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

■ SYNTHESIS OF 2,3,6-TRISUBSTITUTED PYRIDINES FROM ISOXAZOLINONES

Substituted pyridines are an important class of organic compounds and ubiquitous in the chemistry world. Various methodologies have been developed to construct substituted pyridine derivatives. Recently, René Peters and co-workers developed a regioselective Pd-catalyzed synthesis of 2,3,6-trisubstituted pyridines from isoxazolinones (Peters, R., et al. J. Org. Chem. 2015, 80, 6822). The protocol involves a regioselective Pd(II)-catalyzed 1,4-addition of isoxazolinones to enones, followed by a Pd(0)-catalyzed dihydropyridine formation and oxidation. The formation of the dihydropyridine is hypothesized via a vinylnitrene-Pd complex species formed by oxidative addition of Pd(0) to the N−O bond of the 1,4-adduct followed by a decarboxylation. This two-step sequence allows a rapid and regioselective entry to substituted pyridines starting from readily accessible isoxazolinones. Despite these advantages, the safety issue needs to be addressed during application of this approach toward large-scale production as the second step required a mixture of hydrogen and air.

■ STEREOSELECTIVE HETERO-DIELS−ALDER REACTION AND RING CONTRACTION

A hetero-Diels−Alder reaction between dienes and nitroso compounds has been widely utilized to synthesize 3,6-dihydro-1,2-oxazines, valuable intermediates in the organic synthesis. Carboni and co-workers studied on the [4 + 2] cycloaddition between boron substituted dienes and nitrosoarenes, and the results are revealed in a recent report (Carboni, B., et al. J. Org. Chem. 2015, 80, 6574). The researchers demonstrated that using an sp2 boron substituent, i.e., pinacol ester, a one-pot hetero-Diels−Alder/ring contraction cascade afforded N-arylpyroles. The corresponding oxazine cycloaducts were not observed during the course of the reaction. In contrast, reactions of dienes with sp3 boron substituents, i.e., N-methyliminodiacetic (MIDA) borodiene derivatives, led to formation of stable boroxazines in moderate to good yields and high regioselectivity. In addition, the isolated oxazine could participate in Suzuki−Miyaura cross-coupling reaction.

■ HIGHLY REGIOSELECTIVE INDOLINE SYNTHESIS UNDER NICKEL/PHOTOREDOX DUAL CATALYSIS

Nickel-catalyzed cross-coupling reactions involve either a Ni(0/II) pathway for aryl cross-coupling or a Ni(1/III) pathway for C-sp3 cross-coupling. The nickel-catalyzed C-sp3 cross-coupling reaction generally proceeds via an alkyl radical formed from SET process, which is trapped by Ni(II) species to give ArNi(III)RLnX complex. Jamison and co-worker of Massachusetts Institute of Technology, Cambridge, Massachusetts, reported a highly regioselective indoline synthesis under nickel/photoredox dual catalysis (Jamison, T. F., et al. J. Am. Chem. Soc. 2015, 137, 9531). It was found that the visible light photoredox catalyst Ru(bpy)3(PF6)2 improved the indoline yield significantly. Using the optimized protocol, 3-substituted indolines were obtained in good yields. It is demonstrated that various 3-substituted indolines including

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alkyl and aryl substituents could be synthesized. This protocol is able to achieve the challenging C-sp$^3$−N bond formation, avoiding problematic β-hydride elimination.

**ASYMMETRIC SYNTHESIS OF HETEROARYL NITRILES VIA NICKEL-CATALYZED REDUCTIVE CROSS-COUPLING REACTION**

The usefulness of nickel-catalyzed reactions is demonstrated in the asymmetric synthesis of heterocyclic nitriles (Reisman, S. E., et al. *J. Am. Chem. Soc.* 2015, 137, 10480). The method, developed by Reisman and her co-worker of California Institute of Technology, California, utilized NiCl$_2$(dme) in the presence of DMMB-PHOX ligand, TMSCl (40 mol %), and Mn (3 equiv) to enable the reductive cross-coupling between heterocyclic iodides and α-chloronitrile. In this catalytic system, TMSCl additive was employed to activate Mn(0) reductant to turn over the nickel catalyst. As the method uses mild reaction conditions at room temperature, a variety of functional groups in heterocyclic coupling partners were tolerated. Using a new chiral PHOX ligand provided α,α-disubstituted nitriles in good yields and high enantiopurity.

**A COPPER/PALLADIUM COOPERATIVE CATALYSIS FOR ENANTIOSELECTIVE ALLYLBORATION OF ALKENES**

Carboboration of alkenes is a powerful way to generate molecular complexity from simple starting materials. Liao and co-workers at the Chinese Academy of Sciences have developed a Cu/Pd cooperative catalysis system for the enantioselective carboboration of styrenes (*J. Am. Chem. Soc.* 2015, 137, 13760). The strategy involves an enantioselective borylcupration of the alken with CuOAc/SOP and B$_2$(pin)$_2$, followed by a stereoretentive Cu−Pd transmetalation with the achiral Pd(II)-catalyst, Pd-(dppf)Cl$_2$. The formed chiral Pd-complex can react with various allyl electrophiles to form allylboration products. Boc-protected allylic alcohols provide the highest reactivity and selectivity and can be alkyl- or phenyl-substituted. Both branched and linear allylic carbamates can be used to form the linear allylation product. Racemic cyclic allylic carbamates also react in good enantio- and diastereoselectivity. Styrenes with o-, m-, and p-substitution were all tolerated, as were halides, indoles, Bz-protected alcohols, and CF$_3$-groups. Alkyl-substituted alkenes and 1,2-disubstituted styrene derivatives were unsuitable starting materials. Several examples of product utility were shown, as well as a 5-step synthesis of the antipsychotic drug, (−)-preclamol.

**DIRECT SYNTHESIS OF NITRILES FROM ALDEHYDES USING AN O-BENZOYL HYDROXYLAMINE (BHA) AS THE NITROGEN SOURCE**

Safe and efficient methods to synthesize nitriles from simple starting materials are extremely valuable. An and Yu of Nanjing University have described a method utilizing O-benzoyl hydroxylamine (CF$_3$−BHA), as a nitrogen source for the direct synthesis of nitriles from aldehydes (*Org. Lett.* 2015, 17, 5064). The hydroxylamine adds to the aldehyde to form an O-acyl oxime, then requires catalytic strong acid, such as TFA or CSA, along with a protic solvent, to form the nitrile. Several functional groups are tolerated, including alkenes, alkyne, esters, amides, ketals, phenols, pyrroles, pyridines, and indoles. Aliphatic nitriles are formed at room temperature, while aromatic nitriles require heating (80 °C) in DME. α,β-Unsaturated nitriles can be formed from α,β-unsaturated aldehydes without the formation of Michael addition byproducts.
PALLADIIUM-CATALYZED ARYLATION OF ALKYL SULFENATE ANIONS

Several excellent examples of the generation of aryl sulfenate anions (ArSO2−) for palladium-catalyzed arylation have recently been developed, but no general method for the generation of alkyl sulfenate anions exist. Alkyl sulfonites can suffer from base induced β-hydride elimination and α-arylation side reactions. Walsh and co-workers at the University of Pennsylvania have developed a fluoride-mediated fragmentation of 2-(trimethylsilyl)ethyl substituted sulfonites to generate alkyl sulfenate anions that can be coupled to aryl halides with a palladium-catalyst and bulky monodentate phosphine ligands (J. Am. Chem. Soc. 2015, 137, 13887). The required alkyl 2-(trimethylsilyl)ethyl sulfonites can be synthesized in two easy steps from vinyltrimethylsilane. Several examples of successful couplings with sulfonites bearing β-hydrogens were shown, including examples with heterocycles, alcohols, ethers, and sterically demanding α-centers. Electron-rich and electron-withdrawing aryl bromides and chlorides both couple efficiently. Good chemoselectivity for S-arylation is observed with substrates containing amines and amides that could participate in N-arylation.

TERT-BUTYL SULFOXIDE AS A STARTING POINT FOR THE SYNTHESIS OF SULFINYL CONTAINING COMPOUNDS

The tert-butyl sulfoxide moiety is very common in organic synthesis because of its stability and use in enantioselective chemistry popularized by the Elmman group. Wei and Sun of Shanghai University of Engineering Science have developed a method to activate the tert-butyl group for substitution with nitrogen, oxygen and carbon nucleophiles (Org. Lett. 2015, 17, 5396). The method employs N-bromosuccinimide and acetic acid to first activate the sulfoxide, forming a mixed anhydride and molecular bromine, followed by the addition of the nucleophile. Because amines and carbon nucleophiles are incompatible with NBS under acidic conditions, the sulfoxide activation is done separately for 20 min, followed by nucleophile addition. Longer activation times resulted in lower yields. Only aryl and benzylic substituted tert-butyl sulfoxides were demonstrated. Di-tert-butyl sulfoxides were also useful starting materials but require a stronger acid (TFA) for activation. Good yields were observed with a variety of nucleophiles, including primary and secondary amines, Grignard reagents, and indoles. Since bromine is a byproduct, compounds that contain amines or alkynes can suffer from side reactions.

HIGHLY REGIO-AND ENANTIOSELECTIVE ALKOXYCARBONYLATIVE AMINATION OF TERMINAL ALLENES CATALYZED BY A SPIROKETAL-BASED DIPHOSPHINE/PALLADIUM (II) COMPLEX

Ding and co-workers at Shanghai Institute of Organic Chemistry have developed the first enantioselective Pd(II)-catalyzed oxidative carbonylation of allenes to provide useful β-arylamino-α-methylenecarboxylic acid derivatives (J. Am. Chem. Soc. 2015, 10.1021/jacs.5b07764). The reaction utilizes a spiroketal-based diphosphine (SKP) ligand and converts a variety of terminal aryl and aliphatic allenes into Morita–Bayliss–Hillman products, with aromatic primary amines as nucleophiles. Aliphatic or secondary amines provide complicated mixtures or no reaction. Carbon monoxide gas at atmospheric pressure is required; however, a high Pd(II)-loading is required. A Hg(O) test suggests this is due to a large fraction of dormant Pd(O). The use of Cu(OAc)2 as oxidant dramatically increased the branched to linear product ratio, while the use of Cu(OOCOEt)2 allowed for lower catalyst loadings.

THE FUTURE OF PHARMACEUTICAL MANUFACTURING SCIENCES

Written with an emphasis on drug product, this review from the Graz University of Technology and the University of Copenhagen (J. Pharm. Sci. 2015, 104, 3612–3638) about the future of pharmaceutical manufacturing is also discussing aspects of quality by design (QbD) implementation for API. Certain challenging QbD concepts are reviewed, such as “process understanding”. The very visible process analytical technology progress within QbD is addressed as well. Advances in statistical design of experiments (DoE) methods are presented, together with future multivariate analysis tools including artificial neural networks, fuzzy logic, and neuro-fuzzy modeling. Mechanistic process modeling and advanced process simulation techniques are reviewed. Quality risk management is discussed, and a valuable
comment is made: “… relatively demanding quantitative methods such as FMEA (Failure Mode and Effects Analysis) are not an ideal starting point for the first risk assessment efforts or for evaluating early development phases.” The authors comment that because of the increased demand for highly engineered innovative formulations, the role of material science is gaining importance. Active research in continuous manufacturing, including API crystallization, together with related regulatory framework modifications are mentioned. This review has 325 references.

■ CONTROL OF CRYSTAL ASPECT RATIO AND SIZE BY CHANGING SOLVENT COMPOSITION IN OILING-OUT CRYSTALLIZATION OF AN ACTIVE PHARMACEUTICAL INGREDIENT

When crystallization is conducted in a water/water-miscible organic solvent mixture, liquid—liquid phase separation can occur upon cooling or upon antisolvent addition, a phenomenon known as “oiling out” crystallization. This is of course different from the “oiling out” occurring in single phase crystallization due for instance, to “crash” cooling. Most chemists would prefer to avoid both types of oiling-out crystallizations.

Continuing the recent efforts to better understand oiling-out crystallization, groups at Takeda and Osaka City University (Takasuga, M., et al. Cryst. Growth Des. 2015, 10.1021/acs.cgd.5b01192) explain why sometimes mixed solvent oiling out crystallization can be used to control particle size and morphology. The compound used in the experiments executed was a Takeda molecule, API-T (a hemihydrate), for which particle size control in single phase crystallization was challenging. The crystallization solvent was an acetone—water mixture. Crystal characterization was done with digital and scanning electron microscopy. By manipulating API concentration, acetone concentration, temperature, and agitation rate, the authors were able to control particle size and aspect ratio. The dependency of the crystal aspect on acetone concentration in the crystallization solvent mixture is explained by the hydrogen bonds formed between acetone and a carboxylic group of API-T which compete with the hydrogen bonds between API-T and water. In single phase crystallization, the crystal aspect ratio is independent of crystal size, whereas in oiling-out, large particles have a smaller aspect ratio. Large crystals were obtained at small droplet size, which in turn are formed at high agitation rate, a rather counterintuitive observation.

■ INTEGRATED UPSTREAM AND DOWNSTREAM APPLICATION OF WET MILLING WITH CONTINUOUS MIXED SUSPENSION MIXED PRODUCT REMOVAL CRYSTALLIZATION

The design and execution of robust continuous crystallization processes remains to be a challenge. The inclusion of wet milling in a continuous crystallization process is described in a report from Purdue University and the Harbin Institute of Technology (Yang, Y., et al. Cryst. Growth Des. 2015, 10.1021/acs.cgd.5b01290). Compared with dry milling (as a downstream operation), such an integrated process has several advantages, such as process intensification, better process safety, and better physical and chemical milled API stability. Three continuous crystallization processes were compared: without wet milling, with upstream wet milling, and with downstream wet milling (operated in a recirculating loop). In addition to the actual position of the wet mill, this investigation evaluated the impact of operating conditions (tip speed, number of turnovers per residence time) on process results (API average particle size, width of particle size distribution, yield, and startup duration). The API used was paracetamol, and the solvent employed was ethanol. The processes were monitored for 12 residence times, with particle size information collected with an FBRM probe at the 11th residence time. When wet milling is executed downstream, particle size control is achieved by controlled secondary nucleation and breakage. When wet milling is done upstream, the wet mill acts as a continuous seed generator, producing seeds of uniform quality. For the description of particle size, the FBRM square weighted mean chord length (SWMCL) was used. In downstream position, small particles are obtained, whereas in upstream position, particle size can be controlled with the tip speed, which at low values leads to relatively larger particles. Yield estimates were calculated using the “yield index”, the product of the SWMCL, and the total particle counts (FBRM). Overall, operating the wet mill upstream led to the best results of the three processes evaluated. Several challenges exist with wet milling as well, including capital cost, complex process design, and potential risk with temperature sensitive API’s.

■ MOLECULES, MATERIALS, MEDICINES (M3): LINKING MOLECULES TO MEDICINES THROUGH PHARMACEUTICAL MATERIAL SCIENCE

As new chemical entities are optimized for higher efficacy, they tend to be less bioavailable because of their low aqueous solubility, a situation described as the “potency-insolubility conundrum”. As a result, transforming a molecule into a medicine has become far more complex than before, requiring the use of material science methodology. The “M3” concept is sometimes used to describe the complex relationship between Molecules, Materials and Medicine. A recent perspective on the topic was published by scientists at Moderna Therapeutics and InScitech (Cryst. Growth Des. 2015, 15, 5645). This perspective references several recently approved drug products where extensive material science investigations were needed to commercialize highly potent molecules. In the telaprevir case, Vertex disclosed that it took 20 years of R&D to bring the molecule to the market, particularly because of the very low aqueous solubility of the API (4.7 μg/mL). The drug is commercialized as an amorphous dispersion (as Incivek, filed as a QbD submission); however, extensive research was also conducted to identify a suitable cocrystal form with 4-hydroxybenzoic acid. A rather detailed description of the Vertex efforts to develop the telaprevir cocrystal is reviewed in a recent publication: Connelly, P. R., et al. Biophys. Chem 2015, 196, 100–118. The Vertex team explains how they used the hypothesis that there may be a structural similarity between the supramolecular structures of the drug—protein complex and that of the crystalline drug to develop the cocrystal API. In addition to stable amorphous dispersions and cocrystals, the perspective also mentions ionic liquids and cyclodextrin based formulations. In all of these instances, an effective collaboration between the API chemists and engineers with the formulation scientists was found to be critical for the success obtained.
Diphenylmethyl ethers play both a prominent role in a number of biologically active molecules as well as being a common protecting group for alcohols, and as such numerous methods for their preparation have been developed. Chen and co-workers have reported on a metal-free methodology using the Lewis acid BF$_3$·OEt$_2$ to catalyze the formation of diphenylmethyl ethers (Adv. Synth. Catal. 2015, 10.1002/adsc.201500491). Model studies on the reaction between diphenylmethanol with methanol (both as a reagent and solvent) indicated that increasing temperature (with the optimal being 100 °C) led to an increase in yield of the desired ether with loadings as low as 5 mol % of the catalyst being possible to provide a 91% yield after 7 h. Other alcohols also performed well, though yields were shown to be sensitive to increasing steric hindrance. Interestingly, ethanediol could be selectively monoprotected in a synthetically useful yield. While the initial procedure is practical for cheap and volatile alcohols, a solvent screen indicated that it was possible to use almost stoichiometric quantities of both alcohols and obtain high yields if toluene was employed as the solvent. Under the toluene-based conditions, a range of ethers were shown to be successful substrates with improved yields observed for sterically congested alcohols while an attrition of yield was observed in the presence of strongly electron-withdrawing substituents. Tertiary alcohols were observed to give complex mixtures of products. A range of substituents were also well-tolerated on the diphenylmethyl alcohol substrates enabling further functionalization of the products, though depressed yields were observed with either ortho-substitution due to steric hindrance, or the presence of electron-withdrawing groups due to the instability of the carbonium intermediate. An investigation of catalyst-loading under solvent-free conditions showed that it was possible to achieve yields of 84% using 0.5 mol % of the catalyst.

**BORON TRIFLUORIDE-DIETHYL ETHER-CATALYZED Etherification of Alcohols: A Metal-Free Pathway to Diphenylmethyl Ethers**

![Diagram of the reaction between diphenylmethanol with BF$_3$·OEt$_2$](image)

The partial reduction of common bicyclic heterocyclic systems has frequently been utilized as a strategy to break away from planarity in the discovery of novel biologically active compounds. Reductions using metal hydrides suffer from a number of disadvantages such as generation of large amounts of waste, and though catalytic homogeneous and heterogeneous hydrogenations have been developed, these often require both high hydrogen pressures and high catalyst loadings to obtain optimum yields and selectivity. Xu and co-workers have reported on a general rhodium catalyst generated in situ from [Cp*RhCl$_2$]$_2$ and 2,2′-bipyridine (bpy) for the selective transfer hydrogenation of a number of such systems under aqueous conditions (Adv. Synth. Catal. 2015, 337, 3115). Initial model studies on the reaction of 2-methylquinoxaline indicated that control of pH was crucial with 4.4 being shown to be the optimal pH indicating that, although substrate activation through protonation is important, lowering the pH too much may lead to reduction of the active rhodium-hydride species. Concentration of the HCOOH/HCOONa aqueous solution was also important with 2 M being the optimum here with only 0.005 mol % of the catalyst being required. Alternative substituted-bpy ligands were also shown to be effective, though the parent was retained for further studies due to its low cost, and ready availability. A range of substituted-quinolines were successfully reduced with good functional group tolerance being observed. Modulation of both the pH to 4, and an increase in the solution concentration to 5 M enabled the reduction of quinoxalinones to take place. Quinolines were also shown to be effective substrates though a further reduction in pH to 3.5 was required accompanied by an increase in catalyst loading to 0.25 mol % was necessary for optimal yields/conversions to be realized. Indoles reacted well under the same conditions, though provided the corresponding indoline-1-carbaldehyde through reaction with formic acid. Removal of the formyl group could be achieved through basic hydrolysis.

**RHODIUM-CATALYZED TRANSNITRILATION OF ARYL BORONIC ACIDS WITH DIMETHYLMALONONITRILE**

![Diagram of the reaction between aryl boronic acids with DIMETHYLMALONONITRILE](image)

The synthesis of aryl nitriles via metal-catalyzed cyanation of aryl halides presents a pivotal methodology for these structurally important motifs though often suffers from issues such as use of toxic cyanide sources, and deactivation of the catalyst through binding of the cyanide anion to the metal. Reeves and co-workers have reported on a novel rhodium-mediated electrophilic cyanation of aryl boronic acids using dimethylmalononitrile (DMMN) as the cyanide source, which is a safe, bench-stable and commercially available reagent (Angew. Chem., Int. Ed. 2015, 10.1002/anie201508122). The key challenges presented here were not only in investigating the reactivity of DMMN the boronic acid, but also controlling the selectivity for the transnitritlation over the formation of aryl ketones. Model studies using phenylboronic acid as the substrate demonstrated that rhodium catalysis with K$_2$CO$_3$ as an additive were optimal for...
reactivity with a slight excess of the aryl boronic acid being utilized to overcome competitive proto-deborylation. Further studies on the additive indicated that this was critical for selectivity, and screening demonstrated that use of Cs₂CO₃ and an increase in temperature from 80 to 100 °C led to both the highest yields and selectivities. Several alternative dialkylmalononitriles also mediated the reaction, though those substituted with either cyclopropane or electron-withdrawing groups (in place of a nitrile) were ineffective in the reaction. A range of electron-rich and electron-deficient aryl and heteroaryl boronic acids were successful substrates with good functional group tolerance being shown. The reaction scope could also be extended to triﬂuoroborates and neopentylglycol aryl boronate esters in place of the aryl boronic acids, but failed for other commonly utilized boron-derivatives. A mechanistic hypothesis is provided suggesting the strength, desiccant ability, and solubility profile of the base are all important parameters in promoting formation of the desired aryl nitrile.

![ONE-STEP CONVERSION OF METHYL KETONES TO ACYL CHLORIDES](image)

The formation of acyl chlorides from arenes or heteroaranes can be achieved either through direct chlorocarbonylation, or through synthetic manipulations of products such as methyl ketones obtained from a Friedel-Crafts acetylation. Whereas the direct approach rarely gives high yields, the latter is attractive though suffers from several drawbacks including high dilution of the classical haloform reaction, formation of chlorinated byproducts as well as a large number of manipulations. Recognizing these issues, Zaragoza has reported on the direct conversion of a range of methyl ketones to the corresponding acyl chlorides using sulfur monochloride with a catalytic amount of pyridine (J. Org. Chem. 2015, 80, 10370). The initial conditions developed utilized an excess (4–6 equiv) of thionyl chloride to mediate the reaction with heating initially at 60–75 °C for some hours followed by heating to 140 °C for 15–20 h. Although somewhat effective, the use of an excess of thionyl chloride was a drawback, though was necessary to prevent the reaction mixture from solidifying, and use of solvents to prevent this led to a dramatic attrition in reaction rate. In addition for electron-rich methyl ketones, yields of over 70% were never observed due to formation of large amounts of insoluble materials. Based on previous observations that “aged” thionyl chloride appeared to be better suited to reactions with ketones than freshly distilled material, Zaragoza concluded that testing sulfur monochloride (a known decomposition product of thionyl chloride) for the reaction may lead to improved conditions. This proved to be the case with a broader range of substrates (including electron-rich and heteroaromatic cases) being effectively chlorinated, and a range of substituents tolerated on the aromatic nucleus. However, the major drawback of this protocol was the generation of the highly flammable CS₂ as a byproduct, which made this unsuitable for large-scale preparations. To circumvent this, sulfonyl chloride (or thionyl chloride) was added to the reaction mixture after the initial step of the reaction to chlorinate any precursors of CS₂. This led to a cleaner reaction and enabled the use of chlorobenzene as a solvent to prevent the reaction becoming viscous and difficult to stir. After evaporation of volatiles from the new protocol the only byproduct should be sulfur, which should not interfere in any downstream reactions of the desired products.

### CAN PALLADIUM ACETATE LOSE ITS “SALTINESS”? CATALYTIC ACTIVITIES OF THE IMPURITIES IN PALLADIUM ACETATE

Palladium acetate is an extremely popular catalyst for a number of organic transformations, which also finds use in the manufacture of a number of pharmaceuticals and agrochemicals. Utilizing the classical synthesis of this material, Pd₃(OAc)₅ can contain variable quantities of two impurities Pd₃(OAc)₅(NO₂) and polymeric [Pd(OAc)₃]ₙ which can be correlated to the concentration of NO₂ and water present. Colacot and co-workers have reported both on an improved method of synthesis for highly pure Pd₃(OAc)₅ involving ligand exchange of Pd₃(OPiv)₅, as well as carried out a systematic analysis of the catalytic ability of the pure material as well as the commonly found impurities across a range of common transformations (Org. Lett. 2015, 17, 5472). For a standard Buchwald–Hartwig amination, all three catalysts showed comparable activity, which is to some extent surprising given the insolubility of the polymer in many organic solvents. Interestingly, it was noted that the polymer readily dissolved at 100 °C when mixed with both the (S)-BINAP ligand, and the reacting amine. The scope of the reaction was evaluated across a series of amines and shown to be similar for all the catalysts though in the case of less reactive amines, a small amount of water needed to be added. For the Suzuki-Miyaura coupling, again all catalysts led to high conversion with the best results being obtained with Pd₃(OAc)₅(NO₂) possibly due to its greater solubility. For a ligandless, α-carbonyl arylation, the polymeric material displayed an inferior performance to the
The increasing sophistication of late-stage C–H fluorination methodologies present significant challenges for their employment to support large scale efforts. Workers at Merck have reported on the direct C–H fluorination of (S)-leucine to form (S)-γ-fluoroleucine, which is an essential structural component of the cathepsin K inhibitor, Odanacatib, under photochemical conditions (Org. Lett. 2015, 17, 5200). The initial process utilizes a decatungstate (TBADT) catalyst with N-fluorobenzenesulfonimide (NFSI) as the source of fluoride in a 2:1 mixture of CH$_2$CN/H$_2$O to minimize formation of the analogous chlorinated side product. High throughput experimentation utilizing a photochemical screening platform allowed simultaneous investigation of the amino-acid salt, catalyst loading and counterion, concentration and solvent composition. From these studies, it was determined that the bisulfate salt was the best with the sodium salt of the catalyst able to replace the more expensive tetrabutyl ammonium counterion. For scale-up, a residence time of 2 h with product purification being precipitation after azeotropic distillation with 2-MeTHF. The authors further provide a comparator of the new synthesis with the previously reported on the direct C–H fluorination of these substrates under copper-catalyzed conditions (J. Am. Chem. Soc. 2015, 137, 13902). Model studies indicated that copper iodide was the optimal copper source with a slight excess of TBACN as the ideal cyanide source. The reactions proceeded smoothly at ambient temperature in acetonitrile with loadings as low as 2.5% of catalyst possible. In addition, although the reaction was somewhat sensitive to air, it appeared to be relatively insensitive to moisture. From a scope perspective, a range of cyclic and acyclic secondary alkyl chlorides were successfully cyanated with a cyanide anion, though elevated temperatures, and side reactions often occur particularly with less reactive substrates such as unactivated secondary alkyl chlorides. Fu, Peters, and co-workers have reported on a photoinduced cyanation of these substrates under copper-catalyzed conditions (Org. Lett. 2015, 17, 5328). Model studies on the reaction of excess benzylic alcohol with p-TsNH$_2$ indicated that KOH was the most effective base to catalyze the reaction, with the observation that aldehyde byproduct generated from oxidation of the alcohol was also observed in the reaction mixture. Use of catalytic quantities of the base were possible if the direct amidation was carried out with the deprotonated sulfonamides with the potassium salts being observed to be the best for this purpose. Under these conditions, a range of sulfonamides were successfully alkylated with both benzylic and heteroaryl alcohols. Utilizing excess base, the reaction was then extended to the alkylation of anilines with both benzylic and the less active aliphatic alcohols. Deuterium labeling indicated a first-order kinetic isotope effect suggesting that C–H cleavage was the rate-determining. Based on this, a series of control experiments and react IR studies, a mechanistic hypothesis was generated involving the crucial initial oxidation to form the aldehyde to trigger the catalytic cycle (however, the observance of the aldehyde in a number of reactions confirms its existence as an intermediate as opposed to a catalyst) along with the intermediacy of a hemiaminal formed from an imine, which was not observed experimentally.

**Development of a Direct Photocatalytic C–H Fluorination for the Preparative Synthesis of Odanacatib**

![Image](image-url)

The reaction is depicted above with the following details:

- **Olefination**: The reaction between CH$_2$CN/H$_2$O and NFSI is catalyzed by TBADT, forming a mixture of CH$_2$CN/H$_2$O.
- **Fluorination**: The reaction proceeds with a residence time of 2 h, allowing for purification by precipitation after azeotropic distillation with 2-MeTHF.
- **Bisulfate Salt**: Sodium bisulfate is used as the most effective salt, with tetrabutyl ammonium counterion as the alternative.

**Direct Alkylation of Amines with Alcohols Catalyzed by Base**

- **Model Studies**: Studies with p-TsNH$_2$ and KOH indicated that KOH was the most effective base for the reaction.
- **Scope**: The reaction was successful with a range of cyclic and acyclic secondary alkyl chlorides.
- **Mechanistic Studies**: Mechanistic studies suggest a radical-based pathway, indicating the importance of oxidation in the reaction mechanism.

**Photoinduced, Copper-Catalyzed Carbon–Carbon Bond Formation with Alkyl Electrophiles: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature**

- **Copper Iodide**: Copper iodide was used as the optimal copper source with a slight excess of TBACN.
- **Model Studies**: Model studies indicated the importance of copper iodide, with a slight excess of TBACN as the optimal cyanide source.
- **Reaction Conditions**: The reactions proceeded smoothly at ambient temperature in acetonitrile with loadings as low as 2.5% of catalyst possible.

**Direct Amidation**: Amidation was carried out with deprotonated sulfonamides, with the potassium salts being observed to be the best for this purpose. Under these conditions, a range of sulfonamides were successfully alkylated with both benzylic and heteroaryl alcohols.
iridium-based photoredox catalysts to facilitate the transformation appears to support that the role of the copper extends beyond simple electron transfer.

**STABLE TEMPO AND ABNO CATALYST SOLUTIONS FOR USER-FRIENDLY (bpy)Cu/NITROXYL-CATALYZED AEROBIC ALCOHOL OXIDATION**

Recent developments in the Cu/nitroxyl catalyst systems have led to aerobic alcohol oxidation methods that rival the scope and selectivity of traditional oxidation methods though avoid many of the problems with waste generation. However, in terms of practicality particularly on small scale, these methods can be somewhat cumbersome involving weighing out four individual components often in milligram amounts. Stahl and Stevies have developed solutions to obviate this need for tedious solid weighing incorporating three key components of the catalyst systems into a single mixture, which can be easily dispensed followed by addition of solid [Cu(MeCN)4]OTf to perform the desired reactions (J. Org. Chem. 2015, 80, 11184). Attempts to mix all four components into either a solid or solution formulation led to decomposition and poor reproducibility of the reaction over time. For the first generation catalyst system for the oxidation of primary alcohols over secondary and sterically hindered primary alcohols, 0.2 M bpy, 0.2 M TEMPO, and 0.4 M NMI were combined in acetonitrile. For the second generation system for the oxidation of both primary and secondary alcohols, the methoxy-substituted bipy ligand was replaced by the parent bipy for solubility reasons with the solution consisting of 0.2 M bpy, 0.04 M ABNO, and 0.4 M NMI. The concentrations were selected to enable convenient dispensing with 2.5 mL of the solution being required for a 10 mmol reaction. As observed previously, a wide range of alcohols are smoothly oxidized with excellent functional group tolerance being observed. The solutions were stored under air in the refrigerator and displayed no loss in catalytic efficiency over storage for a one year period and are now commercially available from Sigma-Aldrich.

**METAL-FREE CATALYTIC C—H BOND ACTIVATION AND BORYLATION**

Compounds containing intramolecular frustrated Lewis pairs (FLPs) present Lewis acid and base moieties that cannot react among them due to steric impediment. Inspired by transition metal based methods for the C—H bond functionalization of heteroarenes, Fontaine and co-workers demonstrate that an FLP compound combining a borane and a hindered tertiary amine can catalyze the borylation of heteroarenes (Science 2015, 349, 6247). The (1-TMP-2-BH2)3– catalyst—TMP, 2,2,6,6-tetramethylpiperidine—was conceived to facilitate a close contact between the heteroarene nucleophilic carbon and the electrophilic BH3 moiety, and a concerted interaction between the basic amine and the proton to be abstracted. Mixing an excess heteroarene with HBpin and 2.5 mol % catalyst affords borylated furans, pyrroles, and electron-rich thiophenes with selectivities directed by the most nucleophilic carbon in the heteroarene. Control experiments demonstrate the existence of an intermediate heteroarene borylated by the catalyst, which undergoes exchange in the presence of HBpin. KIE and DFT studies support rate-determining transition structures that involve concerted deprotonation-borylation geometries.

![](image)

The generation of anisochronous chemical shifts by mixing a chiral analyte with chiral enantiopure species (solvents, metal complexes, Brensted acids, or bases) constitutes the foundation of chiral analysis using NMR spectroscopy. Researchers from two institutions in Korea report a general method for the analysis of charged molecules via ion pairing with Al(III) complexes in J. Am. Chem. Soc. 2015, 137, 14190. A hexadentate N2O4 ligand was rationally designed using a combination of first-principles and DFT calculations to create a chiral Al(III) octahedral complex that was isolated and characterized with the desired configuration. The Al(III) complex can be effectively used as a chiral solvating agent for positively and negatively charged analytes in polar and nonpolar solvents (e.g., CD3OD, CD3CN, CDCl3 or C6D6). 1H NMR spectra of a variety of racemic analytes could be resolved including compounds with stereo-centers located between the α and δ-positions of the charged functional group. For example, the acidic form of the Al(III) complex forms equimolar ionic adducts with rac-1-phenylethylamine that display well-defined doublets corresponding to the CH3 resonance. Similarly, mixing the Na salt of the Al(III) complex with 2-phenylpropiolic acid affords distinct doublets consistent with the CH3 resonance. The authors demonstrated the convenience of this methodology by expanding it to commercially available drugs containing basic and acidic functional groups.
Ag(I)-CATALYZED SYNTHESIS OF ANTI-1,2-HYDROXYBORONATES

The synthetic utility of secondary alkyl boronate esters has prompted an extensive search for catalytic methods that facilitate their preparation in high yields and stereoselectivities. Meek and co-workers at UNC-Chapel Hill report a new methodology for the synthesis of 1,2-hydroxyboronates in Angew. Chem., Int. Ed. 2015, 54, 14141. The process, which involves a deborylative 1,2-addition of alkyl 1,1-diborons to aldehydes, is catalyzed by a Ag(I) salt and requires excess base as stoichiometric activator (t-BuOK or n-BuLi). Thus, anti-1,2-hydroxyboronates can be obtained in good yields from a variety of functionalized 1,1-diboronates and aryl-, alkenyl-, and alkyl-substituted aldehydes in the presence of 10 mol % AgOAc and 1.3 equiv base. NMR spectroscopy investigations demonstrate that excess base mediates the formation of intermediate borates while AgOAc promotes their transmetalation to generate α-boryl alkyl silver species. The anti-selectivity can be explained in terms of standard stereochemical models that do not necessarily exclude the participation of the Ag(I) salt as an activator for the aldehyde.

COPPER-CATALYZED PENTAFULVENE CARBOMETALATION

The stability of cyclopentadienide-metal complexes complicates the development of organometallic catalytic additions to pentafulvenes because it prevents cycle restoration. The importance of advancing such transformations resides in the fact that metal complexes of enantioenriched cyclopentadienyls have multiple applications in catalysis and biology. Chemists at the University of Nottingham have described an asymmetric addition of dialkylzincs to the exocyclic bond of pentafulvenes catalyzed by Cu (Angew. Chem., Int. Ed. 2015, 54, 14179). Careful screening of reaction conditions using catalytic amounts of electron-deficient Cu(OTf)2 led to the discovery that mixtures of a chiral enantiopure phosphoramidite ligand and a racemic phosphoric acid additive could promote the carbometalations with ZnEt2 or ZnBu2 in acceptable enantioselectivities and rates. Control experiments indicate that the phosphoric acid additive is included in the catalytic species and mainly affects the turnover.
rates. Following this procedure, the authors prepared enantio-
merically pure Cp^R_2TiCl_2 complexes with cytotoxic in vitro
activities that were enantiomer-dependent.

**NICKEL-CATALYZED C−N BORYLATION OF
TRIMETHYLAMMONIUM SALTS**

The dimethylamino group, directly attached to an aryl ring or in
benzylic position, has found widespread use in site-selective
directed aromatic functionalization, but a general method to
transform this group into other functionalities hampers its wider
application in organic synthesis. Itami and co-workers from
Nagoya have recently addressed this issue by developing
conditions that allow the C-N borylation of the dimethylamino
group is first converted into the ammonium salt by
quaternarization with methyl triflate. It then undergoes easy
borylation with bis(pinacolatodiboron) in the presence of a
catalytic amount of nickel salt (Ni(cod)_2 or Ni(NO_3)_2
· 6H_2O depending on the nature of the substrate) and tri-
)n-butylphosphine. Sodium tert-butoxide was found to be the base
of choice in an ethereal solvent. The generality of the reaction has
not been investigated in great detail, but ketones, esters, and an
indole were demonstrated to be successful substrates under the
developed conditions. A handful of examples are also provided
involving the use of dimethylamino group as directing group
followed by its borylation and further manipulation of the newly
introduced reactive center.

**PALLADIUM-CATALYZED SYNTHESIS OF
PYRIDINES BY A HECK-TYPE REACTION
OF OXIME DERIVATIVES**

Pyridines are one of the most significant building blocks
which are present in pharmaceuticals, agrochemicals, and
functional material. Although a myriad of methods for
synthesizing this versatile scaffold exists, conceptually new
methods that allow their regioselective assembly continue to
be sought after. Jiang and co-workers from Gangzhou have
recently described the palladium-catalyzed Heck reaction of
oxime acetates with allylic alcohols as a new alternative to
synthesize pyridines and azafluorenones (Chem. Commun.
2016, 52, 84). Screening revealed that two metal sources (palladium
and copper acetate) were required for the reaction together
with potassium carbonate as base and acetonitrile as solvent.
A number of substituted oxime derivatives and allyl alcohols
are suitable substrates for this reaction allowing the assembly
of 2,3,5-trisubstituted pyridines in moderate-to-high yields.
Surprisingly, a small set of indanone oxime acetates led to the
formation of the corresponding azafluorenones under the same
conditions.

**THIOAMIDE SYNTHESIS BY ADDITION
OF ORGANOLITHIUM REAGENTS
TO ISOThIOcyanATES**

Thioamides constitute an important class of intermediates in
organic synthesis for which the current method of preparation
(direct or indirect thionation of carboxamide) are far from ideal
in terms of reactants, conditions, and yields. Holzer’ group from
Vienna have described an interesting alternative for the synthesis
of thioamide that relies on the nucleophilic addition of
organolithium reagents to isothiocyanates (Chem. Eur. J.
2015, 21, 18966). The best conditions simply involved the addition
of the lithium reagent on a solution of the isothiocyanate in
cyclopentyl methyl ether at 0°C for a few hours. An extremely
large variety of organolithium reagents (either commercially available or prepared by classical method such as lithium/halogen exchange or deprotonation) have been found to react with isothiocyanates in almost uniformly high yields. Worthy of note is that the procedure can be applied to the asymmetric synthesis of (almost) enantiopure thioamides by enantioselective deprotonation with sparteine.

**DIARYLKETONE SYNTHESIS BY PALLADIUM-CATALYZED CARBONYLATION WITH FORMIC ACID**

Reuter and co-workers reported the synthesis of a recyclable polyisobutylene-tagged iridium photocatalyst and its use in batch and continuous processes (Green Chem. 2016, 18, 214–219). Recyclability was achieved using a thermomorphic acetonitrile/heptane binary solvent system which occurs as a single phase above 84.6 °C. A continuous flow microreactor was devised to carry out the photocatalyzed isomerization of cinnamyl acetate to (Z)-3-phenylallyl acetate at 90 °C. Cooling of the product mixture resulted in two phases which were separated in-line; the heptane phase containing the iridium photocatalyst was recycled. Catalyst mass balance measurements revealed an initial loss in catalyst presumably due to dissolution of catalyst species containing short polyisobutylene chains in acetonitrile. The isomerization reaction also proceeded at ambient temperature under biphasic conditions at lower flow rates.

**METAL-FREE OXIDATIVE CROSS ESTERIFICATION**

De Luca and co-workers from Italy have recently described a one-pot two-step metal-free protocol for the oxidation of benzyl alcohols into esters (Adv. Synth. Catal. 2016, 358, 154). They employed trichloroisocyanuric acid as a cheap and non-toxic oxidant in dichloromethane as solvent to convert the benzyl alcohols into the corresponding acid chlorides. The latter are converted in situ to the ester by addition of an alcohol and a catalytic amount of DMAP. The reaction proved to be quite general but slow, 5 days being required at room temperature for the oxidation step. A tentative mechanism based on a radical pathway has been proposed by the author.

**CASCADE REACTIONS BASED ON IN SITU GENERATION OF N-ISOCYANATES**

Beauchemin and colleagues reported the development of a synthetic toolbox based on in situ generation of N-isocyanates (Chem. Sci. 2016, 7, 315–328). Upon irradiation with microwaves at high temperatures or addition of DBU at ambient temperatures, substituted phenyl carbazate precursors generated N-isocyanate intermediates which were reacted with amines or α-amino esters to generate a wide variety of heterocycles containing the N–N–C=O motif, which are prevalent in agrochemical and pharmaceutical products.
Alexanian and colleagues reported the site-selective chlorination of aliphatic C-H bonds using N-chloroamides and visible light under mild conditions (J. Am. Chem. Soc. 2016, 10.1021/jacs.5b12308). The sterically and electronically dictated site selectivities of the C–H chlorination gave useful chemical yields (up to 82%) with substrate as the limiting reagent. For instance, a short semisynthesis of chlorolissoclimide started with the high yielding, gram-scale selective chlorination of (+)-sclareolide by incorporation of a halogen-bearing stereogenic center of a natural product via a stereocontrolled C–H halogenation. Then a three-step/two-pot process for the introduction of the β-hydroxysuccinimide was followed towards target product. Remarkably, this free radical alkane chlorination approach tolerates substrate unsaturation that normally poses major challenges in chemoselective, aliphatic C–H functionalization.

Meggers and colleagues reported a visible light-activated iridium catalyzed carbon–carbon bond forming reaction to synthesize 1,2-amino alcohols with high enantioselectivities (91–99% ee) (Angew. Chem. Int. Ed. 2016, 55, 685–688). The reaction proceeds via single electron transfer (SET) from the donor (tertiary amine) to the Re face of the acceptor (trifluoromethyl ketone) and is initiated by coordination of the Lewis acidic iridium catalyst to the ketone.

Hao Xu and colleagues reported a novel catalytic method for the diastereoselective diazidation of functionalized and unfunctionalized olefins (Angew. Chem. Int. Ed. 2016, 55, 534–538). The diastereoselectivity of the reaction could be modulated by the counterion and the ligand of the catalyst. A mechanistic pathway was presented based on control experiments. The method was successfully applied to acetyl quinine and glycal substrates.

The innate reactivity of different C–H bonds within a single molecule can be used to selectively functionalize one carbon vs others. It may be advantageous, however, to modify this reactivity in order to functionalize the strongest C–H bond (i.e., of alcohols). With this objective in mind, and capitalizing on their expertise with photoredox catalysis, MacMillan and co-workers (Science 2015, 349 (6255), 1532–1536) showed that, by activating alcohols via hydrogen bonding with acceptors such as tetrabutylammonium phosphate, a strong (i.e., 92 kcal-mol)
C(sp³)–H bond can be selectively broken in the presence of other, weaker, C–H bonds.

Thus, under irradiation with blue light (catalytic cycle 1), the Bernhard photocatalyst \( \text{Ir}[\text{dF(CF}_3\text{)ppy}]_2(\text{dtbbpy})\text{PF}_6 \) (where \( \text{dF(CF}_3\text{)ppy} = 2-(2,4\text{-difluorophenyl})-5\text{-} (\text{trifluoromethyl})\text{pyridine}, \text{dtbbpy} = 4,4′\text{-di-tert-butyl-2,2′-bipyridine} \)) becomes excited to \( \text{Ir}[\text{dF(CF}_3\text{)ppy}]_2(\text{dtbbpy})^+ \). Reductive quenching of this complex via oxidation of quinuclidine generates the radical cation (catalytic cycle 2) that will abstract a hydrogen atom from the H-bond-activated alcohol (catalytic cycle 3) to afford an alpha-hydroxy radical and quinuclidinium ion. This nucleophilic radical will then add to the electron-deficient methyl acrylate, and single-electron reduction of the formed electron-deficient radical by \( \text{Ir}^{\text{II}} \), followed by re-protonation and lactonization, will regenerate both the photocatalyst and the quinuclidine.

A variety of lactones can be produced under these mild conditions in a two-step-one-pot procedure. The selectivity of this reaction is very high, allowing activation of \( \alpha \)-hydroxy C–H bond in the presence of potentially reactive allylic, benzylic, alkoxy, secondary C–H bonds.

**MITSUNOBU REACTIONS CATALYTIC IN PHOSPHINE AND A FULLY CATALYTIC SYSTEM**

The venerable Mitsunobu reaction has been of tremendous value over the past 30 years. However, this remarkable reaction presents different hurdles that somewhat prevents its use on large scale, i.e., a large amount of by-products generated (triphenylphosphine oxide and hydrazine carboxylate derivative) as well as hazardous azodicarboxylate reagents. A way to solve those issues has been recently disclosed by Aldrich and Buonomo (Angew. Chem., Int. Ed. 2015, 54, 13041–13044) utilizing a system catalytic in both phosphine and azodicarboxylate.

A first system, using a mild reducing agent (\( \text{PhSiH}_3 \)) and easy-to-reduce phosphine oxide in catalytic amount is described and shows reactivity and yield comparable to the stoichiometric version (except for benzylic alcohols, for which a \( \sim 20 \% \) decreased in yield was observed, due to competitive reduction of benzyl alcohol by \( \text{PhSiH}_3 \)).

Then, the search for a fully catalytic system was pursued. The main difficulty was the seemingly incompatible existence of two catalytic cycles with opposite requirements in the same pot, i.e., a reductive system for the phosphine oxide-to-phosphine transformation plus an oxidative system for the hydrazine-to-azo conversion.

By using a combination of the above reductive conditions with a mild oxidative system (based on Tanigushi’s iron (II) phthalocyanine \( \text{Fe(Pc)} \) in the presence of \( \text{O}_2 \) or hypervalent iodine \( \text{PhI(OAc)}_2 \)) the two catalytic cycles are compatible, and provide the first fully catalytic Mitsunobu reaction. The addition of 5 Å MS was also beneficial for the reaction system.

Compared to the “classical” conditions of Mitsunobu’s reaction (stoichiometric amounts of triphenylphosphine and diazodicarboxylate), the fully catalytic system needs a longer reaction time (48 h) and higher temperature (70°C).

Although amenable to improvements, the work presented here represents a sustainable, safe, and economic alternative to the Mitsunobu’s reaction.

**GRAPHENE AND GRAPHENE-LIKE MOLECULES IN SOLAR CELLS**

This Perspective (J. Am. Chem. Soc. 2016, 138, 10.1021/jacs.5b10917) collects evidence from research over the years with regard to the application of graphene and graphene-like molecules in solar cells. Graphene was constantly hyped as a game-changer for flexible transparent displays. However, compared with transparent and conducting metal oxides (such
as indium tin oxide), graphene may not have competitive advantages in power conversion efficiency (PCE). Instead of replacing silicon-based photovoltaics, it is more realistic to consider graphene as a performance enhancer in these devices. The unique strength of graphene lies in its ability to perform various enabling roles in solar cell architectures, leading to overall improvement in PCE. For instance, graphene can serve as an ultrathin and transparent diffusion barrier in solar cell contacts, as an intermediate layer in tandem solar cells, and as an electron acceptor. Inspired by the properties of graphene, chemists are also learning about the design principles in graphene-like molecules (bottom-up synthesis) that can afford strong light harvesting and efficient exciton separation with diverse and tailor-made structural motifs for various functions. An ideal flexible solar cell is supposed to consist of a photoactive layer made from graphene-like molecules for absorption and exciton generation, and hole or electron transport layers made from solution processed graphene, as well as a flexible, large-area graphene electrode for final integration.

### PROTON-PROMOTED AND ANION-ENHANCED EPOXIDATION OF OLEFINS BY HYDROGEN PEROXIDE IN THE PRESENCE OF NONHEME MANGANESE CATALYSTS

![Reaction Scheme](image)

An unexpected novel effect of sulfuric acid (1–3 mol %, instead of carboxylic acid) in the catalytic asymmetric epoxidation of olefins by aqueous H₂O₂ catalyzed by a nonheme manganese complex bearing a tetradentate N₄ ligand was reported by W. Nam et al. (J. Am. Chem. Soc. 2016, 138, 10.1021/jacs.5b11579). As shown in the graphic, the presence of H₂SO₄ dramatically increased the yields of epoxide products as well as the chemoselectivity and enantioselectivities under the catalysis of a mononuclear nonheme manganese complex bearing a tetradentate N₄ ligand, Mn(II)(Dbp-MCP)(OTf)₂; no formation of epoxides was observed in the absence of H₂SO₄. It was found that product yields and enantioselectivities (up to 90% yield and 98% ee) of this catalytic epoxidation of olefins were similar to those obtained when using other oxidants such as peracids, alkyl hydroperoxides, and iodosylbenzene, but dependent on the manganese catalysts and Bronsted acids. This suggested that a common epoxidizing intermediate, a high-valent manganese-oxo species, was generated in the reactions of [Mn(II)(Dbp-MCP)]²⁺ and the oxidants, which was further proved by using ¹⁸O-labeled water (H₂¹⁸O) and cumyl hydroperoxide in the following mechanistic studies. The roles of H₂SO₄ namely, both the proton and SO₄²⁻ anion, were proposed to facilitate the formation of the Mn-oxo species via heterolytic O−O bond cleavage of a presumed Mn(III)−OOH precursor and to increase the oxidizing power and enantioselectivity of the Mn-oxo epoxidation reactions.

### ENANTIOSELECTIVE HYDROSILYLATIONS OF 1,2-DICARBONYL COMPOUNDS BY CHIRAL FRUSTRATED LEWIS PAIRS

![Hydrosilylation Reaction](image)

A highly enantioselective hydrosilylation of 1,2-dicarbonyl compounds was recently reported under the catalysis a frustrated Lewis pair catalyst, which was the combination of tricyclohexylphosphine and alkenylborane derived in situ from chiral diyne (H. Du et al., J. Am. Chem. Soc. 2016, 138, 10.1021/jacs.5b13104). As shown in the graphic, a variety of optically active α-hydroxy ketones and esters were obtained in 52−98% yields with 96%−99% ee’s. This catalytic hydrosilylation system can be further extended to α-keto esters to give the desired α-hydroxy esters in excellent yields and ee’s. Moreover, no diol byproducts were observed although 3 equiv of PhMe₂SiH were used. It is worthwhile to mention that chiral diyne exhibited a clear advantage over chiral diene in the hydrosilylation.

### CONVERSION OF CO₂ FROM AIR INTO METHANOL USING A POLYAMINE AND A HOMOGENEOUS RUTHENIUM CATALYST

A highly efficient homogeneous catalyst system for the production of CH₃OH from CO₂ and H₂ using pentaethylenehexamine and Ru-Macho-BH at 125–165 °C in an ethereal solvent has been developed recently (G. A. Olah et al., J. Am. Chem. Soc. 2016, 138, 10.1021/jacs.5b12354). The high efficiency of this catalytic system was reflected by an initial turnover frequency of 70 h⁻¹ at 145 °C, as well as a turnover number of >2000 by recycling the catalyst over five runs without significant loss of activity. Various sources of CO₂ including air, despite its low CO₂ concentration (400 ppm), could be directly converted to CH₃OH in 79% yield through this catalysis. Another advantage is that a simple distillation from the reaction mixture could conveniently separate the desired CH₃OH product. In addition, continuous production of CH₃OH can be achieved by implementing this method in a flow system.

### ANHYDROUS TETRAMETHYLAMMONIUM FLUORIDE FOR ROOM-TEMPERATURE S_N_Ar FLUORINATION

Fluorinated arenes and heteroarenes are finding increasing application in agrochemicals and pharmaceuticals. One common synthetic technique for the industrial preparation of aryl and heteroaryl fluorides is nucleophilic aromatic fluorination, S_N_Ar. Typically, high temperatures and long reaction times are required, due to the poor solubility of the fluorinating species. Sanford and co-workers at the University of Michigan and Dow Chemical reported the utilization of anhydrous tetrakis(dimethylamino)fluoride (NMMe₄F) as a superior reagent for S_N_Ar reactions (J. Org. Chem. 2015, 80, 12137). The reagent was readily prepared from inexpensive, commercially available raw
materials and was rigorously dried. The SNAr reactions were typically performed at room temperature in DMF solvent. Generally, high yields were obtained, due to lower byproduct formation as a result of the mild reaction conditions. Water was shown to have a deleterious effect on the conversion. The relative rate of displacement were NO2 >> Br > Cl > I >> OTf. Cost calculations indicated that anhydrous NMe4F was more cost-effective than CsF for difficult fluorinations.

### PALLADIUM ACETATE CATALYZED, SILVER ACETATE PROMOTED Z-SELECTIVE DIRECTED β-ARYLATION OF ACRYLAMIDE SYSTEMS AND STEREOSELECTIVE CONSTRUCTION OF Z-CINNAMAMIDE SCAFFOLDS

Cinnamamide derivatives represent an important class of biologically active compounds, exhibiting diverse indications in both agrochemicals and pharmaceuticals. These compounds are also utilized as building blocks for assembling heterocyclic compounds, such as quinolones. Typical synthetic procedures afford the cinnamamides with the E geometry as the major isomer. Babu and co-workers at the Indian Institute of Science Education and Research disclosed a palladium catalyzed synthesis of cinnamamides which affords the Z isomer predominately (J. Org. Chem. 2015, 80, 12379). This reaction was catalyzed by palladium acetate, mediated by silver acetate and directed by the bidentate ligand 8-aminoquinoline (Q). Aryl and heteroaryl iodides were demonstrated as the coupling partner. Replacement of silver acetate with potassium carbonate in the reaction reversed the predominate product to the thermodynamically preferred E stereochemistry. The method-ology was extended to the preparation of β,β-diarylated acrylamide derivatives. The reaction was compatible with various functional groups on the aryl iodide, including: nitro, ether, fluoro, chloro, and bromo.

### DIRECT BORYLATION OF BENZYL ALCOHOL AND ITS ANALOGS IN THE ABSENCE OF BASES

Organoboron compounds are valuable as key ingredients in the Suzuki–Miyaura coupling reaction. The preparation of benzylboron moiety typically requires either a strong base or the prior activation (halogenation, sulfonation, etc.) of the corresponding arylmethanol. Shi and co-workers at Peking University reported a reliable method to synthesize arylmethylboronic acid esters from commercially available arylmethanols under mild conditions (Org. Chem. Front. 2015, 2, 1505). This Miyaura type borylation reaction was catalyzed by palladium acetate, and the preferred ligand was bis(dicyclohexylphosphino)ferrocene (DCPF). Only bis(pinacolato)diboron was an effective borylating agent in this reaction. The addition of titanium isopropoxide was required to convert substituted benzenemethanols into the corresponding benzylboronate ester. This additive was not required with more complex aromatic substrates.

### CHEMOSELECTIVE SYNTHESIS OF 1-SUBSTITUTED 4-AMINO-2-(TRIFLUOROMETHYL)-1H-PYRROLES THROUGH THE HETEROCYCLIZATION REACTION OF 4-METHOXY-5-BROMO-1,1,1-TRIFLUOROPENTANE-3-EN-2-ONES WITH AMINES

The pyrrole moiety is an important heterocyclic scaffold which is frequently found in natural products, pharmaceuticals, and functional materials. The 2- or 5-substituted pyroles are easily synthesized by electrophilic aromatic substitution; however, the 3- and 4-substituted motifs are less accessible. Zanatta and co-workers from the Universidade Federal De Santa Maria described a novel, chemoselective one-pot synthesis of N-substituted 4-amino-2-(trifluoromethyl)pyrroles via an intramolecular cyclization (J. Org. Chem. 2015, 80, 12453). The starting material was synthesized via allylic bromination of the enone. The methoxy group was displaced with a primary or secondary amine under mild conditions. Reaction with a primary amine under solvent-free conditions afforded the corresponding pyrrole chemoselectively in good-to-excellent yields.

### SYNTHESIS OF [18F]-ARENES VIA COPPER-MEDIATED [18F]-FLUORINATION OF BORONIC ACIDS

The growing prevalence of fluorine in pharmaceutical scaffolds also affords rich opportunities for the simultaneous development of PET radiotracers as companion diagnostics. The development of new 18F radiotracers is complicated by the limited number of reactions available for the introduction of 18F into bioactive molecules, particularly on electron-rich aromatic rings. Sanford, Scott, and co-workers at the University of Michigan disclosed a
mild, copper-mediated radiofluorination of aryl- and vinylboronic acids with K\textsuperscript{18}F which afforded high radiochemical conversion (RCC) (\textit{Org. Lett.} \textbf{2015}, \textit{17}, 5780). Copper (II) triflate was identified as the most effective catalyst; pyridine was an essential component for the reaction, and DMF was the preferred solvent. The reaction was compatible with aryl, heteroaryl, and vinyl boronic acid substrates. Further, the radiofluorination of boronate esters and potassium trifluoroborates was demonstrated. This synthetic methodology fills an important gap in the late stage fluorination space.

\section{Lewis Acid Catalyzed Synthesis of \(\alpha\)-Trifluoromethyl Esters and Lactones by Electrophilic Trifluoromethylation}

The introduction of a trifluoromethyl group at an enolizable position of carbonyl compounds significantly alters their physicochemical properties. There are a relatively limited number of synthetic methods to construct a trifluoromethylated quaternary carbon adjacent to a carbonyl center, so new methodology is of interest. Togni and co-workers at the ETH Zürich reported an operationally simple and highly efficient method for the \(\alpha\)-trifluoromethylation of substituted ester- and lactone-derived ketene silyl acetals (\textit{Org. Lett.} \textbf{2015}, \textit{17}, 5898). The hypervalent iodine-(III)-CF\textsubscript{3} reagent, 1, served as a convenient source of the trifluoromethyl group. A catalytic amount of a Lewis acid, for instance trimethylsilyl triflimide (TMSNTf\textsubscript{2}), was beneficial. Methylene chloride was identified as the preferred solvent. Isolated double bonds and aromatic substituents were not impacted by the reaction. Generally good yields were observed across a range of ester and lactone derived ketene silyl acetals.

\section{Nickel-Catalyzed Reductive Cross-Coupling of (Hetero)aryl Iodides with Fluorinated Secondary Alkyl Bromides}

The trifluoromethyl group (\(-\text{CF}_3\)) is of paramount importance in the discovery of new bioactive molecules and advanced functional materials owing to its strong electron-withdrawing ability and high lipophilicity. While much attention has been devoted to the preparation of trifluoromethylated aromatic compounds, limited attention has been paid to the development of trifluoromethylated aliphatic compounds with a \(-\text{CF}_3\) substituted tertiary carbon center. Jiang at Wuhan University and Zhang at the Shanghai Institute of Organic Chemistry and their co-workers have detailed a mild and efficient nickel-catalyzed reductive cross coupling of fluorinated secondary alkyl bromides and (hetero)aryl iodides (\textit{Org. Lett.} \textbf{2015}, \textit{17}, 5570). The catalyst system was optimized to 5 mol\% NiCl\textsubscript{2}·DME, 6 mol \% 2,2′-bipyridine (bpy). The addition of 0.4 equiv of FeBr\textsubscript{2} promoted the desired cross coupling reaction and expanded the substrate scope. Good-to-high yields of the desired coupling product were obtained, irrespective of the electronic nature of the aryl iodide. The reaction exhibited excellent functional group compatibility, including: ester, ketone, nitrile, hydroxyl, phenol, aniline, and halide.

\section{Palladium-Catalyzed Cyclization for Synthesis of Tricyclic [3.2.1] Bridged Compounds}

Natural products containing bridged [3.2.1] carbocyclic moiety show attractive biological activities. Synthesis of such tricyclic bridged [3.2.1] compounds remains challenging, and only a limited number of synthetic methods are available in the literature. Researchers of Tsinghua University, Beijing, China developed a one-pot approach for access to these bridged compounds (G. Liu, et al. \textit{Org. Lett.} \textbf{2015}, \textit{17}, 4110). The Tsinghua researchers designed a cascade process involving a bridged palladacycle intermediate which would undergo reductive elimination to afford the desired tricyclic product after in situ removal of allyl group. CuCl\textsubscript{2} plays dual roles: to oxidize Pd(0) to Pd(II) and to act as chloride source. The reaction is sensitive to reaction solvents, and THF proved to be the solvent of choice.

\section{Stereospecific Cross-Coupling Reaction of Boronic Esters with N-Heteroarenes}

The trifluoromethyl group (\(-\text{CF}_3\)) is of paramount importance in the discovery of new bioactive molecules and advanced functional materials owing to its strong electron-withdrawing ability and high lipophilicity. While much attention has been devoted to the preparation of trifluoromethylated aromatic compounds, limited attention has been paid to the development of trifluoromethylated aliphatic compounds with a \(-\text{CF}_3\)
Functionalization of pyridine rings has attracted great attention. Alkylation (arylation) of an electron-deficient pyridine via transition metal-catalyzed cross-coupling reaction such as Suzuki–Miyaura reaction presents challenges due in part to the instability of pyridyl boronic acids and the chelating effect of the pyridine nitrogen. Aggarwal and coworkers of University of Bristol, Bristol, UK developed a transition metal-free synthesis for access to alkylated (or arylated) pyridine derivatives (V. K. Aggarwal, et al. J. Am. Chem. Soc. 2015, 137, 10958). The new methodology of Csp²−Csp³ (or Csp²−Csp²) cross-coupling involves six steps: formation of 4-lithiopyridine via I-Li exchange, reaction of the resulting 4-lithiopyridine with alkyl (or aryl) boronic ester to form an ‘ate complex’, activation of the complex by TrocCl, 1,2-migration, and oxidation/hydrolysis. Without isolation of intermediates, the reaction gave the corresponding cross-coupling products in good yields and complete stereospecificity (with R being the chiral group). In addition, this methodology could be extended to quinoline and isoquinoline.

SYNTHESIS OF CYCLOPROPANES VIA NICKEL-CATALYZED STEREOSELECTIVE REDUCTIVE CROSS-ELECTROPHILIC COUPLING REACTIONS

A nickel-based catalyst system has become one of the active research areas that are under extensive investigations. As inexpensive alternatives to palladium catalysts, Ni catalysts present unique reactivity patterns, thereby provide advantages over palladium-based catalysis system. For example, Ni catalysts are playing a critical role in developing reductive cross-electrophile coupling reactions due primarily to the reduced propensity for β-hydride elimination. Substituted cyclopropanes are important organic compounds found in many natural products and medicinal agents. Jarvo and her coworkers of University of California revealed a Ni-catalyzed cyclopropane synthesis (E. R. Jarvo, et al. J. Am. Chem. Soc. 2015, 137, 9760). The stereospecific reductive cross-electrophile coupling reaction of 2-aryl-4-chloro-tetrahydropyrans afforded disubstituted cyclopropanes. The Grignard reagent acts as a reducing agent to effect the Ni catalyst turnover. This new methodology appears to be amenable for large-scale preparations.

RADICAL OXYFUNCTIONALIZATION OF ALKENES TO ACCESS OF CHIRAL LACTONES

Chiral γ- and δ-lactones are valuable compounds and present in a large number of biologically active molecules. In addition to the existing literature methods, Buchwald and his coworker of Massachusetts Institute of Technology, Cambridge, Massachusetts, developed a new synthetic strategy, allowing to access various functionalized lactones (S. L. Buchwald, et al. J. Am. Chem. Soc. 2015, 137, 8069). Depending on the reaction conditions, the following enantioselective functionalizations of alkenes could occur:

1. Oxyazidation (Cu(MeCN)₃PF₆/L, 5%)/PhI(OAc)₂ (2.5 equiv)/TMSCI (2.4 equiv))

2. Oxsulfonylation ((Cu(MeCN)₃PF₆ (10%)/L, 10%)/AgOAc or Ag₂CO₃)

3. Oxyarylation ((Cu(MeCN)₃PF₆ (10%)/L, 10%/DTBP)

4. Oxytrifluoromethylation ((Cu(MeCN)₃PF₆ (7.5%)/L (7.5%))

It was proposed that the C−O bond formation involves two stages: the radical addition to Cu(II) to form a Cu(III) complex, followed by reductive elimination. It was assumed that the Cu−C bond formation between Cu(II) and the prochiral allyl radical is the enantiodetermining step as the reductive elimination is generally a rapid process.

CHIRAL PYRIDOXAL-CATALYZED ASYMMETRIC TRANSAMINATION OF α-KETO ACIDS

Previously, pyridoxal/pyridoxamine-based biomimetic asymmetric transamination of α-keto acids had been carried out using stoichiometric chiral pyridoxamines as the amine sources. Such asymmetric transamination has limited applications due to the use of the expensive chiral pyridoxamine in stoichiometric amounts. Recently, a report (B. Zhao, et al. Org. Lett. 2015, 17, 5784) revealed a chiral pyridoxal-catalyzed asymmetric transamination of α-keto acids, which avoided the use of stoichiometric amounts of chiral pyridoxamine analogues. Mechanistic investigations suggest that the protonated pyridoxamine serves as the resting state of the catalyst. The presence of water is crucial for the success of the reaction. Under optimal
conditions, various \( \alpha \)-keto acids were successfully converted to their corresponding \( \alpha \)-amino acids, except \( \beta \)-substituted keto acids which may be due to steric hindrance.

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