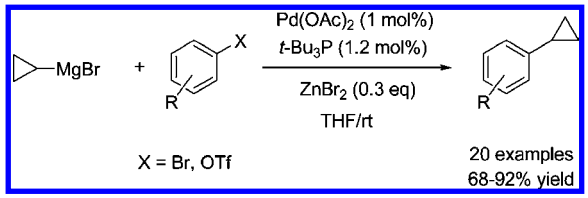
Organic Process Research & Development **2010,** *14,* 1276–1286

Highlights from the Literature

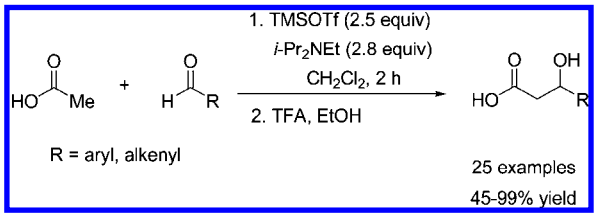
Some Items of Interest to Process R&D Chemists and Engineers

Cyclopropylmagnesium Bromide in Pd-Catalyzed Cross-Coupling Reactions



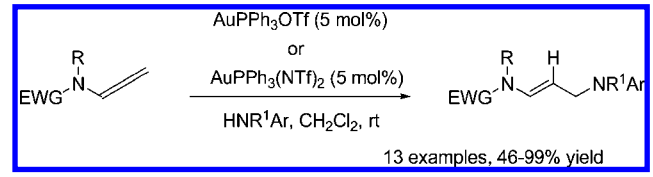
The cyclopropyl group is a common structural motif in natural products and pharmaceutical molecules. Cyclopropyl group incorporation via Pd-catalyzed coupling has been extensively studied, mainly using boron-, zinc-, and bismuth-based reagents. These soft organometallic reagents offer wide functional group compatibility, but their high cost severely limits their attractiveness for large-scale synthesis. The less expensive cyclopropylmagnesium bromide, on the other hand, suffers from poor functional group tolerance and low reactivity (in cross-coupling reactions), often ascribed to the "hardness" of the magnesium species. Now Wang and co-workers at Boehringer Ingelheim report (*J. Org. Chem.* **2010**, *75*, 6677−6680) that the addition of a substoichiometric amount of zinc bromide, even as low as 0.15 equiv, can effectively "soften" the Grignard reagent and provide significantly improved results in Pd-catalyzed coupling reactions of aryl and heteroaryl halides/triflates. The scope of nucleophiles was further extended to other alkyl, cycloalkyl, and aryl Grignard reagents with good results.

Acetic Acid Aldol Reactions



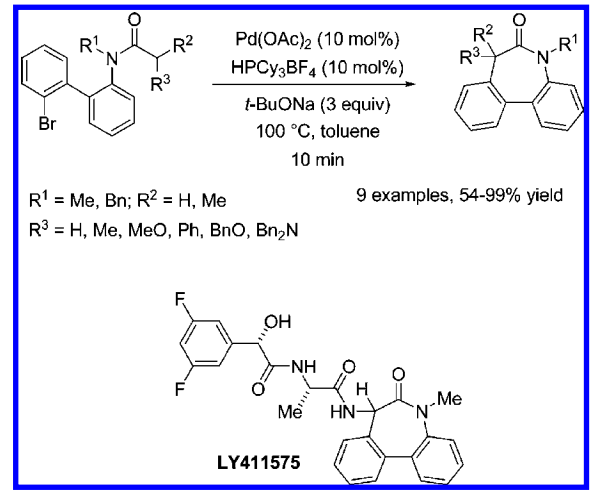
The use of carboxylic acid derivatives in α-substitution reactions, including aldol addition reactions, is well developed. The parent carboxylic acids, however, are seldom employed in aldol reactions because their inherent Brønsted acidity results in deprotonation of the acid proton rather than the α-carbon. A second deprotonation to yield the dianion is possible, but harshly basic conditions are required and the highly reactive dianion is difficult to control. The development of a mild and general aldol reaction of carboxylic acids would be a desirable addition to the field of organic synthesis because of the synthetic versatility of the carboxylic acid group, which can be easily converted to the corresponding ester, anhydride, or acid halide. Now the Downey group reports (*J. Org. Chem.* **2010**, *75*, 5351−5354) that acetic acid undergoes one-pot bis-silyl ketene acetal formation−Mukaiyama aldol reactions in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and an amine base, yielding β-hydroxy carboxylic acids. The crude reaction mixtures contain products silylated at one, both, or neither of the hydroxyl groups, but subjection to ethanolic TFA results in rapid cleavage to unmask the desired β-hydroxy carboxylic acids. Commercially available trimethylsilyl acetate can also be employed in a similar process that requires one less equivalent each of TMSOTf and *i*-Pr_2NEt.

Intermolecular Hydroamination of Allenamides



The addition of the N−H bond over alkene and alkyne π-systems, the hydroamination transformation, represents a powerful method for the introduction of the amine functionality. Such transformations give access to a range of valuable nitrogen-containing building blocks such as amines, imines, and enamines. An intermolecular hydroamination of allenamides with arylamines is reported by the Kimber group (*J. Org. Chem.* **2010**, *75*, 5406−5409). The reaction is achieved under mild Au(I) catalysis conditions delivering allylamino (*E*)-enamides stereoselectively and in high yield. The reaction is made possible via a convenient method for conjugated *N*-acyliminium formation, which involves alkylation with propargyl halides followed by base-mediated rearrangement to the allene.

Dibenzazepinones via Pd-Catalyzed Intramolecular Arylation



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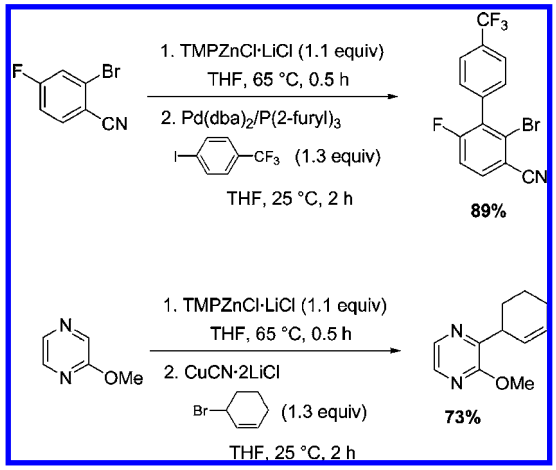
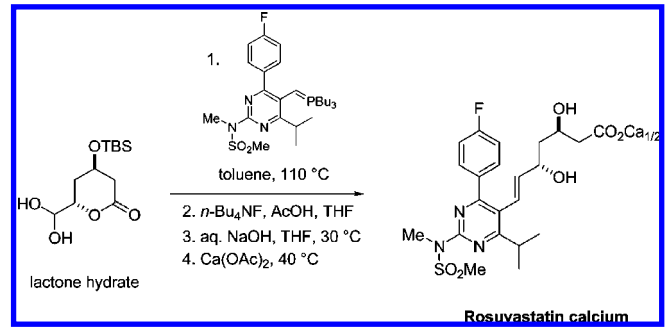
Benzazepinones and dibenzazepinones feature frequently in pharmaceutical compounds. One example is γ-Secretase inhibitor LY411575, a potential drug candidate for Alzheimer's disease, known to reduce brain and cerebrospinal fluid levels of Aβ-peptides. A new approach for the convenient synthesis of dibenzazepinones is reported by the Wilcox group (*J. Org. Chem.* **2010**, *75*, 6445−6451). The key step is the formation of the seven-membered ring through Pd-catalyzed intramolecular arylation of an anilide enolate. The reactions are typically complete in 10 min at 100 °C with moderate to excellent yields. Application of this method to the synthesis of the core structure of the aforementioned γ-Secretase inhibitor LY411575 resulted in a five step, 60% overall yield process starting from 2-bromophenylboronic acid and 2-iodoaniline. The authors note that this approach compares favorably with presently available methods to access this interesting ring system.

Direct Zincation of Aromatic and Heteroaromatic Compounds Using TMPZnCl·LiCl



The metalation of aromatics and heteroaromatics is an important tool since it allows a versatile functionalization of these molecules. The Knochel group continues to expand the scope of this chemistry by developing a direct zincation method for aromatic and heteroaromatic compounds (*J. Org. Chem.* **2010**, *75*, 4686−4695). TMPZnCl·LiCl functions as a mild and highly selective base that allows chemoselective metalations at 25 °C for the directed zincation of molecules containing sensitive functional groups such as an aldehyde or a nitro group. Its higher selectivity is due to the absence of magnesium salts ($MgCl_2$) and to a different stoichiometry (TMPZnX instead of TMP_2ZnX). The mild base TMPZnCl·LiCl is conveniently prepared in a one-pot procedure in quantitative yield, resulting in a 1.3 M final solution concentration. Diverse sensitive functional groups such as a nitro group, an aldehyde, an ester, and a nitrile are readily tolerated and are compatible with high metalation temperatures. Furthermore, the resulting zinc organometallics display an excellent reactivity toward various classes of electrophiles providing functionalized aromatics and heteroaromatics in high yields. Two examples are shown here, and yields are generally good for the >20 examples described in the manuscript.

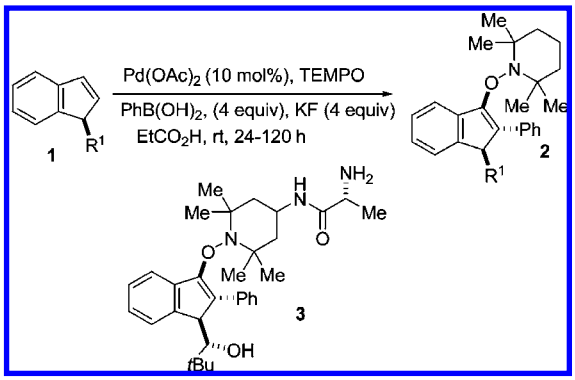
Rosuvastatin Synthesis via Lactone Intermediate



The first entry into statins via a lactone intermediate is reported by Căsar, Košmrlj and co-workers at Lek Pharmaceuticals and the University of Ljubljana (*J. Org. Chem.* **2010**, *75*, 6681−6684). The chemistry is demonstrated by the preparation of rosuvastatin. The key step of this approach is a highly selective Wittig olefination between the appropriate heterocyclic ylide and β-TBSO functionalized δ-formyl-δ-valerolactone into 4-O-TBS-protected statin lactone. The lactone-aldehyde (isolated as a stable hydrate) has only recently become more readily available via a new enzymatic/oxidation process already described elsewhere by the same authors (see *Synlett* **2009**, (7), 1144−1148 and references therein). Following Wittig coupling, deprotection, lactone hydrolysis, and cation exchange reaction into rosuvastatin calcium has been achieved in a one-pot reaction in excellent overall yield and without any detectable epimerization. The authors note that this new convergent route, which is also free of any steps requiring cryogenic conditions, is superior to other methods for the preparation of rosuvastatin.

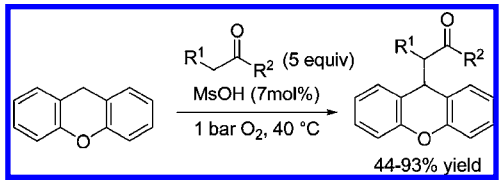
Miscellaneous Uses of TEMPO: Pd-Catalyzed Oxyarylation

Amido Studer and cowokers from Westfälische Wilhelms-Universität (Germany) reported a highly stereoselective intermolecular Pd-catalyzed oxyarylation of indenes with various aryl boronic acids and the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as an oxidant and trapping reagent to provide 1,2,3-trisubstituted indanes (*Angew. Chem., Int. Ed.* **2010**, *49*, 6877−6880). Treatment of indene **1** with 10% $Pd(OAc)_2$ in the presence of TEMPO, $PhB(OH)_2$, and KF (4 equiv each) in propionic acid at room temperature provided carboaminoxylation product **2** bearing three contiguous stereogenic centers as a single isomer in 45−79% yield. The alkoxyamine moiety can be transformed into the corresponding alcohol by reductive N−O bond cleavage. Diastereoselectivity of the oxyarylation remained excellent even when small, unbranched R^1 substituents (Me, Bn) were used. The methodology allows for the installation of interesting functionalities in the 1-position of the indane core: reaction of the amino acid-conjugated nitroxide Boc-Ala-NH-TEMPO with indane afforded compound **3** in 80% yield and with perfect diastereocontrol.



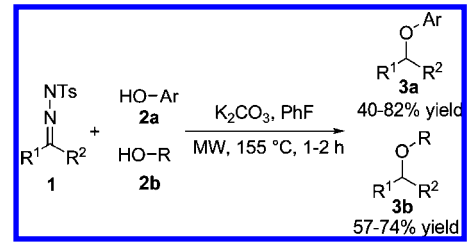
Oxidative Coupling: Autoxidative Carbon−Carbon Bond Formation

Arón Pintér and co-workers at Max-Planck-Institut für Kohlenforschung (Germany) recently reported an oxidative cross-coupling reaction for the formation of C−C bonds from two C−H bonds, requiring only catalytic amounts of MsOH and elemental oxygen (*Angew. Chem., Int. Ed.* **2010**, *49*, 5004−5007). This remarkable reaction does not involve any redox-active metal catalyst or reagent commonly used for C−H bond activation, allowing for the design of sustainable couplings that generate minimal waste. Under the optimized conditions (1 bar O_2, 7% MsOH, 40 °C), treatment of xanthane with cyclic or aliphatic ketones yielded the desired coupled products in 44−93% yield. When the reaction stalled, further additions of acid or different amounts of ketone did not improve the reaction outcome, and most of the unreacted xanthene was recovered. The mechanistic pathway may involve the radical formation of a hydroperoxide that reacts with the ketone via an acid-catalyzed SN_1 reaction. This theory is supported by the following: (a) reaction of the proposed hydroperoxide and cyclopentanone to yield the desired coupling product without further addition of oxygen; (b) addition of catalytic amounts of a radical inhibitor (5 mol % 2,4,6-tris-*tert*-butylphenol) completely blocked the reaction.



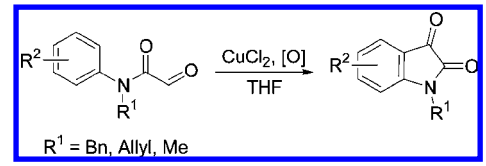
Ether Synthesis: Coupling of Tosylhydrazones with Alcohols or Phenols

Celebrating his 70th birthday in class, Jose Barluenga (University of Oviedo; for recent profiles see *Chem.—Eur. J.* **2010**, *16*, 9696−9697 and *Angew. Chem. Int. Ed.* **2010**, *49*, 6250−6252) has infused the literature with yet another beautiful example of creativity in the chemistry of carbenes. In *Angew. Chem., Int. Ed.* **2010**, *49*, 4993−4996 his group reported a metal-free process for the synthesis of ethers by reductive etherification of tosylhydrazones with phenols or alcohols. Combination of the diazo compound generated by base-promoted decomposition from the tosylhydrazone **1** with a hydroxylic compound **2** resulted in the formation of an ether, through an insertion of the incipient carbene into the O−H bond. When optimizing reaction conditions, the breakthrough came from the utilization of microwave irradiation (MW) to accelerate the process. The transformation proceeds very efficiently with a wide range of tosylhydrazones derived from aldehydes and ketones and a diversity of phenols. Reductive etherification with alcohols, even the sterically encumbered and benzylic species, was achieved after a slight modification in the reagent's ratio. This metal-free C−O bond-forming reaction is achieved from readily available starting materials, is operationally simple, and features a remarkable functional group tolerance.



Cu-Catalyzed Cyclization of Formyl-*N*-arylformamides

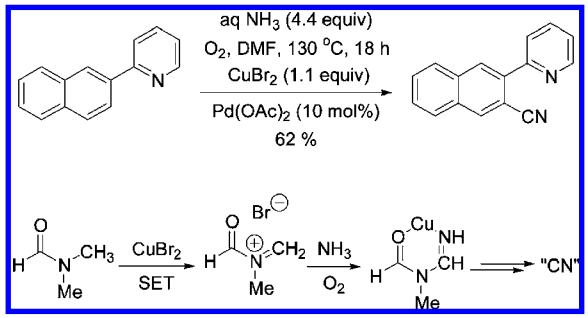
Tang and co-workers at Hunan Normal University report the direct intramolecular C−H oxidation and acylation of formyl-*N*-arylformamides to give indoline-2,3-diones in *J. Am. Chem. Soc.* **2010**, *132*, 8900−8902. The treatment of N-substituted formyl-*N*-arylformamides with 0.2 mmol of $CuCl_2$ and 1 atm of O_2 in THF at 100 °C affords the desired isatines in reasonable yields (>60%). The reaction tolerates a variety of functional groups on the aromatic ring with the exception of strong electron-withdrawing substituents at the *para* position (i.e., R^2 = Ac, CF_3) since they give lower yields. The analysis of inter- and intramolecular kinetic isotope effects and a series of control experiments suggest that the aldehyde C−H bond cleavage constitutes the rate-limiting step and that the reaction does not proceed via a Friedel−Crafts acylation.



Pd-Catalyzed Cyanation of Aryl C−H Bonds

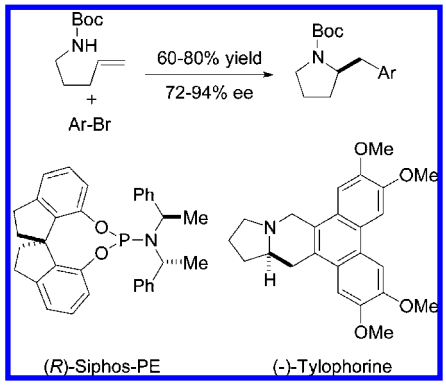
A novel cyanation of 2-(2-pyridyl)arenes has been developed by Kim and Chang (*J. Am. Chem. Soc.* **2010**, *132*, 10272−10274). The method uses a mixture of aqueous NH_3 and DMF as a combined source of CN along with $CuBr_2$ and $Pd(OAc)_2$. Whereas stoichiometric $CuBr_2$ and 1 atm of O_2 are required to mediate the NH_3/DMF reaction that generates the CN precursor, the 10 mol % $Pd(OAc)_2$ catalyzes the cyanation step. Labeling studies indicate that NH_3 serves as the nitrogen supply of CN in a step that presumably involves a single electron transfer oxidation catalyzed by the Cu(II) species. Interestingly, the use of a combination of $^{15}NH_3$ and $^{13}C_2$-DMF generates valuable $^{13}C^{15}N$ doubly labeled nitriles with excellent isotopic

incorporation (>96%). The cyanation occurs with good yields and high regioselectivities.



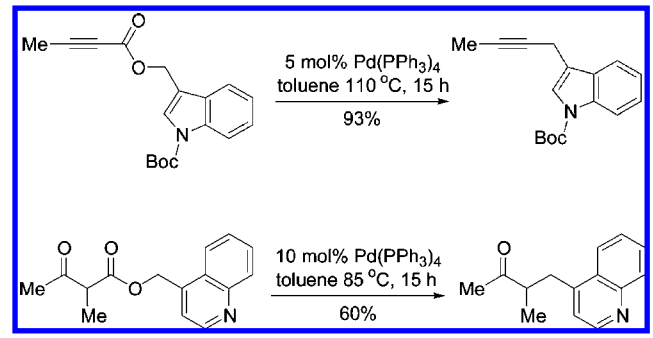
Asymmetric Pd-Catalyzed Alkene Carboaminations

The reaction between alkenyl or aryl bromides and *N*-boc-pentenylamines via Pd-catalyzed carboamination affords enantiomerically enriched 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidines (Mai and Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 12157−12159). A screening of catalysts resulted in the identification of Siphos-PE as an effective phosphoramidite ligand that promoted the carboaminations in good yields and acceptable ee's (72−94%). Optimized reaction conditions involve the use of 2 equiv of RBr, 1−2 equiv of NaO^{t}Bu, 2.5 mol % $Pd_2(dba)_3$, and 7.5 mol % (*R*)-Siphos-PE in toluene at 90 °C during 12 h. Aryl chlorides did not react under these conditions, whereas aryl triflates gave low yields due to the undesired reaction of the sulfonates with base. The proposed mechanism implicates intramolecular alkene insertion into the Pd−N bond of the intermediate complex followed by C−C bond forming reductive elimination. The synthetic utility of the transformation was demonstrated in the enantioselective synthesis of (−)-tylophorine.



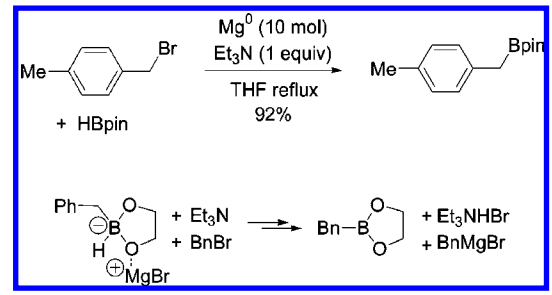
Pd-Catalyzed Decarboxylative Benzylations of Alkynes and Ketones

The group of Prof. Jon A. Tunge at the University of Kansas reported the catalytic benzylation of propiolic and β-keto esters under mild, base-free, and organometallic-free conditions in *J. Am. Chem. Soc.* **2010**, *132*, 9280−9282. The methodology affords sensitive benzylic alkynes from propiolates including heteroaromatic intermediates of pharmaceutical interest. Remarkably, the decarboxylative benzylation of β-keto esters enables the formal regioselective benzylation of ketones that otherwise would be difficult to obtain using standard methods. Moreover, the benzylation of α,α-disubstituted ketones affords hindered quaternary carbon centers. The benzylations of alkynes and unsubstituted ketones require the use of $Pd(PPh_3)_4$ as catalyst. In contrast, benzylations of highly substituted ketones need PBu_3 as the ligand.



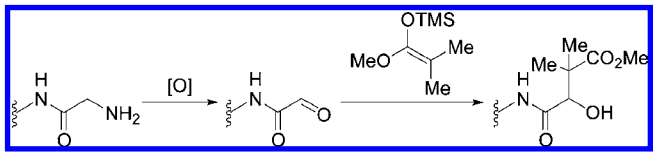
Mg-Catalyzed Coupling of Benzylic Halides with Pinacolborane

Pintaric and co-workers at CNRS developed a simple direct coupling of benzyl halides with pinacolborane using 10 mol % Mg in the presence of 1 equiv of Et_3N (*J. Am. Chem. Soc.* **2010**, *132*, 11825−11827). The procedure circumvents the formation of benzylic dimers from homocoupling and was successfully applied to the synthesis of a variety of benzylboronic picacol esters in good yields. The overall transformation involves a Barbier-type reaction with recycling of the Mg catalyst in which HBpin acts as both an electrophile and a reducing agent. Based on ^{11}B NMR spectroscopic and DFT computational studies, the authors propose the formation of a Mg-dialkoxy alkylborohydride that generates BnMgBr instead of toluene upon reaction with BnBr.



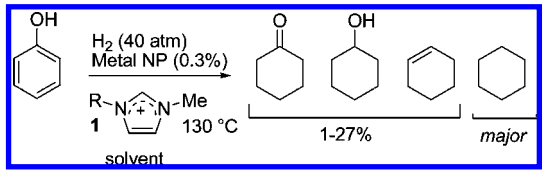
Functionalization of Peptides by Mukaiyama Aldol Reaction

As the result of an academia−industry collaboration, Alam and co-workers describe the functionalization of peptides and proteins using a catalyst-free water-based Mukaiyama aldol reaction between N-terminal aldehydes and a series of ketene acetals (*J. Am. Chem. Soc.* **2010**, *132*, 9546−9548). The choice of oxidant to generate the aldehydes depends on the complexity of the substrate. Thus, in the case of peptide substrates, the aldehydes were generated by periodate oxidation, whereas for proteins pyridoxal-5′-phosphate was more convenient. In general, the addition of 2 equiv of ketene acetal to a 10 mM sodium phosphate buffer solution of peptide aldehyde at pH = 7 at rt during 24 h gives acceptable adduct yields (~50%). 190 equiv of ketene acetal were needed to modify proteins with near quantitative yields (~95%). In the case of myoglobin, the functionalization did not alter its enzymatic activity.

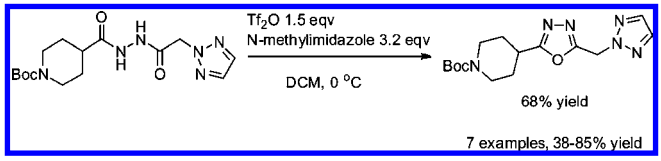


Nanoparticle Catalysts and Brønsted Acidic Ionic Liquids: Hydrodeoxygenation of Lignin-Derived Phenols into Alkanes

Current strategies to produce biofuel from lignin, a promising feedstock with lower oxygen content than polysaccharides, are two-step processes: (1) depolymerization into simple aromatic compounds (mostly phenols) by hydrogenation, hydrolysis, or fast pyrolysis; (2) upgrade of phenolic mixture to fuels, by hydrodeoxygenation into alkanes. The latter step remains a challenge, chiefly due to high energy demands, sulfur accumulation, and catalyst deactivation. In *Angew. Chem., Int. Ed.* **2010**, *49*, 5549−5553, a joint paper between the groups of Yuan Kou and Paul J. Dyson describes the development of a bifunctional catalytic system based on metal nanoparticles (NPs) and ionic liquids (ILs), which effectively converts lignin-derived phenols into alkanes under mild conditions. The catalytic system is composed of metal NPs and a functionalized Brønsted acidic IL immobilized in a nonfunctionalized IL as a solvent (bmim][BF_4] or [bmim][TF_4]) allowing hydrogenation and dehydration reactions to occur in tandem. Brønsted acidic IL **1** (R = CH_2SO_3H; A = CF_3SO_3) performed best in the dehydration of cyclohexanol to cyclohexene. Particles of different metals (Ru, Rh, and Pd) were efficient (>95% conversion) in the one-pot hydrogenation−dehydration of phenols that took place in water at 130 °C and 40 atm of H_2 to yield cyclohexane as the main reaction product.

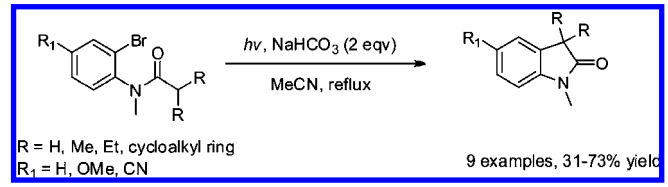


Improved Synthesis of Oxadiazoles



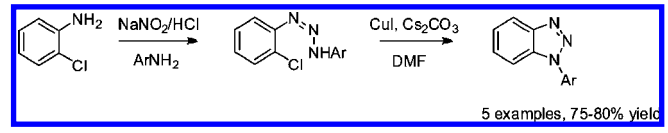
The oxadiazole ring is a common medicinal chemistry motif that occurs in a number of APIs including zibotentan and raltegravir. These heterocycles are typically obtained from diacylhydrazines by use of dehydrating reagents such as $POCl_3$, P_2O_5, PPh_3/DEAD, and Tf_2O/pyridine amongst others. After mixed results with existing methodology, Wheeler et al. (*Synth. Commun.* **2010**, *40* (20), 3021−3026) of Pfizer Sandwich report an optimised procedure using triflic anhydride and *N*-methylimidazole. This converted a range of functionalised diacylimidazoles to oxadiazoles in good yield. This appears to be an economical and mild alternative to existing methodology.

Synthesis of Oxindoles via Photocatalytic Cyclisation



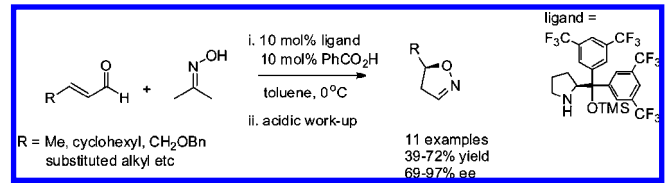
Chaozhong et al. (*Chin. J. Chem.* **2010**, *28*, 1640−1644) report a convenient synthesis of oxindoles via photochemical cyclisation of *o*-bromoanilides. Thus irradiation of an *o*-bromoanilide in refluxing acetonitrile with a high-pressure mercury lamp (125 W) in the presence of base afforded the α,α-dialkyl oxindoles in modest to good yields. Examples were restricted to oxindoles with simple alkyl or cycloalkyl side chains. The absence of any requirement for transition metal catalysis, Bu_3SnH initiation, or prior functionalisation of the amide is a clear advantage in this methodology.

Synthesis of N_1-Arylbenzotriazoles via Diazonium Chemistry



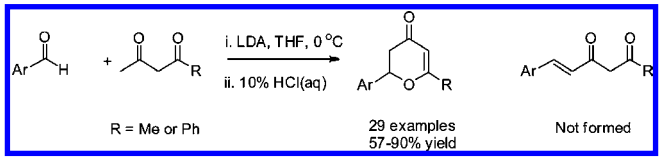
N_1-Arylbenzotriazoles can be prepared via benzyne click cycloaddition and direct N^1-arylation using metal catalysis or SnAr reaction with aryl fluorides. Tiwari et al. (*Tetrahedron Lett. 51*, **2010**, 5740−5743) at Banaras Hindu University, India report a complementary means for their synthesis via sequential diazotisation, reaction with a second aniline followed by intramolecular N-arylation. The intermediate benzotriazenes are prone to rearrangement to *p*-aminoazoarynes thus requiring immediate use in the arylation reaction. This approach to N_1-arylbenzotriazoles appears particular attractive due to the well established chemistries employed and no competing N_2-aryl isomer formation.

Organocatalytic Asymmetric Synthesis of 2-Isoxazolines



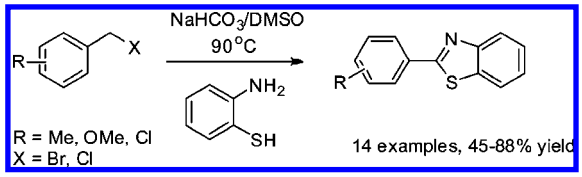
Pihko et al. (*Chem.—Eur. J.* **2010**, *16*, 11325−11339) of the University of Jyvaskyla report an efficient asymmetric synthesis of 2-isoxazolines from enals and acetone oxime catalysed by (*S*)-α,α,3,5-bis(trifluoromethyl)phenyl]prolinol trimethylsilyl ether. Thus initial Michael addition via the oxygen atom of the oxime followed by acidic hydrolysis of the intermediate *O*-alkyl oxime yields a variety of isoxazolines in good yield and high enantiomeric excess (typically >90% ee). Notably the second generation MacMillan catalyst gave neglible asymmetric induction and low yield under these conditions.

Facile Synthesis of Aryl Dihydropyran-4-ones



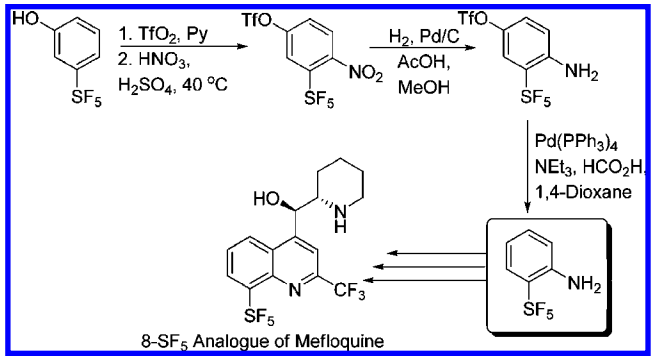
Existing methodologies to 2-aryl-2,3-dihydro-4*H*-pyan-4-ones include cycloadditions with Danishefsky's diene and Pd-catalysed oxidative cyclisation of β-hydroxyenones. Langer et al. (*Helv. Chim. Acta* **2010**, *93* (9), 1705−1715) have developed a facile one pot synthesis of these compounds via addition of aryl aldehydes to the dianion of acetylacetone followed by quench with 10% HCl(aq). The choice of acid proved crucial to promoting the cyclisation; for example TsOH yielded the unwanted acyclic enone. This appears to be a robust means to this class of compound.

One Pot Synthesis of Benzothiazoles from Benzyl Halides



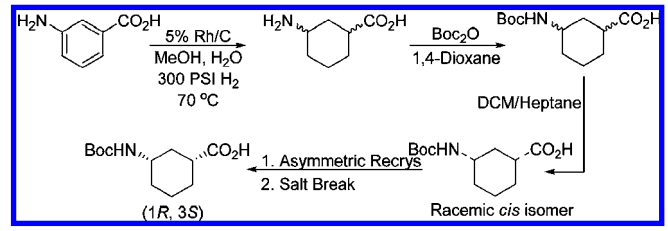
Akiyama et al. (*Synlett* **2010**, (16), 2457−2460) of Gakushuin University report a direct oxidative conversion of benzyl bromides or chlorides to 2-aryl benzothiazoles. The reaction appears to proceed via initial Kornblum oxidation to the aldehyde followed by condensation with the *o*-aminothiophenol and in situ oxidation to the product. Examples given are limited to unsubstituted *o*-aminothiophenol and benzyl halides with simple methyl, methoxy, and chloro substitutents. The ready availability of many different benzyl halides makes this approach worth consideration.

Accessing *ortho*-SF_5-Aniline



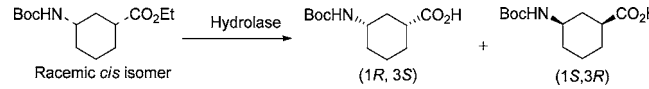
As part of a research program towards the development of improved antimalarial drugs Wipf et al. have been working on pentfluorosulfanyl analogues of their lead compound Mefloquine (*Tetrahedron Lett.* **2010** *51*, 5137−5140). Their work hit a stumbling block with the lack of commercial availability and literature precedent for the synthesis of *ortho*-SF_5-aniline; as a result they have developed a simple and efficient route in to the desired compound. Starting from the commercially available *meta*-SF_5-phenol they perform a triflation to insert a better SeAr directing group followed by a regioselective nitration to giving their first intermediate. The nitro group was then reduced to the aniline by palladium catalyzed hydrogenation; unfortunately the triflate group was not so straightforward to remove. Classical Pd(II) transfer hydrogenation did not work cleanly, and the group was finally removed utilizing a Pd(0) hydrogen transfer reaction to give the key intermediate *ortho*-SF_5-aniline. Five additional synthetic steps were then carried out to give the Mefloquine analogue.

An Improved Synthesis of (1*R*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]cyclohexanecarboxylic Acid



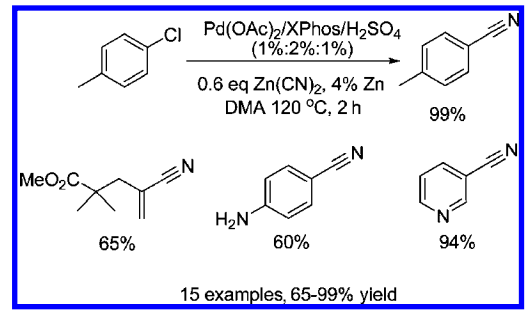
Work by Newman and Badland from Pfizer UK (*Tetrahedron: Asymmetry* **2010**, *21*, 864−866) towards an improved synthesis of this racemic *cis* cyclohexane carboxylic acid has been driven by the need for a shorter scalable route compared to the several known procedures already published.

The initial hydrogenation of 3-aminobenzoic acid was performed using a rhodium on a charcoal catalyst and proceeded at lower pressure (300 PSI) to give a 5:1 *cis*/*trans* mix of isomers. The free amine was then subjected to BOC protection, and the desired compound was then recrystalised to give a racemic mix of *cis* isomer. It was then found that asymmetric resolution using (*R*)-1-phenylethylamine gave rise to the desired (1*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]cyclohexanecarboxylic acid as a single enantiomer.



The authors then tested an alternative resolution approach by screening hydrolase enzymes to selectively convert one stereoisomer of racemic ethyl 3-[(*tert*-butoxycarbonyl)amino]cyclohexanecarboxylic acid into the enantiomerically enriched *cis*-(1*R*,3*S*)-acid and unreacted *cis*-(1*S*,3*R*)-ester. After screening 96 enzymes, the results confirmed the enzymatic approach was viable with cholesterol esterase from *Candida cylindracea* exhibiting the highest stereoselectivity and >99% substrate ee and product ee at 50% conversion.

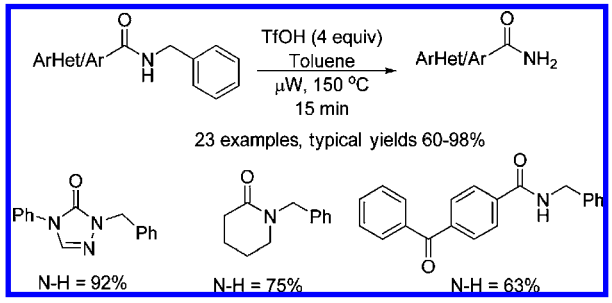
Cyanation of Aryl Chlorides



The cyanation of aryl halides is a widely used method for preparing substituted benzonitriles. Whilst this chem-

istry is robust and requires mild temperatures for aryl iodides, bromides, and triflates, the conversion of aryl chlorides is a particularly difficult transformation to perform. This difficulty is due to the rate of oxidative insertion being slower than the the case for iodide and bromide. As a result the catalyst is left vulnerable to poisoning by the cyanide in solution. To overcome this problem Shevlin (*Tetrahedron Lett.* **2010**, *51*, 4833−4836) has performed a comprehensive study into solving this issue. Using 4-chlorotoluene as his starting material and performing a palladium ligand screen, the author discovers that XPhos gave the best conversion. He then turned his attention to reaction additives for preventing decomposition of the precatalyst by the cyanide. After a vast screen it was shown that $PdSO_4 \cdot 2H_2O$ gave the most robust precatalyst and, as a result, the "best" overall yielding reactions. The author then went further and demonstrated the wide scope of this reaction with various aryl, heteroaryl, and vinyl chloride examples.

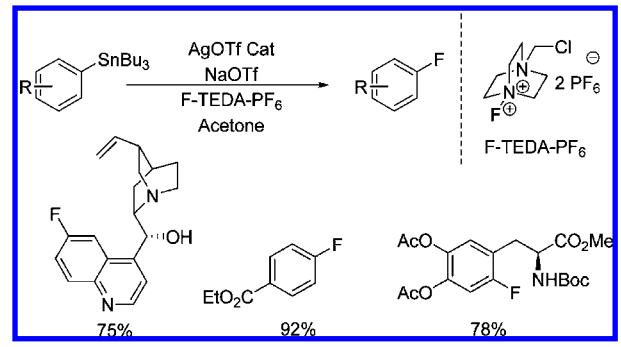
Facile Deprotection of *N*-Benzyl Amides



Whilst the deprotection of *N*- and *O*-benzylated intermediates is a commonly used strategy in organic synthesis, deprotection of *N*-benzylated amides is more challenging and often the removal conditions may be incompatible with other functional groups present in the molecule. With the limitations involved Rombouts and Trabanco from Johnson & Johnson (*Tetrahedron Lett.* **2010**, *51*, 4815−4818) have developed a milder method for the deprotection of these *N*-benzyl amides. Their initial work was based on thermal deprotection in neat trifluoroacetic acid; however this lead to variable yields. Upon reaction optimization the reaction was attempted using microwave irradiation; pleasingly they found this to accelerate the reaction and give more reproducible yields. A key development for this procedure is the use of toluene as a cosolvent. As it is immiscible with trifluoroacetic acid it sits on the top layer and as a result traps any corrosive fumes in the reaction mixture. A second added bonus is the nucleophilic nature of toluene towards radicals, and as a result fewer byproducts are observed due to the ability of toluene to scavenge benzyl radicals. The authors next screened a range of substrates and demonstrate a general application for secondary/tertiary, aliphatic/aromatic, and acyclic/cyclic amides.

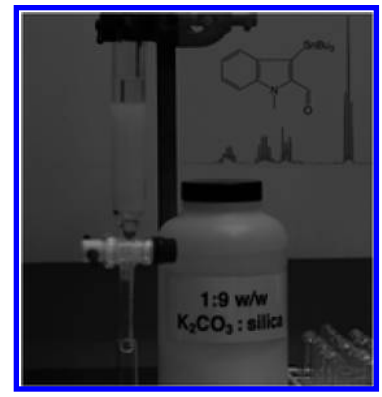
Late Stage Fluorination

Fluorinated aromatic compounds have a wide range of uses throughout the chemical industry. However, the synthesis of



fluorinated arenes is often challenging due to the properties of fluorine and the routinely harsh reaction conditions required. More recently Sanford and Yu have reported palladium catalysed electrophilic fluorination; however high temperatures and regioselectivity issues hold this methodology back. To complement this technique Ritter has recently published (*J. Am. Chem. Soc.* **2010**, *132*, 12150.) a method based on silver catalysis for C−F bond formation. Ritter demonstrates a level of functional group tolerance and substrate scope that have never been demonstrated for a fluorination reaction before. This is done by formation of a number of stannylated natural products such as Taxol, Strychnine, and Rifamycin just to mention a few and their conversion to aryl fluorinated analogues in good to excellent yield. Of course one down side to this chemistry is the use of arylstannanes. However, this does give access to mild conditions making it an attractive piece of methodology for the chemist's war chest.

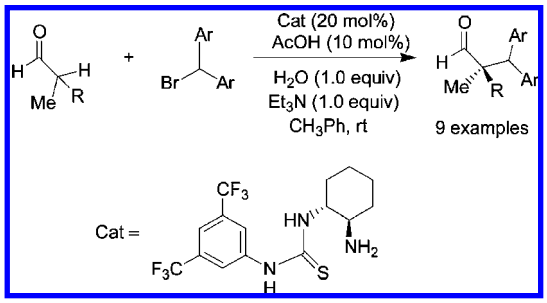
K_2CO_3−Silica - a Highly Effective Stationary Phase for the Chromatographic Removal of Organotin Impurities



Work by Curran and Harrowen (*Chem. Commun.* **2010**, *46*, 6335−6337) has shown that a stationary phase composed of 10% powdered anhydrous K_2CO_3 and silica is remarkably effective for the removal of organotin impurities from product mixtures, reducing these from stoichiometric levels to ∼15 ppm. The K_2CO_3−silica mixture may be stored for months without significant loss in fluidity or activity.

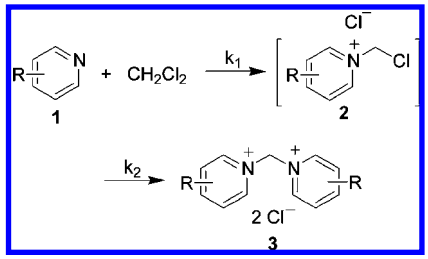
The method is compatible with tetraorganotin and hexaorganylditin compounds which pass through the stationary phase as distinct bands at similar rates observed using silica alone. Separation of other organic components relies on polarity differences, while organotin halides and oxides are captured by the stationary phase.

Enantioselective α-Alkylation of Aldehydes



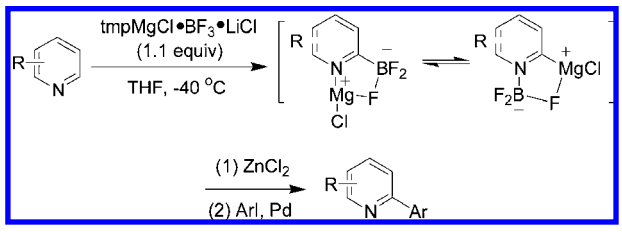
Chiral aldehydes bearing α-quaternary stereocenters are valuable synthetic intermediates. An enantioselective synthesis of the chiral aldehydes was realized by a catalytic α-alkylation of aldehydes with diaryl halides in the presence of thiourea derivatives (*J. Am. Chem. Soc.* **2010**, *132*, 9286−9288). Investigation, by Jacobsen and co-workers at Harvard University, shows that the substitution reaction underwent a stepwise, S_N1 mechanism, induced by anion binding to the catalyst.

Reaction of Pyridine Derivatives with Dichloromethane

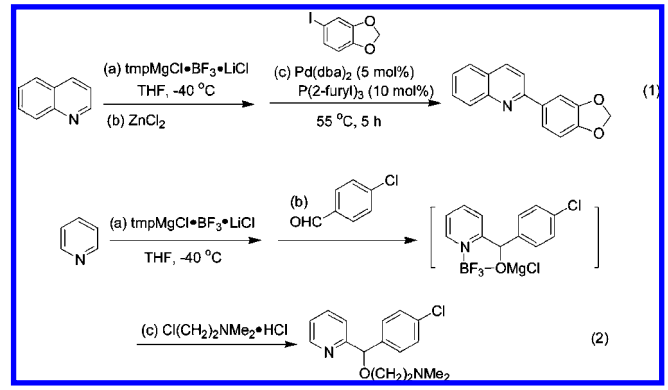


When selecting a reaction solvent, one should consider if the solvent of interest is compatible with the starting material and reagent(s). For example, dichloromethane can react with 4-(dimethylamino)pyridine through an S_N2 consecutive process, giving methylenebispyridinium dichloride (*J. Org. Chem.* **2010**, *75*, 4292−4295). The two consecutive S_N2 reactions proceeded at rate constants of k_1 (2.56×10^{-8} M^{-1} s^{-1}) and k_2 (4.29×10^{-4} M^{-1} s^{-1}), respectively. Because of the high reaction rate of the second substitution, the monosubstitution product **2** could not be detected during the course of the reaction and only the methylenebispyridinium dichloride **3** was isolated. However, it appears that the steric effect can suppress the S_N2 substitution reactions; for example, no reaction was observed between 2- (or 2,6-) substituted pyridines and dichloromethane.

Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs

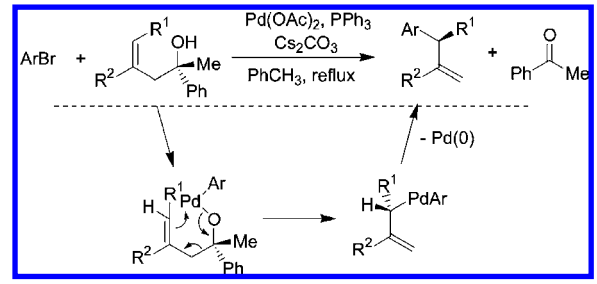


A highly selective metalation of pyridines mediated with a new class of frustrated Lewis pairs based on BF_3·OEt_2 and LiCl-complexed 2,2,6,6-tetramethylpiperidyl (tmp) metal amide bases was developed by Knochel's group in Germany (*Angew. Chem., Int. Ed.* **2010**, *49*, 5451−5455). This approach constitutes an expeditive preparation of versatile magnesium chloride heteroaryl trifluoroborates by treatment of pyridine derivatives with tmpMgCl·BF_3·LiCl formed by mixing a solution of BF_3·OEt_2 (1.1 equiv) with tmpMgCl·LiCl (1.1 equiv, −40 °C, 10 min). Application of the selective metalation reaction toward organic synthesis was demonstrated by a subsequent Negishi cross-coupling of aryl iodides affording the 2-arylated pyridines.



Further demonstration of the synthetic potential of this approach is illustrated in eqs 1 and 2. Two biologically active molecules, the haplophyllum alkaloid, dubamine (eq 1), and an antihistaminic drug, carbinoxamine (eq 2), were conveniently prepared in two one-pot procedures, respectively.

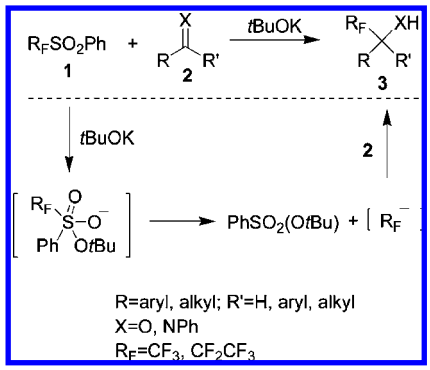
Chirality Transfer Reaction



A palladium-catalyzed arylation of homoallyl alcohols was reported by Oshima and co-workers in Japan (*J. Org. Chem.* **2010**, *75*, 4337−4343). A unique feature of this transformation is that the chirality in the homoallyl alcohols could be transferred into the products. The scope of the chirality transfer reaction was examined. Various aryl halides could be used, including poor substrates for oxidative addition, such as chlorobenzene and electron-rich 4-bromoanisole, and aryl bromides bearing the electron-withdrawing formyl, benzoyl, or cyano group. It was noticed that the steric hindrance in homoallyl alcohols could either prolong the reaction time or lead to an *O*-arylated byproduct.

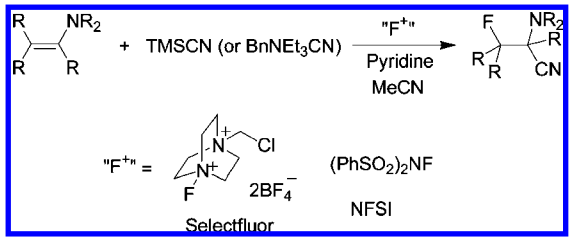
Nucleophilic Perfluoroalkylation of Imines and Carbonyls

Fluorine-containing compounds possess unique properties, such as lipophilicity and bioavailability, and are



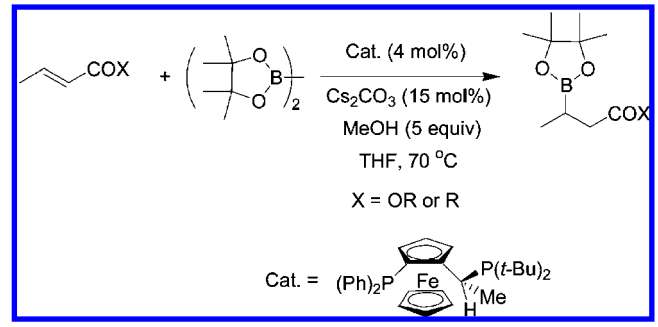
widely used in pharmaceutical, agrochemical, and material fields. Thus, introducing fluorine into organic compounds has attracted much attention. Alkoxide-induced nucleophilic perfluoroalkylation of aldehydes, ketones, and imines using pentafluoroethyl phenyl sulfone ($PhSO_2CF_2CF_3$) or trifluoromethyl phenyl sulfone ($PhSO_2CF_3$) was successfully achieved (*Org. Lett.* **2010**, *12*, 2932−2935). Nucleophilic addition reactions between **1** and **2** were performed under argon atmosphere by slowly adding a base into the mixture of **1** and **2** in THF at −75 °C. A variety of structurally diverse imines **2** (X = NPh) was used to react with **1** in the presence of *t*-BuOK to give the corresponding pentafluoroethyl amines with excellent yields. Imines bearing an α-hydrogen atom were also suitable substrates for the perfluoroalkylation under the basic environment. Extension of this reaction to carbonyl compounds resulted in good yields of the corresponding perfluoroalkyl carbinols though enolizable aldehydes gave lower yields due to the competing enolization occurring in the presence of the base. The nucleophilic attack of the alkoxide ion on the thio center of **1** resulted in the generation of perfluoroalkyl anion (R_F^-) in situ. Ultimately, the subsequent nucleophilic addition of R_F^- onto **2** afforded the observed products **3**.

Fluorocyanation of Enamines



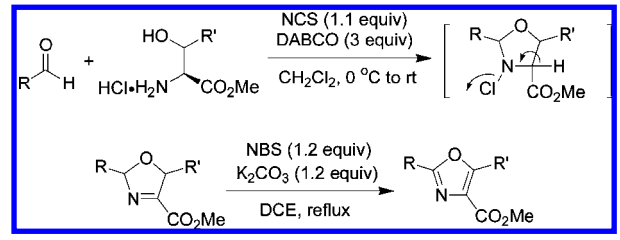
A method for the fluorocyanation of enamines was described by Dilman and co-workers in Russian Federation (*J. Org. Chem.* **2010**, *75*, 5367−5370). The three-component reaction involves fluorination of the electron-rich double bond with a N−F reagent (Selectfluor or NFSI) accompanied by trapping of a β-fluoroiminium cationic intermediate with a cyanide nucleophile. Two cyanides, trimethylsilyl cyanide (TMSCN) and benzyltriethylammonium cyanide, were used as terminating nucleophiles. The presence of pyridine (1.2 equiv) resulted in a cleaner reaction. Pyridine may serve for the stabilization of intermediate fluoroiminium carbocation and/or as a scavenger of trimethylsilyl cation. Various enamines bearing two substituents at the β-position were subjected to the fluorocyanation reactions giving reasonable product yields. Good nucleophilicity of the enamines was required in order to achieve the desired reaction efficiency.

Metal-Free Catalytic Boration of α,β-Unsaturated Compounds



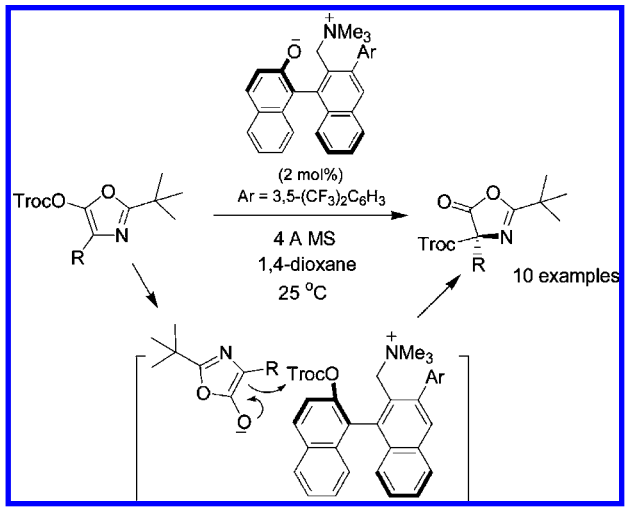
Although the development of a metal-free asymmetric boron-addition reaction with achiral boron reagents is challenging, a method for the synthesis of β-borated carbonyl compounds was reported by Gulyás and co-workers in Spain (*Angew. Chem., Int. Ed.* **2010**, *49*, 5130−5134). A reaction of B_2pin_2 with either α,β-unsaturated esters or ketones in the presence of chiral phosphine catalyst afforded the desired β-borated carbonyl compounds in moderate to good yields with 36−83% ee. The metal-free reaction requires tertiary phosphorus compounds as catalyst, and MeOH and a base as additives. The tertiary phosphorus catalyst acts as a chiral auxiliary to induce the chiral center in the product. The method is particularly advantageous if the borylation reaction needs to be scaled up.

A New Oxidation Method for Conversion of Oxazoline to Oxazole



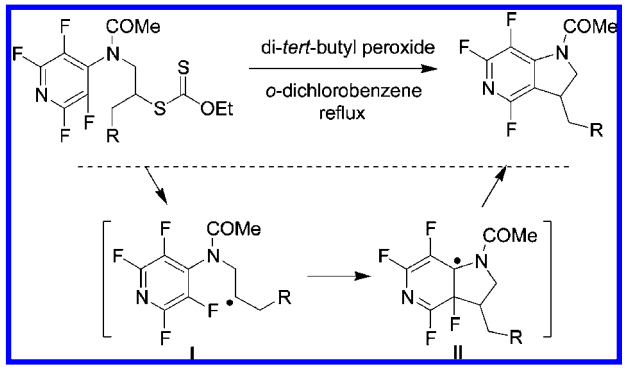
A new oxidation method was developed during the synthesis of oxazole-4-carboxylates (*Org. Lett.* **2010**, *12*, 3456−3459). A one-pot condensation of aldehydes and oxidation with NCS gave 3-oxazoline-4-carboxylate intermediates, followed by oxidation of the intermediates with NBS furnishing oxazole-4-carboxylates. This first oxidation occurred via a *N*-chlorination of oxazolidine and subsequent E2 elimination to lead to a 3-oxazoline-4-carboxylate intermediate. The second oxidation reaction probably proceeded via bromination of the 5-position of 3-oxazolines or a nitrogen atom and then aromatization. K_2CO_3 was used as an acid scavenger for HBr formed in situ. A total of 11 examples were presented, and good yields in both 3-oxazoline-4-carboxylates and oxazole-4-carboxylates were obtained.

A Highly Enantioselective Steglich Rearrangement Catalyzed by Chiral Ammonium Betaines



Acyl transfer reactions by means of nucleophilic catalysts are one of the fundamental molecular transformations in synthetic organic chemistry. A highly enantioselective Steglich rearrangement using chiral ammonium betaines as nucleophilic ionic catalysts was presented by Ooi's group in Japan (*Angew. Chem., Int. Ed.* **2010**, *49*, 5567−5569). The catalytic Steglich rearrangement of 5-oxazolyl carbonate into 4-carboxyazlactones offers an attractive process for establishing a tetrasubstituted stereogenic center. It was observed that the stereoselectivity was strongly dependent on the substrate concentration: a low concentration of the substrates favors the formation of a high enantiomeric excess of the products. Thus, the reaction was generally conducted by the addition of a 1,4-dioxane solution of the substrate to a stirred mixture of catalyst (2 mol %) and powdered 4 Å molecular sieves in 1,4-dioxane at 25 °C. This chiral ammonium betaine catalyzed asymmetric transformation opens new opportunities for the development of asymmetric nucleophilic catalysis.

An Uncommon Radical *ipso* Substitution of a C−F Bond



A report by Zard and co-workers in France demonstrates a synthetically useful method for the preparation of highly functionalized fluoroazaindoline derivatives by means of radical *ipso* substitution of a C−F bond (*Org. Lett.* **2010**, *12*, 3426−3429). Employing inexpensive and readily available substrates and reagents under refluxing in *o*-dichlorobenzene in the presence of lauroyl peroxide, trifluoroazaindolines were obtained in moderate yields. The formation of the products was hypothesized to proceed via a radical *ipso* substitution pathway involving secondary alkyl radicals (**I**) and tertiary radicals (**II**). The radicals **II** are highly stable due to the delocalization with the allylic and adjacent nitrogen plus its inherent tertiary nature. Although the yields are relatively modest because of the competing premature reduction of the intermediate radicals, such radical cycloaddition would be a valuable approach addition to the existing synthetic methodology.

Salt or Co-crystal? Determination of Protonation State by X-ray Photoelectron Spectroscopy

In the salt−co-crystal continuum, determining the accurate location of the proton is not always straightforward. For crystalline materials, established methods to accomplish this task include single crystal X-ray diffraction, XRPD, and solid-state NMR. A collaboration between Sanofi-Aventis and the University of Manchester (Stevens, J. S., et al. *J. Pharm. Sci.*, **2010**, *99* (11), 4453.) aims to identify additional analytical methods that can accurately determine the degree of proton transfer in solids, including those that are amorphous. The proposed method is X-ray photoelectron spectroscopy (XPS), and the model compounds used in this work were salts and co-crystals of theophylline with oxalic acid and 5-sulfosalicylic acid (dihydrate). The XPS results were successfully corroborated with the data obtained from XRPD and solid-state NMR. Among the limitations identified for the XPS methodology, the authors report the requirement that the materials exhibit vapor pressures below 10^{-7} mbar, surface effects must be accounted for, and the method is considered, for practical purposes, an invasive one. The capital cost for XPS is relatively high comparable with that required to acquire a solid state NMR instrument.

Evaluation of the Effect of Seed Preparation Method on the Product Crystal Size Distribution for Batch Cooling Crystallization Processes

Crystallization process development and scale-up are considered to be both a science and an art; the latter includes also seeding methodology. Seeding is used for the control of crystallization processes and the particle size distribution of the crystallized material. The impact of seed quality on crystal size and shape is not well understood from a quantitative perspective, and the open literature contains relatively limited information about this topic. A contribution from Nagy's group at Loughborough University (Aamir, E., et al. *Cryst. Growth Des.* **2010**, in press; DOI: 10.1021/cg100305w) sheds further light into this matter. The model system investigated was potassium dichromate in water. Three types of seed were analyzed: (A) sieved; (B) milled, washed (with isopropanol), and sieved; and (C) milled and sieved.

Crystallizations were monitored using FBRM, ATR-UV/vis, and online laser diffraction. The use of an in-line diffraction method for particle size measurement is rather unusual, given the challenges posed by the slurry transport from the crystallizer to the diffractometer. Seed of 106−125 μm were added at approximately the 1.5% level, at 29 °C, 1 °C below the corresponding saturation level. Cooling was according to a cubic profile from 29 to 20 °C in 1 h. Crystals obtained when seed of type (A) were used exhibited the most growth and presented a monomodal particle size distribution. When seed of type (C) were used, the least growth was observed, and the product exhibited a bimodal distribution. One of the interesting findings in this work is the fact that the fines ("dust", <

1 μm) barely grow. Limited corroboration between the FBRM and the Malvern data is presented. Amongst the conclusions reported by the authors are the importance of using seed of consistent quality in order to obtain product of consistent quality and that seed washing is a valuable technique for seeding methodology. Simulation calculations were also executed, leading to results that were in good agreement with the experimental findings for the case when seed of "good quality" were used that are without fines.

Computer-Aided Solvent Selection for Improvong the Morphology of Needle-like Crystals: A Case Study of 1,6-Dihydroxybenzoic Acid

One of the crystallization process engineers' wishes is to be able to use a software program wherein one inputs the structure of a compound, and the software provides as output crystallization solvents suitable for the engineering of various crystal morphologies. Such a need is of particularly important practical relevance when an active pharmaceutical ingredient exhibits needle-like morphology, associated with poor processability. A contribution from MIT (Prof. Trout's group) describes a systematic approach for the rational selection of a solvent system for the engineering of 2,6-dihydroxybenzoic acid crystals form 2 (Chen, J., et al. *Cryst. Growth Des.* **2010**, in press; DOI: 10.1021/cg1004903). The proposed rational solvent selection methodology is based on rather complex computational methods, including the analysis of molecular dynamics trajectories and of the interactions between functional groups in the solvent and solute molecules. A morphology improvement, with a reduced aspect ratio, was observed when using a solvent toluene−diethyl ether (4:1 molar) mixture as demonstrated by microscopy. Experimental confirmation of the predicted (numeric) aspect ratio remains challenging. Further complications are associated with solute purity levels and with the morphology upon crystallization process scale-up. Future work will include the use of this solvent selection methodology for other compounds.

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