Organic Process Research & Development

HIGHLIGHTS FROM THE LITERATURE

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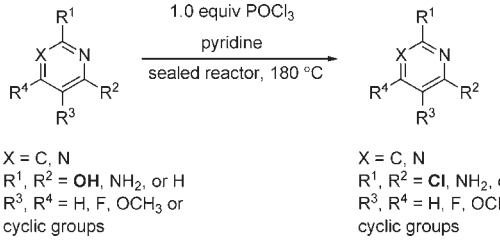
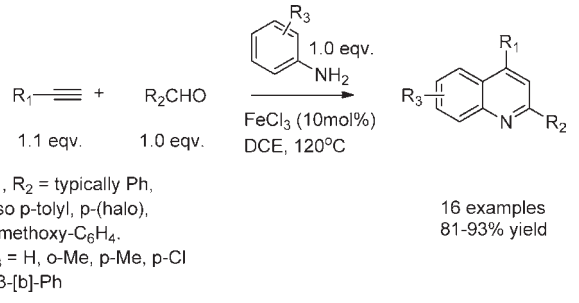
Some Items of Interest to Process R&D Chemists and Engineers

■ LARGE-SCALE PREPARATION OF CHLORINATED PYRIMIDINES



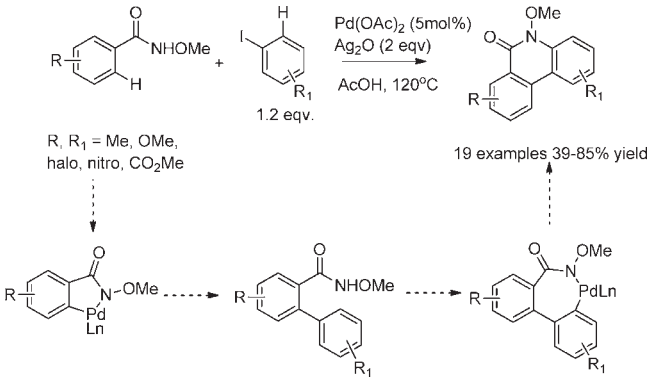
Chloropyrimidines and other *N*-containing aromatic heterocyclic analogues can be efficiently prepared from the corresponding hydroxylated precursors under solvent-free or low-solvent conditions with equimolar or less chlorinating reagents. This high-yielding protocol reported by the Sun group (*J. Org. Chem.* **2011**, *76*, 4149) allows the preparation of multigram and kilogram batches of these important synthetic intermediates. Reasonable to very good yields were obtained for many different kind of starting materials, at tens of grams to 12-kg scales. The workup and purification process also limited the use of solvents, therefore making this procedure more friendly to the environment and suitable for routine production of a variety of important chlorinated synthetic intermediates with pyrimidine and analogous moieties. Details from an experiment conducted at 12-kg scale are provided.

■ $FeCl_3$-CATALYZED THREE-COMPONENT SYNTHESIS OF QUINOLINES



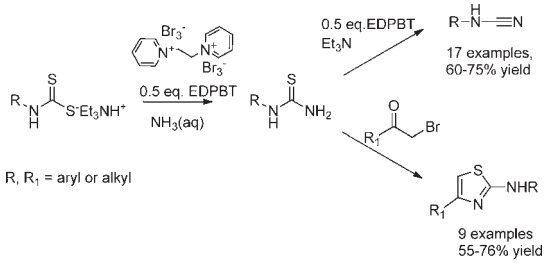
There are numerous well-known methodologies for the synthesis of quinolines; such as Doebner–Miller, Friedlander, Skraup and Povarov reactions. Wang et al. (*J. Heterocycl. Chem.* **2011**, *48*(1), 157) have reported what appears to be a flexible approach to 2,4-disubstituted quinolines from the condensation of an alkyne, aldehyde, and aniline promoted by $FeCl_3$. The authors speculate that the metal additive promotes both addition of the alkyne to the Schiff's base (formed in situ) and cyclization of the resultant proparylic amine. Final step aerobic oxidation is assumed to yield the quinoline.

■ Pd-CATALYZED SYNTHESIS OF PHENANTHRIDINONES FROM WEINREB AMIDES



Wang et al. (*Angew. Chem., Int. Ed.* **2011**, *50*, 1380) have reported a Pd-catalyzed cascade formation of C–C and C–N bonds between an aromatic Weinreb amide and an aryl iodide to yield phenanthridinones. In essence, the reaction is assumed to proceed via the first five-membered palladacycle shown above followed by cross coupling with the aryl iodide, then a second seven-membered palladacycle is formed followed by reductive elimination to the phenanthridinone. Yields in most cases were 60–80% with lower results obtained for *m*-iodonitrobenzene. Aryl bromides and chlorides did not react under these conditions, whilst other silver salts (acetate, sulfate) proved less efficient oxidants; oxone and $Cu(OAc)_2$ gave poor yields.

■ SYNTHESIS OF CYANAMIDES AND THIAZOLES FROM DITHIOCARBAMATE SALTS



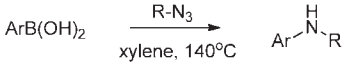
1,1′-(Ethane-1,2-diyl)dipyridinium bis-tribromide (EDPBT) is a known brominating agent capable of the alpha bromination of ketones. Patel et al. (*Synth. Commun.* **2011**, *41*, 792) report on its desulfurizing capabilities by the conversion of dithiocarbamate salts to thioureas and ultimately cyanamides or thiazoles. Thus, treatment of either an aryl or alkyl dithiocarbamate triethylammonium salt with 0.5 equiv of EDPBT in aqueous ammonia afforded the thiourea. Removal of excess ammonia by heating >60 °C followed by addition of triethylamine and EDPBT (0.5 equiv) yielded the

Published: June 28, 2011

   dx.doi.org/10.1021/op200150j | *Org. Process Res. Dev.* 2011, 15, 730–735

N-aryl or alkyl cyanamide in reasonable yield. Alternatively, treatment of the intermediate thiourea with a bromoketone (formed by treatment of parent ketone with EDPBT) gave good yields of the 2,4-disubstituted thiazoles. The brominating agent could be recycled by treatment of the 1,1′-(ethane-1,2-diyl)dipyridinium dibromide salt with KBr/oxone.

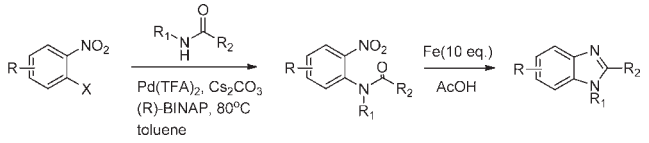
■ PREPARATION OF ANILINES FROM ARYL BORONIC ACIDS AND AZIDES



Ar = Ph, 3,4,5-F-Ph 19 examples
3-CHO-Ph, 3-F-Ph. 35-85% yield
R = octyl, substituted benzyl.

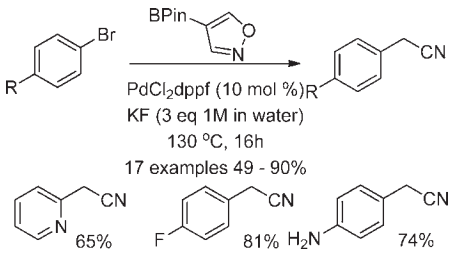
Aryl boronic acids are versatile building blocks for organic synthesis, most notably in the Suzuki cross-coupling reaction. Likewise organic azides are often employed in Click chemistry for the synthesis of triazoles or tetrazoles. Yu et al. (*Tetrahedron Lett.* **2011**, *52*, 1430) have shown that the reaction of aryl boronic acids with either aryl or benzyl azides furnished bis(aryl)amines and *N*-benzylanilines, respectively. Higher yields were obtained with electron-poor aryl boronic acids (e.g., 3,4,5-trifluorophenylboronic acid) and electron-rich azides (e.g., *p*-methoxybenzyl azide). No product was obtained with heterocyclic boronic acids (4-pyridyl or 2-thienyl), whilst octyl azide gave modest yield (35% with phenylboronic acid).

■ SYNTHESIS OF BENZIMIDAZOLES BY SEQUENTIAL CROSS-COUPLING AND REDUCTION



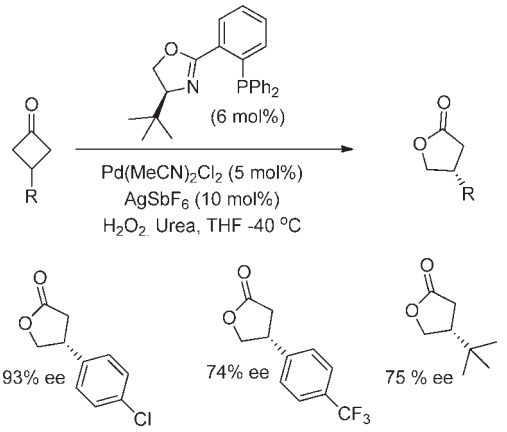
Lindenschmidt et al. (*Eur. J. Chem.* 2011, 234) of Sanofi-Aventis Frankfurt have demonstrated a flexible approach to the synthesis of benzimidazoles from 2-halonitrobenzenes and secondary amides. Thus, initial Pd-catalyzed cross-coupling yielded an *N*-arylated amide which underwent nitro reduction and cyclization after treatment with iron in glacial acetic acid. The reaction proved amenable to a variety of substituents on either reactant with the exception of 2-pyridyl derivatives (i.e., 2-nitro 3-chloropyridine or 2-acetamidopyridine) which gave low yields. A one-pot variant was also described which gave comparable yields.

■ CYANOMETHYLATION VIA ISOXAZOLE FRAGMENTATION

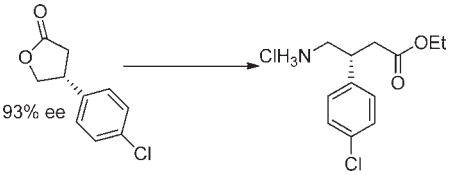


The use of the arylacetonitrile motif is highlighted in several important drugs which include *verapamil* and *anastrozole*, not to mention the wide use of their reduced forms, phenethylamines, as linkages in medicinal chemistry. Interestingly a team lead by Velcicky of Novartis (*J. Am. Chem. Soc.* **2011**, *133*, 6948) accidently stumbled across a side reaction to generate these species whilst trying to Suzuki couple isoxazole-4-boronic acid to aryl halides. During the Suzuki reaction a large amount of decomposition of the heterocycle was occurring; upon further investigation it was found to decompose to an arylacetonitrile. This prompted further investigation and a screen of coupling conditions which highlighted the use of a 1 M solution of potassium fluoride and a reaction temperature of 130 °C. The author then applied this methodology over a range of 17 aryl halides with average to good yields. The main drawback for this chemistry is the limited commercial availability of the isoxazole boronic acid.

■ Pd CATALYZED ASYMMETRIC BAEYER–VILLIGER



Catalytic asymmetric oxidation chemistry has had a profound effect on modern organic chemistry. Over a century after the discovery of the Baeyer–Villiger oxidation Stoltz has turned his attention to increasing the levels of enantioselectivity for this reaction compared to the work that has been reported previously (*Tetrahedron* **2011**, 4352). To achieve this, Stoltz applies the use of his PHOX family of ligands in the palladium-catalyzed Baeyer–Villiger oxidation of prochiral cyclobutanones to provide enantioenriched lactones in up to 99% yield and 81% ee. Pleasingly, he then demonstrates that the lactones can be recrystallised in greater than 66% yield to give material with 93% ee.



(R)-(-)-baclofen

With the optimized systems in hand the strength of the methodology is demonstrated for the key building block for (*R*)-(−)-baclofen.

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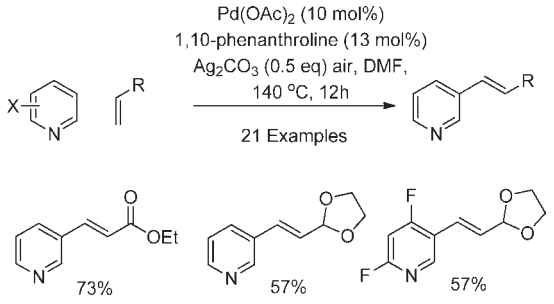
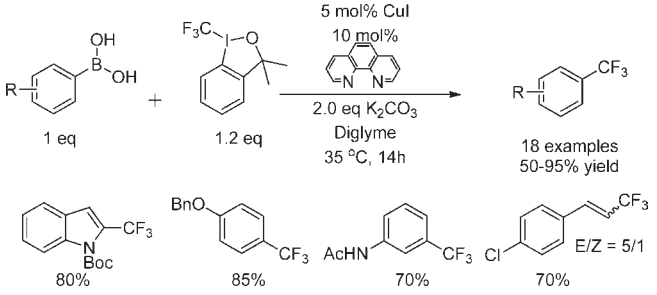
■ PYRIDINE C-3 SELECTIVE C−H OLEFINATION



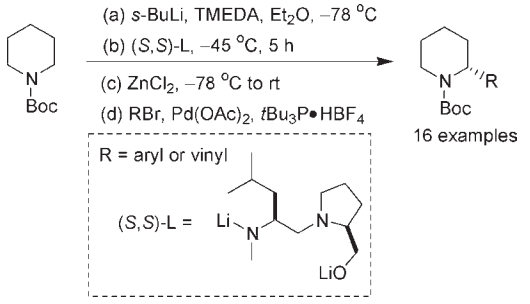
With atom economy proving to be a key part of route optimization in recent years, the arena of C−H activation has gathered great momentum, with the preliminary work developed by Fagnou for pyridine *N*-oxide C-2 activation; it has taken a number of years for C-3 activation to reach its full potential. In an effort to address this gap, Yu of Scripps has reported the first Pd-catalyzed C-3 selective olefination of pyridines (*J. Am. Chem. Soc.* **2011**, *133*, 6964). Yu initially designed experiments to address the low reactivity of pyridyl C−H bonds due to the poor electron density of the ring and the strong coordination of the pyridine N atom with the Pd(II) centre blocking access to the desired site. Yu and co-workers initially screened a wide range of bidentate pyridyl ligands to take advantage of the coordination; this gave rise to the simple and readily available 1,10-phenanthroline as the most efficient ligand to facilitate the reaction. In total Yu then demonstrated the broad scope of these simple, nonsensitive reaction conditions. In total 21 examples demonstrate the functional group compatibility.

■ TRIFLUOROMETHYLATION OF ARYL VINYL BORONIC ACIDS



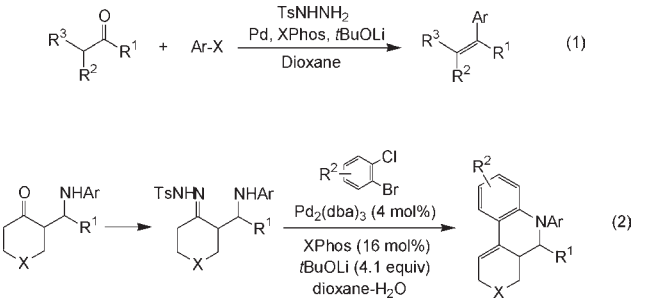
Trifluoroethyl-subsituted arenes are prominent structural motifs that are found in a wide variety of fine chemicals. In particular, in medicinal chemistry where their incorporation into drug-like molecules has become a powerful and widely used tactic in drug discovery. In the past several years many strategies have emerged for the preparation of trifluoromethyl-substituted arenes; however, in this paper Shen, based at the Key Laboratories of Organofluorine Chemistry (*Org. Lett.* **2011**, *13*, 2342), describes an alternative strategy where trifluoromethyl arenes are prepared by reaction of nucleophilic [$ArCu^-$] species and an electrophilic [$CF3^+$] (Togni's reagent). The initial screen for conditions was based upon CuI and 1,10-phenantroline, where a range of copper sources and ligands were evaluated, the result of which highlighted the importance of a 2:1 ligand/copper source ratio. A further screen of solvent and bases then gave rise to the optimized reaction conditions. The author then applied this methodology to 18 different substrates, showing the applicability of the reaction and the benefits it brings compared to the alternative approaches available to the bench chemist.

■ ASYMMETRIC SYNTHESIS OF 2-SUBSTITUTED PIPERIDINES



A highly enantioselective synthesis of 2-aryl- and 2-vinylpiperidines was accomplished through a tandem process involving a catalytic dynamic resolution (CDR) of *N*-Boc-2-lithiopiperidine followed by transmetalation and Negishi coupling (*Org. Lett.* **2011**, *13*, 394). The reaction tolerated various functional groups in the aryl bromides such as methyl, *tert*-butyl, methoxy, acetyl, trifluoromethyl, cyano, and amino groups. Vinylation with 1-bromo-1-propene and β-bromostyrene afforded the corresponding vinylated products in 63% yield (98:8 er) and 66% yield (93:7), respectively.

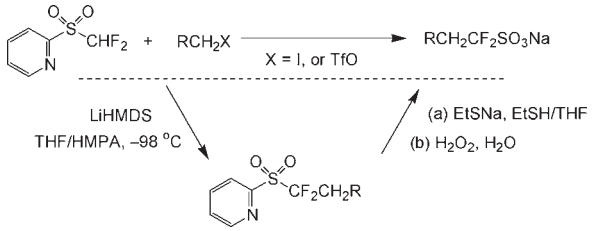
■ TOSYLHYDRAZIDE-PROMOTED PALLADIUM-CATALYZED REACTION OF β-AMINOKETONES WITH *o*-DIHALOARENES



On the basis of the recently developed Pd-catalyzed tosylhydrazide ($TsNHNH_2$)-promoted cross-coupling reaction (eq 1) (*Chem. Eur. J.* **2008**, *14*, 4792), a new Pd-catalyzed process consists of the cross-coupling of the tosylhydrazone of a Mannich adduct with a 1,2-dihalogenated aromatic system, and a subsequent intramolecular C−N bond formation (eq 2) (*Angew. Chem., Int. Ed.* **2011**, *50*, 2350). The reaction can be applied to diverse 1-bromo-2-chlorobenzene derivatives bearing electron-donating and electron-withdrawing groups. The reaction proceeds efficiently through hydrazone intermediates derived from different types of cyclic ketones, including 4-substituted cyclohexanones, cycloheptanone, and heterocyclic derivatives of 4-piperidone, dihydro-2*H*-pyran-4-one, and dihydro-2*H*-thiopyran-4-one.

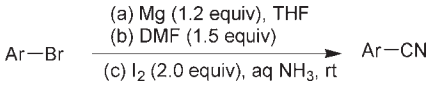
dx.doi.org/10.1021/op200150j |*Org. Process Res. Dev.* 2011, 15, 730–735

■ SYNTHESIS OF SUBSTITUTED DIFLUOROMETHYL SULFONATES FROM DIFLUOROMETHYL 2-PYRIDYL SULFONE AND ALKYL IODIDES (OR ALCOHOLS)



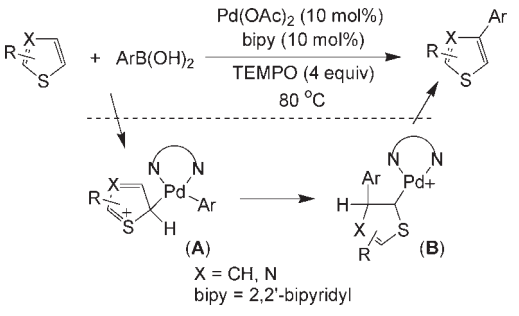
An efficient method for the synthesis of alkyl α,α-difluorosulfonates from difluoromethyl 2-pyridyl sulfone was developed (*Angew. Chem. Int. Ed.* **2011**, *50*, 2559). The synthetic process involves three steps: nucleophilic substitution between difluoromethyl 2-pyridyl sulfone and alkyl iodides (or triflates), followed by ipso substitution and the subsequent oxidation of the resulting sulfinates to afford the α,α-difluorosulfonates. The nucleophilic substitution appeared very sensitive to steric hindrance; for instance, reactions with primary alkyl iodides afforded α,α-difluoroalkyl 2-pyridyl sulfones in good yields, while the secondary alkyl iodide did not give the anticipated product. The ipso substitution and the oxidation step were telescoped into a one-pot operation furnishing the desired α,α-difluorosulfonates in excellent overall yields.

■ A NEW METHOD FOR TRANSFORMATION OF AROMATIC BROMIDES TO NITRILES



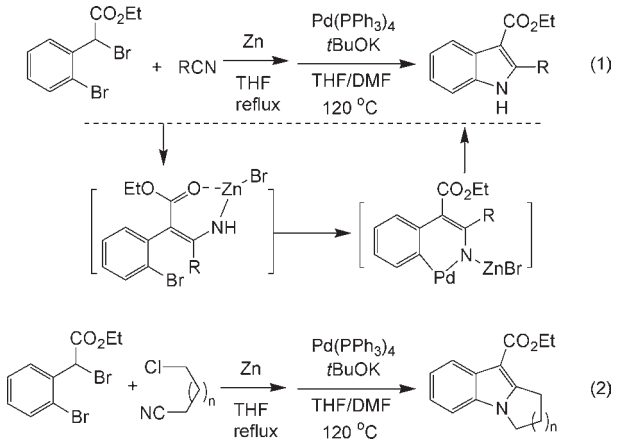
A research group from Japan developed a new method for transformation of aromatic bromides into the corresponding aromatic nitriles (*Tetrahedron Lett.* **2011**, *52*, 2404). The transformation involves the formations of Grignard reagents and *N*,*N*-dimethyl formamide adducts, followed by treatment with molecular iodine in aqueous NH_3 at room temperature to produce the nitriles in good yields. The reactions tolerate various aromatic bromides bearing electron-rich or electron-deficient groups and are less sensitive to steric hindrance.

■ REGIOSELECTIVE BIARYL COUPLING OF THIOPHENES OR THIAZOLES WITH ARYLBORONIC ACIDS IN THE PRESENCE OF PALLADIUM CATALYST



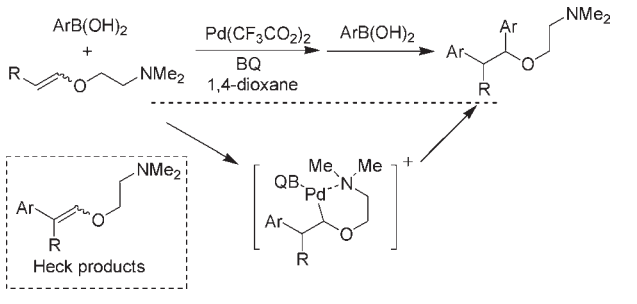
A new method for the C4-selective C—H arylation of thiophenes or thiazoles with arylboronic acids was developed (*Angew. Chem. Int. Ed.* **2011**, *50*, 2387). The reactions were catalyzed with palladium acetate in the presence of TEMPO, affording the cross-coupling products in high yields and excellent regioselectivities. Mechanistic studies revealed that the reaction occurred through intermediates **A** and **B**, and the presence of excess boronic acid is the key in achieving the otherwise difficult C4 regioselectivity. A range of thiophene derivatives including 2-substituted, 3-substituted, and 2,3-disubstituted thiophenes as well as thiophene-containing fused arenes underwent C—H bond arylation with very high regioselectivity. Various arylboronic acids, such as phenyl, 4-methylphenyl, and 4-methoxyphenyl acids, coupled with 2-phenylthiazole yielding regioselectively the corresponding C4-arylated thiazoles in good yields.

■ ONE-POT SYNTHESIS OF INDOLE DERIVATIVES VIA PALLADIUM-CATALYZED AMINATION OF THE BLAISE REACTION INTERMEDIATE



On the basis of Pd-catalyzed intramolecular *N*-arylative or *N*-alkylative/*N*-arylative trappings of the Blaise reaction intermediates, a one-pot approach for the construction of indoles and *N*-fused indole moieties was developed (*Org. Lett.* **2011**, *13*, 1350) from reaction of aryl bromide and nitriles. Various aromatic nitriles with electron-donating and -withdrawing substitutents, heteroaromatic nitriles, and aliphatic nitriles could be converted into the corresponding indoles in a one-pot manner. Under these reaction conditions, *N*-fused indoles were accessed via highly chemoselective *N*-alkylations followed by Pd-mediated *N*-arylations.

■ CHELATION-MEDIATED PALLADIUM(II)-CATALYZED DOMINO HECK—MIZOROKI/SUZUKI —MIYAURA REACTIONS



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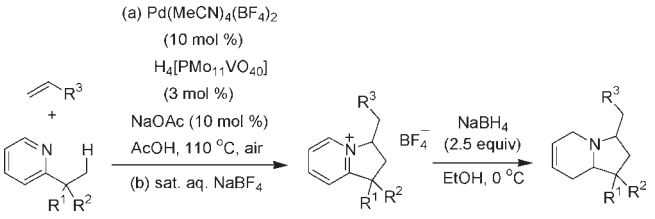
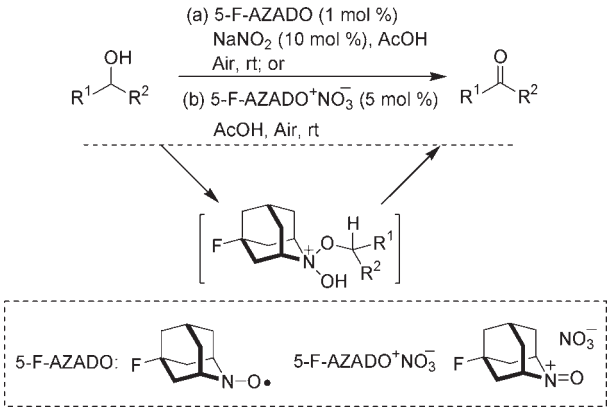
Domino Heck−Mizoroki/Suzuki−Miyaura reactions were developed utilizing arylboronic acids as arylating agents (*J. Org. Chem.* **2011**, *76*, 2433). These oxidative palladium(II)-catalyzed, base-free reactions occurred in a dimethylamino auxiliary-controlled manner, affording 2-(1,2-diarylethoxy)-*N*,*N*-dimethylethanamines (R = H) and 2-(1,1,2-triarylethoxy)-*N*,*N*-dimethylethanamines (R = Ph) from electron-deficient arylboronic acids and mono- (R = H) or 1,2-disubstituted vinyl ethers (R = Ph) in high selectivity without the formation of Heck coupling products. The reactions proceeded through the palladacycle intermediates that could be stabilized by two-carbon tethered dimethylamino moieties in combination with *p*-benzoquinone (BQ). However, the methylamino-substituted vinyl ether yielded only traces of monoarylated Heck product, indicating a strong Pd(II) coordination and poisoning of the catalyst.

AEROBIC Pd-CATALYZED sp^3 C−H OLEFINATION



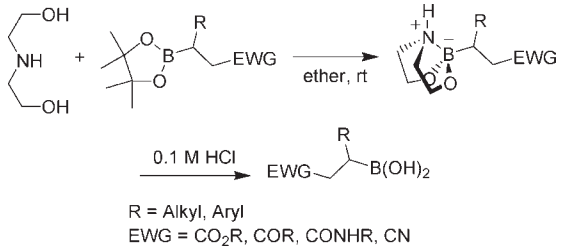
A new method for the Pd/polyoxometalate-catalyzed aerobic olefination of unactivated sp^3 C−H bonds was reported by Sanford and co-workers from University of Michigan (*J. Am. Chem. Soc.* **2011**, *133*, 6541). This selective C−H bond activation is attributed to the nitrogen heterocycles serving as directing groups. The products undergo reversible intramolecular Michael addition, which protects the monoalkenylated products from overfunctionalization. Various alkenes with functional groups such as α,β-unsaturated ester, amide, carboxylic acid, and ketones appeared to be effective coupling partners. In contrast, electron-rich olefins such as styrene and 1-hexene exhibited low reactivity under the same conditions. A variety of other 2-alkylpyridine derivatives participated in this sp^3 C−H olefination/cyclization reaction. Generally, C−H activation/C−C coupling proceeded with >20:1 selectivity for primary over secondary sp^3 C−H bonds. Further hydrogenation of the Michael adducts provides access to bicyclic nitrogen-containing scaffolds that are prevalent in alkaloid natural products.

HIGHLY EFFICIENT, ORGANOCATALYTIC AEROBIC ALCOHOL OXIDATION



The oxidation of alcohols to the corresponding carbonyl compounds, a fundamental reaction in organic chemistry, often requires the use of dangerous and harmful reagents. A highly efficient oxidation reaction was developed by Iwabuchi and coworkers from Japan for the transformation of alcohols to the corresponding carbonyl compounds (*J. Am. Chem. Soc.* **2011**, *133*, 6497). Two sets of catalytic conditions were identified as the methods of choice: method (a) and method (b) employing 5-F-AZADO and 5-F-AZADO$^+NO_3^-$, respectively. Under each set of conditions, oxidation of a wide range of alcohols occurred readily, leading to the carbonyl compounds in good yields. Both primary and secondary alcohols could be oxidized; however, the former was accompanied by a small amount of carboxylic acid. The reaction was hypothesized to proceed via the oxoammonium ion−alcohol adduct intermediate.

A TWO-STEP PROCEDURE FOR THE DEPROTECTION OF ALKYLPINACOLYL BORONATE ESTERS



Although boronate esters exhibit stability under air and chromatographic conditions, and usually benign to various reaction conditions, the removal of these groups has been troublesome and unpredictable. A method for deprotection of alkylpinacolyl boronate esters was developed via transesterification with diethanolamine (DEA) followed by hydrolysis (*J. Org. Chem.* **2011**, *76*, 3571). A variety of pinacolyl-β-alkylboronic esters underwent transesterification with DEA to form sp^3-hybridized boron−DEA adducts in good yields. This reaction proceeded fast (<30 min), and the product purification was simply done by filtration. The subsequent hydrolysis was realized under acidic conditions to yield boronic acid derivatives. This new approach tolerated various function groups including ester, amide, ketone, and cyano groups.

SOLVENT SELECTION GUIDE FOR PROCESS AND MEDICINAL CHEMISTS

GSK scientists and engineers have published their solvent-selection guide based on sustainable design principles (Henderson, R. K.; et al. *Green Chem.* **2011**, *13*, 854). This updated version revises the assessments of factors that impact process safety, separates reactivity from fire and explosion rankings, more than doubles the number of solvents in the guide to 110, and adds a selection guide more suitable for low-level users such as medicinal chemists and analytical laboratories. For each solvent, waste and health environmental factors are scored along with flammability and explosion, reactivity scores, and physical data information. There is also a life-cycle analysis score. Red flags for EHS issues and for legislative problems are also provided, allowing the process chemist to make key judgements re the choice of solvent.

dx.doi.org/10.1021/op200150j |*Org. Process Res. Dev.* 2011, 15, 730–735

HAZARDS OF PREPARING 2(-*tert*-BUTYLSULFONYL)-IODOSYLBENZENE

An original publication on a new class of iodonium ylides (*J. Am. Chem. Soc.* **1999**, *121*, 7164) has been found to be unsafe, although this may be because the workers repeating the published study ventured outside the reported hydrogen peroxide concentration (addition/correction has been published: *J. Am. Chem. Soc.* **2011**, *133*, 4151) The procedure involved working with concentrated hydrogen peroxide and acetic anhydride, and anyone using this combination should ensure that appropriate safety precautions are observed and that the scale of operation is tiny unless adequate safety testing has been carried out. The explosion that caused injury to a laboratory worker was reported in some detail in a letter to *Chem. Eng. News* **2011**, *89*(2), 2).

STRATEGIES FOR BRINGING DRUG DELIVERY TOOLS INTO DISCOVERY

There is no simple explanation for the recently observed 43% decrease in productivity in the pharmaceutical industry, while the R&D costs have increased by 80%. A major challenge for innovation in the pharmaceutical industry remains the high attrition rate of the compounds investigated. A team from Merck (Kwong, E.; et al. *Int. J. Pharm.* **2011**, *412*, 1) suggests that an important tool enabling the "fail-fast/fail cheap" paradigm can be an early holistic approach for the discovery/development process. The main justification for this strategy relates to the profound impact that formulation can have on go/no-go decision for drug candidates. The authors indicate that the use of such early integrated discovery/development teams is productive and does not prolong the discovery process. Challenges associated with the very small amounts of API typically available in the discovery stage were addressed using suitable miniaturization techniques. Examples are given for the successful use of HT solubility measurements (2−5 compounds per day, using 10 mg of material).

THE ROLE OF MESOMIXING IN ANTISOLVENT CRYSTALLIZATION PROCESSES

Occasionally, antisolvent crystallization process studies include amongst the parameters investigated either addition rate or agitation rate, or both but investigated separately. In many crystallization processes, it is both addition rate *and* agitation rate that impact the process results (such as particle size distribution). Mesomixing time is in fact the entity that links the two, characterizing the dispersion of the antisolvent plume. Mesomixing relevance to antisolvent crystallization is analyzed in a publication from the University College in Dublin (Barrett, M.; et al. *Chem. Eng. Sci.* **2011**, *66*, 2523). The impact of mesomixing on crystallization processes has been discussed for nearly two decades, and yet it appears that the concept has not been widely adopted by the chemical community. The model compound used in this work was benzoic acid, with ethanol as the solvent and water as the antisolvent. Crystallization was executed under fully developed turbulence (Re = 12,500), and computational fluid dynamics (CFD) were used to map the fluid velocities in the reactor. In addition to addition rate and agitation rate, mesomixing controlled processes also exhibit sensitivity to the location of the addition point (through the local value of turbulent dissipation of energy). The formulas suggested for the calculation of the mesomixing time are in part similar to such formulas reported earlier.

LEAPFROGGING OSTWALD'S RULE OF STAGES: CRYSTALLIZATION OF STABLE γ-GLYCINE DIRECTLY FROM MICROEMULSIONS

A group from Durham University (Chen, C. et al. *Cryst. Growth Des.*, **2011**, 10.1021/cg 101597q) reports about another success of controlled crystallization in microemulsions. Whereas bulk crystallization is often under kinetic control leading to the formation of metastable polymorphs (Ostwald's rule of stages), crystallization in three-dimensional nanoconfined systems can allow for thermodynamic control. By using certain nonionic surfactants such as AOT (sodium dioctyl sulfosuccinate) the authors were able to crystallize the γ isomer of glycine in preference to the α and β metastable polymorphs. The difference in energy between these polymorphs is approximately 0.2 kJ/mol. A possible physical chemical explanation for the observations reported is provided.

Mark McLaughlin,[†] Ian Wilson,[‡] Patrick Delaney,[§] Wenyi Zhao,[⊥] Andrei Zlota,[¶] and Trevor Laird*[∥]

[†]Merck & Co., Process Research, Rahway, New Jersey 07065, United States

[‡]Almac Sciences, Seagoe Industrial Estate, Portadown, Craigavon, Co. Armagh BT63 5QD, U.K.

[§]Peakdale Molecular Ltd., Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak SK23 0PG, U.K.

[⊥]Jacobus Pharmaceutical Co. Inc., Princeton, New Jersey 08540, United States

[¶]The Zlota Company LLC, 15, Fairbanks Road, Sharon, Massachusetts 02067-2858, United States

[∥]Scientific Update LLP, Maycroft Place, Stone Cross, Mayfield, East Sussex TN20 6EW, U.K.

AUTHOR INFORMATION

Corresponding Author

trevor@scientificupdate.co.uk.