Organic Process Research & Development

HIGHLIGHTS FROM THE LITERATURE

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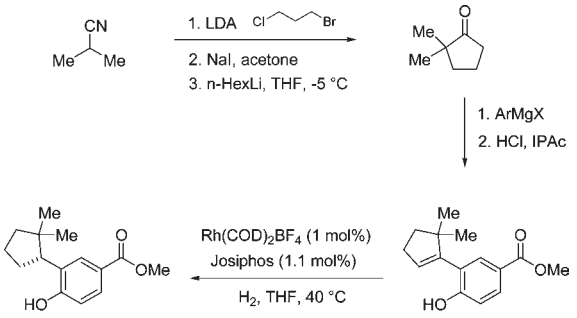
Some Items of Interest to Process R&D Chemists and Engineers

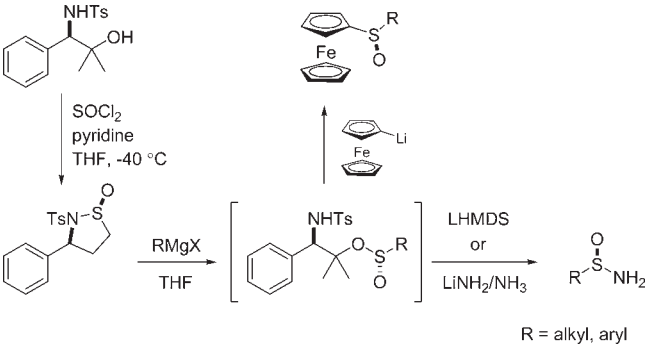
■ CATALYTIC ASYMMETRIC SYNTHESIS OF A TERTIARY BENZYLIC CARBON CENTER VIA PHENOL-DIRECTED ALKENE HYDROGENATION



99% yield, 99 %ee

An expeditious synthetic approach to a chiral phenol, a key building block in the preparation of a series of drug candidates, is reported by Caille and co-workers at Amgen (*J. Org. Chem.* **2011**, *76*, 5198−5206). The strategy includes a cost-effective and readily scalable route to 2,2-dimethylcyclopentanone from isobutyronitrile. The sterically hindered and enolizable 2,2-dimethylcyclopentanone was subsequently employed in a challenging Grignard addition mediated by $LaCl_3 \cdot 2LiCl$. A novel preparation of the lanthanide reagent required for this transformation is also described. To complete the process, a highly enantioselective Rh-catalyzed hydrogenation afforded the target chiral phenol. The importance of the phenol group to the success of this asymmetric transformation is discussed.

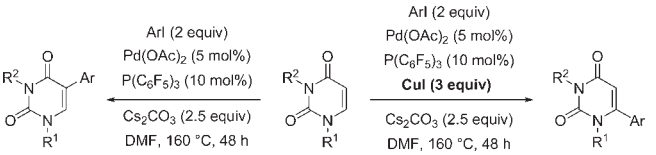
■ PHENYLGLYCINE-DERIVED CHIRAL SULFINYL TRANSFER AGENT



R = alkyl, aryl

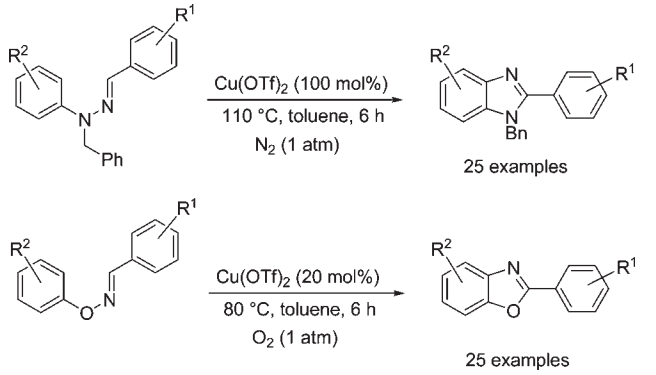
Chiral sulfinyl-containing reagents, such as sulfoxides and sulfinamides, have been recognized as useful tools in the asymmetric synthesis of complex organic molecules. Although the power of chiral sulfinyl reagents in synthetic chemistry has long been recognized, methods for their synthesis have emerged slowly. Now Han and co-workers at Boehringer Ingelheim report on a new chiral sulfinyl transfer auxiliary derived from readily available phenylglycine (*J. Org. Chem.* **2011**, *76*, 5480−5484). This auxiliary can be utilized to synthesize a diverse array of alkyl- and arylsulfinamides and sulfinylferrocenes in high yields and excellent ee's. The desired products are produced in a one-pot sequence from the oxathiazolidine 2-oxide by two sequential nucleophilic additions that proceed in a stereospecific manner.

■ REGIOSELECTIVE DIRECT C−H ARYLATIONS OF PROTECTED URACILS



Diverse uracil bases and nucleosides bearing aryl groups at positions 5 or 6 display a wide range of biological activities (cytostatic, antiviral, antagonists of GnRH, etc.). Arylation at position 5 is often used for labeling of nucleotides and DNA for applications in bioanalysis or chemical biology. A new regioselective synthesis of 5- and 6-aryluracil bases based on direct C−H arylations of diverse 1,3-protected uracils has been developed by the group of Hocek in the Czech Republic (*J. Org. Chem.* **2011**, *76*, 5309−5319). Benzyl-protected uracils were selected as the most practical in terms of stability during the arylation and because of their facile cleavage when desired. Pd-catalyzed C−H arylations in the absence of CuI gave preferentially 5-aryl-, whereas the reactions in the presence of CuI gave 6-aryl-1,3-dibenzyluracils. Final debenzylation either by transfer hydrogenolysis over Pd/C or by treatment with BBr_3 gave the desired free arylated uracil bases in good yields.

■ Cu-MEDIATED BENZIMIDAZOLE AND BENZOXAZOLE SYNTHESIS



Benzimidazoles and benzoxazoles are privileged structural units that are encountered in a wide range of biologically active and medicinally significant compounds. An efficient method for the transformation of *N*-benzyl bisarylhydrazones and bisaryloxime

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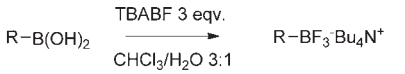
ethers to functionalized 2-aryl-*N*-benzylbenzimidazoles and 2-arylbenzoxazoles is described in a full article by Punniyamurthy and coworkers (*J. Org. Chem.* **2011**, *76*, 5295−5308). The protocol involves a copper(II)-mediated cascade C−H functionalization/C−N/C−O bond formation under neutral conditions. Substrates having either electron-donating or -withdrawing substituents undergo the cyclization to afford the target heterocycles at moderate temperature. The authors present a detailed account of their optimization studies and provide a large number of examples across two substrate tables, with yields ranging from 31 to 88%.

HF-FREE SYNTHESIS OF TETRABUTYLAMMONIUM TRIFLUOROBORATES

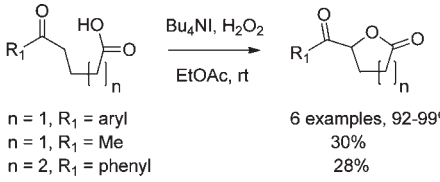


R = sub. aryl	17 examples 74-98% yield
= heteroaryl	6 examples 50-94% yield
= cyclopropyl	50%
= cyclohexyl	86%
= *E*-styryl	98%

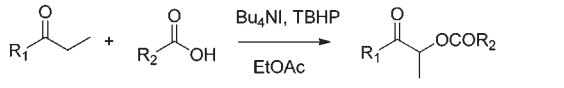
TBABF = $Bu_4N^+HF_2^-$

The Suzuki−Miyaura cross-coupling reaction has established the importance and versatility of boronic acids in organic synthesis. Yet in some cases these reagents may suffer from long-term instability (e.g., alkyl/vinyl boronic acids) and protiodeboronation. This has led to increased use of potassium trifluoroborates and more recently their more soluble tetrabutylammonium salts. The existing methodology to prepare this latter class of reagent requires use of corrosive aqueous HF. Prakash et al. (*Synthesis* **2011**, *2*, 292−302) have demonstrated that treatment of both aromatic and alkyl boronic acids with tetrabutylammonium bifluoride under very mild conditions provided a wide range of substituted tetrabutylammonium trifluoroborates in typically good−high yield.

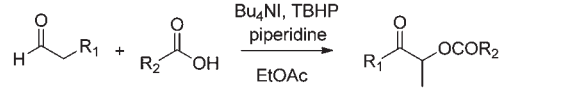
METAL-FREE α-OXYACYLATION OF CARBONYLS



n = 1, R_1 = aryl	6 examples, 92-99%
n = 1, R_1 = Me	30%
n = 2, R_1 = phenyl	28%



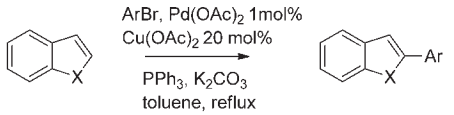
R_1 = aryl R_2 = aryl 15 examples, 76-99% yield



R_1 = alkyl, Me R_2 = aryl, vinyl 10 examples, 62-89% yield

α-Oxyacylation of aldehydes and ketones is a desirable transformation in organic synthesis. Existing methodology for this includes reaction of carbonyl compounds with hypervalent iodides, *O*-acyl hydroxylamines, and $Pb(OAc)_4$. Ishihara et al. (*Angew. Chem., Int. Ed.* **2011**, *50*, 5331−4) have reported efficient and mild conditions to effect this transformation by the use of tetrabutylammonium iodide and hydrogen peroxide (in case of intramolecular cyclisations) or *tert*-butyl hydroperoxide (for intermolecular reactions). Both aldehyde and ketones proved to be suitable substrates yielding oxyacylated products in generally good−high yield.

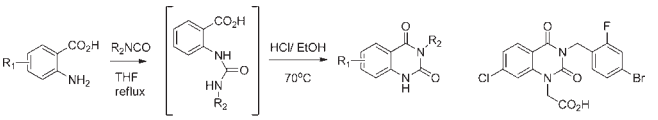
PRACTICAL Pd−Cu CATALYSED ARYLATION OF BENZAZOLES



X = O, S, NMe 27 examples, 75-92% yield

Huang et al. (*Heterocycles* **2011**, *83*(6), 1371−1376) have reported a simple direct arylation of benzoxazole, benzothiophene, and *N*-methylbenzimidazole using a palladium−copper cocatalytic system with the cheap and widely available ligand triphenylphosphine. This methodology proved insensitive to the presence of air. The electronic nature of the aromatic bromide did not effect the reaction: bromoanisole, fluorobenzene, and 2-bromopyridine all gave high yields of products.

EFFICIENT PREPARATION OF 3-SUBSTITUTED QUINAZOLINEDIONES

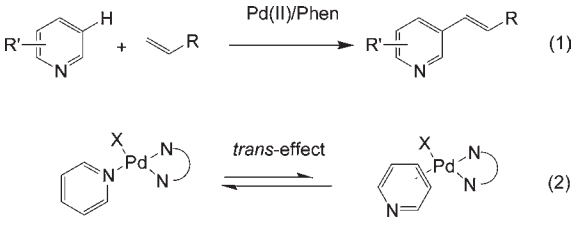


R_1 = Me, OMe, halo, CO_2H
R_2 = cyclopentyl, allyl, aryl, benzyl

15 examples, 67-89% yield Zenarestat

Campeau and Koay (*J. Heterocycl. Chem.* **2011**, *48*, 473) of Merck Frosst have developed a scalable one-pot procedure for the conversion of anthranilic acids to 3-substituted quinazolinediones. Thus treatment of anthranilic acid with an isocyanate in THF, followed by heating with 12 M hydrochloric acid, afforded the desired diones in typically good yield. This methodology was successfully applied to a key intermediate of the known aldose inhibitor zenarestat.

LIGAND-PROMOTED SELECTIVE C(3)−H OLEFINATION OF PYRIDINES WITH Pd CATALYSTS



Pd-catalyzed C3 selective olefination of pyridines was developed by Yu's laboratory at the Scripps Research Institute using 1,10-phenanthroline as the ligand (eq 1) (*J. Am. Chem. Soc.* **2011**, *133*, 6964−6967). The bisdentate ligand 1,10-Phenanthroline (Phen) plays a key role in this olefination, in which Phen weakens the coordination of the Pd(II) catalyst with the pyridyl N atom through the *trans*-effect to allow the activation of the C(3)−H bond by Pd(II) (eq 2). The

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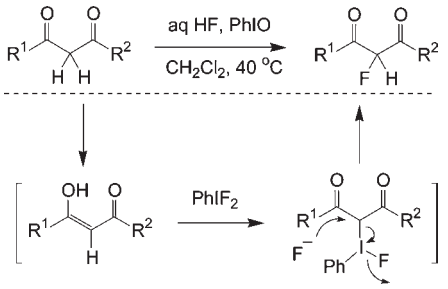
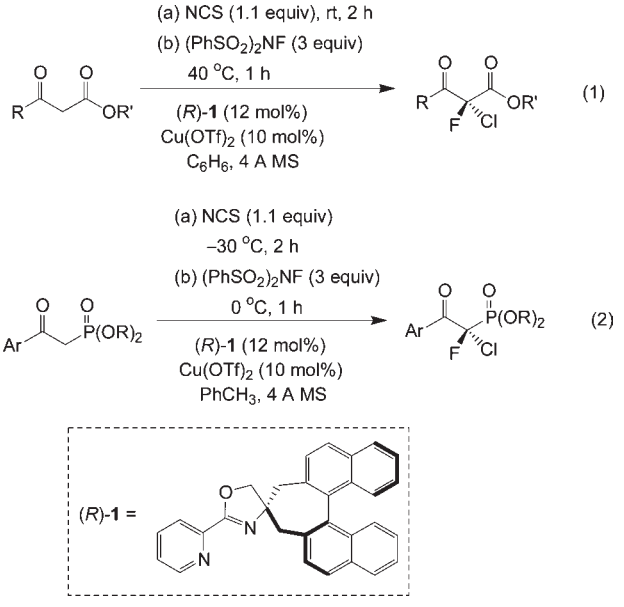
pyridine substrates containing both electron-donating and -withdrawing groups were olefinated selectively to furnish the corresponding olefins in synthetically useful yields. Substitution at the C2 position by methoxy, chloride, or fluoride was also tolerated. However, substitution at the para position reduced the yield significantly.

FLUORINATION OF 1,3-DICARBONYL COMPOUNDS USING AQUEOUS HF IN THE PRESENCE OF IODOSYLBENZENE



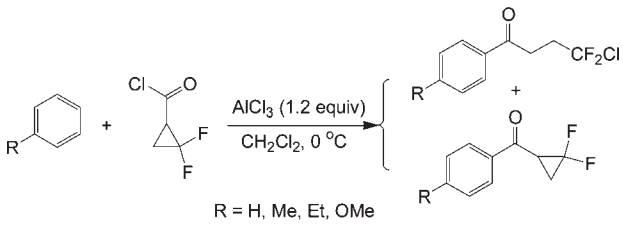
Fluorination of 1,3-dicarbonyl compounds was achieved by direct use of aqueous hydrofluoric acid and iodosylbenzene (PhIO) (*Org. Lett.* **2011**, *13*, 2392−2394). This one-pot operation includes the generation of difluoroiodobenzene ($PhIF_2$) in situ, its activation for the fluorination reaction, and the subsequent electrophilic attack onto the enols, followed by reductive S_N2 displacement of hypervalent iodine with fluoride. Among 3-ketoesters, aliphatic 3-ketoesters showed higher reactivity toward fluorination than aromatic ones, giving the corresponding 2-fluorinated 3-ketoester in high yields. In addition to 3-ketoesters, 1,3-diketones and 3-ketoamides also underwent fluorination to give the corresponding 2-fluorinated products.

ENANTIOSELECTIVE GEM-CHLOROFLUORINATION OF ACTIVE METHYLENE COMPOUNDS USING A CHIRAL SPIRO OXAZOLINE LIGAND



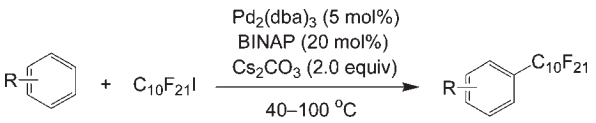
An approach for the preparation of α-chloro-α-fluoro-*β*-keto esters and α-chloro-α-fluoro-*β*-keto phosphonates was developed by Shibatomi and co-workers of Toyohashi University of Technology, Japan (*Org. Lett.* **2011**, *13*, 2944−2947). These preparations were carried out in a one-pot fashion in the presence of the (*R*)-**1**/$Cu(OTf)_2$ complex including chlorination of *β*-keto esters (or phosphonates) with NCS followed by fluorination with *N*-fluorobenzenesulfonimide (NFSI). The stereochemical outcome of the double halogenation is determined by the fluorination step. Various *β*-keto esters, including aliphatic, aromatic, and heterocyclic ketoesters, were exposed to the double halogenation conditions affording the corresponding gem-chlorofluorinated products with good to high optical purity. Analogously, several α-chloro-α-fluoro-*β*-keto phoshonates were prepared under the same conditions in moderate to good yields with high enantioselectivity (85−92% ee).

FRIEDEL−CRAFTS REACTIONS OF 2,2-DIFLUOROCYCLOPROPANECARBONYL CHLORIDE



The Friedel−Crafts reactions of 2,2-difluorocyclopropanecarbonyl chloride with various arenes led to aryl 3-chloro-3,3-difluoropropyl ketones or aryl 2,2-difluorocyclopropyl ketones (*J. Org. Chem.* **2011**, *76*, 3450−3456). Depending on the substituent, the product distribution between aryl 2,2-difluorocyclopropyl ketones and ring-opened aryl 3-chloro-3,3-difluoropropyl ketones varied. Employing unreactive arene substrates such as benzene, toluene, and *p*-xylene, aryl 3-chloro-3,3-difluoropropyl ketones were obtained exclusively in high yields. However, the regioselectivity reversed when the reactive substrate thiophene was used favoring the cyclopropane ring intact product.

PALLADIUM-CATALYZED C−H PERFLUOROALKYLATION OF ARENES



A Pd-catalyzed reaction was developed for the coupling between perfluoroalkyl iodides (R_FI) and simple aromatic substrates to afford the corresponding perfluoroalkylated arene products in good to excellent yields (*Org. Lett.* **2011**, *13*, 2548−2551). In the presence of a phosphine-ligated Pd catalyst and Cs_2CO_3 as a base, a variety of aromatic substrates underwent facile perfluoroalkylation with R_FI. Arenes containing electron-rich groups such as methyl and alkoxy substituents were perfluoroalkylated smoothly to provide perfluoroalkylated products. However, significantly lower reactivity was observed with aromatic substrates containing electron-poor substituents, except 1,2-dichlorobenzene that did undergo perfluoroalkylation in modest yield. In addition, *N*-methylpyrrole afforded the 2-perfluoroalkylated product as a single detectable isomer.

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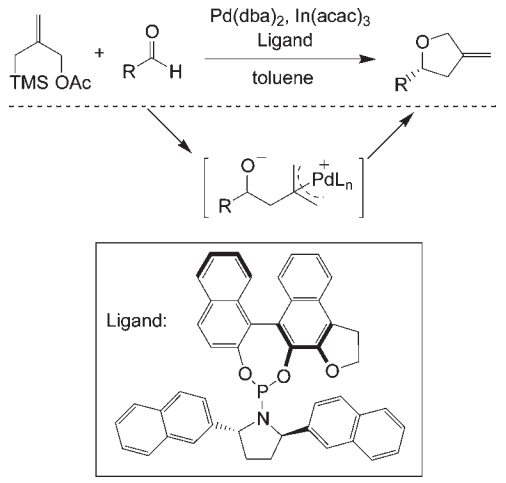
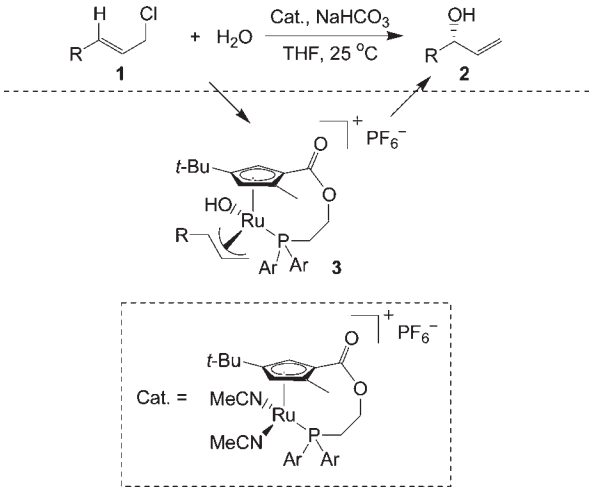
■ PALLADIUM-CATALYZED [3 + 2] CYCLOADDITION OF TRIMETHYLENEMETHANE WITH ALDEHYDES



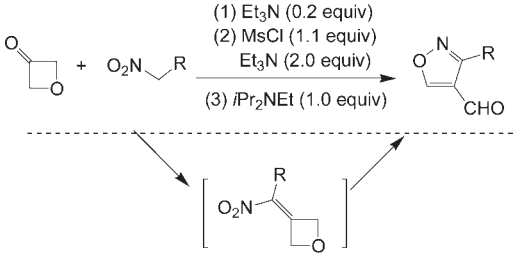
An asymmetric synthesis of methylenetetrahydrofurans was realized by utilizing a palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane (TMM) with aldehydes (*J. Am. Chem. Soc.* **2011**, *133*, 7664−7667). In the presence of a phosphoramidite ligand possessing a stereogenic phosphorus, reactions of electron-rich benzaldehydes bearing mono- and disubstituted groups in various substitution patterns led to methylenetetrahydrofurans in good to excellent yields and enantioselectivities. While the reaction of 4-chlorobenzaldehyde proceeded with good yield and selectivity, 4-nitrobenzaldehyde gave the product with only 36% ee. Other aldehydes such as heterocyclic aldehydes and α,β-unsaturated aldehydes also gave cycloadducts in good optical purity.

■ SYNTHESIS OF CHIRAL ALLYLIC ALCOHOLS VIA RUTHENIUM-CATALYZED REGIO- AND ENANTIOSELECTIVE ALLYLIC SUBSTITUTION



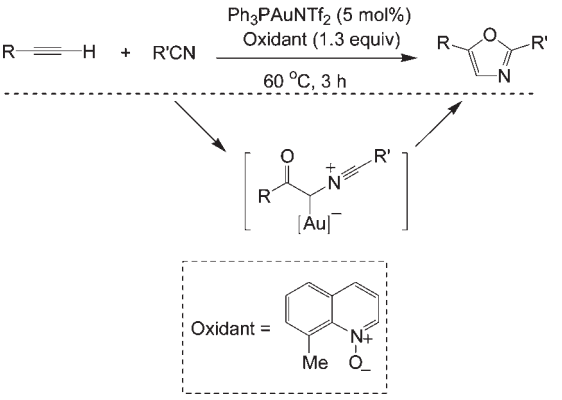
A direct synthesis of chiral allylic alcohols by regio- and enantioselective allylic substitution using water as the nucleophile was reported by Onitsuka and his co-worker of Osaka University, Japan (*Angew. Chem., Int. Ed.* **2011**, *50*, 5197−5199). Treatment of allylic chlorides **1** with a mixture of THF/water (8:1) at 25 °C with sodium hydrogen carbonate (1.2 equiv) in the presence of 1 mol % of the ruthenium complex as the catalyst resulted in a selective formation of the branched allylic alcohols **2**. The reactions of cinnamyl chloride derivatives with various substituents selectively produced the corresponding branched allylic alcohols in good yields with high enantioselectivities, though substrates with electron-withdrawing groups required longer reaction times for complete conversion. Due to the mild reaction conditions, methoxycarbonyl and formyl groups are well tolerated. Mechanistically, the reaction proceeds via π-allyl intermediates **3** that are generated by the oxidative addition of allylic chlorides followed by reaction with water in the presence of sodium hydrogen carbonate.

■ FORMATION OF ISOXAZOLES VIA FACILE BASE-MEDIATED REARRANGEMENT



A synthetic approach to 3-substituted isoxazoles-4-carbaldehydes was developed via a condensation reaction of nitroalkanes with 3-oxetanone, followed by a base-mediated rearrangement (*Angew. Chem., Int. Ed.* **2011**, *50*, 5379−5382). The rearrangement of oxetane intermediates was initiated by deprotonation. Tertiary amines (in particular iPr_2NEt) are superior to other bases (e.g., Cs_2CO_3, LiHMDS, NaOMe, or pyridine) for the rearrangement, favoring the formation of isoxazoles. This rearrangement is also solvent dependent: when the reaction was conducted in THF, clean product formation was observed; in contrast, in CH_3CN, pyridine, or MeOH, significant amounts of oligomeric side products were observed. The reaction tolerated a wide range of nitroalkanes in which the R groups include both aromatic and aliphatic groups. The aromatic rings can bear electron-rich and electron-deficient substituents, and the aliphatic groups include a variety of functionalities such as remotely positioned ester groups, terminal alkenes, and protected amines and alcohols.

■ SYNTHESIS OF 2,5-DISUBSTITUTED OXAZOLES VIA GOLD-CATALYZED ALKYNE OXIDATION



A synthetic method for access to 2,5-disubstituted oxazoles was developed by Zhang and co-workers of University of California, Santa Barbara (*J. Am. Chem. Soc* **2011**, *133*,

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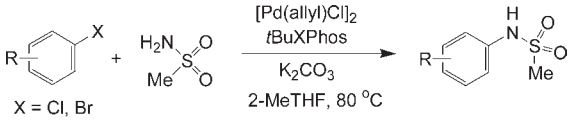
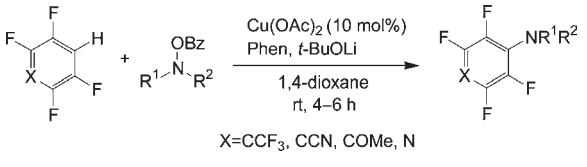
8482−8485). This new approach utilizes gold-catalyzed alkyne oxidation to generate gold carbene intermediates, followed by intermolecular trapping of the intermediates with nitriles and intramolecular cycloaddition. The nitriles were used as both the reacting partner and the reaction solvent. The overall reaction is a [2 + 2 + 1] annulation of a terminal alkyne, a nitrile, and an oxygen atom from an oxidant. Due to the relatively mild reaction conditions, a range of functional groups was easily tolerated. A variety of terminal alkynes was allowed including functional groups such as hydroxy, carboxylic acid, TBSO, THP, Boc, PhS, and chloride. In addition, aryl groups having different electronic and steric natures were also tolerated. Besides acetonitrile, propionitrile, benzonitrile, and phenylacetonitrile were shown to be suitable reagents to afford the corresponding oxazoles in good yields.

MILD Pd-CATALYZED *N*-ARYLATION OF METHANESULFONAMIDE AND RELATED NUCLEOPHILES



The *N*-arylsulfonamides are frequently prepared via reactions of anilines with sulfonyl chloride. Although the synthetic method is generally effective, this approach is less than ideal from the perspective of contamination of products by potential genotoxic impurities as both the anilines and the sulfonyl chloride raise alerts for genotoxicity. A Pd-catalyzed cross-coupling of methanesulfonamide with aryl halides was devised to eliminate the concerns over the formation of genotoxic impurities (*Org. Lett.* **2011**, *13*, 2564−2567). The reaction was conducted in the presence K_2CO_3 (2.0 equiv), $[Pd(allyl)Cl]_2$ (0.5 mol %), and *t*-BuXPhos (2 mol %) in 2-MeTHF at 80 °C. Under these conditions, excellent product yields were obtained with all aryl bromides examined including those with electron-rich (Me, OMe, NMe_2), electron-deficient (CN, CF_3, Ac, CO_2Me), and those bearing ortho substituents (2-Me, 2-OMe). Analogously, aryl chlorides reacted efficiently under these conditions.

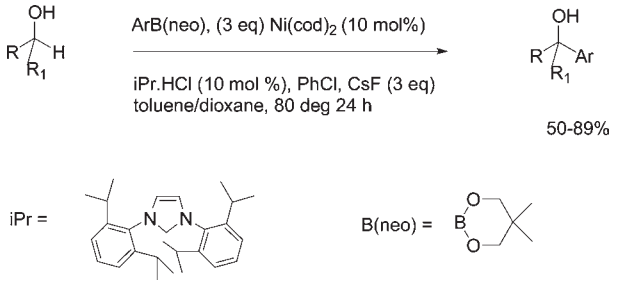
COPPER-CATALYZED AMINATION OF ELECTRON-DEFICIENT ARENES WITH HYDROXYLAMINES



Copper-catalyzed amination of electron-deficient arenes involving fluoroarenes as well as azoles was developed by Miura and co-workers of Osaka University, Japan (*Org. Lett.* **2011**, *13*, 2860−2863). Generally, the amination reaction of electron-deficient arenes with hydroxyamines in the presence of the $Cu(OAc)_2$/phen catalyst and lithium *tert*-butoxide in 1,4-dioxane furnished the corresponding anilines or aminoazoles in good yields. Reactions with a number of acyclic hydroxyamines ($R^1 = R^2$ = Et, allyl; R^1 = H, Me, R^2 = Bn) proceeded smoothly under these conditions, in which the resultant benzyl and allyl moieties could be readily deprotected into the free N−H bond. Hydroxyamines with cyclic systems such as pyrrolidine, piperidine, and morpholine are also good substrates in the couplings.

CONTROLLED ALCOHOL CARBONYL INTERCONVERSION BY NICKEL CATALYSIS

The group of Itami at Nagoya (Japan) has recently established that nickel catalysts can promote the reaction of arylboronic acid esters with aldehydes and ketones under mild conditions (*Org. Lett.* **2009**, *11*, 4410). In a recent paper (*Angew. Chem., Int. Ed.* **2011**, *50*, 7022−7026) the same group found that the catalysts can catalyse the oxidation and reduction of alcohols/carbonyls to allow a combined sequence of reactions where an alcohol can be added to an aromatic nucleus to form another alcohol, usually tertiary, in good yield. Unfortunately yields are calculated based on the alcohol component rather than, as process chemists would have done, on the more expensive aryl boronate, which is present in vast excess. Nevertheless this is an interesting one-pot transformation proceeding via initial oxidation and then C−C bond formation.



CAPROLACTAM FROM RENEWABLE RESOURCES

Lignocellulosic biomass is a promising feedstock for the production of biobased chemicals, and a key intermediate is hydroxymethylfurfural (HMF), which can be made from sugars, such as fructose, in high yield. It is hoped that in the future HMF can be made directly from cellulose. It has now been shown by a group from the University of Groningen in collaboration with DSM in The Netherlands that HMG can be converted easily to caprolactam, the precursor of Nylon-6 and other polymers, which is made at an annual production rate of about 4 million metric tonnes. A number of routes to caprolactone were identified, the reaction of caprolactone to caprolactam being already known and used on production scale. Overall the conversion of HMF to caprolactone proceeded via a 5-step process with 95% selectivity, whereas the shorter 2-step process had only 85% selectivity and it is calculated that 1.44 kg of HMF could make 1 kg of caprolactam using 0.11 kg of hydrogen and 0.17 kg of ammonia, which compares favorably with the current production process of 6 steps from benzene and ammonia. Key factors in the process economics will be the efficiency of the Rh−Re/silica hydrogenation catalysts and the Ru(cymene)chloride−DPPF

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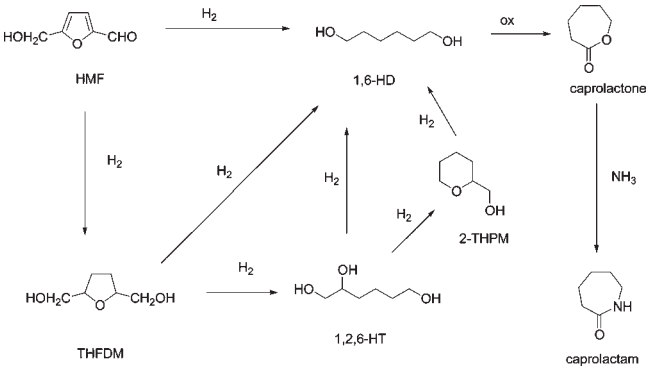
oxidation catalyst (Buntara, T. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 7083−7087).



■ SALT EFFECTS IN ORGANOMETALLIC RECIPES

A recent highlight (Hevia, E. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 6448−6450) reviews the latest results on the importance of added salts such as lithium chloride (added intentionally or inadvertently, for example, as an impurity in BuLi or LDA) on the course of organometallic reactions. Even levels as low as 0.5 mol % can change the course of the chemistry (a 100-fold rate acceleration is not unusual), and the authors indicate that its effects need to be explored before the chemistry can be fully understood (I would add especially during scaleup). Salt effects are particularly important when handling diaryl or dialkylzinc reagents (except possibly diethylzinc, which can be purchased salt-free − this is why most academics use this in enantioselective reactions, which may not then extrapolate to other reagents because of salt effects).

■ PACKED-BED MICROREACTOR FOR SUCCESSFUL ARYLATIONS IN CONTINUOUS MODE

The latest results from the group of Buchwald at MIT on continuous processing concern the palladium catalysed arylation of oxindoles (Li, P. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 6396−6940). Key to the success was a two-phase system with KOH as base, a palladocycle-XPhos precatalyst, which is rapidly activated, and a packed bed as microreactor which enables efficient mixing. This enables some residence times to be under a minute, depending of course on the aryl halide used.

■ LABORATORY METHODS FOR ASSESSING API SENSITIVITY TO MECHANICAL STRESS DURING AGITATED DRYING

The selection of suitable drying equipment at scale can be complicated by active pharmaceutical ingredient (API) sensitivity to mechanical stress, especially when efficient agitated drying equipment is considered. A very small number of techniques, including nanoindentation methods, are available to assess such sensitivity; the main disadvantage of such methods is the use of a relatively small number of crystals in the analysis, leading to results with limited value for the bulk behavior of the API crystals. A team from Merck reports on the development of two new such techniques (Lamberto, D. J. et al. *Chem. Eng. Sci.* **2011**, *66*, 3868). In one method the crystals are investigated (PSD) when a normal force is applied and the solids are mixed (wet or dry); in another, the crystals are monitored when they are carried by a pressurized gas stream. Based on corroboration with data obtained at scale, the results thus obtained can lead to a practical classification of solids: hard, medium, or easy to break. Several examples are presented, discussing crystals of various morphologies, solvated or not, including interesting correlations made by the authors about certain types of APIs; for example, milling reduces the breakage category by one. These methods require relatively small amounts of material, which the authors hope could be further reduced by using more sophisticated instrumentation.

■ MORPHOLOGICAL DIVERSITY OF CAFFEINE ON SURFACES

A less commonly investigated process parameter in crystal engineering is the nature of the surface on which crystals are formed and grown. A group from Humboldt University and the BAM Federal Institute for Material Research and Testing (Berlin, Germany) report their recent work on the topic (Sarfraz, A. et al. *Cryst. Growth Des.* **2011**, DOI 10.1021/cg 101358q). The model compound used is caffeine (known since 1820 but with an elucidated crystal structure only in 2007). Various crystallization techniques (including those using an ultrasonic levitator, in the absence of any contact surface) produce caffeine as high aspect ratio (10−100) needles for all of its known forms. The experiments discussed employed special crystallization methods including RESS (Rapid Expansion of Supercritical Solutions) and Drop-Casting. Using the Drop-Casting method in certain solvents such as dichloromethane produced, in addition to needles, also "hexagons" (hexagonal prisms), with the latter in higher ratios when subsurface ion-exchanged soda lime silicate glass was used. A mechanism for the formation of the hexagons is proposed, and future work including determination of the hexagon crystal structure is indicated.

■ THE ICH Q8 DEFINITION OF DESIGN SPACE: A COMPARISON OF THE OVERLAPPING MEANS AND THE BAYESIAN PREDICTIVE APPROACHES

Every key concept in the ICH Quality by Design (QbD) guidelines continues to be debated, including that of design space. A certain consensus has been reached, and careful use of statistical designed experiments (DoE) is considered capable to lead to a design space. The challenge with the methodology of overlapping mean responses is the quantification of the level of quality assurance, or of the risk associated with possible failure. An effective approach, for cases where no correlations exist between responses, is provided by Monte Carlo calculations. A more general methodology is afforded by Bayesian predictive approaches. Statisticians at GlaxoSmithKline have developed such Bayesian procedures, and their findings are summarized in a recent report (Peterson, J. J. et al. *Stat. Biopharm. Res.* **2010**, *2*(2), 249). Unfortunately a very small number of commercially available software platforms allow nonexperts to execute Bayesian computations. This article challenges several influential publications discussing methods for the definition of design space.

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