Organic Process Research & Development

Highlights from the Literature

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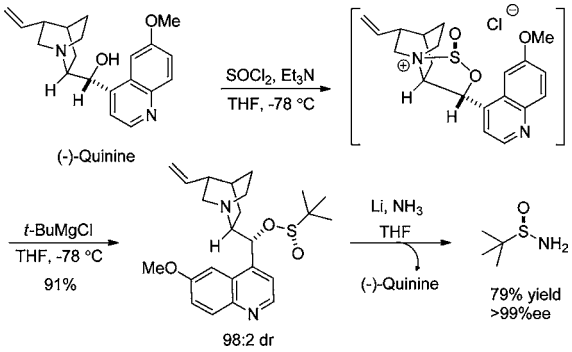
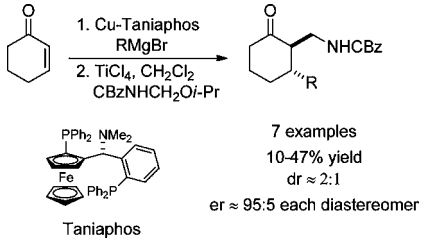
Some Items of Interest to Process R&D Chemists and Engineers

■ ASYMMETRIC SYNTHESIS OF SULFINAMIDES USING (−)-QUININE AS CHIRAL AUXILIARY



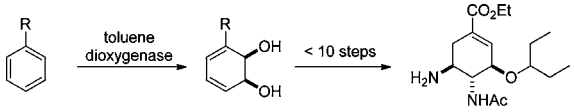
Over the past three decades, chiral sulfinamides such as *p*-toluenesulfinamide and *tert*-butanesulfinamide have been widely exploited in chemical synthesis because of their unique roles and importance in the generation of chiral nitrogen-containing functionalities. The corresponding sulfinylimines, derived from the condensation of sulfinamides with aldehydes and ketones, have been extensively utilized as versatile intermediates for the synthesis of a variety of chiral amines, including α-branched amines, α- and β- amino acids, 1,2-amino alcohols, 1,3-amino alcohols, aziridines, aminooxetanes, and amino phosphoric acids. Now Zhang and co-workers at Boehringer Ingelheim report on the asymmetric synthesis of sulfinamides using quinine as auxiliary (*J. Org. Chem* **2012**, *77*, 690). A variety of chiral sulfinamides including *N*-alkyl sulfinamides with diverse structures were prepared in good yields and excellent enantioselectivity, starting from easily available and inexpensive reagents. The auxiliary quinine could be recovered and recycled.

■ ENANTIOSELECTIVE ONE-POT CONJUGATE ADDITION OF GRIGNARD REAGENTS TO CYCLIC ENONES FOLLOWED BY AMIDOMETHYLATION



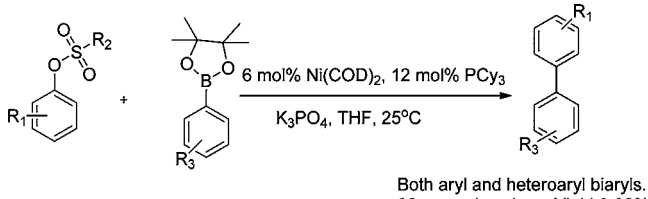
The development of new methods for efficient and stereocontrolled construction of complex molecules is an ongoing challenge in organic chemistry. Stepwise processes, in which each reaction step is followed by a purification operation, are slow and laborious. In contrast, stereoselective domino or cascade processes represent a significant improvement in terms of step economy. The Sebesta group in Slovakia describes an interesting application of this concept to the synthesis of β-aminoketones (*J. Org. Chem* **2012**, *77*, 760). Enantioselective conjugate addition of Grignard reagents to enones, catalyzed by Cu−Taniaphos or −Josiphos complex, affords chiral Mg enolates. A subsequent one-pot Mannich reaction mediated by $TiCl_4$ leads to aminocarbonyl compounds with a CBz-protected nitrogen atom. Both diastereomers of these compounds are isolated in moderate yields but high enantiomeric purities (up to er 97.5:2.5). Diastereoselectivities were relatively low because of Ti-mediated epimerization of the products.

■ QUEST FOR A PROCESS-QUALITY SYNTHESIS OF OSELTAMIVIR (TAMIFLU)



Interest in the synthesis of oseltamivir continues despite the fact that the compound seems to be less effective against recent mutations of the influenza virus. New approaches to this molecule continue to appear regularly in the literature. In a recent article, Hudlicky, Andraos, and co-workers report on the evolution of a chemoenzymatic strategy toward oseltamivir through four generations of design (*J. Org. Chem* **2011**, *76*, 10050). In addition, an evaluation of overall efficiency and comparison with existing syntheses are provided for the successful approaches. Interestingly, the authors note that yield values reported in publications from academic groups are frequently subject to wide fluctuations for a variety of reasons that have recently been analyzed (*Synlett* **2010**, 2701; see editorial in *Org. Process Res. Dev.***2011***15*305). Thus, only the industrial protocols that have been subjected to focused optimization and that have been performed on large scale can be taken as reliable in terms of the reported values.

■ $Ni(COD)_2/PCy_3$-CATALYZED CROSS-COUPLING OF ARYL AND HETEROARYL NEOPENTYLGLYCOLBORONATES WITH ARYL AND HETEROARYL MESYLATES AND SULFAMATES IN THF AT ROOM TEMPERATURE



Aryl−aryl and aryl−heteroaryl couplings remain the best and most robust strategy for the synthesis of functional substituted biaryls, heterobiaryls, and other complex aromatic compounds. Traditional Suzuki−Miyaura couplings need the use of high temperature to achieve good yields. In a recent article V. Percec

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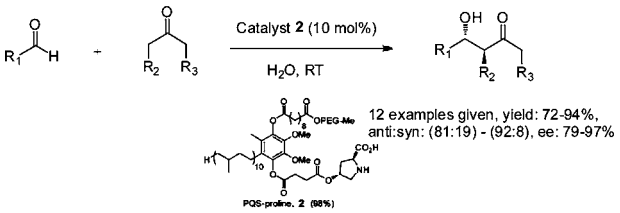
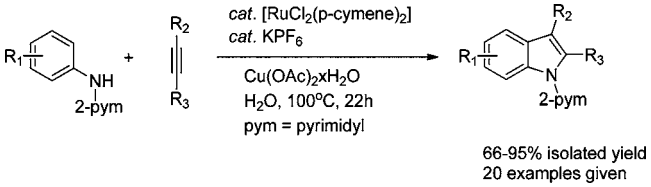
et al. showed an optimized method to generate complex molecules using Ni-catalyzed Suzuki–Miyaura reactions at room temperature in THF (*J. Org. Chem* **2011**, *76*, 9946) using either mesylates or sulfamates and neopentylglycolboronates. The article covers the successful synthesis of a variety of molecules, some with sensitive structural motifs in varied yields. The level of Ni catalyst varied between 6 and 10%, and the PCy_3 ligand was varied between 12 and 20%. The base of choice used in the experiments was potassium phosphate.

ORGANOCATALYSIS IN WATER AT ROOM TEMPERATURE WITH *In-Flask* CATALYST RECYCLING



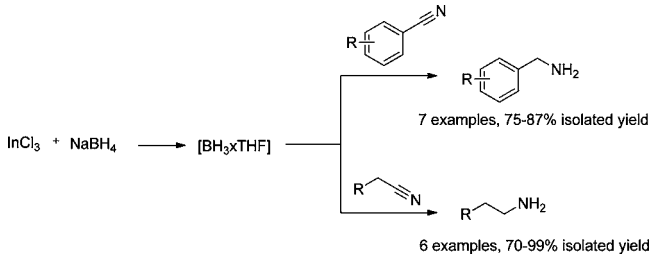
Organocatalysis is an exciting area of research with a plethora of articles coming out each year. Lipshutz et al. (*Org. Lett.* **2012**, *14*, 422) describe a new proline derivative linked to a designer surfactant which increases the solubility. The new catalyst forms nanomicelles in water and was shown to be able to catalyze aldol reactions with a number of aldehydes and ketones at room temperature. By using this catalyst the authors managed to drop the loading down to 10% compared to the usually much higher loading required when using proline. The reaction time varied from 18 h to 48 h with a range of yields from reasonable to excellent, and the same goes for the selectivity.

CATIONIC RUTHENIUM(II) CATALYSTS FOR OXIDATIVE C–H/N–H BOND FUNCTIONALIZATION OF ANILINES WITH REMOVABLE DIRECTING GROUP: SYNTHESIS OF INDOLES IN WATER



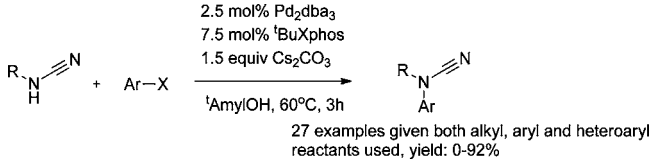
The literature contains a plethora of examples on using transition metal catalysis to prepare indoles from a diverse number of substrates. Ackermann et al. (*Org. Lett.* **2011**, DOI: 10.1021/ol203309y) recently published an article using pyrimidine as a nitrogen protection group on substituted anilines. The authors described several successful reactions using anilines to form indoles using a C–H oxidative functionalization via a cationic ruthenium catalyst. The reactions worked best in water and used copper(II) acetate as the oxidant. A mechanistic study is also included in the article.

REACTION OF $InCl_3$ WITH VARIOUS REDUCING AGENTS: $InCl_3$–$NaBH_4$-MEDIATED REDUCTION OF AROMATIC AND ALIPHATIC NITRILES TO PRIMARY AMINES



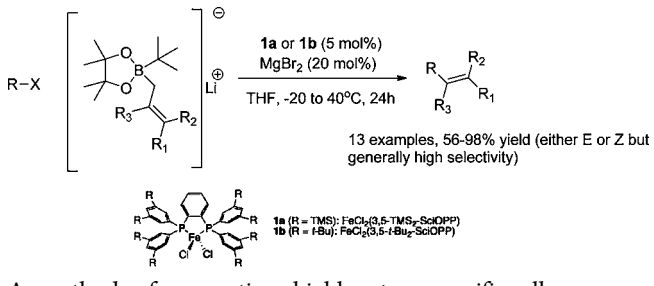
Indium(III) chloride, reduced using sodium borohydride, was found by Singaram, et al. (*J. Org. Chem* **2012**, *77*, 221) to efficiently reduce both aromatic and aliphatic nitriles to primary amines. It was also found that both alkyl halide and nitrile functional groups could be reduced in tandem using $HInCl_2$/BH_3·THF. A final interesting find was that, if the indium(III) chloride was reduced by sodium borohydride in acetonitrile or lithium dimethylaminoborohydride in THF, a selective reduction of a carbon–bromine bond could be effected, leaving the nitrile functionality intact.

PALLADIUM-CATALYZED ARYLATION OF CYANAMIDES



Amination of aromatic compounds have been around for several years, and research into amination reactions is still going on. Louie et al. (*Org. Lett.* **2012**, *14*, 322) recently reported the successful arylation of cyanamides using a modified amination protocol. The mild conditions facilitate a very selective reaction for a wide selection of vinyl compounds, aromatics, and heteroaromatics containing either halides or pseudohalides as leaving groups. The article describes the screening of ligands and conditions during their research into this variation of the amination of aromatic compounds.

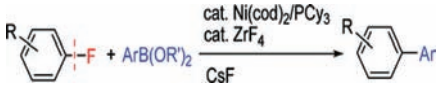
STEREOSPECIFIC CROSS-COUPLING BETWEEN ALKENYLBORONATES AND ALKYL HALIDES CATALYZED BY IRON–BISPHOSPHINE COMPLEXES



A method of generating highly stereospecific alkenes was reported by Nakamura et al. (*J. Org. Chem.* **2011**, DOI: 10.1021/jo202151f) using an iron-catalyzed Suzuki reaction. By preparing the boron species using a boronate and an organolithium compound and reacting said species with an alkyl halide

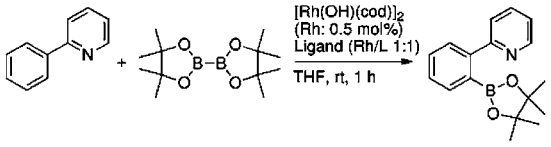
using the iron catalyst, the authors were able to generate the desired stereochemistry of the target compounds in moderate to high yields. Several examples of substituted alkyl halides were tested in this article.

NICKEL-CATALYZED SUZUKI–MIYAURA REACTION OF ARYL FLUORIDES



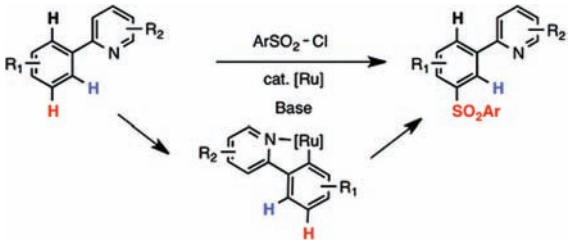
Over the past few decades, the Suzuki –Miyaura reaction has emerged as a powerful tool for the construction of carbon–carbon bonds. Organic iodides, bromides, chlorides, and sulfonates have been employed as typical substrates for the reaction. In a recent article, *J. Am. Chem. Soc.* **2011**, *133*, 19505, the coupling of aryl fluorides with aryl boronic esters in the presence of $Ni(COD)_2$ and PCy_3 and CsF has been described. Two protocols have been described for the same. The first method employs the use of fluoride salts, ZrF_4 and TiF_4, which enables the coupling of aryl fluorides bearing electron-withdrawing substituents (ketones, esters, CF_3). Aryl fluorides with extended π systems such as biaryl, stilbene, and naphthalene could also be arylated using bimetallic catalysis with Ni and Zr. It needs to be emphasized that the coupling failed to proceed in the absence of CsF. The second protocol involves the coupling of aryl fluorides bearing ortho-directing substituents, wherein the C–F bond formation proceeds via a stable cyclometalated intermediate. Directing groups possessing an sp2-hybridized nitrogen atom including pyridine, pyrazole, and oxazoline were found to promote coupling with a vast array of aryl and alkenyl boronic esters.

Rh-CATALYZED ORTHO-SELECTIVE C–H BORYLATION



Direct C–H borylation of arenes presents a simple and efficient route for the synthesis of aryl boronic acids. M. Sawamura and his group of the University of Hokkaido have disclosed in a recent article, *J. Am. Chem. Soc.* **2011**, *133*, 19310, a Rh-catalyzed ortho-selective C–H borylation of N-functionalized arenes with silica-supported bridgehead monophosphine ligands. The method described complements the Ir-catalyzed borylation of arenes bearing oxygen-based directing groups. The said borylation was conducted in the presence of $[Rh(OH)(cod)]_2$ and immobilized phosphine Rh systems with a P/Rh ratio of 1:1(prepared from silica-supported bridgehead monophosphine ligands Silica-SMAP and Silica-TRIP). The reaction exhibited excellent regioselectivity with various N-directing groups, including saturated and unsaturated N-heterocycles, *tert*-aminoalkyl groups, and imino groups. In addition, the reaction showed significant tolerance towards steric hindrance around the reaction centre. The effect of the ligands on the borylation reaction has been discussed at length.

Meta SULFONATION OF 2-PHENYLPYRIDINES

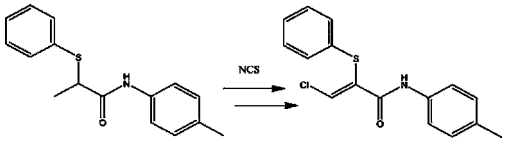


A common approach for functionalization of aromatic substrates (carbon–carbon/carbon–halogen) proceeds via chelation-assisted cleavage of a C–H bond. Despite advances in the aforementioned reaction categories, methods for C–S bond formation remain relatively undeveloped. Christopher Frost and coworkers, have described in *J. Am. Chem. Soc* **2011**, *133*, 19298, a ruthenium-catalyzed method for the meta sulfonation of 2-phenylpyridines with sulfonyl chlorides. The reaction proceeds through an (arene)ruthenium(II) complex, the formation of which is facilitated by the 2-pyridyl group. Variations of the sulfonyl chloride (with respect to functionality and substitution) were well-tolerated in the reaction.

HYDRIDE AS A LEAVING GROUP IN THE SYNTHESIS OF PINACOLBORONIC ESTERS

In a recent development, *J. Org. Chem* **2011**, *76*, 9602, an alternate method for the preparation of boronic esters, which stands in contrast to the established Brown–Cole transmetalation protocol, has been described. The authors have developed a mild and simple method for the synthesis of pinacolboronates using PinBH and commercially available Grignard reagents. Preparation of aryl, vinyl, allyl, and benzyl boronic esters under Barbier conditions from the corresponding halides has also been demonstrated. Boronate ester synthesis by these methods is advantageous as it avoids the use of low temperatures and transition metal catalysts. It is suggested that the reaction proceeds by a unique pathway where hydridomagnesium bromide (HMgBr), which further disproportionates to magnesium hydride and magnesium bromide, acts as the leaving group. Magnesium hydride was identified as a disproportionation product by trapping with 1equiv of BH_3·THF and by hydride analysis.

ReactNMR AND ReactIR FOR REACTION MONITORING AND MECHANISTIC ELUCIDATION



The article, *J. Org. Chem* **2011**, *76*, 9630 outlines the utility of flow NMR and IR for reaction monitoring and in situ intermediate characterization. The method has been applied to the investigation of *N*-chlorosuccinimide-mediated chlorination of a thioamide. The above investigation enabled the identification of the chlorosulfonium ion as a key intermediate

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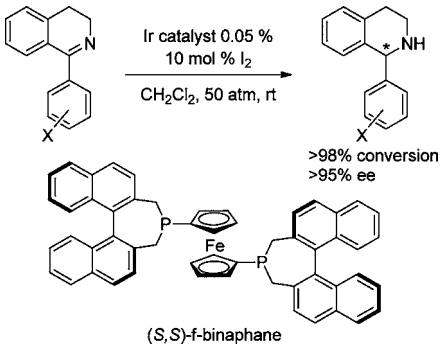
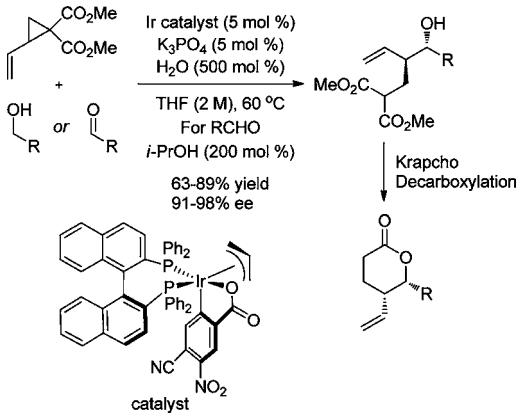
in the reaction. It needs to be emphasized that, though the intermediacy of the chlorosulfonium ion has been widely accepted in chlorination of sulfides, direct determination of the intermediate has been enabled by the above method for the first time in 15 years. In addition, this NMR study also provided direct evidence for the generation of the dichlorosulfonium ion as a side product which has clear implications in the yield of the reaction.

Ir-CATALYZED ASYMMETRIC HYDROGENATION



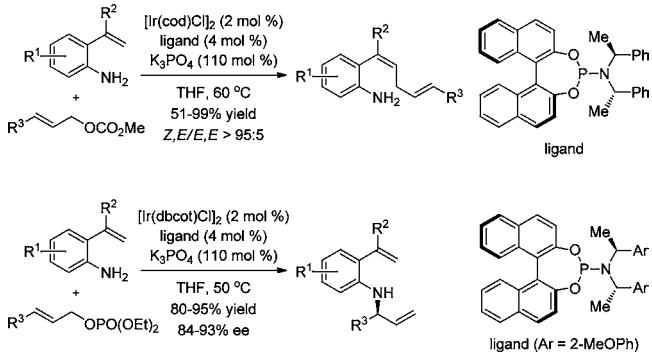
The first asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinolines was reported by Chang, Li, and Zhang (*Angew. Chem., Int. Ed.* **2011**, *50*, 10679). The perennial complexity of this transformation has been attributed to the rigidity and steric demands of the imine substructure. The team at Rutgers University investigated the ability of Ir−diphosphine complexes to reduce the imines by screening a series of Ir precursors, ligands, additives, and solvents and discovered that an iodine-bridged dimeric iridium complex of (*S,S*)-*ϕ*-binaphane gives excellent yields and enantioselectivities. The catalyst $[\{Ir(H)[(S,S)\text{-}\phi\text{-binaphane}]\}_2(\mu\text{-I})_3]^+I^-$ was prepared by mixing $[\{Ir(cod)Cl\}_2]$ and 2.2. equiv (*S,S*)-*ϕ*-binaphane in toluene at rt for 2 h followed by (1) addition of an excess of HI, (2) overnight stirring, (3) evaporation under reduced pressure, and (4) redissolution in CH_2Cl_2 and hexanes to precipitate the desired complex. Optimal hydrogenation conditions involved the use of Ir-complex/I_2/substrate 0.05:10:100 ratios at 50 atm of H_2 and rt during 24 h.

DISUBSTITUTED *δ*-LACTONES VIA ENANTIOSELECTIVE Ir CATALYSIS



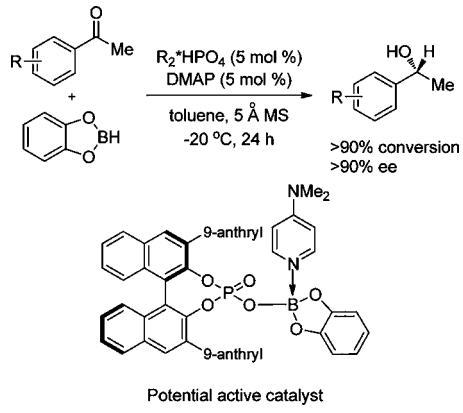
The treatment of cyclopropanes incorporating the malonic ester substructure with (*S*)-BINAP complexes of cyclometalated iridium catalysts triggers the umpolung of the donor−acceptor cyclopropanes (Johnson, Krische, and co-workers in *J. Am. Chem. Soc.* **2011**, *133*, 18618). Thus, the electrophilic trapping of nucleophilic *π*-allyls generated from donor−acceptor cyclopropanes with aldehydes leads to diastereo- and enantioselective C−C couplings to afford allyl alcohols. These adducts can be transformed in a subsequent step into *cis*-4,5-disubstituted *δ*-lactones via Krapcho decarboxylation. The Ir-catalyzed reductive couplings use alcohols as terminal reductants (e.g. *i*-PrOH 200 mol %), allowing formal carbonyl trapping from the alcohol or the aldehyde in the absence of stoichiometric metallic reagents. The vinylcyclopropane reactant can be prepared from commercially available (*E*)-1,4-dibromobut-2-ene and dimethyl malonate.

Ir-CATALYZED ALLYLIC VINYLATION AND AMINATION REACTIONS WITH *o*-AMINOSTYRENES



You and co-workers at the Shanghai Institute of Organic Chemistry describe allylic substitution reactions with *o*-aminostyrene derivatives in *J. Am. Chem. Soc.* **2011**, *133*, 19006. The transformations include allylic vinylations and asymmetric allylic aminations catalyzed by phosphoramidite−Ir complexes. The reaction of *o*-aminostyrenes with allylic carbonates as electrophiles provides skipped (*Z,E*)-dienes with good yields and chemo- and stereoselectivities. Optimal conditions for the allylic vinylations include the use of 4 mol % $[Ir(cod)Cl]_2$, 8 mol % ligand, and 2.6 equiv of DABCO in THF at 60 °C. The nature of the leaving group of the allylic precursors influences the chemoselectivity of the allylation. Thus, the reaction between cinnamyl diethyl phosphate and substituted *o*-aminostyrenes affords allylic amination products that can be readily transformed into enantioenriched 1,2-dihydroquinolines by subsequent RCM reactions. Typical conditions for the allylic amination involve the use of 2 mol % $[Ir(dbcot)Cl]_2$, 4 mol % ligand, and 110 mol % K_3PO_4 in THF or dioxane at 50 °C.

ASYMMETRIC REDUCTION OF KETONES BY PHOSPHORIC ACID CATALYSTS



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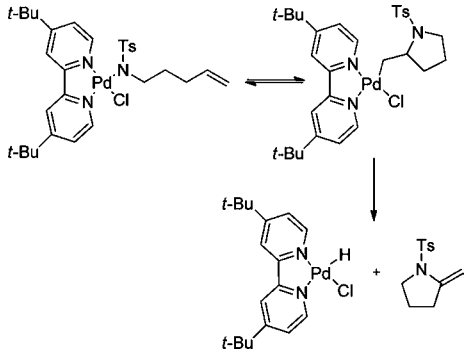
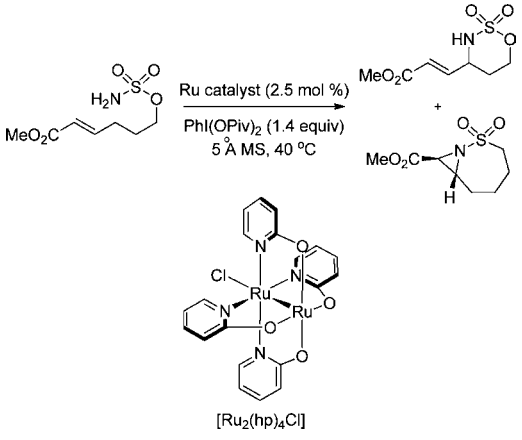
The applications of chiral phosphoric acids continue to expand. Antilla and co-workers at the University of South Florida developed a catalyst system for the asymmetric reduction of aryl ketones using catecholborane as the reducing agent (*Angew. Chem., Int. Ed.* **2011**, *50*, 10961). Thus, a variety of chiral secondary alcohols could be obtained with high enantioselectivities by treating the ketone precursors with a binol-derived phosphoric acid (5 mol %), 4-(dimethylamino)pyridine (5 mol %), catecholborane (1.6 equiv), and molecular sieves in toluene at −20 °C. The methodology tolerates diverse functional groups on the aromatic ring, such as nitrile, nitro, ester, iodide, and bromide. ^{11}B NMR studies indicate that catecholborane reacts with the phosphoric acid and 4-(dimethylamino)pyridine to generate hydrogen and form a phosphoryl catechol borate as the active catalyst.

REVERSIBLE ALKENE INSERTION INTO THE Pd−N BOND OF Pd(II)−SULFONAMIDATES



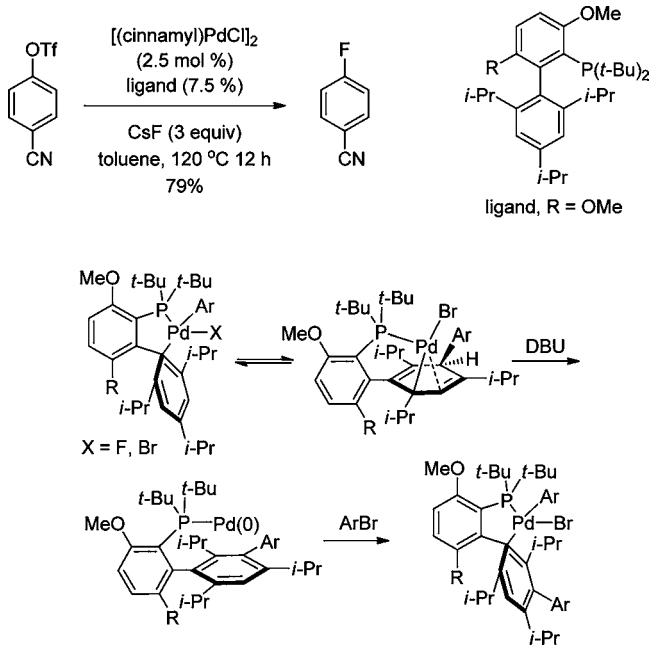
White and Stahl describe mechanistic studies on the insertion of alkenes into Pd−N bonds, a key step in the Pd-catalyzed oxidative amidation of olefins (*J. Am. Chem. Soc.***2011***13*318594). A model Pd(II)−sulfonamidate chloride complex was prepared and crystallographically characterized. The *cis*-aminopalladation of this complex occurred in polar solvents (e.g., DMSO) and was strongly inhibited by the addition of chloride to the reaction mixture, in agreement with a mechanism involving dissociation of chloride prior to the insertion. Notably, the regeneration of the original complex from the intermediate alkyl-Pd species indicated that the alkene insertion is reversible under anaerobic conditions. Electron-rich amidates accelerate the alkene insertion into the Pd−N bond, endorsing a mechanism that involves the intramolecular nucleophilic attack of the amidate to the Pd-coordinated alkene.

Ru-CATALYZED INTRAMOLECULAR ALLYLIC C−H AMINATION



Tetrakis-(2-oxypyridinato)diruthenium chloride, $[Ru_2(hp)_4Cl]$, catalyzes the intramolecular allylic C−H amination of unsaturated sulfamate esters under oxidative conditions. In contrast to the related Rh dimeric catalyst $[Rh_2(esp)_2]$, the Ru system displays high selectivity for the C−H amination relative to the competing aziridination. Typical reactions are performed with 2.5 mol % $[Ru_2(hp)_4Cl]$, 1.4 equiv of $PhI(O_2Ct\text{-}Bu)_2$, and powdered 5 Å molecular sieves in CH_2Cl_2 at 40 °C to afford product mixtures with insertion-to-aziridination ratios larger than 20:1. A comprehensive combination of mechanistic and DFT computational studies reveals the prevalence of a stepwise mechanism involving initial H-atom abstraction followed by diradical recombination instead of a closed-shell singlet nitrene concerted insertion (Harvey, Musaev, Du Bois in *J. Am. Chem. Soc.* **2011**, *133*, 17207).

Pd-CATALYZED CONVERSION OF ARYL TRIFLATES TO ARYL FLUORIDES



Buchwald and co-workers described the conversion of aryl triflates to aryl fluorides catalyzed by Pd complexes with bulky biaryl phosphines in *Angew. Chem., Int. Ed.* **2011**, *50*, 8900. More recently, the team reported additional studies revealing that the actual ligand is an arylated form of the original phosphine generated during the reaction (*J. Am. Chem. Soc.* **2011**, *133*, 18106). L-Pd(Ar)F oxidative addition complexes believed to be intermediates in the fluorination and their L-Pd(Ar)Br analogues were independently prepared, isolated, and characterized by X-ray crystallography. In the Br series, the original L-Pd(Ar)Br species was found to be in equilibrium with a dearomatized Pd(II) complex that could also be crystallized. Rearomatization of the Pd(II) complex took place in the presence of DBU and aryl bromide with concurrent oxidative addition. The tetraarylphosphine ligand of the resulting complex could be detected as a byproduct of the fluorination reactions and was found to be catalytically active in the fluorination of 4-*n*-BuPhOTf. The formation of terarylphosphine ligands may influence the outcome of the reactions mediated by their biaryl phosphine precursors.

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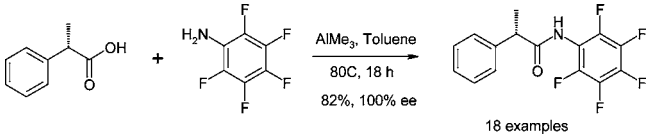
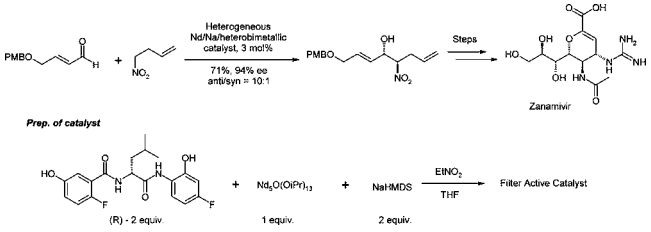
$AlMe_3$-PROMOTED FORMATION OF AMIDES FROM ACIDS AND AMINES



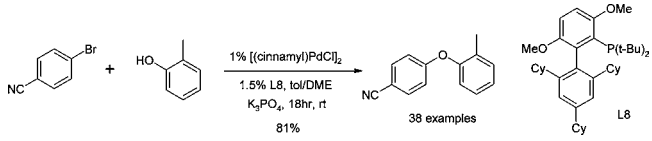
Amide bond formation represents one of the most fundamental reactions in organic chemistry, playing a key role in both peptide synthesis and medicinal chemistry. Numerous methods are available to achieve this transformation with each having advantages and limitations. Li and co-workers at Bristol-Myers Squibb (*Org. Lett.* **2012**, *14*, 214) have reported on a novel method for the direct preparation of amides from acids and amines mediated by $AlMe_3$. The reaction is operationally simple with initially $AlMe_3$ and the amine being mixed to generate the dimethylaluminium amide, which is then reacted with the carboxylic acid at 80 °C in toluene. The reaction time is typically between 16 and 24 h with good to excellent yields of products being isolated. A wide range of both acids and amines can be coupled including both weakly nucleophilic, and sterically encumbered amines, as well as acids with poor solubility. The coupling of chiral acids occurs without any observed racemization. Initial studies on the couplings of some unprotected amino acids were carried out. In the case of proline, the reactions proceeded smoothly without any cross coupling being observed although 5−15% of racemization was noticed. For primary amino acids such as 2-phenylglycine, the reactions became complex, owing to the cross-coupling products being predominant. The major limitations of the methodology is that functionality such as ester, nitro, and cyano groups are not tolerated under these conditions, and that 3 equiv of both the amines and $AlMe_3$ are required for optimal yields.

CATALYTIC ASYMMETRIC *anti*-SELECTIVE NITROALDOL REACTION EN ROUTE TO ZANAMIVIR



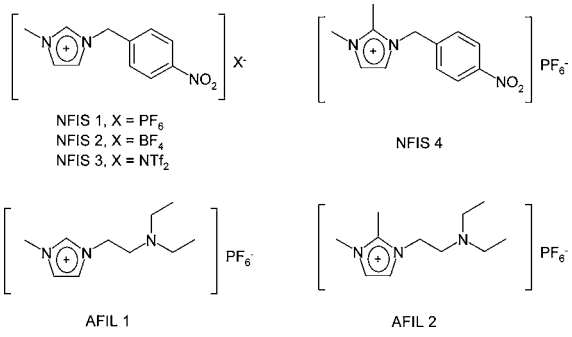
Zanamivir is a potent neuraminidase inhibitor, which has been marketed since 1999 for the treatment of influenza. It is a densely functionalized dihydropyran entity bearing five consecutive stereogenic centers, and a synthetic derivative of sialic acid. Given its molecular complexity, all the previously reported synthetic approaches in the literature are semi-syntheses from natural chiral building blocks, such as sialic acid. Given this, there are inherent problems with limited structural variation in derivatization and the high cost of the chiral building blocks. Shibasaki and co-workers have reported a de novo enantioselective synthesis of zanamivir. The key initial C−C bond-forming step is an *anti*-selective catalytic asymmetric nitroaldol reaction promoted by a Nd/Na heterobimetallic complex (*Angew. Chem., Int. Ed.* **2012**, *51*, 1644). The catalyst is easy to prepare and is isolated by precipitation. Three mol % of the active complex is utilized to promote the nitroaldol reaction, which delivers the desired vicinal nitroalkanol in 71% yield with an *anti/syn* = 10: 1 ratio and 94% ee (*anti*). A series of synthetic manipulations are required to convert the nitroalkanol into zanamivir. Of interest amongst these is a Sharpless asymmetric epoxidation, which requires stoichiometric amounts of both ligand and titanium to obtain full conversion. It is important to note that the novel nitroaldol reaction is amenable to scale-up, and various aldehydes can be utilized to enable preparation of analogues of zanamivir, although its value for this purpose might be somewhat limited with the point of diversity being introduced at the beginning of a lengthy synthesis.

A NEW BIARYLPHOSPHINE LIGAND FOR THE Pd-CATALYZED SYNTHESIS OF DIARYL ETHERS UNDER MILD CONDITIONS



The formation of diaryl ethers under mild conditions is a major challenge. Buchwald has reported on a new bulky biarylphosphine ligand (L8), which allows the Pd-catalyzed C−O cross-coupling to proceed between a wide range of aryl halides and phenols under milder conditions than previously possible (*Org. Lett.* **2012**, *14*, 170). Studies on a series of new ligands indicated the importance of steric bulk in the 2-, 4-, and 6-positions of the nonphosphine-containing aromatic ring. A large substituent was beneficial, but if the group became too large, it inhibited the reaction. The reactions proceeded in toluene/DME with potassium phosphate being utilized as the base. $[(Cinnamyl)PdCl]_2$ was chosen as the optimal palladium source since it is able to generate the active Pd(0) species at lower temperatures than other commonly used precursors. The substrate scope of the reaction is good with electron-deficient aryl bromides being coupled at room temperature with electron-rich and neutral phenols. Electron-neutral and -rich aryl bromides could also be coupled successfully, but in general elevated temperatures were required (up to 100 °C). Five- and six-membered heterocyclic bromides were also shown to be successful coupling partners, thus extending the scope of this methodology.

AN ALTERNATIVE TO NITROMETHANE AS SOLVENT: THE PROMOTING INFLUENCE OF NITRO-FUNCTIONALIZED IMIDAZOLIUM SALTS FOR SYNTHESIS AND CATALYSIS



The replacement of volatile and toxic organic solvents with environmentally benign alternatives continues to be an area of significant interest. Gu, Peng, and co-workers have reported a series of functionalized ionic liquids which could potentially replace nitromethane in organic and catalytic reactions (*Adv.*

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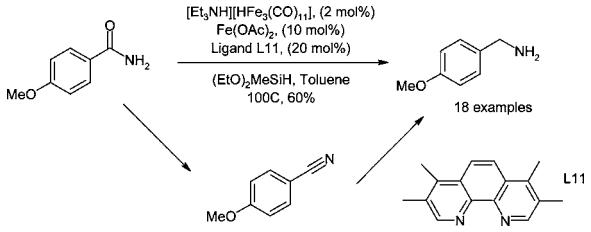
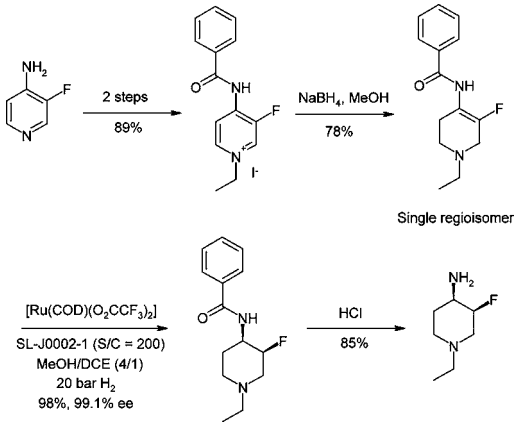
Synth. Catal. **2011**, *353*, 3473). It should be noted that three of these imidazolium salts (NFIS 1, NFIS 2, and NFIS 4) are solids at room temperature, and their melting points are higher than 80 °C. Given that the nitro group is attached directly to an aromatic ring, it is not unreasonable to expect that the potential of these imidazolium salts for explosion should be much lower than that of nitromethane. These novel ionic liquids were tested in a series of reactions. For silylation with HMDS, use of 10 mol % of NFIS 1 was sufficient to promote the reaction for a wide range of alcohol substrates in good yield at room temperature. In addition, as the salt was a solid under these conditions, it could be easily recovered and recycled through the reaction without loss of activity. In a similar manner, NFIS 1 was able to promote and enhance the reactivity of the manganese-catalyzed ring-openings of dihydropyrans with thiols. Finally, a study was carried out on the Glaser coupling reaction, and it was shown that a combination of AFIL 1 and NFIS 1 had a profound effect on the reactivity of these systems. Interestingly, if the 2-methyl-substituted salt, AFIL 2, was employed, the reaction shut down, leading the authors to postulate on a potential structure for the catalytically active copper species. In all these cases, isolation of the products is trivial, and the catalysts can be recycled.

TWO IRON CATALYSTS ARE BETTER THAN ONE: A GENERAL AND CONVENIENT REDUCTION OF AROMATIC AND ALIPHATIC PRIMARY AMIDES



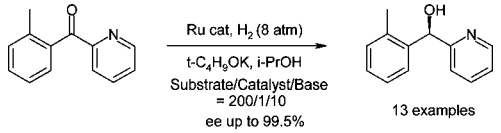
The conversion of primary amides to amines is traditionally carried out using a metal hydride-mediated reduction. However, given both the air and moisture sensitivity of these reagents, and the costly purification of the products, selective catalytic methods such as hydrogenation or hydrosilylation are highly desired. Beller's group has described a stepwise system, which employs two discrete iron catalysts for the reduction of a primary amide to a primary amine via the intermediacy of the nitrile (*Angew. Chem., Int. Ed.* **2012**, *51*, 1662). The reaction is simple to perform with both reductions occurring in toluene at 100 °C with inexpensive methyldiethoxysilane being the key reagent to enable the reactions. The initial dehydration of the amide to the nitrile was mediated by 2 mol % of $[Et_3NH]-[HFe_3(CO)_{11}]$, while 10 mol % of $Fe(OAc)_2$ with 20 mol % of a phenanthroline ligand (note ligands with electron-donating groups show the best activity) completed the reduction to the primary amine. The substrate scope is good with both aromatic and aliphatic examples being reported, and it is interesting to note that both halide and amine substituents are tolerated in the reaction. Furthermore, no secondary or tertiary amines are observed as side products. A mechanism has been proposed focusing on the different reactivities of the two iron species.

KILOGRAM-SCALE ASYMMETRIC RUTHENIUM-CATALYZED HYDROGENATION OF A TETRASUBSTITUTED FLUOROENAMIDE



Workers at Genentech needed access to kilogram quantities of an enantiomerically pure piperidine to facilitate one of their development programs (*Adv. Synth. Catal.* **2011**, *353*, 3367). They envisioned that the easiest way to access the desired compound would be from the commercially available 3-fluoro-4-amino pyridine. The 4-amino group was initially protected with a benzoyl group to provide a chromophore as well as a potential coordinating group for a metal catalyst. After quaternization, reduction with sodium borohydride was completely selective to give the tetra-substituted enamide in 68% overall yield on a 20 kg scale. The crucial hydrogenation was subjected to a screen looking at Ru, Rh, and Ir in conjuction with a wide variety of chiral diphosphine ligands. From these experiments, it was found that using a Ru complex of the Josiphos ligands SL-J011-1 and SL-J00201 provided high levels of enantiomeric excess (97%), minimal amounts of the defluorinated compound (2−3%), and none of the undesired *trans*-isomer. The transformation was quickly optimized with one key parameter found to be the choice of Ru precursor. Utilization of $[Ru(COD)(CF_3CO_2)_2]$ with SL-J002-1 proved to be the optimum conditions, and the reaction was successfully scaled in methanol/DCE (4:1) under 20 bar hydrogen pressure to 12 kg scale. Simple acidic hydrolysis of the benzamide group provided the desired final product.

RUTHENIUM-CATALYZED ENANTIOSELECTIVE HYDROGENATION OF ARYL-PYRIDYL KETONES



Ru Cat = *trans*-$RuCl_2$[(S)-XylSunPhos][(S)-Daipen]

The asymmetric hydrogenation of prochiral ketones represents one of the most efficient ways for producing enantiomerically pure secondary alcohols. However, in this regard the reduction of aryl-pyridyl ketones has met with limited success. Zhang and co-workers have designed a series of atropisomeric C_2-symmetric biaryl biphosphines-SunPhos ligands with complementary steric and electronic properties, which have been successful in a series of previous asymmetric hydrogenations (*J. Org. Chem* **2012**, *77*, 612). In the present study, they combine these SunPhos ligands with the chiral diamine, Daipen, to prepare Noyori-type complexes, $RuCl_2$(diphosphine)(diamine). During

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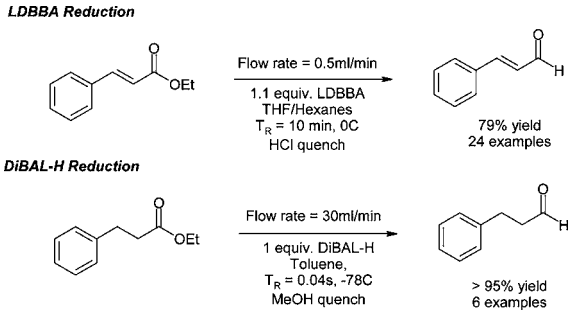
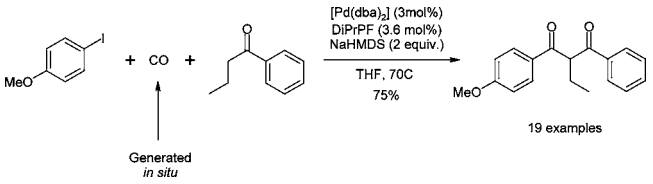
screening, the group identified that the 3,5-dimethyl substituents on the phenyl rings of the ligands Xyl-SunPhos were essential for high enantioselectivity. Furthermore, *i*-PrOH was the solvent of choice for the transformation with potassium *tert*-butoxide as the base. Enantioselectivity decreased as the temperature increased, though unexpectedly, hydrogen pressure had little impact on the enantioselectivity. The substrate scope was investigated, and it was found that ortho-substituted substrates gave excellent results (>98% ee) regardless of the electronics of the ring. Simple meta- and para-substrates led to moderate enantioselectivities with electronic effects having more impact. Finally, an asymmetric synthesis of a key intermediate for both carbinoxamine and bepotastine besilate was demonstrated using this methodology.

FLOW CHEMISTRY ENABLED SELECTIVE REDUCTION OF ESTERS TO ALDEHYDES



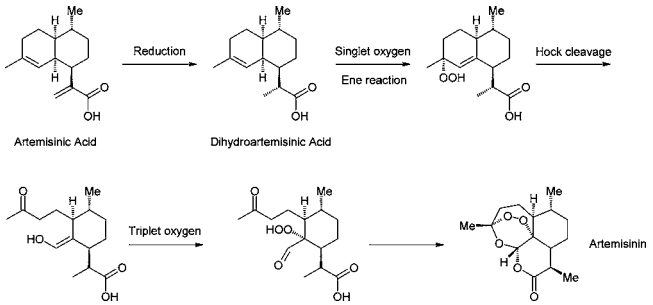
The selective reduction of esters to aldehydes is an important transformation in organic chemistry, though reactions to achieve this often require cryogenic temperatures and are not robust due to over-reduction to the corresponding alcohol. In many synthetic endeavors, better control can be achieved by carrying out a two-step sequence initially reducing the ester to the alcohol prior to oxidation back to the aldehyde. The precise parameter control and optimal mixing offered by running reactions in Flow offer potential solutions to this long-standing problem, and two research groups have reported on this selective reduction. Alcázar and co-workers have demonstrated the reaction using a commercial flow system using lithium diisobutyl-*tert*-butoxyaluminium (LDBBA) as the reagent of choice (*Eur. J. Org. Chem* **2012**, 260). The optimal conditions employed a residence time of 20 min with 1.1 equiv of reducing agent at 0 °C. A wide variety of esters was reduced in excellent yield, and the authors were also able to demonstrate several selective ester reductions. In contrast, Jamison has optimized this transformation using DiBAL-H as the reducing agent, employing an inline methanol quench (*Org. Lett.* **2012**, *14*, 568). In this study, residence time, temperature, and flow rate are optimized for each substrate, taking advantage of the ability to quickly generate data to find the optimum conditions. An important factor to note in this study is the key role that mixing plays in obtaining an efficient reaction with higher conversions and yields being observed at higher flow rates despite the shorter residence times. This observation indicates that the reaction is very fast, and at increased flow rates, additional energy is provided for mixing. One limitation of the methodology is that simple aromatic esters are not successful substrates in this reduction.

PALLADIUM-CATALYZED CARBONYLATIVE α-ARYLATION FOR ACCESSING 1,3-DIKETONES



The addition of carbon monoxide into the catalytic cycle of a palladium-catalyzed α-arylation would provide a straightforward entry to β-ketocarbonyl compounds from simple aryl halides and carbonyl derivatives having one or two protons in the α-position. Skyrdstrup has successfully developed a system to achieve this, using only stoichiometric amounts of carbon monoxide (*Angew. Chem., Int. Ed.* **2012**, *51*, 798). The reactions are run using a two-chamber system using 9-methyl-9*H*-fluorene-9-carbonyl chloride to generate carbon monoxide. The optimized reaction system initially premixes the ketone with NaHMDS to generate the enolate prior to addition of the aryl halide, palladium catalyst, and exposure to carbon monoxide. THF is the solvent of choice, and switching to toluene leads to exclusive formation of the α-arylated product without CO insertion. Ligands with a rigid ferrocene backbone gave cleaner reactions and higher yields of the desired products, and the steric bulk of the ligand was shown to be a key factor in determining the selectivity of the products. As expected, aryl iodides performed better than the corresponding bromides, and the substrate scope in terms of the ketones employed was generally good. This new method allowed for facile ^{13}C labeling of the 1,3-diketones, which are themselves precursors to a range of heterocyclic compounds.

CONTINUOUS-FLOW SYNTHESIS OF THE ANTI-MALARIA DRUG ARTEMISININ



Artemisinin is currently the most effective treatment of malaria. The compound is produced by extraction from the plant *Artemisia annua*, though reliance on this method both restricts the supply of the drug and elevates costs for the patients. While a total synthesis is considered too laborious, the much less complex precursor artemisinic acid can be extracted from the same plant in higher yields or produced in engineered yeast. Seeberger has utilized the reduced acid as the starting material for the continuous flow synthesis of artemisinin (*Angew. Chem., Int. Ed.* **2012**, *51*, 1706). In this sequence, the acid is initially subjected to an ene reaction with singlet oxygen, which is photochemically generated in situ. Carrying out this transformation in Flow has significant advantages over a batch method with the most notable being the highly efficient illumination of the entire reaction solution. The hydroperoxide on exiting the photochemical reactor is treated with TFA, which promotes the Hock cleavage, leading to a highly reactive enol. This in turn reacts with triplet oxygen to again generate a hydroperoxide, which

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undergoes a series of condensations to generate the three missing rings of artemisinin. Remarkably, this entire sequence is carried out in one continuous flow system to generate the natural product in 50% yield after chromatographic purification. On the basis of this result, Seeberger estimates that the setup described can generate 200 g of artemisinin a day and represents a viable process to meet the ever-growing demand for low-cost artemisinin.

NANOMEDICINE(S) UNDER THE MICROSCOPE

Nanotechnology is very widely discussed in both the scientific literature and in the general press. A critical and comprehensive review of nanomedicines was recently published (Duncan R.; et al. *Mol. Pharm.* **2011**, *8*, 2101). It may be encouraging to know that over 40 nanomedical products have made it to routine clinical use (tabulated in the paper), and 70 ongoing clinical trials focus on nanomedicines (selected nanodrugs in development are also tabulated). This review discusses key aspects of pharmaceutical nanotechnology including nomenclature, rational design of new drug products, nanotoxicology, and regulatory aspects. The focus in nanomedicines has been on novel, high-performing drug delivery systems (using "old" drugs). On the border perhaps between drug substance and drug product, nanocrystals are mentioned amongst novel nanodrugs. Synthetic and analytical challenges continue to exist in this field, such as the case of robust manufacturing for dendrimer production and characterization. Apparently the "nanomedicinista" complain about insufficient industry support; however, an expert report quoted indicates that "it has been increasingly clear to the industrial sector that an academic-driven or "laissez faire" approach to Nanomedicine will be an inefficient process". The review briefly discusses the older question of whether "noanotechnology is too broad to practice", indicating that to overcome such complexity, "overall...Quality by Design (QbD) should be applied" in the development of new nanomedicines. The authors caution against "extreme" approaches when discussing nanomedicines: no "hype" and no "nanoparticles can wreak havoc in the body". This review is 41 pages long, featuring 518 references.

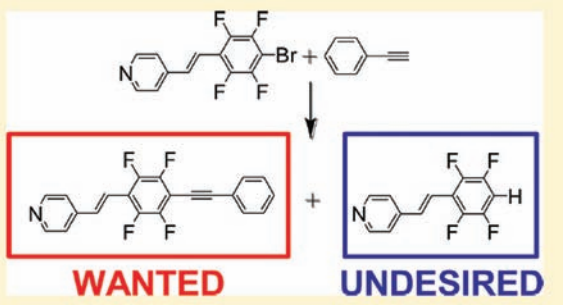
OVERCOMING INHERENT LIMITS TO PHARMACEUTICAL MANUFACTURING QUALITY PERFORMANCE WITH QbD (QUALITY by DESIGN)

When the QbD initiative was announced nearly 10 years ago, it was rather difficult to make a convincing business case for QbD implementation. However slowly, the results of QbD implementation of the past decade provide now a sufficient data set for a meaningful business analysis.

Using some of the results of his Ph.D. thesis at The George Washington University and his experience at Pfizer, Blackburn published a report discussing key aspects of the business value that QbD adds to pharmaceutical process R&D and manufacturing (Blackburn, T. D.; et al. *J. Pharm. Innov.* **2011**, *15*, 69). The paper summarizes the findings of a systems engineering analysis for a case study focused on understanding the gap between the pharmaceutical production systems ($\sim 3.5\sigma$) and supplied quality to the patient ($\sim 6\sigma$). The research analyzed four hypotheses: (1) the gap between shipped quality and production sigma is significant; (2) the current QbT (Quality by Testing) model hits a fundamental upper limit for quality improvement; (3) pharmaceutical production systems behave like other manufacturing systems, specifically exhibiting the S-curve technological profile; (4) QbD can eliminate or minimize typical negative effects of manufacturing systems. A systematic analysis showed that each of these hypotheses is correct. On the basis of the case study available, the cost of quality was estimated to be 8% of sales. At a 50% cost reduction target, when extrapolating to the top 20 pharmaceutical companies with revenues of $427 billion (2008 dollars), such savings would amount to $17 billion (or 17 blockbusters per year for this group). The synergy between Six Sigma methods and QbD is discussed, as is the use of the Theory of Constraints and that of TRIZ (an acronym for "Theory of Inventive Problem Solving", in Russian).

PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS WITH FLUORINATED SUBSTRATES: MECHANISTIC INSIGHTS INTO THE UNDESIRED HYDRODEHALOGENATION OF ARYL HALIDES

A mechanistic investigation of the Sonogashira reaction with fluorinated aryl halides was recently published by van der Boom's group at the Weizmann Institute (Orbach, M.; et al. *Organometallics* **2011**, DOI: 10.1021/om200898t). The focus of this investigation was understanding the mechanism for the formation of the undesired hydrodehalogenation products. The authors showed how selectivity can be controlled by varying the phosphine ligands, identifying water as the most probable hydrogen source for the formation of the undesired product. Under certain reaction conditions, it was shown that the phosphine, and not CuI, induces hydrodehalogenation.



Using computational chemistry, it was shown that significant hydrodehalogenation occurs prior to the formation of Ar_F–Pd(II)–Br complexes. The authors may consider executing similar work for other platinum-group metal-catalyzed cross-coupling reactions with fluorinated aryl halides. The Supporting Information to this paper is quite informative (44 pages).

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