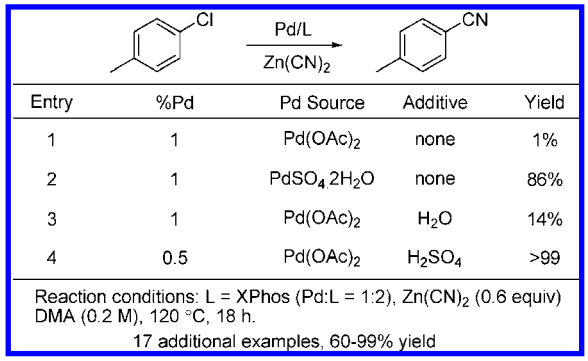
Highlights from the Literature

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

Improved Pd-Catalyzed Aryl Chloride Cyanations Using Sulfate Additives



Entry	%Pd	Pd Source	Additive	Yield
1	1	$Pd(OAc)_2$	none	1%
2	1	$PdSO_4 2H_2O$	none	86%
3	1	$Pd(OAc)_2$	H_2O	14%
4	0.5	$Pd(OAc)_2$	H_2SO_4	>99

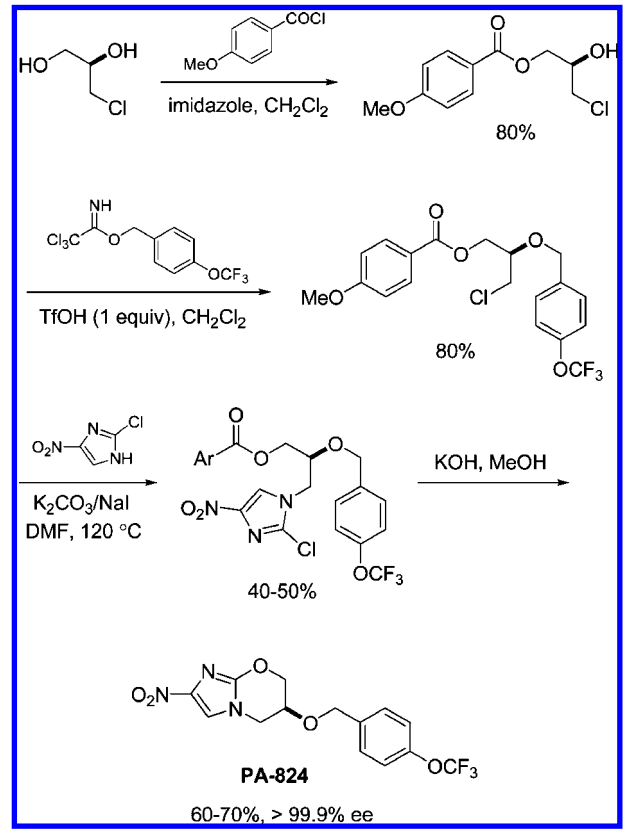
Reaction conditions: L = XPhos (Pd:L = 1:2), $Zn(CN)_2$ (0.6 equiv) DMA (0.2 M), 120 °C, 18 h.

17 additional examples, 60-99% yield

The Pd-catalyzed cyanation of aryl chlorides can still be challenging due to the more difficult oxidative insertion step into C−Cl bonds and competing catalyst deactivation caused by soluble cyanide. A recent report from Shevlin at Merck describes the use of sulfate additives to improve the robustness of Pd-catalyzed cyanations (*Tetrahedron Lett.* **2010**, *51*, 4833−4836). Additives such as H_2SO_4 greatly increase the reactivity of palladium catalysts for the cyanation of aryl and heteroaryl chlorides and render these reactions more robust toward adventitious air. Using this method, a wide variety of aromatic and heteroaromatic nitriles were prepared in high yield. Experiments to completely understand the role of the sulfate additives are ongoing.

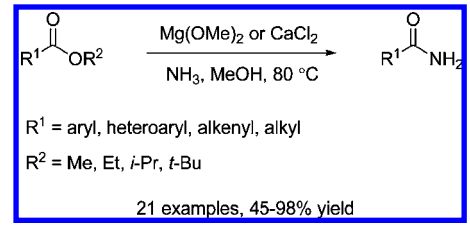
Synthesis of Antituberculosis Candidate PA-824

Tuberculosis (TB) is a devastating bacterial infection that kills more than 1.8 million people each year worldwide. Compound PA-824 is being developed by the Global Alliance for TB Drug Development (GATB) and is now in advanced phase II clinical trials. The original synthesis used to obtain material for clinical trials provides PA-824 in five linear steps from 2,4-dinitroimidazole, an intermediate with risk of explosion. Furthermore, the synthesis requires four chromatographic separations and an inefficient protection−deprotection sequence in order to selectively construct the oxazine core. Now Reider, Sorensen, and Marsini at Princeton report a new efficient four-step synthesis of PA-824 (*J. Org. Chem.* **2010**, *75*, 7479−7482). This new route employs (*R*)-3-chloro-1,2-propanediol, which is readily available from epichlorohydrin via HKR. Selective protection with a *p*-methoxybenzoyl group yields an intermediate that can be benzylated on the secondary alcohol and then reacted with 2-chloro-4-nitroimidazole under basic conditions to displace the chloride. Last, treatment with a stronger base (KOH in MeOH) results in cleavage of the benzoate ester and cyclization to form the oxazine ring. This concise approach



offers significant improvements over the synthetic route currently used for large-scale production.

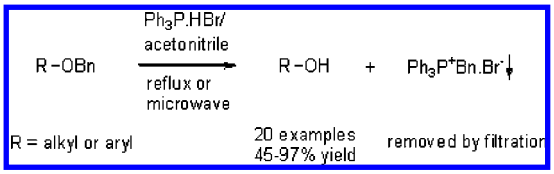
Amidation of Esters Assisted by $Mg(OMe)_2$ or $CaCl_2$



Wright and co-workers at Pfizer report that magnesium methoxide ($Mg(OMe)_2$) and calcium chloride can facilitate the direct aminolysis of esters by ammonia to primary amides (*Tetrahedron Lett.* **2010**, *51*, 3879−3882). Methyl, ethyl, isopropyl, and *tert*-butyl esters are converted to the corresponding carboxamides in good yields. The authors note that these reactions can be run on large scale without the safety liability inherent in the use of the alternative magnesium nitride (Mg_3N_2). Ammonium chloride and amine hydrochlorides can also be used successfully in place of ammonia with magnesium methoxide

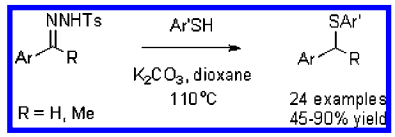
Published on Web 12/23/2010
10.1021/op100321t

Cleavage of Benzyl Ethers with Triphenylphosphine Hydrobromide



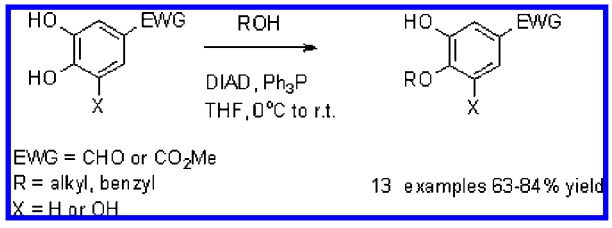
The protection of hydroxyl groups by the formation of benzyl ethers is a long established and common strategy in organic synthesis. Typically these ethers are cleaved via hydrogenolysis using Pd/C or Ra−Ni, although Greene and Wuts does list over 40 other conditions to effect this (*Protective Groups in Organic Synthesis*; Wiley and Sons: New York, 1999; see pp 76−84 therein). Regardless, Hou et al. (*Tetrahedron Letters 51 (* ***2010***) 6143−6145) have reported the use of $Ph_3P{\cdot}HBr$ in refluxing acetonitrile as an effective reagent to cleave benzyl ethers. This provides clear advantages such as compatibility with hydrogen-sensitive groups (e.g., carbon−carbon multiple bonds, nitro groups) and simple workup by filtration of $Ph_3P^+BnBr^-$ and removal of solvent. Notably, *O*-benzyl groups could be removed selectively over *N*-benzyl groups and a PMB group cleaved preferentially over benzyl.

Synthesis of Thioethers from Tosylhydrazones



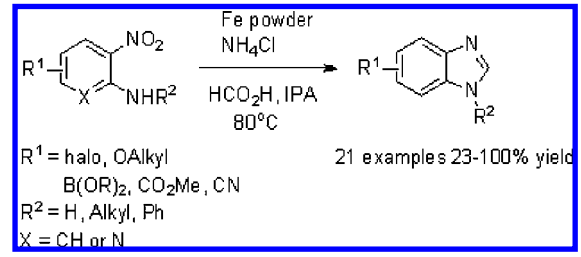
Aryl sulfides are typically prepared by reaction of the appropiate thiophenol with an alkyl (or benzyl) halide or sulfonate. Ding et al. (*Org. Biomol. Chem.* **2010**, DOI: 10.1039/C0OB00639D) have reported an alternative synthesis of benzyl arylsulfides by reaction of *N*-tosyl hydrazones with thiophenols in presence of potassium carbonate. The reaction failed with alkyl *N*-tosylhydrazones and was only exemplified with thiophenols. Thus the reaction appears to proceed via carbene formation from base decomposition of the hydrazone followed by insertion into the S−H bond.

Regioselective Alkylation of Catechols



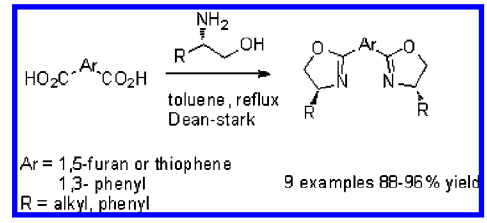
Since its first report in 1967 the Mitsunobu reaction has developed into a well established protocol to prepare ethers of various types. A key feature being stereoinversion with chiral substrates. Another intriguing facet of this reaction is the selective alkylation of diols or phenols. Wang et al. (*Synlett* **2010**, *19*, 2947−2949) demonstrate that 3,4-dihydroxy-benzaldehyde or -benzoic acid undergo selective alkylation under Mitsunobu conditions at the 4-OH group. None of the product arising from 3-OH alkylation was detected by 1H NMR. The results can be rationalised due to the greater acidity of the 4-OH proton. This approach looks applicable to substrates with other EWG groups and thus provides a clear benefit to the unselective alkylations obtained under basic conditions.

One-Pot Reductive Cyclisations of Nitroanilines to Imidazoles



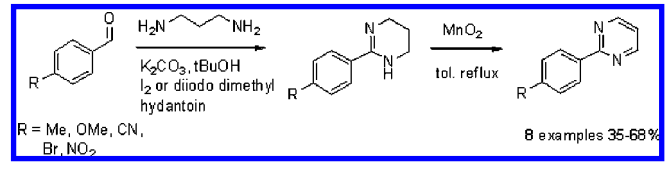
Hana and co-workers (*Synlett* **2010**, *18*, 2759−2764) from Genentech have developed a single-step procedure for conversion of 2-nitro aromatic amines to benzimidazoles. Addition of ammonium chloride proved necessary as Fe powder and formic acid alone was ineffective for nitro reduction. These conditions were compatible with a variety of functional groups on the aromatic, including boronate esters. The methodology was also extended to nitro aminopyridines but failed to deliver the desired product with isoxazole or pyrazole reactants.

Easy Access to Bis(oxazolines)



Reported methodology for the synthesis of bis(oxazolines) typically relies on the reaction of either aromatic bis-nitriles or bis-acid chlorides with the requisite β-amino alcohol. Hence this entails either modest yields or multiple steps to yield the oxazoline. Li et al. (*J. Heterocyclic Chem.*, *47*, 1340, **2010**) have demonstrated that simply heating a 1,3 bis-carboxyaromatic acid and β-amino alcohol in toluene under Dean−Stark conditions gives high yields of bis(oxazolines) after flash chromatography. Examples were restricted to 1,3-benzene dicarboxylic acid and 1,5-furan/thiophene dicarboxylic acids.

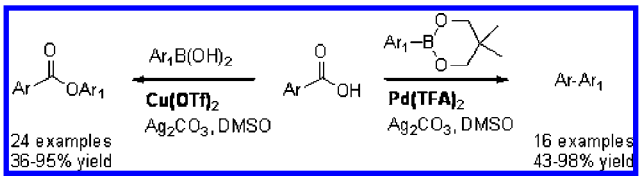
Oxidative Conversion of Aldehydes to Pyrimidines



Togo et al. (*Heterocycles*, DOI: 10.3987/COM-10-S(E)29) have reported an efficient one pot synthesis of 2-arylpyrimidines from aromatic aldehydes by condensation with 1,3-propanamine and subsequent oxidation with iodine or 1,3-diiodo-5,5-dim-

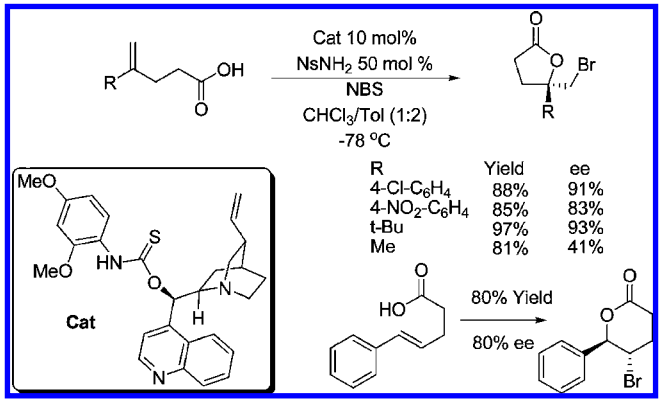
ethylhydantoin and MnO_2 aromatisation. The MnO_2 oxidation failed when aliphatic aldehydes were employed, except for 1-adamantane carboxyaldehyde.

Divergent Esterification and Decarboxylative Suzuki Couplings of Carboxylic Acids



Liu et al. (*Chem. Commun.* **2011**, *47*, 677) have reported an interesting example of orthogonal reactivity of aromatic carboxylic acids towards boronic acids and esters. Under palladium catalysis, carboxylic acids underwent decarboxylative coupling with aryl boronic acids and esters to yield biaryls in generally good yield. This is very similar to Chan-Lam conditions and thus represents its extension to carboxylic acids as substrates. Conversely when copper(II) triflate was used decarboxylation did not take place, rather aryl esters were formed in good yield. Both reactions worked well with electron-poor and -rich substrates; thus, this appears to be an interesting addition to the field of Suzuki couplings.

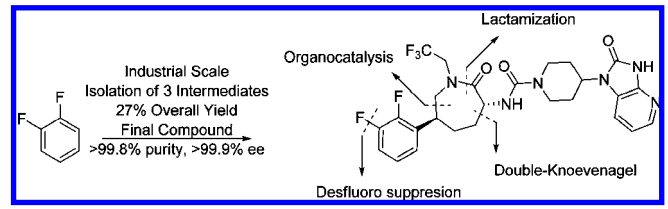
Asymmetric Bromolactonization Using Organocatalysis



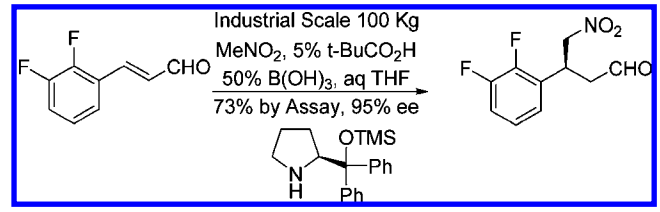
The halocyclization of olefins is an important class of organic transformations. Whilst these reactions are well documented, the catalytic enantioselective version has not been reported until now by Yeung (*J. Am. Chem. Soc.* **2010**, *132*, 15474−15476). He postulated that the use of a thiocarbamate organocatalyst would be a suitable activator of NBS as well as providing a rigid pocket for the bromonium ion to form within leading to high levels of enatioselectivity. Yeung then demonstrates a wide range of substrate compatibility albeit with low enantiomeric excess in the electron rich examples and a negative enantiomeric excess in the case of ortho substituted aryl groups. Yeung then applies the optimized conditions to the synthesis of δ-lactones giving the desired products in good yield and enantiomeric excess.

Asymmetric Synthesis of Telcagepant

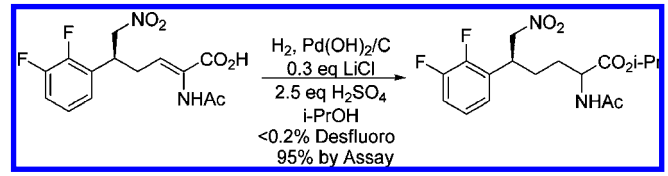
As part of the process of bringing a new API to market, it is often required to use an alternative synthetic strategy to the



initial medicinal chemistry approach. Here Xu et al. of Merck Rahway disclose their efforts towards an improved multikilogram synthesis of telcagepant, a CGRP receptor antagonist for the treatment of migraines (*J. Org. Chem.* **2010**, *75*, 7829−7841). The route described in the report is an example of a synthetic target driving the discovery of new chemistries.



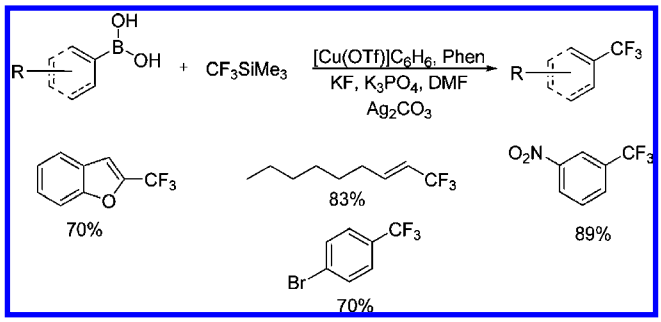
Of note are the challenges they faced and overcame in particular the asymmetric Michael addition of nitromethane to a cinnamyl aldehyde. Initial attempts under Hayashi's conditions gave promising results (50−75% yield) and moreover confirmed a high enantioselectivity could be achieved using the Jorgensen−Hayashi catalyst. However, the use of benzoic acid as the acidic cocatalyst gave rise to undesired byproducts. After performing a comprehensive screen of conditions Xu showed that the combination of the weak acids t-$BuCO_2H$ (5 mol %) and $B(OH)_3$ (50 mol %) minimized the level of impurities. Of specific note is that this is the first reported application of iminium organocatalysis on industrial scale.



The second milestone achieved in the strategy was the prevention of the protodefluorination under hydrogenative conditions. During the initial studies between 1.06−2.5% of the desfluoro compounds were formed by using $Pd(OH)_2/C$ in 100% conversion. To suppress the by product formation Xu screened a range of inorganic additives and found that 0.3 eq of LiCl gave a reproducible reaction where less than 0.2% of the desfluoro compounds were generated.

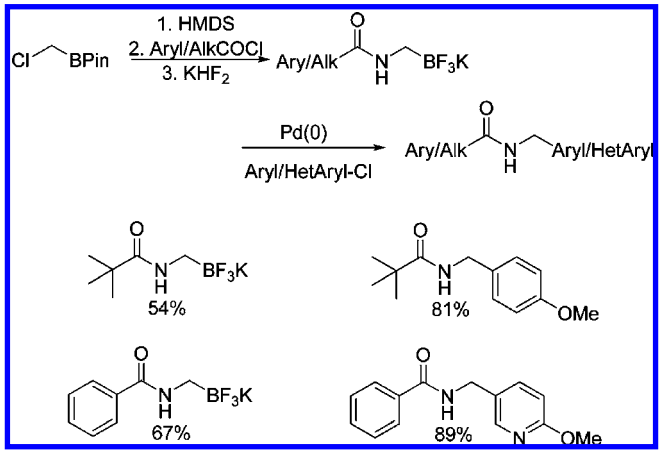
Copper-Mediated Oxidative Trifluoromethylation of Boronic Acids

Recently palladium mediated reactions for the introduction of trifluoromethyl groups on to aromatic rings has been intensely sought. In addition to recent research by Buchwald the Qing group has developed a mild oxidative trifluoromethylation of aryl- and alkenyl boronic acids (*Org. Lett.* **2010**, *12*, 5060−5063). Through a screen of oxidants the investigator shows that the in situ generation of $CuCF_3$ has given rise to substantial scope for functional group compatibility. In the paper the author goes



on to show that both electron rich and electron deficient groups are tolerated as well as halogenated intermediates. With the plethora of boronic acids commercially available to chemists in this day and age Qing's protocol opens a new door to trifluoromethyl groups in highly functionalized molecules.

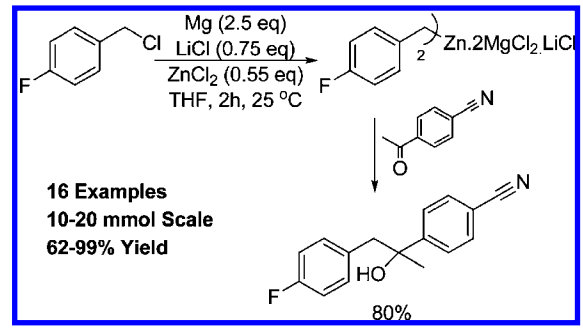
Cross-Coupling of Amidomethyltrifluoroborates



Over the years several strategies have been developed to access amidomethylarenes which are widely found in biologically active compounds. In addition to the plethora of classical methodology Molander has recently disclosed a one pot synthesis of amidotrifluoroborates and their subsequent cross coupling to aryl and heteroaryl chlorides (*Org. Lett*, **2010**, *12*, 4876−4879). Initially a tertiary amine is formed by treating 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane with KHMDS, this is then deprotected with methanol giving rise to the primary amine which is trapped with a variety of acyl chlorides to form the corresponding amides. The crude amidomethylboronic ester is then converted to the more stable boronate form by treatment with KHF_2. Molander then went on to show that both alkyl and aryl substrates underwent Suzuki-Miyaura coupling demonstrating the generality of this method.

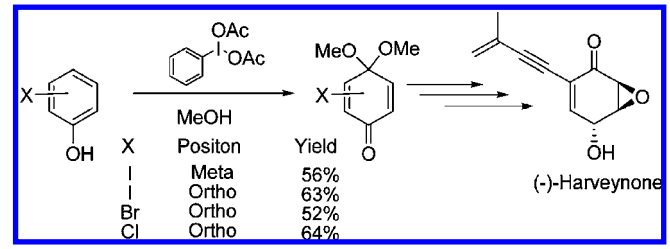
Direct Addition of Functionalized Organozinc Reagents to Carbonyls in the Presence of $MgCl_2$

The addition reactions of organometallic reagents to carbonyl electrophiles are essential transformations in organic synthesis as they provide access to various types of alcohols or carboxylic acids. Among the wide range of organometallics that are easily prepared or readily available through commercial sources organozincs display one of the highest functional group tolerances. In the following paper Knochel provides practical procedures for the synthesis (20 mmol scale) for zinc reagents



that are activated thanks to stoichiometric $MgCl_2$ (*Synthesis*, **2010**, *22*, 3802−3810). The author then shows that the zinc reagents undergo smooth addition reactions to various carbonyl derivatives and carbon dioxide at room temperature without the use of polar cosolvents. The author gives practical scale-up procedures for a wide range of organozincs followed by the trapping with electrophiles. In total 16 examples are cited typically on a 20 mmol scale with yields between 62−99%.

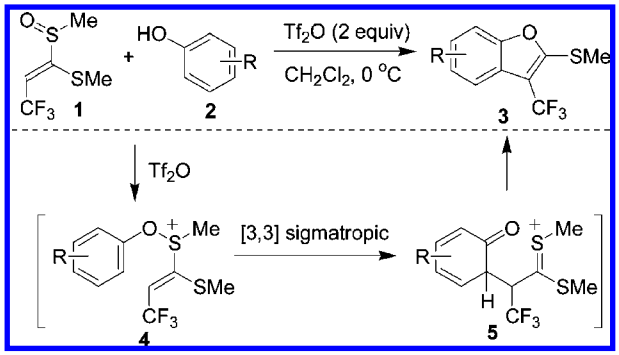
Preparation of *p*-Benzoquinone Monoketals



The halide substituted 1,4-benzoquinone monoketals have been widely used as building blocks in the synthesis of complex natural products, for example (−)-asperpentyn and (+)-ottelione. However, their synthesis is normally performed via electrochemical oxidation or by the use of thallium trinitrate; both of these processes are laborious and require synthesis of highly substituted aromatics. Now Prof. Taylor has shown an approach where commercially available halo phenols are oxidized by phenyliodoso diacetate in methanol to give the desired 1,4-benzoquinone monoketals (*Tetrahedron Lett.* **2010**, *51*, 6619−6621), albeit the yields are from good to average (38−64%) the cost of starting materials and ease of reaction makes this a very attractive approach. Taylor then demonstrates the synthetic utility of these halogen-substituted 1,4-benzoquinones by the short and efficient synthesis of (−)-harveynone, a microspindle formation inhibitor.

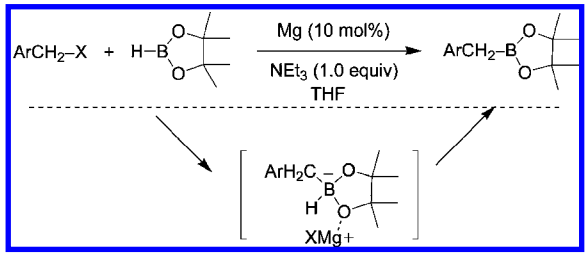
Synthesis of 3-Trifluoromethylbenzo[b]furans by Extended Pummerer Reaction

A report (*J. Am. Chem. Soc.* **2010**, *132*, 11838−11840) describes the synthesis of 2-methylthio-3-trifluoromethylbenzo[*b*]furan derivatives **3** via an extended Pummerer rearrangement. Treatment of a mixture of phenols **2** and 3,3,3-trifluoro-1-methanesulfinyl-1-(methylsulfanyl)propene **1** with trifluoromethanesulfonic anhydride (Tf_2O) in dichloromethane at 0 °C provided trifluoromethyl-substituted dihydrobenzo[*b*]furans **3** in good yields. Investigation of the reaction scope revealed that phenols with electron-withdrawing groups at the para position



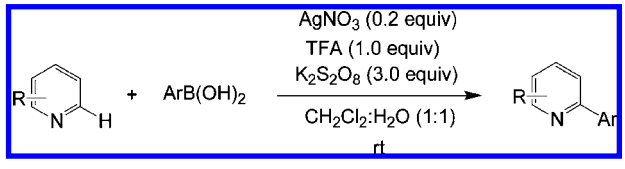
required a relatively high temperature (40 °C); in contrast, *p*-methoxyphenol is not a suitable substrate due to its high reactivity. The meta-substituted phenols gave a mixture of two regioisomers in favor of the sterically less demanding isomer. Although *o*-cresol reacted smoothly, the reaction of 2,6-dimethylphenol afforded a complex reaction mixture. Mechanistically, it was proposed that upon activation of **1** by Tf_2O, a nucleophilic attack by phenols **2** would yield sulfonium intermediates **4** whose subsequent [3,3] sigmatropic rearrangement could form a carbon−carbon bond at the ortho position of the phenols. The following cyclization of **5** would afford the desired dihydrobenzo[*b*]furans **3**.

Magnesium-Catalyzed Coupling of Benzylic Halides with Pinacolborane



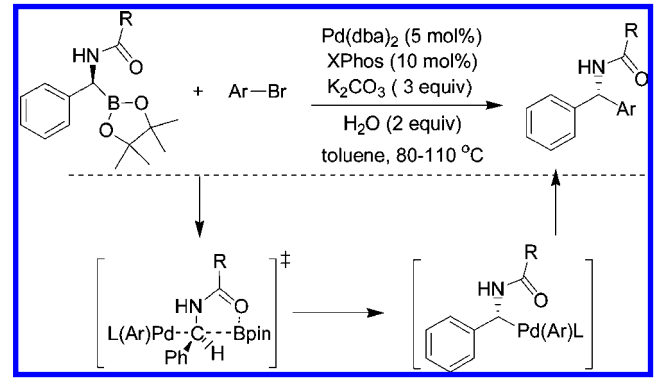
Magnesium-catalyzed reductive coupling between benzyl halides and pinacolborane (HBpin) was realized (*J. Am. Chem. Soc.* **2010**, *132*, 11825−11827). HBpin acts both as an electrophile and as a reducing agent to regenerate an organomagnesium species *in situ*. Among the solvents (THF, diethyl ether, THF-DMF mixtures) and bases (NEt_3, *t*-BuOK, or 2,6-di-*tert*butylpyridine) screened, THF together with triethylamine proved the ideal combination leading to the best product yields. Notably, no benzylic dimers (Wurtz coupling) or benzyl triethylammonium salts were observed and $ArCH_3$ was the only byproduct which was easily removed from the reaction mixture. These catalytic Grignard-type reactions using inexpensive magnesium as catalyst are of particular interest in large-scale syntheses.

Direct C−H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids



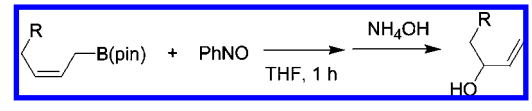
A new synthetic method for C−H arylation of heterocycles with arylboronic acids was developed by Baran and his co-workers at the Scripps Research Institute (*J. Am. Chem. Soc.* **2010**, *132*, 13194−13196). Practically, the reaction was conducted by addition of silver(I) nitrate (0.2 equiv) and $K_2S_2O_8$ (3.0 equiv) to a solution of the heterocycle·TFA salt (1.0 equiv) (generated in situ) and arylboronic acid (1.5 equiv) in CH_2Cl_2/H_2O (1:1, v:v) at room temperature. The reactions occurred regioselectively on the 2- or 4-positions on the heterocycles and bis-addition proved to be minimal. Arylboronic acids bearing electron-rich substitutes are more reactive giving good product yields. The reactions tolerate halogenated arylboronic acids providing handles for further functionalization. This arylation protocol is operationally simple, and presumably involves aryl radicals derived from the arylboronic acids.

Stereospecific Suzuki−Miyaura Coupling Reaction



A useful method for the synthesis of enantioenriched benzylamine derivatives was developed by Ohmura and co-workers in Japan (*J. Am. Chem. Soc.* **2010**, *132*, 13191−13193). Reactions of enantioenriched α-(acetylamino)benzylboronic esters and aryl bromides were carried out in toluene at 110 °C in the presence of $Pd(dba)_2$ (5 mol %), Xphos ligand (10 mol %), K_2CO_3 (3 equiv), and H_2O (2 equiv) as an additive. This highly stereospecific Suzuki-Miyaura cross-coupling reaction proceeds with inversion of configuration. Reactions of various aryl bromides including both electron-rich and electron-deficient took place efficiently to give the corresponding amides in high yields. High es [% es = (product ee/starting material ee) × 100] was achieved with sterically demanding aryl bromides. Analogously, aryl chlorides could also be used for the invertive Suzuki-Miyaura coupling under the optimized conditions. Various boron compounds bearing different acyl group on the nitrogen atom, such as propionyl, benzoyl, or pivaloyl group afforded the corresponding coupling products with high es.

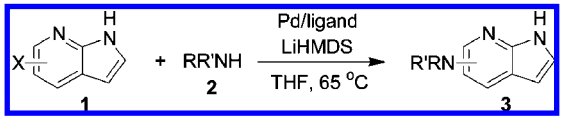
A New Method for the Preparation of Allylic Alcohols



An approach for the synthesis of allylic alcohols by oxidation of pinacol allylboronates in the presence of 3 equiv of nitrosobenzene with concomitant rearrangement

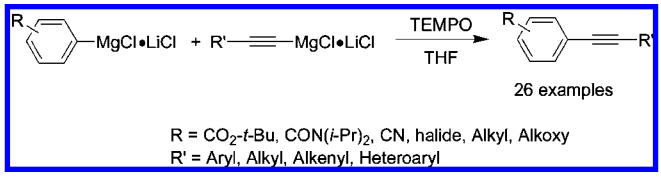
was developed by Morken and his co-workers at Boston College (*Org. Lett.* **2010**, *12*, 3796−3799). This nitrosobenzene-mediated allylboronate oxidation tolerates a number of different substituted allylboronates delivering moderate yields of the secondary allylic alcohols. For example, reactions of the protected oxygen functional groups and steric encumbrance of the allylboronates occurred smoothly leading to the corresponding alcohols in good yields. The drawback of the approach is the use of 3 equiv of nitrosobenzene in order to achieve appreciate product yields.

Palladium-Catalyzed Amination of Unprotected Halo-7-azaindoles



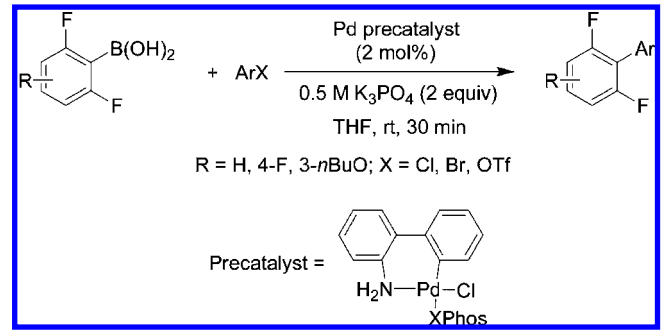
Amino-substituted azaindoles **3** are an important type of compounds which appear in a variety of biologically active molecules. The synthesis of such compounds via cross-coupling of unprotected haloazaindoles **1** with amines can be particularly challenging due to chelating for metals by the two adjacent nitrogens in **1** and the potential for homocoupling between the halide and azaindole *N*-H. Buchwald and co-workers at Massachusetts Institute of Technology developed an efficient method for Pd-catalyzed cross-coupling of amines with haloazaindoles (*Org. Lett.* **2010**, *12*, 4438−4441). Under the reaction conditions (Pd precatalyst/ligand/LiHMDS), haloazaindoles **1** reacted smoothly with amines (alkyl or aryl, primary or secondary) giving the corresponding aminated azainoles in good to excellent yields. The cross-coupling reactions are applicable for both bromo- and chloro-azaindoles. Furthermore, the approach tolerated amines containing a second protic functional group such as phenol, aliphatic alcohol, or more hindered secondary amine by addition of an extra equivalent of LiHMDS.

Transition Metal-Free Sonogashira-Type Coupling Reaction



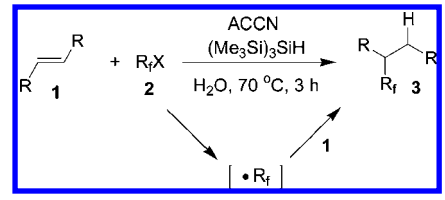
A transition metal-free Sonogashira-type coupling reaction was described by Studer and co-workers in Germany (*Org. Lett.* **2010**, *12*, 3878−3881). In the absence of transition metal, the reaction of aryl or alkenyl Grignard reagents with alkynyl magnesium compounds by using 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as an environmentally benign organic oxidant provided Sonogashira cross-coupling products. This coupling reaction can be performed on various substituted aryl Grignard reagents tolerating functional groups such as esters, amides, and cyanides. Arylalkynyl Grignard reagents bearing either electron-donating or electron-withdrawing substituents at the aryl moiety gave the corresponding cross coupling products in excellent yields and selectivities. Slightly lower yields were obtained for less reactive alkylalkynyl Grignard reagents. It was noticed that the undesired oxidative homocoupling reaction of aryl Grignard reagents could be suppressed by installing substituents at the ortho position of the aryl-Mg derivatives.

A New Palladium Precatalyst for the Fast Suzuki−Miyaura Coupling Reactions



A new palladium precatalyst was developed for the fast Suzuki−Miyaura cross-coupling reactions of polyfluorophenylboronic acids by Buchwald and co-workers (*J. Am. Chem. Soc.* **2010**, *132*, 14073−14075). Generally, Suzuki coupling reactions are performed at elevated temperatures which are problematic for polyfluorophenylboronic acids or five-membered two-heterocyclic boronic acids due to deboronation. The use of palladium precatalyst allows the Suzuki coupling reactions under mild conditions (room temperature or 40 °C) avoiding the deboronating boronic acids. The precatalyst can be easily obtained in a one-pot procedure by combining $Pd(OAc)_2$ with 2-aminobiphenyl, followed by addition of LiCl and the ligand (XPhos). Several aryl halides or pseudohalides are good substrates for the coupling reactions, such as aryl chlorides, bromides, and triflates, while only low conversions were observed with aryl iodides. Substrates with ortho-steric hindrance groups were well tolerated, however, with ortho substituents, such as esters or ketones, could not be coupled efficiently due to competitive coordinations.

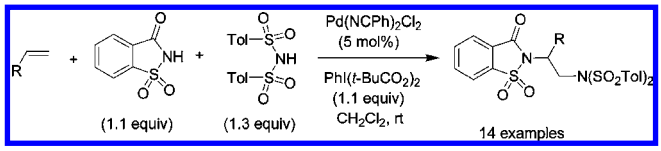
$(TMS)_3SiH$-Mediated Radical Perfluoroalkylations of Olefins in Water



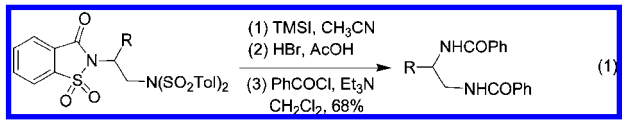
As the synthesis of perfluoroalkyl compounds cannot be achieved through classical nucleophilic substitutions on perfluoroalkyl halides (R_fX), compounds bearing the perfluoroalkyl moiety bond, however, have been synthesized by different routes, such as radical addition to double bonds of olefins. Recently, Postigo and co-worker in Argentina developed a silyl radical-mediated radical perfluoroalkylation reaction of olefins in water (*J. Org. Chem.* **2010**, *75*, 6141−6148). The reactions occurred in the presence of $(Me_3Si)_3SiH$ as the radical mediator and 1,10-azobis(cyclohexanecarbonitrile) (ACCN) as the radical initiator.

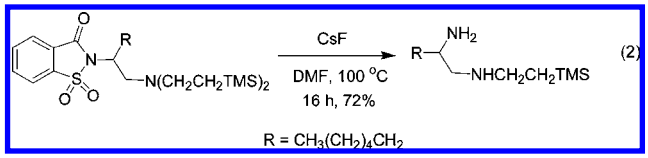
These radical additions are compatible with electron-rich or electron-deficient alkenes to provide the radical addition products in fairly good yields.

Palladium-Catalyzed Diamination of Unactivated Alkenes



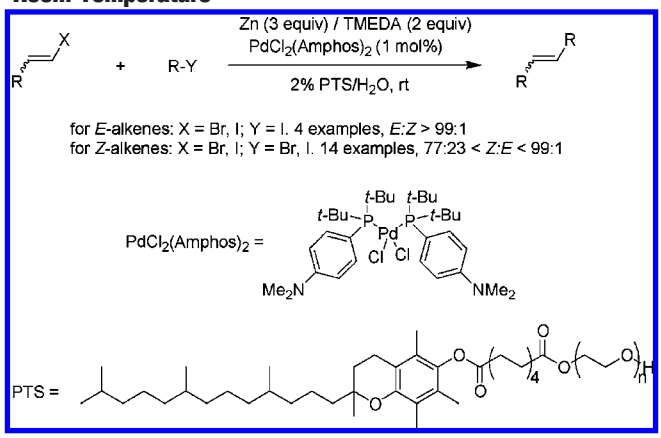
A general method for an intermolecular 1,2-diamination of unactivated alkenes was developed by Muñiz and co-workers in Spain (*Angew. Chem. Int. Ed.* **2010**, *49*, 8109−8111). Under the conditions of the combination of saccharin and bistosylimide as nitrogen sources a series of terminal alkenes was converted into the corresponding diamines. High chemoselectivity and complete regioselectivity were observed for all representative examples. In addition, a number of commonly used functional groups, such as esters, amides, halogenides, azides, and sulfones are tolerated under these reaction conditions.





Further transformations of the aminated products were demonstrated in eqs 1 and 2. The deprotection of the amino groups proceeded under acidic conditions to produce the free diamine which was converted into the corresponding bisbenzoylamide (eq 1). Treatment of the di(trimethylsilylethyl) (TSE) derivative with an excess of cesium fluoride led to 1-(trimethylsilylethyl)octane-1,2-diamine in which one of the TSE groups was selectively removed (eq 2).

Stereoselective Negishi-Like Coupling Reactions in Water at Room Temperature



An environmentally benign Negishi-like coupling reactions were developed by Lipshutz and co-workers at University of California, Santa Barbara (*Org. Lett.* **2010**, *12*, 4742−4744). The reactions were carried out in water at room temperature giving the corresponding cross-coupling products in high yields and with good stereoselectivity. It was claimed that the combination of TMEDA (2 equiv) as an additive, $PdCl_2(Amphos)_2$, amphiphile PTS, and Zn dust is crucial to the success of the couplings. Functional groups such as benzyl ether, ketone, chloride, ester, and trimethylsilyl within the starting halides are tolerated in the reactions with various functionalized *Z*-olefins. When both substrates are unactivated, the "homo halide" pairs such as alkenyl iodide-alkyl iodide and alkenyl bromide-alkyl bromide, led to efficient cross-couplings with anticipated *Z*-stereochemistry. In contrast, the "mixed halide" pairs gave low levels of conversion and/or significant amounts of the alkenyl halide reduction product.

Crystallization from Solutions Containing Multiple Conformers: A New Modeling Approach for Solubility and Supersaturation

Most of the organic compounds of pharmaceutical interest exhibit solubilities that increase with temperature (a rule of thumb proposes doubling of the solubility for every 20° of temperature increase). During certain API crystallization investigations, Bristol Myers Squibb researchers encountered two drug substances for which the solubility either stayed constant, or decreased with temperature increase (Derdour, L.; . *Chem. Eng. Sci.*, **2011**, *66* (1), 88.). Such "retrograde" solubility, documented for a relatively small number of organic compounds, requires the design of atypical crystallization processes. The API's at stake exhibit several conformers, with the highest energy one being the "right" conformer, desired to be preferentially crystallized. The estimated difference in the energy of such conformers is approximately 10 kcal/mol, higher than the previously studied comparable crystallization cases. The "wrong" conformers may act as "impurities" and also reduce the crystallization driving force. The new approach proposed by the BMS scientists takes into account the unique physicochemical properties of such systems, and introduces entities such as ISS (Intrinsic Supersaturation) which is the concentration of the "right" conformer minus the intrinsic solubility; the latter is the saturation concentration of the "right" conformer. The modeling approach discussed was capable to explain unexpected experimental observations such as the slow crystallization at low temperatures (0.5%/h at 20 °C) compared to the faster crystallization occurring at higher temperatures (63%/h at 50 °C). This article has 60 references.

Mixing and Packing of Fine Particles of Different Sizes

A challenge in powder mixing exists when the solids to be mixed are of significantly different sizes; in such cases segregation can occur, leading to poor content uniformity. A team from

the New Jersey Institute of Technology (Lin, H.; et al. *Ind. Eng. Chem. Res.*, in press, DOI: 10.1021/ie1008844) has addressed this issue with two pairs of solids to be mixed effectively without segregation and with suitable (high) packed density of the mixture. The team studied in one case aluminum oxide particles of 300 and 30 μm (the former acting as a surrogate for an explosive compound), and in the other course (2,300 μm) and fine (65 μm) silica aerogel particles. Rather creative solutions were found for each case. For the alumina particles, a sequence of adding and removing moisture solved the problem. For the aerogel particles, vacuum with either sound waves, or vibration (in a vertical tube) accomplished the mixing objectives. Unfortunately each such method worked very well only for the solids at stake; neither method is considered to be of general applicability.

Solid-State Interactions of a Drug Substance and Excipients and Their Impact on Tablet Dissolution: A Thermal−Mechanical Facilitated Process-Induced Transformation or PIT

Drug product development is often more challenging than drug substance development because excipients science is much less developed than active pharmaceutical ingredients science. Prior experience is often invoked when certain excipients are used to design formulations. During formulation optimization for drug "Z", Bristol Myers Squibb scientists working with Prof. K. Morris (University of Hawaii) have discovered that when stearic acid is used to reduce stickiness, tablet dissolution was negatively impacted under certain manufacturing conditions (Wang, J.; et al. *J. Pharm. Sci.*, **2010**, *99 (9), 3849.).* A very thorough investigation was conducted in order to develop suitable process understanding for the development of this drug product. The team learned that there are two forms for drug "Z", form I, and form II; form I is anhydrous, with a defined crystal structure, whereas form II is actually a mixture of hydrates. The desired solubility is provided by a formula containing a mixture of the 2 forms. Depending on the form, when stearic acid is used, premixing shear and drying temperature during wet granulation can impact tablet dissolution behavior. Understanding such process induced transformations (PIT) and their relationship with the proposed design space is an important QbD element.

Mark McLaughlin
Merck & Co. Inc., Rahway, New Jersey 07065, U.S.A.
E-mail: mark_mclaughlin@merck.com

Ian Wilson
Almac Sciences, Craigavon, Northern Ireland, BT63 5QD, U.K.
E-mail: ian.wilson@almacgroup.com

Patrick Delaney
Peakdale Molecular Ltd., Peakdale Science Park, Sheffield Road, Chapel-en-le-Firth, High Peak SK23 0PG, U.K.
E-mail: patrick.delaney@peakdale.co.uk

Wenyi Zhao
Jacobus Pharmaceutical Company, Inc., P.O. Box 5290, Princeton, New Jersey 08540, U.S.A. E-mail: Wenyi38@hotmail.com

Trevor Laird*
Editor

Andrei Zlota
The Zlota Company, LLC 15, Fairbanks Road, Sharon, Massachusetts 02067-2858, U.S.A. E-mail: andrei.zlota@thezlotacompany.com

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