Organic Process Research & Development

Highlights from the Literature

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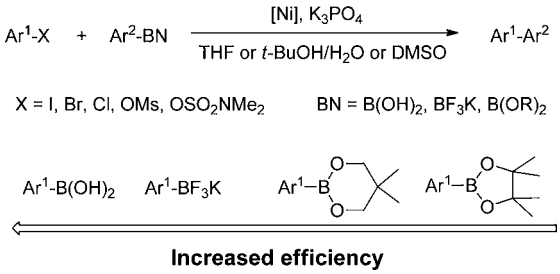
# Some Items of Interest to Process R&D Chemists and Engineers

## COMPARISON OF ARYLBORON-BASED NUCLEOPHILES IN Ni-CATALYZED SUZUKI–MIYAURA CROSS-COUPLING WITH ARYL MESYLATES AND SULFAMATES

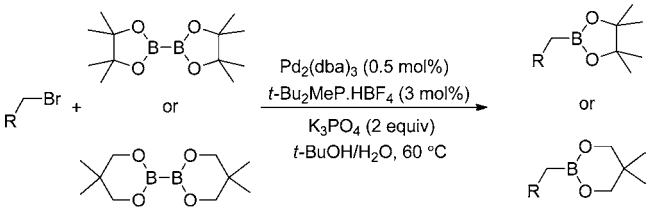
In a recent report from the Percec group (*J. Org. Chem.* **2012**, *77*, 5956) the efficiency of arylboron-based nucleophiles, boronic acid, potassium trifluoroborate, neopentylglycolboronate, and pinacol boronate in Ni-catalyzed Suzuki–Miyaura cross-coupling reactions with the two C–O electrophiles, mesylates, and sulfamates is compared. The conclusion from




this study is that arylboronic acids are the most reactive and most atom-economic of the four boron species examined. Arylpotassium trifluoroborates cross-couple efficiently only in the presence of water. In the absence of water, aryl neopentylglycolboronate is more efficient, less expensive, and more atom-economic than aryl pinacolboronate. Data for cost per mole of boron nucleophile and comparison of relative kinetics from competitive cross-coupling experiments are presented.

## PALLADIUM-CATALYZED BORYLATION OF PRIMARY ALKYL BROMIDES

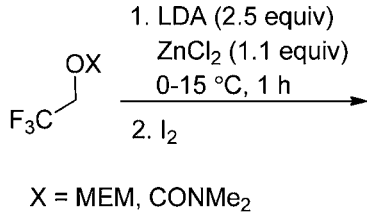
Continuing with the Suzuki–Miyaura cross-coupling theme, the Biscoe group reports that a mild Pd-catalyzed process for the borylation of alkyl bromides has been developed using bis(pinacolato)diboron as a boron source (*J. Org. Chem.* **2012**, *77*, 6629). This process accommodates the use of a wide range

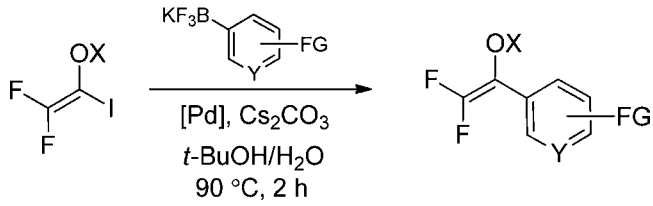



of functional groups on the alkyl bromide substrate. Primary bromides react with complete selectivity in the presence of a secondary bromide. The generality of this approach is demonstrated by its extension to the use of alkyl iodides and alkyl tosylates, as well as borylation reactions employing bis(neopentyl glycolato)diboron as the boron source. A total of 12 examples are presented with yields ranging from 63 to 96%. Overall this method provides a useful alternative to the hydroboration of terminal alkenes for access to primary alkylboron intermediates.

## SUZUKI–MIYAURA COUPLING REACTIONS OF IODO(DIFLUOROENOL) DERIVATIVES, FLUORINATED BUILDING BLOCKS ACCESSIBLE AT NEAR-AMBIENT TEMPERATURES

In another report related to Suzuki–Miyaura cross-coupling, the Percy group describes a new method for access to difluorovinylzinc reagents that can be operated at near ambient temperatures (*J. Org. Chem.* **2012**, *77*, 6384). The utility of




these reagents has been investigated in Suzuki–Miyaura couplings with a range of potassium trifluoroborate coupling partners, with the scope of successful couplings proving wide. Deiodinated species appeared as significant side products, but a solvent change from *i*-PrOH to *t*-BuOH suppressed the pathway to these species and improved coupling yields. These procedures afford cross-coupled products in moderate to excellent yield, overcoming a limitation in scope described in previous publications and signaling a further advance in the coupling of useful difluorovinyl synthons.

## A SOLUBLE COPPER(I) SOURCE AND STABLE SALTS OF VOLATILE LIGANDS FOR COPPER-CATALYZED C–X COUPLINGS

Although widely reported in the literature, anecdotal reports suggest that Cu-catalyzed C–N and C–O couplings can be notoriously unreliable, due in part to the insolubility of the copper source and base in the reaction medium. In addition, many of the high performance ligands which have been developed for this class of reactions possess nonideal physical and chemical properties such as volatility, hygroscopicity, and in some cases air sensitivity. To address these issues, Maligres and co-workers at Merck report on the development of stable, nonvolatile, and nonhygroscopic salts of certain high-perform-

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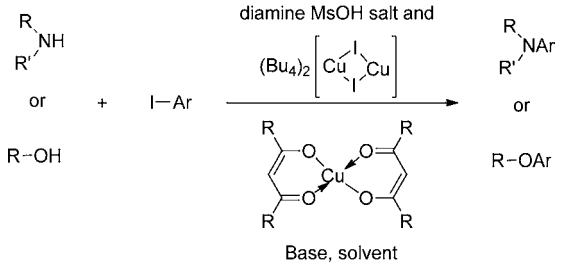
ance ligands and their use in Cu-catalyzed cross-coupling reactions (*J. Org. Chem.* **2012**, *77*, 7646). In addition, a stable

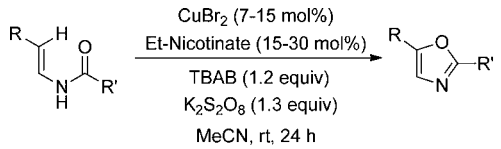



> 20 examples, 42-97% yield

Cu(I) double salt which is readily soluble in most organic solvents was identified and demonstrated to be a superior metal precursor for these reactions compared to traditional copper salts.

## ROOM TEMPERATURE COPPER(II)-CATALYZED OXIDATIVE CYCLIZATION OF ENAMIDES TO 2,5-DISUBSTITUTED OXAZOLES VIA VINYLIC C—H FUNCTIONALIZATION

Substituted oxazoles can be found in a wide variety of biologically active molecules of interest to the drug discovery community. A copper(II)-catalyzed oxidative cyclization of enamides to oxazoles via vinylic C—H bond functionalization at room temperature is now reported by Buchwald (*J. Org. Chem.* **2012**, *77*, 7526). Various 2,5-disubstituted oxazoles bearing



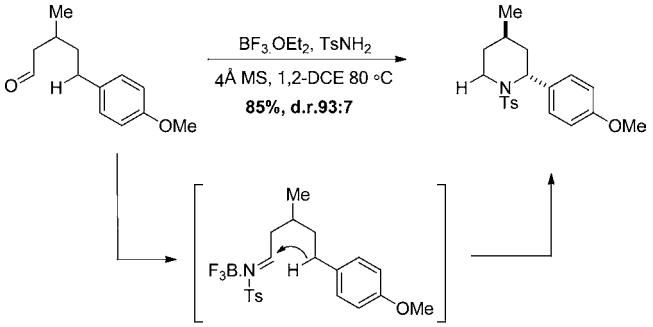

R, R' = aryl, vinyl, alkyl, heteroaryl

28 examples, up to 90% yield

aryl, vinyl, alkyl, and heteroaryl substituents could be synthesized in moderate to high yields. This reaction protocol is complementary to a previously reported iodine-mediated cyclization of enamides to afford 2,4,5-trisubstituted oxazoles.

## C—H BOND FUNCTIONALIZATION VIA HYDRIDE TRANSFER: FORMATION OF α-ARYLATED PIPERIDINES AND 1,2,3,4-TETRAHYDROISOQUINOLINES VIA STEREOSELECTIVE INTRAMOLECULAR AMINATION OF BENZYLIC C—H BONDS

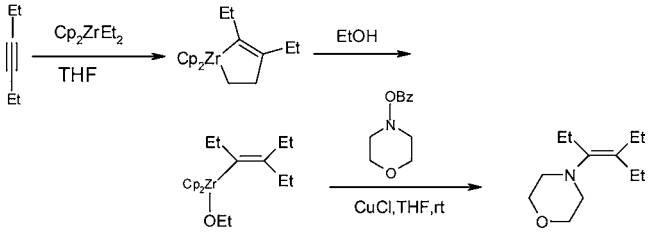
C—H bond functionalization represents a process of broad synthetic potential owing to the ubiquity of C—H bonds in organic compounds. The Sames group reports on a study of the intramolecular amination of $sp^3$ C—H bonds via the hydride transfer (HT) cyclization of *N*-tosylimines (*J. Org. Chem.* **2012**, *77*, 6689). In this transformation, 5-aryl aldehydes are subjected to *N*-toluenesulfonamide in the presence of $BF_3{\cdot}OEt_2$ to effect imine formation and HT-cyclization, leading to 2-arylpiperidines and 3-aryl-1,2,3,4-tetrahydroisoquinolines in a one-pot procedure. The reactivity of a range of aldehyde substrates was examined as a function of their conformational flexibility. Substrates of higher conformational rigidity were more reactive, giving higher yields of the desired products. However, a single substituent on the alkyl chain linking the *N*-tosylimine and the




benzylic $sp^3$ C—H bonds was sufficient for HT-cyclization to occur. In addition, an examination of various arenes revealed that the electronic character of the hydridic C—H bonds dramatically affects the efficiency of the reaction. The transformation is highly stereoselective and the stereoselectivity is reported to be a consequence of thermodynamic control.

## COPPER-CATALYZED ELECTROPHILIC AMINATION OF ALKENYLZIRCONOCENES WITH *O*-BENZOYLHYDROXYLAMINES: AN EFFICIENT METHOD FOR ENAMINE SYNTHESIS

Enamines, owing to their participation in a variety of synthetic transformations, occupy an important position in organic synthesis. The present article (*Org. Lett.* **2012**, *14*, 4750) describes a novel process for the preparation of highly substituted enamines, via, electrophilic amination of alkenyl zirconocenes. The alkenyl zirconocenes were prepared by the




alcoholysis of the corresponding zirconacyclopentene, which, in turn had been obtained by the action of the Schwartz reagent on the corresponding alkyne. In a typical reaction protocol, the enamine was obtained in two hours after the addition of CuCl(10 mol %) and 4-benzoyloxymorpholine to a solution of the alkenylzirconocene, which was generated as above. 4-Benzoyloxymorpholine was reacted with a variety of alkenyl zirconocenes with alkyl, aryl, alkenyl, and alkynyl substituents; all the reactions proceeded with moderate to good yields (74—86%). Amination with a range of *O*-benzoylhydroxyl amines and *O*-benzoylhydroxylamine derived piperidines proceeded equally well. Reduction of the enamines to the corresponding amines with $NaB(OAc)_3H$ further highlights the synthetic potential of the reaction. Mechanistically, it has been proposed that the alkenyl zirconocene undergoes transmetalation with CuCl which is followed by amination.

## RuHCl(CO)(PPh)$_3$-CATALYZED ALKYLATION OF KETONES WITH PRIMARY ALCOHOLS

The article (*Org. Lett.* **2012**, *14*, 4703) discloses a novel protocol for the α-alkylation of ketones with primary alcohols using $RuHCl(CO)(PPh)_3$ as a catalyst. The reaction conditions were optimized with acetophenone and 4-methylbenzyl alcohol as test substrates. Optimization studies revealed the use of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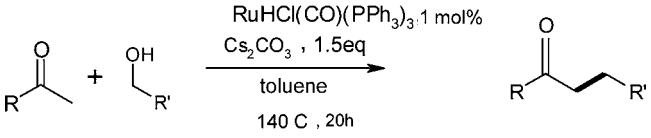
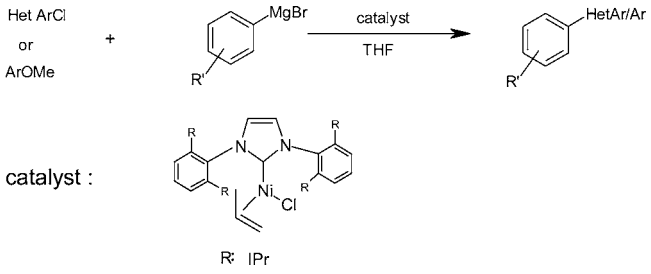



cesium carbonate as base and a catalyst loading of 1 mol % in refluxing toluene (140 °C) to be the conditions of choice. At lower temperatures, however, addition of a catalytic quantity (3 mol %) of 1,10-phenanthroline was essential for reaction completion. The reaction showed good substrate tolerance as alkylation with substituted benzyl alcohols as well as several hydroxymethyl heteroayls proceeded in good yields. Alkylation with aliphatic alcohols, however, proceeded only in the presence of 1,10 phenanthroline. It has been proposed that the alcohol, upon metal catalyzed transfer dehydrogenation under the given conditions, yields the corresponding aldehyde; condensation of the aldehyde with the ketone then affords the $\alpha,\beta$-unsaturated ketone which again undergoes transfer hydrogenation with primary alcohols to yield the $\alpha$-alkylated ketones and also generates the aldehyde for further participation in the catalytic cycle.

## KUMADA–TAMAO–CORRIU COUPLING OF HETEROAROMATIC CHLORIDES AND ARYL ETHERS CATALYZED BY (iPr)Ni(ALLYL)Cl

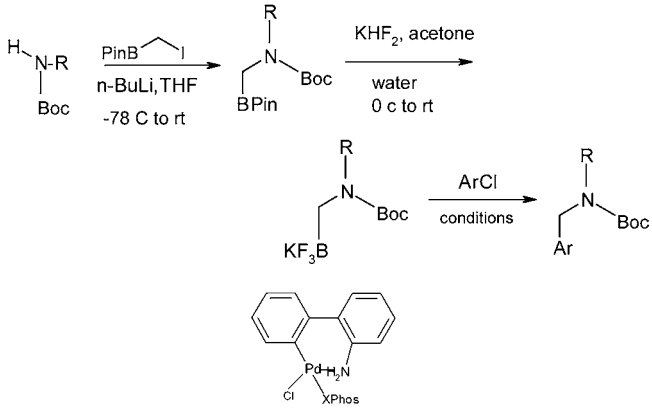
The Kumada–Tamao–Corriu reaction presents a simple approach to biaryls. In a recent development, Nicasio and coworkers have reported (*Org. Lett.* **2012**, *14*, 4318) (iPr)Ni(allyl)Cl (iPr = 1,3 bis(2,6-diisopropylphenyl)imidazolidene)-catalysed coupling of heteroaromatic chlorides and anisoles with aryl Grignard reagents, thus, further extending the scope of the reaction. A variety of heteroaryl chlorides were reacted with




variously substituted arylmagnesium bromides under optimized conditions with the reactions proceeding with good to excellent yields (74–99%). A turnover frequency of 190–990/h was obtained for the above reaction. Coupling of differently substituted anisoles, prompted by the high-yielding reactions of 2-methoxynaphthalene, with both PhMgBr and (*p*-Me)-PhMgBr, was also investigated. Reaction with anisoles, which proceeded better at 60 °C than at room temperature, showed excellent substrate tolerance (even a secondary amine substituent was tolerated) and proceeded smoothly to yield the corresponding biaryls. Heteroaromatic ethers, also reacted smoothly, under the above conditions.

## POTASSIUM BOC-PROTECTED SECONDARY AMINOTRIFLUOROMETHYL BORATES: SYNTHESIS AND SUZUKI–MIYAURA REACTIONS

Aminomethylated arenes, especially secondary aminomethyl arenes, are attractive synthetic targets, due to their presence in APIs and biologically active compounds. The present paper (*Org. Lett.* **2012**, *14*, 4458) reports a novel protocol for the synthesis of the above class of compounds via the Suzuki–Miyaura cross-coupling reactions of potassium Boc-protected secondary aminotrifluoromethyl borates. *N*-alkylation of Boc-

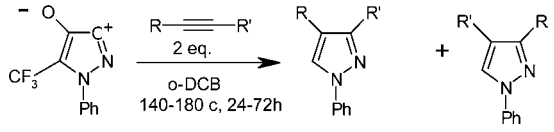



XPhos-Pd- G2 A

protected amines with iodomethylpinacolboronate followed by treatment with $KHF_2$ in presence of $K_2CO_3$ yielded the required aminotrifluoromethyl borates which were subjected to cross-coupling reactions with aryl and heteroaryl chlorides. Optimization studies revealed that a combination of 4 mol % of the ligand XPhos-Pd-G2A and 3 equiv of $Cs_2CO_3$ at 85 °C in a 4:1 mixture of toluene/water yielded the best results. Using the above conditions, the aminotrifluoromethylborates were subjected to coupling with variously substituted aryl chlorides which yielded the corresponding products in good-to-excellent yields. Interestingly, aryl chlorides with sterically demanding substituents at the ortho positions reacted better than the less hindered ones. Heteroaryl chlorides also reacted smoothly under the optimized conditions. Coupling with aryl mesylates, however, did not yield any product.

## A GENERAL AND REGIOSELECTIVE SYNTHESIS OF 5-TRIFLUOROMETHYL PYRAZOLES

A novel approach to 5-trifluoromethyl pyrazoles (important building blocks in the fine chemicals sector) via the cycloaddition of alkynes and 4-trifluoromethylsydnones (a novel class of mesoionic reagents) has been reported (*Org. Lett.* **2012**, *14*, 4858). Cycloaddition of the sydnones with differently




substituted acetylenes proceeded smoothly with good yields and excellent regioselectivity. In case of tetrasubstituted pyrazoles, better regioselectivities were obtained with alkynylboronates as they preferentially afforded the 4-borylated isomer. The syntheses of the trifluoromethylated sydnones are also described.

## Fe(II)-CATALYZED ASYMMETRIC OXYAMINATION OF ALKENES

Although osmium tetroxide is a valuable catalyst for the functionalization of alkenes, its use in industrial processes is limited by its high toxicity and volatility. Williamson and Yoon report a new advance in the context of a program for the development of osmium-free oxyaminations in *J. Am. Chem. Soc.* **2012**, *134*, 12370; an iron(II) bis(oxazoline) complex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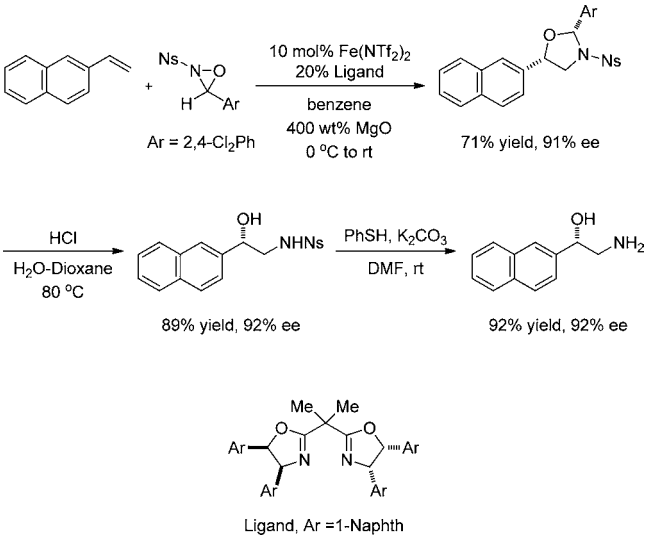
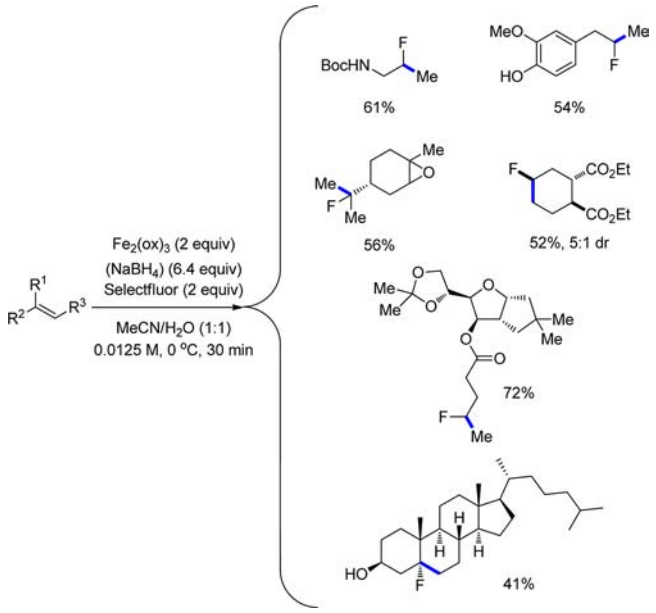
catalyzes the enantioselective intermolecular oxyamination of alkenes with *N*-sulfonyl oxaziridines. The reaction, which is




highly efficient for the functionalization of styrenes, fused polycyclic aromatics, and 1,3-dienes, does not work for aliphatic alkenes. Good yields and enantioselectivities can be achieved for a variety of styrenes bearing electron-withdrawing or electron-donating substituents that include halides, esters, and protecting groups for alcohols and amines. Interestingly, the oxyamination of 1,3-dienes affords complete chemoselectivity for the terminal olefin. The success of the oxyamination relies on the minimization of unwanted side reactions by increasing the loading of the catalyst, adding a drying reagent or using high dilution. A series of control experiments indicate that the remarkable diastereoselectivity of the reaction results from the selective transformation of one of the enantiomers of the racemic oxaziridine in a kinetic resolution process. Deprotection of the oxyamination product by sequential aminal hydrolysis and *N*-nosyl group removal affords the corresponding amino alcohols with stereochemical integrity and high yields.

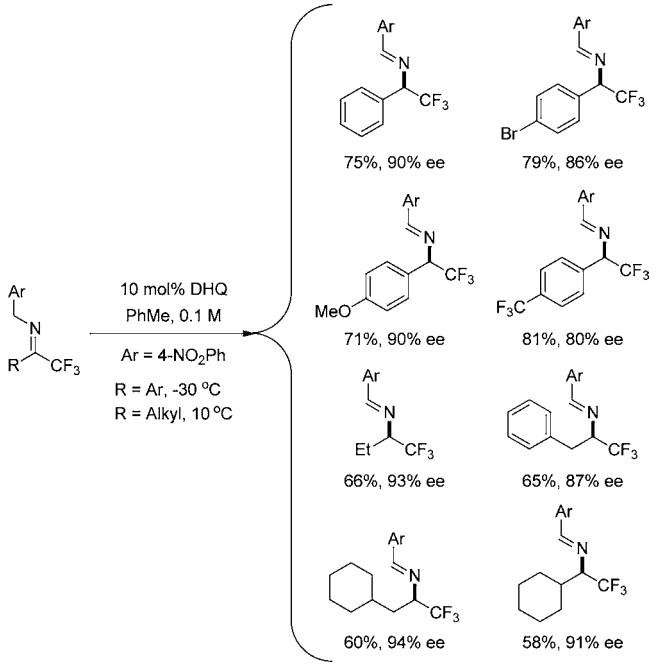
## Fe(III)-MEDIATED HYDROFLUORINATION OF ALKENES

Despite the growing interest in the development of practical routes to introduce fluorine in organic molecules, there is a shortage of methods to hydrofluorinate alkenes. Barker and Boger describe a mild hydrofluorination of unactivated alkenes using Fe(III) oxalate, $NaBH_4$, and Selectfluor (*J. Am. Chem. Soc.* **2012**, *134*, 13588). The functionalization, which is very fast (~30 min, 0 °C) and can be carried out open to the air with water as a cosolvent, occurs with exclusive Markovnikov regioselectivity and displays a remarkable scope and functional group tolerance. For example, terminal, di- and trisubstituted alkenes undergo hydrofluorination in good yields in the presence of a variety of functional groups such as unprotected alcohols and amines, phenols, epoxides, ketals, acetals, carboxylic acids, carbamates, amides, esters, peptides, and carbohydrates. The reaction follows a free radical mechanism in which $NaBH_4$ acts as the source of the hydrogen atom and Selectfluor donates atomic fluorine. Since $^{18}F$ Selectfluor is available, the methodology enables the preparation of substrates with potential utility in positron emission tomography (PET) molecular imaging based on $^{18}F$ labeling.




## ASYMMETRIC SYNTHESIS OF TRIFLUOROMETHYLATED AMINES

In another example of the increasing efforts to facilitate the preparation of valuable fluorinated compounds, Wu and Deng (Brandeis University) report the synthesis of optically active trifluoromethylated amines by the enantioselective isomerization of trifluoromethyl imines (*J. Am. Chem. Soc.* **2012**, *134*, 14334). Relative to their methyl-substituted counterparts, 2-




trifluoromethyl amines display increased lipophilicity and metabolic stability and have been explored in medicinal chemistry as nonbasic nitrogen-bearing pharmacophores. A comprehensive screening of catalysts and reaction conditions resulted in the discovery of a 9-OH cinchona alkaloid (DHQ) as an effective catalyst for imine isomerization via proton-transfer catalysis. A range of different aryl and alkyl trifluoromethyl imines could be transformed into the corresponding chiral trifluoromethylated amines in good yields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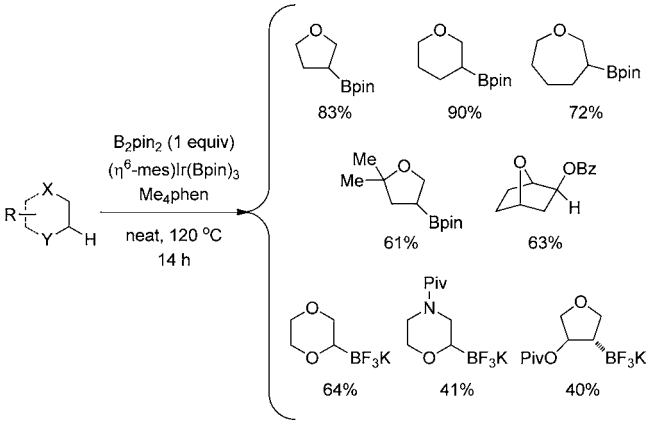
and high enantioselectivities in the presence of 10 mol % DHQ. Maintaining low temperatures was crucial to avoid racemization of the product, and the use of toluene accelerated the reaction and increased the yields relative to that of dichloromethane. Under hydrolytic treatment with acid, aryl and alkyl imines gave the desired chiral trifluoromethylated amines in excellent yields.

## Ir-CATALYZED BORYLATION OF SECONDARY C−H BONDS OF CYCLIC ETHERS

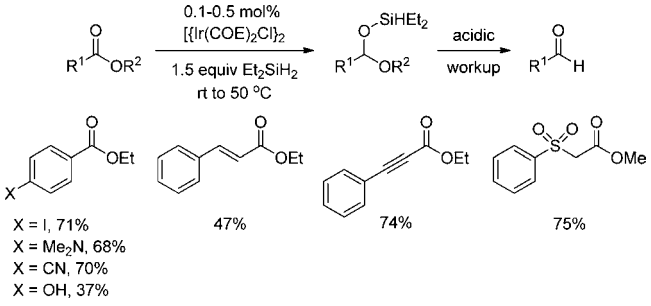
Liskey and Hartwig report a new methodology to functionalize cyclic ethers in *J. Am. Chem. Soc.* **2012**, *134*, 12422. Thus, an




electron-rich boryl complex generated by combining the strongly electron-donating ligand, 3,4,7,8-tetramethyl-1,10-phenanthroline ($Me_4$phen), and ($\eta^6$-mes)IrBpin$_3$, as the source of iridium, promotes the selective C−H borylation of secondary C−H bonds in cyclic ethers. The borylation takes place in good yields for five-, six-, and seven-membered ethers, and can occur $\alpha$ to the oxygen atom when the substrate lacks C−H bonds $\beta$ to oxygen. 1,4-Dioxane affords the borylated product in 64% yield upon isolation as its corresponding trifluoroborate salt. A combination of labeling experiments and kinetic isotope effect measurements using tetrahydrofuran as the substrate support a direct C−H activation at the 3-position instead of an initial C−H activation at the 2-position followed by isomerization to the 3-position. A plausible explanation for the high $\beta$-selectivities depicts the coordination of the oxygen atom of the cyclic ether to the $\beta$-pin Lewis acidic component of the catalyst to form a six-membered transition state. The synthetic importance of the reaction is enhanced by the development of single-pot conditions for the conversion of the tetrahydrofuranylboronate esters to the corresponding trifluoroborates, boronic acids, and alcohols. From a process-oriented perspective, understanding the borylation of THF and other cyclic ethers commonly used as solvents in the pharmaceutical industry may help to characterize and minimize the formation of related process impurities.

## Ir-CATALYZED REDUCTION OF ESTERS TO ALDEHYDES

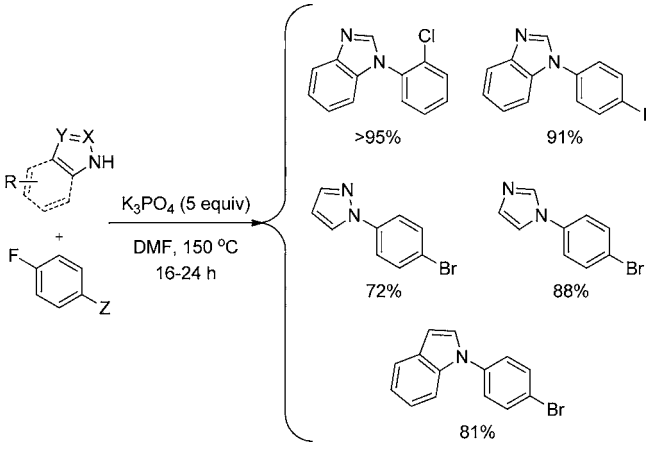
As an extension of previous studies on the reduction of secondary amides to amines through hydrosilylation with diethylsilane and the binuclear iridium complex [{Ir(COE)$_2$Cl}$_2$] (COE = cyclooctene, *J. Am. Chem. Soc.* **2012**, *134*, 11304), Cheng and Brookhart report an efficient reduction of esters to aldehydes through Ir-catalyzed hydrosilylation (*Angew. Chem., Int. Ed.* **2012**, *51*, 9422). The reduction of methyl, ethyl, and benzyl esters to the corresponding silyl




acetals occurs with low catalyst loading under mild conditions. The intermediate silyl acetals can be hydrolyzed following a treatment with acid to give the final aldehydes. The overall transformation accepts a range of functional groups including aryl halides, alkyl halides, ethers, alkenes, alkynes, tertiary amines, nitriles, sulfones, and alcohols. The iridium catalyst, however, is incompatible with nitro groups and can competitively hydrosilylate carbonyl groups in amides, aldehydes, and ketones. The new methodology constitutes a complementary method for the preparation of aldehydes from esters, which circumvents tedious isolation procedures, the need to exclude air and moisture, and the formation of over-reduction byproducts associated with the use of standard aluminum hydrides.

## CATALYST-FREE N-ARYLATION OF AZOLES

Cu-catalyzed Ullmann-type N-arylations and Pd-catalyzed Buchwald−Hartwig couplings are common methods for the assembly of *N*-aryl azoles of pharmaceutical interest. Although these cross-coupling reactions solve the limitations of S$_N$Ar-based arylations that require highly electron-deficient arenes, catalyst cost and availability, oxygen tolerance, and stringent controls for trace metal contaminants limit their use in industrial settings. Diness and Fairlie from The University of Queensland (Brisbane, Australia) discovered that under optimized conditions S$_N$Ar arylations of azoles with fluorobenzenes can occur rapidly and with full conversion in the absence of a transition metal catalyst (*Angew. Chem., Int. Ed.* **2012**, *51*, 8012). Thus, addition of an excess of inorganic base




($K_3PO_4$ or $Cs_2CO_3$) to a heated solution of the azole derivative and an unactivated fluorobenzene in a dipolar aprotic solvent affords the desired N-arylated azoles in high yields. The choice of base and its stoichiometric excess are extremely important for the reaction success since, in addition to deprotonating the azole, the base accelerates the substitution rates. The examples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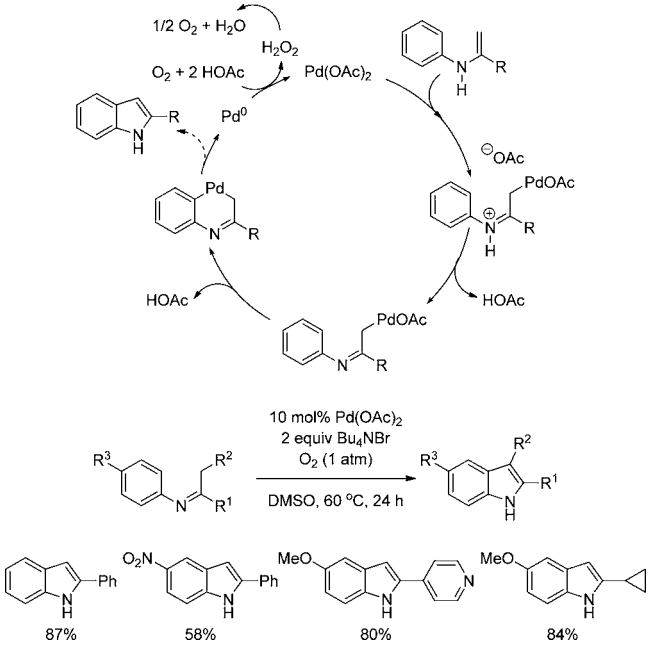
shown in the communication highlight the selective displacement of the fluorine atom in the presence of bromo and iodo substituents to afford bromo- and iodo-substituted *N*-phenyl azoles that would be difficult to obtain by other methods.

## SYNTHESIS OF INDOLES FROM ENAMINES AND IMINES BY CROSS-DEHYDROGENATIVE COUPLING

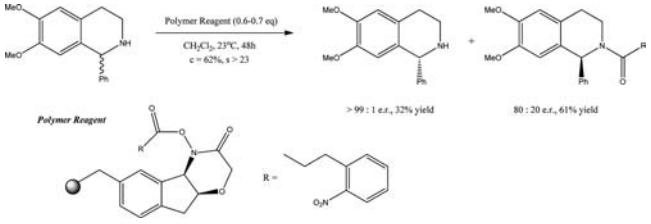
Shi and Glorius summarize new developments on the preparation of indoles by cross-dehydrogenative coupling (CDC) in *Angew. Chem., Int. Ed.* **2012**, *51*, 9220. This




approach follows the C3−C3a disconnection characteristic of the Fischer synthesis of indoles while avoiding the use of carcinogenic hydrazines and the potential functional group incompatibilities due to the use of acidic conditions. The CDC sequence of transformations involves (a) the condensation between an aniline and a ketone to give the corresponding enamine, (b) an electrophilic aromatic palladation mediated by a Pd(II) catalyst, and (c) a reductive elimination that affords the indole product and a Pd(0) complex. The catalytic cycle is completed following the reoxidation of the Pd(0) complex to the original Pd(II) species by a stoichiometric oxidant. Optimized conditions reported by Yoshikai and co-workers promote this transformation with catalytic $Pd(OAc)_2$ and 2 equiv $NBu_4Br$ in DMSO under an oxygen atmosphere (*J. Am. Chem. Soc.* **2012**, *134*, 9098). Yoshikai's indole synthesis has been demonstrated in gram scale and tolerates a variety of functional groups on both the aniline and the acetophenone subunits.

## KINETIC RESOLUTION OF NITROGEN HETEROCYCLES WITH A REUSABLE POLYMER-SUPPORTED REAGENT

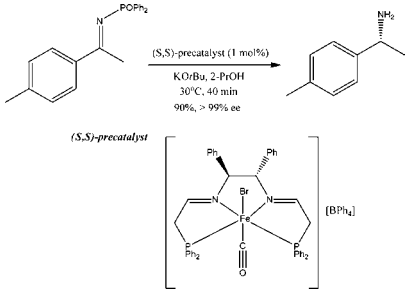
Although alternative approaches have been investigated, the preparation of enantioenriched N-heterocycles is still typically achieved by diastereomeric salt formation or resolution by chiral chromatographic methods. One potential alternative for this transformation is utilize a stoichiometric chiral acylating agent to enantioselectively acylate the amine. Bode and co-workers have pursued this approach using a chiral *O*-acyl hydroxamic acid, and have now developed a polymer-supported version of their reagent (*Angew. Chem., Int. Ed.* **2012**, *51*, 10660). This reagent is easy to prepare, and the resolutions are




simply performed by mixing the racemic amine with the polymer (~0.6 equiv) followed by filtration then aqueous extraction or column chromatography to separate the acylated product from the enantioenriched amine. In addition, the reagent can easily be regenerated, and reused without any deterioration in performance by treatment with an acylating agent. The optimal solvent was found to be dichloromethane due to the efficient swelling of the resin, and a wide range of N-heterocycles (for example piperidines, morpholines and tetrahydroisoquinolines) all performed well displaying high selectivity and good product recovery. Initial experiments focused on acylation to form a hydrocinnamyl amide, though this proved difficult to cleave under mild conditions. Owing to this, chiral reagents were developed which promoted the formation of either 3-(2-nitrophenyl)propanoyl or pent-4-enoyl amides. These amides are easily cleaved under mild conditions in contrast to those used in the previously developed procedure, and as such at short reaction times allow access to highly enantioenriched amines.

## ASYMMETRIC TRANSFER HYDROGENATION OF KETIMINES USING WELL-DEFINED IRON(II)-BASED PRECATALYSTS CONTAINING A PNNP LIGAND

A significant amount of effort is devoted to developing new methodology for the synthesis of chiral amines. Amongst these, the catalytic reduction of imines with chiral transition metal catalysts using either molecular hydrogen or cheap and safe 2-propanol as the reducing agent is most attractive. However, several challenges exist with developing such an approach amongst which are the reactivity of the imine, and the potential for the amine product to deactivate the catalyst. Morris and co-workers have developed a protocol to alleviate these issues by addition of a substituent to the imine prior to hydrogenation to provide the required steric and electronic properties for successful reduction (*Org. Lett.* **2012**, *14*, 4638). They




evaluated a series of iron(II) chiral complexes with a range of substituted imines. These studies demonstrated that only imines featuring bulky and strongly electron-withdrawing N-substituents such as *N*-diphenylphosphinoyl or *p*-tolylsulphonyl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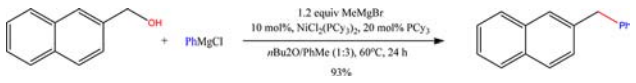
were successfully reduced to the corresponding amines with the former providing a significantly faster reaction. Gratifyingly exceptional enantioselectivities (>95% ee) were observed in the reduction of both imines, particularly with the PNNP ligands that form 5,5,5-membered rings around the metal center. The absolute stereochemistry of the reduction is controlled by the stereoorientation of the diamine incorporated into the ligand backbone. The substrate scope is good, and even a thiophene-based substrate is successfully reduced, indicating no coordination of sulfur to the active complex. The results obtained indicate that the catalyst displays high sensitivity towards the sterics around the imine carbon, but variation of the electronic properties of the substrate has a negligible effect on its reactivity.

## DIRECT ARYLATION/ALKYLATION/MAGNESIATION OF BENZYL ALCOHOLS IN THE PRESENCE OF GRIGNARD REAGENTS VIA Ni-, Fe-, OR Co-CATALYZED $sp^3$ C–O BOND ACTIVATION

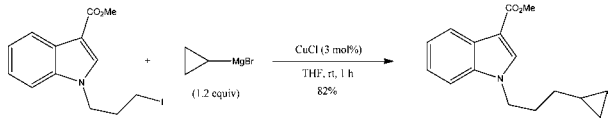
Direct transformations of cheap and abundantly available alcohols represent an attractive goal for the synthetic chemistry community, given its step and atom economic nature. However, due to the high C–O bond dissociation energy, good coordinative properties and low leaving ability of the OH group, alcohols typically have to be activated to utilize their latent reactivity. Shi and co-workers have reported on the direct cross-coupling of benzyl alcohols with Grignard reagents (*J. Am. Chem. Soc.* **2012**, *134*, 14638). Catalyst screening revealed




$NiCl_2(PCy_3)_2$ to be the optimal catalyst for coupling alcohols with aryl Grignards, with a switch to a bidentate ligand (1,1′-bis(dicyclohexylphosphino)ferrocene, DCyPF) being required to obtain good yields for alkyl Grignards. A range of both aromatic and heteroaromatic benzylic alcohols coupled well, and $\alpha$-arylated benzylic alcohols also worked, but displayed lower reactivity. In the initial coupling experiments with alkyl Grignard reagents, reductive products were often observed in the reaction. Screening a variety of metal catalysts led to successful benzylic alcohol reduction using iron, cobalt, or nickel catalysis, and a range of substrates was successfully reduced under the optimal conditions. Mechanistic studies using deuterium labeling indicated that deuterium was incorporated from the quench solvent, strongly supporting benzylic C–M bond formation through the transition metal-catalyzed magnesiation of the alcohol C–O bond.

## COPPER-CATALYZED CROSS-COUPLING OF FUNCTIONALIZED ALKYL HALIDES AND TOSYLATES WITH SECONDARY AND TERTIARY ALKYL GRIGNARD REAGENTS

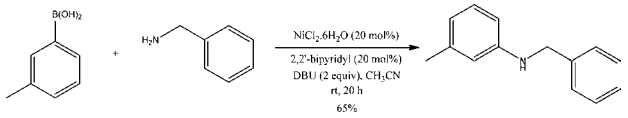
Efficient alkyl–alkyl cross coupling reactions are a synthetic challenge due to the reluctance of alkyl electrophiles to undergo oxidative addition accompanied by the propensity of the metal–alkyl intermediates to undergo $\beta$-hydride elimination. Several couplings with Grignard reagents have been reported though have limited synthetic utility due to poor functional group compatibility of the reagents employed. Hu and co-workers have reported on a remarkably simple copper-mediated coupling of secondary and tertiary Grignard reagents with alkyl halides and tosylates containing a range of functional groups (*Angew. Chem., Int. Ed.* **2012**, *51*, 9110). The reaction took




place at room temperature using a range of simple copper salts such as CuCl as the catalyst. Yields of over 90% were obtained in the solvents THF, toluene, and ether. A range of functional groups, and heterocyclic substrates coupled smoothly under the optimal conditions. Acids and alcohols required an additional equivalent of Grignard reagent to be added, presumably to deprotonate the substrate, but smooth coupling still ensued. Ketones were tolerated if NMP was introduced as an additive in the reaction, whereas aldehyde, nitro, and succinimide groups were not compatible with this method. Neither secondary alkyl halides nor alkyl chlorides participated in the coupling protocol, allowing selective couplings to take place. Attempts to develop an enantioselective variant of the reaction adding chiral ligands to the copper source have so far proven unsuccessful. Mechanistic studies suggest that a radical process is not operating, and given that alkyl tosylates are also successful substrates, an $S_N2$ mechanism seems likely.

## NICKEL-MEDIATED N-ARYLATION WITH ARYLBORONIC ACIDS: AN AVENUE TO CHAN–LAM COUPLING

The oxidative amination of arylboronic acids with amines and other nucleophiles (Chan–Lam coupling) has been widely exploited since its discovery in 1998, and has been exclusively mediated by a copper(II) species. Singh and co-workers have explored the development of a variant of this reaction using an alternative transition metal catalyst (*Org. Lett.* **2012**, *14*, 4326).




Screening a range of different species led to the discovery that only nickel salts could promote the desired conversion, and it was found that the optimum catalyst was $NiCl_2 \cdot 6H_2O$ (20 mol %). The potential for copper contamination was conclusively eliminated by control experiments using ppm quantities of $Cu(OAc)_2$. Addition of 2,2′-bipyridyl as a ligand (20 mol %), and use of 2 equiv of DBU as a base were required for optimum conversion with acetonitrile being the solvent of choice. A wide range of amine and amide substrates were effectively coupled with this protocol. Pyrazole coupled in a more sluggish manner and required extended reaction times at elevated temperature (60 °C). Some secondary amines and amides proved difficult to couple, possibly due to steric congestion at the reactive center. A range of boronic acids was also successfully utilized and a model reaction successfully scaled to 20 mmol (gram) scale to illustrate the potential applicability of this protocol for larger-scale preparations.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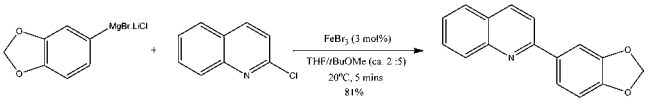
## IRON-CATALYZED CROSS-COUPLING OF N-HETEROCYCLIC CHLORIDES AND BROMIDES WITH ARYLMAGNESIUM REAGENTS

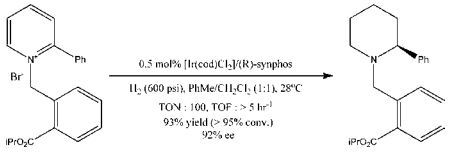
There has been a growth in the exploitation of alternative metals to palladium in cross-coupling reactions. Of these, iron catalysis has been of particular interest due to the environmentally friendly properties of iron combined with its moderate price. Knochel and co-workers have reported on the iron-mediated cross-coupling of N-heterocyclic halides (chlorides or bromides) with aryl Grignard reagents to form arylated heterocycles, which can often display useful biological activity (*Org. Lett.* **2012**, *14*, 4818). $FeBr_3$ was the catalyst of choice




with solvent selection being critical for a successful reaction. In model studies, it was shown polar solvents inhibited the reaction, nonpolar solvents led to moderate yields, and that addition of ethereal solvents was key for optimum yields, with the industry-friendly *t*BuOMe being selected for substrate scope studies. Bromides reacted faster than chlorides though both substrates led to the same yield. Substituted heterocycles were also well tolerated, though both chloropyrazine and chloropyridazines performed relatively poorly in the reaction sequence. The scope of Grignard reagents was also investigated, and a wide range coupled successfully with a number of functional groups tolerated in the rapid iron-catalyzed cross-couplings. The mechanism has not been elucidated at this time, but it has been shown that the use of either Fe(II) or Fe(III) salt led to the same result. Prior reduction *in situ* of the Fe(III) catalyst with *i*PrMgCl deactivated the system and hampered the catalyst, and use of an aprotic cosolvent (*t*BuOMe) was vital to achieve high yields primarily by avoiding homocoupling products.

## IRIDIUM-CATALYZED ASYMMETRIC HYDROGENATION OF PYRIDINIUM SALTS

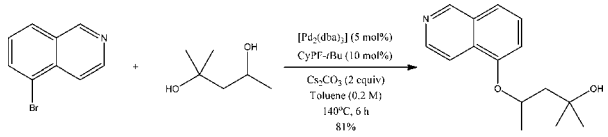
Chiral piperidines are important building blocks in the pharmaceutical industry, and are most easily accessed by asymmetric reduction of pyridines. Hydrogenation of simple pyridines still represents a significant challenge due to the aromaticity of the ring system, and the coordinating ability of both the substrate and product leading to deactivation of the catalysts examined. Zhou and co-workers have reported on the iridium-mediated hydrogenation of *N*-benzyl pyridinium salts (*Angew. Chem., Int. Ed.* **2012**, *51*, 10181).They proposed that




formation of the salt would activate the ring system for reduction whilst simultaneously eliminating the coordinating ability of the ring nitrogen. A solvent screen indicated that toluene/$CH_2Cl_2$ (1:1) was the best choice with the bromide counterion being critical to achieve optimal reactivity and enantioselectivity. Introduction of an electron-withdrawing group ($CO_2R$) at the 2-position of the benzyl group led to a significant increase in enantioselectivity, probably as this group can coordinate further to the catalyst species. Choosing a more sterically encumbered ester group (R = *i*Pr > Me) also had a positive effect on enantioselectivity. Several commercially available chiral bisphosphine ligands were evaluated, and the electron-rich species (*R*)-segphos and (*R*)-synphos displayed the highest enantioselectivity. The substrate scope was evaluated, and electronic properties appeared to have little influence on the enantioselectivity of the reaction. However, introduction of steric hindrance led to diminished enantioselectivity although the reduction still proceeded in good yield. The hydrogenation of *N*-benzyl-2-phenylpyridinium bromide was demonstrated on gram scale (93%, 92% ee), and the product obtained was utilized in the formal synthesis of an orally active NK1 receptor antagonist, with the optical purity being upgraded by a simple crystallization.

## C–O CROSS-COUPLING OF ACTIVATED ARYL AND HETEROARYL HALIDES WITH ALIPHATIC ALCOHOLS

Aromatic ethers are frequently found in natural and synthetic biologically active compounds. Traditional methods to access this functionality typically involve $S_NAr$ reactions or Ullman-type couplings necessitating the use of reactive aryl halides or forcing conditions, thus, significantly limiting the substrate scope of the transformation. Workers at Merck have demonstrated a mild and robust methodology for the alkoxylation of activated aryl and heteroaryl halides with primary, secondary, and select tertiary alcohols (*Angew. Chem., Int. Ed.* **2012**, *51*, 9071). Screening of a series of ligands across




the coupling of three structurally diverse heteroaryl halides with 2-phenylethanol demonstrated that only the Josiphos analogue CyPF-*t*Bu had activity for all three systems. This ligand proved to be the optimal choice amongst over 70 ferrocenyl-type phosphine ligands evaluated. THF and toluene proved to be the best solvents, and cesium carbonate was demonstrated to be the preferred base, with $[(allylPdCl)_2]$ being the most active catalyst. In contrast to the previously disclosed RockPhos system developed for this transformation (*Angew. Chem., Int. Ed.* **2011**, *50*, 9943), catalyst preformation is not required, and the Merck system is not sensitive to the addition order of the reagents, providing a robust protocol for the transformation. The current system tolerates a wide range of electron-deficient aromatic and heteroaromatic substrates, and only one equivalent of the alcohol is required. However, electron-neutral aryl halides react poorly due either to alcohol displacement or to reductive elimination being disfavored at the highly hindered electron-rich metal center. A wide range of structurally diverse alcohols also coupled well, and excellent functional group tolerance was displayed as well as complete selectivity for primary over secondary over tertiary alcohols.

## PALLADIUM-CATALYZED BORYLATION OF ARYL AND HETEROARYL HALIDES UTILIZING TETRAKIS(DIMETHYLAMINO)DIBORON: ONE STEP GREENER

The palladium-catalyzed borylation of aryl halides with bis(pinacalato)diboron ($B_2Pin_2$) by Miyaura in 1995 repre-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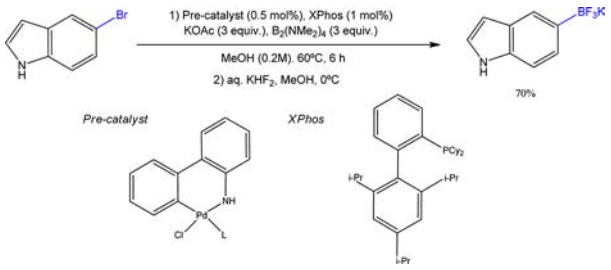
sented a significant advance in the synthesis of arylborons for cross-coupling reactions. The drawbacks of this methodology are the relatively poor atom efficiency and the potential for pinacol contamination throughout the process. Recently, a new methodology using bis-boronic acid (BBA) for the synthesis of boronic acids and derivatives has been developed, although this material is not commercially available. Molander has reported on a new protocol for palladium-catalyzed borylation using tetrakis(dimethylamino)diboron ($(Me_2N)_2BB(NMe_2)_2$) (*Org. Lett.* **2012**, *14*, 4814). This material is both the direct precursor




to BBA and $B_2Pin_2$. The optimized protocol is a minor modification of that developed for the use of BBA and uses Buchwald's second-generation palladium precatalyst (XPhos-Pd-G2) (0.5 mol %) with X-Phos (1 mol %, 3:1 ligand/catalyst ratio) with 3 equiv of KOAc. Unlike the BBA method, which is run in EtOH, the current method performs better in MeOH. Operationally, the methods are very similar with the reagents being combined, followed by addition of solvent, and the borylating reagent last. The major difference in the operation is that the borylating reagent is a liquid as opposed to BBA, which is charged as a solid. The methods are highly comparable in terms of yields, but examples exist in which a degree of complementarity is displayed. For example, the new protocol allows a 10-fold decrease in loading when used for heteroaryl substrates, and allows access to some compounds (e.g., 3-thienyltrifluoroborate) previously unavailable *via* the BBA methodology.

## UNDERSTANDING REFLECTION BEHAVIOR AS A KEY FOR INTERPRETING COMPLEX SIGNALS IN FBRM MONITORING OF MICROPARTICULATE PREPARATION PROCESSES

Due to its complexity, however not obvious, particle sizing using focused beam reflectance measurement (FBRM) continues to attract research interest aimed at better understanding this method. A recent account investigating the impact of particle reflection behavior on FBRM results was published (Vay, K.; et al. *Int. J. Pharm.* **2012**, *437*, 1; DOI: 10.1016/j.ijpharm.2012.07.072)). The Sandoz team found a strong dependence of the FBRM results on the optical properties of the particles analyzed. For particles with good scattering properties the FBRM chord length distribution (CLD) is comparable with the particle size distribution measured with laser diffraction or optical methods. With translucent particles, FBRM CLD overestimates particle size, whereas with transparent emulsion droplets, FBRM CLD underestimates particle size. The team also found that the FBRM results exhibit a solids concentration (nonlinear) dependence, and they are also sensitive to certain instrument settings such as the focal point position; the latter is an instrument parameter not routinely varied. The materials used were transparent and black polystyrene microspheres and poly(D,L-lactide-*co*-glycolide) 75:25 (Resomer 755 S) particles with and without API. The instrument used was the D600 Lasentec FBRM and its manufacturer bench setup. The probe was inserted in the beaker at a 30−60° incidence angle, with the flow directed obliquely toward the probe window, as recommended. The fine discrimination mode and the default setting of (−20 $\mu$m) for the focal position were used. As was reported before, the authors found the statistic of the square-weighted mean of the CLD to be the best approximation for comparisons with particle size. One of the conclusions from the study is that FBRM is "not a trivial method".

## ATMOSPHERIC PRESSURE COLD PLASMA SYNTHESIS OF SUBMICROMETER-SIZED PHARMACEUTICALS WITH IMPROVED PHYSICOCHEMICAL PROPERTIES

Achieving suitable bioavailability for active pharmaceutical ingredients (APIs) with low solubility requires particle reduction. Because milling can be costly and ridden with safety challenges, the most desirable approach towards particle reduction is controlled crystallization. However, sometimes supersaturation, mixing and seeding control are insufficient to accomplish the desired particle size distribution. A novel method for the production of submicrometer-sized APIs using atmospheric pressure cold plasma was recently reported (Radacsi, N.; et al. *Cryst. Growth Des.* **2012**, *12*, 5090; DOI: 10.1021/cg301026b)). The API solution is nebulized under an inert atmosphere in the cold plasma, and because of the heat produced, solvent evaporation occurs, generating the supersaturation necessary for crystallization. The device used appears to have been built specifically for this research effort. The model compound was niflumic acid, investigated with and without Poloxamer 188, a typical excipient used in niflumic acid formulations. The mean particle size of niflumic acid obtained using the cold plasma method was 700 nm (as expected, micrometer-sized clusters were observed). When dissolution rates (30 min) were measured, a significant improvement was noticed, from 20% for the conventionally obtained niflumic acid (30% formulated with Poloxamer 188 and D-mannitol) to 89% for the formulated niflumic acid obtained by cold plasma technology. Additional advantages offered by the new method include minimal particle shape change and minimal amorphous material formation.

## CONTINUOUS SONOCRYSTALLIZATION OF ACETYLSALICYLIC ACID (ASA): CONTROL OF CRYSTAL SIZE

Even though ultrasound has been used for many years in crystallization processes, we still do not have a sufficiently comprehensive theory explaining sonocrystallization. This fact does not discourage process scientists from using ultrasound to manipulate particle size distribution. The current drive to develop continuous crystallization processes is an additional incentive for the use of sonocrystallization. An innovative combination of several known crystallization technologies was recently reported (Eder, R. J. P.; et al. *Cryst. Growth Des.* **2012**, *12*, 4733; DOI: 10.1021/cg201567y)). Crystallization was accomplished in a tubular reactor (27 m long, 2 mm in diameter), with a Y-inlet fitting; the seed slurry and the ASA ethanolic solution were fed through this fitting. The controlled temperature trajectory, together with suitably designed hydrodynamic conditions afforded ASA of a very narrow particle size

distribution. Sonication was accomplished in a commercial bath operating at 35 kHz, and the production rate was approximately 2 g/min. The optimized hydrodynamics through the tubular reactor was a segmented gas−slurry flow, developed using air bubbles injected in the tube. Seed was generated in situ, and temperature cycling was used to remove excess fines. Future work will investigate scale-up, cleaning in place options as well as the impact of the material of construction on the outcome of such sonocrystallizations.

## MICROMIXING EFFICIENCY OF A SPINNING DISK REACTOR

The selectivity of fast chemical reactions occurring in nonideally mixed reactors depends on mixing at the molecular level: micromixing. Lowering micromixing times is not trivial in batch reactors. A good alternative, allowing also for continuous processing, is the spinning disk reactor. A recent account discusses micromixing in spinning disk reactors (Jacobsen, N. C.; et al. *Ind. Eng. Chem. Res.* **2012**, *51*, 11643; DOI: 10.1021/ie300411b)). The test reaction used to "finger-print" the reactor was the Villermaux−Dushman iodide/iodate competitive-parallel reaction system. Parameters investigated for their impact on micromixing efficiency included rotation speed, feed location and type (multipoint injection), flow rate, and disk surface structure (textured or smooth). Disk speed was found to be a key process parameter influencing micromixing. Not surprisingly, when several theoretical models were used to calculate micromixing, the corresponding results were 2 orders of magnitude apart. An important advantage of spinning disk reactors over microreactors is the lack of fouling or blocking.

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