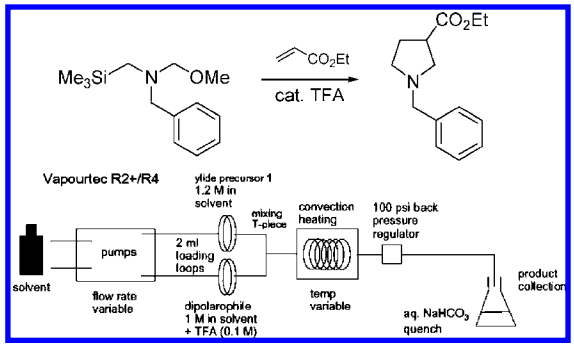
Organic Process Research & Development **2010,** *14,* 300–310

Highlights from the Literature

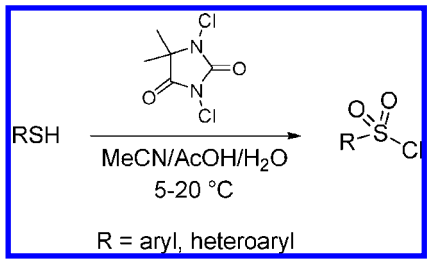
Some Items of Interest to Process R&D Chemists and Engineers

[3 + 2] Dipolar Cycloadditions in Flow Reactors



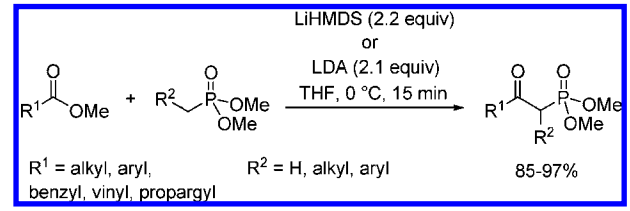
The [3 + 2] dipolar cycloaddition of unstabilized azomethine ylides can be used to construct susbstituted pyrrolidines, which can be useful building blocks in pharmaceutical and natural product synthesis. A common experimental procedure involves in situ generation of the intermediate ylide in the presence of the dipolarophile; however, this technique can produce a significant exotherm when reactive dipolarophiles (e.g., acrylates, maleimides) are employed. Now Fray and co-workers at Pfizer describe efforts to conduct this chemistry using continuous flow technology, which is often beneficial when applied to systems involving highly energetic intermediates (*Tetrahedron Lett.* **2010**, *51*, 1026−1029). The authors provide a description and schematic for the flow apparatus used and optimized the system for flow-rate/residence time, temperature, and pressure. It was found that the residence times could be reduced to 15 min if a higher operating temperature (100 °C) was used. The best conditions were then applied to a series of substrates, but it was determined that differences in reactivity required adjustment of parameters to achieve optimal results. For comparison, the authors also conducted the reaction in typical batch mode and found the yield to be higher. Nonetheless, the flow process was demonstrated to be capable of processing 30 g substrate within 1 h of operation (87% isolated yield after chromatography).

Synthesis of Arenesulfonyl Chlorides via Oxidative Chlorination



Aryl and heteroarylsulfonyl chlorides are an important class of compounds primarily used in the preparation of sulfonamides. Sulfonamide motifs are prevalent in a variety of biologically active compounds with a broad range of biological and pharmaceutical activities. Pu and co-workers at Abbott report that 2,4-dichloro-5,5-dimethylhydantoin (DCDMH) is a mild and efficient reagent for the direct oxidative conversion of sulfur compounds to the corresponding arenesulfonyl chlorides via oxidative chlorination (*Tetrahedron Lett.* **2010**, *51*, 418−421). The method is suitable for many types of sulfur substrates (thiols, disulfides, or benzylic sulfides). The overall process is simple and practical, and it provides convenient access to a variety of aryl or heteroarylsulfonyl chlorides. The mild reaction conditions and the broad substrate scope render this method attractive and complementary to existing syntheses of aryl or heteroarylsulfonyl chlorides.

Synthesis of β-Ketophosphonates



β-Ketophosphonates are versatile intermediates for the synthesis of α,β-unsaturated carbonyl compounds via the Horner−Wadsworth−Emmons (HWEs) reaction. Two related reports from Millburn and co-workers at Amgen (*Tetrahedron Lett.* **2009**, *50*, 870−872) and from Maloney and co-workers at Merck (*J. Org. Chem.* **2009**, *74*, 7574−7576) describe practical, non-cryogenic procedures for the synthesis of β-ketophosphonates. Researchers at Amgen developed a procedure (employing LiHMDS as the base) that is applicable to various aryl and heteroaryl esters substrates. Additionally, the Amgen researchers point out that in many cases the lithio-ketophosphonates may be isolated directly to give stable, non-hygroscopic salts, which have been successfully used directly in subsequent HWE reactions with aldehydes. Alternatively, researchers at Merck developed a procedure (using LDA as the base) that extends the reaction conditions to the use of aliphatic ester substrates that bear relatively acidic α-protons in a mild, non-cryogenic procedure for the synthesis of β-ketophosphonates. Combined, these reports feature around 20 examples of this reaction.

Synthesis of a Prostaglandin E Synthase-1 Inhibitor

Selective inhibitors of prostaglandin E synthase-1 are of interest due to their potential as anti-inflammatory agents for use in the treatment of osteoarthritis, rheumatoid arthritis, and other conditions of chronic pain. Gosselin and co-workers at

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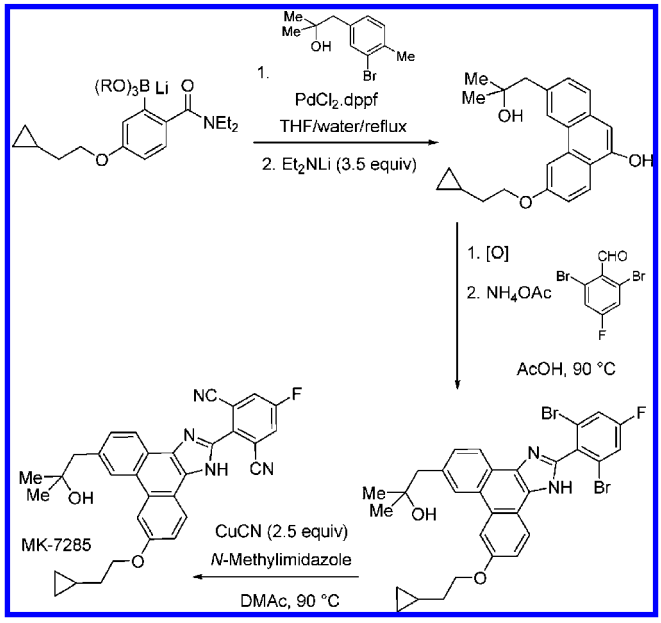
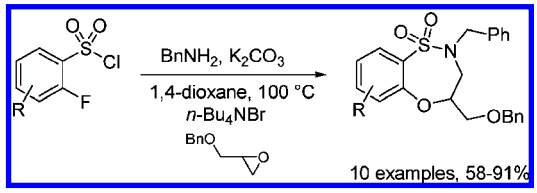


Merck report on the synthesis of MK-7285, a preclinical drug candidate in this therapeutic area (*J. Org. Chem.* **2009**, *74*, 7790−7797). The route features a convergent assembly of the core phenanthrene unit via amide-directed ortho metalation and proximity-induced anionic cyclization, followed by imidazole synthesis and late-stage double cyanation. A total of 12 synthetic steps were involved, with 8 steps in the longest linear sequence starting from 3-bromo-4-methylaniline. Multikilogram-scale experimental details are provided.

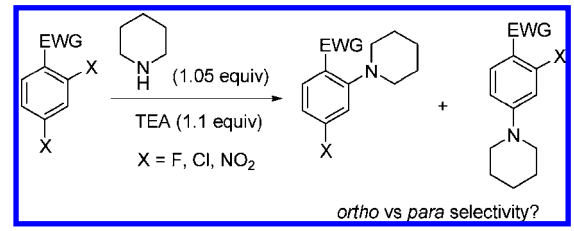
One-Pot Synthesis of Benzoxathiazepine-1,1-dioxides



Benzo-fused rings are prevalent in pharmacologically active drugs. In particular, benzoxathiazepines have generated interest as potential treatments for hypertensive disorders as well as diabetes. Multicomponent reactions (MCRs) can have distinct advantages over stepwise processes, particularly with respect to minimization of purification steps and overall efficiency. Cleator and co-workers at Merck describe their application of the MCR concept to the rapid construction of benzoxathiazepine-1,1-dioxides (*Tetrahedron Lett.* **2010**, *51*, 1079−1082). Starting from 2-fluorobenzenesulfonyl chlorides, a one-pot reaction involving treatment with benzylamine, an epoxide, and potassium carbonate in DMF ultimately leads to the desired benzo-fused heterocycles in yields ranging from 58 to 91% for the 10 examples shown. Additional halogens on the arene ring were subsequently used for structural elaboration via metal-catalyzed cross-coupling reactions.

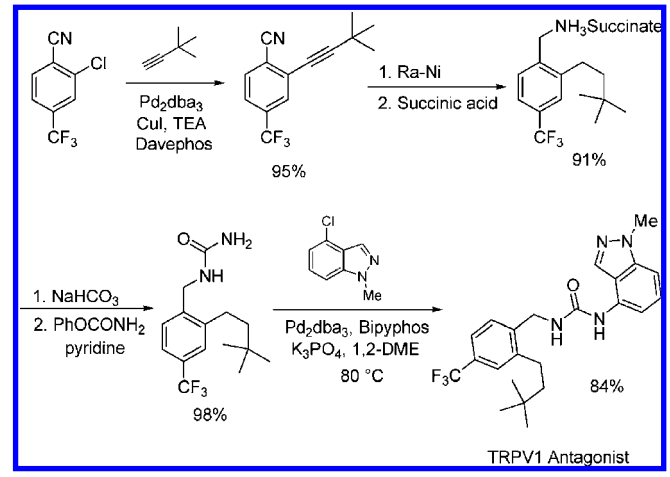
Ortho-Selectivity in S_NAr Reactions of 2,4-Dihalogenated Arenes

A broad survey of S_NAr reactions between piperidine and aromatic compounds with halogens positioned both ortho and



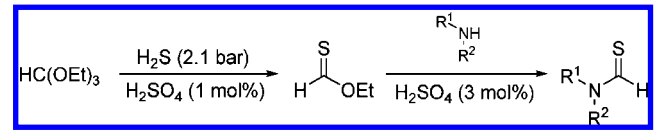
para to activating groups is reported by Wendt and co-workers at Abbott (*Tetrahedron Lett.* **2010**, *51*, 641−644). Regioselectivities varied with the substituent group and the polarity of the solvent. Many activating groups exhibited an overall bias toward ortho substitution, and this led in non-polar solvents to very high ortho selectivity. More polar solvents uniformly shifted the product ratio toward para substitution. Evidence is presented that argues for coordination via hydrogen bonding as a driver of much of the ortho selectivity observed. The data presented show ample evidence of the generality and synthetic utility of the ortho-directing ability of several common activating groups for this reaction type.

Synthesis of a TRPV1 Receptor Antagonist



TRPV1 Receptor antagonists represent a non-NSAID, non-opiate approach for pain management with reduced potential for substance abuse. Yu and co-workers at Abbott describe their efforts to develop a scalable synthesis of a drug candidate in this therapeutic area (*J. Org. Chem.* **2009**, *74*, 9539−9542). The synthesis involves a C−N bond-forming reaction between a non-symmetric *N*-benzylurea and a 4-chloroindazole with readily available non-proprietary Bipyphos as the ligand as well as a high-yielding Sonogashira coupling of an aryl chloride.

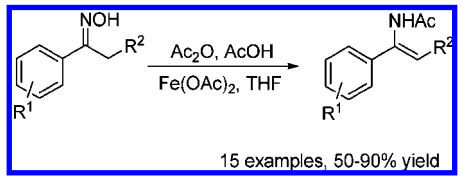
Synthesis of *O*-Ethyl Thioformate and Thioformylation of Amines



O-Ethyl thioformate is an effective reagent for the preparation of thioformamides, which themselves are synthetically useful intermediates in organic synthesis. Existing procedures for the synthesis of *O*-ethyl thioformate are inefficient and/or

potentially hazardous. Now Borths, Chan, and co-workers at Amgen have developed a more practical procedure that allows safe generation of this reagent on preparative scale (*Synlett* **2009**, 3139−3142). Key modifications include replacing perchloric acid with sulfuric acid and conducting the reaction under a positive pressure (2.1 bar) of hydrogen sulfide to ensure high conversion. The product can be isolated as a neat liquid in 83% overall yield or stored as a 40 wt % solution in ethanol. Both the crude ethanol solution and purified *O*-ethyl thioformate can be used to thioformylate a variety of amines in good to excellent yields.

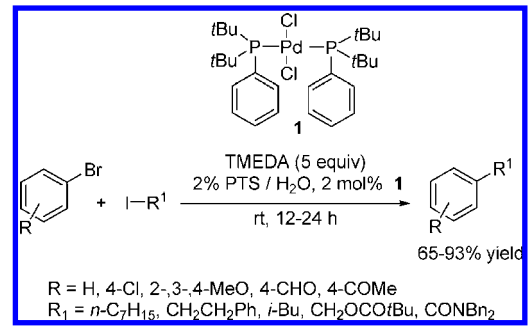
Synthesis of *N*-Acetyl Enamides



Tang and co-workers at Boehringer Ingelheim report on a practical method for the synthesis of *N*-acetyl α-arylenamides (*J. Org. Chem.* **2009**, *74*, 9528−9530). Using easily derived ketoximes as the starting materials, treatment with ferrous acetate as the reducing reagent leads to intermediate enamines that are acylated in situ by acetyl chloride. Compared to the traditional method with iron metal as the reducing reagent, the new method provides milder reaction conditions, simpler purification procedures, and higher yields for a variety of *N*-acetyl α-arylenamides. The mild reaction profile is amenable for scale-up activities, which would facilitate the industrial application of asymmetric hydrogenation of *N*-acetyl α-arylenamides for chiral amine syntheses.

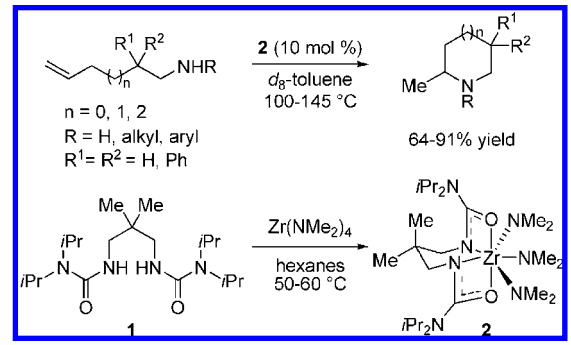
No Preformed Organozinc Required: Aqueous Micellar Catalysis

Krasovski, Duplais, and Lipschutz recently utilized homogeneous micellar technology to conduct Pd-catalyzed, Zn-mediated cross-couplings in water at room temperature (*J. Am. Chem. Soc.* **2009**, *131*, 15592−15593). The technology takes advantage of catalytic nanoreactors spontaneously formed upon dissolution in water of the commercially available amphiphile PTS and does not require the preformation of stoichiometric amounts of the organometallic species RZnI. Cross-coupling of a variety of aryl bromides with primary alkyl iodides takes place at room temperature in the presence of excess TMEDA, without formation of homocoupling byproducts. The diamine may play a dual role: the activation of the Zn surface towards insertion into an alkyl halide, and stabilization of the organozinc species. Substituents on the aryl bromides (aldehydes, ketones) or the alkyl halides (esters, amides) tolerated the standard conditions (TMEDA, 2% PTS/H_2O, 2 mol % L_nPd **1**). The rate of formation of the RZnI·diamine complex on the Zn surface was faster for secondary iodides (i.e., cyclohexyl) than for their bromide counterparts. Interestingly, the rate of this step was amenable to modulation by using bulkier amines such as TEEDA.

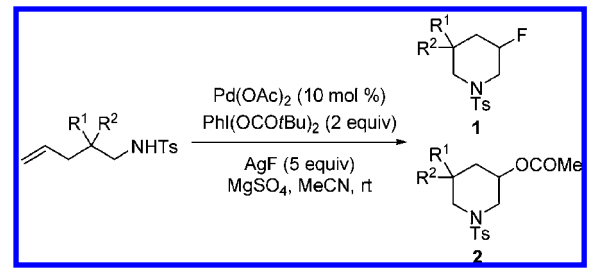


Intramolecular Amination and Aminofluorination of Unactivated Alkenes

In *J. Am. Chem. Soc.* **2009**, *131*, 18246−18247, Schafer and co-workers report the use of a tethered ureate ligand to support a Zr precatalyst with excellent activity for the intramolecular hydroamination of alkenes. The urea proligand **1,** which incorporates σ-electron-withdrawing substituents that make the metal center more electropositive, generates the most active catalyst for the conversion of primary and secondary amino alkenes. Precatalyst **2** can be prepared in multigram scale from readily available materials, and was effective for the hydroamination of alkenes that do not have *gem*-substituents and in the unprecedented formation of azepanes. The precatalyst is chemoselective and effective in the presence of acid-sensitive protected catechol, pyrrole, and tertiary anilines.

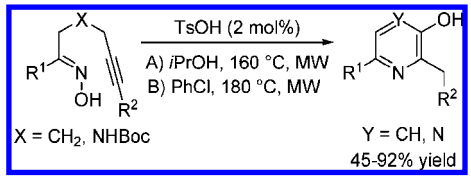


Scientists at the Shanghai institute of Organic Chemistry disclosed a highly regioselective Pd-catalyzed intramolecular aminofluorination of alkenes using AgF as the fluorinating agent in the presence of $PhI(OPiv)_2$ (*J. Am. Chem. Soc.* **2009**, *131*, 16354−16355). The transformation provides direct access to valuable fluoropiperidines **1**, but also generates small amounts of the aminocarboxylated side product **2**. $Pd(OAc)_2$ emerged as the most effective catalyst. Aminofluorination products were not observed in the absence of Iodine(III) oxidants nor using other oxidants such as oxone, NCS, and H_2O_2. Tosyl amines converted in larger extents than nosyl amines, whereas Boc-protected amines failed to react. In all cases, the addition of $MgSO_4$ increased the reaction yields by 10%.



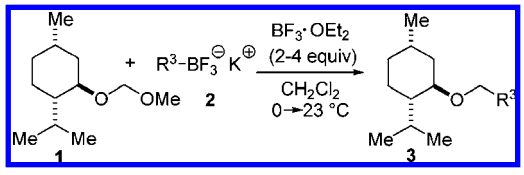
Synthesis of Pyridines and Pyrazines by Intramolecular Hydroamination

Hydroamination routes to aromatic nitrogen heterocycles are rare. Therefore, the recent findings that pyridines and pyrazines can be obtained via an acid-catalyzed hydroamination/isomerization/aromatization sequence from acyclic alkynyl oxime precursors (*Angew. Chem., Int. Ed.* **2009**, *48*, 8325−8327) are energizing. Whereas several N-containing substrates could provide the required oxidation state (e.g., NOH, NSO_2Ar, NNR_2), oxime precursors were selected since the only byproduct of the reaction would be H_2O. The optimized sets of conditions (A and B, see below) included the use of catalytic TsOH in a Biotage microwave reactor at high temperatures (160−180 °C). The procedure proved applicable to a variety of aldoximes and ketoximes, and alkynes bearing ester and amide moieties on their terminal position. It also allowed access to various bicyclic ring systems as well as pyrazine derivatives by in situ removal of the Boc protecting group.



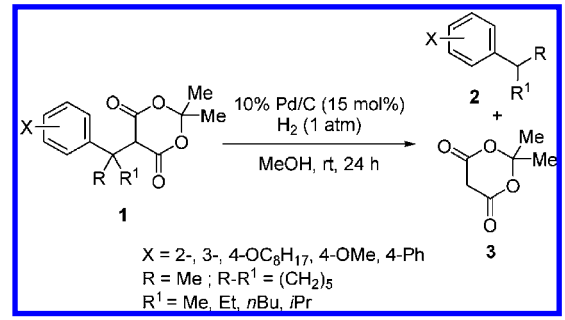
C−O Bond Formation No More: Synthesis of Dialkyl Ethers by C−C Bond Formation

In seeking a general approach to ether construction from readily available starting materials, Mitchell and Bode identified a versatile C−C formation via cross-coupling of potassium organotrifluoroborates and acetals (*J. Am. Chem. Soc.* **2009**, *131*, 18057−18059). (−)-Menthol-MOM (**1**) was treated with a variety of potassium organotrifluoroborates **2** in the presence of $BF_3{\cdot}OEt_2$ (CH_2Cl_2, 0 °C→rt) to provide the desired ethers **3** in moderate to good yields. In the case of alkynyl-, allyl-, and alkenyltrifluoroborates, it was necessary to premix **2** with the Lewis acid prior to the addition of the acetal. Primary, secondary, and tertiary MOM-protected alcohols gave the desired products under these conditions. Several of the products obtained (i.e., from bromo-substituted acetals) would have been challenging to prepare by Williamson's classic approach. Secondary kinetic isotope effects indicated that the sp^3 to sp^2 hybridization change (oxocarbenium formation) was the rate-limiting step.



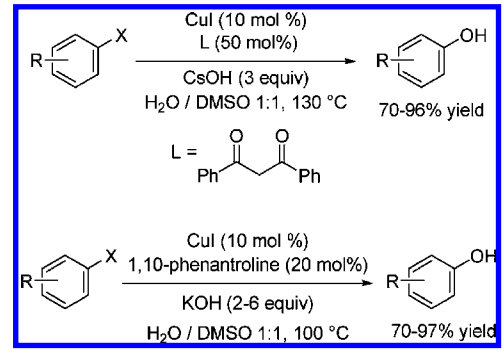
Hydrogenolysis of Unstrained Carbon−Carbon σ Bonds

Whereas the hydrogenolysis of C=Z bonds (Z = N, O, S, halogen) is an integral part of the synthetic chemist toolbox, the hydrogenolysis of C−C bonds under mild conditions remains unprecedented. In the course of preparing a series of Meldrum's acids **1**, Fillon and co-workers discovered that their exposure to Pd/C in the presence of H_2 induced the C−C σ bond scission with release of the corresponding aromatic rings **2** and Meldrum's acids **3** (*J. Am. Chem. Soc.* **2009**, *131*, 15606−15607). Para- and ortho substrates underwent facile hydrogenation in comparison with their meta analogues. Moreover, crowding the quaternary benzylic center (R_1 = *i*Pr) resulted in modest conversions. Both the solvent and the H_2 gas transfer H atoms during the reaction: the use of D_2 and D_3OD led to full deuterium incorporation at the benzylic position, whereas the use of D_2 or D_3OD led to partial incorporation. Hydrogenolysis of enantioenriched Meldrum's acids took place with complete inversion of configuration, supporting an S_N2 mechanism. In the C−C scission process, the Meldrum's acid moiety is displaced by either a Pd hydride or Pd(0) to yield a benzylic organopalladium intermediate that undergoes protonation by MeOH (see mechanism proposed for hydrogenation of benzylic nitro groups by Carreira and co-workers in *Angew. Chem., Int. Ed.* **2007**, *46*, 2078−2081).



Synthesis of Phenols Using Copper Iodide

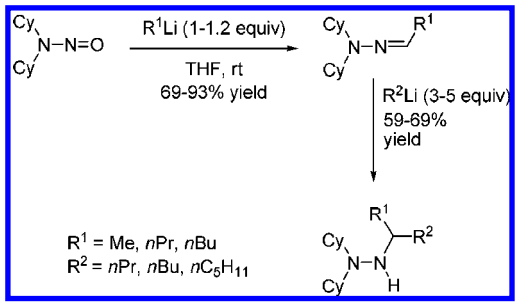
Their manuscripts separated by mere pages, two groups report the direct Cu-mediated coupling of aryl halides with hydroxides to yield phenols. The group of Taillefer selected diketone **L** as the Cu ligand and CsOH as the source of hydroxyl group to promote the hydroxylation (*Angew. Chem., Int. Ed.* **2009**, *48*, 8725−8728), whereas Your and co-workers chose 1,10-phenanthroline and KOH (*Angew. Chem, Int. Ed.* **2009**, *48*, 9318−9321). Various phenol derivatives were obtained from both non-activated and activated aryl iodides as well as aryl bromides bearing electron-withdrawing groups. The mild reaction conditions (DMSO/water, 100 or 130 °C) were compatible with a variety of functional groups, which could be further elaborated. In the latter manuscript, alkyl halides were converted into alkyl aryl ethers, and 2-iodoaryl alkynes were transformed into benzofuranes using the one-pot phenoxide-alkylation protocol.



Synthesis of Trialkylhydrazines

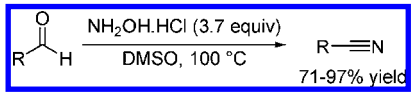
The addition of organolithiums to *N*,*N*-dialkyl *N*-nitrosamines was recently developed for the synthesis of substituted

hydrazones and trialkyl hydrazines by the group of Sbarbati Nudelman at the Universidad de Buenos Aires, Argentina (*Synth. Commun.* **2009**, *39*, 3958−3972). The reaction outcome is determined by the RLi/nitrosamine ratio. Using 1−1.2 equiv RLi, an almost quantitative conversion to *N*-alkylidene hydrazines occurs, whereas using 3−5 equiv RLi leads to a second addition that gives branched trialkyl hydrazines with variable amounts of the intermediate alkylidene hydrazines. Since the addition to the N═C bond is slower than that to the N═O bond, the one-pot procedure can use two different alkyllithiums ($R^1 \neq R^2$) and quickly provide a wide array of trialkyl hydrazines in good yields (59−69%, 2 h rt).

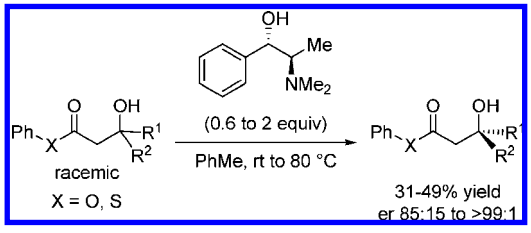


One-Pot Conversion of Aldehydes to Nitriles

Chill and Mebane recently reported a one-pot synthesis of nitriles starting from aldehydes using hydroxylamine hydrochloride in DMSO at 100 °C (*Synth. Commun.* **2009**, *39*, 3601−3606). Aldoximes were prepared by reacting aromatic or aliphatic aldehydes with hydroxylamine hydrochloride. These were dehydrated *in situ* using DMSO at high temperatures to yield the corresponding nitriles after conventional aqueous workup.



Kinetic Resolution of Quaternary and Tertiary β-Hydroxy Esters

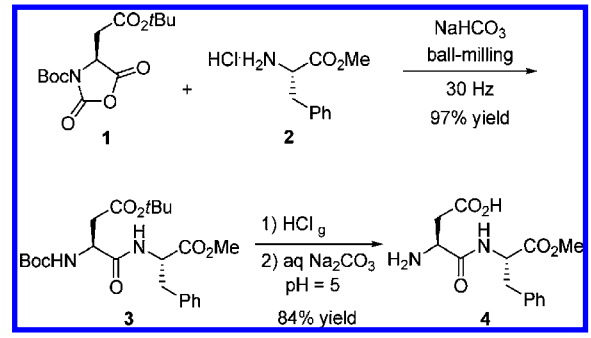


Schipper, Rousseaux, and Fagnou disclosed the unique reactivity and selectivity of (1*S*,2*R*)-*N*-methylephedrine in the resolution of tertiary alcohols arising from ketone aldol reactions (*Angew. Chem., Int. Ed.* **2009**, *48*, 8343−8347). Even though the tertiary stereogenic center is three atoms removed from the reactive site, high selectivities are obtained with *s* factors >20 in many instances. Presence of a base is key to enhance the reactivity of the alcohol nucleophile through hydrogen-bonding interactions, a property further enhanced when the alcohol and the amine are tethered, such as in (1*S*,2*R*)-*N*-methylephedrine. In addition, the β-hydroxy moiety plays a pivotal role establishing high reactivities and selectivities. The reaction is performed in toluene without exclusion of air or moisture, and its progress can be monitored by chiral HPLC.

Solvent-Free Synthesis of Peptides

In spite of the well-established procedures for the preparation of peptides, both stepwise synthesis in solution and solid-phase synthesis are tainted by the large amount of solvents required. The group of Prof. Lamaty at the University of Montpellier (France) described a streamlined process for the synthesis of peptides using ball-milling technology without the use of solvents (*Angew. Chem., Int. Ed.* **2009**, *48*, 9318−9321).

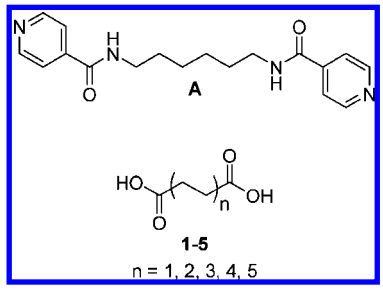
Coupling of urethane-protected α-amino acid *N*-carboxyanhydride derivatives (UNCA, **1**) with α-amino acids, amides, or esters was carried in the presence of $NaHCO_3$ (1.5 equiv) in a hardened-steel vessel with steel balls agitated for 1 h at a frequency of 30 Hz. After analysis, the reaction mixture was recovered directly from the milling jar, washed with water to remove the inorganic salts, and dried to provide the clean dipeptide. It is paramount for this technology that all components remain solid, since the adequate physicochemical state is required to obtain good yields. In-process analysis was performed using two solid-state IR and solid-state cross-polarization magic angle spinning ^{13}C NMR, whereas chiral HPLC was used to check for potential epimerization (nondetected). The authors applied this methodology to the preparation of the dipeptide aspartame (**4**, 82% overall yield) by coupling Boc-Asp(O*t*Bu)-NCA **1** and HCl·H-Phe-OMe, followed by the removal of the acid-labile protecting groups and pH adjustment.



Cocrystals as Tools to Modulate Physical Properties of APIs

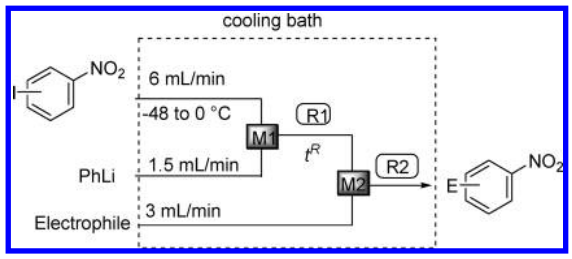
In cocrystals, two or more molecular compounds may exist within the same crystalline lattice in specific stoichiometric amounts. In *J. Am. Chem. Soc.* **2009**, *131*, 11316−11317) Aackeröy and co-workers studied a series of cocrystals of hexamethylenbisacetamide **A**, an homologue of the FDA-accepted diacids **1**−**5** that prevents the proliferation of lung cancer cells. Single-crystal X-ray diffraction showed that the cocrystals **A1**−**A5** are isostructural, with larger cell volumes reflecting the larger size of the cocrystallizing agent. The cocrystal of **A** and diacid **1** shows a primary O−H---N interaction between the carboxylic acid and the pyridine moiety, resulting in chains organized into layers via interchain N−H---O hydrogen bonds. Similar discrete structures were obtained for longer diacids. The melting points of the cocrystals **A1**−**A5** were directly related to the ones of the dicarboxylic acids; therefore, the melting point of the API can be modulated over a 144−188 °C range, with the API itself featuring a melting point of 181−182 °C. Most notably, the solubility of **A** can be

enhanced by a factor of 2.5 without altering the structure of the API. The trend, albeit not linear, can be rationalized on the basis of the properties of the dicarboxylic acids, with the longer-chain (and less polar) diacid cocrystals being less soluble than the API itself. By exerting control over the supramolecular assembly and incorporating an API within a series of structurally consistent crystalline solids, it would be possible to fine-tune its melting point and aqueous solubility.



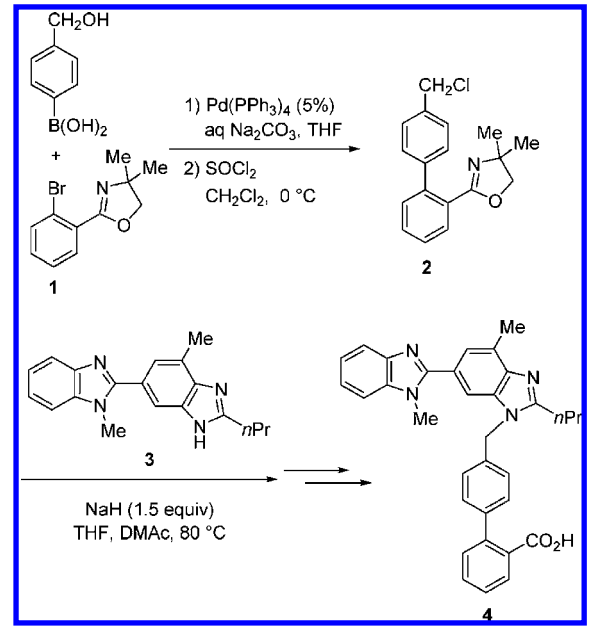
Microreactors: Synthesis of Nitro-Substituted Aryl Lithium Compounds

The nitro group reacts very rapidly with organolithium reagents, challenging the generation of nitroaryllithium compounds. The use of a microflow system allowed a team at Kyoto University to generate and transform *o*-, *m*-, and *p*-nitro-substituted aryllithiums in a controlled manner (*Angew. Chem., Int. Ed.* **2009**, *48*, 8063−8065). Furthermore, either the kinetically or thermodynamically preferred aryllithium could be selectively used through control of the residence time. The I/Li exchange of *o*-, *p*-, and *m*-iodonitrobenzenes was examined in a microflow system consisting of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) varying the temperatures of the cooling bath and residence times (t^R) in R1 (= 0.01 to 10 s). Alkyllithiums were trapped with MeOH in R2. Irrespective of the substitution pattern, the products formed in good yields (>80%) at 0 or −28 °C at t^R 0.01 s. Contour maps provided optimal conditions for the I/Li exchange of each iodonitrobenzene, which reacted with different electrophiles (MeI, Me_3SiCl, MeSiOTf, PhCHO, and ROH) with acceptable yields (44−93%).



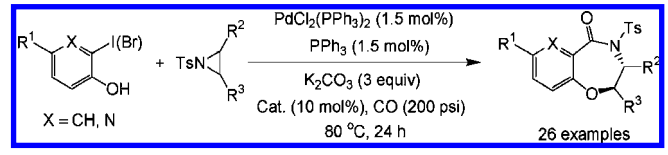
Synthesis of Telmisartan

Telmisartan (**4**, Micardis, Boeringher Ingelheim) is an angiotensin II receptor antagonist used as an antihypertensive. Scientists at the Sardar Vallabhbhai National Institute of Technology (India) reported a synthetic process suitable for scale-up (*Synth. Commun.* **2009**, *39*, 4149−4157). The key intermediate **2** was prepared by Suzuki coupling of 4-(hydroxymethyl)phenylboronic acid and bromophenyl oxazoline **1**, followed by chlorination with $SOCl_2$ (95% overall yield). Condensation with dibenzimidazole derivative **3** followed by hydrolysis and crystallization provided the desired API in good yield.



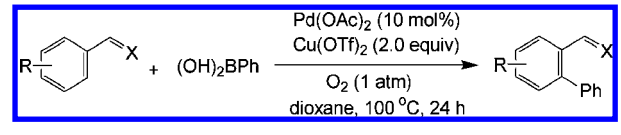
One-Pot Synthesis of 1,4-Benzo- and Pyrido-oxazepinones

Domino reactions have attracted significant attention by many organic chemists due to the fact that they can improve synthetic efficiency, avoid the separation of intermediates, and reduce the amount of waste. A one-pot protocol for the preparation of 1,4-benzo- and pyrido-oxazepinones was developed by the group of Alper at the University of Ottawa (*Org. Lett.* **2010**, *12*, 192−195). The synthesis involves a domino ring-opening/carboxamidation reaction of *N*-tosylaziridines and 2-halophenols/pyridinol under phase-transfer conditions.



Pd-Catalyzed C−H bond Activation

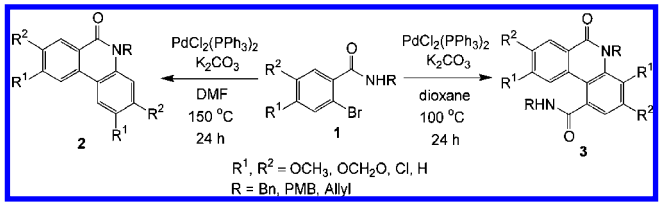
Cross-coupling of arylboronic acid with aromatic compounds via direct C−H activation is one of the challenging tasks for organic chemists. Shi's group at Peking University in China has developed a synthetic method to construct ortho arylated aryl aldoximes and ketoximes via Pd(II)-catalyzed cross-coupling of *O*-methyl oximes with arylboronic acids (*Org. Lett.* **2010**, *12*, 184−187). This reaction occurred through palladium(II)-catalyzed C−H activation in the presence of Cu(II) species and oxygen as co-oxidant.



Pd-Mediated Biaryl Coupling Reactions

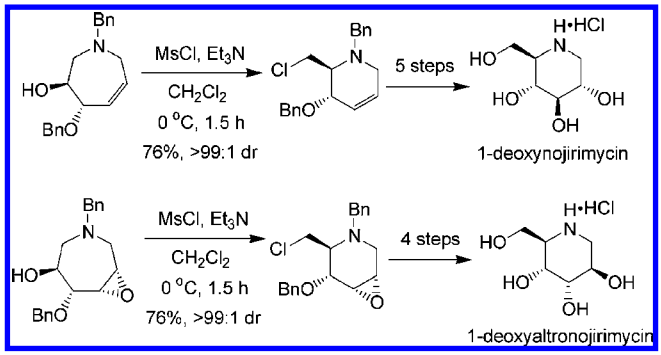
It was found by Porée and co-workers (*Org. Lett.* **2010**, *12*, 156−158) that a one-step Pd-catalyzed reaction of an *O*-bromobenzamide allowed the selective formation of either

phenanthridinones **2** or phenanthridinone-1-carboxamides **3** via a common aryl−aryl Pd(II) intermediate. A direct correlation between the solvent polarity and the carbonate base on the selectivity has been observed. Depending on the reaction condition, this intermediate can go through either an ipso substitution to lead to **2** or *N*-arylation to **3**.



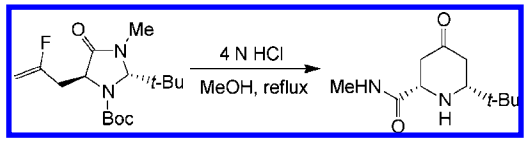
Ring Contraction of Tetrahydroazepine and Azepane

A team of scientists from the University of Oxford and Pfizer in the U.K. developed a practical ring contraction protocol to access the key intermediates in the synthesis of 1-deoxynojirimycin and 1-deoxyaltronojirimycin (*Org. Lett.* **2010**, *12*, 136−139). Treatment of azepane or tetrahydroazepine with MsCl promoted ring contraction to give piperidine or tetrahydropyridine, respectively in good yields.



Ring Expansion of 4-Oxoimidazolidine

Under acid conditions, Haufe and co-workers in Germany demonstrated that *tert*-butyl (2*S*,5*S*)-2-*tert*-butyl-5-(2-fluoroallyl)-3-methyl-4-oxoimidazolidine-1-carboxylate underwent ring-expansion rearrangement leading to pipecolic acid derivative (*J. Org. Chem.* **2010**, *75*, 222−225). Interestingly, vinylchloro and vinylbromo groups do not show such transformation under the same conditions. Thus, the vinylfluoro group can be utilized as an acetonyl cation equivalent under acidic conditions.

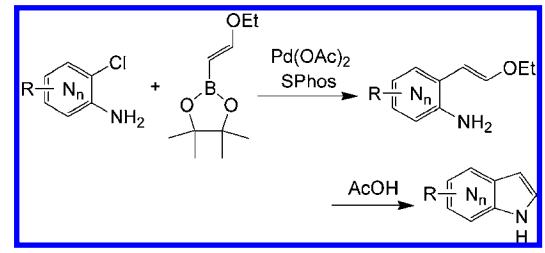


Synthesis of Aza- and Diazaindoles

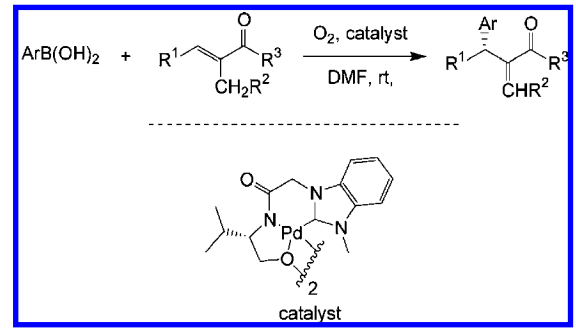
An efficient two-step protocol to access a broad range of aza- and diazaindoles was established by Hoelder's group in the U.K. (*J. Org. Chem.* **2010**, *75*, 11−15). The feature of the method includes an optimized Suzuki−Miyaura coupling of chloroamino-*N*-heterocycles with (2-ethoxyvinyl)borolane, without the need for protecting groups.

Asymmetric Intermolecular Heck-Type Reactions

Jung's group at University of Southern California revealed asymmetric Heck-type reactions of aryl boronic acids with both

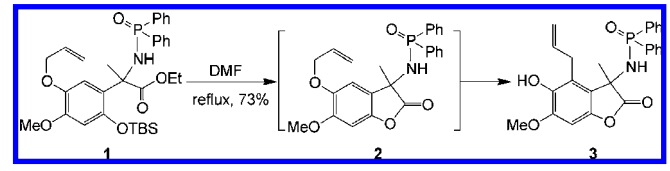


acyclic and cyclic alkenes (*J. Org. Chem.* **2010**, *75*, 95−101). In the presence of chiral dimeric tridentate NHC-amidate-alkoxide palladium(II) complexes, the Heck-type coupling reaction was effected at room temperature to afford the corresponding coupling products with high enantioselectivities. The high degree of enantioselection was due to the influence from bulky substituents of the alkene substrates and the "counter axial groups" of the palladium(II) catalysts.

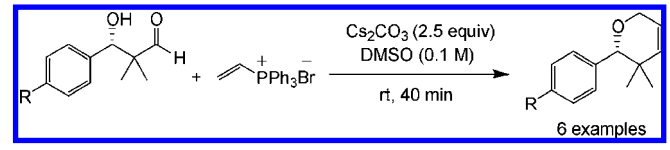


Tandem Lactonization−Claisen Rearrangement

A one-pot process in the synthesis of (±)-methoxyfumimycin, a potential new bacterial peptide deformylase (PDF) inhibitor, is reported by Bräse and co-workers (*J. Org. Chem.* **2010**, *75*, 229−232). Heating of **1** in dry DMF at 120 °C first led to the formation of the lactone ring **2**. Further heating of the lactone **2** at 153 °C finally led to a rearrangement of the allyl ether to the desired product **3**. In addition, this lactonization−Claisen rearrangement synthesis avoided an extra TBS-deprotection step, giving **3** in an overall 73% yield.

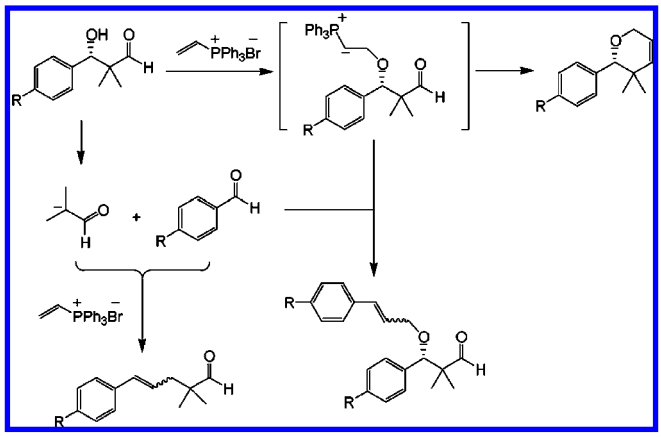


Tandem Conjugative Addition−Intramolecular Cyclization

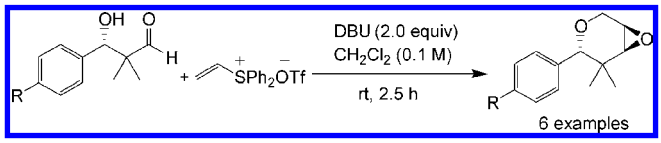


A tandem sequence for the synthesis of 3,6-dihydropyrans starting from enantiomerically *β*-hydroxy aldehyde is described by Ley's group at University of Cambridge in the U.K. (*Eur. J. Org. Chem.* **2010**, 183−190). This tandem sequence consists of a base-promoted conjugative addition, followed by an intramolecular Wittig process to provide 3,6-dihydropyran derivatives in moderate yield with

high optical purity. The moderate product yield is presumably due to the competing retro aldol reactions.

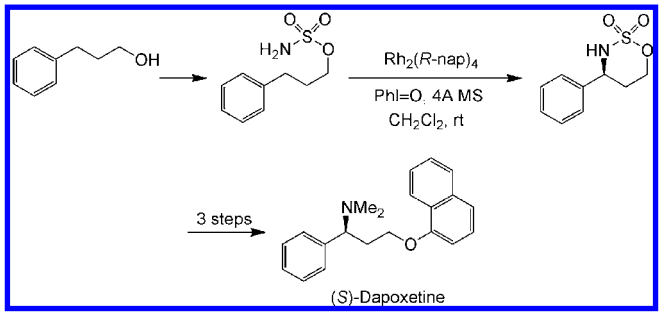


Exploring this reaction further led to an analogous tandem sequence, which consists of a conjugative addition, followed by an intramolecular cyclization/epoxidation process to afford 4,5-epoxytetrahydropyrans



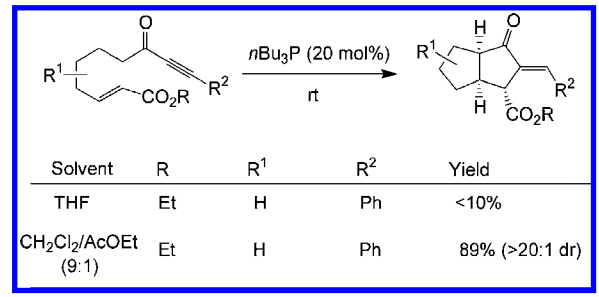
Du Bois Asymmetric C−H Amination Reactions

In spite of currently available strategies for the asymmetric synthesis of (*S*)-(+)-dapoxetine, Lee and co-worker in Korea developed a highly efficient, enantioselective sequence for the synthesis of (*S*)- and (*R*)-dapoxetine starting from 3-phenyl-1-propanol (*J. Org. Chem.* **2010**, *75*, 237−240). This method involves a 6-membered-ring sulfamate ester intermediate produced via Du Bois asymmetric C−H amination reaction catalyzed by a chiral dirhodium(II) complexes.



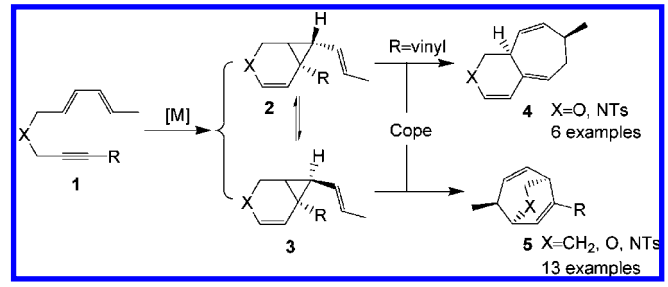
Stereoselective Synthesis of Bicyclic Rings

(A). Phosphine-Catalyzed Synthesis of Diquinanes. Fu's group at MIT has developed a versatile new method for the room-temperature synthesis of diquinanes from acyclic precursors (*Angew. Chem., Int. Ed* **2010**, *49*, 161−163). The product diquinane bears three new contiguous stereocenters and an E double bond, as a single diastereomer. It appears that this reaction is solvent sensitive; for example, a reaction in a mixture of CH_2Cl_2/EtOAc (9:1) produced 89% of product yield with high diastereoselectivity (20:1 dr), while in THF only less than 10% product was observed.



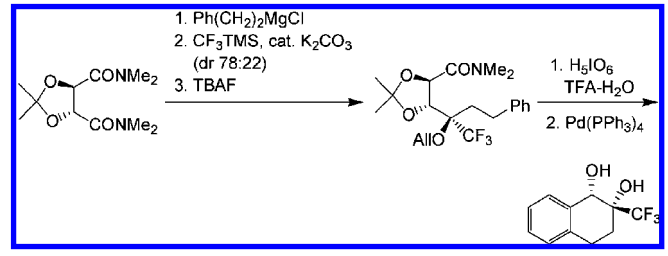
Solvent	R	R^1	R^2	Yield
THF	Et	H	Ph	<10%
CH_2Cl_2/AcOEt (9:1)	Et	H	Ph	89% (>20:1 dr)

(B). Platinum-Catalyzed Cycloisomerization and Cope Rearrangement of Dienynes. Chung and co-workers at Seoul National University in Korea presented a facile method for the stereoselective construction of bicyclic compounds using a $PtCl_2$-catalyzed cycloisomerization and subsequent Cope rearrangement (*Angew. Chem., Int. Ed* **2010**, *49*, 415−418). With two vinyl groups (R = vinyl in **2**) the Cope rearrangement of **2** afforded bicyclo[5.4.0]undecadiene rather than bicyclo[3.2.2]-nonadienes **5**.



Nucleophilic Trifluoromethylation

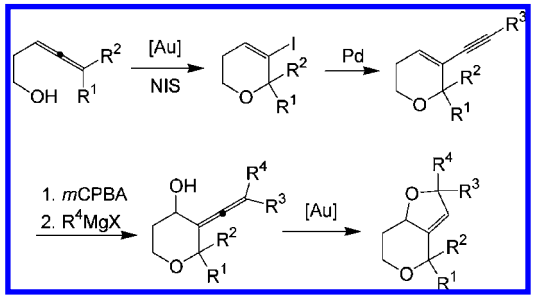
The synthesis of enantiopure stereoisomers of 2-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1,2-diol was reported by Portella et al. in France (*Eur. J. Org. Chem.* **2010**, 275−279). The key step in this method was the diastereoselective nucleophilic trifluoromethylation reaction with CF_3TMS by using L-tartaric acid as a simple chiral pool-derived starting material.



Stereoselective Synthesis of Bicyclic Ethers

A method of stereoselective synthesis of furopyrans from *β*-hydroxyallenes as starting material was developed by Krause's group in Germany (*Eur. J. Org. Chem.* **2010**, 311−316). This method involves a sequence containing gold-catalyzed 6-*endo* cyclization, palladium-catalyzed cross-coupling, epoxidation and allene formation, and second gold-catalyzed cyclization. The first gold-catalyzed cyclization occurred with various *β*-hydroxyallenes in the presence of *N*-iodosuccinimide (NIS) affording iodinated dihydropyrans in good yield. It was found

that NIS has a tremendous accelerating effect on the gold-catalyzed cyclization of β-hydroxyallenes.



C−H Activation for the Construction of C−B Bonds

Much research has been devoted to the selective oxidation of alkyl C−H bonds, but the development of a catalyst for the conversion of methane to methanol, for example, remains an important, unsolved problem in catalysis. Several groups have made great progress toward selective conversions of aryl C−H bonds to C−C, C−O, C−N, and C−X [(X) F, Cl, Br, and I] bonds, and several groups have made progress toward the conversion of alkyl C−H bonds to C−C, C−O, and C═C bonds. In contrast, the direct conversion of C−H bonds to C−B bonds is a more recently developed class of metal-catalyzed C−H bond functionalization. Significant progress has been made toward the development of systems that catalyze such borylation reactions of C−H bonds in alkanes, alkenes, and arenes in high yields and with high selectivity. This reaction has developed from curious stoichiometric reactions of transition metal−boryl complexes to a synthetic method now being studied by several groups and being used by synthetic chemists in the fields of materials, science, fine chemical synthesis, and natural product synthesis (Hartwig, J. F.; et al. *Chem. Rev.* **2010**, *110*, 890−931).

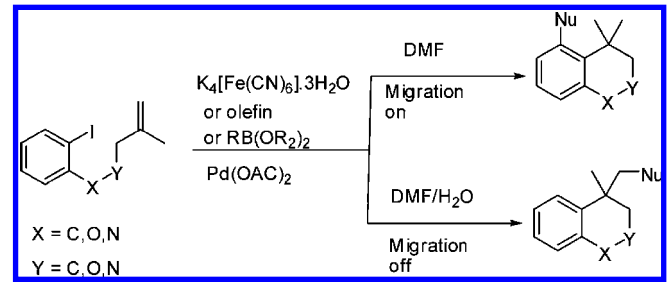
Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions

The development of methods for the direct conversion of carbon hydrogen bonds into carbon−oxygen, carbon−halogen, carbon−nitrogen, carbon−sulfur, and carbon−carbon bonds remains a critical challenge in organic chemistry. Mild and selective transformations of this type will undoubtedly find widespread application across the chemical field, including in the synthesis of pharmaceuticals, natural products, agrochemicals, polymers, and feedstock commodity chemicals. Traditional approaches for the formation of such functional groups rely on prefunctionalized starting materials for both reactivity and selectivity. However, the requirement for installing a functional group prior to the desired C−O, C−X, C−N, C−S, or C−C bond adds costly chemical steps to the overall construction of a molecule. To circumvent prefunctionalization will not only improve atom economy but also increase the overall efficiency of multistep synthesis.

Sanford M. S. and Lyons, T. W. (*Chem. Rev.* **2010**, *110*, 1147−1169) have reviewed the topic with the focus specifically on ligand-directed C−H functionalization reactions catalyzed by palladium.

Water-Controlled Regioselectivity of Pd-Catalyzed Domino Reaction Involving a C−H Activation Process: Rapid Synthesis of Diverse Carbo- and Heterocyclic Skeletons

Domino reactions have proven to be very useful for the construction of complex molecules through formation of multiple bonds in one-pot reactions. A palladium-catalyzed domino reaction involving a C−H activation process to synthesize diverse carbo- and heterocyclic skeletons has been developed by Jia, Y.; et al (*Org. Lett.* **2010**, *12*, 480.). The palladacycle intermediate is successfully trapped by cyanation, Heck reaction, secondary C−H activation, and Suzuki coupling. The regioselectivity is controlled by manipulating the reaction conditions using water as cosolvent to give either an arylfunctionalized product with yields in the 47−95% range or alkyl-functionalized product with yields in the 60−95% range. Moreover, only sodium carbonate and no expensive bases, which are usually employed in C−H activation, and phosphorus ligands, which are usually not friendly to the environment are used. Diverse products can be prepared starting from the same substrate by using this method.



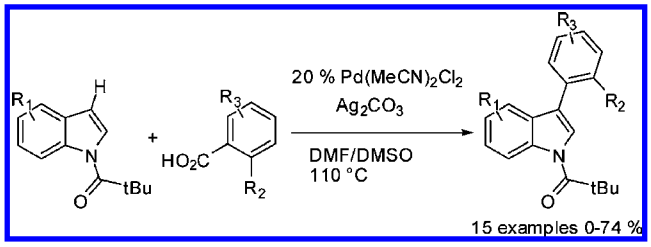
Synthesis of 2-Hydroxymethyl Ketones by Ruthenium Hydride-Catalyzed Cross-Coupling Reaction of α,β-Unsaturated Aldehydes with Primary Alcohols

The cross-coupling reaction of α,β-unsaturated aldehydes with primary alcohols to give 2-hydroxymethyl ketones has been achieved using $RuHCl(CO)(PPh_3)_3$ as a catalyst (Ryu, I.; et al. *Org. Lett.* **2010**, *12*, 1.). This atom-economical reaction is likely to proceed via the hydroruthenation of α,β-unsaturated aldehydes followed by an aldol reaction of the resultant enolates with aldehydes to give α-formylated ketones, which undergo transfer hydrogenation with primary alcohols leading to 2 -hydroxymethyl ketones. The reduction step can generate aldehydes, participating in the next catalytic cycle.

Intermolecular Decarboxylative Direct C-3 Arylation of Indoles with Benzoic Acids

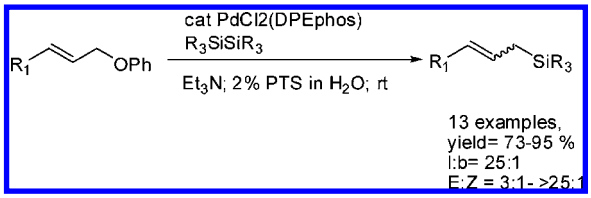
A palladium-catalyzed C−H activation of indoles and a silver-catalyzed decarboxylative C−C activation of ortho-substituted benzoic acids have been combined to synthesize indoles arylated exclusively in the C-3 position by Larrosa, I.; et al. (*Org. Lett.* **2009**, *11*, 5506.). This novel decarboxylative

C−H arylation methodology is compatible with electron-donating and -withdrawing substituents in both coupling partners.



Pd-Catalyzed Synthesis of Allylic Silanes from Allylic Ethers

Allylic silanes are among the most important and widely used reagents in organic synthesis. Well known transformations, such as the Hosomi−Sakurai reaction, or Hiyama couplings, underscore their value as building blocks. Although a vast array of synthetic methods for the preparation of allylic silanes now exists, further development of selective entries to allylic silanes are still of considerable interest. Now Lipschutz, B. H.; et al. (*Org. Lett.* **2010**, *12*, 28.) have found that allylic phenyl ethers serve as electrophiles toward Pd(0) en route to a variety of allylic silanes. The reactions can be run at room temperature in water as the only medium using micellar catalysis. Readily available disilanes serve as the stoichiometric source of silicon. Both the regio- and stereoselectivity associated with the catalysis are well-controlled.



Prediction of Drug Particle Size and Content Uniformity in Low-Dose Solid Dosage Forms

Content uniformity in low-dose solid dosage forms is known to depend on Active Pharmaceutical Ingredient (API) particle size distribution. This dependency is non-linear, and the API particle size distribution to be used in the manufacture of drug product must be optimized. Often, particle size distribution is a critical quality attribute for the API. Regardless of organizational culture, some decisions regarding the API solid state properties must be made in the early stages of process R&D, when relatively small amounts of API are available. A group from Wyeth (Pfizer) (Huang, C−Y.; et al. *Int. J. Pharm.* **2010**, *383*, 70−80) reports their theoretical work for deriving a correlation between the skewness of potency distribution, API particle size distribution and target dose. The authors found that both the skewness of potency distribution as well as the coefficient of variation (quantifying the mixing quality in the solid dosage form) depend on the inverse square root of the target dose. It was shown that for very low target doses, the potency distribution significantly deviates from normality before the coefficient of variation becomes significantly large. A nomograph of the median particle size and target dose that meets a 99% pass rate (based on USP 905) was constructed. Such nomographs can assist with particle engineering, including defining the high limit that can be imposed on API particle size, in order to allow for a lower target dose. The advantage of using particle populations with low standard deviations of their particle size distribution is quantified in these nomographs.

Polymorphism of *trans*-1,4-Cyclohexanediol: Conformational Isomorphism

In addition to job security for pharmaceutical process scientists, polymorph investigations continue to provide interesting findings, some challenging existing dogmas. Until recently, only one solid form of trans-1,4-Cyclohexanediol was known and characterized. An academic team from Portugal (Maria, T. M.; et al. *Cryst. Growth Des.* **2010**, DOI: 10.1021/cg901160v) investigated further the polymorphism in *trans*-1,4-cyclohexanediol to find two novel forms (I and II), in addition to the already known form (III). Form III can be obtained from crystallization in solution or sublimation; form I is obtained by heating form III, and form II can be obtained by controlled sublimation. Forms I and III are enantiotropic (with a transition temperature of 79 °C), whereas forms I and II are monotropic (with melting points of 138 and 141 °C respectively). The solid state transformations were investigated using DSC, and polarized light thermomicroscopy. DSC for form II could not be achieved due to insufficient material, but the single crystal X-ray analysis for form II was solved. Polymorphs II and III exhibit unusual conformational isomorphism, characterized by the *coexistence* of the biequatorial *and* of the biaxial conformers in the same crystal structure. The authors indicated that a search in the Cambridge Structural Database for *trans*-1,4-disubstituted cyclohexanes showed no other structures comprising both biequatorial and biaxial conformers.

Microreactor Numbering-up in Multiscale Networks for Industrial-Scale Applications: Impact of Flow Maldistribution on Reactor Performance

Among the advantages that microreactors could bring to process engineering is rapid scale-up by numbering-up (also known as "scale-out"). An academic team from France (Saber, M.; et al. *Chem. Eng. Sci.* **2010**, *65*, 372.) analyzed the impact of flow non-uniformity and channel clogging on catalytic microreactor performance. Just as non-ideal mixing in classical reactors impacts reaction selectivity (especially for fast heterogeneous processes), so does flow maldistribution in numbered-up microreactors. Simulated microreactor clogging was shown to also impact reaction selectivity. The authors plan on continuing such investigations for exothermic reactions, for which they expect a stronger dependence of reaction selectivity on flow uniformity and clogging.

Monitoring a Lab-Scale Fluidized Bed Dryer: A Comparison between Pressure Transducers, Passive Acoustic Emissions, and Vibration Measurements

Effective implementation of process analytical technology (PAT) in the quality by design paradigm is based on the use of a relatively large number of sensors at lab scale. Monitoring of a fluidized bed dryer has been investigated by a group from Delft University in The Netherlands

(Vervloet, D.; et al. *Powder Technol.* **2010**, *197*, 36.). For this purpose, the authors looked at pressure fluctuations, passive acoustic emission, and at accelerometry. The pressure fluctuation measurements were found the most reproducible for the monitoring of the drying of a pharmaceutical placebo. Improvements in passive acoustic emission and vibration measurements are sought, given the non-intrusive nature of such sensors (microphones). Suitable data analysis algorithms were developed, and sophisticated statistical analysis was employed in the mining of the data obtained.

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