Organic Process Research & Development

HIGHLIGHTS FROM THE LITERATURE

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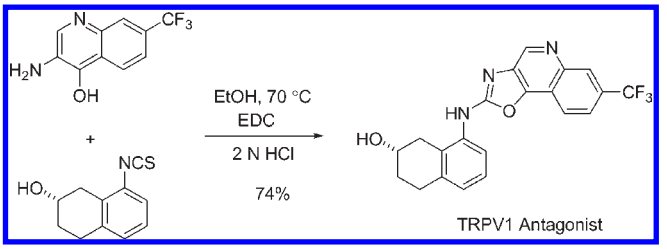
Some Items of Interest to Process R&D Chemists and Engineers

SYNTHESIS OF A TRPV1 ANTAGONIST

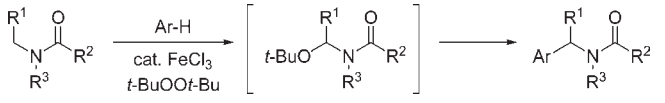


In preclinical models of inflammatory and neuropathic pain, TRPV1 antagonists have shown promising analgesic efficacy; however, clinical proof-of-concept remains a challenge for the field. An efficient synthesis of 2-amino-oxazolo[4,5-*c*]quinoline TRPV1 antagonists via a thiourea formation/carbodiimide cyclization sequence is described by Voight and co-workers at Abbott (*J. Org. Chem.* **2010**, *75*, 8713−8715). At the heart of this chemistry is a three-step, one-pot synthesis of pentacyclic 2-amino-oxazolo[4,5-c]quinoline structures starting from 3-amino-4-hydroxyquinolines and chiral isothiocyanates derived from 1-amino-7-hydroxynaphthalenes. The chemistry developed for the specific structure of interest was applied to the preparation of six additional related compounds.

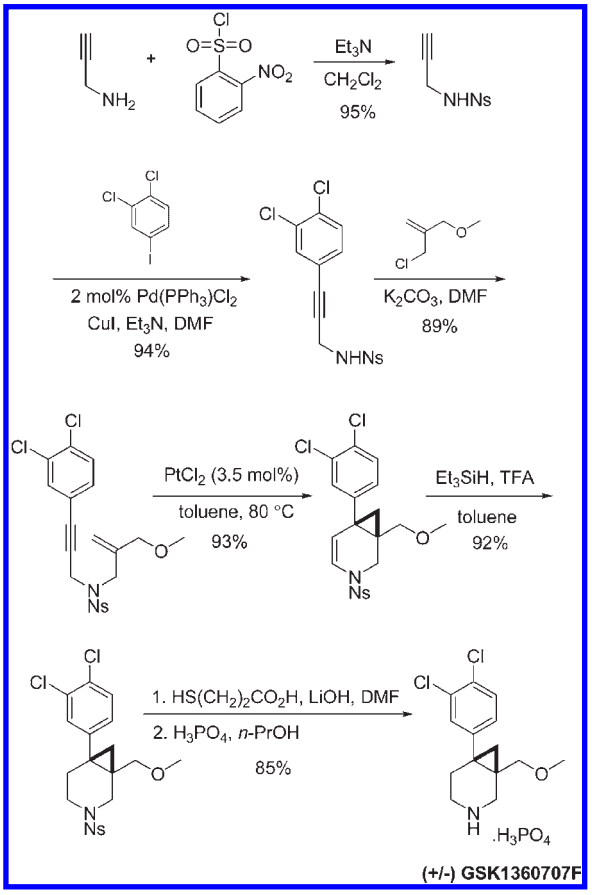
CYCLOISOMERIZATION APPROACH TO TRIPLE REUPTAKE INHIBITOR GSK1360707F

GSK1360707F is a potent serotonin, noradrenaline, and dopamine reuptake (triple reuptake) inhibitor under development at GlaxoSmithKline (GSK) for the treatment of major depressive disorder (MDD). Elitzin and co-workers at GSK describe a novel approach to this target that features a Pt-catalyzed cycloisomerization of a readily prepared ene−yne substrate (*J. Org. Chem.* **2011**, *76*, 712−715). Key aspects of this work, such as the choice of the nitrogen protecting group and initial enantioselectivity studies, are discussed. The researchers observed stereoselectivity to the extent of 59% ee when the reaction was run in the presence of a Au(I) catalyst and (*R*)-tol-BINAP ligand. Application of chiral ligands to the Pt-catalyzed system resulted in suppressed reaction rates.

OXIDATIVE COUPLING OF ALKYLAMIDES AND ARENES

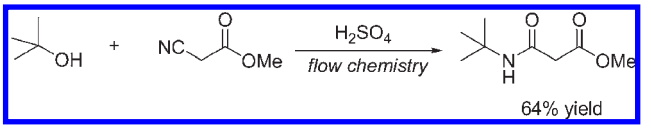


Shirakawa, Hayashi, and co-workers report on the oxidative coupling of alkylamides with electron-rich arenes (*J. Org. Chem.* **2011**, *76*, 25−34). $FeCl_3$ in combination with *t*-BuOO*t*-Bu as an oxidant was found to be an efficient catalytic system for oxidation of alkylamides to α-(*tert*-butoxy)alkylamides. $FeCl_2$ and CuCl showed, respectively, almost the same and slightly lower activities compared with that of $FeCl_3$ in the *tert*-butoxylation of *N*-phenylpyrrolidone, whereas no *tert*-butoxylated product was obtained by use of $Fe(OTf)_3$, $RuCl_3$, or $Zr(OTf)_4$. Further,



$FeCl_3$ was found to be an effective catalyst for the Friedel−Crafts alkylation of electron-rich arenes with the obtained α-(*tert*-butoxy)alkylamides. Considering these observations, $FeCl_3$ was then applied to a one-pot oxidative coupling of alkylamides with arenes, proceeding via intermediate α-(*tert*-butoxy)alkylamides. This method is applicable to a wide variety of alkylamides and arenes. The researchers discuss plausible mechanisms for each step, including an Fe(II)/Fe(III) radical-type process for the *tert*-butoxylation and a typical two-electron Lewis acid-type process promoted by Fe(III) for the Friedel−Crafts step. Numerous examples are presented with yields ranging from 55 to 99%.

FLOW CHEMISTRY



One of the foremost advantages of microflow procedures in synthetic chemistry is the superior kinetic and thermodynamic

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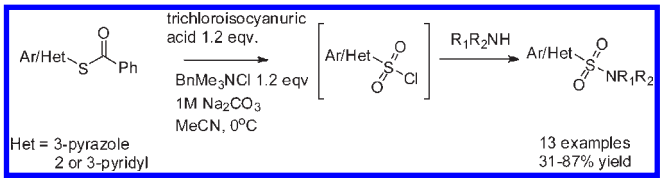
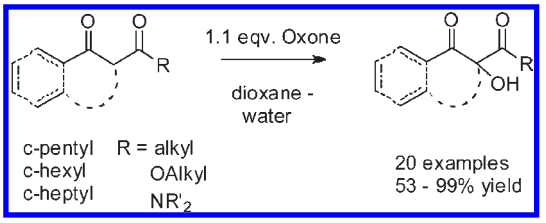
control over the course of a reaction when compared to the batch process. Microfluidic mixing has been proven to be much more efficient and quicker than even rapid stirring in a flask. Additionally, the dimensions of the microstructured devices together with the flow rate can allow very short and very accurately adjusted reaction times. Wirth and co-workers at Pfizer report on optimization of the Ritter reaction for flow conditions, leading to short reaction times and higher yields (*Synlett* **2010**, 3099−3103). The authors note that running this reaction under flow conditions is also more feasible with regard to safety, productivity, and tolerance toward substrate functionalities. In a related report (*J. Org. Chem.* **2011**, *76*, 993−996), Dolman and co-workers at Merck describe an economical and simple flow mixer based on magnetically driven agitation in a tube (MDAT). Mixing via MDAT compared favorably to both tee and multilaminar mixers at low flow and was successfully used to screen and optimize two challenging organometallic reactions at low temperature without clogging or the need for high dilution.

■ CONVERSION OF AROMATIC THIOBENZOATES TO SULFONAMIDES



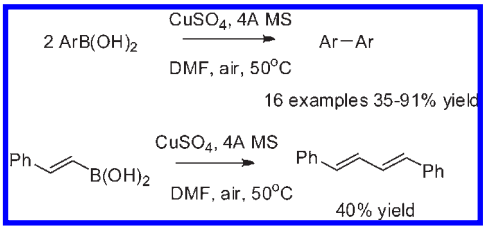
Ho et al. (*Tetrahedron Lett.* **2011**, *52*, 820−823) of Pfizer Sandwich have developed a two-step synthesis of aromatic sulfonyl chlorides from aromatic iodides. The required thiobenzoates were prepared in typically good yield via copper(I)-catalyzed coupling of aryl/heteroaryl iodides with thiobenzoic acid. A one-pot process comprising oxidative chlorination with trichloroisocyanuric acid and amine displacement yielded a range of sulfonamides in satisfactory yield. Other chlorinating agents such as NCS produced inferior results, whilst ortho-substituted thiobenzoates gave low yields of sulfonamide.

■ OXONE HYDROXYLATION OF CYCLIC *B*-DICARBONYLS



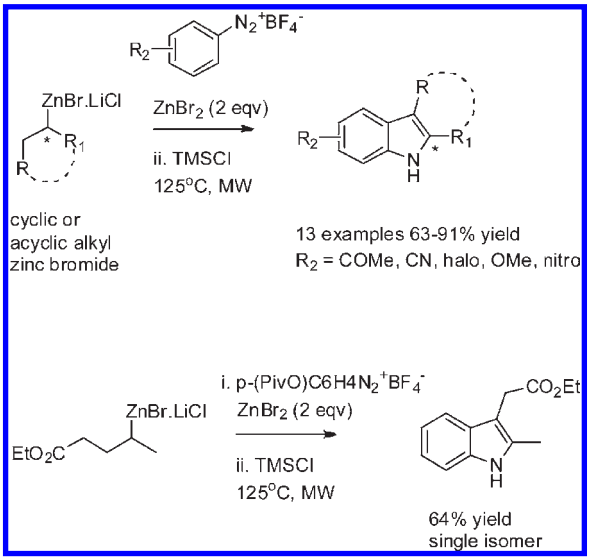
Various reagents are capable of hydroxylating β-dicarbonyl compounds including dimethyldioxirane, hydrogen peroxide, and MCPBA. Zhang et al. (*Eur. J. Org. Chem.* **2010**, 7020−7026) report a simple method for this transformation using Oxone in dioxane−water. Modest to high yields of hydroxylated products were obtained for all cyclic β-dicarbonyls irrespective of whether amide, ketone, or ester side chains were present. Acyclic substrates reacted sluggishly with Oxone or failed to react at all; thus, this methodology is only suitable for cyclic substrates.

■ COPPER SULFATE DIMERIZATION OF BORONIC ACIDS



Kaboudin et al. (*Synthesis* **2011**, (1), 91−96) provide an efficient method for the oxidative dimerization of both aryl and vinyl boronic acids. Thus, treatment of a variety of aryl and heteroaryl boronic acids with a stoichiometric equivalent of copper(II) sulfate in *N*,*N*-dimethylformamide at 50 °C led to dimerization in generally good yield. This protocol was amenable to aryl boronic acids possessing a wide variety of functional groups including aldehyde and nitro. In addition, thiophenyl- and benzofuranyl boronic acids could be dimerized successfully. A single example was provided for the oxidative dimerization of a vinyl boronic acid (see above) leading to the diene in modest yield.

■ ORGANOZINC FISHER INDOLE VARIANT



Knochel et al. (*Synthesis* **2011**, (1), 23−29) report an interesting variant of this classic reaction. Both primary and secondary alkyl zinc halides underwent addition to diazonium salts to afford an azo intermediate. This then rearranged on treatment with trimethylsilyl chloride and microwave heating to afford the indole. Unsymmetrical secondary alkylzincs afforded a single regioisomer (see above). Zinc(II) bromide was required in the initial step to prevent double addition of the alkylzinc to the diazo salt, whilst both conventional and microwave heating could be employed in the rearrangement step. This protocol was successfully applied to a wide range of substituted diazonium salts.

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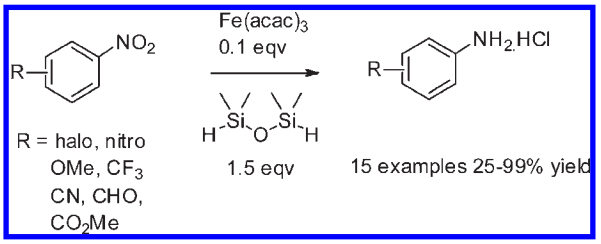
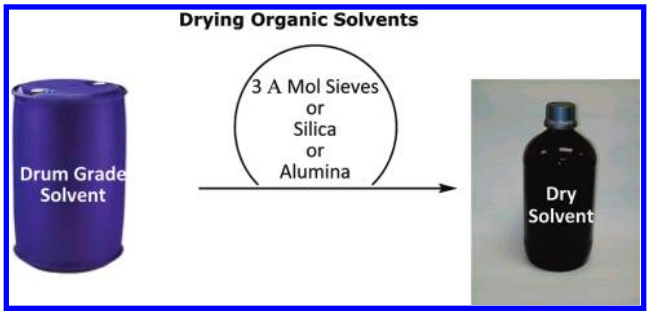
■ TMDS/IRON REDUCTION OF NITRO GROUPS



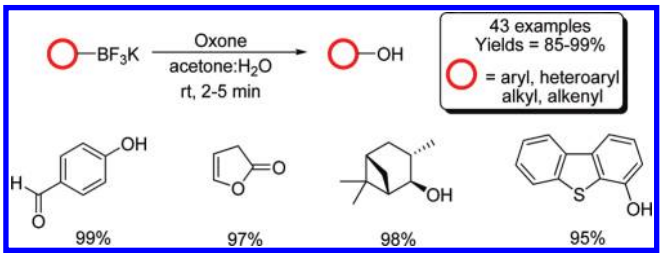
Lemaire (U. of Lyon) and collaborators from Minakem and Rhodia (*Tetrahedron* **2011**, 10.1016/j.tet.2010.12.070) have reported an optimized procedure for the tetramethyldisiloxane (TMDS)/$Fe(acac)_3$ reduction of aromatic nitro groups. Initial attempts to effect the reduction with polymethylhydrosiloxane (PMHS) and iron salts gave modest yields (~50%) due to the coagulation of PMHS during the reaction. No such issues were observed with TMDS which with catalytic $Fe(acac)_3$ gave consistently high yields of 4-cyanoaniline in a variety of solvents (THF, MeTHF, toluene, and tBuOH). No reactions took place under copper catalysis (with $Cu(acac)_2$ for instance), confirming that iron was the true catalyst. The optimized conditions were employed on a series of nitro aromatics, and only ortho-substituted substrates gave low yields (20−66%), whilst other substrates reduced in typically >80% yield.

■ DRYING ORGANIC SOLVENTS



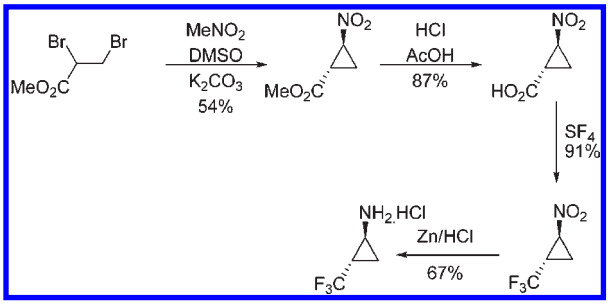
Laboratories involved in synthetic chemistry frequently require the need for dry organic solvents. Typically, methods used call for the use of highly reactive metals or metal hydrides, which increase the risk of fires or explosions in the laboratory. To alleviate these risks some laboratories have now turned to relatively expensive commercially available drying trains that used prepacked cartridges to dry solvents. However, a large number of laboratories do not have access to such facilities. In a bid to remedy these shortcomings Williams from the University of Johannesburg (*J. Org. Chem.* **2010**, *75*, 8351−8354) undertook a study of the efficiency of a number of drying agents. From this study it was shown that 3 Å molecular sieves (silica or alumina) readily and reliably provide dry solvents with residual moisture in the sub-10-ppm range. The main drawback of this research is that the author did not test for the removal of peroxides from solvents such as THF.

■ IMPROVED STRATEGY FOR PHENOL SYNTHESIS



Traditionally, phenols have been widely used as versatile synthetic intermediates; unfortunately, these have been synthesized under harsh reaction conditions which lend themselves to poor yields and substrate scope. More recently the oxidation of boronic acids using hydrogen peroxide has proven an industry standard protocol. Unfortunately, these conditions have reduced appeal on large scale. To address this, Molander and Cavalcanti (*J. Org. Chem.* **2011**, *76*, 623−630) have turned their attention to the oxidation of trifluoroborate salts. A number of reports into this reaction suggest elevated temperature and elongated time periods are required; however, this paper demonstrates that Oxone facilitates this reaction within 5 min at room temperature. The major advantage, however, is that simple workup by filtration through a pad of silica/charcoal gives analytically pure phenols in virtually quantitative yields. Molander and Cavalcanti apply this methodology to a wide range of substrates, proving that this is indeed a key development for synthetic chemistry.

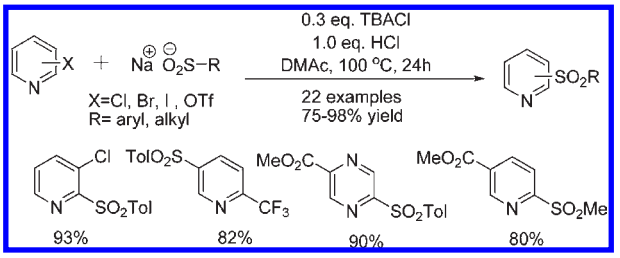
■ MULTIGRAM SYNTHESIS OF *TRANS*-2-(TRIFLUOROMETHYL)CYCLOPROPANAMINE



The introduction of privileged motifs into compounds with biological activity is a well-known strategy in medicinal chemistry. The cyclopropyl group is one such privileged motif, the use of which has become increasingly popular in drug design. The introduction of the cyclopropyl group is frequently done via cyclopropyl amine. When one does a literature search for cyclopropyl amines, a number of examples are retrieved where only the 1-(trifluoromethyl)cyclopropanamine is readily synthesized. To address this limited scope the scientists at Enamine have developed a route to *trans*-2-(trifluoromethyl)cyclopropanamine (*Synthesis* **2011**, (1), 119−122). The initial cyclopropanation was performed by the addition of nitromethane to the dibromide which proceeded in good yield. Of note is that addition of the nitromethane over 12 h was required; otherwise the product yield decreased significantly. The ester moiety was then hydrolyzed under acidic conditions, giving the carboxylic acid. Treatment of the acid with 2.5 equiv of sulfur tetrafluoride in the presence of catalytic amounts of water (to generate HF) afforded the trifluoromethyl-substituted cyclopropane in excellent

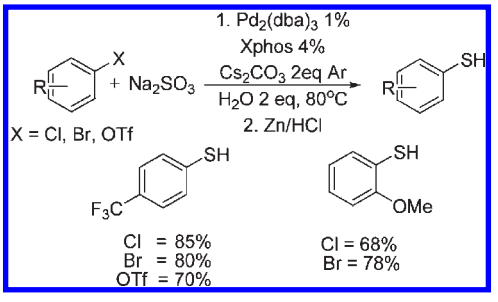
yield. Finally, reduction of the nitro group to the hydrochloric salt of the target compound was facilitated by the use of aqueous hydrochloric acid with zinc powder. Importantly, the synthesis of *trans*-2-(trifluoromethyl)cyclopropamine hydrochloride was easily scaled up so that 20 g of the product was prepared in a single batch from the starting dibromide.

■ ONE-POT SYNTHESIS OF SULFONYLATED PYRIDINES



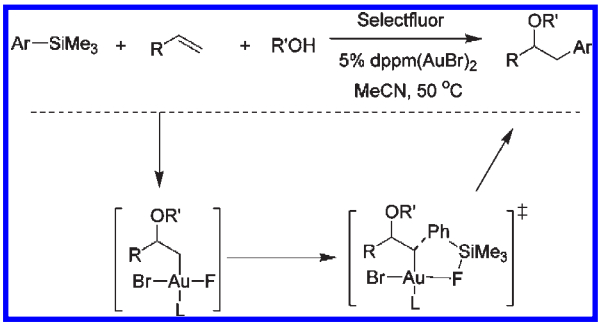
Throughout medicinal and agricultural chemistry the pyridyl sulfone moiety is a building block with a distinguished track record; these have been shown to be anti-inflammatory, anti-hyperglycemic, and immunosuppressive agents. The most common approach for their preparation has typically involved displacement of a halo-pyridine with a thiol followed by an oxidation of the corresponding sulfide. To address the problems associated with the traditional procedures a team led by Maloney and Kuethe from Merck based in Rahway (*Org. Lett.* **2011**, *13*, 102−105) have developed a concise one-pot protocol for the rapid preparation of highly functionalized sulfonylated pyridines. They began their work by performing a thorough catalyst screen to promote SnAr reactions of chloropyridines with sulfinic acids salts; from this they obtained tetrabutylammonium chloride as the most effective additive and dimethylacetamide as the most appropriate solvent regardless of which metal or ligand was present. They then turned their attention to phase transfer catalysis and the application of these conditions to a range of chloropyridines; pleasingly, several examples gave yields ranging from 85 to 98% yield. During transfer to 2- and 4-chloropyridines the standard conditions failed; to resolve this issue an equivalent of HCl was required which gave access to all analogues. In total the authors demonstrate 22 examples in good to excellent conversion.

■ SYNTHESIS OF ARYL THIOLS

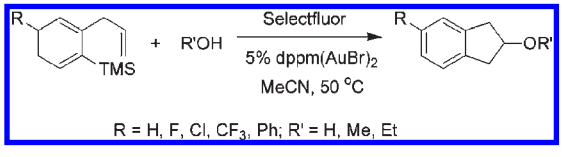


Aryl thiols are an important class of building blocks often used in natural product and pharmaceutical compounds. Unfortunately, few aryl thiols are commercially available. In this paper Guo (*Tetrahedron Lett.* **2011**, *52*, 205−208) reports the cross coupling of aryl chlorides, bromides, and triflates with sodium thiosulfate to give rise to a range of aryl thiols. This approach was taken due to the relatively cheaper cost of aryl chlorides and bromides compared to that of their iodide analogues. In addition, sodium thiosulfate is an odorless white powder, which can be easily handled and is a nontoxic and an inexpensive reagent. After an initial catalyst screen Guo discovered that a palladium(0) source using Xphos in combination with cesium carbonate gave the optimal and most robust coupling conditions. The crude reaction mixture was then directly treated with zinc/hydrochloric acid to give the desired thiols. During the course of the study it was found that the presence of ortho-hindrance diminishes the efficiency of the reaction. Functional groups that are compatible with this protocol include CF_3, F, Ph, and methoxy groups. With the mild conditions utilized for the transformation, one can envisage a new range of building blocks becoming commercially available with new substitution patterns previously unattainable.

■ GOLD-CATALYZED OXIDATIVE COUPLING REACTIONS WITH ARYLTRIMETHYLSILANES



Toste and co-workers of the University of California, Berkeley have described gold-catalyzed oxidative coupling reactions using organosilicon reagents (*Org. Lett.* **2010**, *13*, 4728−4731). The reactions employ acetoxy-, trifloxy-, and sulfonamide-substituted aryltrimethylsilanes to give the corresponding adducts in good to excellent yields. The reactions were general for a variety of alcohol nucleophiles including primary and secondary alcohols, although incomplete conversions were observed with tertiary alcohols. These transformations tolerated a variety of functional groups in the olefins, including esters, sulfonamides, carbamates, and halides.



Analogously, gold-catalyzed two-component cycloadditions proceeded smoothly with methanol, ethanol, or water providing tetrahydronaphthalenes in excellent yields. With a scope similar to that of the three-component reaction, a variety of ring substitutions was tolerated.

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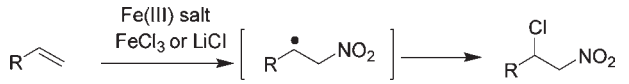
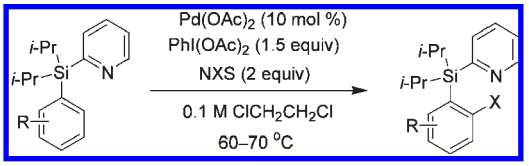
■ IRON-MEDIATED RADICAL HALO-NITRATION OF ALKENES

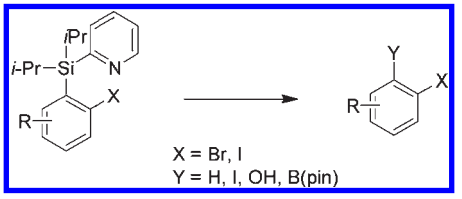


Iron complexes as nontoxic and inexpensive green elements and potential replacements for expensive transition metal catalysts attract increasing attention from the chemistry community. Taniguchi and co-workers in Japan developed an approach for preparation of halogenated nitro compounds via an iron-mediated radical reaction (*J. Org. Chem.* **2010**, *75*, 8126−8132). The radical addition of alkenes with nitrogen dioxide generated by thermal decomposition of iron(III) nitrate results in alkyl radicals which are trapped by halogen atoms in the presence of halogen salts. The reaction protocol using nontoxic and inexpensive iron reagents appears applicable to acyclic, cyclic, electron-deficient, or electron-rich alkenes to afford the corresponding chloro-nitro compounds in moderate to good yields.

■ PALLADIUM-CATALYZED ORTHO HALOGENATION OF PYDIPSI-ARENES

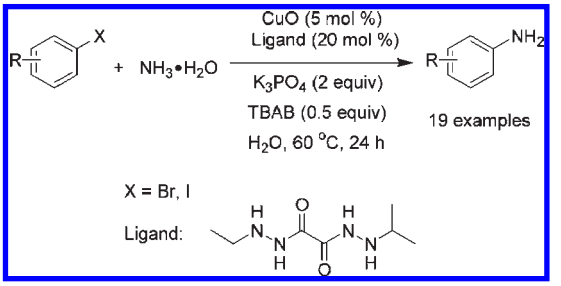


Currently, C−H bond activations are one of the most active research fields in organic chemistry. Gevorgyan and co-workers at the University of Illinois at Chicago developed palladium-catalyzed ortho halogenation reactions of easily accessible pyridyldiisopropylsilyl (PyDipSi) arenes into 1,2-ambiphiles (*Angew. Chem., Int. Ed.* **2010**, *49*, 8729-8732). Investigations on the generality of the halogenation reactions showed that a number of functional groups, including OMe, F, Cl, Br, ester, and amide, were tolerated under the halogenation reaction conditions. Iodination of para-substituted aryl silanes possessing both electron-donating and electron-withdrawing substituents proceeded with equal efficiency. PyDipSi arene derivatives of various heterocycles, such as benzofuran, carbazole, indole, and benzoxazole, were monoiodinated in good yields.



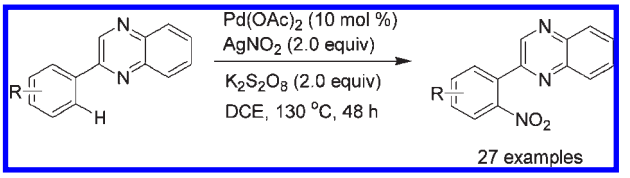
Further transformations of pyridyldiisopropylsilyl arenes to a variety of valuable building blocks were briefly demonstrated.

■ COPPER-CATALYZED AMINATION OF ARYL HALIDES IN WATER

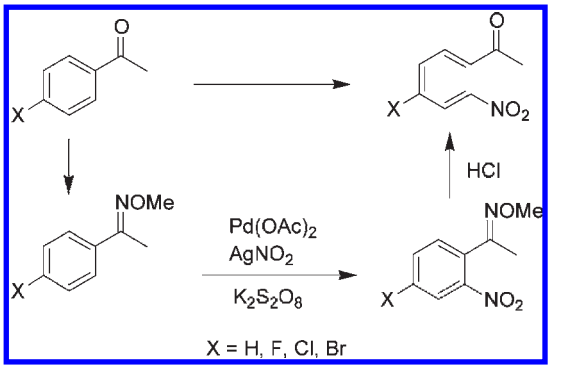


A general and practical protocol for the direct coupling of aryl or heteroaryl halides with aqueous ammonia was developed by scientists in China (*Eur. J. Org. Chem.* **2010**, 6149−6152). The use of $N^2,N^{2\prime}$-diisopropyloxalohydrazide/CuO as catalytic system in the aminations of heteroaryl halides in the presence of K_3PO_4 and tetrabutylammonium bromide (TBAB) provided the aminated product in good to excellent yields. The reactions tolerated electron-donating and electron-withdrawing substituents and could be performed at 60 °C for 24 h or at 120 °C for 20−30 min. Moreover, the reactions are attractive to process chemists in terms of large-scale application due to the easy availability of the ligand, copper source, and the use of a green solvent and aqueous ammonia.

■ PALLADIUM-CATALYZED REGIOSPECIFIC SYNTHESIS OF NITROARENES



A direct ortho nitration of aryl C−H bonds was developed by Liu and co-workers of Zhejiang University of Technology, China (*Chem. Eur. J.* **2010**, *16*, 13590−13593). The palladium-catalyzed nitration occurred in the presence of $AgNO_2$ (2.0 equiv) as nitrogen source and $K_2S_2O_8$ (2.0 equiv) as an oxidant. Further studies revealed that the nitration is sensitive to the functional R groups: with electron-rich R groups, such as methyl, methoxyl, and hydroxyl groups, providing products in good yields (76−93%) and electron-deficient R groups, such as F, Cl, and Br, leading to products in lower to moderate yields (35−51%).



The *O*-methyl oxime group was shown to be a good directing group under the nitration conditions. Thus, 2-nitrated acetophenones were prepared by ortho nitration of oximes followed by treatment with hydrochloric acid.

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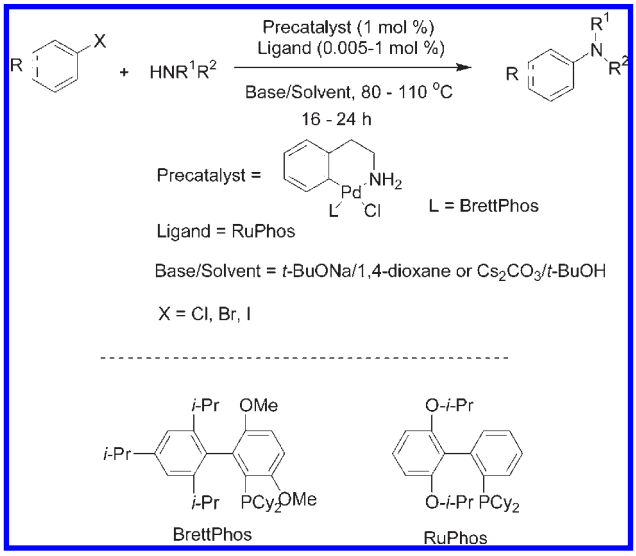
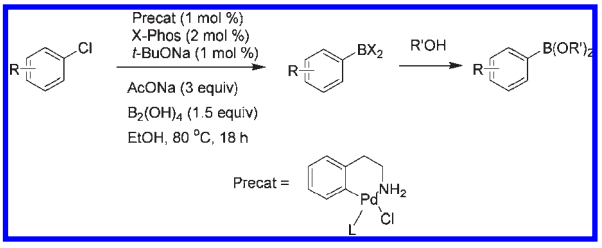
■ TWO BIARYLPHOSPHINE-BASED PD CATALYSTS FOR C−N CROSS-COUPLING REACTIONS

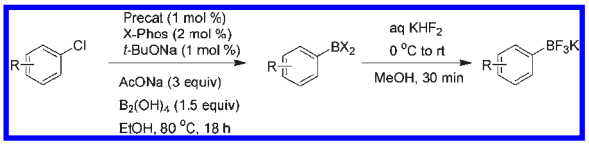


Buchwald and co-workers from Massachusetts Institute of Technology have developed a new catalytic system for C−N cross-coupling reactions (*J. Am. Chem. Soc.* **2010**, *132*, 15914−15917). Generally, a given catalyst system developed previously has a limited reaction scope; for example, a BrettPhos-based catalyst system works well for the monoarylation of primary amines but is inefficient for reactions involving secondary amines, while RuPhos is highly efficient for the arylation of secondary amines. Remarkably, the new catalyst system works for all Pd-catalyzed amination reactions including both primary and secondary amines. The use of Cs_2CO_3 as the base in *t*-BuOH allowed for substrates containing base-sensitive functional groups such as esters, nitriles, ketones, or nitroarenes to be converted to product in high yields. Furthermore, by employing a 1:1 mixture of precatalyst and ligand, anilines were coupled with aryl chlorides, bromides, or iodides in good to excellent yields (using only ppm levels of Pd, 0.005−0.01 mol %). The catalyst system was not suitable for substrates such as imidazoles, benzimidazoles, pyrazoles, or secondary acyclic amides.

■ PALLADIUM-CATALYZED, DIRECT SYNTHESIS OF BORONIC ACID AND DERIVATIVES FROM ARYL CHLORIDES

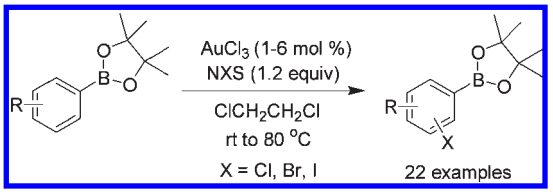


A palladium-catalyzed, direct synthesis of boronic acids and derivatives from aryl chlorides was reported by a collaborative team of University of Pennsylvania and Merck (*J. Am. Chem. Soc.* **2010**, *132*, 17701−17703). Exposure of aryl chlorides to general conditions (1 mol % of precatalyst, 2 mol % of X-Phos, 1 mol % of NaO*t*-Bu, 3 equiv of KOAc, 1.5 equiv of tetrahydroxydiboron) in EtOH (0.1 M) at 80 °C for 18 h afforded the desired products which then were converted to boronate analogues in good yields. The method allowed easy and direct access to a diverse set of boronic acids, boronate esters, and trifluoroborates.



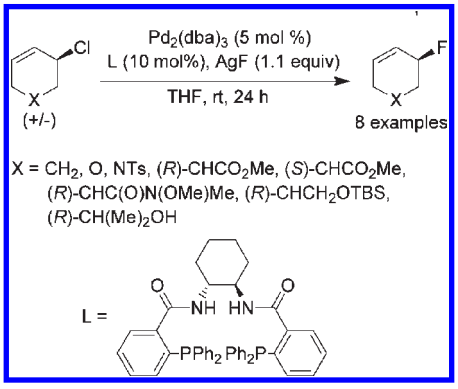
In addition, this protocol allowed the preparation of the more robust aryltrifluoroborates. The method tolerated a wide range of substituents, including nitro, cyano, ester, and aldehyde groups.

■ GOLD(III)-CATALYZED HALOGENATION OF AROMATIC BORONATES WITH *N*-HALOSUCCINIMIDES



Aromatic boronates bearing halogen substituents are valuable synthetic intermediates due to the availability for multiple transformations in addition to Suzuki−Miyaura cross-coupling reaction. Scientists in China developed a Au(III)-catalyzed halogenation approach to access to halogenated aromatic boronates with *N*-halosuccinimides (*Org. Lett.* **2010**, *12*, 5474−5477). The results showed that $AuCl_3$ could catalyze a wide range of arylboronates, including those bearing heterocyclic rings. The reactions worked well with arylboronates bearing either electron-rich or -poor substituents on aromatic rings, although the latter required relatively higher catalyst loading and temperature. In general, the reactions were conducted under relatively mild conditions (rt to 80 °C), leading to high yields of products.

■ PD-CATALYZED ENANTIOSELECTIVE ALLYLIC FLUORINATION



A palladium-catalyzed enantioselective fluorination of readily available cyclic allylic chlorides with AgF was accomplished in the presence of Trost bisphosphine ligand (*J. Am. Chem. Soc.* **2010**, *132*, 17402−17404). In contrast to the popular Pd(II)-electrophilic "F^+" mechanism, the authors demonstrated that the C−F bond formation occurs by an S_N2-type attack of fluoride on a Pd(II)−allyl intermediate. The driving force for the C−F bond formation was presumably generated from the precipitation of AgCl since substrates possessing traditional leaving groups for

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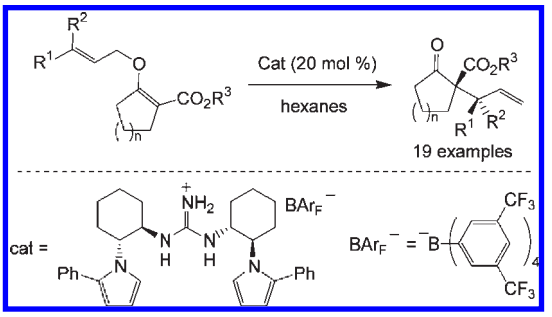
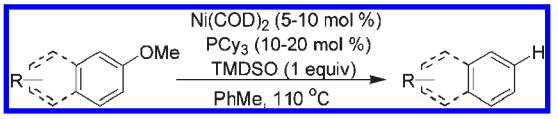
Pd-catalyzed allylic alkylation, such as allylic acetates and carbonates, were unreactive under the same conditions. The initial Pd(0) S_N2-type attack on the allylic chloride to activate the C−Cl bond was followed by chloride abstraction by Ag^+ and addition of fluoride on the allyl−Pd intermediate, resulting in a product with overall retention of configuration. The reactions allowed access to highly enantioenriched cyclic allylic fluorides under mild conditions.

■ CATALYTIC ENANTIOSELECTIVE CLAISEN REARRANGEMENTS OF *O*-ALLYL *B*-KETOESTERS



Jacobsen and co-workers of Harvard University have reported chiral guanidinium-catalyzed Claisen rearrangements of cyclic *O*-allyl β-ketoesters as a method of broad scope for the formation of branched allylation products with both enantio- and diastereocontrol (*Angew. Chem., Int. Ed.* **2010**, *49*, 9753−9756). The rearrangements were effective for substrates of a variety of ring sizes and of those containing unsaturation, fused aromatic rings, and heteroatoms, affording the isolated products in high yields and enantiomeric excesses in the range of 79−87%. The drawback of the rearrangements is long reaction times (2−6 days), albeit under mild conditions (<40 °C).

■ NI-CATALYZED REDUCTION OF INERT C−O BONDS



An efficient Ni-catalyzed protocol for the reductive cleavage of inert C−O bonds was developed by Martin and his co-worker in Spain (*J. Am. Chem. Soc.* **2010**, *132*, 17352−17353). The use of PCy_3 as the ligand and tetramethyldisiloxane (TMDSO) as the hydride source was critical for obtaining the desired arenes in good yields. The reactions tolerated a variety of functional groups such as silyl, ester, amide, acetal, tertiary amine groups, or nitrogen-containing heterocycles. Lower conversions were observed for the substrates bearing ethoxy, acetoxy, mesylate, tosylate, or pivalate groups. A proposed pathway consists of C−O oxidative addition, σ-bond metathesis with the Si−H bond, and reductive elimination from a nickel(II) hydride intermediate. Nevertheless, the new C−O bond cleavage approach shows great potential in practical applications due to its simplicity and wide scope.

■ QUALITY-BY-DESIGN (QBD): AN INTEGRATED PROCESS ANALYTICAL TECHNOLOGY (PAT) APPROACH FOR A DYNAMIC PHARMACEUTICAL COPRECIPITATION PROCESS CHARACTERIZATION AND PROCESS DESIGN SPACE DEVELOPMENT

Among the concerns that some pharmaceutical companies have regarding QbD implementation is the lack of specific guidance from the regulatory agencies. It was a pleasant surprise to see a publication from the FDA (Division of Product Quality Research/Office of Pharmaceutical Sciences/CDER) on the topic of QbD implementation for the development of the design space in a coprecipitation process (Wu, H. et al. *Int. J. Pharm.* **2011**, *405*, 63−78). The proposed design space was developed using an approach based on PAT and DoE, executing the experiments at 1-L scale. Interestingly, the process understanding was extended from the end point (after reaching steady state) to several intermediate stages of the precipitation processes. Three factors were selected for a full factorial investigation (27 experiments): temperature, agitation rate, and antisolvent addition rate. FBRM and PVM probes (Mettler-Toledo AutoChem) were employed for process monitoring and response data collection. In addition to classical ANOVA DoE analysis, neural network models were also developed. Data analysis was supported with the scientific first principles available. No explicit correlations between the reported chord length distributions and the corresponding particle size distributions are mentioned. It will be interesting to see in a subsequent publication the approach taken for the scale-up of the design space.

■ STABLE POLYMORPHS CRYSTALLIZED DIRECTLY UNDER THERMODYNAMIC CONTROL IN THREE-DIMENSIONAL NANOCONFINEMENT: A GENERIC METHODOLOGY

Crystallization events are often under kinetic control, and as discovered by Ostwald over 100 years ago, there is a certain likelihood that the crystalline material obtained is metastable. One of the "holy grails" in pharmaceutical crystallization process design is our ability to execute the crystallization under thermodynamic control or to "leap-frog" Ostwald's rule of stages.

A group from Durham University proposes a "universal" approach to thermodynamic control of a crystallization process (Nicholson, C. E., et al. *Cryst. Growth. Des.* **2011**, *11*, 363−366). The proposed strategy requires crystallization in microemulsions where, because of the three-dimensional (3D) nanoconfinement, at suitable levels of supersaturation and emulsion characteristics the stable polymorph is expected to crystallize. The approach was experimentally demonstrated using three "problem" compounds: mefenamic acid, glycine, and 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophencarbonitrile] (ROY). This paper was published in communication format, and we look forward to the full paper which will likely further discuss the design of such crystallization processes, in particular with respect to surfactant selection, and supersaturation control.

■ AGGLOMERATION OF PHARMACEUTICAL, DETERGENT, CHEMICAL AND FOOD POWDERS: SIMILARITIES AND DIFFERENCES OF MATERIALS AND PROCESSES

A thorough paper written by an experienced food scientist at Nestle (Palzer, S. *Powder Technol.* **2011**, *206*, 2−17) reviews key aspects of powder agglomeration. After proposing an original

method of powder classification based on polarity and supramolecular structure, together with the discussion of fundamental physical aspects of agglomeration, the paper reviews in detail agglomeration processes as practiced in several industries. Roller compaction and tableting, of great pharmaceutical interest, are explained very clearly. This review has 65 references.

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