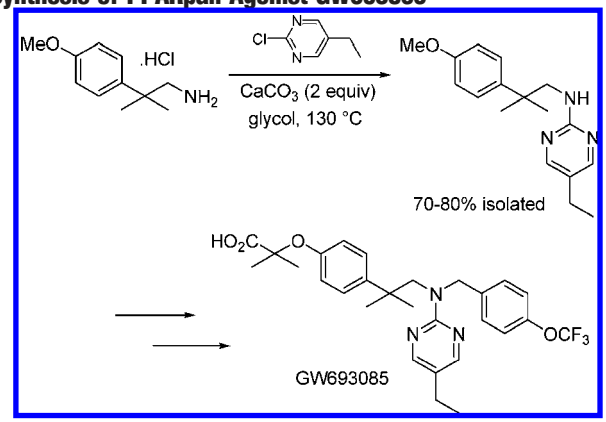
Highlights from the Literature

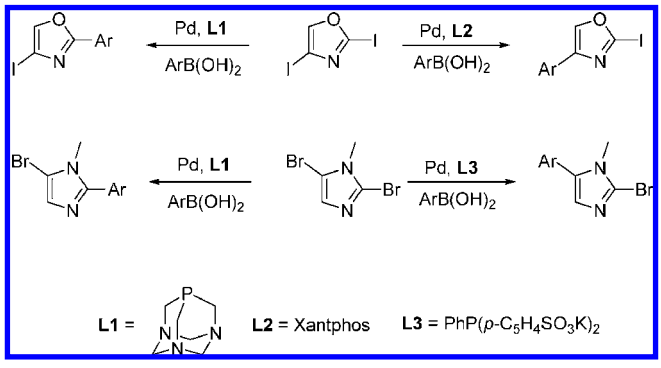
Some Items of Interest to Process R&D Chemists and Engineers

Synthesis of PPARpan Agonist GW693085



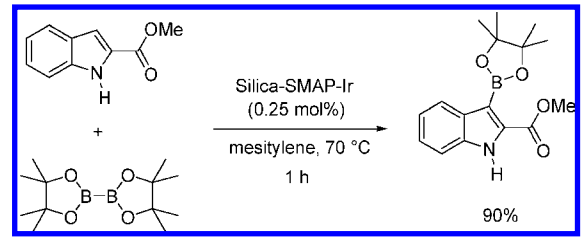
Recently, selective PPAR agonists were dosed in combination to show that there could be synergy in lowering glucose and triglycerides. GW693085 is a PPARpan agonist, combining the activity of the three known subtypes of the PPAR agonists into a single molecule. As a drug candidate for type 2 diabetes, a supply of multikilogram quantities for preclinical and clinical investigation was required. Xie and co-workers at GSK describe process development of this compound (*J. Org. Chem.* **2010**, *75*, 3904−3907). Following a study of how to most efficiently prepare the central tertiary amine, a unique buffering effect of various bases (i-Pr_2NEt and $CaCO_3$) in particular, was observed for the acid-catalyzed chloro displacement of 2-chloro-5-ethylpyrimidine with a 2-methyl-2-phenylpropanamine. The use of the carefully chosen bases was essential for the progression of the chloro displacement as well as the stability of the product because of the formation of HCl. Research work leading to an efficient synthesis of PPARpan agonist GW693085 is described, featuring highly selective sequential *N*- and *O*-alkylations.

Catalyst-Controlled Regioselective Suzuki Couplings at Both Positions of Dihaloimidazoles, Dihalooxazoles, and Dihalothiazoles



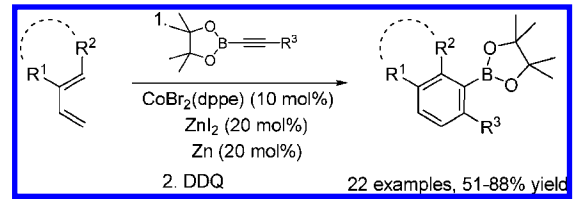
Although diaryl-imidazoles, -oxazoles, and -thiazoles are common subunits in pharmaceutical and natural products, these compounds are not always easily accessed in modular fashion. Now Strotman, Chobanian, and coworkers at Merck report that various dihaloazoles can be monoarylated at a single C−X bond with high selectivity via Suzuki coupling (*J. Org. Chem.* **2010**, *75*, 1733−1739). By changing the palladium catalyst employed, the selectivity can be switched for some dihaloazoles, allowing for Suzuki coupling at the other, traditionally less reactive C−X bond. These conditions are applicable to coupling of a wide variety of aryl-, heteroaryl-, cyclopropyl-, and vinylboronic acids with high selectivities and enable the rapid construction of diverse arrays of diarylazoles in a modular fashion.

Ester-Directed Regioselective Borylation of Heteroarenes



Catalytic C−H borylation of arenes allows direct access to various borylated arenes, often with regiochemical control that is otherwise difficult to achieve. Application of this reaction to heterocylic substrates broadens the scope of this process with respect to the synthesis of pharmaceutical products. Now Sawamura and co-workers report on an ester-directed regioselective borylation of aromatic heterocycles (*J. Org. Chem.* **2010**, *75*, 3866−3858). This borylation is catalyzed by a silica-supported monophosphine−Ir complex, which displays broad substrate scope, including thiophene, pyrrole, furan, benzothiophene, benzofuran, indole, and carbazole derivatives. The regioselectivity is complementary to the selectivities observed in the heteroarene C−H borylation with the dtbpy−Ir catalyst system.

Ambient-Temperature Cobalt-Catalyzed Cycloaddition Strategies to Aromatic Boronic Esters



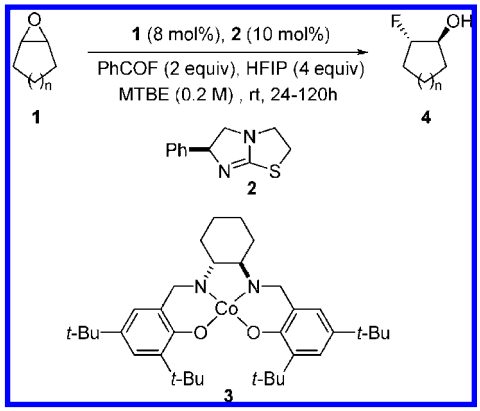
In a separate report concerning the synthesis of arylboronic esters, Harrity, Hilt and co-workers describe an interesting alternative approach to these widely used synthetic intermediates (*J. Org. Chem.* **2010**, *75*, 3893−3896).

Published on Web 06/30/2010
10.1021/op100166w

The room-temperature cobalt-catalyzed [4 + 2] cycloaddition of alkynylboronates and 1,3-dienes provides a convenient and general method for the synthesis of benzene-based aromatic boronic esters. For aromatization postcycloaddition, two complementary strategies are presented. The first involves in situ elimination, and the second is a DDQ oxidation, with the latter finding more generality. Finally, the potential of this technique to generate highly functionalized biaryls has been demonstrated via the synthesis of chiral (racemic) DMAP catalysts.

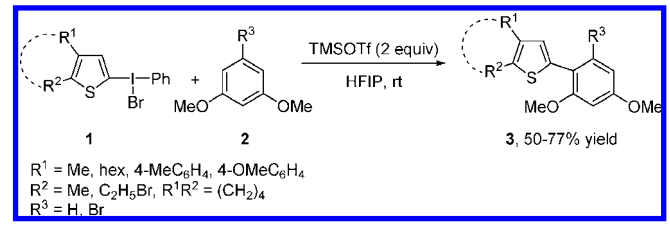
Enantioselective Ring-Opening by Fluoride Anion

Julia A. Kalow and Abigail G Doyle (Princeton University) reported the use of a dual catalyst system that promotes the fluoride ring-opening of meso and terminal epoxides in an enantioselective fashion (*J. Am. Chem. Soc.* **2010**, *132*, 3268−3269). The reaction proceeds at room temperature and uses commercially available benzoyl fluoride as the source of nucleophilic fluoride. The protocol takes place via an intermediate chiral amine-HF salt or via a chiral Lewis acid/amine cocatalysis. The amine-catalyzed generation of HF from benzoyl fluoride and an alcohol overcomes both background reactivity and catalyst inhibition. In short, treatment of meso-epoxides **1** with a combination of (-)-tetramisole **2** and chiral (salen)Co complex **3** in the presence of benzoyl fluoride and 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) afforded fluorohydrins **4** in 85−95% ee. The transformation can be carried out in regular glassware and is well-tolerated by alkenes, esters, and protected amine functionalities.



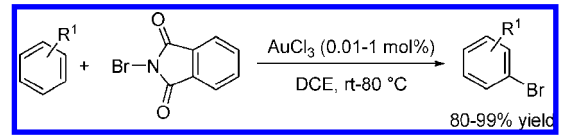
ipso Substitution of Diaryliodonium Bromides

Despite their rich chemistry, the utility of diaryliodonium salts $Ar^1I^+Ar^2X^-$ as heteroaryl transfer agents in ligand coupling processes has been somewhat limited. In *Angew. Chem., Int. Ed.* **2010**, *49*, 3334−3337, the group of Prof. Kita at Osaka University reported a unique single-electron-transfer (SET) oxidizing strategy using diaryliodonium salts as selective heteroaryl transfer agents during *ipso* substitution. Activation of the heteroaryl iodonium salt **1** using TMSOTf led to the carbon−carbon bond formation between its *ipso* carbon atom and the unfunctionalized aromatic nucleophiles **2** to yield products **3**. The reaction does not occur through the classically proposed tricoordinated intermediates $Ar^1I^+Ar^2Nu$. Instead, the SET oxidizing properties of thiophene iodonium-bromides towards electron-rich aromatic compounds play a key role; with the aid of TMSOTf in HFIP at room temperature, **1** generates a stable radical species in the presence of 1,4-dimethoxybenzene that can be detected by ESR spectroscopy. The method facilitates the production of a variety of heteroaryl-containing biaryl compounds under metal-free conditions.



Gold-Catalyzed Halogenation of Aromatics by *N*-Bromosuccinimide

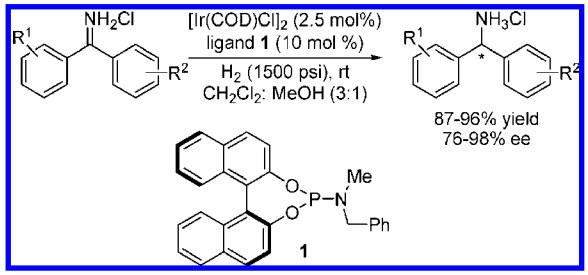
The group of Prof. Wang (College of Chemistry at Peking University, Beijing) recently disclosed an efficient protocol for the $AuCl_3$-catalyzed bromination of arenes with *N*-bromosuccinimide (NBS) under mild conditions (*Angew. Chem., Int. Ed.* **2010**, *49*, 2028−2032). $AuCl_3$ promotes the dual activation of NBS through complexation to its carbonyl oxygen atom and its aromatic ring by formation of a C_{Ar}−M bond following direct metalation of a C_{Ar}−H bond. The treatment of a variety of aromatic substrates with NBS (1 equiv) and $AuCl_3$ in DCE originates clean reactions, with succinimide as the only byproduct. GC/MS analysis indicated the exclusive formation of monobrominated arenes. Moreover, benzylic bromination did not occur when toluene or xylenes were subjected to the reaction conditions. To further the applications of the method, the authors successfully combined it with other metal-catalyzed C−N and C−C bond formation reactions: in situ synthesis of anilines by reaction with succinimide (Cu, MW, 150 W, 150 °C, 57−83% yield) and palladium-catalyzed transformations such as Suzuki−Miyaura cross-coupling, Miyaura borylation, and Sonogashira coupling.



Asymmetric Hydrogenation of Substituted Benzophenone N−H Imines

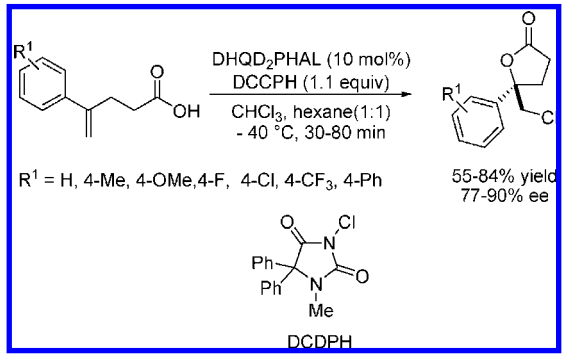
A joint publication of the Department of Process Research at Merck and the Department of Chemistry at Rutgers, The State University of New Jersey, describes the protection-free asymmetric hydrogenation of substituted benzophenone imines (*J. Am. Chem. Soc.* **2010**, *132*, 2124−2425). The authors capitalized on their recently reported enantioselective hydrogenation of N−H imines using iridium-*f*-binaphane (see *J. Am. Chem. Soc.* **2009**, *131*, 9882−9883) and present a concise, economical approach to the asymmetric synthesis of diarylmethylamines. Benzophenone imines were prepared on multigram scale by organometallic addition to benzonitriles. The precatalyst of choice was $[Ir(COD)Cl]_2$, while the inexpensive, commercially available (*S*)-*N*-benzyl-*N*-methyl-MonoPhos (**1**) was selected as the ligand. Remarkably, the process maintained its selectivity even if the H_2 pressure was increased to 1500 psi, and the catalyst was not affected by excess of the (counterion) chloride. Ortho substitution is a key

feature to obtain high enantioselectivities; chloro, bromo, and methyl substituents at the 2-position gave 82−91% ee's, whereas coordinating 2-methoxy, and smaller 2-fluoro substituents afforded lower selectivities.



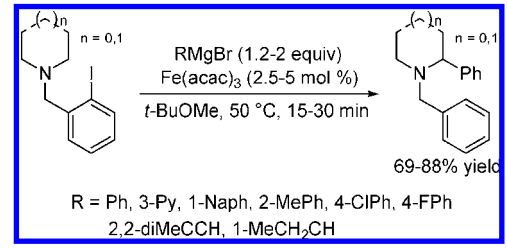
Organocatalytic Asymmetric Chlorolactonization

Examples of synthetically useful electrophilic halogenations of olefins are notably absent from the arsenal of catalytic asymmetric oxidations. Borhan and co-workers at Michigan State University report the discovery of an organocatalytic enantioselective protocol for the chlorolactonization of 4-substituted 4-pentenoic acids that yields chiral halolactones with synthetically useful enantioselectivities (*J. Am. Chem. Soc.* **2010**, *132*, 3298−3300). Hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$ (10 mol %)] was the chiral auxiliary employed, while 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) was the ultimate chlorenium transfer reagent. Extensive parallel additive and cosolvent screening revealed that both the addition of benzoic acid (1 equiv) and the solvent system ($CHCl_3$/hexane, 1:1) independently increased the reaction selectivities. Improved enantioselectivities could be obtained as the steric demand of the C-5 substituents on the terminal chlorine source were augmented. ^1H NMR experiments provided underlying mechanistic insights: association between the *N*,*N*-dichlorohydantoin species and the chiral catalyst was evidenced by the split of the singlet corresponding to the C-5 protons into an AB quartet that coalesced upon raising the reaction temperature. A panel of 4-substituted pentenoic acids was subjected to the optimal reaction conditions to yield phenyl-substituted lactones (55−84% yield, 77−90% ee).



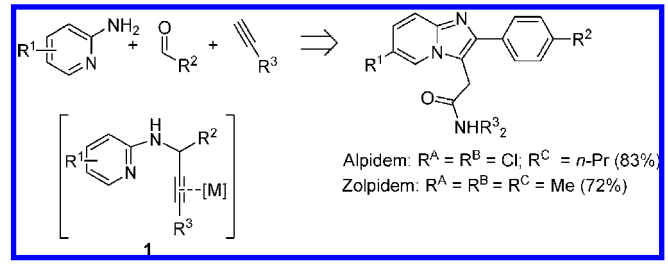
Iron-Catalyzed α-Alkylation of Aliphatic Amines through 1,5-Hydrogen Transfer

The group of Professor Eiichi Nakamura at the University of Tokyo reported an iron-catalyzed C(sp^3)−H bond activation reaction of cyclic and aliphatic amines bearing an *N*-(2-iodophenyl)methyl moiety. The substrates react with Grignard or diorganozinc reagents to yield the corresponding α-alkylated products through an intramolecular 1,5-hydrogen transfer followed by reductive elimination (*J. Am. Chem. Soc.* **2010**, *132*, 5568−5569). While $Fe(acac)_3$ was chosen as the iron source, $FeCl_3$ or $FeCl_2$ gave comparable results; however, in the absence of the iron catalyst, only unreacted starting material could be recovered. The choice of the ethereal solvent was important: among Et_2O, *t*-BuOMe, and THF, THF was less suitable because of competitive arylation. The observed reactivity and selectivity support the author's hypothesis that the iron intermediate exhibits properties of both a carbon radical and a d-block organometallic. Therefore, iron-catalyzed reactions could capitalize on synthetic strategies developed for free radical chemistry, such as radical translocations.



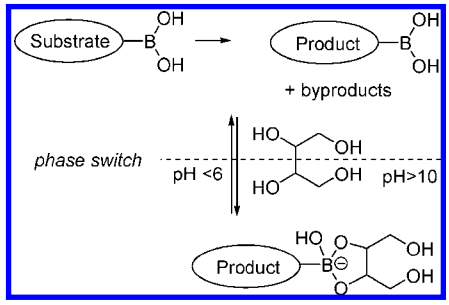
One-Pot Synthesis of Alpidem and Zolpidem

The imidazopyridine motif is a relevant pharmacophore shared by drugs used to treat anxiety (alpidem, Anaxyl) as well as insomnia (zolpidem, Ambien). Chernyak and Gevorgyan (University of Illinois at Chicago) described a general and efficient synthesis of imidazopyridines using a copper-catalyzed three-component coupling (TCC) reaction of 2-aminopyridines with aryl aldehydes and terminal alkynes (*Angew. Chem., Int. Ed.* **2010**, *49*, 2743−2746). The imidazo[1,2-*a*]pyridyl core was assembled by a π-philic metal-catalyzed 5-exodig cyclization of propargylamine **1**. In turn, the latter compound was accessible through the three-component coupling described above. Best results were obtained when the reaction was conducted using the $CuCl/Cu(OTf)_2$ binary catalytic system in toluene at 120 °C. The transformation is applicable to a wide range of aldehydes and alkynes, and provides access to densely substituted imidazopyridine derivatives (61−89%). The synthesis of alpidem and zolpidem posed as a special challenge the requirement of propiolamides as starting materials. These Michael acceptors were amenable to the dehydrocondensation step, and therefore were added once this step was complete. By using this newly developed protocol, alpidem and zolpidem were obtained in 83% and 72% yields, respectively.

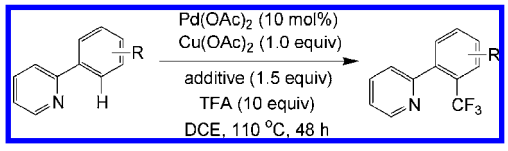


Multistep Phase-Switch Synthesis: Liquid−Liquid Partitioning of Boronic Acids

New strategies are needed to facilitate the synthesis and isolation of organic compounds while minimizing the use of silica gel and solvents in chromatography. In phase-switching strategies, reactions take place under homogeneous conditions, and the product is separated by liquid−liquid partition or precipitation/filtration. Phase migration is enabled through functionalization with a phase "tag' (perfluoroalkyl groups, polyethylene glycol chains, metal chelators, etc.), but only a few strategies can be applied to multistep synthesis, as the tagging/detagging process is unproductive. The latter operation destroys the phase tag and often leaves undesired traces on the product. Mothana, Grassot, and Hall developed a less invasive strategy using boronic acid as built-in phase tags that can be selectively derivatized instead of cleaved at the end of the synthetic sequence (*Angew. Chem., Int. Ed.* **2010**, *49*, 2883−2887). The phase-switching system is a mixture of sorbitol and boronic acids, which forms a strong water-soluble complex at high pH but is insoluble in the organic phase, thereby avoiding contamination, while excess reagents and nonpolar side products can be eliminated at the end of the reaction. The stability of boronic acids was tested under a variety of transformations: oxidations of alcohols, carbonyl reductions, esterifications, organometallic additions, Wittig olefinations, and the expected products isolated in good to high yields after phase-switch purification. The usefulness of the protocol was highlighted in a multistep synthesis of the antihyperlipidemic drug, ezetimibe.

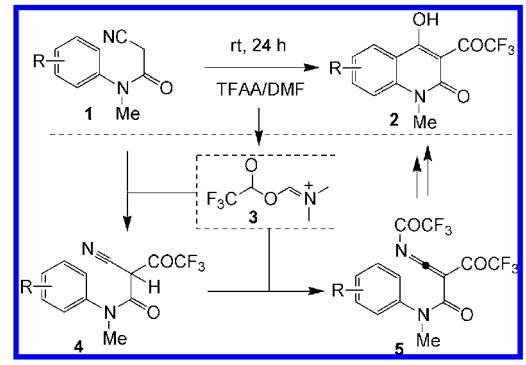


Pd(II)-Catalyzed Ortho-Trifluoromethylation of Aromatics



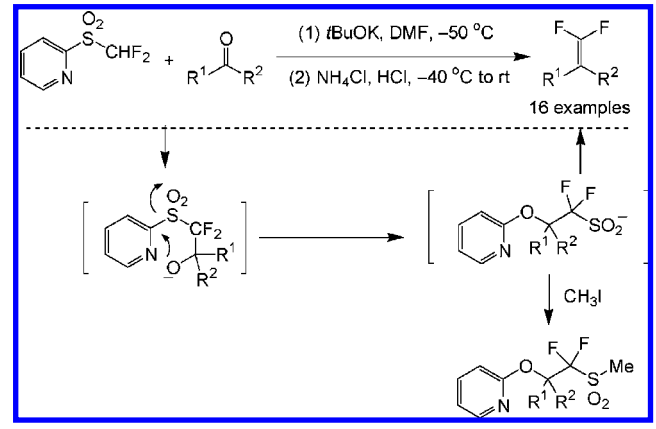
Incorporation of CF_3 groups into drug molecules can improve their physical and biological properties such as binding selectivity, lipophilicity, and metabolic stability. Such unique properties of fluorinated compounds attract considerable attention; as a consequence, much effort was made in developing new synthetic methods. A new Pd(II)-catalyzed trifluoromethylation reaction of arenes through C−H functionalization was uncovered by Yu and co-workers at the Scripps Research Institute (*J. Am. Chem. Soc.* **2010**, *132*, 3648−3649). This transformation occurred in dichloroethane in the presence of $Cu(OAc)_2$ and TFA as additive, giving the desired ortho-trifluoromethylated arenes in good yields. Exploring the scope of this protocol revealed that electron-donating groups are well tolerated. Low yields of coupling products were observed with strong electron-withdrawing groups, albeit moderately electron-withdrawing groups such as Cl are compatible. Substrates with other heterocyclic ring systems as directing groups to replace pyridine performed equally well.

Sequential Trifluoroacetylation−Cyclization Reactions



The synthesis of 4-hydroxy-*N*-methyl-3-trifluoroacetylquinolin-2(1H)-ones **2** was achieved via trifluoroacetic anhydride-mediated tandem trifluoroacetylation−cyclization of cyanoacetanilides **1** (*J. Org. Chem.* **2010**, *75*, 2741−2744). This transformation occurred under mild conditions. However, higher reaction temperature was required when ortho-substituted groups presented in the substrates **1**. Notably, reactions of 2-cyano-*N*-methyl-*N*-phenyl-acetamide (R = H) with anhydrides, such as acetic anhydride or benzoic anhydride, failed to produce the desired products. In contrast, fluorine-containing acid anhydrides, such as $(CF_2ClCO)_2O$, $(CF_3CF_2CO)_2O$, or $(CF_3CF_2CF_2CO)_2O$, efficiently promoted the tandem reaction to furnish the corresponding quinolinones in good yields. Mechanistically, this synthetic protocol is envisaged to occur via double-trifluoroacetylation of **1** by **3**, generated in situ by an interaction of DMF-trifluoroacetic anhydride, leading to **5** followed by cyclization of **5** to the desired quinolinones **2**.

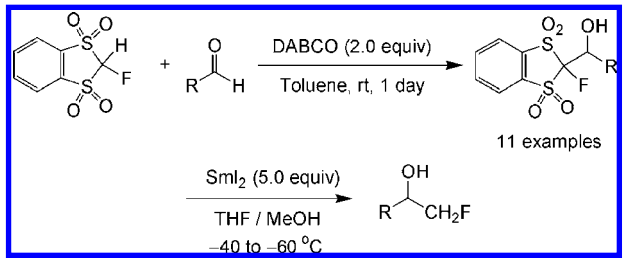
gem-Difluoroolefination of Aldehydes and Ketones



In addition to the existing methods of difluoroolefination, an efficient *gem*-difluoroolefination of aldehydes and ketones was developed by scientists in Shanghai Institute of Organic

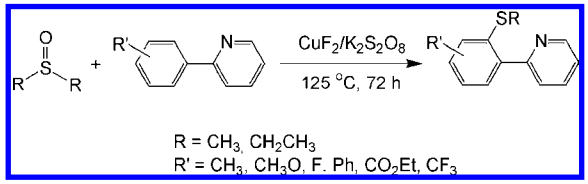
Chemistry, China (*Org. Lett.* **2010**, *12*, 1444−1447). Difluoromethyl 2-pyridyl sulfone acting as a *gem*-difluoroolefination reagent reacted smoothly with the carbonyl group in aldehydes or ketones to furnish *gem*-difluorinated vinyl products. The formation of relatively stable intermediates, sulfinate salts, could be confirmed by trapping with iodomethane to give an isolable sulfone.

Nucleophilic Monofluoromethylation of Aldehydes



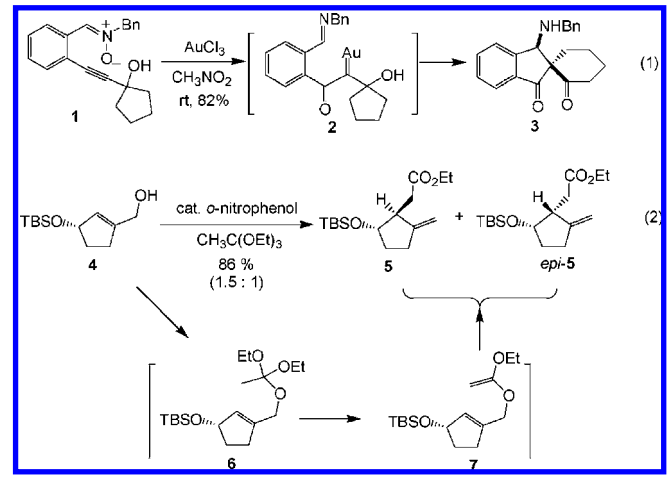
Similar to trifluoromethyl-containing organic compounds, monofluorinated analogues possess unique biologically activity. A two-step approach to access monofluoromethylated alcohols was developed by Shibata and co-workers in Japan via a nucleophilic monofluoromethylation of aldehydes (*Angew. Chem., Int. Ed.* **2010**, *49*, 1642−1647). In their report, a novel nucleophilic monofluoromethylation occurred between various aldehydes and 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide, affording the corresponding monofluoromethylated products in good yields. The subsequent transformations of the resulting 1,2-adducts into the monofluoromethylated alcohols were carried out by reductive desulfonylation using SmI_2.

Cu-Mediated Alkylthiolation of Arenes



Alkyl aryl thioethers are important compounds due to their biological activities. The common method for preparation of aryl sulfides involves lithiation and subsequent alkylthiolation with dialkyl disulfide. A new approach for the synthesis of such sulfur compounds was reported by Qing and co-workers in China (*Org. Lett.* **2010**, *12*, 1644−1647). This transformation occurred in the presence of CuF_2 (4.0 equiv), $K_2S_2O_8$ (2.0 equiv), and excess of dialkyl sulfoxide, leading to alkyl aryl sulfide with ortho-selectivity. It was claimed that no reaction was observed in the absence of copper salt and that the nitrogen in the pyridine moiety was responsible for the ortho-selectivity. The drawbacks of this method are that the reactions were carried out at a relatively high temperature (125 °C) using a large excessive amount of copper salt (CuF_2) with long reaction time (72 h).

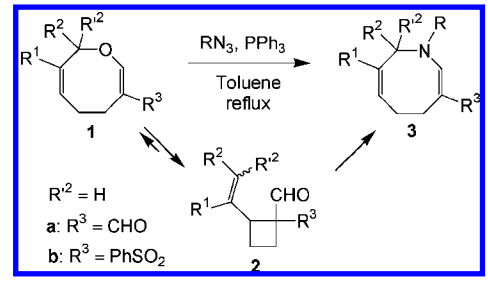
Cascade Reactions



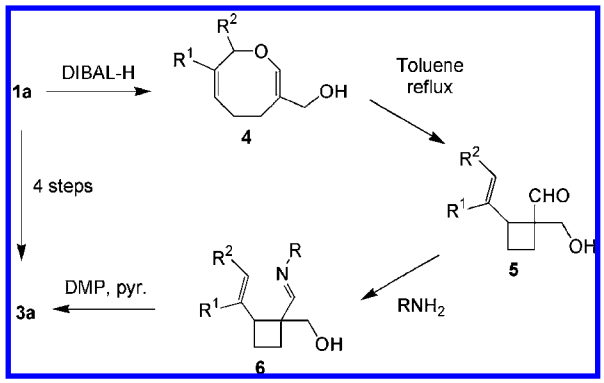
Cascade reactions can improve not only the redox economy but also the synthetic efficiency through a rapid increase in molecular complexity. A cascade reaction, developed by Shin et al. in Korea (*Angew. Chem., Int. Ed.* **2010**, *49*, 1611−1614), involved a $AuCl_3$-catalyzed reduction/oxidation reaction leading to a gold-carbenoid **2**. The subsequent pinacol-type rearrangement and Mannich reaction afforded a spiro product **3** (eq 1 above). In this Au(III)-catalyzed redox step both the C-1 oxidation state adjustment and skeletal bond formation were realized in a highly efficient manner.

A cascade reaction was designed by Nicolaou et al. (*J. Am. Chem. Soc.* **2010**, *132*, 3815−3818) to access a key intermediate **5** in the total synthesis of echinopines A and B. A displacement of ethanol by hydroxy group in **4** gave a mixed ortho ester **6** which upon losing another ethanol molecule led to **7**, the precursor of Claisen rearrangement. The subsequent Claisen rearrangement of **7** led to γ,δ-unsaturated carboxylate **5** in 86% overall yield as a mixture of diastereoisomers in which the desired *anti*-product was predominating (dr ≈ 1.5:1).

Claisen/Aza-retro-Claisen Rearrangement

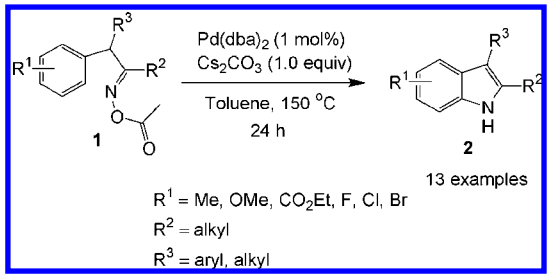


A nice one-pot process was established by Boeckman's group at the University of Rochester involving a novel aza-retro-Claisen rearrangement (*Org. Lett.* **2010**, *12*, 1628−1631). Upon heating, Claisen rearrangement of oxacenes **1** provided cyclobutanecarboxaldehydes **2** which, in turn, reacted with Staudinger reagent, generated in situ via a reaction of azide with triphenylphosphine, followed by aza-retro-Claisen rearrangement leading to the medium-sized *N*-heterocycles **3**. One limitation of this one-pot approach is that the aza-retro-Claisen rearrangement failed with terminally disubstituted olefins ($R'^2 \neq H$).



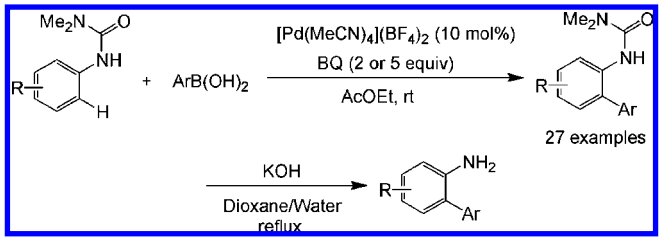
Furthermore, this one-pot procedure features redox economy as it avoided the need for additional redox transformations (**1a**→**4** and **6**→**3a**) used in the stepwise synthesis.

Indole Synthesis via Palladium-Catalyzed Intramolecular Cyclization



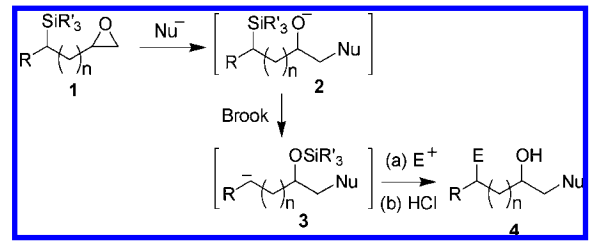
Hartwig and his co-worker (*J. Am. Chem. Soc.* **2010**, *132*, 3676−3677) demonstrated a one-step synthesis of 2,3-disubstitituted indoles via a palladium-catalyzed amination of aromatic C−H bonds with oxime esters. This cyclization tolerates various functional groups (R^1) ranging from strong EDG to strong EWG albeit only in 40% yield with R^1═OMe. Interestingly, aryl−halogen (Cl, Br) bonds are inert under these conditions, indicating that the N−O bonds of the oxime acetate are more reactive than the aryl−Cl or aryl−Br bond toward the Pd-catalyzed oxidative insertion. The drawback is that the reactions were conducted at a relatively high temperature (150 °C).

C−H Activation/Suzuki−Miyaura Couplings at Room Temperature



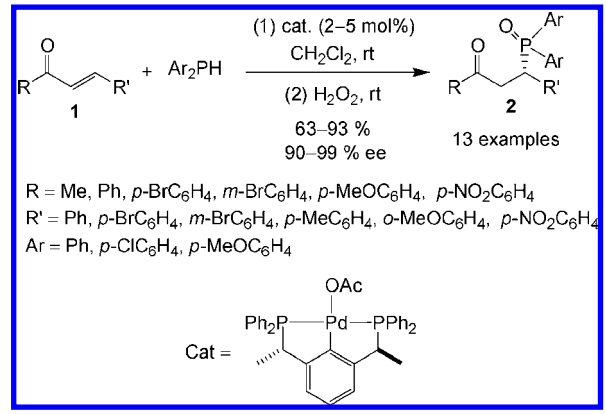
Room temperature Suzuki−Miyaura coupling reactions were realized via C−H bond activation under cationic palladium(II) catalysis conditions (*J. Am. Chem. Soc.* **2010**, *132*, 4978−4979). In this approach, the use of aromatic ureas as Suzuki coupling partners to replace common aryl halides allows C−C bond formation under mild conditions in the presence of 1,4-benzoquinone (BQ). It is notable that this method involves nitrogen- or oxygen-based directing groups (DG) for ortho C−H activation. Various arylboronic acids having electron-donating or -withdrawing groups reacted smoothly with aromatic ureas in high yields. The dimethylurea moiety was easily removed under general hydrolysis conditions to produce the corresponding amines quantitatively.

Brook Rearrangement in Anion Relay Chemistry



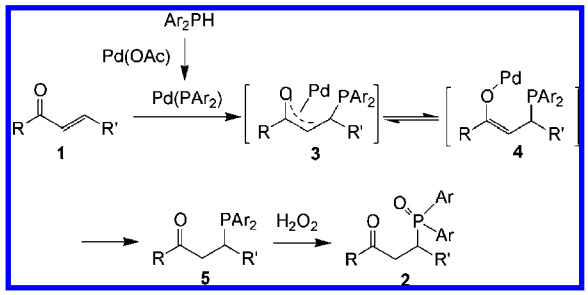
Anion relay chemistry (ARC), a one-pot tricomponent union approach, has proven highly effective in organic synthesis. The ARC is based on Brook rearrangement which allows the migration of the negative charge on the alkoxide **2** onto C(sp^3) in **3** (*Org. Lett.* **2010**, *12*, 1260−1263). This silyl migration requires R to be a viable anion stabilizing group in order to generate a new anionic site. A variety of electrophiles can be used to trap the newly generated anion **3** in a one-pot fashion to furnish the three-component adduct **4**.

Palladium-Catalyzed Synthesis of Chiral Phosphines

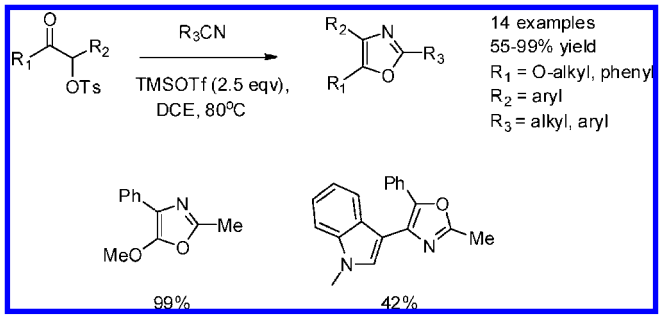


Chiral phosphines, as the most fundamental ligands for transition metals, have been extensively employed in asymmetric synthesis. Available methods to prepare the chiral phosphine ligands are limited to the use of stoichiometric amounts of chiral auxiliaries or optical resolution of racemates. Duan and his cowokers in China developed a synthetic protocol to access the chiral phosphines via a palladium-catalyzed reaction (*J. Am. Chem. Soc.* **2010**, *132*, 5562−5563).

This transformation is envisaged to occur via the initially formed mixture of π-oxa-allylpalladium adducts **3** and σ-oxa-allylpalladium adducts **4** which undergo protonolysis followed by oxidation with hydrogen peroxide to the products **2**.

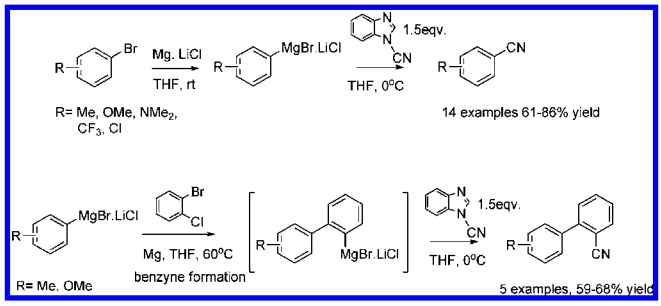


Synthesis of Oxazoles via Ritter Reaction



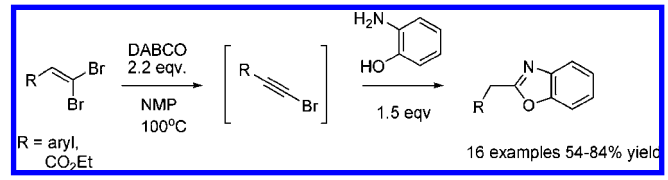
Taylor et al. from the University of Toronto (*Synthesis*, **2010**, *9*, 1449−1452) have reported the synthesis of oxazoles via a Ritter-type reaction of α-tosyl esters or ketones with nitriles under Lewis acidic conditions. In cases where cation stabilising substituents were present, a trifluoroacetyl group was used rather than tosyl. Highest yields are obtained with use of trimethylsilyl triflate as Lewis acid catalyst, and in most cases oxazoles are obtained in 65−99% yield. This reaction appears to be a versatile approach to the synthesis of oxazoles, for example, as an alternative to the Gabriel synthesis for 5-ethoxyoxazoles or for more complex oxazoles such as the indole derivative above.

Electrophilic Cyanation of Grignard Reagents



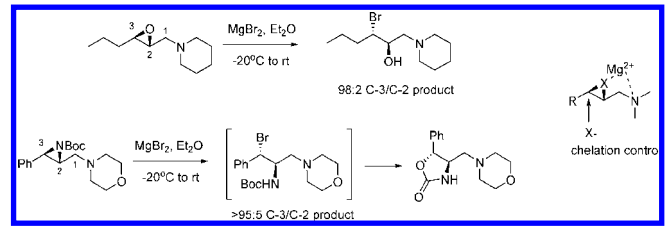
The conversion of aryl halides to aryl nitriles can be effected by reagents such as CuCN (Rosenmund von-Braun), $Zn(CN)_2$, or potassium ferrocyanide/transition metal and of course the Sandmeyer reaction using a diazonium salt/CuCN. Viable electrophilic cyanations of aryl organometallics appear restricted to aryl zinc halides with tosylcyanide or aryl Grignards with 2-pyridylcyanate. To overcome these limitations Beller et al. (*Chem.—Eur. J.* **2010**, *16*, 4725−4728) reports the reaction of aryl Grignards with *N*-cyanobenzimidazole, acting as an electrophilic cyanide source, to afford a range of benzonitriles in good yield (61−86% yield). Of note is a successful tandem Grignard formation, benzyne trapping, and electrophilic cyanation to yield a biphenyl nitrile.

Synthesis of Benzoxazoles from 1,1-Dibromoalkenes



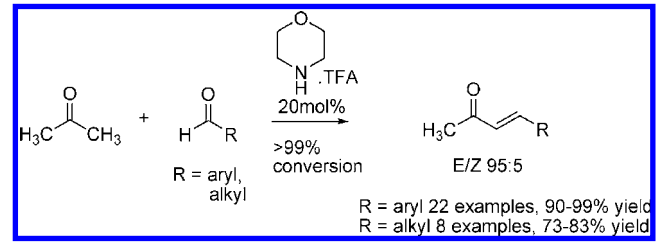
Benzoxazoles are typically synthesised by reaction of *o*-aminophenols with carboxylic acid derivatives followed by acid cyclisation or by a condensation/oxidation sequence with aldehydes. A markedly different approach is reported by Zhang et al. (*Tetrahedron Lett.* **2010**, *51*, 3246−3249) which utilises terminal dibromoalkenes, which themselves are readily available via Corey−Fuchs homologation of aldehydes. Thus treatment of the dibromoalkene with base (DABCO) and *o*-aminophenol afforded benzoxazoles in modest-high yield. The authors speculate the reaction proceeds via an intermediate bromoalkyne.

$MgBr_2$ Regioselective Opening of Epoxides and Aziridines



As part of a programme towards the development of saquinavir analogues, Righi et al. (*J. Heterocycl. Chem.* **2010**, *47*, 564.) have demonstrated a novel regioselective ring-opening of 2,3-epoxy and 2,3-aziridinyl amines with $MgBr_2$ in diethyl ether. In all cases the regioselectivity was >90:10 in favor of the C-3 bromo adduct. Benzylic bromide products derived from *N*-Boc aziridines rearranged *in situ* to afford oxazolidinones. This methodology appears generally applicable for the diastereoselective syntheses of *syn*-amino alcohols and *syn*-diamines through further elaboration of the bromo products.

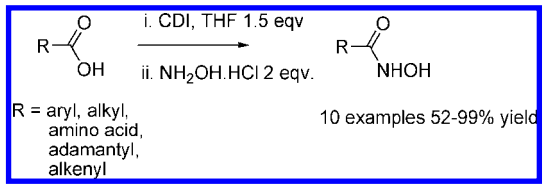
Facile Monoaldol Condensation of Acetone with Enolisable Aldehydes



List et al. (*Adv. Synth. Catal.* **2010**, *352*, 1135−1138) have demonstrated morpholinium trifluoroacetate (TFA) to be a superior catalyst for the selective mono-Aldol reaction of acetone with a variety of aryl and alkyl aldehydes. The authors surveyed a number of piperidine, morpholine, and thiomorpholine salts and found morpholinium TFA salt to provide the highest conversion and selectivity for monoaldol products. Most significant was the cross-aldol with enolisable aliphatic aldehydes. For example, morpholinium TFA-catalysed aldol cross

reaction of acetone and octanal gave the mono-aldol adduct in 85% selectivity and 81% isolated product on 45-g scale. Other examples with aliphatic aldehydes generally gave high yields of monoadducts after chromatography. Further investigations are required to elucidate whether the mechanism of this reaction proceeds via aldol or Mannich pathways.

Efficient Conversion of Carboxylic to Hydroxamic Acids Using Carbonyl Diimidazole



The carbonyl diimidazole (CDI)-promoted Lossen rearrangement was recently reported in a publication from the Pfizer Groton development group (*Org. Lett.* **2009**, *11*, 5622.). The authors commented that a significant limitation was the availability of the precursor hydroxamic acid and provided some preliminary results on the use of CDI to prepare them. In an unconnected report, Usachova et al. at the Latvian Institute of Organic Synthesis (*Synth. Commun.* **2010**, *40*, 927−935) provide a high- yielding protocol to convert carboxylic acids to hydroxamic acids with 2 equiv of CDI followed by treatment with either solid $NH_2OH \cdot HCl$ or aqueous 2 M NH_2OH. In most cases products were isolated in 70−99% yield with the exception of an alkynyl carboxylic acid which gave low yields of products (<25%). This methodology in combination with the earlier Pfizer work should promote the Lossen rearrangement as a scalable and safe alternative to the Curtius or Hoffmann rearrangements.

A PAT Approach to Improve Process Understanding of High Shear Wet Granulation (HSWG) Through In-Line Particle Measurement Using FBRM C35

The successful implementation of Quality by Design (QbD) in the pharmaceutical industry requires the use of statistical design of experiments (DoE), of scale-up science, and of process analytical technology (PAT). Knowledge-rich experiments are designed so that they can use more than one QbD tool. A group from Wyeth (Pfizer), Excella, and Mettler-Toledo (Huang, J.; et al. *J. Pharm. Sci.* **2010**, *99*, 3205.) reports about such a DoE experimental matrix executed using an in-line particle measurement instrument, the FBRM C35. The FBRM C35 has been recently commercialized, and among the improvements that it includes, a mechanical scraper ("windshield wiper") is worth noting. The objective of the team was to develop process understanding for a high shear wet granulation (HSWG) process, in particular to determine the end point of the operation. As before, issues and limitations were encountered during the evaluation of the FBRM probe; expected challenges were probe location, sampling, and data analysis. The authors emphasize that "FBRM should not be considered as a particle size analyzer in the traditional analytical sense. It is really an in situ processing monitoring tool that tracks the rate and degree of change to particle count and size as the particles naturally exist in the process". The conclusion of the team is that the FBRM C35 could be a potential technique for HSWG end-point determination. Hopefully the analysis of the DoE data will be published in a sequel to this paper.

Single-Crystal-to-Single-Crystal Reactivity: Gray, Rather than Black or White

Good understanding of the stability of solid dosage forms benefits from a good understanding of solid-state reactivity. Rather unique cases of solid-state reactivity are single-crystal-to-single-crystal (SCSC) reactions. In such SCSC reactions, a single crystal undergoes a chemical transformation to yield a product that is also a single crystal. This perspective summarizing the state-of-the art in the SCSC reactivity was published recently (Halasz, I. *Cryst. Growth Des.* **2010**. In press. DOI: 10.1021/cg100338t). A possible reason for the renewed interest in SCSC reactivity is the opportunity that they provide for investigating solid-state reaction mechanisms. Among the experimental challenges encountered are the characterization of single crystals. The author comments that often solid-state NMR spectroscopy must be used in conjunction with single-crystal X-ray diffraction. Scientific and technical limitations together with related terminology confusion are reviewed for key concepts such as crystallinity quantification and the definition of a (perfect) single crystal. This mini-review has 42 reference entries, including nearly 100 individual references. For the philosophical aspects of the discussion the author also references a recent book: *Not Exactly: In Praise of Vagueness* (van Deemter, K. Oxford University Press: London, New York, 2010).

Coupling between Membrane Processes and Crystallization Operations

The ideal approach to control particle morphology during a crystallization process is to control supersaturation, especially if this task is uncoupled from nucleation and growth. A team from Université Lyon 1 (Charcosset, C.; et al. *Ind. Eng. Chem.. Res.* **2010** *49*, 5489−5495; DOI: 10.1021/ie901824x) reviews the use of membrane processes in crystallization operations. Some of the relevant features of a membrane crystallization system are: (a) to control and limit the maximum level of supersaturation (due to defined mass transfer capability across the membrane); (b) to act as heterogeneous nucleation-inducing substrates; (c) to control certain solid state properties such as polymorphic form, shape, and purity. Four types of membranes are discussed, including principles of operation, applications, and limitations: (1) osmosis and reverse osmosis, (2) evaporative membrane crystallization, (3) membrane contactors, and (4) membrane templates. Interestingly, in spite of the fact that the first reports of membrane crystallization were published nearly 25 years ago, none of these membrane-based crystallization processes was implemented at industrial scale.

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