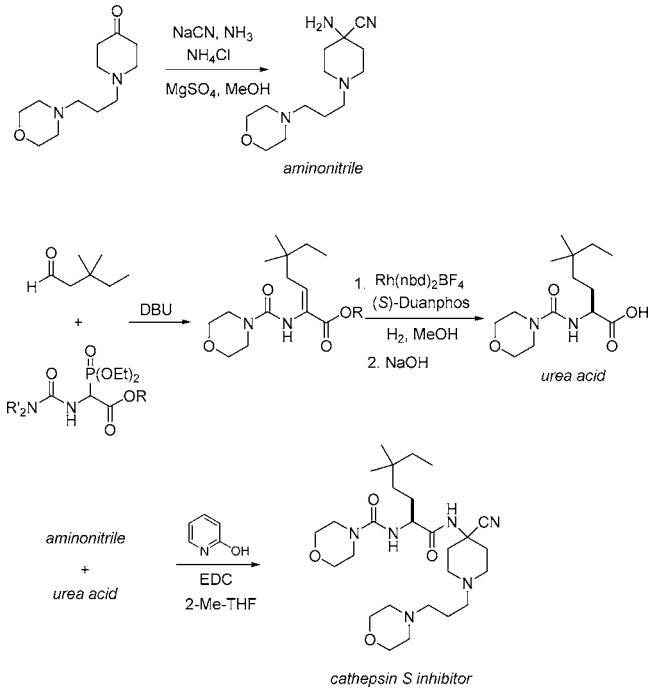
Organic Process Research & Development **2010,** *14,* 485–491

Highlights from the Literature

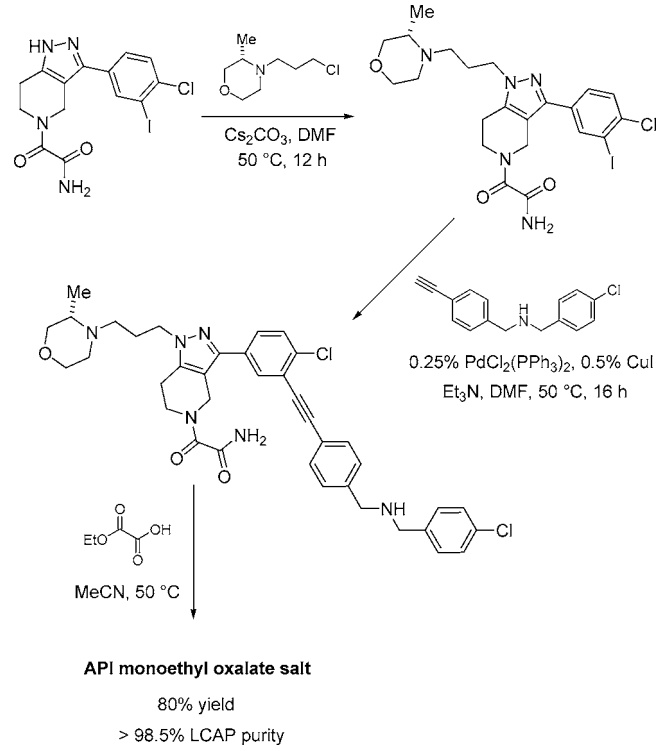
Some Items of Interest to Process Chemists and Engineers

Large-Scale Asymmetric Synthesis of a Cathepsin S Inhibitor



Inhibition of cathepsin proteases has been identified as a potential mechanism for the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. In connection with a drug development program, Lorenz, Busacca, and co-workers at Boehringer Ingelheim report on a large-scale asymmetric synthesis of a potent reversible inhibitor of cathepsin-S (*J. Org. Chem.* **2010**, *75*, 1155−1161). The target API was prepared on large scale using a convergent synthetic route, free of chromatography and cryogenics. Late-stage amide coupling of a chiral urea acid fragment with a functionalized aminonitrile was employed to construct the amidonitrile group, linking the two halves of the molecule. Following an extensive additive study 2-hydroxypyridine was identified as a robust, nonexplosive replacement for HOBT. The two halves of the molecule were prepared using a modified Strecker reaction for the aminonitrile and a phosphonation-olefination rhodium-catalyzed asymmetric hydrogenation sequence for the urea. A palladium-catalyzed vinyl transfer coupled with a Claisen reaction was used to produce the aldehyde required for the side chain. Key scale-up issues, safety calorimetry, and optimization of all steps for multikilogram production are discussed.

Serendipitous Discovery of API Crystalline Salt Form



In a separate article relating to process development of a cathepsin S inhibitor, Deng and co-workers at Johnson and Johnson provide a detailed description of route identification, purification strategy, and serendipitous discovery of a relatively unusual crystalline salt form of the active pharmaceutical ingredient (API) (*J. Org. Chem.* **2010**, *75*, 1940−1947). The authors discuss various synthetic sequence modifications investigated to access crystalline intermediates that allowed for purity upgrade at intermediate stages. More importantly, the nature of the final target API (large, flexible molecule with high rotational freedom) led to difficulties in identification of a suitable final crystalline form to provide purity upgrade. An extensive screen of acids generated only three solid salts, and these were not crystalline. During parallel solubility determinations, the team observed a crystalline precipitate when the API free-base was dissolved in diethyl oxalate. Characterization of this precipitate revealed it was the salt of the API with oxalic acid monoethyl ester. Subsequent deliberate attempts to form this salt confirmed the initial characterization and that the material was crystalline, offering high potential for purity upgrade. Careful examination of the single-crystal X-ray structural data suggested that both carbonyl groups and the length of its alkyl side chain were essential for the construction of the crystal lattice. A study of related 2-oxocarboxylic acids

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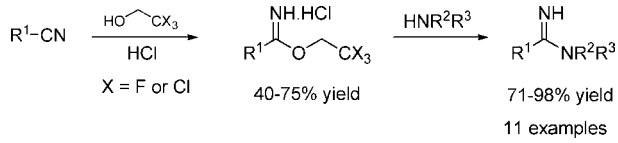
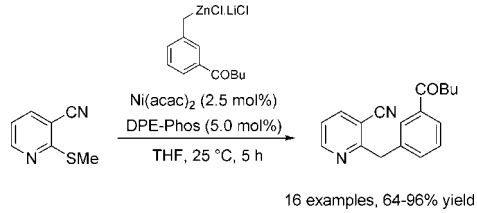
revealed that, other than monoethyl oxalate, only 2-oxopentanoic acid fits the structural requirements to provide a crystalline salt.

Trihaloethyl Imidates for Amidine Synthesis



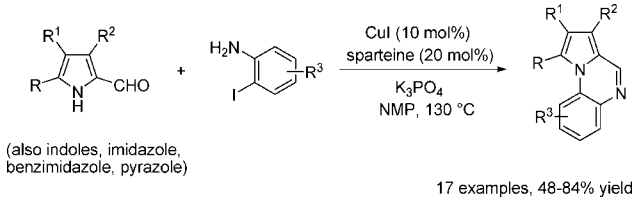
2,2,2-Trifluoro- and trichloroethyl imidates, which are easily prepared by reaction of a nitrile and a trihaloethanol in the presence of HCl, are excellent reagents for the preparation of amidines under mild reaction conditions, as reported by Caron and co-workers at Pfizer (*J. Org. Chem.* **2010**, *75*, 945−947). Depending on the nature of the amine nucleophile, the imidates can react either as the free-base or the hydrochloride salt in a telescoped process. In several cases, the *p*-bromobenzoate salt of the desired product was directly isolated from the reaction mixture. A total of 11 examples are included with yields ranging from 71 to 98%.

Ni-Catalyzed Coupling of Organozinc Reagents with Thiomethyl Heterocycles



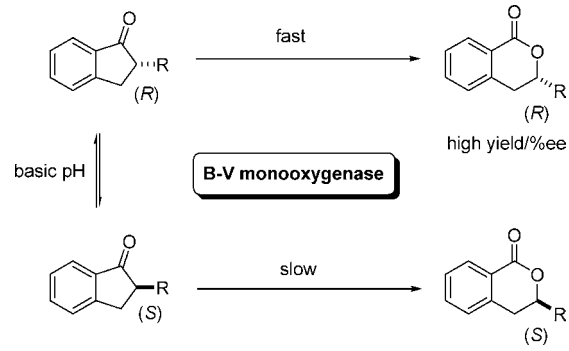
The first transition-metal-catalyzed cross-coupling reactions of thioethers with Grignard reagents were independently reported by Takei and Wenkert in 1979. This method allows direct conversion of a carbon−sulfur bond into a carbon−carbon bond. Liebeskind has also described a Ni-catalyzed cross-coupling reaction using various sulfur functionalities as leaving groups. Now the Knochel group reports that a variety of thiomethyl-substituted *N*-heterocycles such as pyridines, isoquinolines, pyrimidines, pyrazines, pyridazines, quinazolines, triazines, benzothiazoles, or benzoxazoles undergo smooth Ni-catalyzed cross-coupling reactions with functionalized aryl-, heteroaryl-, alkyl-, and benzylic zinc reagents using an inexpensive $Ni(acac)_2$/ DPE-Phos catalytic system at 25 °C (*J. Org. Chem.* **2010**, *75*, 2131−2133). Many functional groups are tolerated, and across 16 examples the yields are good (64−96%).

Synthesis of Pyrrolo[1,2-*a*]quinoxalines via Cu-Catalyzed Intramolecular *N*-Arylation



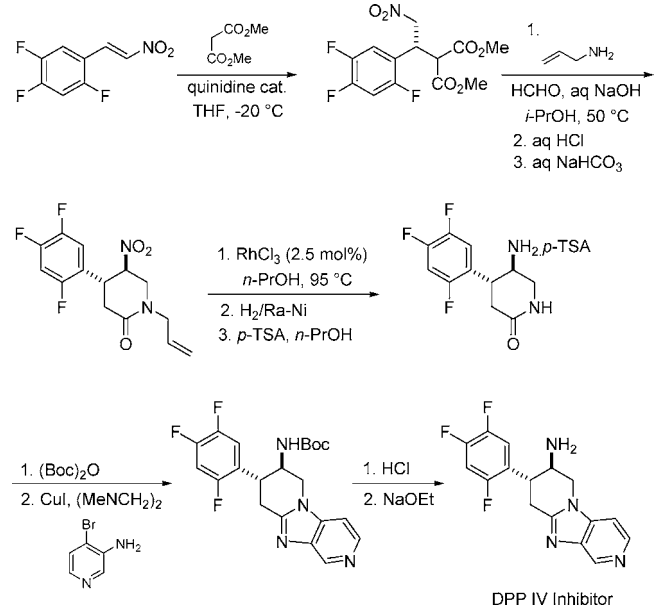
As described by Reeves and co-workers at Boehringer Ingelheim, in the presence of catalytic CuI and sparteine, 2-formylpyrroles can be annulated with *o*-aminoiodoarenes to give substituted pyrrolo[1,2-*a*]quinoxalines and related heterocycles (*J. Org. Chem.* **2010**, *75*, 992−994). The reaction also works for annulation of 2-formylindoles, 2-formylimidazole, 2-formylbenzimidazole, and a 3-formylpyrazole. A total of 17 examples are provided with yields ranging from 48 to 84%.

Dynamic Kinetic Resolution (DKR) Using Baeyer−Villiger Monooxygenase



Baeyer−Villiger monooxygenases (BVMOs) are flavoproteins that are able to catalyze the oxidation of carbonylic and heteroatom-containing compounds employing atmospheric oxygen as oxidant. BMVOs have now been tested in the oxidation of racemic benzofused ketones, as reported by Gotor and co-workers (*J. Org. Chem.* **2010**, *75*, 2073−2076). When employing a single mutant of phenylacetone monooxygenase (M446G PAMO) under the proper reaction conditions, it is possible to achieve an effective DKR and convert racemic 2-substituted indanones into enantiomerically enriched 3-substituted 3,4-dihydroisocoumarins with high yields and high % ee. Addition of 5% methanol increases the enzymatic activity with a loss of selectivity, while the use of hexane leads to the best selectivities. Higher conversions are obtained when ketones bearing short alkyl chains are oxidized. This enzymatic oxidation has been scaled up to 250-mg scale using cell-free extract.

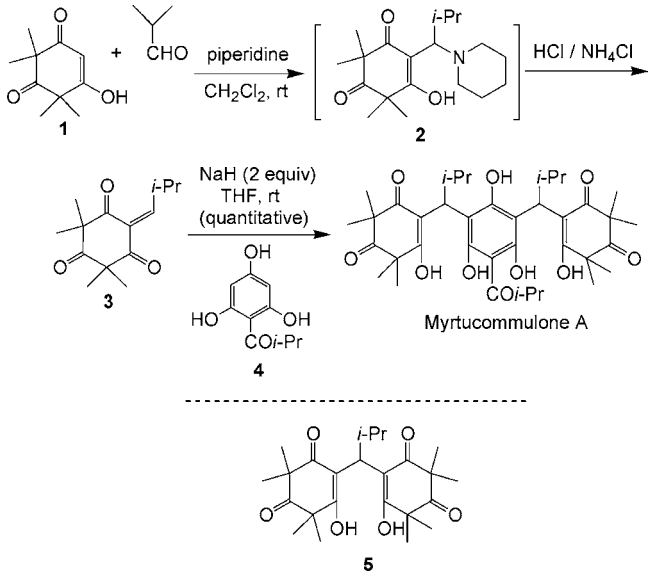
Asymmetric Synthesis of a Dipeptidyl Peptidase IV Inhibitor



A practical asymmetric synthesis of a novel aminopiperidine-fused imidazopyridine dipeptidyl peptidase IV (DPP-4) inhibitor

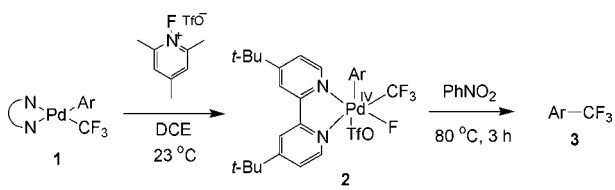
is described by Xu and co-workers at Merck (*J. Org. Chem.* **2010**, *75*, 1343−1353). This article provides a detailed account of the process development around this particular API. Key features include an asymmetric Henry addition to generate the substrate for a three-component cascade coupling that ultimately formed the functionalized piperidinone skeleton in one pot. A base-catalyzed dynamic crystallization-driven process was developed to access the -piperidinone in practical fashion, allowing direct crystallization from the crude reaction stream in high yield and purity. Isomerization/deprotection of the allyl-protected amide in the presence of $RhCl_3$ was achieved without any epimerization of the acid/base labile stereogenic center adjacent to the nitro group on the piperidinone ring. The amino lactam, obtained through hydrogenation and hydrolysis, was directly isolated as a crystalline *p*-TSA salt from the reaction solution. Finally, a Cu(I)-catalyzed coupling-cyclization produces the final tricyclic structure of the potent DPP-4 inhibitor 1. The synthesis, which is suitable for large-scale preparation, was accomplished in 23% overall yield. Multikilogram-scale experimental details are provided.

Total Synthesis of Myrtucommulone A



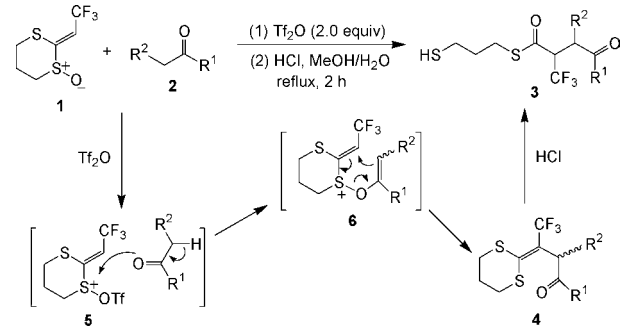
A highly efficient three-step synthesis of myrtucommulone A was accomplished by Jauch's group in Germany (*Angew. Chem., Int. Ed.* **2010**, *49*, 2045−2049). Condensation of syncarpic acid **1** with 2-methyl-propionaldehyde in the presence of piperidine gave the desired Mannich base **2**, avoiding the formation of byproduct **5**. Without isolation, the intermediate **2** was converted to **3** by addition of HCl/NH_4Cl. The yield of myrtucommulone A in the Friedel−Crafts reaction was significantly improved by conducting the alkylation under basic conditions.

Aryl−CF_3 Bond Formation

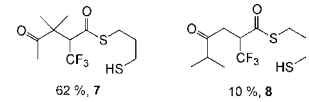


The installation of a trifluoromethyl unit into an organic molecule is a challenging task due to its extraordinary chemical properties. Owing to the fact that trifluoromethyl group (CF_3) can dramatically change the physical properties and biological activity of organic molecules, tremendous effort has been directed at the introduction of CF_3 group into organic structures. Sanford and her co-workers at the University of Michigan have developed a novel palladium-catalyzed cross-coupling reaction (*J. Am. Chem. Soc.* **2010**, *132*, 2878−2879). It was demonstrated that the Ar−CF_3 bond-forming reaction involves a Pd(IV) complex **2**, formed by oxidation of Pd(II) complex **1** with *N*-fluoro-2,4,6-trimethylpyridinium triflate at room temperature. This Pd(IV) complex **2** thus formed, in turn undergoes reductive elimination at 80 °C for 3 h, resulting in the 4-trifluoromethylbenzene derivative **3** in good yields. Furthermore, the proposed Pd(IV) complex **2** was isolated, and its structure was confirmed by ^{19}F NMR spectroscopy and X-ray crystallographic data. These transformations proceed under mild conditions with diverse nitrogen- and phosphorus-based ancillary ligands.

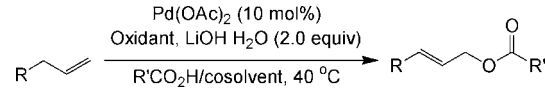
Novel Pummerer Transformation



Oshima and co-workers devised a novel Pummerer transformation using ketones as substrates (*Angew. Chem., Int. Ed.* **2010**, *49*, 2340−2343). The formation of **3** occurred via an intermediate **4**, produced by nucleophilic attack of the carbonyl oxygen atom of **2** onto the activated cationic sulfur atom of **5** and a subsequent [3,3]-sigmatropic rearrangement of **6**. A wide variety of ketones **2** provides suitable substrates for this reaction wherein R^1 equals aryl or alkyl groups and R^2 ranges from hydrogen and alkyl to acetyl groups. Interestingly, a high regioselectivity was observed in the reaction of unsymmetrical aliphatic ketone such as 3-methyl-2-butanone, furnishing predominantly **7** (62%) along with 10% of **8**.



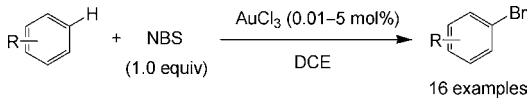
Palladium-Catalyzed Allylic Acyloxylation of Terminal Alkenes



Palladium(II)-catalyzed allylic oxidation of olefins in carboxylic acid is an efficient process for the synthesis of acyloxylated product. It was found by Bras and co-workers in France (*J. Org. Chem.* **2010**, *75*, 1771−1774) that the use of base strongly improved the efficiency and the selectivity of the Pd-catalyzed oxidation of terminal alkenes, resulting in the

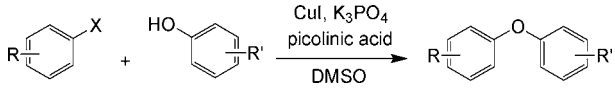
acyloxylated products selectively as *E*-isomers in fair to good yields. Two oxidation protocols were developed including $Pd(OAc)_2$ (10 mol %)/benzoquinone (2.0 equiv)/$LiOH \cdot H_2O$ (2.0 equiv)/$C_2H_5CO_2H$ without cosolvent and $Pd(OAc)_2$ (10 mol %)/benzoquinone (0.05 equiv)−MnO_2 (2.0 equiv)/$LiOH \cdot H_2O$ (2.0 equiv)/*t*-$BuCO_2H$−CH_3CN.

Gold-Catalyzed Halogenation of Aromatics



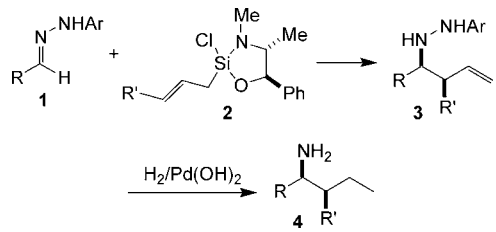
Halogenated aromatic compounds are one of the valuable organic intermediates in organic synthesis. Albeit various halogenation systems using NXS (X = Br, I, or Cl) being available in the literature, halogenation of unactivated aromatics remains challenging due to harsh reaction conditions including high reaction temperature, high catalyst loading, or strong acidic medium. A $AuCl_3$-catalyzed bromination protocol was developed by a group of scientists in China using NBS as bromination agent (*Angew. Chem., Int. Ed.* **2010**, *49*, 2028−2032). This new protocol offers several advantages, such as low catalyst loading, mild reaction conditions, as well as clean transformations in almost quantitative yield.

Cu-Catalyzed O-Arylation of Phenols



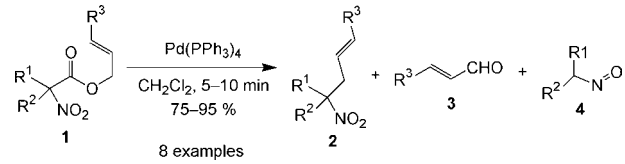
Buchwald and co-worker at Massachussetts Institute of Technology revealed a Cu-catalyzed O-arylation of phenols with aryl halides (X = I, Br) under mild DMSO/K_3PO_4 conditions (*J. Org. Chem.* **2010**, *75*, 1791−1794). This economical method utilizes less expensive copper iodide as catalyst and picolinic acid as ligand and is especially attractive for large production scale. Exploring the scope of the reaction shows that this C−O coupling reaction tolerates a variety of functional groups and is effective in the synthesis of hindered diaryl and heteroaryl ethers.

Chiral Amine Synthesis

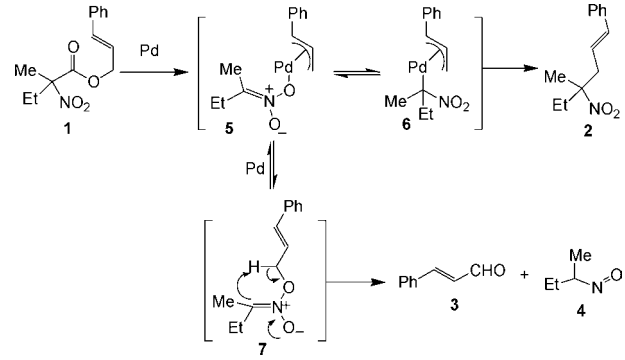


A two-step process was designed by Leighton's group at Columbia University to synthesize chiral amines **4** via intermediates **3** formed by asymmetric allylation, crotylation, or cinnamylation of *N*-heteroaryl hydrazones **1** (*Org. Lett.* **2010**, *12*, 688−691). The N−N bonds in the intermediates **3** are easily cleaved by $Pd(OH)_2$-catalyzed hydrogenation. The hydrazones **1** as a nitrogen source are inexpensive starting materials and can be readily prepared.

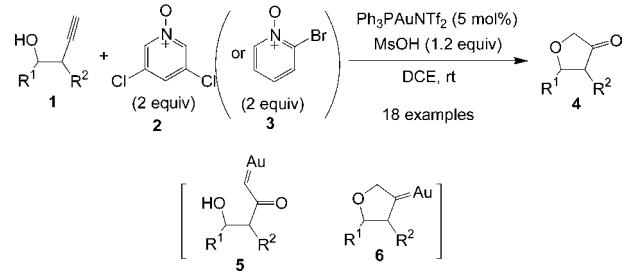
Decarboxylative Allylation of Nitroakanes



An efficient decarboxylative allylation of allyl nitroacetates was reported by Tunge and co-worker at the University of Kansas (*Org. Lett.* **2010**, *12*, 740−742). This palladium-catalyzed transformation features mild reaction conditions (room temperature), fast reaction rate (complete within several minutes), and high product yield. Due to these mild conditions, the reaction is tolerant of functionality including α-fluorine, as well as esters or ketones. In addition to the *C*-allylation product **2** two byproducts, propenal **3** and nitroso compound **4** derived from *O*-allylation, were observed when using cinnamyl derivative (R^1 = Me, R^2 = Et, R^3 = Ph) as starting material. It was noticed that reactions that run at higher concentration or with higher catalyst loading (10 mol %) produced more *C*-allylation product **2**. A hypothesis suggests that a palladium π-allyl complex **5** has two equilibria with palladium π-allyl complex **6** and O-allylated intermediate **7**, respectively. Thus, more palladium promotes conversion of **7** to **5** which in turn pushes the equilibrium in the direction of **6**. A reductive elimination of palladium π-allyl complex **6** (via Pd σ-allyl complex) furnishes the desired *C*-allylated product **2**.

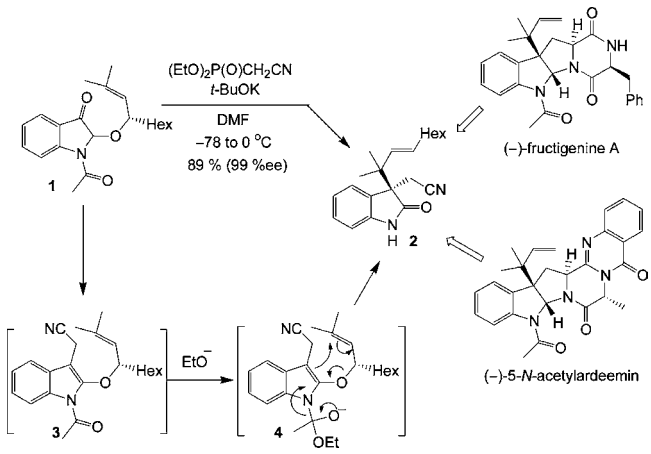


A Gold-Catalyzed Synthesis of Dihydrofuran-3-ones



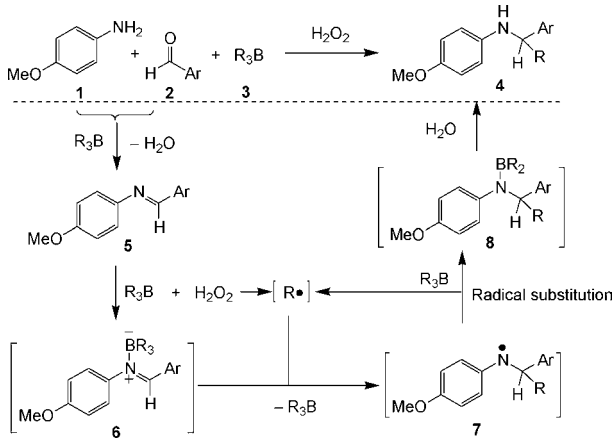
Zhang's research group at the University of California, Santa Barbara, developed a gold-catalyzed oxidation of terminal alkynes (*J. Am. Chem. Soc.* **2010**, *132*, 3258−3259). Many functional groups were tolerated including Boc and MOM groups. The reaction can occur via α-oxo gold carbenoid **5** followed by 5-exotrig cyclization (or **6** followed by oxidation with the oxidant). The drawback of this approach is the use of 2 equiv of *N*-pyridine oxide and 1.2 equiv of strong acid MsOH.

Domino Olefination/Isomerization/Claisen Rearrangement



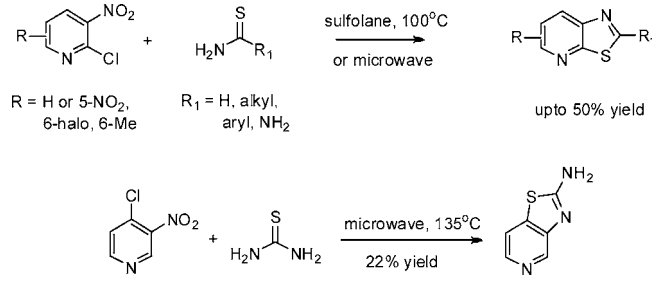
Of critical importance is the design of an innovative route for the synthesis of a complex target molecule. As one of the principals in the organic synthesis, redox economy gains increased attention. Redox economy was described in a review paper by Hoffmann, Baran, and co-worker (*Angew Chem., Int. Ed.* **2009**, *48*, 2854−2867) as "*to reduce the number of nonstrategic (those that do not set stereochemistry or are not skeleton-building) or corrective oxidation and reduction steps in synthesis, not only because these steps lower the overall efficiency of a synthesis, but also since many redox reactions are difficult to scale up in industrial settings and are frequently the source of noxious byproducts and environmental problems*". A domino olefination/isomerization/Claisen rearrangement synthetic sequence was devised by Kawasaki and co-workers in Japan (*J. Org. Chem.* **2010**, *75*, 1126−1131) to prepare a common intermediate **2** in the total synthesis of (−)-fructigenine A and (−)-5-*N*-acetylardeemin. This redox economy synthetic sequence accomplished two targets, the oxidation state transformation from C3 to C2 and the establishment of C3 stereogenic center in one single operation. Horner−Wadsworth−Emmons reaction of **1** with diethyl cyanomethylphosphonate in the presence of *t*-BuOK at −78 to 0 °C sets out the domino sequence involving olefination/isomerization to lead to **3** whose reaction with ethoxide affords intermediate **4**. The subsequent acetyl removal of **4** initiates Claisen rearrangement to furnish the desired oxindole **2** in 89% yield and 99% ee.

One-Pot, Three-Component Alkylative Amination



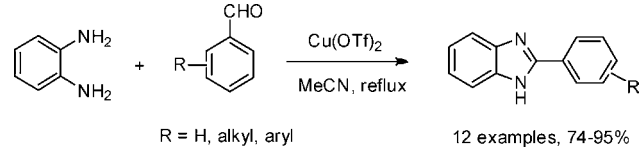
A three-component reaction of an aryl aldehyde **2**, an arylamine **1**, and a trialkylborane **3** in the presence of hydrogen peroxide was accomplished in one-pot fashion to afford alkylated arylamine products in good yields. A mechanistic hypothesis (a minor modification was made based on the original one) for this transformation (*Eur. J. Org. Chem.* **2010**, 1934−1942), reported by Valpuesta and co-workers in Spain, involves imine **5** which is activated via the imine−borane complexes **6**. The subsequent radical addition of **6** leads to radical **7** whose radical substitution with R_3B in turn produces **8** and radical R•. Theoretically, this reaction may require 2 equivalents of Et_3B: one equivalent for the formation of imine **5** and one for **8**. Additionally, catalytic quantity of R_3B is needed for the formation of **6** and the radical initiation with hydrogen peroxide. The reaction can be applied to arylamines and differently substituted aryl aldehydes including heteroaryl aldehydes.

One-Step Synthesis of Thiazolopyridines



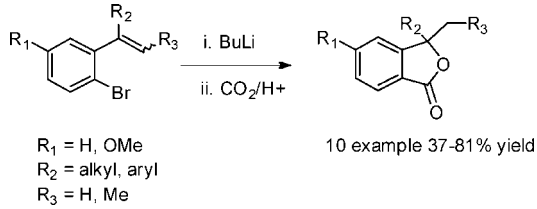
The thiazolo[5,4-*b*]pyridine nucleus has been utilised in a number of agricultural and medicinal programmes (e.g., a recent report from Schering Plough: *Bioorg. Med. Chem Lett* **2009**, *19*, 6176−6180). As part of their ion modulators project, Duncton and co-workers from Evotec San Francisco (*J. Heterocycl. Chem.* **2009**, *46*, 1125) report an efficient one-step synthesis of such thiazolopyridines from chloro-nitropyridines. Simple heating of reagents in either sulfolane or under microwave irradiation gave products with a range of thiazole substituents, albeit in modest yields. Highest yields were obtained with a 4-fold excess of the thioamide, whilst microwaves promoted the reaction with less activated pyridines. The authors considered the reaction to proceed via nucleophilic chloro displacement followed by *in situ* reduction of the nitro group by excess thioamide prior to cyclisation. A single example with thiourea provides access to a thiazolo[5,4-*c*]pyridine. Whilst some yields are quite low, this methodology may be competitive to the other multistep processes that exist.

Mild Synthesis of Benzimidazoles



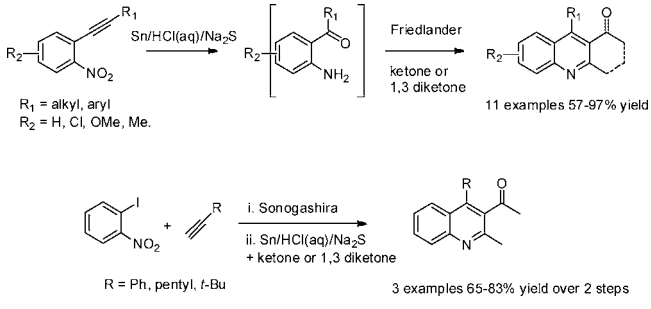
Chari and colleagues (*J. Heterocycl. Chem.* **2010**, *47*, 153) disclose a one-pot oxidative synthesis of benzimidazoles from 1,2-phenylenediamine and alkyl or aryl aldehydes. Whilst the reaction does require a molar equivalent of copper triflate, it is noteworthy for the mildness of conditions required. This provides an alternative to other methodologies which utilise sodium thionite, benzoquinone, or air, for example.

Efficient Synthesis of Phthalides



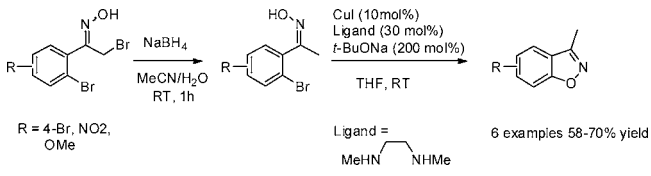
Kobayashi et al. (*Heterocycles* **2010**, *81*, 1, 163−169) describe a facile synthesis of differentially 3,3-disubstituted phthalides from *o*-bromostyrenes via lithium−bromine exchange and quench with carbon dioxide. Examples are restricted to styrenes with $R_2 \neq H$, and in all but one case $R_3 = H$. Nevertheless, this provides useful methodology due to the ready availability of precursor styrenes via Wittig chemistry.

Tandem Sonogashira−Friedlander Synthesis of Quinolines



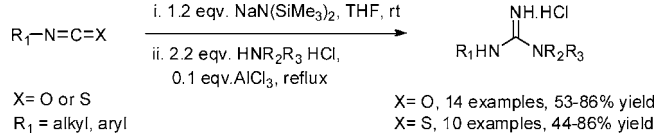
The Sonogashira and Friedlander reactions are well-established protocols in organic synthesis for the preparation of alkynes and quinolines, respectively. Okuma (*Heterocycles* **2010** *81*. Pre-press) have reported a tandem process which delivers 2,3,4-substituted quinolines from an *o*-alkynyl nitrobenzene precusor via in situ reduction and alkyne hydration to afford intermediate aminoketone followed by standard Friedlander cyclisation. A few examples are reported which describe a one-pot synthesis from *o*-iodonitrobenzenes via Sonogashira, reduction−hydration, and subsequent Friedlander sequence.

Synthesis of Isoxazoles from *o*-Bromoacetophenone *Z*-Oximes



Intramolecular cyclisation of oximes to form isoxazoles typically requires the presence of an ortho-fluoro group and proceeds under strongly basic conditions via the SnAr mechanism. Tois and co-workers (*Tetrahedron Lett.* **2010**, *51*, 1030−1033) report a mild Cu(I)-/diamine-promoted cyclisation of *o*-bromo analogues. Key to the utility of this approach is the selective formation of the *Z*-oxime by borohydride reduction of an α-bromo oxime. Subsequent cyclisation under optimum conditions of copper iodide/*N*,*N*′-dimethylethylenediamine and sodium *tert*-butoxide afforded a range of 3-methylisoxazoles in good yield. No cyclisation occurred with NaO*t*Bu alone, whilst *E*-oximes failed to undergo cyclisation under optimised conditions.

Simple One-Pot Synthesis of Guanidines



Classical methodologies to form the guanidine group involve addition of amines to *S*-alkylisothiouronium salts or carbodiimides. Wong (*Tetrahedron* **2010**, *66*, 1892−1897) describe the reaction of isocyanates or isothiocyanates with NaHMDS (acting as an ammonia equivalent) to form a cyanamide anion which is trapped *in situ* with an amine hydrochloride salt to afford range-substituted guanidines in a one-pot procedure. The reaction proceeds in good overall yield for isocyanates or isothiocyanates with either anilines/aliphatic amine hydrochloride salts.

Solubility and Micronization of Griseofulvin in Subcritical Water

Controlling particle morphology is one of the common challenges of a pharmaceutical process scientist. One of the "dream" green, but often forbidden, solvents for particle engineering is water. Creative use of water as a solvent for organic, hydrophobic compounds, involves the use of water under subcritical conditions. Hydrophobic compounds were solubilized in superheated (subcritical) water at temperatures between 130 to 170 °C and at 70 bar. A novel method for API particle morphology control using subcritical water was reported by a group from The University of New South Wales (Australia) (Carr, A. G.; et al. *Ind. Eng. Chem. Res.* **2010**, *49*, 3403−3410). Subcritical solutions of griseofulvin were injected in RT water, leading to griseofulvin precipitation. The morphology of the particles produced could be modified by using concentration, temperature, and mixing. Surprisingly, unimodal particle size distributions were obtained. XRPD found irregularities with particles obtained under certain operating conditions, whereas DSC did not show any difference between the various forms produced. A known limitation of this methodology is thermal stability of the API. It will be interesting to see the results of similar investigations using other APIs, and the development of a better theory explaining the interactions between subcritical water and such organic, hydrophobic molecules.

Multiscale Pharmaceutical Process Understanding: From Particle to Powder to Dosage Form

One of the goals of the Quality by Design (QbD) paradigm is multiscale process understanding based on an integrated informatics database. Related multiscale modeling can effectively remove the artificial separation of API and excipient properties from the manufacturing process. Such a holistic approach for pharmaceutical development is discussed in a report from the University of Hawaii, Purdue University, and Harris Co. (Hamad, M. L.; et al. *Chem. Eng. Sci.* **2010**. In press,

DOI: 10.1016/j.ces.2010.01.037). The paper reviews key aspects of pharmaceutical material development at all three scales: particle, powder, and solid dosage form, while presenting key examples. The authors comment on the lag in pharmaceutical material R&D compared to advances in materials science in general; they explain that this delay is the result of different development criteria used for pharmaceutical material development (primarily solubility and stability), compared with the criticality of mechanical properties that need to be optimized for "typical" new materials. Because of the high complexity associated with pharmaceutical R&D, first principles can rarely be used for reliable predictive modeling of such processes. The "next best" tool, multivariate analysis (chemometrics), is discussed in some detail. The authors predict that the future of pharmaceutical development lies in multiscale modeling, advanced analytics, and informatics.

Protecting-Group-Free Synthesis As an Opportunity for Invention

A key objective when converting a medicinal chemistry route into a potential manufacturing process is reducing the number of synthetic steps. An approach considered for accomplishing this goal (as well as that of an "ideal synthesis") has been the exclusion, or at least minimization, of the use of protecting groups. A review from The Scripps Research Institute (the Baran group) discusses the relevant historical background, as well as the recent developments in this field (Young, I. S.; et al. *Nat. Chem.* **2009**, *1*, 193). Protecting-group-free ("PGF") synthetic procedures have been published during the last century, but the authors indicate that in the past 5 years a surge was noticed in this area. Several natural product synthesis examples are presented, and new chemoselective reagents and processes are discussed. The unique challenge of PGF synthesis in the area of "naked" biomolecules (polypeptides, polynucleotides, and polysachharides) is mentioned. The authors comment that the required reaction innovation and optimization are a justified price for PGF synthesis. This review has 105 references.

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