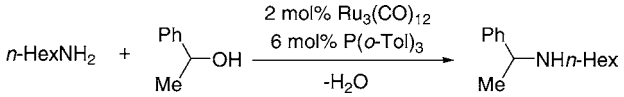
Organic Process Research & Development **2007**, *11*, 166–177

Highlights from the Literature

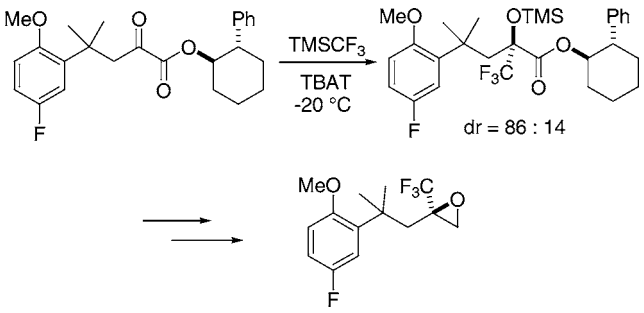
Some Items of Interest to Process R&D Chemists and Engineers

Ruthenium-Catalyzed Amination of Primary and Secondary Alcohols



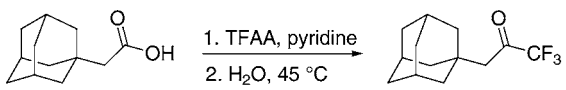
The catalytic formation of carbon−nitrogen bonds is of a broad interest to synthetic organic chemists since a large number of nitrogen-containing molecules are of importance for both the bulk and fine chemical industries. Among the various catalytic amination methods, palladium-catalyzed amination of aryl halides, hydroamination, and hydroaminomethylation of olefins or alkynes have received close attention in the past decade. Less interest has been paid to the further development of catalytic alkylations of amines. Compared to the frequently applied *N*-alkylations with alkyl halides and reductive aminations, an economically and environmentally attractive method is the *N*-alkylation of amines using primary and secondary alcohols. In a recent report, Beller and co-workers describe the ruthenium-catalyzed *N*-alkylation of amines with alcohols in the presence of different sterically hindered phosphine ligands (*Tetrahedron Lett.* **2006**, *47*, 8881−8885). The reactions can be performed under significantly milder conditions (110 °C) compared to known ruthenium systems. At present, a 5-fold excess of the alcohol partner was required for good conversion of the amine, and the substrate scope with respect to the amine is rather limited; however, a variety of primary and secondary alcohols are viable in this process.

Practical Diastereoselective Trifluoromethylation Reaction



A practical stereoselective synthesis of an α-trifluoromethyl-α-alkyl epoxide (**1**), which is an important pharmaceutical intermediate, is reported by Song and co-workers at Boehringer Ingelheim (*J. Org. Chem.* **2007**, *72*, 292−294). The key step involves a chiral auxiliary-controlled asymmetric trifluoromethylation reaction for the introduction of the unique trifluoromethyl-substituted tertiary alcohol stereogenic center in the target molecule. After examination of reaction parameters, operating at −20 °C in toluene with TBAT as the fluoride source proved optimal. The fluoride-initiated CF_3 addition to the chiral keto ester proceeded with a diastereoselectivity up to 86:14. The major diastereomer was readily obtained (in 50% isolated yield) with a >99.5:0.5 dr through a simple crystallization of the crude product mixture. The authors note that it was possible to efficiently recover the chiral auxiliary following ester hydrolysis and acid−base extractive workup.

Direct Conversion of Carboxylic Acids to Trifluoromethyl Ketones



8 examples 41-82% yield

Primary and secondary carboxylic acids can be converted in one step to the corresponding trifluoromethyl ketones by treatment with trifluoroacetic anhydride (TFAA) and pyridine in toluene at 60−100 °C followed by hydrolysis/decarboxylation with water at 45 °C, as reported by Reeves and co-workers at Boehringer Ingelheim (*Tetrahedron Lett.* **2007**, *48*, 189−192). The described process eliminates the need for an additional step for the conversion of carboxylic acids to acid chlorides prior to trifluoromethyl ketone formation. In addition, these conditions allow for the successful reaction of substrates which previously afforded low yields (hindered primary substrates) or no reaction (secondary substrates) using the previously described procedure for acid chlorides. The use of inexpensive reagents and readily available, easily handled carboxylic acids as starting materials makes this a practical method for accessing enolizable trifluoromethyl ketones.

Catalytic Asymmetric Strecker Reaction of Phosphinoyl Ketoimines

The Strecker reaction is one of the most attractive methods for the synthesis of α-amino acids and their derivatives. An enantioselective variant of this reaction, with *N*-diphenylphosphinoyl ketoimines as substrates, is reported by the Feng group (*J. Org. Chem.* **2007**, *72*, 204−208). The optimal chiral *N*,*N*′-dioxide catalyst is prepared in situ from the piperidinamide shown and *m*-chloroperoxybenzoic acid (*m*-CPBA). Excellent yields (up to 99%) and high enantioselectivities (up to 92% ee) can be obtained, and the reaction had tolerance of moisture and air. It was shown that the piperidinamide-derived *N*,*N*′-dioxide could be recycled and

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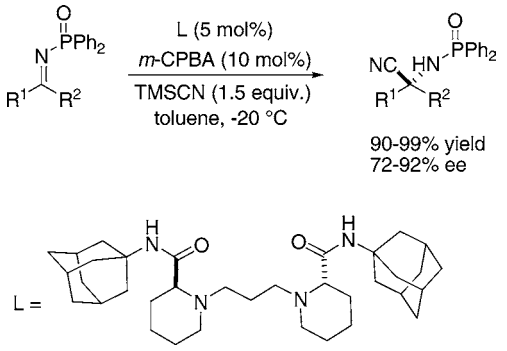
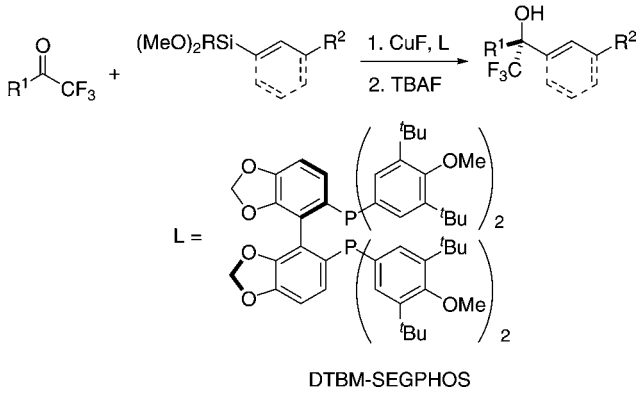


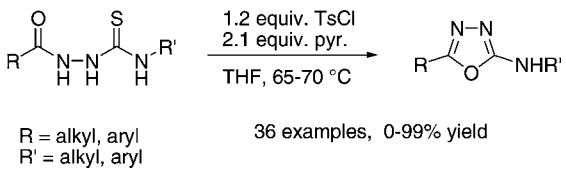
reused at least five times without any loss of either catalytic activity or enantioselectivity. Unfortunately, there are several drawbacks to the current procedure, including very dilute operating conditions (0.1 M) and the necessity of prolonged reaction times (68−196 h at −20 °C) in order to achieve reasonable conversion.

Catalytic Enantioselective Alkenylation/Phenylation of Trifluoromethyl Ketones



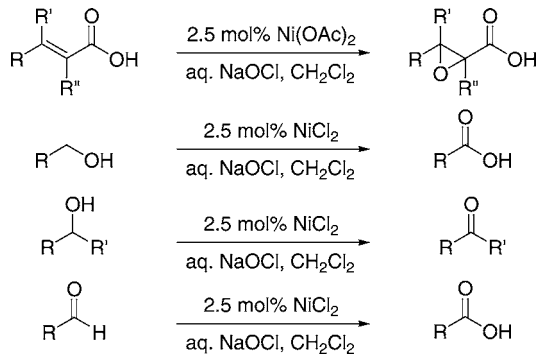
Catalytic enantioselective alkenylation and phenylation of trifluoromethyl ketones is described in a recent report from Kanai and Shibasaki (*Tetrahedron Lett.* **2006**, *47*, 8083−8086). Enantioselectivities up to 84% were observed in additions to aryl trifluoromethyl ketones using a CuF−DTBM−SEGPHOS complex as the catalyst (5−10 mol %). Air-stable alkenylsilanes, phenylsilane, and alkynylsilane can be used as nucleophiles. The method allows for an entry to the catalytic enantioselective synthesis of chiral trifluoromethyl-substituted tertiary alcohols. These products are versatile chiral building blocks, which contain a trifluoromethyl-substituted tertiary alcohol moiety.

Thiosemicarbazides for the Synthesis of 2-Amino-1,3,4-oxadiazoles



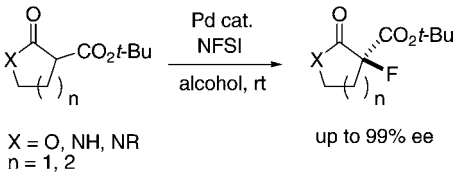
A facile and general protocol for the preparation of 2-amino-1,3,4-oxadiazoles is reported by Dolman and coworkers at Merck (*J. Org. Chem.* **2006**, *71*, 9548−9551). This method relies on a tosyl chloride/pyridine-mediated cyclization of a thiosemicarbazide, which is readily prepared by acylation of a given hydrazide with the appropriate isothiocyanate. Cyclization of the thiosemicarbazide outperformed the analogous semicarbazide cyclization under these conditions, for 18 examples. Utilizing this protocol, numerous 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles were prepared in 78−99% yield.

Catalytic Oxidation of Alcohols, Aldehydes, and α,β-Unsaturated Carboxylic Acids



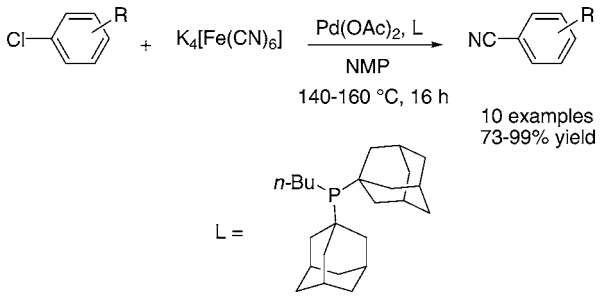
An ongoing area of research is the facile oxidation of alcohols using relatively benign and inexpensive catalysts. Typically, oxidations can be accomplished in the lab through the stoichiometric use of Collins reagent, Jones' reagent, pyridinium chlorochromate (PCC), or potassium permanganate. These routes are generally undesirable due to the large amounts of toxic-metal-containing waste that they produce in addition to the fact that the reagents are always used in excess to ensure reaction completion. They do, however, tend to be selective and very reliable. Many industrial organic oxidations can be accomplished with oxygen or hydrogen peroxide using heterogeneous catalysts, but the reaction conditions can often lead to over-oxidation of the product to give carbon dioxide and water. Nevertheless, heterogeneous systems are industrially useful for synthesizing commodity chemicals from abundant feedstocks because modest selectivity is often compensated by the low cost of the oxidant, usually oxygen gas. However, with complex and expensive alcohols (fine chemical synthesis), a more selective route is desirable. In a recent full article, the Miller group describes the facile oxidation of primary alcohols, secondary alcohols, aldehydes, and α, β-unsaturated acids to give carboxylic acids, ketones, carboxylic acids, and epoxy acids, respectively, using rather inexpensive and commonly available reagents (*J. Org. Chem.* **2006**, *71*, 9291−9296). The oxidation proceeds rapidly in the presence of various nickel(II) salts (2.5 mol %) and excess commercial bleach under ambient conditions and appears to be quite general, giving predictable products with high yields (70−95%) and high purities (90−100%) in most cases. With a few exceptions, these oxidations can be performed without the use of an organic solvent. For the oxidation of water-insoluble organics, a small amount of added dichloromethane (or diethyl ether in certain cases) greatly facilitates the reaction.

Pd-Catalyzed Enantioselective Fluorination



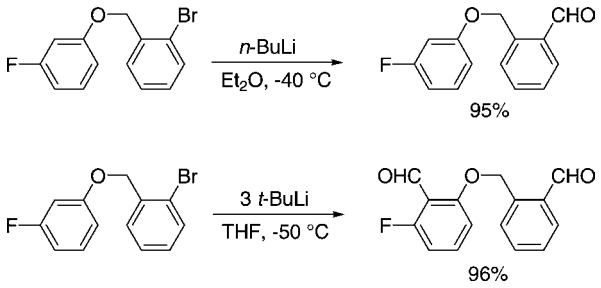
Replacement of hydrogen atoms or hydroxyl groups in the parent compounds with fluorine atoms sometimes leads to improvement of their biological activity profiles. Consequently, the development of efficient methods for the synthesis of optically active fluorinated compounds is extremely important. After pioneering work on enantioselective fluorination using chiral fluorinating reagents, catalytic asymmetric fluorination has witnessed great progress in recent years. In this regard, an efficient catalytic enantioselective fluorination of *tert*-butoxycarbonyl lactones and lactams is reported by Sodeoka and co-workers at Riken in Japan (*J. Org. Chem.* **2007**, *72*, 246−250). Reactions of the lactone substrates proceeded smoothly in an alcoholic solvent with a catalytic amount of chiral Pd(II) complex (BINAP or SEGPHOS ligands). In the case of the less acidic lactam substrates, concurrent use of the Pd complex and 2,6-lutidine as a cocatalyst was effective. Under the reaction conditions, the fluorinated lactones and lactams were obtained in good yield with excellent enantioselectivity (94−99% ee).

A New Pd Catalyst System for the Cyanation of Aryl Chlorides with $K_4[Fe(CN)_6]$



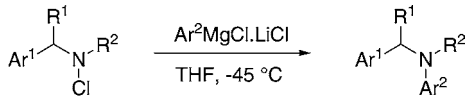
The synthesis of aryl nitriles via transition metal-catalyzed cyanation of aryl halides using inexpensive cyanide salts (such as potassium cyanide or sodium cyanide) is a commonly used method in organic synthesis. In order to fully exploit the synthetic potential of this reaction it is important that all kinds of aryl and heteroaryl halides can be used as starting materials for this transformation. From an environmental point of view and for applications in the fine chemical industry the efficient activation of inexpensive and readily available aryl bromides and chlorides instead of aryl iodides is desirable. Having previously demonstrated the use of potassium hexacyanoferrate(II) as cyanide source for the cyanation of aryl bromides, the Beller group now reports on the extension of this method to aryl chlorides (*Tetrahedron Lett.* **2007**, *48*, 1087−1090). This novel protocol avoids the use of highly toxic alkali cyanides and proceeds in the presence of small amounts (0.5 mol %) of palladium catalysts. High yields and selectivities of the corresponding aryl nitriles were achieved applying di(1-adamantyl)-1-butylphosphine (cataCXium A) as the ligand.

Halogen−Lithium Exchange Versus Deprotonation



Lithiation of aryl groups can occur via deprotonation (ortho lithiation) or via a lithium−halogen exchange mechanism. It is generally accepted that fluorine atoms accelerate ortho lithiation and Br or I atoms undergo HLE easily. Lithiation of a series of aryl benzyl ethers containing halogen substituents (−F, −Br, −I) was investigated by Klis and Serwatowski, and their results are presented in a recent communication (*Tetrahedron Lett.* **2007**, *48*, 1169−1173). The mono- and diorganolithium intermediates were converted into the corresponding aldehydes or diboronic acids in good yields. The dilithiation of aryl benzyl ethers containing a reactive hydrogen atom and a halogen atom capable of halogen−lithium exchange proceeds quantitatively in THF at −50 °C. It was found that mono-aryllithiums formed in the reaction can remove the reactive hydrogen atom from a molecule of aryl benzyl ether, thus decreasing the yield of dilithiated species. This effect does not occur when *t*-BuLi is used instead of *n*-BuLi.

Electrophilic Amination of Arylmagnesium Compounds Using *N*-Chloroamines

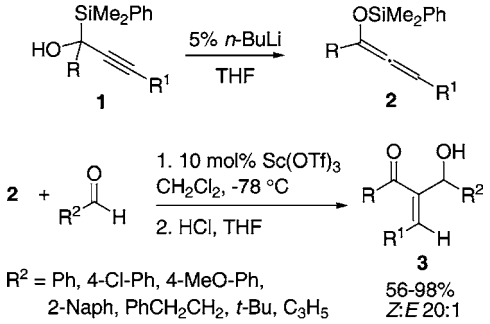


12 examples, 27-73% yield

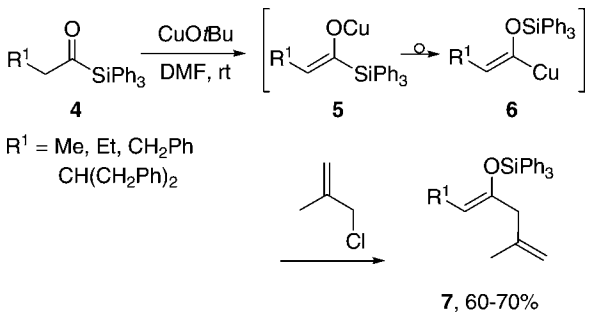
The electrophilic amination reaction of organometallic species using mono-, di-, and trihaloamines has attracted a lot of attention for the synthesis of amines. Only a few cases have been reported using alkylchloroamines as precursors for the synthesis of tertiary amines. Knochel now reports that functionalized arylmagnesium compounds, prepared via a halogen−magnesium exchange reaction using aryl iodides or bromides and *i*-PrMgCl·LiCl, react rapidly with benzyl-*N*-chloroamines at −45 °C providing polyfunctional tertiary amines in good yields (*Synlett* **2006**, 3304−3308). The procedure was also applied to the preparation of chiral *N*-chloroamines with retention of chirality. However, the amination process is limited to benzyl-*N*-chloroamines only. This method offers a possible alternative strategy to transition-metal-catalyzed amination reactions.

Unconventional Reactivity of Silyloxyallenes, Acylsilanes, and Alkenylsilanolates

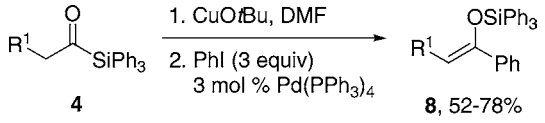
The group of Scheidt at Northwestern University reported a novel method to exploit α-acylvinyl anion reactivity: the Lewis acid-catalyzed addition of silyloxyallenes to carbonyl compounds (*J. Am. Chem. Soc.* **2006**, *128*, 15382−15383). The methodology grants access to α,*β*-unsaturated carbonyl compounds with control over the alkene geometry and the stereochemistry of the newly formed carbinol. Allenes **2** were prepared by treatment of propargyl silanes **1** with 5% *n*-BuLi followed by removal of THF in vacuo. $Sc(OTf)_3$ emerged as the most efficient catalyst for the addition of **2** to benzaldehyde. Using the optimized conditions, 10 mol % $Sc(OTf)_3$ generated the desired addition product **3** with excellent selectivity for the *Z* isomer (20:1). The procedure accommodates a variety of *β*-substituents, notably *t*-Bu and CH_2TBDPS moieties, as well as aromatic and unbranched aliphatic aldehydes.



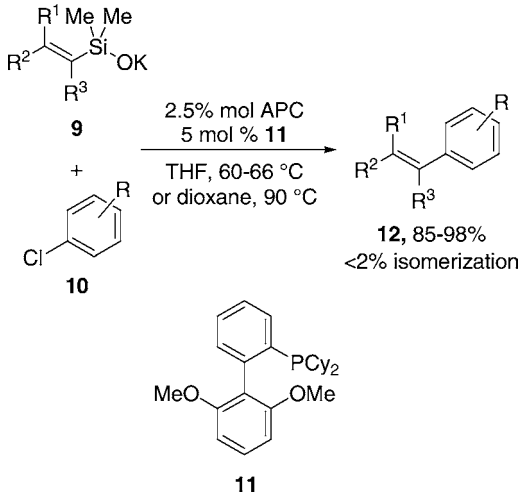
Whereas the Brook-type rearrangement of silicon from sp^3 carbons to oxygen has attracted much attention, there has been limited application of the silyl migration from sp^2 carbons to oxygen. Tsubouchi, Onishi, and Takeda developed a method for the generation of functionalized alkenyl copper species based on the 1,2-migration (*J. Am. Chem. Soc.* **2006**, *128*, 14268−14269). Acyltriphenyl silanes **4** were converted into their corresponding copper enolates **5** using Cu(I)O*t*-Bu. Enolates underwent 1,2-Csp^2-to-O silyl migration to yield alkenyl copper species **6** bearing a (*Z*)-silyl enol ether moiety. These intermediates reacted at room temperature with methallyl chloride or other electrophiles (allyl chloride, MeI, BnBr, Bu_3SnCl) to yield exclusively (*Z*)-silylenol ethers **7** in good yields. Stereoselectivity stems from the relative stability of the (*E*)- and (*Z*)-copper enolates, which is determined by the steric repulsion between the $SiPh_3$ and R^1 groups.



The process was extended to the Pd-catalyzed cross-coupling of acylsilanes with aryl iodides. Treatment of **4** with iodobenzene (2 equiv) in the presence of $Pd(PPh_3)_4$ (3 mol %) gave **8** as single isomers in good yields.



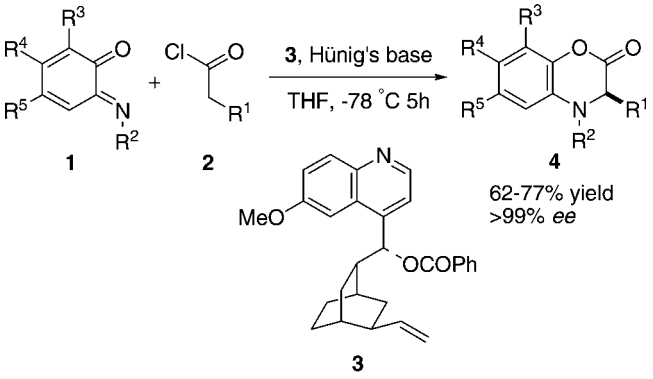
The low reactivity of alkenyl boronic acids and aryl chlorides in cross-coupling reactions results in isomerization of the double bond. The group of Denmark has developed organosilanol reagents as highly reactive, easy to prepare, and stable substrates for cross-coupling reactions. The use of silanolates eliminates the need for adding an external activator, lowering the overall cost of the reaction. In a recent communication, Denmark and Kallemeyn described a highly stereospecific Pd-catalyzed reaction of (*E*)- and (*Z*)-alkenyldimethylsilanolates with a variety of aryl chlorides (*J. Am. Chem. Soc.* **2006**, *128*, 15958−15959). Since the intermediate is an organo-Pd(II) silanolate complex, the transformation takes place via (1) an oxidative addition followed by (2) displacement of the strong Pd−Cl bond by the silanolate. In the optimized conditions, (*E*)- and (*Z*)-potassium silanolates **9** reacted with aryl chlorides in the presence of Buchwald's biphosphine ligands **11** and allyl palladium (APC). The coupling products were obtained in good yields and high stereospecificity (<2% isomerization) in less than 2 h. Fastidious substrates required fine-tuning the conditions: the reaction of tri- and tetrasubstituted silanols went to completion at slightly higher temperatures (66 °C), and (*E*)- and (*Z*)-stiryl silanolates reacted in dioxane (90 °C). The methodology represents an entry to the synthesis of aryl-substituted alkenes.

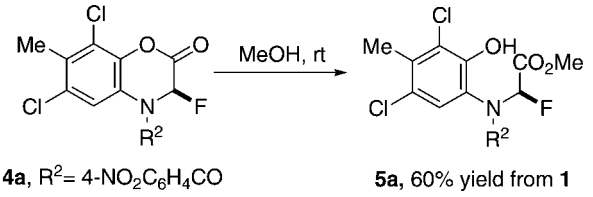


Catalytic Synthesis of 1,4-Benzoxazines en Route to α-Amino Acids

Lectka and co-workers reported the first catalytic asymmetric synthesis of 1,4-benzoxazinones and used these compounds as precursors for the efficient preparation of α-amino acids (*Angew. Chem., Int. Ed.* **2006**, *45*, 7398−7400). The success of this methodology relies on the highly enantioselective [4 + 2] cycloaddition of *o*-benzoquinone imides **1** with chiral ketene enolates derived from acid

chlorides **2** and cinchona alkaloid **3**. Electron-withdrawing substituents on the nitrogen (4-$NO_2C_6H_4CO$, FMoc) and halogenated substituents on positions 3 or 4 increased the reactivity of the quinine towards cycloaddition. Since benzoxaziones underwent rapid methanolysis at room temperature to afford α-amino acids (i.e., **5**), the authors performed the conversion in one pot. Following the cycloaddition (5 h at −78 °C), MeOH was added to the reaction mixture, which was warmed overnight to yield products **4** (60−90%) with excellent ee's (>99%). Remarkably, the synthesis of α-fluoro amino acids derivatives (**5a**) was achieved for the first time using asymmetric catalysis.

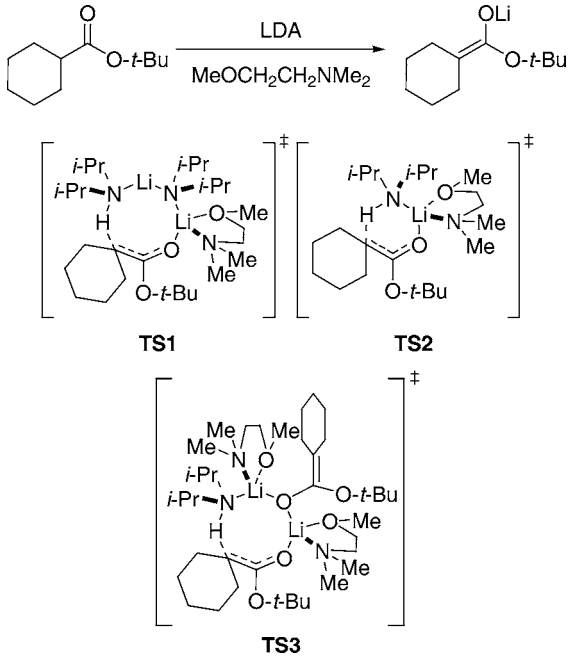




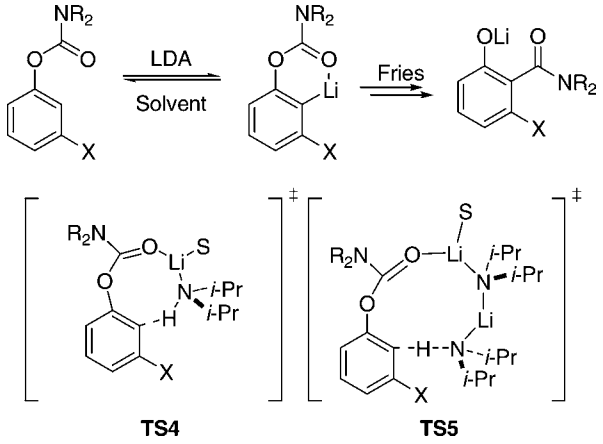
Organolithium Chemistry: Mechanisms Underlying Routine Transformations

Collum and co-workers at Cornell University reported mechanistic details of two lithium diisopropylamide (LDA)-mediated reactions of tremendous importance to process chemists: the enolization of esters and the ortholithiation of arenes. The investigations combine in situ NMR and IR techniques to scrutinize the processes in real time and correlate kinetic data with the structure of the species in solution. A common theme to these studies is that lithiated products generated during the reactions combine (i.e., aggregate) with the original LDA reactant to generate new species (i.e., mixed aggregates) that modify the equilibrium concentrations of the organolithiums in solution, inhibiting reaction rates and revealing new reaction pathways. In short, the mechanisms of these reactions change as the reactions proceed.

In *J. Am. Chem. Soc.* **2006**, *128*, 10326−10336, the authors disclose the complexities of an ester enolization. Thus, whereas at the onset of the reaction an LDA dimer effects the deprotonation (**TS1**), as the reaction generates the desired lithium enolate, the latter aggregates with LDA and diverts the enolization through monomer- and dimer-based pathways (**TS2** and **TS3**, respectively). The mechanistic understanding of the reaction coordinate precedes a ligand-catalyzed ester enolization from first principles. Readily available hemilabile ligand $MeOCH_2CH_2NMe_2$ accelerates the enolization 10,000-fold compared with isostructural *n*-BuOMe via selective chelation of the transition structure.

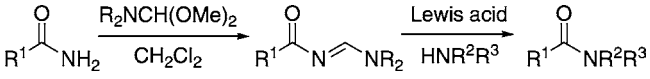


In *J. Am. Chem. Soc.* **2006**, *128*, 13753−13760, Singh and Collum report investigations on the LDA-mediated ortholithiation and anionic Fries rearrangement of aryl carbamates. Rate studies show monomer- and dimer-based ortholithiations (**TS4** and **TS5**, respectively) as well as monomer- and mixed aggregate-based Fries rearrangements. Most interestingly from a process development perspective, observed solvent effects upon per cent conversion find an explanation on the selective stabilization of the organolithiums in solution: whereas some ortholithiations proceed to <10% conversion at equilibrium in strongly coordinating THF, the same ortholithiations in poorly coordinating Me_2NEt proceed to >90% conversion. Rate studies show a higher order dependence in THF for the Fries rearrangement compared with the ortholithiation. Therefore, lower THF concentrations in hydrocarbons or poorly coordinating Me_2NEt selectively inhibit the Fries. The full manuscripts are obliged readings for organolithium chemistry practitioners.



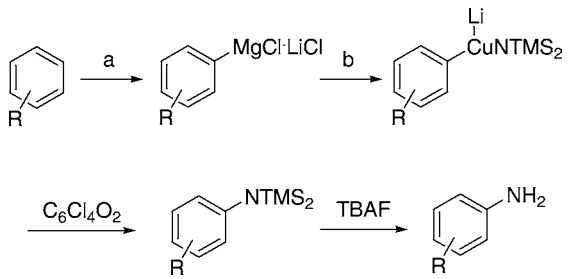
Transamidation of Primary Carboxamides

The Myers group at Harvard University discovered two procedures for the transamidation of a variety of primary amides with primary and secondary amines that generate secondary and tertiary amides, respectively (*J. Am. Chem. Soc.* **2006**, *128*, 16406−16409). The protocols are based on the activation of the primary amides using *N*,*N*-dialkylformamide dimethyl acetals to afford *N*′-acyl-*N*,*N*-dialkylformamidines as reactive intermediates. These formamidines promote the acyl transfer in the presence of catalytic amounts of Lewis acids $Sc(OTf)_3$ or $ZrCl_4$. Whereas the procedure using $Sc(OTf)_3$ uses lower catalyst loadings, the method using $ZrCl_4$ is more general and operationally simpler. A number of dipeptides were synthesized in high yields using $ZrCl_4$ without detectable epimerization, and the acid-labile *tert*-butoxycarbonyl amide and *tert*-butyl ester groups were not affected under the transamidation conditions.



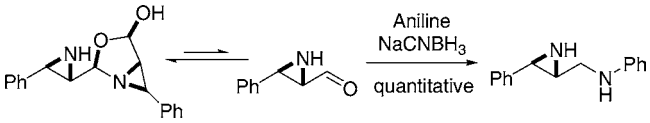
Synthesis of Aryl Amines via Amidocuprates

A general method for the assembly of primary, secondary, and tertiary aryl amines based on the oxidative coupling of aryl and heteroaryl amido cuprates has been reported by Knochel and co-workers at University of Munich (*Angew. Chem., Int. Ed.* **2006**, *45*, 7838−7842). In a representative synthesis of primary amines, magnesiation of an activated arene with TMPMgCl·LiCl (a) is followed by treatment with CuCl·2LiCl, bis[2-(*N*,*N*-dimethylamino)ethyl]ether, and LiHMDS (b) to afford the corresponding amidocuprate. Treatment of this amidocuprate with chloranil ($C_6Cl_4O_2$) leads to the *N*,*N*-bis(trimethylsilyl)amine derivative that can be desilylated at room temperature with TBAF to give the desired aryl amine. All steps preceding the desilylation require cryogenic conditions, and typical isolated yields for the overall transformation fall within 69−80%. Notably, the amination can be extended to the preparation of highly hindered amines such as 2,2,6,6-tetramethylpiperidyl derivatives.



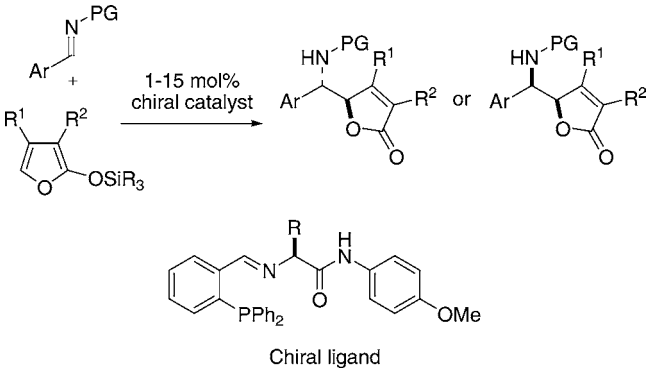
Readily Available Unprotected Amino Aldehydes

Quoting Hili and Yudin (University of Toronto, *J. Am. Chem. Soc.* **2006**, *128*, 14722−14723): *it is difficult to see how an unprotected secondary amine could coexist with an aldehyde in the same molecule for a prolonged period of time*. The authors overcame the compatibility dilemma using an unprotected aziridine as a secondary amine and, thus, describe previously unknown unprotected aziridine aldehydes. This class of compounds does not self-condense because the thermodynamic driving force to undergo iminium ion formation is compensated by the aziridine ring strain. The aziridine aldehydes can be generated as crystalline homodimers from the corresponding aziridine esters by treatment with DIBAL. Interestingly, the reductive amination of these homodimers with external amines affords the desired amino aziridines in excellent yields, demonstrating that the aziridine is orthogonal to the aldehyde. The synthetic utility of aziridine aldehydes is established in the synthesis of complex alkaloid substructures.



Asymmetric Vinilogous Mannich Reactions

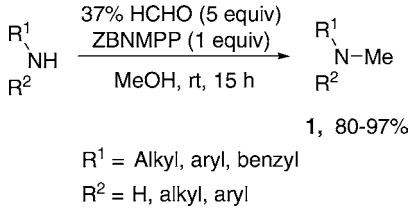
Despite the synthetic utility of vinylogous Mannich (AVM) reactions, they have not enjoyed a practical catalytic asymmetric version until Carswell, Snapper, and Hoveyda at Boston College reported the first highly diastereo- and enantioselective protocol for promotion of AVM reactions by catalytic AgOAc (*Angew. Chem., Int. Ed.* **2006**, *45*, 7230−7233). Representative conditions to transform an aldimine and a siloxyfuran into γ-butenolides (>98% de, >95% ee, >82% yield) include the use of 1 mol % chiral phosphine, 1 mol % AgOAc, and 1.1 equiv of *i*-PrOH. The methodology is highly functional since the reactions are carried out in air with undistilled solvent and additives, in the presence of commercial AgOAc without further purification, and with an easily accessible ligand. Moreover, siloxyfurans are commercially available or readily prepared with excellent yields. The resulting γ-butenolides are δ-amino carbonyl equivalents of enormous value as chiral building blocks.



Reductive Methylation of Amines

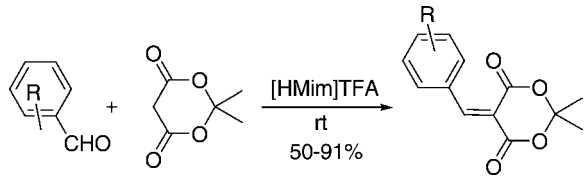
Alinezhad and co-workers expanded the repertoire for the reductive methylation of amines by using *N*-methylpiperidine zinc borohydride (ZBNMPP, *Synth. Commun.* **2006**, *36*, 3609−3615). The reaction does not require an inert atmosphere, and the workup is simple and eliminates the risk of residual cyanide in the product or waste streams. ZBNMPP is a stable white solid prepared by the addition of *N*-methylpiperidine over a solution of zinc borohydride. Meth-

ylation of primary and secondary amines with formaldehyde (37% aqueous, 5 equiv) in MeOH proceeded smoothly in the presence of ZBNMPP (1 equiv) in neutral conditions. Dimethylated tertiary amines (anilines, benzyl amines) were cleanly obtained in 80−97% yields with no apparent reduction of functional groups (NO_2, Br). Secondary amines reacted faster, and steric hindrance posed no problem. Overall, ZNBNMPP proved to be a good substitute for $NaBH_3CN$ and $NaBH_3CN/ZnCl_2$ for the preparation of tertiary methylated amines.

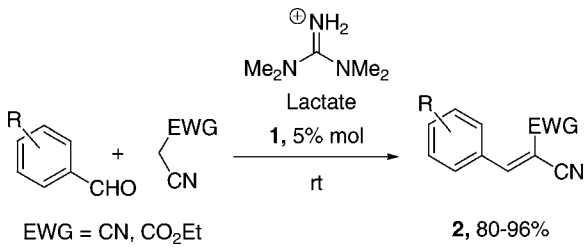


Knoevenagel Condensation Catalyzed by Ionic Liquids

Among the fascinating properties of ionic liquids is playing a dual role as solvent and catalyst in a variety of reactions. Two reports of their use in Knoevenagel condensations using aromatic aldehydes showcase their versatility (see *Synth. Commun*. **2006**, *36*, 3043−3051 and 3305−3317). In the first communication, benzaldehydes with different substitution patterns react with Meldrum's acid using 1-methylimidazolium trifluoroacetate ([Hmim]TFA) at room temperature. Ylidene products were isolated by filtration from the reaction mixture upon addition of water. The ionic liquid was recycled by removing excess water under reduced pressure, and extracting unreacted components with toluene.

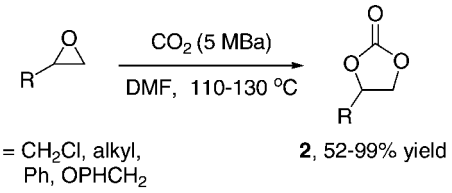


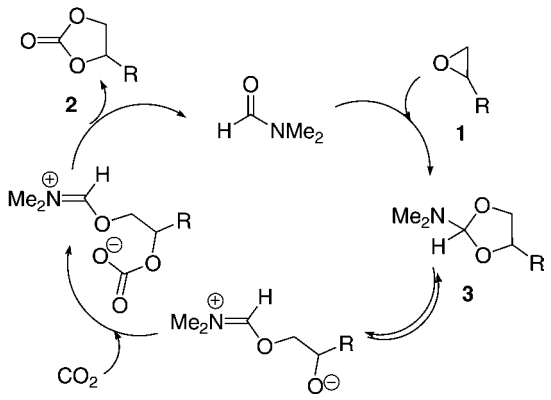
In the second communication, the authors use a catalytic amount of 1,1,3,3,-tetramethyl guanidyl lactate (**1**) to promote the condensation between aldehydes and ethyl cyanoacetate or malononitrile. The reactions were sluggish in the absence of **1** but upon addition of the guanidinium salt proceeded to completion in less than 1 h. In the case of cyanoacetate, the (*E*)-products were exclusively obtained in high yields.



Coupling of Epoxides and CO_2: Formation of Cyclic Carbonates

Jiand and Hua from Tsinghua University in China reported the coupling of epoxides with CO_2 using DMF as an efficient organocatalyst (*Synth. Commun*. **2006**, *36*, 3141−3148). The reaction of epichlorohydrin and CO_2 at 110 °C (autoclave, 5 MPa, 20 h) using DMF (10−20%) provided the target cyclic carbonate in good yields. Different epoxides (R = alkyl, Ph, $PhOCH_2$) were subjected to the optimized conditions. In the case of alkyl epoxides, the reaction required high temperatures (130−160 °C) and/or the addition of water. The proposed mechanism is showed below. One important piece of supporting data is that, when DMF−dimethyl acetal (**3**, R = H) was heated in the presence of CO_2, ethyl carbonate (**2**, R = H) formed in quantitative yield.



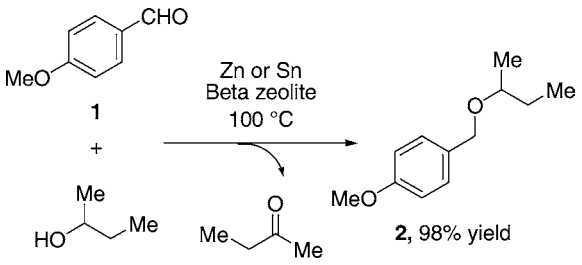


Protocol for the Formation and Cleavage of THP ethers

In two separate communications, scientists from Azzahra University and Shahrekord University in Iran report the use of green heterogeneous catalysts for the formation and cleavage of tetrahydropyranyl ethers (*Synth. Commun*. **2006**, *36*, 2705−2710 and 3103−3107). In the first manuscript, the reaction of a variety of alcohols (alkyl, aryl, allyl, propargyl) and phenols with 3,4-dihydro 2*H*-pyran (DHP, 1.2−1.5 equiv) in the presence of silica gel-supported $AlCl_3$ (0.1 equiv) provided the THP−ethers in excellent yields (91−98%). Whereas alcohols reacted in 1,2-dichloroethane at room temperature, more vigorous conditions (CH_2Cl_2, reflux) were required for phenols. The mild catalyst did not lead to isomerizaton or elimination products; neither caused the polymerization of DHP. Moreover, the methodology allowed the selective protection of alcohols in the presence of phenols and the mono-THP protection of symmetrical diols. The catalyst was recovered by filtration and used up to four times without detriment in the yield. The second manuscript illustrates the use of heteropolyacids with superacidic properties as electrophilic catalysts. Alcohols, DPH (1.1 equiv) and $H_{14}[NaP_5W_{30}O_{110}]$ (0.1 mol %) were refluxed in CH_2Cl_2 (toluene in the case of phenols) to yield the corresponding THP−ethers in high yields (75−94%). By simply switching the solvent to MeOH, the heteropolyacid catalyzed the deprotection of the THP−ethers in quantitative yields.

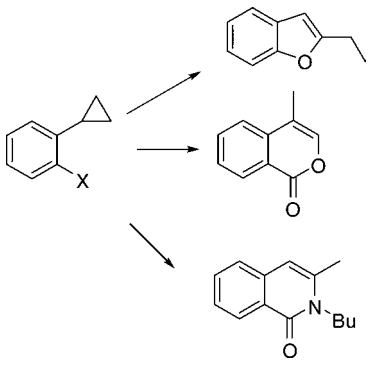
Preparation of Ethers Using Lewis Acid Catalysis

The Williamson reaction, discovered more than a century ago, remains as the best general method for the preparation of ethers from readily available starting materials and reagents. Corma and Renz from the Universidad Politécnica de Valencia developed water-stable Lewis acid catalysts for the synthesis of ethers from commercial alcohols (*Angew. Chem., Int. Ed.* **2007**, *46*, 298−300). In these Sn- and Zr-containing catalysts, the metal is isolated in the framework of β-zeolites. This circumvents the need for water removal, since the site remains active, and the reaction proceeds further. The experimental procedure is strikingly simple: The higher-molecular weight alcohol (typically, an aromatic one) is reacted with an excess of the alkyl alcohol (MeOH, BuOH) and catalyst at 60 °C. Complete conversion occurs in a few hours, with minimal formation of dimeric products. The catalyst is then filtered and the excess alcohol distilled and recovered. The communication is peppered with examples relevant to the fragrance industry and includes a one-pot process for the Meeewein−Ponndorf−Verley reduction of aldehyde **1** followed by the reaction with 2-butanol. Ether **2** has a fruity pear odor and was isolated in quantitative yield and high purity.



Palladium-Catalyzed Oxidative Activation of Arylcyclopropanes

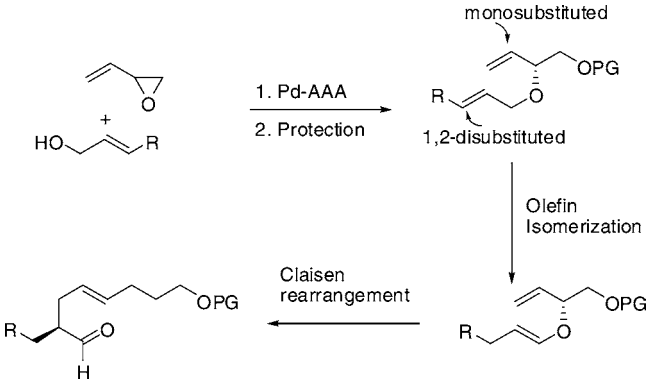
Yudin, A. K. et al. (*Org. Lett.* **2006**, *8*, 5829) have found that palladium chloride-catalyzed intramolecular activation of electroneutral cyclopropane derivatives results in cleavage of the cyclopropane ring followed by formation of heterocyclic derivatives. Phenols, carboxylic acids, and amide groups were investigated as neighbouring groups. The regioselectivity observed in the case of amide-containing derivatives was found to be different from that of carboxylic acid substrates. The difference in regioselectivity rules out a simple isomerisation of the cyclopropane ring followed by a Wacker oxidation.



The method delivers the corresponding heterocycles in good yields without a detailed optimization.

Asymmetric Synthesis of α-Substituted Aldehydes by Pd-Catalyzed Asymmetric Allylic Alkylation−Alkene Isomerization−Claisen Rearrangement

Enantiospecific aliphatic Claisen rearrangement was realized with generally high chirality transfer (Trost, B. M.; Zhang, T. *Org. Lett.* **2006**, *8*, 6007). The requisite substrates were synthesized via Pd-catalyzed asymmetric allylic alkylation from easily obtainable starting materials. After protection, the resultant bis-allyl ethers underwent olefin isomerisation and subsequently in situ Claisen rearrangement to generate α-chiral aldehydes. A remarkable chemoselectivity in the olefin isomerisation step was observed.



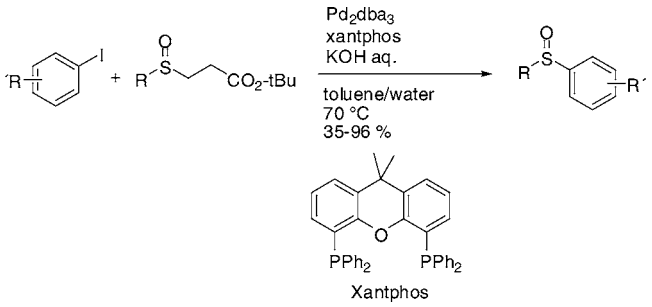
The Mg-Oppenauer Oxidation as a Mild Method for the Synthesis of Aryl and Metallocenyl Ketones

Magnesium alkoxides undergo a hydride-transfer oxidation with benzaldehyde as the oxidant. This magnesium variant of the Oppenauer oxidation was used by Knochel et al. (*Chem. Eur. J.* **2007**, *13*, 215) for the synthesis of polyfunctional biaryl ketones. LiCl was found to promote this reaction by enhancing the solubility of magnesium alkoxides. The mild reaction conditions enable the synthesis of various ketones bearing a metallocene unit. These ketones were reduced with CBS catalyst to chiral benzhydrol complexes with high enantioselectivities, enabling an asymmetric synthesis of electron-rich or -poor benzhydrol alcohols.

Aryl Sulfoxides via Palladium-Catalyzed Arylation of Sulfenate Anions

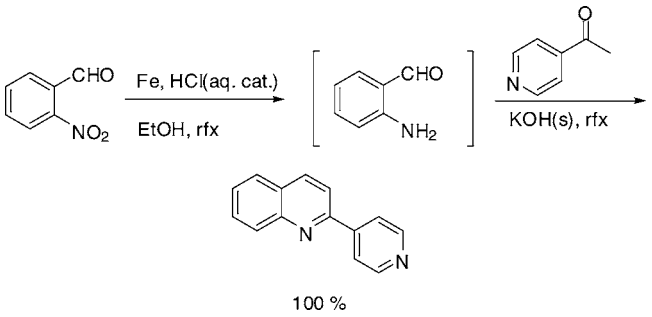
Palladium-catalyzed arylation of sulfenate anions generated from β-sulfinyl esters can take place under biphasic conditions. This hitherto unexplored reaction provides a simple, mild, and efficient route to aryl sulfoxides in good yields (Maitro, G.; et al *Org. Lett.* **2006**, *8*, 5951).

The work discloses a new synthetic route toward aryl sulfoxides eliminating the need for an oxidation step that in many cases is poorly selective for the sulfoxide.



An Efficient One-Pot Synthesis of Quinolines from *o*-Nitroarylcarbaldehydes

Mulvihill, M. J. et al. (*Org. Biomol. Chem.* **2007**, *5*, 61) have developed a highly efficient one-pot Friedländer quinoline synthesis using inexpensive reagents. *o*-Nitroaryl carbaldehydes are reduced to the corresponding *o*-amino arylaldehydes with iron in the presence of a catalytic amount of aqueous HCl. The obtained product is treated in situ with aldehydes or ketones to form mono- or disubstituted quinolines in good to high yields. The basic condensations are mild enough to tolerate substrates that are prone to self-condensation.



Catalytic Applications of Metal Nanoparticles in Imidazolium Ionic Liquids

Transition-metal nanoparticles (MNPs) with a small diameter and narrow size distribution can be prepared by H_2 reduction of metal compounds or decomposition of organometallic species in imidazolium ionic liquids (ILs) (Dupont, J.; et al. *Chem. Eur. J.* **2007**, *13*, 32). MNPs dispersed in ILs are catalysts for reactions under multiphase conditions. These soluble MNPs possess pronounced surfacelike catalytic properties rather than single-site catalytic properties. In reduction of aromatic ketones with Ir(0) the reduction of the aromatic ring is preferred, probably due to a higher affinity for surface coordination of the aromatic ring.

The Heck−Mizoroki Cross-Coupling Reaction: A Mechanistic Perspective

The Heck−Mizoroki cross-coupling reaction is an important part of the modern synthetic chemists toolbox and it has been applied to a huge variety of different substrates. In contrast, the mechanism of the process is less studied and consequently much less understood. There have been numerous studies reported over the years aiming at uncovering the inner workings of this palladium-mediated coupling process. Knowles, J. P. and Whiting, A. (*Org. Biol. Chem.* **2007**, *5*, 31) have reviewed these works to provide an up-to-date view of this reaction.

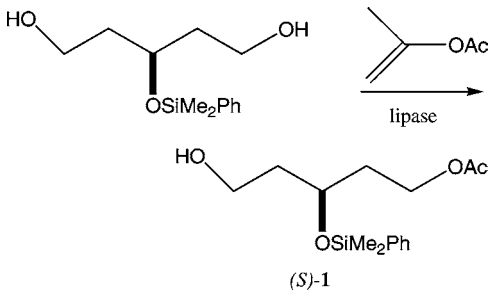
At best it can be said that the mechanism of the oxidative addition is strongly dependent on the conditions. Clearly, not one proposed mechanism for the oxidative addition explains all the phenomena observed, and it seems likely that several mechanisms may be in operation, either independently, depending on the reaction conditions, or in parallel.

For subsequent steps, the mechanism is more poorly understood due to the difficulties of investigation.

For a full understanding of the mechanism in operation, further studies are required, although it may well be the case that due to the reactive nature of the intermediates involved a comprehensive understanding will be challenging to achieve.

Lipase-Catalyzed Desymmetrization of 1,3,5-Pentanetriol

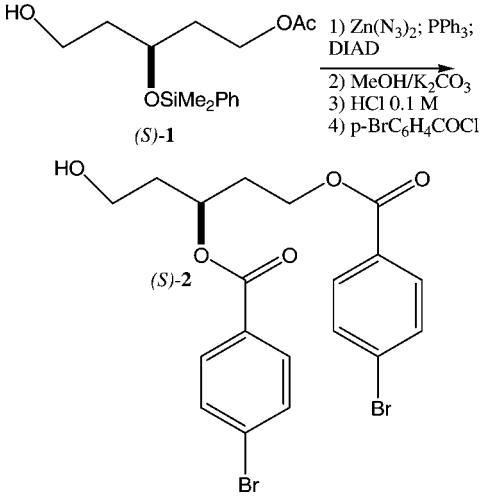
The enantiospecific desymmetrization of 3-*O*-dimethylphenyl-1,2,3-pentanetriol was investigated using lipases from different sources (Köhler and Wünsch *Tetrahedron: Asymmetry* **2006**, *17*, 3091). The most successful transformation took place using lipase of *Burkholderia cepacia* immobilized on ceramic particles. The (*S*)-monoacetate (**1**) was obtained in 52% yield and over 99% ee (at −10 °C using *tert*-butylmethyl ether).



(*S*)-**1**

A derived compound, (*S*)-azido, via Mitsunobu reaction, was used to produce a suitable compound, (*S*)-bromobenzoyl ester (**2**), to carry out a circular dichroism study to determine absolute configuration in this series.

A very detailed study concerning conversions and ee's versus reaction times is disclosed in this paper.



(*S*)-**1**

(*S*)-**2**

Immobilized Alcohol Dehydrogenase

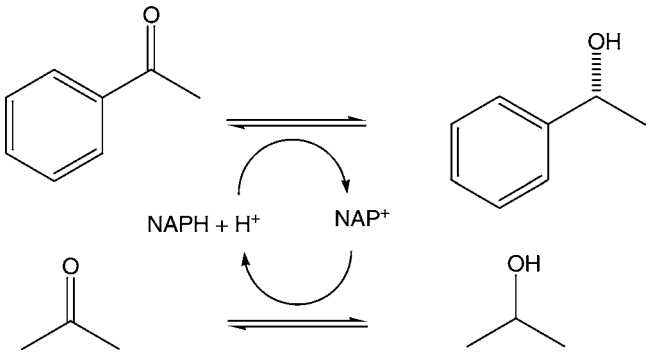
Hildebrandt and Lutz (*Tetrahedron: Asymmetry* **2006**, *17*, 3219) described a smart protocol to immobilize an alcohol dehydrogenase from *Lactobacillus brevis* (*Lb*-ADH; E.C.1.1.1.2) on an amino epoxy support.

A 4-fold increase in stability was found by blocking the remaining functional groups on the enzyme-support preparations with glycine or mercaptoethanol. The multipoint attachment was only achieved by cross-linking the adsorbed proteins with glutaraldehyde.

An overall 60-fold increase in stability was found compared to that with the soluble enzyme.

The enzyme-support preparation was applied to the production of (*R*)-phenylethanol from acetophenone in a plug-flow reactor. This system could be operated in up to 10 weeks, showing excellent enzyme performance.

Recycle of the coenzyme was made possible via oxidation of 2-propanol.

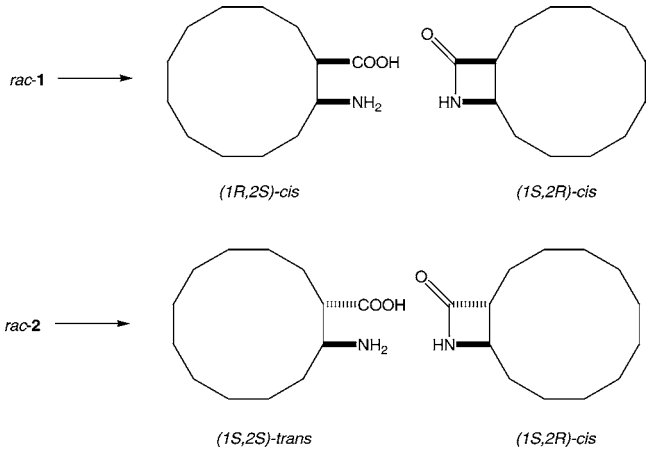


Turnover numbers of 2,500,000 were made possible by decreasing volumetric productivity.

Ring Cleavage of β-Lactams

The enantiospecific ring cleavage of (±)-*cis*- and (±)-*trans*-β-lactams to chiral β-amino acids using lipases was described by Forró and Fülöp (*Tetrahedron: Asymmetry* **2006**, *17*, 3193).

The importance of the chiral synthetic targets, reagents and products, is linked to their potential biological activity, as exemplified by *cis*-pentacin, and to the fact that (chiral) β-amino acids have increasing importance in peptide and combinatorial chemistry.



The substrates, (±)-*cis*- and (±)-*trans*-β-lactams (*rac*-1 and *rac*-2, respectively), were produced via 1,2-dipolar addition of chlorosulfonyl isocyanate to cyclododecene.

On the basis of previous experiences of this group lipolase, *Candida antartica* lipase B, in *i*-Pr_2O, was chosen to carry out these transformations.

No significant changes in enantiospecificity ($E > 200$) or reaction rate (45−46% conversion after 8 h for *rac*-**1** and 45−50% conversion after 137 h for *rac*-**2** at 60 °C) were achieved. Increasing temperature kept *E* values and reduced reaction times, at 50% conversion, to 16 h and 91 h for *rac*-**1** and *rac*-**2**, respectively.

Unreacted (1*S*,2*R*)-*cis*- and (1*R*,2*R*)-*trans*-β-lactams and reaction products, (1*R*,2*S*)-*cis*- and (1*S*,2*S*)-*trans*-β-amino acids, were obtained with ees over 98%.

Carbon Nanotube Oxidation

The structures of carbon nanotubes, graphite, and amorphous carbon are different, which is revealed in their reactivity and the resistance to oxidation. The stability of single- and multiwalled nanotubes, and their true oxidation rates have been studied on the basis of conversion to CO_2 when heated in the presence of oxygen. Nonisothermal techniques were used to establish the kinetics of oxidation of nanotubes, amorphous carbon, and graphite. Single-walled nanotubes are found to be the most reactive, followed by multiwalled nanotubes, amorphous carbon, and graphite. The oxidation rates of different single-walled tube samples containing different residual catalysts vary significantly. (*J. Mater. Chem.* **2007**, *17*, 619−623).

One-Pot Synthesis of C_8 Aldehydes/Alcohols from Propylene

The group of Jasra at CSMCRI, India, have synthesized a multifunctional catalyst [HF/HT] containing a rhodium complex, $HRh(CO)(PPh_3)_3$ [HF] and a solid base, hydrotalcite $Mg_{1-x}Al_x(OH_2)^{x+}(CO_3^{2-})_{x/n}{\cdot}mH_2O$ [HT]. This catalyst was synthesized by impregnation of [HF] onto the surface of [HT] and employed for the one-pot synthesis of C_8 aldehydes or alcohols from propylene. The catalyst was found to be efficient to carry out hydroformylation, aldol condensation, and hydrogenation reactions in one pot. The catalytic activity of [HF/HT(*X*)] was studied in detail as functions of Mg/Al molar ratio (*X*) of [HT], amount of [HF] complex and [HT], and reaction temperature. The selectivity for 2-ethylhexanal is enhanced with increasing *X* and amount of [HT]. The highest selectivity for 2-ethylhexanol was observed for [HT] Mg/Al molar ratio of 3.5 at 250 °C. The kinetic profiles of the various products obtained were in agreement with the reaction pathway proposed to understand the role of the [HF/HT] catalyst on the formation of C_8 aldol derivatives. Thermal stability of the [HF/HT] catalyst system was also investigated. (*New J. Chem.* **2007**, *31*, 277 − 286).

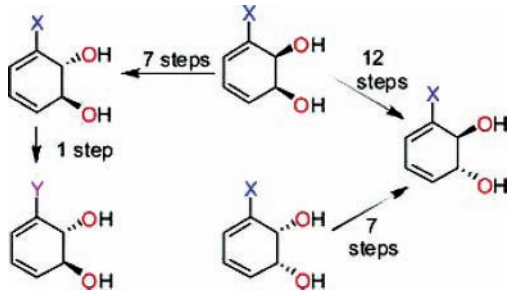
Light-Driven Organometallic Catalysis by Heterooligonuclear Ru(II) Complexes

Development of new photocatalytic systems modeling natural photosynthesis is vigorously pursued in view of their

importance in the energy sector. Recent investigations have shown that supramolecular devices consisting of photosynthetic reaction centres and organometallic complexes are capable of performing light-driven catalytic reactions such as hydrogen production, reduction of CO_2, and conversion reactions of olefins. The extensive synthetic chemistry known for these compounds makes them ideal starting points for the construction of light-driven catalysts (*Dalton Trans.* **2007**, published online, http://dx.doi.org/10.1039/b615987g).

Chemoenzymatic Synthesis of *trans*-Dihydrodiol Derivatives of Monosubstituted Benzenes

Enantiopure *trans*-dihydrodiols have been obtained by a chemoenzymatic synthesis from the corresponding *cis*-dihydrodiol metabolites, obtained by dioxygenase-catalysed arene *cis*-dihydroxylation at the 2,3-bond of monosubstituted benzene substrates. This generally applicable, seven-step synthetic route to *trans*-dihydrodiols involves a regioselective hydrogenation and a Mitsunobu inversion of configuration at C-2, followed by benzylic bromination and dehydrobromination steps. The method has also been extended to the synthesis of both enantiomers of the *trans*-dihydrodiol derivatives of toluene, through substitution of a vinyl bromine atom of the corresponding *trans*-dihydrodiol enantiomers derived from bromobenzene. Through incorporation of hydrogenolysis and diMTPA ester diastereoisomer resolution steps into the synthetic route, both *trans*-dihydrodiol enantiomers of monohalobenzenes were obtained from the *cis*-dihydrodiols of 4-haloiodobenzenes (*Org. Biomol. Chem.* **2007**, *5*, 514−522).



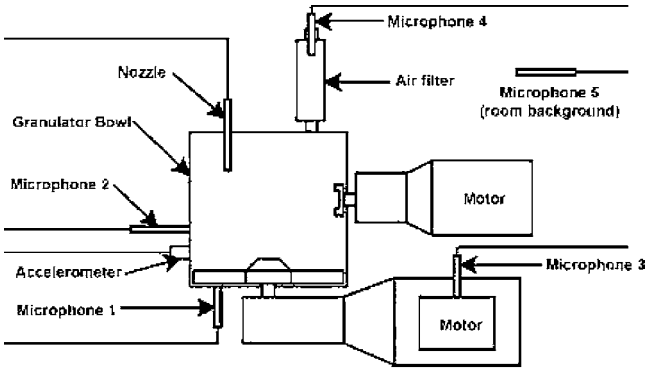
The Chemometric Analysis of Point and Dynamic Data in Pharmaceutical and Biotech Production (PAT): Some Objectives and Approaches

In spite the relatively large number of Process Analytical Technologies (PAT) publications produced so far, certain hurdles in PAT implementation continue to be reported. Hence, every success deserves attention, even if only limited details can be made available.

A team from Novartis, Umea University, and Umetrics (Wold, S. et al. *Chemom. Intell. Lab. Syst.* **2006**, *84*, 159) reports such a success. The paper reviews and clarifies the different types of risk that the FDA included in its PAT-QbD (Quality by Design) initiative: total, chemical, physical, biological, engineering, analytical, data analytical, interpretation, and communication. More importantly, the paper describes the various levels of chemometrics that can be practiced: the more common four levels (PAT-1 through PAT-4) as well as level 5, "still a thing of the future", which includes feedback control from the PAT models to the process settings. The Novartis successful example is one of PAT-3 and PAT-4 applications, one which started with a retrospective data analysis. This analysis was based on a database that was generated through passive collection (not DoE-generated) over about 2 years and 314 batches. The critical quality attribute at stake was the dissolution rate of the final product; drying and compaction were the key process steps impacting process results. Because of confidentiality, limited experimental data are reported. The readers are reminded (perhaps not necessarily the target audience for this reminder) that "the easiest and fastest way to reach such representativity is to employ design of experiments during process development...in laboratory and pilot scale".

Monitoring High-Shear Granulation Using Sound and Vibration Measurements

Many may have heard people speaking about "listening" to a piece of processing piece of equipment such as a mill, a granulator, etc. (while others "talk" to their reaction, etc.). Now a team from GlaxoSmithKline and the University of Western Ontario (Briens, L.; et. al *Intl. J. Pharm. Sci.* **2007**, *331*, 54) reports that good listening can add to process understanding and assist with process monitoring. High-shear granulation in 10- and 25-L granulators was monitored using sound and vibration measurements. Of several positions tested for the microphones, the optimal one was found to be in the filtered air exhaust of the granulators (microphone 4 in the figure below).



The location of the microphones and the accelerometer.

Batch sizes of 2 kg and 8 kg of a placebo formulation were used for the 10- and 25-L Niro-Fielder granulators, respectively. The main impeller was operated at 250 rpm and the intensifier (chopper) at 1500 rpm. As expected, because of the difference in size, different frequency bands were deemed to be process-sensitive in the two granulators. Better monitoring was apparently possible in the larger granulator. Advanced signal analysis was needed in order to extract useful information from the data.

Diastereomeric Salt Crystallization Synthesis for Chiral Resolution of Ibuprofen

Continuing a series of interesting process synthesis accounts, Professor Ng's group reports now on the industrially important topic of chiral resolution through diastero-

emeric salt crystallization (Lam, W. H.; et al. *AIChE J.* **2007**, *53* (2), 429). This paper appears to be based on the MPhil thesis that W. H. Lam worked on in Prof Ng's group. The resolution of ibuprofen using *N*-methyl-D-glucamine as a resolving agent was used as an example. The general process includes, besides solvent screening and crystallization process development, an in-depth determination of solid−liquid equilibrium behavior. The analysis of the solid−liquid equilibrium is deemed to play a key role in this approach. Interesting findings are reported for the dependency of the induction time on supersaturation and temperature. The recommended crystallization process is a seeded one, using a nonstoichiometric amount of resolving base. To improve process economics a racemization step is proposed, and several process options are discussed conceptually. The integrated methodology employed is believed to be of general use, especially when all the relevant compounds are available for solubility and crystallization measurements. Further work is planned to verify the feasibility of this conceptual design. Racemization kinetics, crystal filtration, and scale-up investigations are undoubtedly already under way.

An Analysis of Firm-Level Innovation Strategies in the U.S. Biotechnology Industry

Given the fewer than expected new drugs introduced in the market, many business analysts embarked on complex studies examining the factors that affect innovation strategies and innovation performance in the biotechnology industry. One such recent NSF-funded study reported its findings (Hall, L. A.; et al. *Technovation* **2007**, *27*, 4), along with the challenges encountered during the data gathering and analysis. Interesting "secondary" findings are also reported, such as geographic clustering, the widespread utilization of strategic alliances, and collaboration, etc. Gathering meaningful data for such a study is not trivial; in 1999, a sample of 424 U.S. biotechnology companies received questionnaires, and 126 of the respondents' sets were deemed usable in the analysis. A more recent survey (2003) is used for comparison, showing good agreement between the two studies. The primary measure of commitment to innovation employed by the study was R&D intensity: the percentage of firm revenues expended on research and development. The metrics for innovation performance were divided into two groups: research-based innovation and production-based innovation. For research-based innovation the metrics were domestic and international patent applications and approvals, and for production-based innovation the metrics were new product and process introductions, and redesigned products and processes. High R&D intensity firms were considered those for which the R&D intensity was above 20%. Firm performance measures utilized were growth in sales and export revenues, employment, and net profits. Many interesting statistical results are reported, some perhaps of value to organizational development strategies. Some of those statistics are not surprising, such as a positive correlation between R&D intensity and innovation. However, other findings were less expected, such as the nonexistence of a significant relationship between research-based innovation and firm performance measures.

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