*-selective olefins are formed but invariably some starting materials are recovered. Because of its cost and safety, after some optimization of reaction conditions, this methodology may find use in large-scale synthesis.



Catalytic Enantioselective Quaternary Carbon Center Formation

The Conia-ene reaction is one of the most useful reactions for carbon–carbon bond formation in organic synthesis. Now, its use is extended to the enantioselective quaternary carbon compounds using yttrium metal salts in the presence of optically active phosphine palladium complex such as **1**. The ideal experimental condition for this reaction is the use of protic acid (acetic acid) and ethereal solvents (diethyl ether) at 0.02 M concentration. Under these conditions, high yield and impressive enatioselectivity are obtained. (B. K. Corkey and F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 17168–17169).

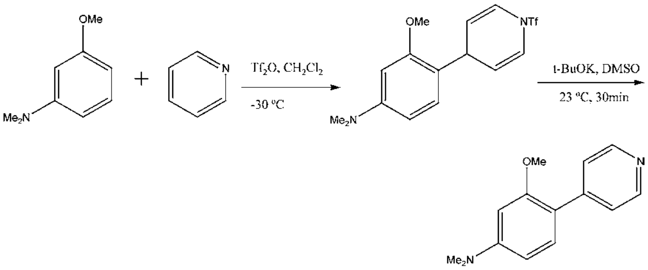




(1)

Selective 4-Arylation of Pyridines

Typically, aryl pyridines are prepared using metal-catalyzed reactions such as Suzuki, Stille, Negishi reactions or organometallic reagents. Corey and Tian (E. J. Corey and Y. Tian, *Org. Lett.* **2005**, *7*, 5535–5537) reported a convenient 4-arylation of pyridine derivatives by activating the pyridine nucleus with trifluoromethanesulfonic acid anhydride. These salts thus obtained undergo nucleophilic substitution with π basic aromatic compounds such as *N*-dialkylamino and *O*-methoxy aryl compounds, *N*-alkyl indoles, and pyrroles. The trifluoromethanesulfonyl group is ideal for the activation of the pyridine ring compared to other electron-withdrawing groups. Yields are generally very high. The reaction is sensitive to the bulkiness of substituents at the 2- and 6-positions of pyridine.



“Heterogeneous” or “Homogeneous”

Andrew et al. (*Adv. Synth. Catal.* **2005**, *347*, 647) reported the use of Pd-containing perovskite catalysts in the Suzuki reaction. Turnover numbers up to 400,000 were obtained. For the seven perovskite catalysts, conversions over 80% were achieved in less than 2 h. The commercial catalyst $LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$ (originally developed for automotive emission control) displayed a short, but measurable, induction period of approximately 4 min. This induction period was correlated with production of a solution-phase Pd species, via oxidative addition.

To further study the reaction pathway, both oxidized and reduced forms of the Pd-containing perovskite catalysts were tested. The oxidized form proved to be superior, achieving 100% conversion in much shorter reaction times.

Interestingly, it is proposed that Pd^{III} in the oxidized form of the catalyst is present; however, to be active, this species must be reduced to Pd^0 species prior to any oxidative addition.

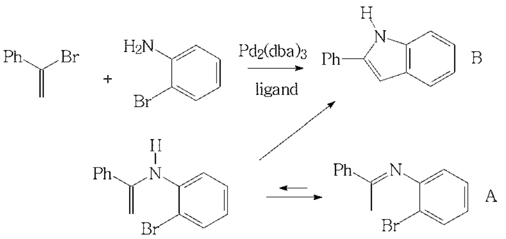
To prove the formation of soluble Pd species the Maitlis filtration test was carried out. It was found that the filtrates (of the reaction media) were catalytically active and that the reactions progressed to significantly higher conversions in the absence of solid perovskite catalyst even when the reaction was stopped after only 4% conversion.

Catalyst poisoning with CS_2, PPh_3, or polymer-supported thiophenol indicated that the true catalysts are the Pd-soluble species.

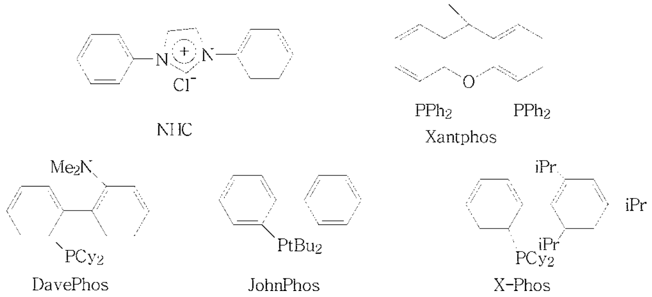
Cascade Alkenyl Amination/Heck Reaction

Barluenga and co-workers (*Chem. Eur. J.* **2005**, *11*, 2276) reported the one-pot synthesis of indoles from *o*-haloanilines and alkenylhalides.

Reaction was made possible by the addition of 3 equiv of NaOtBu as base.



BINAP, Xantphos, JohnPhos, P(*o*-Tol)$_3$, and NHC afforded Schiff base A in 100% conversion, while DavePhos and X-Phos led to B in 100% conversion, using 4% mol $Pd_2(dba)_3$.



Although all the ligands used in this work are bulky, electron-rich ligands, DavePhos and X-Phos are more basic ligands.

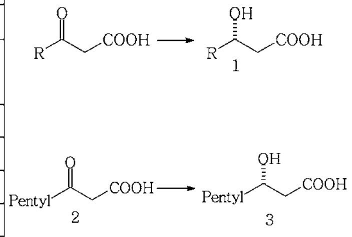
The use of DavePhos as ligand allowed the generalization of the protocol. Therefore, the production of either 2- or 3-substituted indoles has been made possible.

Engineered *Streptomyces coelicolor*

The soil bacterium *Streptomyces coelicolor* is known to produce antibiotics. The dimeric benzoisochromanequinone, actinorphodin, is the most significant of them.

Booker-Milburn and co-workers (*Angew. Chem., Int. Ed.* **2005**, *44*, 1121) while working on the molecular biology of mutant and recombinant strains of this microorganism discovered that the CH999/pIJ5675 strain is able to carry out, as a whole-cell biotransformation system, the enantioselective reduction of β-ketoacids to the corresponding (*S*)-β-hydroxy acids.

R	ee [%]
Bn	> 00
β-naphtylCH_2	77
o-$MeOC_6H_4CH_2$	99 (low yield)
m-$MeOC_6H_4CH_2$	99
p-$MeOC_6H_4CH_2$	98
3,5-di$MeOC_6H_3CH_2$	98
3,4-di$MeOC_6H_3CH_2$	98
2,4-di$MeOC_6H_3CH_2$	99
$CyCH_2$	99
n-pentyl	> 95

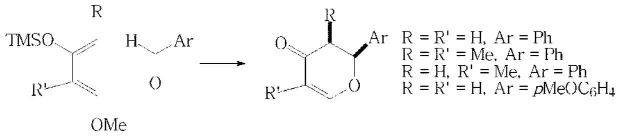


This system is encouraging since reduction of *n*-pentyl derivative **2** is known to produce (*R*)-**3** using baker’s yeast while the present system yielded the *S*-enantiomer.

Biocatalytic Hetero-Diels−Alder

Gouverneur and Reiter (*Chem. Eur. J.* **2005**, *11*, 5806) reviewed a series of examples of catalytic production of hetero-Diels−Alder adducts.

First, the use of Danishefsky diene (and analogues) was described.

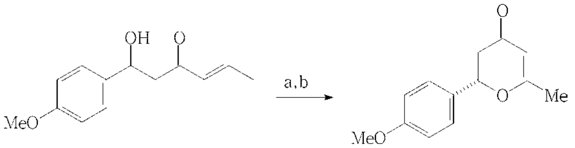


Binol, oxazaborolidine, camphor, and chiral salen derivatives, as ligand, yielded ee's between 55 and 96%, using aluminum, chromium, titanium, boron, europium, or ytterbium as Lewis acids.

Next, examples of biocatalytic approaches were displayed, including the use of macrophomate synthase, a natural Diels−Alderase enzyme.

It was emphasized that few examples of man-made catalytic antibodies displaying Diels−Alderase activity are known and that almost nothing is known about the existence of natural hetero-Diels−Alderase systems.

A beautiful combination of the use of catalytic antibodies (84G3) and palladium chemistry (Wacker oxidative addition) was showed to be useful in a multigram-scale production of an enantioenriched (97% ee) aldol adduct (Sinha, Lerner, and Barbas, III. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14603; Sinha et al. *Chem Eur. J.* **2001**, *7*, 1692; Turner et al. *Chem. Eur. J.* **2000**, *6*, 2772).



a) 1 mol % ab 84G3, PBS/toluene, 50% conversion;
b) $PdCl_2$, CuCl, O_2, PBS/toluene, 100% conversion

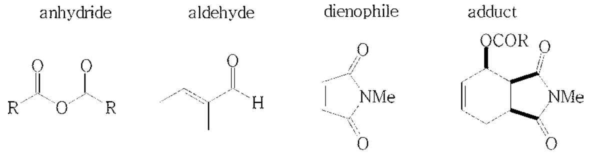
The key step for the delivery of the enantioenriched aldol intermediate was the retro-aldolization catalyzed by antibody 84G3.

The biphasic sequential approach reported presents the advantage of allowing easy separation of the protein catalyst for recycling purposes.

Novel Multicomponent Reaction

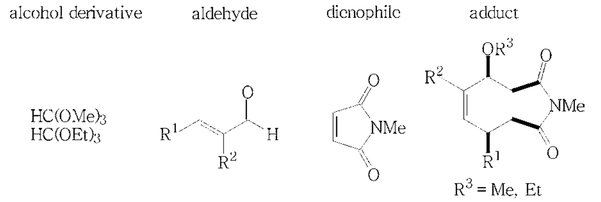
Beller and co-workers (*Chem. Eur. J.* **2005**, *11*, 4210) developed a new domino chemical enzymatic system.

The AAD (**a**mide, **a**ldehyde, and **d**ienophile) reaction between 1-acyloxy-1,3-butadienes (from the corresponding aldehyde and carboxylic acid anhydrides) and *N*-methyl maleiimide yielded the corresponding adducts in good yields.



One- and two-dimensional NMR experiments unambiguously established the stereochemical structure of all new MRC products as all-*syn*, thus showing the *endo*-addition reaction course.

To extend the versatility of this MCR, in situ formed 1-alkyloxy-1,3-butadienes were allowed to react with *N*-methyl maleiimide, affording the corresponding adducts in up to 70% yield.



To obtain pure MCR compounds kinetic resolution processes were chosen. Therefore, the use of different lipases and estearases were investigated in the esters series.

Enzyme	Time (h)	Conversion (%)	ee_s (%)	ee_p (%)	E
pNBE	0.5	50	99	99	> 100
BCL	24	49	95	> 99	> 100
pNBE	8	50	97	n.d.	> 100
Chyrazyme E-3	25	50	>99	n. d.	> 100
PGA-450	72	48	91	98	> 100
Chyrazyme E-3	48	51	94	93	79
CAL-B	1.5	50	> 99	99	> 100

Several enzymes showed $E > 100$. Enantiomeric excess $>90\%$ were observed for both reagents and products.

This exceptional system allowed, therefore, in a two-pot reaction system the production of enantioenriched Diels−Alder products in very good yields.

The multicomponent alternative combined with enzyme chemistry is compatible with atom economy and green chemistry, since the process minimizes waste production and energy consumption and makes use of water chemistry and optimizes human labour.

Hydrolytic Kinetic Resolution of Epoxides

Enantioselective hydrolysis of epoxides has a tremendous importance in organic synthesis since the corresponding diols can be used in several applications.

Faber et al. developed a quite interesting enzymatic cascade system in which up to 100% enantiomeric excesses are obtained from epoxide hydrolysis (*J. Org. Chem.* **2002**, *67*, 9115; *Chem. Soc. Rev.* **2001**, *30*, 332).

The chemical alternative makes use of chiral salen complexes, which also allowed enantioselective azide addition to epoxides (Jacobsen et al. *J. Org. Chem.* **1997**, *62*, 4197).

Recently, Kineshy et al. (*Chirality* **2005**, *17*, 590) reported the use of chiral dimeric cobalt−salen complexes which allowed the resolution of terminal racemic epoxides in very good ee's both for the diol product and for the remaining epoxides.

Lipases in Ionic Liquids

For the past years several applications of the use of lipase in ionic liquids have appeared in the literature. Industrially, the use of lipases in ionic liquids can allow the convenient recycling of the enzyme and can avoid organic solvent consumption; thus, there is a need for a new process employing ionic liquids.

In this way Hongwei, Jinchuan, and Bun (*Chirality* **2005**, *17*, 16) showed the use of *Candida rugosa* lipase in ionic liquids for the esterification (kinetic resolution) of ibuprofen, showing that BMIM PF_6 could be applied to substitute isooctane in such a process. Although ee's were modest, the use of ionic liquids improved this ee compared with isooctane and appears to better stabilize the system.

In a related paper, *N*-ethylpyridimine trifluoro acetate was employed by Malhotra and Zhao (*Chirality* **2005**, *17*, 5240) in the hydrolysis of esters of α-*N*-acetyl-amino acids. Good ee's and isolated yields were obtained in the hydrolysis of the *N*-acetyl moiety. Porcine pancreas lipase (PPL, lipase 3126) was shown to give best results. The enantioselective production of α-amino acids has obvious importance. The employment of lipase to carry out the diacetylation is an alternative to the use of hog kidney acylase I (Machado et al. *Process Biochem.* **2005**, *40*, 3186).

However, as stated above, the ionic liquid−enzyme system can be recycled, thus playing an important role in green chemistry.

Wastewater Dye Destruction with Ozone-Rich Decamethylcyclopentasiloxane

Decamethylcyclopentasiloxane (Volasil245), originally developed as a heat-exchange fluid, has been found to dissolve 10 times more ozone than does water. Extracting wastewater contaminants to ozone-loaded Volasil245 was achieved by Ward and co-workers as a means of enhancing reaction kinetics, thus providing more rapid wastewater decontamination. Using a continuous flow pilot plant, ozone-loaded Volasil245 contact was applied to dye-contaminated waters. Process kinetics and efficacy have been assessed in terms of colour, COD and TOC reductions, and also in relation to direct ozone gas contact. Design and operating conditions for the prototype Volasil245 liquid−liquid/ozone wastewater treatment plant were proposed. It was found that counter-current ozone-loading of the solvent is required instead of co-current loading. The dyes used were not extracted into the solvent, and expected kinetic enhancement was not realised compared to direct gas/water treatment. Other contaminant chemicals are being studied to assess the process further (*Chem. Eng. Process* **2006**, *45, 124−139).*

Cresols were obtained in 19% yield by recharging air and CO under these conditions. A variety of substituted benzenes were hydroxylated by this method to give the corresponding phenol derivatives in higher selectivity.

Asymmetric Catalyst Preparation in a Fluidized Bed

The production of supported catalysts by impregnation method of porous supports can be carried out in a fluidized bed. This technique allows, in only one apparatus, obtaining catalysts which by the traditional way must successively undergo the stages of impregnation, filtration, drying, and calcination/activation. The work of Desportes et al. *(Powder Technol.* **2005**, *157*, 12−19) deals with the results of experiments related to the manufacture of traditional catalysts and new-generation catalysts containing various metals (nickel, manganese, copper, palladium) deposited on a porous support such as alumina or silica gel. Moreover, it is shown that the reproducible synthesis of metallic nanoparticles of size, composition, and controlled surface quality can be carried out under mild conditions with organometallic precursors. The principle of this technique consists of the spraying of a solution containing a metallic precursor into a hot fluidised bed of porous fine particles as chosen support. The adequate choice of operating conditions makes possible a uniform deposit of the metal precursor inside the porous matrix. After the impregnation step, the decomposition of the metallic precursor and metal activation can be operated in the same reactor. For organometallic complexes the decomposition/activation is achieved at low temperature ($T < 80$ °C) under a reactive atmosphere (H_2/N_2 mixture) giving rise to the synthesis of metal nanoparticles with controlled size and composition. Feasibility studies and optimisation of the operating conditions have been carried out, and solid characterization and catalytic tests have been conducted to validate the process. In the case of asymmetric catalysts, Pd nanoparticles associated with cinchonidine as an asymmetric ligand inside silica particles have been prepared by this process for the ethyl pyruvate hydrogenation.

Gas-Phase Oxidation of Alcohols over Silver

Oxidation of alcohols (including C_2-C_6 alkyl alcohols, cyclohexanol, benzyl alcohol, 1-octanol and allyl alcohol) to corresponding aldehydes or ketones has been performed over silver catalyst by Yang et al. (*J. Mol. Catal. A: Chem.* **2005**, *241*, 15−22); the silver catalyst is highly active and selective to the reaction. The mechanism of oxidation of alcohols is inclined to oxidative dehydrogenation at low-temperature region (<550 K). The facets of silver are ideal versatile facets to activate molecular oxygen and generate oxidative, strong basic oxygen species ($O^{\delta-}$) and weak acidic sites ($Ag^{\delta+}$) which can stabilize the organic intermediates, quickly. The facets of silver containing oxygen integrate several active catalytic sites existing in liquid-phase catalytic oxidation of alcohols and make catalytic reaction more effective.

Kinetic Models of Complex Reaction Systems

Papadaki and Gao have used reaction calorimetry for the desired *N*-oxidation of β-picoline (3-methylpyridine), 2,6-lutidine, 3,5-lutidine, and 2,4,6-collidine and the undesired hydrogen peroxide decomposition accompanying the syntheses reactions *(Comput. Chem. Eng.* **2005,** *29*, 2449−2460). The power generation measurements have been used for the development of a kinetic model that will represent satisfactorily the *N*-oxidation of this family of reactions, and it can be used towards the prediction of selected runaway scenarios of the respective reactions. Modelling of the reaction of 2-methylpyridine using hydrogen peroxide and a complex metal catalyst. It was found that the model represents well the *N*-oxidation of methylpyridines. Due to the limited miscibility of di- and trimethylpyridines with hydrogen peroxide, water, and catalyst, only partial agreement with the model was achieved. These reactions need further study under conditions where homogeneous mixtures can be formed. A simple methodology was employed for the evaluation of the model coefficients. Accurate evaluation of the kinetic model constants can be achieved if the noise of measurements is reduced or if conditions where it is less pronounced are employed.

Separation of Aromatics with Aqueous Cyclodextrins

The separation of aromatic compounds (toluene and *o*-xylene) from heptane and of benzyl alcohol from toluene with aqueous solutions of cyclodextrins has been experimentally investigated by Meindersma and co-workers. Cyclodextrins and its derivatives can selectively incorporate several organic compounds, whereas the separation of the aqueous solution of complexed cyclodextrins from the organic feed is simple (*Chem. Eng. Process.* **2006**, *45*, 175−183). Cyclodextrins are not soluble in organic liquids, but cyclodextrin derivatives are highly soluble in water. Hydroxypropyl-β-cyclodextrins with different degrees of substitution and methylated β-cyclodextrin were selected for the extraction of toluene and *o*-xylene from heptane. Hydroxypropyl-β-cyclodextrin (two different substitution degrees) and hydroxypropyl-α-cyclodextrin were selected for the extraction of benzyl alcohol from toluene. The liquid−liquid distribution experiments were carried out at room temperature. Toluene and *o*-xylene form 1:1 complexes with different cyclodextrins, and heptane can form 1:1 to 1:3 complexes. Benzyl alcohol forms 1:3 complexes with hydroxypropylated cyclodextrins. The models developed describe the experimental data reasonably well, considering the large deviations in the analyses. Aqueous cyclodextrin solutions are not feasible for the separation of aromatic components from aliphatic hydrocarbons, due to low distribution ratios of toluene (0.05) and *o*-xylene (0.023) between the aqueous and organic phase. With high distribution ratios of benzyl alcohol, between 0.3 and 2.2 depending on the CD concentration (at a solvent-to-feed ratio of 1) and a benzyl alcohol/toluene selectivity of at least 100, aqueous hydroxypropylated cyclodextrin solutions have sufficient potential for extracting benzyl alcohol from toluene.

Pt Catalysts Supported on Activated Carbon Felt and Granular Carbon for Nitrobenzene Hydrogenation

Vilella et al. have studied the catalytic behavior of the Pt (1 wt %) catalysts supported on purified activated carbon felt (ACF) and powder carbon (C) in the nitrobenzene (NBZ) hydrogenation reaction in liquid phase after activation under a H_2 atmosphere between 298 and 623 K. Hydrogen chemisorption measurements, temperature-programmed reduction (TPR), and X-ray photoelectron spectroscopy (XPS) were used to characterize the metallic phase of the catalysts. For Pt/ACF catalysts, the catalytic activity in nitrobenzene hydrogenation after reduction at 298 K was very high, and it decreased as the reduction temperature increased up to 373 K. On the other hand, the Pt/C catalyst after reduction at 298 K was inactive. The activity of the Pt/C catalysts increased in a moderate way when the reduction temperature increases up to 373 K. Between 373 and 623 K of reduction temperature, the hydrogenation rate was modified in a minor proportion for both catalysts. The Pt/ACF catalyst previously reduced at 298 K showed a lag step before the reaction ignition. This effect could be attributed to the tendency for the metallic centers to conform the proper arrangement to hydrogenate the nitrobenzene molecule (*Chem. Eng. J.* **2005**, *114*, 33−38).

Direct Synthesis of Hydrogen Peroxide from H_2 and O_2 Using TiO_2-Supported Au−Pd Catalysts

Hydrogen peroxide is the “Mr. Clean” oxidant of the chemical industry and is favoured for several green processes. Its production from H_2 and O_2 is beset with several technological problems including hazard and safety, and several patents are being claimed. A group of British and American scientists from Cardiff and Lehigh Universities have reported the direct synthesis of H_2O_2 at low temperature (2 °C) from H_2 and O_2 using TiO_2-supported Au, Pd, and Au−Pd catalysts. The Au−Pd catalysts performed significantly better than the pure Pd/TiO_2 and Au/TiO_2 materials. Au−Pd particles were found with a core−shell structure, with Pd concentrated on the surface. The highest yields of H_2O_2 were observed with uncalcined catalysts, but these were particularly unstable, losing both metals during use. In contrast, samples calcined at 400 °C were stable and could be reused several times without loss of performance. These catalysts exhibited low activity for CO oxidation at 25 °C; conversely, catalysts effective for low-temperature CO oxidation were inactive for H_2 oxidation to H_2O_2. This anticorrelation is explored in terms of the mechanism by which the catalysts function and the design of catalysts for the selective oxidation of one of these substrates in the presence of the other (Edwards et al. *J. Catal.* **2005**, *236*, 69−79).

A Molecular Modeling Study of the Crystal Morphology of Adipic Acid and Its Habit Modifications by Homologous Impurities

Crystal morphology prediction via molecular modelling-based simulation techniques continues to evolve. An academic (Heriot-Watt University and University of Leeds) and industrial (DuPont Pharmaceuticals and Pfizer) collaboration calculated adipic acid (AA) crystal morphologies, and compared them with those experimentally observed (Clydesdale, G. et al. *Cryst. Growth Design* **2005**, *5*, 2154). The calculations and experiments included the case of AA crystallization in the presence of impurities. The impurities investigated are homologous compounds obtained during AA synthesis, such as caproic, glutaric, and succinic acids. The theory of “tailor-made” additives (Lahav, M. et al.) was also employed. Such “designer impurities”, resembling the host system, were successfully used in certain cases to engineer crystal growth. The AA-predicted morphologies agreed well with those experimentally observed in sublimation growth experiments. However, when compared with data generated in crystallization from aqueous solutions, such predictions were of lower quality. An explanation for the observed discrepancy may be the possible adsorption of water molecules onto exposed carboxylic acid groups through hydrogen bonding. An earlier study (one of the author's Ph.D. thesis) investigated the effect of solvent molecules, including ethanol and water, on crystal growth.

Just Because It's Small Doesn't Mean It's Well Mixed: Ensuring Good Mixing in Mesoscale Reactors

High-throughput experimentation, frequently used in polymorph and salt screenings, employs very small vessels in the microliter range (10^{-9} m^3). The first process "scale-up" often occurs in milliliter-scale "reactors" (10^{-6} m^3), usually magnetically stirred vials. The next step in scale-up may be executed in hundreds-of-milliliters-range vessels (10^{-4} m^3), sometimes fitted with overhead stirrers. Most of the correlations currently available for mixing and scale-up were developed on the basis of experimentation executed in much larger reactors, typically in the liters range (10^{-3} to 10^{-2} m^3). Work from Johnson Matthey Catalysts and University of Birmingham (Hall, J. F. et al. *Ind. Eng. Chem. Res*. **2005**, *44*, 9695) addresses this latter stage in the scale-up of high-throughput procedures, to hundreds-of-milliliters-range vessels (10^{-4} m^3). Experiments using particle image velocimetry and CFD calculations were used to describe the fluid flow in such reactors, in single- and two-phase (air−water) systems. In the single-phase case, low- (water) and high-viscosity (400 cP, PPG 2000) fluids were used. The authors indicate that at high viscosity, the flow is fully laminar, whereas in the low viscosity case, the flow is characterized by low turbulence. Because high-throughput equipment is sometimes unbaffled, the authors found that, in some cases when baffles are not present, eccentric agitation can improve mixing performance. It will be interesting to see the behavior of certain test reactions, such as a Bourne reaction, in such configurations. For air−water systems, two positions for a sparger were evaluated, concluding that positioning the sparger away from the impeller (rather than directly below it) may be a better choice.

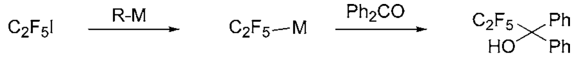
Review on Mixing Characteristics in Solid−Liquid, and Solid−Liquid−Gas Reactor Vessels

Scale-up of three-phase reactive systems is often challenging because of the complexity of such systems. Work from the University of Mumbai (Kasat, G. R. et al. *Can. J. Chem. Eng.* **2005**, *83* (4), 618−643) reviews (89 references) several aspects of solid−liquid and solid−liquid−gas mixing characterization. Various methods used for the experimental measurement of "just-suspended" agitator speeds are discussed, mentioning the effects of gas sparging in solid−liquid media. Certain agitator types are presented, referencing the literature addressing the impact of type, geometry, and position of the agitator. Several recommendations are made, for example for the position of spargers. A separate section reviews the case of multiple-impeller systems, a topic for which open literature data are relatively limited, especially for the case of different types of agitators on the same shaft, with applications to heterogeneous systems. Another section presents some of the literature data available for the challenging case of floating particles in three-phase reactors.

Microreactors

A review of micro-reaction technology and its application in organic chemistry and chemical processes has appeared with the intriguing title "Development of Microstructured Reactors to Enable Organic Synthesis Rather than Subduing Chemistry" (Hessel, V. et al. *Curr. Org. Chem.* **2005**, *9*, 765−787). The emphasis in the review is on reactions which have difficulties in standard-batch or semi-batch reactors and which would be much better carried out in continuous mode. The use of microreactors enables small-scale processes to be quickly evaluated in the laboratory and for kilograms to be generated in a short time.

For example, Grignards prepared from pentafluoroethyl iodide are very unstable, and reactions with ketones are hard to scale-up with good yield, since side products formed by C−F bond cleavage accumulate. In continuous mode, the intermediate Grignard, which is only stable for a few minutes at −78 °C can be quickly reacted with the ketone, and high yields result.



mode	Reagent RM	T °C st. 1	T °C st. 2	Yield	% side product
Batch	BuLi	-61	-10	51	36
Batch	MeMgCl	-30	0	0	90
Cont.	MgMgCl	-6	-4	86	5
Cont.	MgMgCl	1	-4	80	7
Cont.	MgMgCl	-8	-6	82	11

Fluorinations have recently been examined in microreactors using 10% F_2 in N_2, and excellent results have been achieved with β-ketoesters.

Diazomethane has recently been made in a microreactor and reacted immediately with substrates, as have other hazardous reagents such as N_2O_5, ethyl diazo-acetate, and hydrogen peroxide.

In general, microreactors are excellent for liquid and gaseous reagents, but there are more and more applications now with solid reagents and products.

A discussion on the type of reactions most appropriate for use in microreactors is covered in a review by Dominque Roberge of Lonza (Microreactor Technology: A Revolution for the Fine Chemical and Pharmaceutical Industries. *Chem. Eng. Technol.* **2005**, *28*, 318−323) This article is one of a series of articles devoted to microreactors in issues of *Chemical Engineering and Technology* in the last few months.

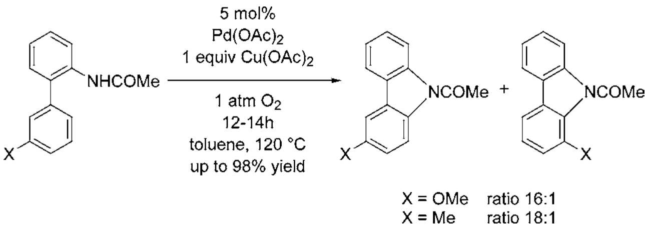
Other papers of interest are on Fine Chemicals and Contract Manufacturing Industry Applications of Microreactors (Schwalbe, T. et al. *Chem. Eng. Technol.* **2005**, *28(4)*, 408−419); Applications of Microreactors for Small Scale Organic Synthesis (Watts, P. et al. *Chem. Eng. Technol.* **2005**, *28*(3), 290−301); Versatile Gas−Liquid Microreactors for Industry (Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Chem. Eng. Technol.* **2005**, *28*(3), 344−352).

Chemical Engineering and Technology also had a special issue on Preparative Chromatography [**2005**, *28* (11)].

Synthesis of Carbazoles

A new route to carbazoles using combined C−H functionalisation and C−N bond formation has been disclosed by the group of Buchwald at MIT. (Tsang, W. C. P. et al. *J. Am. Chem. Soc.* **2005**, *127*, 14560). The catalyst for the conversion of *o*-phenyl acetanilides is a mixture of palladium and copper acetates, with an oxygen atmosphere.

The reaction probably proceeds via preassociation of the NH to palladium, followed by insertion into the aromatic H bond, formation of a six-membered palladacycle, and then carbazole formation with release of Pd. The reaction shows some regioselectivity as shown in the scheme below.



Green Chemistry

A recent issue of *Green Chemistry* contains a review by Roger Sheldon on "Green Solvents for Sustainable Organic Synthesis: State of the Art" (*Green Chem.* **2005**, *7*, 267−278). Ionic liquids are discussed briefly in this paper, but more about this topic is in two other papers in the same issue. One is concerned with the toxicity of ionic liquids (Jastorff, B. et al. *Green Chem.* **2005**, *7*, 362−372), where the toxicity increased with the length of the hydrocarbon chain.

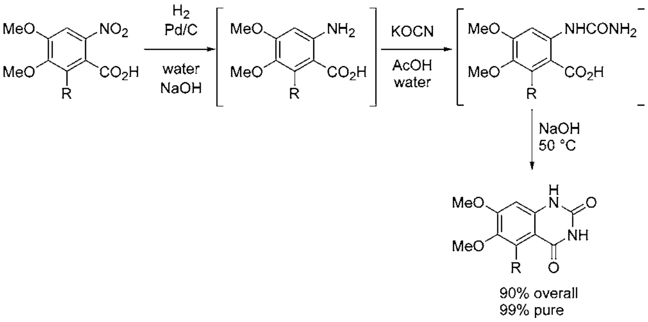
The second paper concerns the corrosion behaviour of ionic liquids towards standard metals of construction of chemical reactors (carbon steel, austenitic stainless steel, nickel alloys such as Hastelloy C22, copper, brass and aluminium alloy) (Uerdingen, M. et al. *Green Chem.* **2005**, *7*, 321−325). The corrosion depended very much on the chosen anion in the ionic liquid (IL) and on whether pure IL or a water-diluted IL mixture was tested.

Polymorphism of Benzamide

The polymorphism of benzamide is historically interesting since it was Wöhler and Liebig in 1832 who first described that slow cooling of a hot aqueous benzamide solution resulted first in production of a solid mass of white silky needles, which later transformed to rhombic crystals−the stable form. Now the group of Davey at Manchester, UK (David, W. I. F. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 7032−7035) has, 173 years after its discovery, determined the crystal structure of the metastable form using an "in situ" synchrotron XRPD experiment. The structure of this transient polymorph was determined quickly in the presence of solvent and other crystalline phases, even though the metastable form only persists for around 60 min.

Pilot Plant-Scale Synthesis of Quinazolinediones

A group at Roche, Palo Alto, has published a paper in *Green Chemistry* (Connolly, T. J. et al. *Green Chem.* **2005**, *7*, 586−589) describing an ecoefficient process for making two quinazoline-2,4-diones from *o*-nitrobenzoic acids. A unique feature is that all the steps were conducted in water (including a catalytic hydrogenation), giving products in high yield. The only waste streams were the aqueous filtrates and the catalyst, which presumably could be reused or recycled.



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