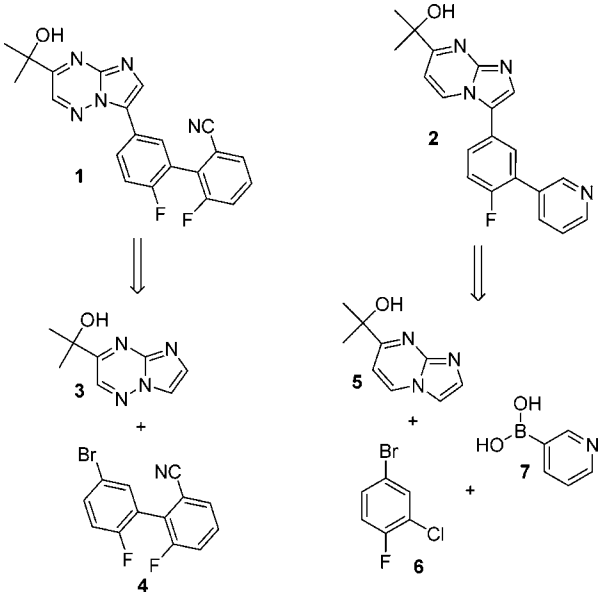
Organic Process Research & Development **2005**, *9*, 522–536

Highlights from the Literature

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

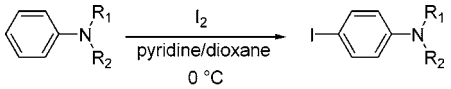
Efficient Syntheses of Selective GABA Agonists



Two papers from Merck describe synthetic approaches towards two structurally similar $GABA_A$ $\alpha_{2/3}$-selective agonists **1** and **2**. In both cases, a tactic was to use regioselective Pd-catalyzed direct arylation of the imidazotriazine **3**/imidazopyrimidine **5** substrates, although at different stages in the respective routes. In the first paper, Gauthier and co-workers describe a seven-step, chromatography-free route to **1** that was demonstrated on a multikilogram scale (*J. Org. Chem.* **2005**, *70*, 5938−5945). This synthesis is highlighted by an efficient preparation of the required imidazotriazine **3**, based on the regioselective cyclization of aminoguanidine with a bis-morpholine ketoaminal. A selective bromination of a biaryl intermediate furnished key biaryl coupling partner **4**. In the second paper, Jensen, Hoerrner and co-workers present their efforts towards **2**, which culminated in a 40% overall yield, five-step process (*J. Org. Chem.* **2005**, *70*, 6034−6039). Key aspects of this synthesis include the consecutive functionalization 4-bromo-2-chloro-1-fluorobenzene **6** (in which the choice of ligand for these Pd-catalyzed reactions was crucial for regioselectivity) and the identification of an undesired Dimroth rearrangement during the final Suzuki coupling that could be suppressed under appropriate conditions. Last, both papers address the problem of removal of Pd-residues from the API.

Cheap and Efficient Method for Selective *para*-Iodination of Anilines

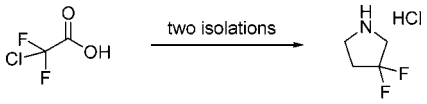
A new and cheap protocol for controlled iodination in the *para*-position of various aniline derivatives has been



80-98%

developed by Blart, Odobel, and co-workers (*Tetrahedron Lett.* **2005**, *46*, 5421−5423). The reaction operates under mild conditions by reacting the aniline derivatives with molecular iodine in a mixture of pyridine/dioxane (1/1 vol) at 0 °C. The authors do not discuss whether cosolvents other than 1,4-dioxane can be used.

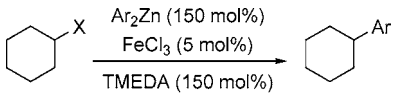
Practical Preparation of 3,3-Difluoropyrrolidine



59% overall, no chromatography

Faced with the requirement for a practical large-scale synthesis of 3,3-difluoropyrrolidine, Xu and co-workers at Merck sought an alternative to the previously reported procedure employing an expensive starting material and the unstable fluorinating reagent DAST (*J. Org. Chem.* **2005**, *70*, 6105−6107). The result is a practical and cost-effective synthesis of 3,3-difluoropyrrolidine involving the isolation of only two crystalline intermediates and requiring no chromatography. The overall sequence comprises two efficient through processes: (1) a Claisen rearrangement followed by a Ru(VIII)-catalyzed oxidation to prepare the 2,2-difluorosuccinic acid and (2) an efficient cyclization to form *N*-benzyl-3,3-difluorosuccinimide followed by borane reduction.

Iron-Catalyzed Cross-Coupling of Alkyl Halides and Diarylzinc Reagents



88-98%

X = Cl, Br or I

Nakamura and co-workers report on a cross-coupling reaction between alkyl halides and diarylzinc reagents, catalyzed by $FeCl_3$ in the presence of TMEDA (*Synlett* **2005**, 1794−1798). The method offers advantages in terms of functional group compatibility over existing procedures involving the use of more aggressive Grignard reagents as the organometallic species. The required diarylzinc reagents are prepared in situ from the air- and moisture-stable

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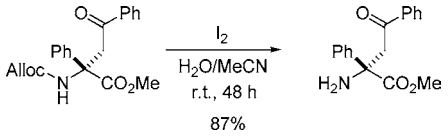
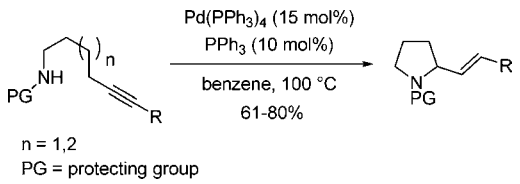
$ZnCl_2$·TMEDA complex and 2 equiv of an aryl Grignard. The by-product magnesium halide from this step was found to be essential for success in the coupling step since diarylzinc reagents prepared from $ZnCl_2$ and aryllithiums did not couple. A drawback of using diarylzinc reagents is that only one aryl group is available for coupling, although the authors comment that, by using a mixed diorganozinc reagent bearing Me_3SiCH_2 as a dummy ligand, this problem can be circumvented. As shown, secondary alkyl chlorides, bromides, and iodides react efficiently and the paper includes several other more complex substrates (both primary and secondary). A variety of alkylated aromatic compounds can be obtained in good to excellent yield.

Mild and Metal-Free Deprotection of the *N*-Alloc Group



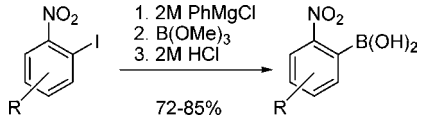
During the course of their research, Miller, Szumigala and co-workers at Merck required a synthesis of methyl (2*S*)-2-amino-4-oxo-2,4-diphenylbutanoate. As a consequence of the synthetic route chosen, the *N*-Alloc protected intermediate was obtained, and the group investigated alternative deprotection conditions that avoid the conventional use of transition metals (*Tetrahedron Lett.* **2005**, *46*, 4403−4405). In short, it was discovered that iodine in wet acetonitrile can efficiently deprotect the *N*-Alloc group via iodocyclization and subsequent facile hydrolysis. The by-product (iodomethyl)ethylene carbonate (neutral) can be separated from the amine (basic) during extractive work-up. The applicability of this transformation was demonstrated by deprotecting a variety of *N*-allyloxycarbonylamines, α-aminomethyl esters, and simple *N*-allyloxycarbonyl alkylamines. Deprotection occurs in high yield (82−93%) without erosion of the optical purity of the chiral substrates.

Catalytic Intramolecular Hydroamination of Alkynes



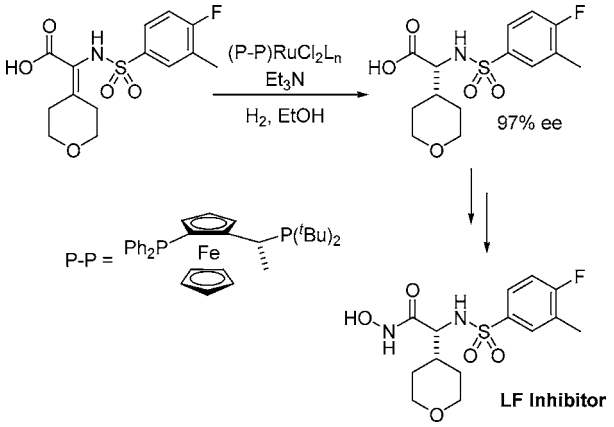
On the basis of chemistry developed previously within their group (and elsewhere), Yamamoto and co-workers have discovered an intramolecular hydroamination of alkynes in the presence of catalytic amounts of $Pd(PPh_3)_4$ and PPh_3 in benzene at 100 °C (*J. Org. Chem.* **2005**, *70*, 4883−4886). Unlike their previously reported work, the present procedure does not require carboxylic acid additives and proceeds under neutral conditions to afford five- and six-membered nitrogen heterocycles in good yields. Curiously, the hydroamination does not take place when conducted using only $Pd(PPh_3)_4$ or PPh_3 alone and succeeds only when these two species are used in conjunction. The authors propose that the excess PPh_3 behaves as a base, initiating the catalytic cycle by deprotonating the NH group and generating the phosphonium ion $[HPPh_3]^+$. This phosphonium species would then interact with Pd(0) to give a complex that can hydropalladate the alkyne. No evidence for this mechanism is currently available, and the authors note that their hypothesis is highly speculative. Nevertheless, the reported results represent a useful starting point for further development.

Convenient Synthesis of Functionalized *ortho*-Nitroarylboronic Acids



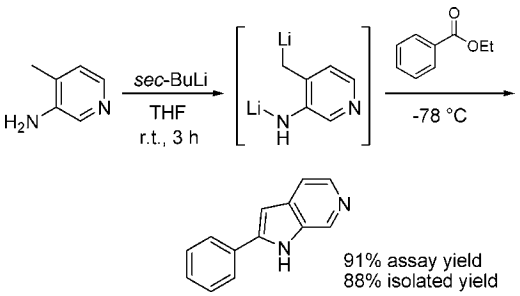
Collibee and Yu at Albany Molecular Research report on a convenient method for the synthesis of functionalized *ortho*-nitroarylboronic acids (*Tetrahedron Lett.* **2005**, *46*, 4453−4455). The method is based upon Knochel's recent discovery that *ortho*-nitroarylmagnesium reagents can be prepared through an I−Mg exchange process. A stability study indicated the prepared Grignard reagents were stable for at least 2 h at temperatures up to −40 °C; however, after 2 h at 0 °C complete decomposition was observed. A variety of *ortho*-nitroarylboronic acids bearing functional groups such as cyano, nitro, halo, α-bromomethyl, and ester were prepared in good yields via I−Mg exchange followed by quenching with trimethyl borate and acidic aqueous work-up.

Asymmetric Hydrogenation of *N*-Sulfonylated-α-dehydroamino Acids



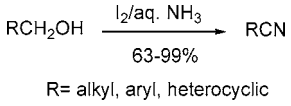
In support of a recent program to develop an anthrax lethal factor inhibitor, Dreher and co-workers at Merck discovered a novel and highly enantioselective Ru-catalyzed hydrogenation of an *N*-sulfonylated-α-dehydroamino acid that allowed for the late-stage installation of the molecule's stereocenter (*Org. Lett.* **2005**, *7*, 3405−3408). The method was used to prepare several *N*-sulfonylated amino acids in up to 98% ee. A ruthenium catalyst is employed (instead of the rhodium-based species commonly used for acylated dehydroamino acids) in conjunction with various chiral phosphine ligands, depending upon the specific substrate to be reduced. An additional notable aspect of this work is the asymmetric hydrogenation of a tetrasubstituted dehydroamino acid derivative.

One Step Synthesis of 2-Substituted 6-Azaindoles



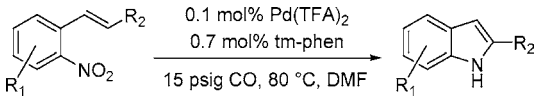
Song and co-workers at Boehringer Ingelheim describe a practical synthetic procedure for the synthesis of 2-substituted 6-azaindoles (*J. Org. Chem.* **2005**, *70*, 6512−6514). Room-temperature dilithiation of 3-amino-4-picoline is achieved with *sec*-BuLi, and condensation of the resulting dianion with carboxylic esters afforded a wide range of 2-substituted 6-azaindoles in good yields. It is notable that no protecting group or oxidation state adjustment is necessary and the entire process can be conducted in one pot. Considering its simplicity, generality, and the ready availability of the starting materials, it appears that this method will be very useful for the synthesis of 6-azaindole-containing compounds.

Direct Oxidation of Alcohols to Nitriles Using Molecular Iodine/Ammonia



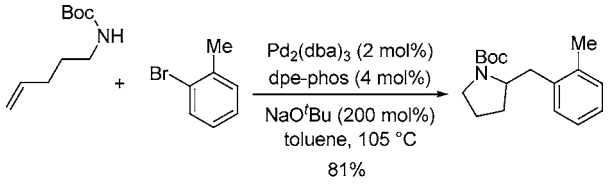
In another paper featuring the use of molecular iodine as a reagent, the group of Togo in Japan describes a simple and high-yielding procedure for the direct oxidation of alcohols to nitriles (*Synlett* **2005**, 1456−1458). By stirring a variety of alcohols with 3 equiv of molecular iodine in aqueous ammonia at 60 °C the requisite nitriles were obtained directly in good to excellent yields.

Catalytic Reductive Cyclization of *ortho*-Nitrostyrenes under Mild Conditions



As part of their development work around a KDR kinase inhibitor, the group of Davies at Merck made a thorough investigation of the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes to afford indoles (*Tetrahedron* **2005**, *61*, 6425−6437). A key aspect of the process optimization was the use of a Parallel Pressure Reactor (PPR) system that allowed for rapid screening of reaction conditions. Importantly, the newly developed conditions are milder than those previously available and avoid the use of phosphine ligands that can compromise the isolation of the indole product. In addition to the Merck target compound, the chemistry was demonstrated to be applicable to a wide variety of substrates. Optimum conditions involve treatment of *ortho*-nitrostyrenes with 0.1 mol % palladium (II) trifluoroacetate [$Pd(TFA)_2$] and 0.7 mol % 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF at 15 psig CO and 80 °C, and afford indoles in good to excellent yields. By using CO as the stoichiometric reductant, CO_2 is the only stoichiometric by-product, a facet of this chemistry which offers definite economic and environmental advantages over the standard triethylphosphite deoxygenation procedure.

Stereoselective Synthesis of *N*-Protected Pyrrolidines

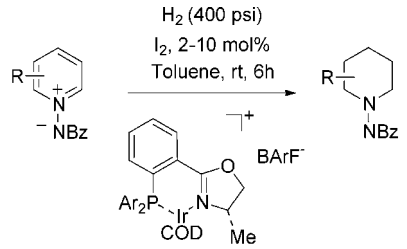


many other examples including cyclic alkenes and various electron-rich and -poor aryl bromides

Following up on their recent reports of a novel catalytic method for the synthesis of *N*-arylpyrrolidines, the group of Wolfe now describes an extension of this chemistry to include the use of starting materials bearing more synthetically flexible groups on nitrogen (*Tetrahedron* **2005**, *61*, 6447−6459). The stereoselective preparation of *N*-acyl- and *N*-Boc-protected pyrrolidines can be achieved via Pd-catalyzed reactions of γ-(*N*-acylamino)alkenes and γ-(*N*-Boc-amino)alkenes with aryl bromides. These reactions effect formation of two bonds in a single operation and proceed with generally high levels of diastereoselectivity. In contrast to the group's previously developed reactions of γ-(*N*-arylamino)alkenes, the present transformations proceed in high yield and high regioselectivity with both electron-rich and electron-deficient aryl bromides as well as vinyl bromide substrates.

Synthesis of Enantioenriched Substituted Piperidine Derivatives

Legault and Charette (Université de Montréal) have used a wide spectrum of pyridines as starting materials to access enantiomerically enriched piperidines via asymmetric catalytic hydrogenation (*J. Am. Chem Soc.* **2005**, *127*, 8966−8967). Mono- and disubstituted pyridinium ylides (2-, and 2,3-, respectively) were prepared using a one-pot amination−benzoylation procedure from the corresponding pyridines (see Legault, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 7912−7922). These compounds were hydrogenated in toluene (400 psi) using a designer iridium catalyst (2 mol %) to yield piperidine derivatives in good to excellent yields (65−98%) and enantioselectivities (58−90% ee). The hydrogenations were carried out in the presence of I_2 (2−10 mol %), which presumably oxidizes Ir^{I} to the active Ir^{III} species. The resulting aminopiperidines are solids that can be crystallized to increase optical purities. Optimization of the catalyst was achieved by tuning the electronic properties of the phosphine substituent (Ar = Ph, *o*-tolyl, *p*-OMe, *p*-F, *p*-CF_3, C_6F_5) and exploring different counterions (BF_4^-, OTf^-, $CF_3CO_2^-$, $BArF^-$).

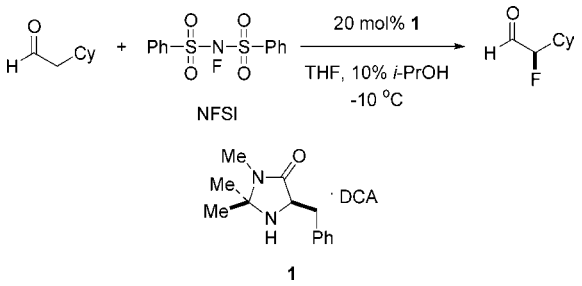


BArF$^-$ = tetrakis [3,5-bis(trifluoromethyl)phenyl]borate

Catalytic Enantioselective Fluorination

The introduction of C−F bonds in organic molecules is a valuable strategy oriented to avoid in vivo C−H oxidation. Different enantioselective methods to fluorinate the α-position of carbonyl groups have been recently described using the commercially available *N*-fluorobenzenesulfonimide (NFSI) as electrophilic fluorinating reagent.

Expanding the theme of enantioselective organocatalysis, the group of MacMillan at the California Institute of Technology reported an enantioselective α-fluorination of aldehydes (*J. Am. Chem Soc.* **2005**, *127*, 8826−8828). The reaction of cyclohexylacetaldehyde with NFSI catalyzed by imidazolidinone **1** (20 mol %) in solvent mixtures with 10% *i*-PrOH affords (*R*)-2-flourocyclohexaldehyde in 98% conversion and 98% ee.



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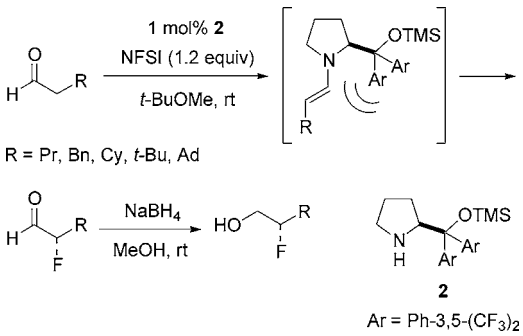
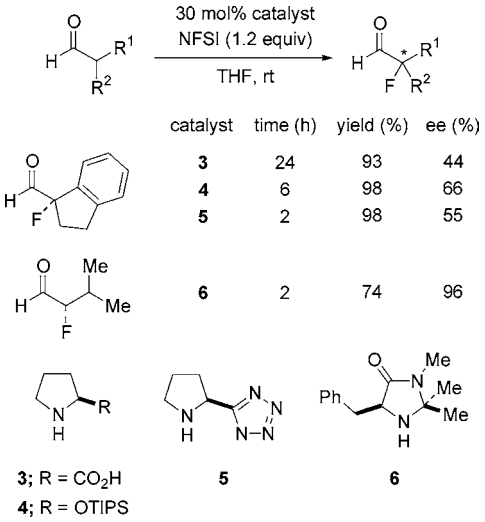
The method is compatible with different aldehydes as well as a wide range of functional groups including olefins, esters, amines, and carbamates. Catalyst loadings as low as 2.5 mol % can be utilized without loss of enantioselectivities. In addition, epimerization of the products was not observed over the reaction time for any of the cases studied.

Jørgensen and co-workers broadened the catalytic use of silylated prolinol **2** to α-fluorinations (*Angew. Chem. Int. Ed.* **2005**, *44*, 3703−3706). The methodology uses stoichiometric amounts of NFSI in conjunction with catalyst **2** (1 mol %) in *t*-BuOMe to generate α-fluoroaldehydes in good yields (55−95%) and excellent stereoselectivities (91−96% ee). Due to the volatility of α-fluoroaldehydes and their instability in silica gel, these compounds were directly reduced to the corresponding (*S*)-*β*-fluoro alcohols. The authors explore the stereoselective course of the reaction with DFT calculations and conclude that shielding of the *re* face of the intermediate *E*-enamine caused by the proline substituent is decisive.

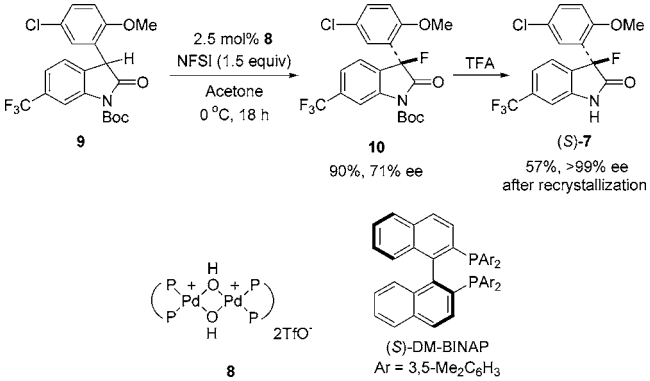
The group of C. Barbas, III reported an alternative organocatalytic α-fluorination (*Angew. Chem. Int. Ed.* **2005**, *44*, 3706−3710). The screening of different catalysts derived from L-proline (e.g., **3**−**6**) as well as a variety of solvents led to optimum conditions for the fluorination of diverse



aldehydes using NSFI (1.2 equiv). Selected results for branched aldehydes are shown below.

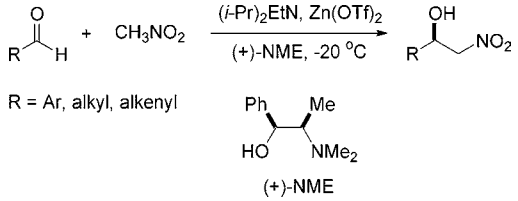


The introduction of a fluorine atom at position 3 of oxindole enhances the efficiency of BMS 204352 (Maxipost, **7**), an agent for the treatment of stroke developed by Bristol-Myers Squibb that is currently undergoing Phase III clinical trials. In this context, Sodeoka and co-workers described the catalytic enantioselective fluorination of oxindoles using chiral Pd complexes (*J. Am. Chem Soc.* **2005**, *127*, 10164−10165). Tuning of the reaction conditions involved: (a) the protection of the nitrogen with Boc to form a configurationally stable Pd enolate and (b) the use of mildly acidic Pd complex **8** to minimize the cleavage of the carbamate. In this fashion, treatment of racemic oxindole **9** with NFSI in the presence of **8** provided its fluorinated derivative **10** (90% yield, 71% ee). Cleavage of the Boc protecting group with TFA followed by crystallization furnished optically pure **7** (> 99% ee).



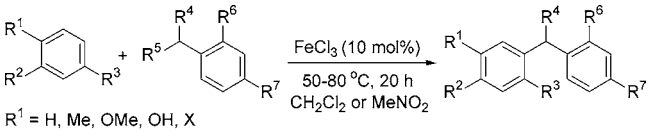
Efficient Catalytic Enantioselective Henry Reaction

Palomo, Oiarbide, and Laso developed a highly enantioselective Henry reaction combining $Zn(OTf)_2$, $(i\text{-Pr})_2EtN$, and chiral amino alcohols such as (+)-*N*-methyl ephedrine (*Angew. Chem. Int. Ed.* **2005**, *44*, 3881−3884). The best results were obtained using 1 equiv of $Zn(OTf)_2$ and $(i\text{-Pr})_2EtN$ relative to aldehyde, and 1.5 equiv of amino alcohol at low temperatures. Although the experimental procedures used nitromethane as solvent, the authors report that dichloromethane and toluene work well. The isolated yields were good for a variety of aldehydes (68−90%). The enantioselectivities were good to excellent (74−90% ee). (+)-*N*-Methylephedrine can be recovered after the reaction by acid−base aqueous workup and reused.



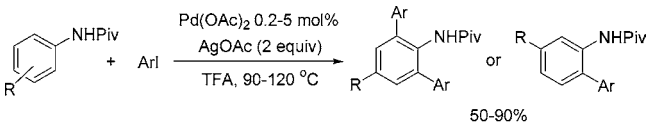
Metal-Catalyzed Arylations

Following a sequence of articles on Friedel−Crafts-like alkylations developed in his group, M. Beller et al. reported the use of iron to promote the arylation of benzyl alcohols and benzyl carboxylates (*Angew. Chem. Int. Ed.* **2005**, *44*, 3913−3917). Iron (III) salts were found to be an alternative to expensive late-transition metal catalysts. Typically, the reactions proceed under mild conditions (50−80 °C) in the absence of strong acids or bases, and the exclusion of air or moisture is not required. The best results were obtained using $FeCl_3$ (anhydrous or hexahydrate). The reaction conditions work with nonactivated arenes, including benzene, and are tolerated by functional groups such as CHO, CHO_2R, halogens, OH, and OMe. Remarkably, thiophene and furan derivatives, which are rarely featured in Friedel−Crafts reactions, afford good yields. The reactions were regioselective at the *para* position of the activating groups (>80%).



R^1 = H, Me, OMe, OH, X
R^2 = H, Me, OMe
R^3 = H, OMe, OH
R^4 = H, Me, Ph, CH_2CO_2Et, CN
R^5 = OH, OAc, OCO_2Me, Cl
R^6 = H, Cl, F
R^7 = H, OMe, Cl, F

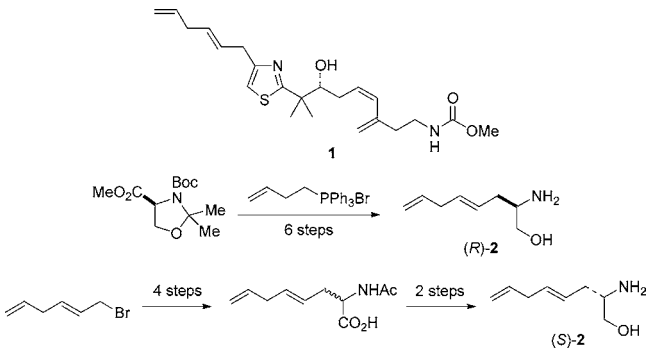
Daugulis and Zaitsev recently investigated the Pd-catalyzed arylation of arenes containing *ortho*-directing groups (*Angew. Chem. Int. Ed.* **2005**, *44*, 4046−4048). The combination of aryl iodides and AgOAc was effective in the catalytic *ortho*-arylation of anilides using $Pd(OAc)_2$. The reaction is highly tolerant with respect to substituents in the anilide ring, including iodine. In addition, it is compatible with bromo substituents on the aryl iodide, which allows further functionalization of the products using conventional Pd couplings. The use of *meta*-substituted anilides results in the selective addition of a single aryl group. In typical reaction conditions, the pivaloyl amide reacts with ArI in the presence of AgOAc (1 equiv per coupled Ar) and $Pd(OAc)_2$ in TFA to give the bis- or mono-arylated products in 50−90% isolated yields.



R = H, 4-Br, 4-I, 4-Me, 3-I
Ar = C_6H_5, 3-Br-C_6H_4, 4-MeO-C_6H_4

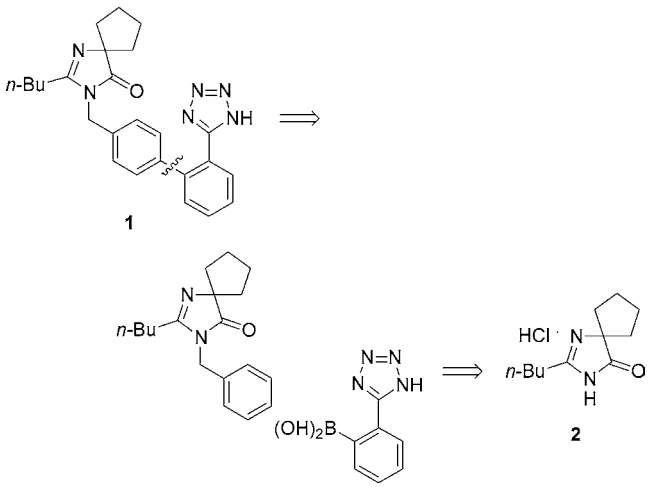
Synthesis of 1,2-Amino Alcohols en Route to Anthelmintic Agents

The marine natural product mycothiazol (**1**) exhibits anthelmintic activity. As part of a program to synthesize oxazoline analogues, Mahler, Serra, and Manta prepared the two antipodes of amino alcohol **2** (*Synth. Commun.* **2005**, *35*, 1481−1492). The absolute configuration of the (*R*)-isomer was correlated to the configuration of an oxazolidine derivative of L-lysine. In contrast, the (*S*)-isomer was prepared via enzymatic resolution of an *N*-acetyl amino acid with aminoacylase EC 3.5.1.14. Stereochemical control of the unsaturated chain in (*R*)-**2** was achieved by using a modified Wittig reaction (PhLi, *t*BuOH/*t*BuOK). The trans isomer of 6-bromo-hexa-1,4-diene was the key intermediate for the preparation of (*S*)-**2**.



Synthesis of the Antihypertensive Drug Irbesartan

Scientists at Dr. Reddy's Laboratories in Hyderabad reported a synthesis of irbesartan (**1**), an angiotensin II receptor antagonist (*Synth. Commun.* **2005**, *35*, 1979−1982). The biaryl system is created in a late stage via Suzuki

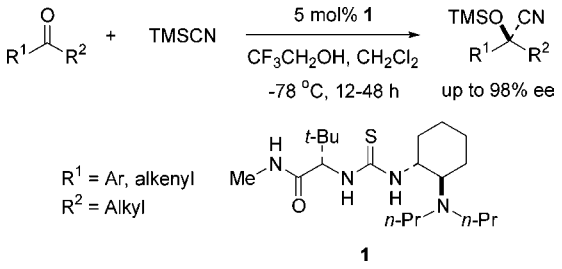


coupling of a boronic acid that features the tetrazole moiety. This strategy circumvents the elaboration of a biphenyl benzyl bromide intermediate that in the previous synthesis was elaborated into the final product. Irbestaran was obtained in 80% yield from diazospiroenone **2**.

Catalytic Enantioselective Cyanosilylation of Ketones

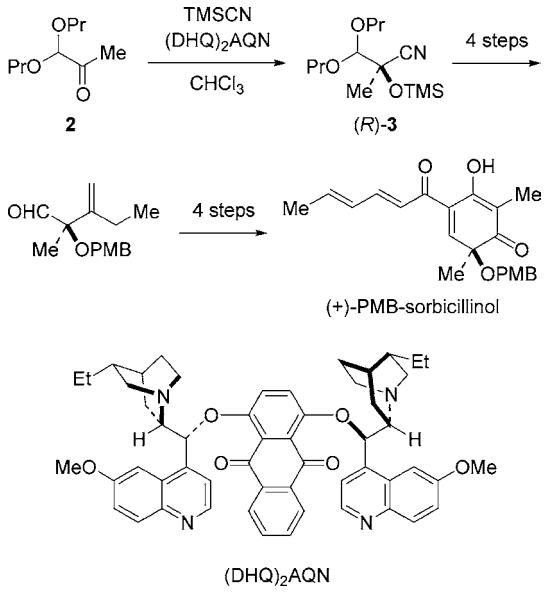
The preparation of chiral cyanohydrins via enantioselective cyanosilylation of carbonyl compounds constitutes a central entry to optically active building blocks. Whereas several catalytic systems exist for the enantioselective cyanosilylation of aldehydes, methodologies for the analogous transformation of ketones lag far behind.

As part of continued efforts to develop new general acid asymmetric catalysts, Fuerst and Jacobsen have reported the use of chiral thiourea **1** for the enantioselective cyanosilylation of a wide range of ketones bearing one sp^2-hybridized substituent (*J. Am. Chem. Soc.* **2005**, *127*, 8964−8965). Common experimental conditions at −78 °C include 5 mol % catalyst, 2.2 equiv of TMSCN, and 1 equiv of CF_3CH_2OH as additive in CH_2Cl_2. The reaction of alkyl aryl ketones, heteroaromatic ketones, and α,β-unsaturated ketones affords the desired cyanohydrins in excellent isolated yields (81−98%) and enantioselectivities (86−98% ee). In addition, 0.05 mol % catalyst promotes the rapid cyanosilylation of aldehydes with excellent ee's. In a 10 mmol scale, the catalyst was recovered in 96% yield by silica gel chromatography.



1

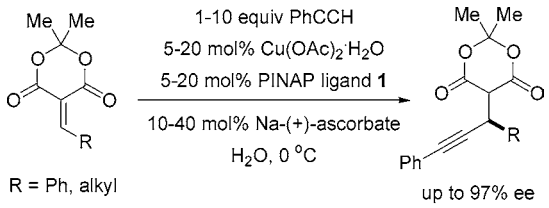
Although the mechanism of catalysis is a current subject of study, the CF_3CH_2OH additive presumably generates HCN as the active nucleophile, and the enantiofacial selectivities are imposed by electronic, rather than steric, effects.

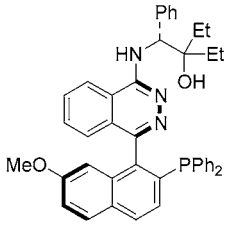


A modified cinchona alkaloid-catalyzed cyanosilylation of ketones developed by Deng and co-workers was used in the enantioselective total synthesis of sorbicillinol derivatives (*Angew. Chem. Int. Ed.* **2005**, *44*, 3478−3481). Thus, cyanohydrin (*R*)-**3** was obtained in 92% ee and quantitative yield on a multigram scale by treatment of acetal ketone **2** with 2 mol % $(DHQ)_2AQN$ and TMSCN. The syntheses were accomplished in 10−11 steps and 12−19% yields, and provided evidence confirming the assignment of absolute configurations for sorbicillinol derivatives based on biosynthetic assumptions.

Cu-Catalyzed Conjugate Additions

The use of copper catalysts to mediate 1,4-additions to α,β-unsaturated carbonyl compounds has been expanded by the Carreira group at ETH to the direct enantioselective conjugate addition of phenylacetylene to Meldrum's acid acceptors (*J. Am. Chem. Soc.* **2005**, *127*, 9682−9683). The catalytic species (5−20 mol % loading) is generated by an equimolar mixture of $Cu(OAc)_2 \cdot H_2O$ and PINAP ligand **1** in aqueous media without need of inert atmosphere. The reactions take place in a 10-fold excess of phenylacetylene relative to acceptor to afford the desired adducts in 94−97% ee and 79−94% yield after 14−66 h at 0 °C. Due to the heterogeneous nature of the process, efficient stirring of the reaction mixture is essential to obtain good yields and to allow for the reduction of the amount of phenylacetylene used. The addition products are crystalline solids amenable to optical purity enhancement by recrystallization.

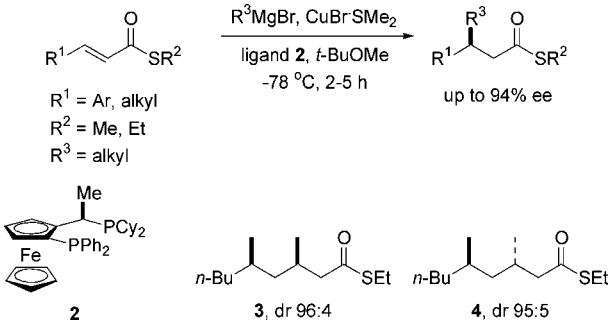




1

Minnaard, Feringa, and co-workers (*J. Am. Chem. Soc.* **2005**, *127*, 9966−9967) have reported a highly enantioselective conjugate addition of Grignard reagents to α,β-unsaturated thioesters using a catalyst prepared in situ from $CuBr \cdot SMe_2$ (5 mol %) and chiral diphosphine ligand (*R,S*)-Josiphos (**2**, 6 mol %). In the optimized conditions, RMgBr (1.2 equiv, R = *n*-alkyl) reacts with an α,β-unsaturated thioester in *t*-BuOMe at −75 °C to afford 1,4-addition products with 85−96% ee and isolated yields of 87−94%. The procedure catalyzes the conjugate addition of the less reactive MeMgBr. In contrast to linear Grignard reagents, their α-substituted counterparts gave poor enantioselectivities

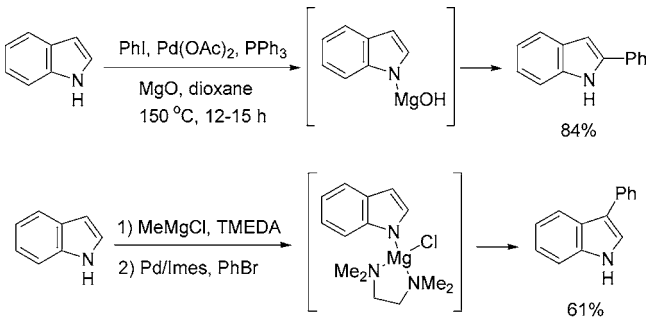
under identical conditions. The sequential application of this methodology provides access to chiral *syn*- and *anti*-1,3-dimethyl arrays (e.g., **3** and **4**, respectively).



2

Direct Regioselective Pd-Catalyzed C-2 and C-3 Arylation of Indoles

General methods for the arylation of azoles require functionalization of the heterocycle followed by introduction of the aryl substituent. The group of Dalibor Sames at Columbia University has recently reported a direct Pd-catalyzed regioselective arylation of indoles (*J. Am. Chem. Soc.* **2005**, *127*, 8050−8057.) 1-Indolyl Mg salts generated with MgO (1.2 equiv) afford C-2 arylated indoles in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %), and PhI (1.2 equiv). The transformation is robust and compatible with a wide variety of functional groups. Under comparable conditions, using CsOAc as base, 1-alkylindoles afford 2-arylindoles in good yields. Following a detailed kinetic study, the authors developed a mechanistic hypothesis to understand the regioselectivities and steer the course of the reaction toward selective C-3 arylations. In short, generation of a hindered 1-indolyl Mg complex using TMEDA or $Mg(HMDS)_2$ leads to C-3/C-2 selectivities greater than 14:1, respectively.



Imes = 1,3-dimesitylimidazol-2-ylidene

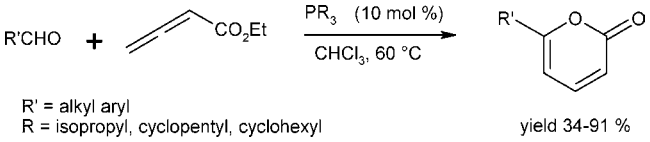
Organic Reactions in Aqueous Media with a Focus on Carbon−Carbon Bond Formations.

Li, C.-J. (*Chem. Rev.* **2005**, *105*, 3095−3166)) has reviewed the topic of organic reactions in aqueous media with focus on C−C bond formation over the past decade. A decade ago the first comprehensive review on carbon−carbon bond formations in water was reported. Since then, there has been an explosion of research activities in this field, which has been partially attributed to the development of the field of Green Chemistry. The review gives a clear overview of the topic and demonstrates that water can promote various old and new reactions. Most importantly, completely new reactivities have been discovered by using water as a solvent.

Phosphine-Catalyzed Synthesis of 6-Substituted 2-Pyrones

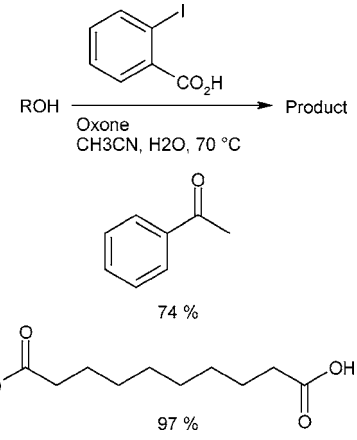
2-Pyrones are found in a large number of natural products that display various biological activities. Consequently, much attention has been paid to the synthesis of 2-pyrones. Despite the plethora of synthetic methods there is still no simple method for the synthesis of 6-substituted 2-pyrones.

Kwon, O. et al. (*Org. Lett.* **2005**, *7*, 2977) have reported a one-step phosphine-catalyzed annelation between aldehydes and ethyl allonate to form 6-substituted 2-pyrones. Sterically demanding trialkyl phosphines are the best catalysts. Various aromatic as well as aliphatic aldehydes undergo the transformation in moderate to good yields.



In Situ Generation of *o*-Iodoxybenzoic Acid (IBX) and the Catalytic Use in Oxidations with Oxone as Cooxidant

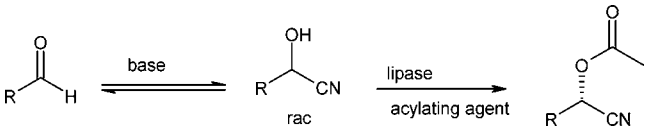
Vinod, T. K. et al. (*Org. Lett.* **2005**, *7*, 2933) have shown that a catalytic use of IBX in the presence of Oxone as the primary oxidant oxidizes primary and secondary alcohols to carboxylic acids and ketones in a mixture of acetonitrile water. The authors show that IBX can be formed in situ from the commercially available 2-iodobenzoic acid through oxidation with Oxone. The reaction is carried out in an acetonitrile−water mixture at 70 °C. Upon cooling to room temperature the insoluble iodine reagent precipitates and can easily be filtered off.



Optimization of the Enantioselective Synthesis of Cyanohydrin Esters

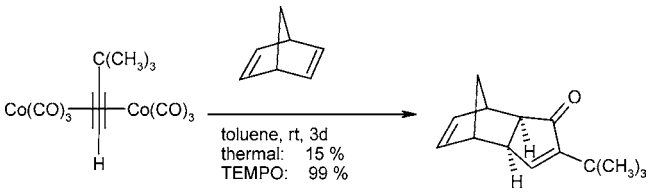
The base- and lipase-catalysed enantioselective synthesis of cyanohydrin esters was investigated, and the problem of low yields due to residual water in the reaction mixture was addressed (Hanefeld, U. et al. *Adv. Synth. Catal.* **2005**, *347*, 1015). When the lipase (CAL-B) was immobilized on Celite R-633 as a carrier and the use of Amberlite IRA-904 in the OH^- form, both enantioselectivity and reaction kinetics for this dynamic kinetic resolution were improved, thus enabling

a highly enantioselective synthesis of aromatic and heteroaromatic cyanohydrin acetates.



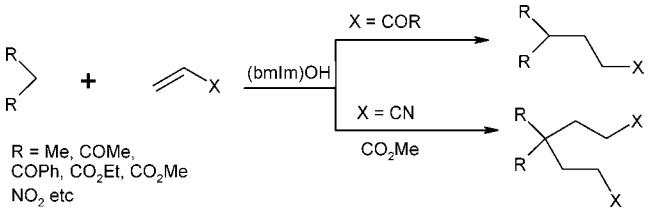
TEMPO-Promoted Pauson−Khand Reaction. Single-Electron Activation of Cobalt−Carbonyl Bonds

Pericàs, M. A. et al. (*Org. Lett.* **2005**, *7*, 3033) have found that the Pauson−Khand reaction can be accelerated by TEMPO. When sterically more demanding alkynes were used, the beneficial effect of TEMPO was accentuated. Thus, the trimethylsilylacetylene complex reacted cleanly in either dichloromethane or toluene, but no product was formed at all in the absence of TEMPO.



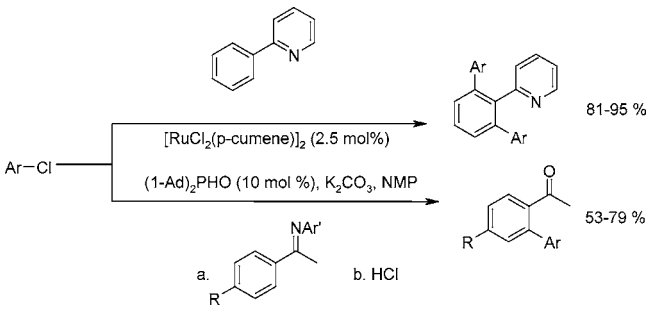
Ionic Liquid as Catalyst and Reaction Medium. The Influence of Task-Specific Ionic Liquid, [bmIm]OH, in Michael Addition of Active Methylene Compounds

Ranu, B. C. et al. (*Org. Lett.* **2005**, *7*, 3049) have used a task-specific ionic liquid 1-butyl-3-methylimidazolium hydroxide ([bmIm]OH) as catalyst and reaction medium in Michael addition. Although the addition to α,β-unsaturated ketones proceeds in the usual way, giving the monoaddition products, the ionic liquid always drives the reaction of open-chain 1,3-dicarbonyl compounds with α,β-unsaturated esters and nitriles towards bis-addition to produce exclusively bis-adducts in one stroke.



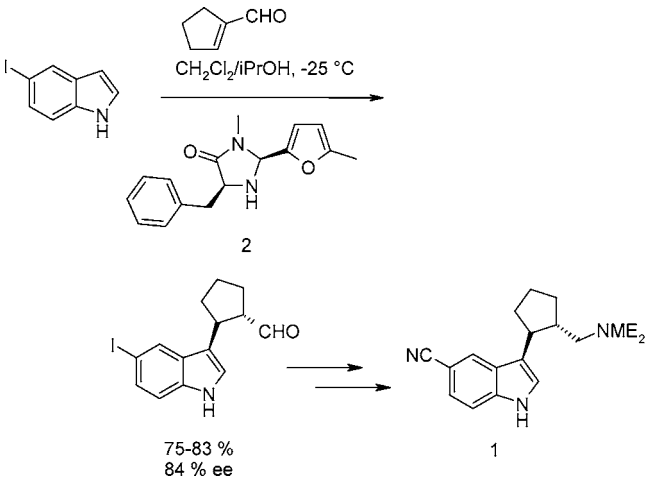
Phosphine Oxides as Preligands in Ruthenium-Catalyzed Arylations via C−H Bond Activation Using Aryl Chlorides

Ackermann, L. (*Org. Lett.* **2005**, *7*, 3123) has found that the use of air-stable electron-rich phosphine oxides as preligands allows for ruthenium-catalyzed arylation reactions of pyridines and imines through C−H bond activation using aryl chlorides. The catalytic system derived from a sterically hindered adamantyl-substituted phosphine oxide was found to be efficient and tolerates a number of functional groups.



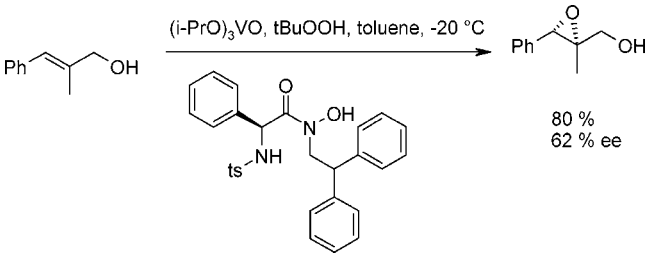
Enantioselective Synthesis of a Highly Potent Selective Serotonin Reuptake Inhibitor. An Application of Imidazolidinone Catalysis to the Alkylation of Indoles

King, H. D. et al. (*Org. Lett.* **2005**, *7*, 3437) have described the enantioselective synthesis of the highly potent and selective serotonin reuptake inhibitor (**1**). In the key construction step, an enantioselective alkylation of the indole nucleus with an α-branched α,β-unsaturated aldehyde was accomplished utilizing Macmillan's imidazolidinone catalyst (**2**).



Amino Acid-Derived Hydroxamic Acids as Chiral Ligands in the Vanadium-Catalyzed Epoxidation

Malkov, A. V. et al. (*Org. Biomol. Chem.* **2005**, Advance Articles) have developed new chiral sulfonamide-derived hydroxamic acids as chiral ligands for the vanadium-catalyzed asymmetric epoxidation. The strong accelerating effect exhibited by this type of ligand can be attributed to the sulfonamide functionality. A range of cinnamyl-type allylic alcohols were epoxidized with up to 74% ee.



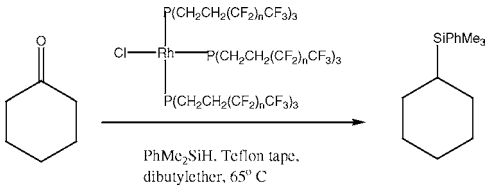
Advances in Homogeneous and Heterogeneous Catalytic Asymmetric Epoxidation

Xia, Q.-H. et al. (*Chem Rev.* **2005**, *105*, 1603) have reviewed the advances in homogeneous and heterogeneous catalytic asymmetric epoxidations. The authors comment that since chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules with biological activity more attention will still need to be

paid to the progress in this field to improve enantioselectivity as well as chemoselectivity.

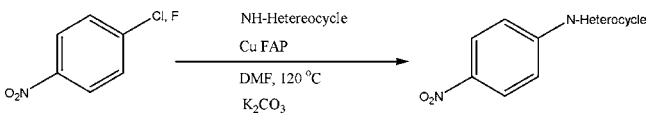
A Novel Delivery and Recovery Method for Noble Metal Catalysts

Recovery and recycling of expensive metal catalysts play important role in economical large-scale synthesis. Although insoluble catalysts or solid support catalysts have been in use, recovery of organic solvent soluble catalysts is generally difficult. Therefore, such processes contribute to the cost and contamination of products with heavy metals and thus render them unacceptable to pharmaceutical application. Fluorous-tagged thermophilic catalysts in usual organic solvents have found application in large-scale synthesis. Yet they have limitations. Dinh and co-workers (*Angew. Chem., Int. Ed.* **2005**, *44*, 4995−4997) found that the metals (rhodium) containing long-chain fluorous hydrocarbon chains can be adsorbed onto Teflon tape and serve as catalysts in the same way as those which are solubilized in either in fluorocarbon or in nonfluorohydrocarbon solvents such as dibutyl ether at higher temperatures. The authors were able to reduce ketones to silyl ethers with $PhMe_2SiH$. This technology can deliver low loading of catalyst without recourse to balance or tedious preparation of standard solutions and has the potential for fabricating reactors with catalysts. Some years ago L. Errede and co-workers (*Chemically Modified Surfaces in Science and Industry: Proceedings of the Chemically Modified Surface Symposium*, Fort Collins, Colorado, 17−19 June, 1987; Gordon and Breach Science Publishers: New York, 1988) embedded palladium on carbon in a Teflon matrix and performed several chemical reactions very efficiently.



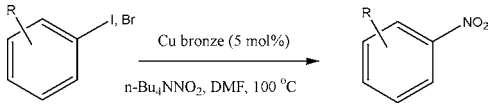
Copper Apatite Catalysts for N-Arylation of Heterocycles

In general, the process of N-arylation of heterocycles is a problem to make it a synthetically useful reaction even after using highly reactive aryliodides or -bromides in the presence of catalysts such as palladium. Chowdary and co-workers (Chowdary, B. M.; Sridhar, C.; Kantham, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948−9949) devised a new recyclable catalyst system, copper fluoro- or *tert*-butoxyapatite. This catalyst is easily prepared and activates chloro and fluoro arenas with ortho or para electron-withdrawing as well as electron-donating substituents on the aromatic ring, successfully arylated with variety of −NH heterocycles.



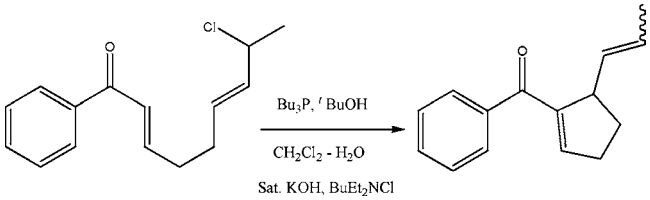
A Mild Procedure for the Nitration of Aromatic Compounds

Due to the importance of aromatic nitro compounds in many commodity and fine chemical industry applications, numerous promising nitration methods in lieu of using hazardous nitric acid mixtures as nitration reagents have been developed. Invariably some contamination of dinitro compound formation is also unavoidable. In addition, the directing group on the aromatic ring plays a critical role. Sato and Koizumi (Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715−4717) report a method of nitration of aromatic halides with a combination of $NaNO_2$ and 18-crown-6 or *tert*-*n*-butylammonium nitrite in the presence of a catalytic amount of copper-bronze. This method circumvents the traditional problems associated with nitration reactions of aromatic compounds. The yields are good to moderate.



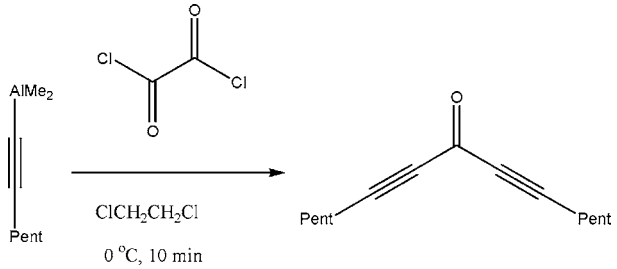
Use of Allylic Chlorides for Intramolecular Morita−Baylis−Hillman with Organocatalysts

Morita−Baylis−Hillman reaction is increasingly finding application in organic synthesis. Krafft and Haxell (Krafft, M. E.; Haxell, T. F. N. *J. Am. Chem. Soc.* **2005**, *127*, 10168−10169) report high-yielding cyclizations to five- and six-membered rings via the intramolecular allylic group as an electrophilic partner in a completely organo-mediated process. In this reaction both mono- and disubstituted alkenes are readily generated. Transition metals are not needed.



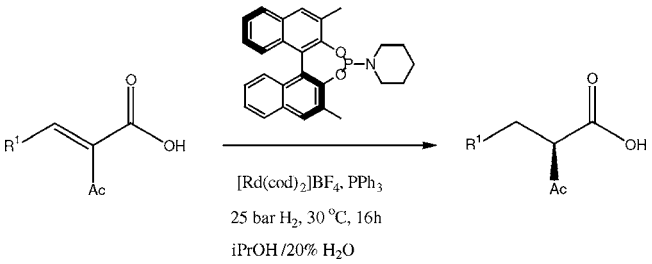
Preparation of Ynones with Dimethylalkynylaluminum

Ynones are useful building blocks for the synthesis of a variety of useful materials for natural products and pharmaceutical syntheses. Although preparation of ynones generally starts with acid chlorides, usually it needs palladium or other metals as catalysts. Wang and co-workers (Wang, B.; Bonin, M.; Micouin, L. *J. Org. Chem.* **2005**, *70*, 6126−6128) used dialkyl aluminumacetylides which are highly reactive and easily prepared, for the condensation with a variety of acid chlorides. In some cases, the reagent adds to the initially formed ynone, but the reaction is complete in few minutes, and work-up is simple. This reaction provides a simple entry into numerous ynones, using readily available, inexpensive, nontoxic metallating agents; it does not require any transition metal as catalyst and gives good yields.



Dramatic High Enantioselectivity with Heterocombination of Chiral and Achiral Monodentate Ligands

For asymmetric reduction of α,β-unsaturated esters, the combination of transition metals and chiral, as well as achiral, mono and bidentate ligands such as phosphoramidites, phosphonites, or phosphates plays an important role. Mixtures of chiral monodentate ligands improve the enantioselectivity and reactivity in several cases. This prompted Hoen and co-workers (Hoen, R. et al. *Angew. Chem., Int. Ed.* **2005**, *46*, 4209−4212) to employ rhodium metal with a mixture made up of a chiral monodentate phosphoramidite and an achiral monodentate phosphine ligand, for high enantioselective reduction of unsaturated esters. A substituent at the α- or β-position does not affect the enantioselectivity. In some cases fine-tuning of the ratio of phosphine and phosphoramidite combination becomes necessary.



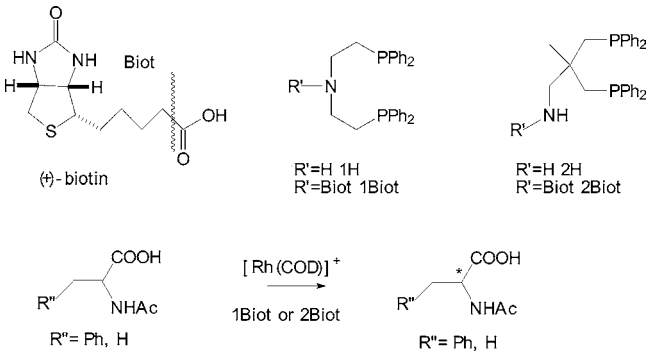
Artificial Metalloenzymes for Enantioselective Catalysis

Thomas R. Ward from the University of Neuchâtel reports (*Chem. Eur. J.* **2005**, *11*, 3798) the design and synthesis of organometallic modified enzymes.

The biotin−avidin system fulfills the necessary requirements to be used as the host−guest system for supramolecular-anchoring purposes. Therefore, biotin was chosen to anchor the catalyst, thus playing the fundamental guest role.

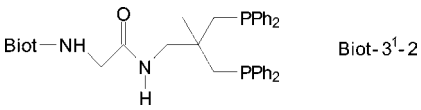
Modified biotin (linked to achiral phosphines) anchored in the convenient enzyme (avidin or other similar enzyme) in the presence of $[Rh(COD)]^+$ was therefore successfully used as catalyst on the reduction of acetamidoacrylic and acetamidocinnamic acids.

In addition to the very high enantiomeric excesses (ee's) obtained and configuration tuning ((*R*) or (*S*) isomers can be produced), the phenomenon of protein-accelerated catalysis was unraveled.



Hydrogenation of acetamidoacrylate in the presence of the guest−host complex, [Rh(1Biot)(COD)$^+$] streptavidin, proceeded quantitatively with up to 94% ee (*R*).

Screening of a number of spacers revealed that the guest−host complex, [Rh(Biot-3^1-2)(COD)$^+$]⊂avidin (host⊂guest complex) afforded acetamidoalanine in 80% ee (*S*).



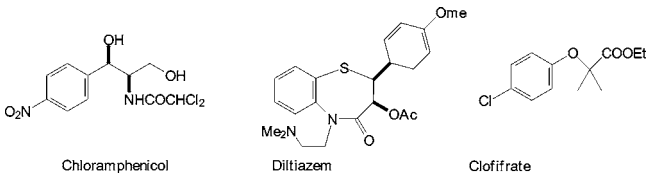
To improve selectivity four streptavidin mutants (S112G, V47G, K80G, and P64G) were expressed in *Escherichia coli* purified and tested with the ligands. In addition, a recombinant glycosylated form of avidin was expressed in *Pichia pastoris* (pI = 5.4) and was tested as well.

From these combinations (18 × 7 ligand−protein) it was demonstrated that the selectivity of artificial metalloenzymes is amenable to a chemogenetic optimization procedure since, depending on the mutations, either (*R*) or (*S*) enantiomer can be produced.

Microbial Stereoselective Reductions

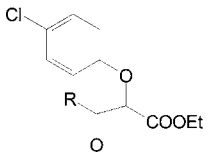
Stereoselective reduction of α-substituted β-keto esters are generally carried out via the Noyori process. However, high pressures and costly ligands are needed in these processes.

The corresponding reduced compounds are important intermediates for the production of active pharmaceutical ingredients (APIs), for example, chloramphenicol and diltiazem. In connection to this need, new analogues of clofibrate with improved pharmacological profiles have been the object of investigation (Feller et al. *J. Med. Chem.* **1987**, *30*, 1265).



To investigate the production of these (chiral) intermediates, Scilimatis's group has been working on the microbial reduction of β-keto esters with remarkable success. They reported the yeast-mediated reduction of ethyl 2-(4-chlorophenoxy)-3-oxo-alkanoates (*Tetrahedron: Asymmetry* **2004**, *15*, 3501; *Tetrahedron: Asymmetry* **2004**, *15*, 3511; *Tetrahedron: Asymmetry* **2005**, *16*, 1473).

First, they used Baker's yeast to mediate the reduction of 2-(4-chlorophenoxy)-3-oxo-alkanoates.



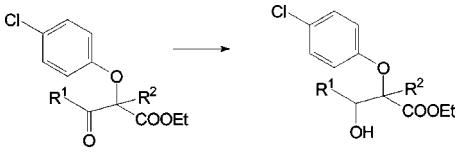
R	de(*syn/anti*)	ee (*syn*)
Me	92	94
Et	50	51
nPr	89	89
iPr	70	70
tBu	low conversion	
Ph	99	99

Conversions were strongly dependent on the R group. Bulky substituents led to reduced conversions (iPr 43%, tBu 2%). However, the phenyl group behaves very well, giving rise to good conversions and 99% ee and de.

Syn stereochemistry predominates and was fully proved via X-ray analysis.

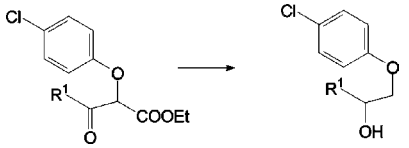
After testing other yeasts, they discovered that *Kluyveromyces marxianus* CBS 6556 afforded quantitative conversion, 99% de (*syn*) and 86% ee (growing cells) or 97% ee (resting cells) on the reduction of ethyl 2-(4-chlorophenoxy)-3-oxobutanoate.

Finally, other oxoesters were tested with different yeasts. *Saccaromyces cerevisiae* (DSM 11 285 and CBS 7336) led to over 99% de on the reduction of ethyl 2-(4-chlorophenoxy)-3-oxo-3-phenylpropanoate.



R^2 = H, R^1 = Me, Et, nPr, iPr, tBu, Ph, Me
R^2 = Me, R^1 = Me

Interestingly, hydrolysis, decarboxylation, and reduction also occurred competitively to the main reaction.



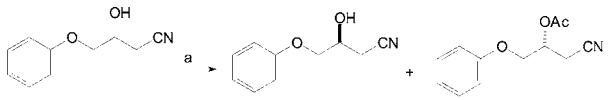
Also concerning the enzymatic/microbial reduction of keto compounds, the reader is invited to the excellent review of Muller et al. (Enzyme-Catalyzed Regio- and Enantioselective Ketone Reductions. In *Technology Transfer in Biotechnology: From Lab to Industry and Production*; Kragl, U., Ed.; *Adv. Biochem. Eng. Biotechnol.* **2005**, *92*, 261) devoted particularly to the access to chiral 1,3-diols and propargylic alcohols.

Lipases in the (Kinetic) Resolution of Racemates

This title comes from a review article of Ghanem and Aboul-Enein (*Chirality* **2005**, *17*, 1) which covers general aspects of lipases in organic solvents and describes several examples of applications of lipases in the resolution of racemates. Very useful is a brief description of what is called enantiomeric ratio (E) which has a tremendous importance to anyone interested in using enzymatic resolution for practical synthetic purposes.

In that way a remarkable description of the use of (*Kluyveromyces marxianus*) in the hydrolysis of (*R,S*)-isopropylideneglycerol acetate shows the use of a multisimplex experimental design optimization system to find the best compromise among reaction variables to achieve the highest enantioselectivity (Molinari et al. *Tetrahedron: Asymmetry* **2004**, *15*, 1945). Of particular importance is to show the enormous importance of this microorganism in organic synthesis once (vide supra) it has been successfully used in enantioselective reductions.

Also related to the use of lipases in resolution of racemates (although there have been described several enzymatic and microbial process to produce beta-blockers related to *S*-propranolol), recently Kamal et al. (*Tetrahedron: Asymmetry* **2005**, *16*, 1485) described the use of *Pseudomonas cepacia* lipase to promote the production of suitable chiral (up to 50% yield, 99% ee) intermediates to these compounds. What is encouraging is the use of such biological systems in very bulky lipophilic substrates. In addition, contrary to the most exploited methodologies, in this case the secondary alcohol is subjected to the acetylation enzymatic process.



a- lipase from *Pseudomonas cepacia* (*Burkholderia cepacia*), vinyl acetate, diisopropyl ether

Green Systems

Sheldon reviewed (*Green Chem.* **2005**, *7*, 267) the general use of environmentally acceptable solvents, showing several examples of the use of supercritical CO_2, ionic liquids, PEG, and other nonaqueous solvents.

In connection to this, recent examples of the use of ionic liquids in Morita−Baylis−Hillman Reactions (Mi, Luo, and Cheng, *J. Org. Chem.* **2005**, *70*, 2338) as well as in oxidations (Kuhn et al. *Tetrahedron Lett.* **2005**, *46*, 47; Valente et al. *J. Mol. Catal. A.: Chem.* **2004**, *218*, 5; Bernini et al. *Tetrahedron* **2005**, *61*, 1821; Li and Xia *J. Mol. Catal. A: Chem.* **2004**, *214*, 95) have been described in the literature.

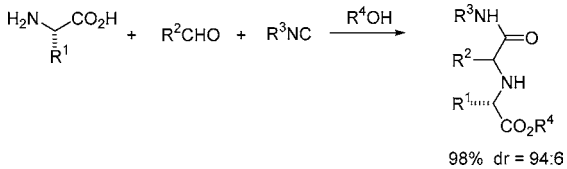
On the homogeneous catalysis side, a recyclable and reusable $Pd(OAc)_2$/DABCO/PEG-400 system for the Suzuki−Miyaura cross-coupling reaction (Li, J.-H.; Liu, W.-J.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 5409−5412) as well as the use of nanosized palladium on chitosan in ionic liquids in the Heck reaction (Caló et al. *Organometallics* **2004**, *23*, 5154) has been described

In addition, the production and characterization of palladium−dendrimer encapsulated nanoparticles have been reported (Scott, R. W. J.; Wilson, O. M.; Crooks, R. M. *J. Phys. Chem. B* **2005**, *109*, 692) with several catalytic applications.

In addition Pd−dendrimer complexes have been used in Heck (Ooe, M. et al. *J. Am. Chem. Soc.* **2004**, *126*, 1604) and Stille (Garcia-Martinez, Lezutekong, and Crooks *J. Am. Chem. Soc.* **2005**, *127*, 5097) reactions, Narayana and El-Sayed (*Langmuir* **2005**, *21*, 2027) described the Suzuki reaction catalyzed by Pt−PVP nanoparticles, and Lu et al. (*Tetrahedron Lett.* **2005**, *46*, 4255) described the use of Pd/C ligandless system in water, also for the Suzuki reaction.

Asymmetric Multicomponent Reactions

A review on this important topic has recently appeared (Ramon, D. J. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602). The review covers reactions such as the asymmetric Strecker, Mannich, Biginelli, Petasis, Hantzsch, Passerini, and Ugi multicomponent reactions as well as cycloaddition-based multicomponent reactions. A recent monograph on a similar topic has also appeared and will be reviewed in *Organic Process Research & Development* (*Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005). These reactions allow the build-up of a high degree of molecular complexity in a one-pot process with high selectivity, as shown in the example below, an Ugi four-component reaction.



98% dr = 94:6

Enantioselective Imino-Reformatsky Reaction

The Reformatsky reaction, discovered in 1887, is still widely used in synthesis (for a review, see: Ocampo, R. et al. *Tetrahedron* **2004**, *60*, 9325). The reaction has high functional-group tolerance and in situ reagent preparation, but examples of successful scale-up are few, partly because of the sometimes difficult zinc activation step. One useful activation method uses Et_2Zn and $RhCl(PPh_3)_3$ in catalytic amounts (Kanai, K. et al. *Org. Lett.* **2000**, *2*, 2549).

The imino version was described over 60 years ago but can lead to mixtures of β-amino esters and β-lactams; this can be overcome by using imines derived from 2-methoxyaniline. A recent paper described an efficient nickel-catalysed imino-Reformatsky reaction in a one-pot process (Adrian, J. C. et al. *J. Org. Chem.* **2003**, *68*, 2143). Now an asymmetric version of that process, using *N*-methylephedrine as the cheap and recoverable chiral component, is described (Cozzi, P. G. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600).

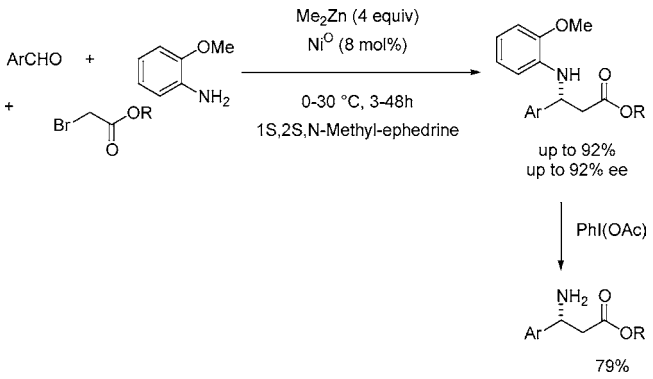
The $NiCl_2(PPh_3)_2$ catalyst described by Adrian is reduced to Ni^0, followed by oxidative addition of the α-bromo ester, then nickel−zinc exchange, leading to the organozinc Reformatsky reagent. By using a chiral chelating ligand in the imine, able to coordinate to zinc (in the same way as Carreira's additions of acetylenes to aldehydes), it was expected that chiral information could be transmitted. This proved to be the case.

The dialkyl zinc performs several functions:

- dehydrating agent in imine formation
- reduction of Ni^{II} to Ni^0
- reaction with the nickel "enolate" to give the zinc "enolate"
- coordination of *N*-methylephedrine

The reaction works well with 4 equiv of dialkylzinc and 1.5−1.6 equiv of *N*-methylephedrine. After acidic work-up, the latter can be recovered. Chloroform and toluene as solvents both give comparable results; however, chloroform dissolves the nickel complex, whereas toluene does not and provides better ee's. A wide variety of aromatic, heteroaromatic, alkyl, and unsaturated groups can be used. Ethyl- and methylbromoacetate gave better results than *tert*-butylbromoacetate.

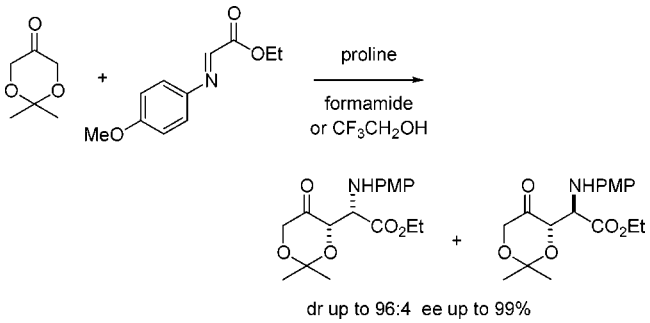
The major disadvantage for scale-up is having to oxidize the 2-methoxyaniline to give the β-amino ester.



Dihydroxyacetone in Amino Acid-Catalysed Mannich-Type Reactions to Form Aza and Amino Sugars

After lying in obscurity for more than 40 years, the potential of amino acid-catalyzed reactions is now being realized, although their potential *was* pointed out in a review article in 1982 (Drauz, K. et al. *Angew. Chem., Int. Ed.* **1982**, *21*, 584). These reactions are now reported to be useful in the synthesis of aza and amino sugars (Westermann, B. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077).

Although hydroxyacetone works well in aldol-type reactions with L-proline as catalyst in DMSO, dihydroxyacetone does not, unless it is protected as the acetonide.



A minimum of 5% proline is required for good diastereoselectivity, and temperature is not a significant factor. Other proline-derived catalysts were unsuccessful. The disadvantage of proline as a catalyst is that reaction times can be long. In this case use of microwaves accelerates the reactions, which are complete in 5−10 min.

In the following paper from the group of Enders (*Angew. Chem., Int. Ed.* **2005**, *44*, 4079), which builds on earlier results using the acetonide of dihydroxyacetone (Enders, D. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210), asymmetric synthesis of selectively protected amino sugars by a Mannich reaction is also described.

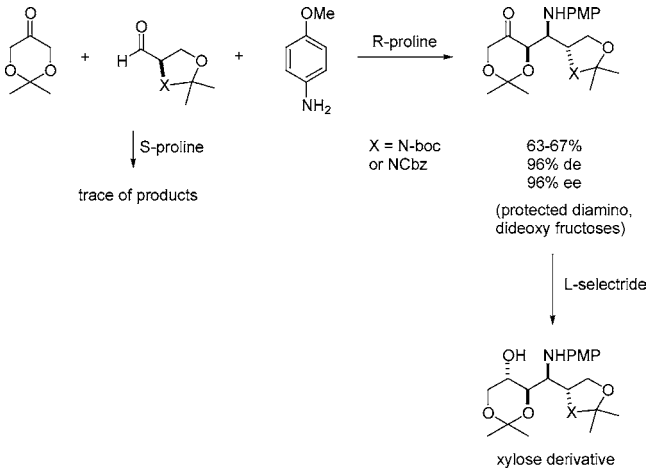
In contrast to the previous paper, the Enders group use DMF, MeCN, and NMP as solvents and either proline or TBS-protected 3-hydroxyproline as catalysts. After extensive optimization they find

(1) The optimal reaction temperature for reasonable rate and good selectivity is between 2 and 20 °C. Lowering the temperature lowered diastereo- and enantioselectivity.

(2) Addition of 1−10 equiv of water led to an increase in selectivity, although at a slower rate.

(3) Use of the TBS protected catalyst gave increased rate and selectivity, possibly owing to its solubility, although this varied from solvent to solvent.

(4) When the TBS protected catalyst is used, addition of water again has a positive effect in stereochemistry.

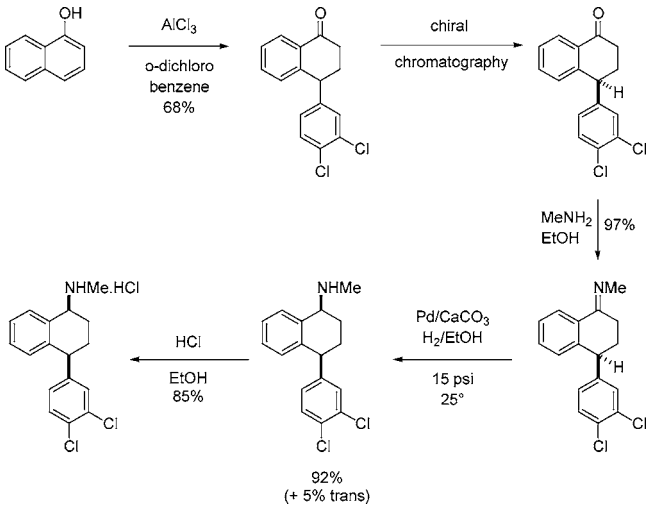


Interestingly, when the aldehyde is chiral, the reaction works only with one enantiomer of the proline catalyst. For *S*-configured aldehydes, *R*-proline is the catalyst of choice whereas for *R*-configured aldehydes, *S*-proline is the catalyst of choice. This methodology allows the synthesis of protected amino-pentoses and hexoses with high diversity and diastereo- and enantioselectivity in one to two steps from readily available materials.

The use of organo catalysis in carbohydrate synthesis has also been highlighted in a short review (Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186).

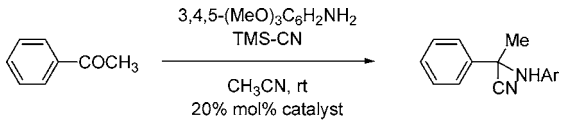
The Commercial Process for Sertraline

A recent article in *Chirality* (Quallich, G. *Chirality* **2005**, *17*, 5120) describes the use of continuous chromatography to separate the key tetralone intermediate in the synthesis of the Pfizer drug sertraline (Zoloft). The chromatographic separation of the enantiomers, followed by racemisation of the unwanted isomer and recycle, was the most cost-effective process, giving the desired product in 98.4% yield and 99.7% ee, with a productivity of 371 kg of enantiomer per kg of chiral stationary phase. The commercial process is detailed below.



Iodine as a Novel Catalyst for Synthesis of α-Aminonitriles

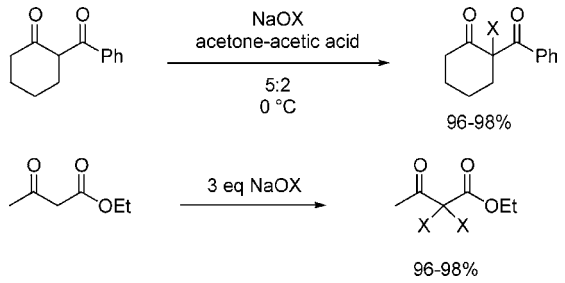
α-Aminonitriles are very important intermediates for the synthesis of amino acids and heterocycles and are normally made by the Strecker reaction. Whilst many catalysts work with aldehydes, ketone substrates are often unreactive. A new procedure (Royer, L. et al. *Tetrahedron Lett* **2005**, *46*, 4595) shows that iodine can catalyse the reaction of carbonyls (including ketones) with TMS−CN and amines, using acetonitrile as solvent at room temperature. A comparison with other catalysts is shown in the table.



catalyst	time	yield
$Sc(OTf)_3$	12	15
$InCl_3$	10	12
$RuCl_3$	12	5
$BiCl_3$	12	8
I_2	8	68

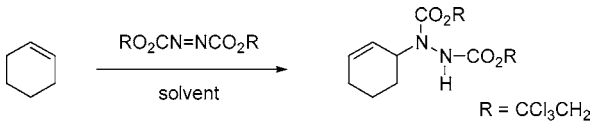
Halogenation of β-Dicarbonyl Compounds under Mild Conditions

Reaction of β-dicarbonyl compounds with sodium hypochlorite in a mixture of acetone and acetic acid (5:2 ratio) leads to dichlorination of the active methylene group or monochlorination if the methylene is already substituted (Meketa, M. L. et al. *Tetrahedron Lett.* **2005**, *46*, 4749). The reaction also works with sodium hypobromite. These simple reaction conditions had previously been used for the conversion of vinyl chlorides to α-chloro ketones (Van Brunt, M. P. et al. *J. Org. Chem.* **2003**, *68*, 3323).



Organic Reactions "on Water": No Need for Any Solubility?

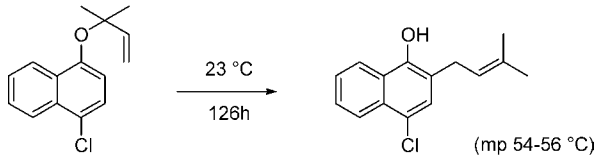
A fascinating paper from the Sharpless group probes the question "do substances need to be dissolved to react?" (Narayan, S. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275). The answer is no! The hydrophobic effect (for a review, see: Otto, S. et al. *Org. Biomol. Chem.* **2003**, *1*, 2809) works if one or both components are not soluble; it is preferable of course if one component is a liquid. The accelerating effect of reactions "on water" is shown in the examples below. These reactions have practical value even if the origins of rate enhancement are unclear.



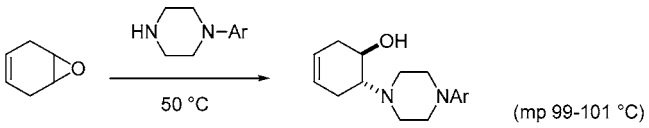
Solvent	T(°C)	t(h)	Yield %
Benzene	80	24	70
Neat	50	36	62
on Water	50	8	91

In cases where the product is a solid, the product crystallizes out during the reaction and can be isolated by simple filtration. From a scale-up viewpoint the amount of water can be adjusted to compensate for the exothermicity of the reaction, but this does *not* cause any dilution and therefore no change in the rate of reaction—it just acts as a heat sink!

The unique properties of molecules at the macroscopic phase boundary between water and insoluble hydrophobic oils is probably of significance, as has been observed



Solvent	Yield
Toluene	16
DMF	21
MeCN	27
MeOH	56
Net	73
on Water	100



Solvent	Conc	t(h)	Yield
Toluene	1	120	<10
Neat	3.88	72	76
EtOH	1	60	89
on Water	3.88	12	88

previously by others such as Breslow (*Acc. Chem. Res.* **1991**, *24*, 159). For Diels−Alder reactions, Breslow found further rate enhancements when surfactants were added, and it would be interesting to see if this occurs in the above examples. However, this would reduce practicality since work-up may be more difficult in the presence of surfactants.

Crystal Size Distribution in Batch Crystallizations

Batch crystallization is used in the production of high-value-added products, such as pharmaceuticals, photo materials, and fine chemicals, mainly because it offers flexible and simple processing steps for plants with frequently changing recipes and product lines. For this kind of material, product purity and crystal size distribution (CSD) are of prime importance. Furthermore, the crystals produced through a crystallization process have a decisive influence on the downstream processing, and therefore, the CSD should be reproducible in each operation and as regular as possible. Recently, a case study has been reported which suggests ways to improve the performance of batch crystallization processes. The batch cooling crystallization of adipic acid is chosen as a case study. In a well-mixed batch crystallizer, the final crystal product is determined by the supersaturation profile, the initial seed mass, and the seed crystal size distribution. The supersaturation evolution in time, during batch crystallization processes, determines the magnitude of the many kinetic phenomena of the process. Since in cooling crystallization processes, the supersaturation magnitude is determined mainly by the cooling rate during the process, the optimization of the cooling trajectory is indispensable to the improvement of the process performance, and a substantial research activity has been devoted to the computation of optimal temperature trajectories. The proposed approach involves the process modeling and its further optimization in a real-time fashion. The modeling of the crystallization process is presented, and it takes into account the contribution of agglomeration. The influence of the process variables on the final crystal size distribution (CSD) and on the quantity of solids is analyzed. This analysis is fundamental because it gives evidence of the role and magnitude of each variable as well as their interaction in the process performance. The optimization of the process is then considered, and it can be focused on finding the optimal cooling trajectory through optimal control theory. A study of the best way to postulate the problem is considered, taking into account the constraints and which is the best performance criterion to be used. The problem is postulated as a nonlinear programming problem, which is solved through sequential quadratic programming (SQP). The nonlinearity feature of the problem is strongly increased by the agglomeration contribution. The results have shown that the developed mathematical model is a good representation of the process, able to reproduce results from the literature. The optimization problem has been shown to be strongly nonlinear and difficult to postulate. Nevertheless, the solutions obtained through the optimization study, although the global optimum may not be guaranteed, lead to a substantial improvement of the end-product quality, expressed in terms of the mean size and the variation coefficient (Costa et al. *Chem. Eng. Process.* **2005**, *44*, 737−753).

Production of Small Uniform Particles

The supercritical antisolvent (SAS) technique is a very popular method currently used for producing microparticles for a variety of applications, such as pharmaceutical compounds, superconductor precursors, and polymers. In making micrometer-sized particles, the significance of the droplet size minimization and droplet mass transfer enhancement, accomplished for example through the decrease in the nozzle diameter, have been well recognized. However, its applicability for reliably producing nanosized particles is somewhat limited due to the lack of detailed understanding of the subprocesses important to this process such as droplet formation, droplet interaction, and coagulation, as well as droplet mass transfer. Droplet formation, droplet interaction, and coagulation together with droplet mass transfer are major subprocesses in the developing technology of nanoparticle production by means of solute nucleation inside the emulsion droplet. The solvent (ethanol) droplets containing the solute form during the solvent jet dispergation in pressurized flow of solvent CO_2. In the formed two-phase flow of solvent−antisolvent emulsion, the solvent diffuses from droplets into antisolvent, while antisolvent dissolves inside solvent droplets. The solvent replacement by the antisolvent causes droplet supersaturation by solute when it occurs near the critical point of solvent−antisolvent emulsion (∼80 bar and 31 °C) and the intradroplet nucleation of solute. To provide the same droplet lifetime and the uniform droplet supersaturation, the hydrodynamic relaxation time for droplets and for two-phase flow has to be shorter than their relaxation time of the mass transfer. Above a critical volume fraction of solvent, droplets dissolve partially. Afterwards, i.e., downstream, antisolvent is saturated with solvent, i.e., phase

equilibrium establishes within two-phase flow with uniform solute supersaturation inside droplets. Under these conditions, an additional mechanism of the supersaturation is identified, which is droplet specific (the supersaturation caused by increasing solute concentration) and is favorable for small particle production (Dukhin et al. *Colloids Surf., A* **2005**, *261,* 163−176*)*.

Real-Time Product Morphology Monitoring in Crystallization Using Imaging Technique

In situ crystal morphology imaging is reported by a team including groups from the University of Leeds, GlaxoSmith-Kline, and Malvern Instruments (Calderon De Anda, J. et al. *AIChE J.* **2005**, *51*, 1406). Crystal morphology is often a critical quality attribute for APIs. Whereas several techniques for in situ crystallization monitoring are available, only few of them achieve crystal-morphology monitoring. The Glaxo-SmithKline group built a prototype that was used to monitor the crystallization and polymorphic transformations of L-glutamic acid that exhibits two polymorphs: prismatic, and needle-shaped crystals. A photomicroscope and an off-line particle characterization instrument (Pharma-Vision System 830, from Malvern Instruments) were used to validate and benchmark the results obtained. At high supersaturation levels big crystals were obtained, with particular growth on the crystallographic face (0 1 1); crystals develop into long needles at low supersaturation levels, with the crystallographic face (1 0 1) showing the fastest growth rate. Future work will include investigating the possibility of adding quantification capabilities to the method.

Scale-Up Study of Retreat Curve Impeller Stirred Tanks Using LDA Measurements and CFD Simulation

Another collaboration including Prof. Roberts' group at the University of Leeds, with colleagues from Heriot-Watt University, describes scale-up investigations of retreat curve impeller stirred tanks (Li, M. et al. *Chem. Eng. J.* **2005**, *108*, 81). Retreat curve impeller stirred tanks are widely used in fine chemical and pharmaceutical manufacturing. For three fully geometrically similar reactors (0.5, 2.0, and 20 L), using CFD (CFX5.5.1) calculations, and laser doppler anemometer (LDA) measurements, the authors show that certain flow characteristics in the three reactors are very similar, such as the power number, pumping efficiency, etc. This is not surprising, especially for homogeneous systems, due to complete geometric similarity between the reactors. Future work will include investigation of additional process parameters.

Incorporation and Characterization of a Mixing Elbow on the Pilot-Plant Scale for a Mixing-Sensitive Crystallization of an API

A group from Merck reports the use of a mixing elbow in a pilot-plant setting to successfully scale-up a challenging, mixing-sensitive API crystallization process (Singh, U. K. et al. *Ind. Eng. Chem. Res*. **2005**, *44*, 4068). The crystallization process had been proven to be very fast and, because of strong secondary nucleation effects, sensitive to scale and geometry. Mixing in the pilot-plant elbow was characterized using the fourth Bourne reaction, wherein the impact of mixing is assessed on two fast competitive reactions: the neutralization of HCl with NaOH, and the NaOH hydrolysis of 2,2-dimethoxypropane.

The semi-continuous crystallization process employed three 200-gal reactors and a mixing elbow; first, a 15% wet milled seed is recirculated through the elbow, followed by mixing through the elbow of a hot toluene solution of the API with a cold *n*-heptane antisolvent stream. Interestingly, the use of a mixing elbow in this crystallization process altered both the particle size distribution as well as particle morphology. Particles obtained using the mixing elbow were smaller and less agglomerated than in the case of conventional stirred tank crystallization.

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