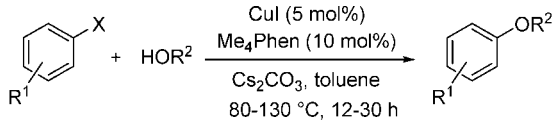
Organic Process Research & Development **2008,** *12,* 358–368

Highlights from the Literature

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

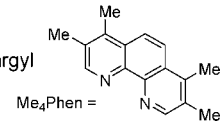
An Improved Cu-Catalyst System for the Synthesis of Aryl Ethers



X = I, Br

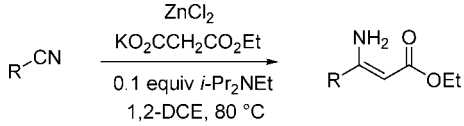
R^2 = 1° and 2° alkyl, benzyl, allyl, propargyl

23 examples, 59-99% yield



The Buchwald group provides a detailed account of their continuing studies on the metal-catalyzed formation of carbon−heteroatom bonds (*J. Org. Chem.* **2008**, *73*, 284−286). Using Pd-based catalysts, the low yields observed in the coupling of certain substrates have been attributed to the slow rate of C−O reductive elimination relative to β-hydride elimination from the $L_nPd^{II}(Ar)(alkoxide)$ intermediate. In these cases, Cu-based catalyst systems can provide complementary reactivities, as the analogous intermediates derived from these catalysts do not readily undergo β-hydride elimination reactions. The use of 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4-Phen) as a ligand improves the Cu-catalyzed cross-coupling reactions of aryl iodides and bromides with primary and secondary aliphatic, benzylic, allylic, and propargylic alcohols. Most importantly, by employing this catalyst system, the need to use an excessive quantity of the alcohol coupling partner is alleviated. The relatively mild conditions, short reaction times, and moderately low catalyst loading allow for a wide array of functional groups to be tolerated on both the electrophilic and nucleophilic coupling partners.

The Decarboxylative Blaise Reaction

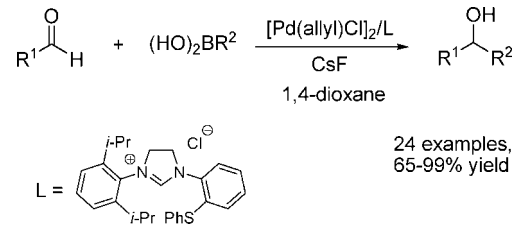


R = aryl, heteroaryl, cyclopropyl

12 examples, 0-86% yield

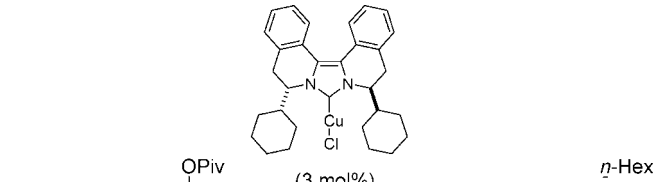
Shin and co-workers in the Chemical Development Division at LG Life Sciences describe a variant of a classical transformation known as the Blaise reaction (*J. Org. Chem.* **2007**, *72*, 10261−10263). Originally, this reaction was conducted between Reformatsky reagents (prepared by zinc insertion into bromoacetates) and nitriles. The current method intercepts the same type of nucleophilic organozinc species via decarboxylation of potassium ethyl malonate in the presence of zinc salts. Although simple on paper, detailed investigations revealed the reaction profile is strongly dependent upon solvent, choice of zinc salt, and water content of the system. The optimal conditions employ dry (<30 ppm H_2O) 1,2-DCE, zinc chloride, and a catalytic amount of Hunig's base. The reaction works best with electron-poor aryl nitriles and fails completely with alkyl nitriles.

Efficient Pd-Catalyzed 1,2-Addition of Arylboronic Acids to Aldehydes



Variants of the Rh-catalyzed 1,2-addition of arylboronic acids to aldehydes have been reported by several groups. Now Kuriyama, Shirai, and co-workers report on a Pd-catalyzed version of this reaction, which can proceed using relatively low catalyst loadings (*J. Org. Chem.* **2008**, *73*, 1597−1600). Specifically, the researchers found that heterobidentate thioether−imidazolinium ligands confer desirable catalyst properties for this particular transformation. In contrast, the widely applicable isopropyl-substituted imidazolinium carbene ligand afforded only 8% yield for this reaction. Optimal conditions employ 1.5 equiv of arylboronic acid, 2 equiv of CsF as the base, and 1,4-dioxane as solvent at 80 °C. Aryl-, heteroaryl-, and alkenylboronic acids add to aromatic, heteroaromatic, and aliphatic aldehydes using this system. There are 24 examples with yields ranging from 65−99%.

Biisoquinoline-Based Chiral Diaminocarbene Ligands



In another report on the use of carbene-type ligands, Hong and co-workers describe an enantioselective S_N2' allylic alkylation reaction that is catalyzed by Cu complexes (*J. Org. Chem.*

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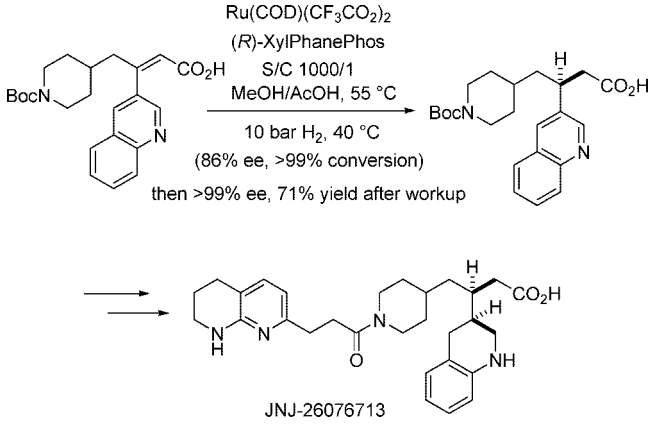
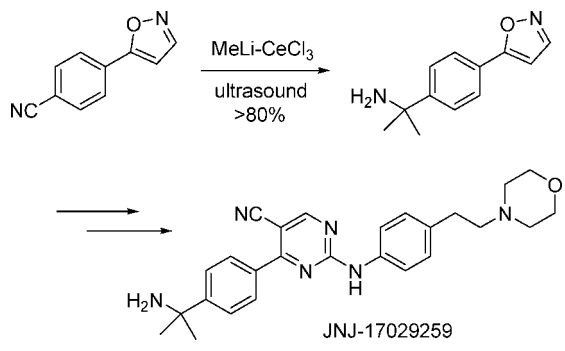
2008, *73*, 1983−1986). The authors report the synthesis of a family of chiral biisoquinoline-based diaminocarbene ligands (BIQ) that were designed to create a chiral environment extended toward the metal center. The solid-state structure of a Pd complex with one of these ligands was determined via X-ray crystal structure analysis, and the span of the chiral environment around the metal was confirmed. The cyclohexyl-BIQ−copper complex was shown to be a catalyst for the enantioselective S_N2' allylic alkylation with Grignard reagents showing S_N2' regioselectivity higher than 5:1 and enantioselectivity in the range of 68−77% ee.

Enantioselective Synthesis of an Integrin Antagonist



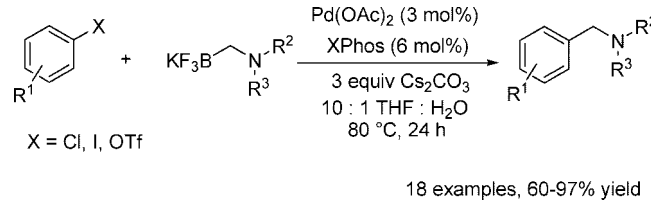
An enantioselective synthesis of an integrin antagonist JNJ-26076713 is reported by Kinney and co-workers at Johnson and Johnson (*J. Org. Chem.* **2008**, *73*, 2302−2310). Key to the overall strategy was the preparation of a stereodefined, quinoline-substituted, trisubstituted unsaturated acid via a Suzuki-Miyaura cross-coupling. Access to this substrate facilitated exploration of multiple methods of asymmetric reduction. The catalytic chiral hydrogenation of this unsaturated acid with a ruthenium-based metal precursor and the (*R*)-XylPhanePhos ligand proved particularly efficient and economical. The resulting (3*S*)-quinoline-bearing intermediate was reduced to an equal mixture of tetrahydroquinoline diastereomers. The undesired diastereomer could be recycled to the desired one by an oxidation/reduction protocol. The absolute stereochemistry was established as 3*S*,3′*S* by a combination of X-ray diffraction and chemical means.

Ultrasound-Mediated Addition of MeLi−$CeCl_3$ to a Nitrile



Also from the Johnson and Johnson laboratories, Reuman and co-workers describe their preparation of a selective VEGF-R2 kinase inhibitor (JNJ-17029259) (*J. Org. Chem.* **2008**, *73*, 1121−1123). A key synthetic intermediate, 4-(5-isoxazolyl)-benzonitrile, undergoes clean transformation to the corresponding cumylamine derivative when treated with $CeCl_3$−MeLi in THF at −70 °C. The sensitive nature of this type of cerium-mediated process is well-known and generally attributable to hydration state and physical properties of the $CeCl_3$ employed. In this report the authors detail a procedure in which commercial anhydrous $CeCl_3$ beads are milled before use and then subjected to sonication during dissolution in THF. The process was scaled to provide 80 g of product (5 L reaction vessel) per batch, consistently obtaining >80% yield.

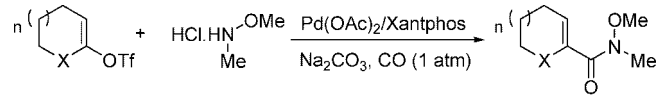
Aminomethylation via Suzuki−Miyaura Cross-Coupling of Organotrifluoroborates



18 examples, 60-97% yield

Following up on several communications on this topic, the Molander group now provides a full account of the scope of the Pd-catalyzed Suzuki−Miyaura aminomethylation reaction using trifluoroborate reagents (*J. Org. Chem.* **2008**, *73*, 2052−2057). Aryl chlorides, iodides, and triflates coupled in good to excellent yields to give *N,N*-dialkylbenzylic amines. Phenyl tosylate did not cross-couple under the standard conditions. A limited selection of alkenyl bromides participated with reasonable efficiency. Overall, the paper provides 18 successful examples with yields ranging from 60−97%.

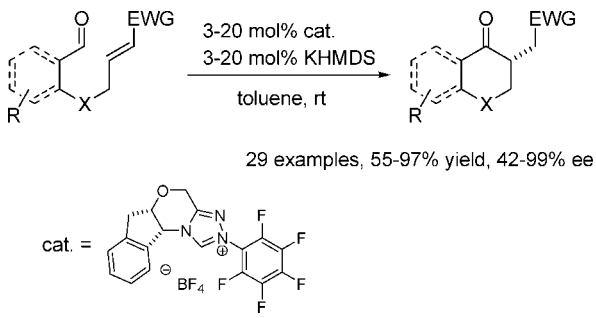
Synthesis of Weinreb Amides via Pd-Catalyzed Aminocarbonylation



13 examples, 50-90% yield

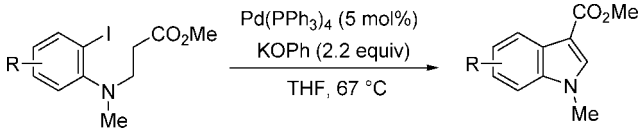
The direct transformation of lactam-, lactone-, and thiolactone-derived triflates into *N*-methoxy-*N*-methyl or morpholine Weinreb amides is reported by the Prandi group in Italy (*J. Org. Chem.* **2008**, *73*, 1941−1945). The optimized process operates at room temperature under 1 atm of carbon monoxide in the presence of 2 mol % $Pd(OAc)_2$/2 mol % Xantphos. The resultant amides react smoothly with organometallic nucleophiles to afford acylated aza-, oxa-, and thio-heterocycles. The authors note in particular that this method could be exploited for the synthesis of heterocycle-bearing dienones, potentially useful as substrates for Nazarov cyclization; recent reports of asymmetric Nazarov cyclizations could prove even more interesting in this regard.

Scope of the Asymmetric Intramolecular Stetter Reaction



The Rovis group at Colorado State provide a full account of the scope of the enantioselective intramolecular Stetter reaction of aromatic and aliphatic aldehydes catalyzed by nucleophilic triazolinylidenes (*J. Org. Chem.* **2008**, *73*, 2033−2040). Two triazolium scaffolds were identified that catalyze the intramolecular Stetter reaction with good reactivity and enantioselectivity. The substrate scope was examined and found to be fairly broad; both electron-rich and -poor aromatic aldehydes undergo cyclization in high yield and enantioselectivity. The tether can include oxygen, sulfur, nitrogen, and carbon linkers with no detrimental effects. In addition, the Michael acceptor component can comprise amides, esters, thioesters, ketones, aldehydes, and nitriles. The catalyst loading may be reduced to 3 mol % without significantly affecting the reactivity or selectivity of the reaction.

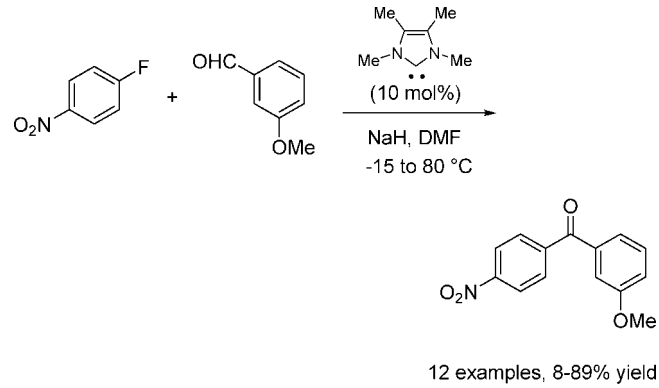
Synthesis of Indole-3-carboxylic Acid Derivatives



The Solé group reports on the synthesis of indole-3-carboxylic acid derivatives via a Pd-catalyzed α-arylation process (*J. Org. Chem.* **2008**, *73*, 2476−2479). *β*-(2-Iodoanilino) esters undergo intramolecular α-arylation in the presence of $Pd(PPh_3)_4$ and potassium phenoxide. The use of KOPh as an additive is significant in determining the outcome of the process since in the absence of this base, the initial product of oxidative insertion undergoes direct reaction with the ester carbonyl to yield a 2,3-dihydroquinolin-4-one. The researchers reasoned that addition of a basic species would serve to enolize the ester, but the potential for elimination of the aniline fragment via an E1cB mechanism steered them from the use of stronger bases such as KO*t*Bu. Depending on the substrate, indolines can sometimes be isolated from this reaction, but in most cases these convert directly to indoles under the reaction conditions.

N-Heterocyclic Carbene-Catalyzed Nucleophilic Aroylation of Fluorobenzenes

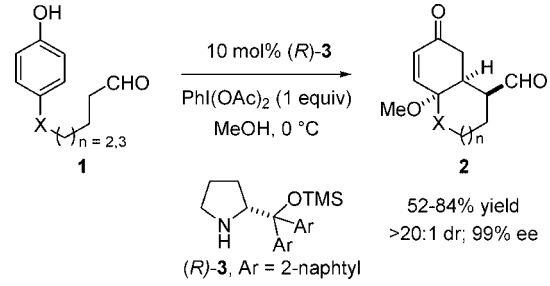
Suzuki and co-workers report on a nucleophilic aromatic substitution reaction that is catalyzed by N-heterocyclic carbenes (NHCs) (*J. Org. Chem.* **2008**, *73*, 2420−2423). Proceeding via a mechanism similar to that exploited in the previous Highlight, NHCs can facilitate polarity reversal in aromatic aldehydes to generate C-nucleophiles that can displace fluoride from certain activated fluorobenzenes. The optimal NHC catalyst was



determined to be 1,3,4,5-tetramethylimidazol-2-ylidene, which can function at 1 mol % loading without a significant decrease in the product yields. Several polysubstituted benzophenones were synthesized in yields ranging from 8−89%.

Catalytic Oxidative Dearomatization

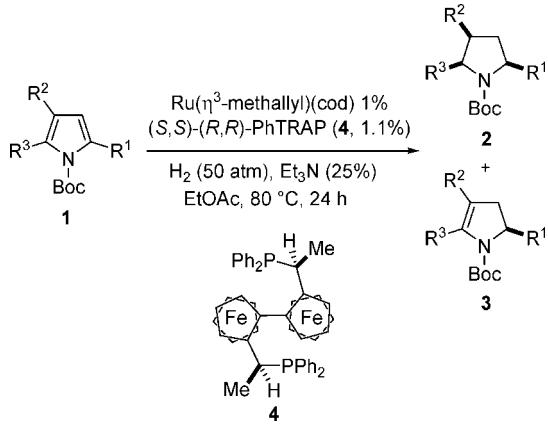
The group of Dr. Matthew Gaunt at the University of Cambridge reported a catalytic method for the enantioselective conversion of *para*-substituted phenols into bicyclic cyclohexanones via oxidative dearomatization followed by amine-catalyzed Michael reaction (*J. Am. Chem. Soc.* **2008**, *130*, 404−405). The protocol requires a rapid oxidation of the phenol ring without affecting the aldehyde moiety. Hypervalent iodine reagent $PhI(OAc)_2$ facilitates the selective oxidation of phenols to *meso*-cyclohexanediones, while MeOH plays the role of solvent and nucleophile in the dearomatization step. Additional tuning of the reaction included the selection of proline catalyst (*R*)-**3**, which displays a hindered nitrogen atom shielded from potential oxidation. Using the optimized conditions, oxidation of **1** with of $PhI(OAc)_2$ (1 equiv) and 10 mol % (*R*)-**3** in MeOH at 0 °C delivers the desired bicycles **2** with high yields (52−84%), diastereoselectivities (dr >20:1) and ee's >99%.



Asymmetric Hydrogenation of Pyrroles

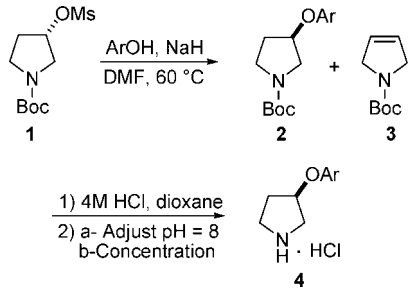
The catalytic enantioselective hydrogenation of heteroaromatics provides chiral heterocyclic skeletons with high efficiencies. Nevertheless, there are just a handful of examples, with a distinct lack of development for the hydrogenation of pyrroles. Using a Ru complex equipped with the *trans*-chelating bisphosphine PhTRAP, Kuwano and co-workers reported a methodology for the hydrogenation of 2,3,5-trisubstituted pyrroles to yield pyrrolidines **1** or dihydropyrroles **2** with up to 97% ee (*J. Am. Chem. Soc.* **2008**, *130*, 808−809). No regioisomers of partially reduced species **3** were detected in the crude product, which suggests that the conversion of **1** into **2** occurs via successive 1,2-additions of hydrogen to the two C−C double bonds. Interestingly, the stereoselectivity in the reduction of **3** to yield

cis-**2** products is controlled by the chirality at the 5-position. The **2**:**3** ratios ranged from 0:100 to 100:0, depending on the substitution pattern of the starting material.



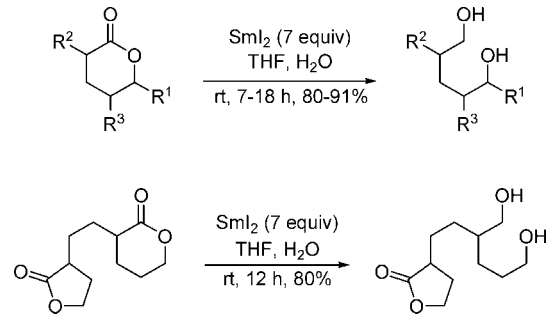
Preparation of Optically Pure 3-Aryloxy-pyrrolidines

The basic framework of the title moieties, incorporated into various biologically active agents, has been generally synthesized using a Mitsunobu reaction between a hydroxypyrrolidine and a phenol. Chemists at Naeja and Pfizer developed an alternate efficient synthesis that avoids the generation of phosphine and hydrazide byproduct (*Synth. Commun.* **2008**, 517−524). Thus, when pyrrolidine mesylate **1** was displaced by the sodium salt of *m*-cresol, a mixture of the desired product **2** and the elimination byproduct **3** (30%) was obtained. Nevertheless, after Boc-deprotection, pH adjustment, and extraction, pyrrolidine hydrochloride **4** was isolated as the only product. The protocol was successfully applied to the synthesis of aryloxypiperidines, which were obtained in moderate yields and purities, as well as high chiral purity.



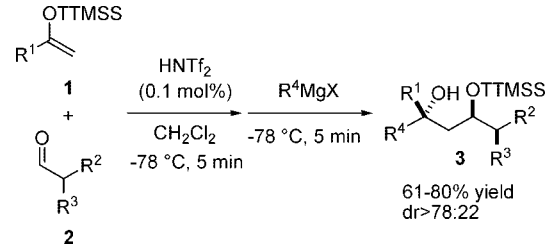
Reduction of Lactones Using SmI_2 and H_2O

Duffy, Matsubara, and Procter describe a ring-size selective reduction of lactones mediated by SmI_2−H_2O (*J. Am. Chem. Soc.* **2008**, *130*, 11361137). Treatment of a variety of lactones with SmI_2−H_2O in THF at room temperature gave the corresponding diols in good yields (80−91%). The procedure is highly chemoselective: when mixtures of esters and lactones were subjected to the reaction conditions, 6-membered lactones were reduced smoothly, with no reduction products arising from esters of 5-, 7-, or 8-membered lactones. The enhanced reactivity of SmI_2 is due to its activation with water, which acts as a proton source and increases the reduction potential (Hasewaga, E. and Curran, D. P. *J. Org Chem.* **1993**, *58*, 5008−5010). The selectivity for the reduction of the 6-membered ring appears linked to the rate of the initial electron transfer to the lactone carbonyl; the stability of the intermediate radical anion compared to the analogous 5, 6, and 7-membered lactones promotes the initial step. Supporting this hypothesis is the observation that oxabicyclo [2.2.2] octanones that cannot adopt the chair conformation required for stabilization do not undergo reduction.



Reactions of Super Silyl Enol Ethers: Generation of Carbinols in One Pot

In a recent communication, Boxer, Akakura, and Yamamoto (University of Chicago) describe a synthetic sequence involving the super silyl group tris(trimethylsilyl)silyl (TTMSS). The transformation involves two steps: (1) addition of a TTMSS ketone to a chiral aldehyde and (2) addition of Grignard reagents to give tertiary alcohols (*J. Am. Chem. Soc.* **2007**, *130*, 1580−1582). The first reaction provides β-oxygenated ketone adducts with high Felkin selectivity (>95:5). These adducts react with alkyl or phenyl magnesium bromide to generate the desired carbinols in one pot. Ketone-derivative silyl ether **1** underwent the aldol reaction with **2** in the presence of 0.1 mol % $HNTf_2$ (CH_2Cl_2, −78 °C, 5 min). PhMgBr was subsequently added dropwise, and product **3** was formed in good yields (70−85%) and moderate *anti* diastereoselectivity (dr >78:22). Distinct stereodefined isomers can be accessed by choosing the TTMSS ketone and Grignard reagents, which indicates that the TTMSS controls the geometry of transition throughout the Grignard addition to the β-TTMSS ketone. DFT calculations suggest that TTMSS creates an umbrella-like structure that restricts the conformational freedom of the remainder of the molecule, determining the stereochemical outcome of the reaction.

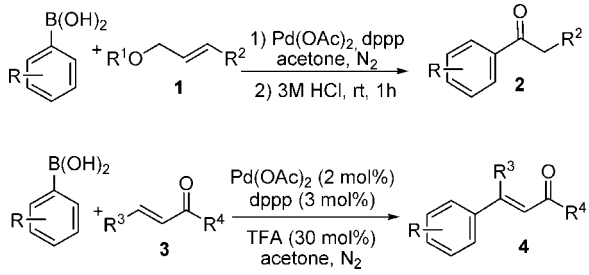


Oxygen and Base-Free Oxidative Heck Reactions of Boronic Acids and Olefins

Xiao and co-workers at the University of Liverpool recently disclosed a new set of conditions for a Heck coupling of aryl boronic acids and olefins that do not require external oxidants to reoxidize Pd(0). (*J. Am. Chem. Soc.* **2007**, *130*, 2424−2425).

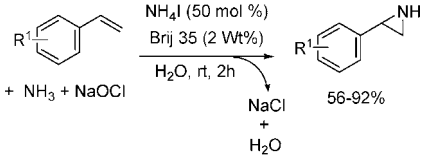
The authors postulated that, following the release of the coupling product (ArCHCHR) from Pd(II), a hydrogen acceptor could be used to intercept the X−Pd-H intermediate regenerating Pd(II) and circumventing the need for oxidants (quinone, $Cu(OAc)_2$) or base. The reaction of various aryl boronic acids with olefins **1** provided, after hydrolysis, ketones **2** in excellent

yields (61−94%). Among the comprehensive list of substrates, outstanding entries are oxygen- sensitive (R= *p*-OH, *p*-SMe, *p*-CH_2OH) and bromo-substituted boronic acids. The latter exclusively provide the product from the oxidative Heck reaction. The use of electron-deficient olefins **3** as substrates required the addition of TFA acid (30 mol%) to the reaction media. The desired products **4** were obtained in excellent yields (75−96%), with no *cis* or branched byproduct detected.



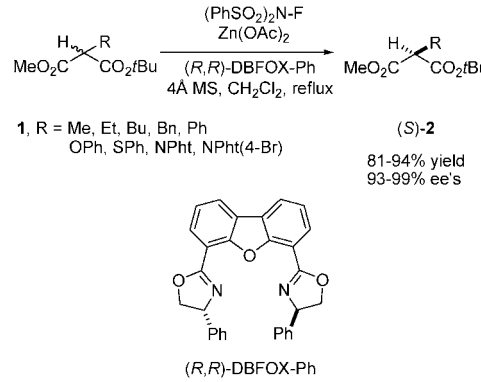
Aziridines from Styrenes and Ammonia

Ammonia, the most obvious source of nucleophilic nitrogen, has barely been considered in aziridination reactions. In *Angew. Chem., Int. Ed.* **2008**, *47*, 1477−1480, De Vos and colleagues from industry (BASF) and academia (Katholieke Universiteit Leuven) report the first catalytic synthesis of unprotected aziridines from NH_3 and simple olefins. Products are formed in one-pot, using NH_4I as the catalyst and aqueous bleach as the oxidant that generate the electrophilic iodonium species. By using excess ammonia, the pH is maintained alkaline, and NH_3 remains a stronger nucleophile than water and hydroxide anions. Effective mixing of aqueous ammonia with the apolar olefin is achieved in a micellar system that results from the addition of the nonionic surfactant Brij 35. The olefin is first attacked by the "I^+" cation formed by oxidation of iodine, and then by NH_3. The resulting 2-iodo-1-phenethylamine intermediate cyclizes to the corresponding aziridine, and the reoxidation of iodide by bleach closes the catalytic cycle.



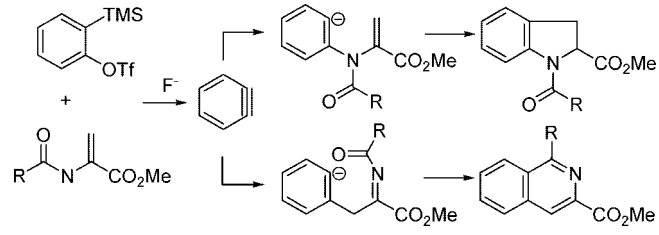
Catalytic Enantioselective Fluorination of Malonates

Examples of enzymatic desymmetrizations leading to fluoromalonate-like synthons abound in the literature. Nevertheless, the enantioselectivity of these reactions is highly dependent on the substrate, narrowing their synthetic utility. In response to these limitations, scientists at the Nagoya Institute of Technology and Kyushu University reported a protocol for the desymmetrization-like enantioselective fluorination of malonates (*Angew. Chem., Int. Ed.* **2008**, *47*, 164−168). A (*R*,*R*)-DBFOX-Ph/$Zn(OAc)_2$ complex (DBFOX = 4,6-dibenzofurandiyl-2,2′-bisoxazoline) proved an effective catalyst for discriminating the ester groups in almost-symmetrical malonates. After careful screening of Lewis acids and reaction conditions, the fluorination of a wide range of substrates could be achieved using *N*-fluorobenzenesulfonimide to yield optically active (*S*)-**2** (81−94% yield; 93−99% ee's). The resulting fluoromalonates were converted into chiral fluorinated hydroxyesters and unsymmetrical ester-amides. The methodology was applied to the synthesis of the ACE inhibitor fluoro-alacepril and an HIV-1 protease inhibitor.



Synthesis of Isoquinolines and Indolines via Aryne Annulation

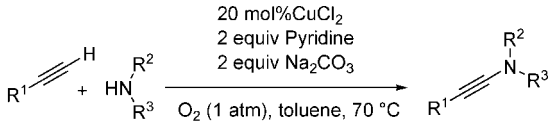
In *J. Am. Chem. Soc.* **2008**, *130*, 1558−1559, the group of Stoltz at California Institute of Technology report two metal-free orthogonal reactions that directly produce either indolines or isoquinolines from arynes and differentially substituted enamines. The aryne precursors (silyl aryl triflates) were reacted with *N*-Boc dehydroalanine esters in the presence of $Bu_4NPh_3SiF_2$ (TBAT) as the fluoride source. In this fashion, a range of substituted indolines was obtained in modest yields (40−61%) resulting from a formal [3 + 2] cycloaddition . When enamide esters were reacted with the aryne under the same conditions, the resulting adduct was an isoquinoline. The product arises from the [4 + 2] addition of the *N*-acyl enamine and the aryne followed by dehydrative aromatization. A range of polyfunctionalyzed quinolines was synthesized (51−87% yield). The reaction tolerates a variety of substitution α to the amide carbonyl, (alkyl, aryl, esters), and the enamine may be also incorporated in a carbocycle to yield tricyclic isoquinoline derivatives. The synthetic utility of the methodology was demonstrated with the preparation of the opium alkaloid papaverine.



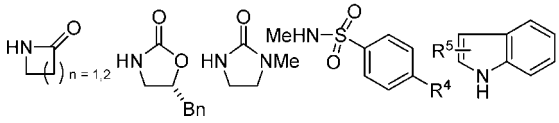
Copper-Catalyzed Aerobic Amidation of Terminal Alkynes

Stahl and co-workers used ubiquitous molecular oxygen for the copper-catalyzed coupling of alkynes with a variety of nitrogen nucleophiles for the synthesis of ynamides (*J. Am. Chem. Soc.* **2008**, *130*, 833−835). The methodology is an efficient alternative to two-step methods, such as alkyne halogenation followed by C−N cross-coupling. Conditions for the coupling of different terminal alkynes with nitrogen nucleophiles were screened to minimize the formation of secondary products, namely alkenyl homocoupling dimers and alkenyl chlorides. Optimized catalytic conditions using 1 atm of O_2 featured 20 mol % $CuCl_2$, 2 equiv of Na_2CO_3, and pyridine in toluene at 70 °C. Cyclic carbamates, amides, and urea nucleophiles gave the desired ynamides in high yields. Selected

benzenesulfonamides and indoles were also viable substrates. In contrast, acyclic nucleophiles (*N*,*O*-dimethyl carbamate, acetanilide, and *N*, *N*′-dimethylurea) showed no reactivity under the above conditions or using a stoichiometric version (2 equiv $CuCl_2$, DMSO). The reaction is compatible with a variety of terminal alkynes, although it is more effective with electron-rich alkynes.

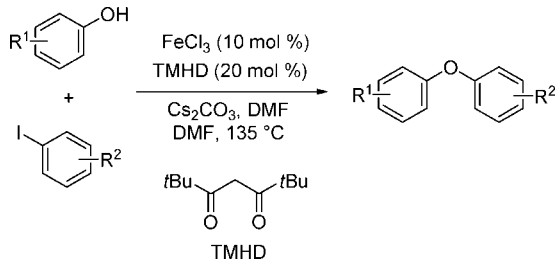


R_1 = TIPS, *n*-hexyl, $TBSO(CH_2)_3$, $TBSO(CH_2)$, 4-$MeOC_6H_4$



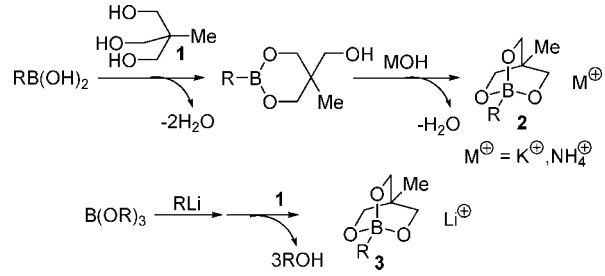
Iron-Catalyzed C−O Cross-Coupling of Phenols with Aryl Iodides

Carlsten Bolm and co-workers reported a novel iron-catalyzed *O*-arylation reaction, which showcases the synthesis of diaryl ethers in high yields using aryl halides (*Angew. Chem., Int. Ed.* **2008**, *47*, 586−588). The transformation proceeds smoothly when using a combination of $FeCl_3$ and 2,2,6,6-tetramethyl-3,5-heptanedione (TMDH) as the chelating ligand. Noteworthy is that the choice of base (Cs_2CO_3) and solvent (DMF) was crucial for the O-arylation. Electron -rich, and -poor phenols are compatible with the coupling, but in the case of *p*-$NO_2C_6H_4OH$ the reaction did not take place. A variety of substituted aryl iodides afforded the corresponding diaryl ethers in high yields (50−95%), with the exception of iodoanisol. The protocol is promising for large-scale applications.



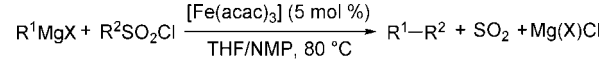
Air-and Water-Stable Complexes of Boronic Acids

Exceptionally air- and water- stable cyclic triolborates have been recently synthesized by Yamamoto, Miyaura, and co-workers at Hokkaido University (*Angew. Chem., Int. Ed.* **2008**, *47*, 942−945). Treatment of organoboronic acids with triol **1** followed by azeotropic water removal gives boronic esters, which are readily converted in triolborates **2** by treatment with KOH or NH_4OH. Potassium triolborates are insoluble in toluene and precipitate as white solids in high yields. Lithium triolborates **3** were synthesized by treatment of $B(OMe)_3$ or $B(OiPr)_3$ with RLi followed by ester exchange with triol **1**. An ORTEP plot of a triolborane (R = Ph, M = NH_4) showed that the structure contains a bicycle [2,2,2]octane ring. The C−B bond is stretched due to the sp^3 hybridization of the tetrahedral boron atom. Potassium and lithium triolborates can be used in Pd- and Cu-catalyzed cross-coupling reactions as surrogates of aryl boronic acids that are unstable due to hydrolytic B−C cleavage (R = 2-pyridyl; 2-thiophenyl).



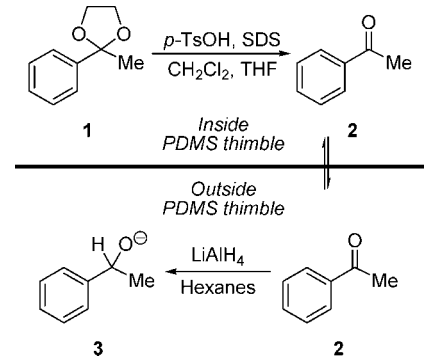
Desulfinylative Coupling of Sulfonyl Chlorides with Grignard Reagents

Alkanesulfonyl chlorides are not suitable substrates in Pd-catalyzed desulfinylative C−C cross-coupling reactions as they experience β-elimination. Volla and Vogel recently reported that these reagents undergo smooth desulfinylative C−C cross-coupling reactions with Grignard reagents in the presence of catalytic amounts of [Fe(acac)$_3$] (*Angew. Chem Int. Ed.* **2008**, *47*, 1305−1307). Using a mixture of THF and NMP at 80 °C, the desired coupling products are obtained in modest to good yields depending on the nature of the R^1 and R^2 groups. Remarkably, the addition of expensive or toxic ligands is not required. The communication contains a detailed table of examples as well as an exhaustive review on the advances of Fe-catalyzed C−C cross-coupling reactions.



Using $LiAlH_4$ in the Presence of Site-Isolated Water

Bowden and co-workers at the University of Iowa report the use of polydimethylsiloxane (PDMS) thimbles to site-isolate water from $LiAlH_4$, Grignard, and cuprate reagents (*Angew. Chem., Int. Ed.* **2008**, *47*, 935−939). Incompatible reagents can be used in cascade reactions, reducing isolation and purifications steps, as well as waste generation. PDMS, a hydrophobic



polymer ($90/kg), is cast in thimbles that cured after several hours at 65 °C. Polar molecules (water, LAH, Grignard, cuprate, and alkyl-liythium reagents) do not diffuse through PDMS. In contrast, nonionic organic molecules show high flux rates and freely diffuse through PDMS. In a typical experiment, the substrate (cyclic acetal, **1**), *p*-TsOH, water, SDS (sodium dodecyl acetate), and the solvent (CH_2Cl_2−hexanes or THF−hexanes) are added to the interior of the thimble, which seats on a glass vessel. After the deprotection is complete, $LiAlH_4$ (1.25 equiv) in hexanes reduces ketone **2** in the exterior of the

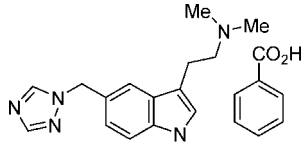
thimbles. Conversion to **3** was complete in 4 h (96−100%) despite of the presence of over 50 equiv of water per LAH mole.

Ultracentrifugation to Separate Racemates from Excess Enantiomers

Collaborative work between Bar-Ilan University in Israel and the Max Planck Institute in Potsdam, Germany, resulted in the development of a method for the separation of crystals of racemic alanine from the enantiomer in excess by using density gradient ultracentrifugation (*J. Am. Chem. Soc.* **2007**, *130*, 2426−2427). Racemic compounds are up to 5% denser than the corresponding pure enantiomers. Gradient ultracentrifugation is a well-established technique that can be applied with high accuracy for separations in the density range of amino acids. The test material was a solution of D,L-alanine, saturated water, and 50.8% w/w Nycodenz (d = 1.394 g/mL), a universal, readily available centrifugation media (see http://www.axis-shield-density-gradient-media.com/200769%20Nycodenz.pdf) as well as crystals of the racemate and the excess enantiomer. The gradient was generated using a standard laboratory preparative ultracentrifuge and a clear boundary formed between D,L-alanine and floating crystals of D- and L-alanine. Separation of the racemic from mixtures containing up to 20% excess enantiomers was achieved using simple filtration with a recovery of 75% (D-Ala) and 90% (L-Ala).

Characterization of Potential Impurities in the Synthesis of Rizatriptan

Rizatriptan benzoate (**1**) is a recently developed drug used for the treatment of migraines and severe headaches. Researchers at Dr. Reddy's Laboratories and JNT University (Hyderabad, India) describe the characterization of six impurities isolated during the bulk synthesis of this product in *Synth. Commun.* **2008**, 603−612. Driven by ever-more-stringent guidelines for the identification of impurities (ICH recommends the characterization of impurities at levels above 0.10%), Praveen and co-workers studied the impurity profile of the product manufactured, painstakingly characterized six related substances, and then engaged in their synthesis. The compounds were characterized as a hydrazone intermediate, rizatriptan *N*-oxide, formed by air oxidation of the product, rizatriptan dimer, two demethylated impurities, and *N*-methyl rizatriptan oxalate.



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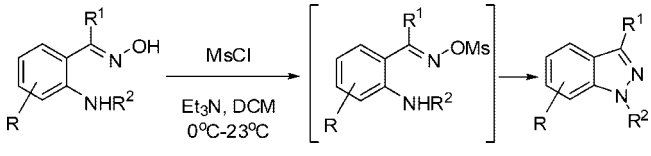
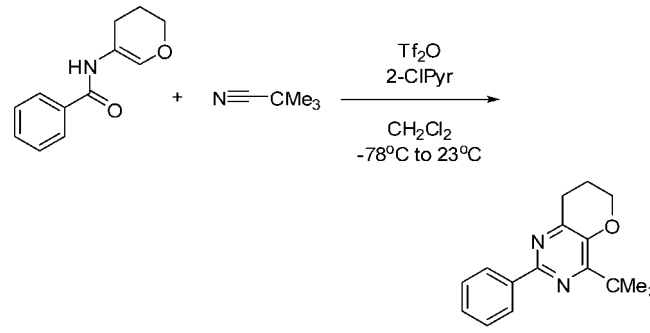
A Practical, Metal-Free Synthesis of 1*H*-Indazoles



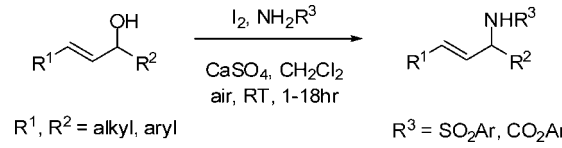
Recently, a number of communications have surfaced to address the synthesis of 1*H*-indazoles, striving to improve on the classic methods of their synthesis that often employ harsh reaction conditions such as diazotization and nitrosation reactions, but many suffer from drawbacks such as high metal-catalyst loading, low yields, or limited substrate scope. A simple, metal-free method utilizing readily available aminobenzoximes has been described by Stambuli and co-workers at The Ohio State University (*Org. Lett.* **2008**, *10*, 1021−1023). The mechanism is thought to occur via mesylation of the oxime, followed by intramolecular nucleophilic substitution by the aniline moiety. The reaction appears general and proceeds in moderate to good yields, while common side reactions such as Beckmann or Neber rearrangement were not observed.

Direct Synthesis of Substituted Pyrimidines and Quinazolines



A single-step reaction to produce pyrimidine and quinazoline derivatives from *N*-vinyl and *N*-aryl amides, respectively, has been reported by Movassaghi and Hill at the Massachusetts Institute of Technology (*Synthesis*, **2008**, *5*, 823−827). The combination of triflic anhydride and 2-chloropyridine activates the amide for nitrile addition, which is followed by annulation to provide the desired azaheterocycles. Electronic effects seem to dominate the reaction. Most utility will be found when employing electron-rich amides and nitriles, which after initial activation at cryogenic temperature proceed smoothly at either room temperature or 45 °C. However, reactions using electron-deficient N-aryl substrates usually required heating in a microwave reactor at 140 °C to achieve reasonable yields. Notably, cyclization reactions allow for retention of optical activity using epimerizable *N*-vinyl amide and nitrile substrates.

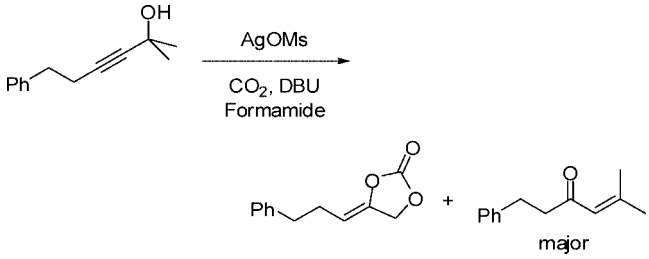
Iodine-Catalyzed Allylic Alkylation of Sulfonamides and Carbamates with Allylic Alcohols at Room Temperature



A process for the allylic alkylation of sulfonamides and carbamates with allylic alcohols at room temperature has been reported by Chan and co-workers at Nanyang Technological University (*Tetrahedron Lett.* **2008**, *49*, 2620−2624). Unlike many of its metal-catalyzed counterparts, the use of catalytic iodine and calcium sulfate allows the procedure to be run in open flasks and promotes reactions in good yield shown in a variety of electron-withdrawing, electron-donating, and sterically encumbered combinations. Although presumably proceeding through an allylic carbocation species, regioselectivity was observed in cases in which two very different substituents were

present on the allylic alcohol, such as an aryl group and an alkyl group, but suffered when similar substituents were present. Lower product yields were observed without the presence of the drying reagent or exchange for other common drying reagents such as magnesium sulfate or molecular sieves.

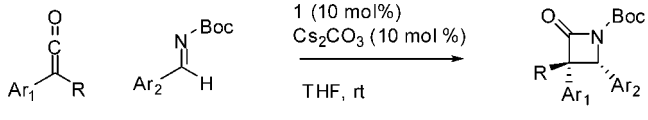
Carbon Dioxide-Mediated Catalytic Rearrangement of Propargyl Alcohols into α,β-Unsaturated Ketones

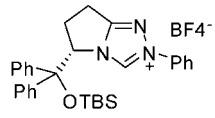


Yamada and co-workers at the Keio University have disclosed a carbon dioxide-mediated catalytic rearrangement of propargyl alcohols to form α,β-unsaturated ketones (*J. Am. Chem. Soc.* **2007**, *129*, 12903−12904). While developing methodology utilizing silver acetate and DBU to provide cyclic carbonates from propargyl alcohols, the authors noticed traces of enones in polar solvents from a Meyer−Schuster type [3,3]-sigmatropic rearrangement. After the carbonate intermediate is generated from propargyl alcohol and carbon dioxide, intramolecular ring closing can occur at either the α-carbon or the β-carbon of the propargyl alcohol. Closure onto the α-carbon activated by the silver salt provides the cyclic carbonate. However, by tuning the reaction with silver methanesulfonate and DBU in formamide, stabilization of the elongated C−O bond transpires, and the favored pathway becomes the [3,3]-sigmatropic rearrangement onto the β-carbon, giving the enone via the allene-enolate. Yields were generally high for a variety of substrates, although a mixture of *E*/*Z* products was obtained when unsymmetrical enones were synthesized.

Chiral N-Heterocyclic Carbene-Catalyzed Staudinger Reaction of Ketenes with Imines: Highly Enantioselective Synthesis of *N*-Boc β-Lactams

N-Heterocyclic carbenes (NHCs) have been demonstrated to be efficient catalysts for the Staudinger reaction of ketenes with *N*-tosyl, *N*-benzyloxycarbonyl, or *N*-*tert*-butoxycarbonyl imines (Ye, S.; et al. *Org. Lett.* **2008**, *10*, 277). Chiral NHC **1**,





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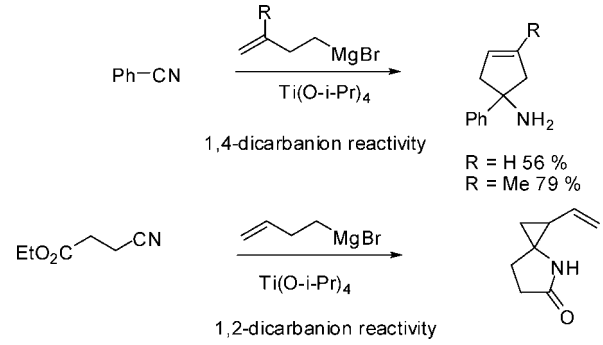
conveniently prepared from L-pyroglutamic acid, catalyzed the reactions of arylalkylketenes with a variety of *N*-*tert*-butoxycarbonyl arylimines to give the corresponding *cis*-β-lactams in good yields with good diastereoselectivities and good to excellent enantioselectivities (up to 99% ee). Two possible catalytic pathways, initiated by the addition of NHC to ketenes or imines, were discussed.

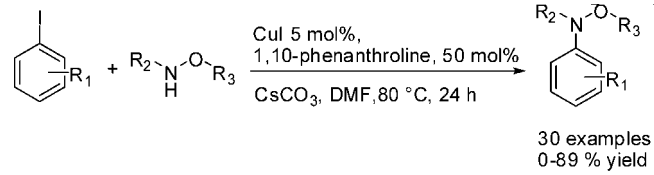
Diene−Titanium Complexes as Synthetic Intermediates for the Construction of Three- or Five-Membered Carbocycles

It has been shown that diene−titanium complexes generated from homoallylic Grignard reagents and Ti(O-*i*-Pr)$_4$ exhibit substrate-dependent 1,2- or 1,4-dicarbanion reactivity (Bertus, P.; et al. *Org. Lett.* **2008**, *10*, 777). On this basis, 3-cyclopentenylamines and spiro-vinylcyclopropane lactams were easily prepared by using homoallylic Grignard reagents, Ti(O-*i*-Pr)$_4$, and nitriles or cyanoesters, respectively. For the 3-cyclopentenyl amine five examples were demonstrated with yields between 42−79%, and the synthesis of spiro-vinylcyclopropane was done with five examples with yields between 40−85%.



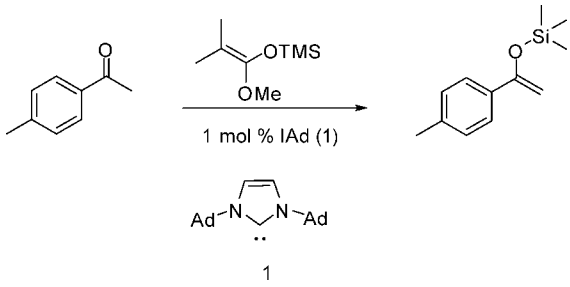
Copper-Catalyzed Coupling of Hydroxylamines with Aryl Iodides

An efficient method for the copper-catalyzed N-arylation of hydroxylamines with aryl iodides is described (Jones, K. L.; et al. *Org. Lett.* **2008**, *10*, 797). A variety of N- and O-functionalized hydroxylamines were transformed in good to excellent yield with a broad range of aryl coupling partners. Methods for the selective deprotection of either the N- or O-substituents for further functionalization are also described. The coupling was demonstrated on nine aryl iodides all either para- or meta-substituted. 2-Iodotoluene failed the coupling, as did phenyl bromide and phenyl triflate.



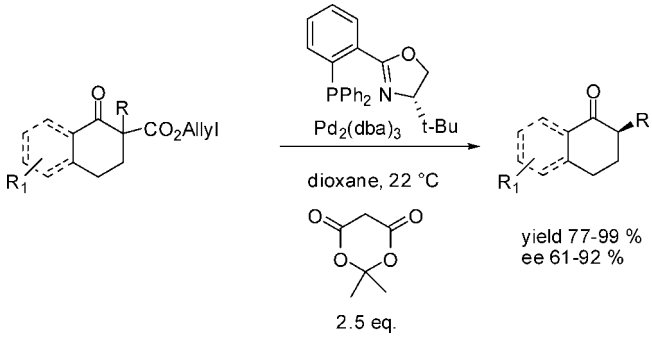
N-Heterocyclic Carbene-Catalyzed Silyl Enol Ether Formation

N-Heterocyclic carbenes (NHCs) were found to catalyze the silyl transfer from trialkylsilyl ketene acetals to ketones (Song, J. J.; et al. *Org. Lett.* **2008**, *10*, 877). In the presence of a catalytic amount of NHC 1 (IAd, 0.1−5 mol %), a series of enolizable ketones as well as cyclohexanecarboxaldehyde were efficiently converted into the corresponding silyl enol ethers at 23 °C in THF. The yield from the 13 examples varies between 46 to 94%.



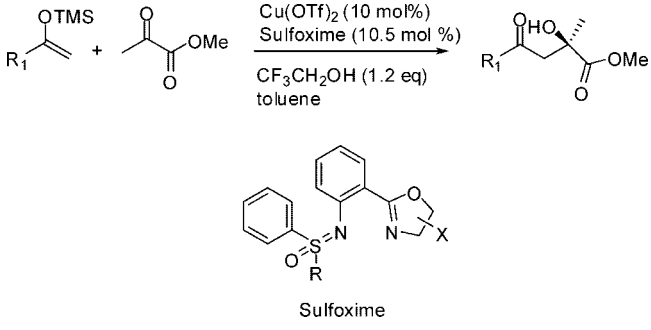
Homogeneous Pd-Catalyzed Enantioselective Decarboxylative Protonation

General homogeneous conditions for the palladium-catalyzed synthesis of carbonyl compounds with tertiary carbon stereocenters at the α-position are reported (Stoltz, B. M.; et al. *Org. Lett.* **2008**, *10*, 1039). The highly reactive catalyst tolerates a variety of substrate substitution and functionality, and generates enantioenriched cyclic ketones from racemic allyl β-ketoester starting materials. The enantiomeric excess from the protonation was found to be scale dependent. At larger scale (0.3 mmol) the ee was found to be lower.



C_1-Symmetric Oxazolinyl Sulfoximines as Ligands in Copper-Catalyzed Asymmetric Mukaiyama Aldol Reactions

Aryl-bridged C_1-symmetric oxazolinyl sulfoximines are applicable in copper-catalyzed asymmetric Mukaiyama aldol reactions with methyl pyruvate (Bolm, C.; et al. *Org. Lett.* **2008**, *10*, 917). The resulting α-hydroxy esters have been obtained with up to 94% ee in good yields. They contain a quaternary stereogenic center and represent valuable precursors for biologically active molecules.



Suzuki–Miyaura Cross-Coupling Reactions of Alkylboronic Acid Derivatives or Alkyltrifluoroborates with Aryl, Alkenyl, or Alkyl Halides and Triflates

Palladium-catalyzed Suzuki–Miyaura cross-couplings of organoboronic acids or organotrifluoroborates with aryl and alkenyl halides or triflates have become classic methods for generating carbon–carbon bonds (Doucet, H. *Eur. J. Org. Chem.*, **2008**, 2013). For this reaction, not only sp^2-hybridized but also sp^3-hybridized organoboron derivatives can be employed. However, alkylboronic acids or trifluoroborates are generally less reactive than arylboron derivatives. The coupling of primary alkylboronic acids or alkyltrifluoroborates with aryl or alkenyl halides is well-known, and the reaction gives the coupling products with high selectivities, relatively high turnover numbers, and in good yields with several catalysts. On the other hand, secondary alkylboronic acids or trifluoroborates, except for cyclopropylboron derivatives, are much less reactive, and very few catalysts are able to activate such compounds. Because of the hybridization of cyclopropanes, which confers significant aromatic character, several reactions have successfully been performed with cyclopropylboronic acids or trifluoroborates. The stereochemistries of substituted cyclopropylboron derivatives were maintained in the course of the reactions. For all these couplings with primary or secondary alkylboron derivatives, aryl iodides, bromides, chlorides, or triflates and alkenyl iodides, bromides, or triflates were employed. Alkenyl chlorides have attracted less attention. The reactions with alkenyl halides are stereoselective. A few examples of couplings between sp^3-hybridized organoboronic acids and alkyl halides have also been reported.

Photochemical Reactions as Key Steps in Organic Synthesis

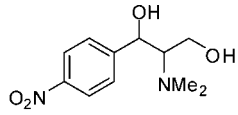
Since the beginning of scientific chemistry, chemists have been interested in light as an energy source to induce chemical reactions. Hoffman, N. (*Chem. Rev.*, **2008**, *108*, 1052) has reviewed the literature where photochemical steps are the key ones in organic synthesis.

This short review on recent applications of photochemical reactions to organic synthesis shows a highly dynamic research field. Almost all domains of organic synthesis are concerned. Photochemistry frequently provides solutions to problems which are difficult to solve with ground-state reactions. This fact results from significant differences between these two reactions modes. Photochemical excitation considerably modifies the electron configuration and consequently the chemical nature of a molecule. The traditionally strong interaction existing between different disciplines of photochemistry on one hand and physical chemistry or physics, on the other, enables a high level of characterization and understanding of the reactions. These circumstances also facilitate their optimization and application in various fields. Organic photochemistry also establishes interdisciplinary links between organic chemistry and biology and other research domains such as material science, supramolecular chemistry, or nanoscience. In this context, research activities will certainly increase in the near future in both directions, in basic and applied research. The fact that many organic photochemical reactions do not need polluting or toxic reagents offers perspectives in the context of sustainable processes and green chemistry.

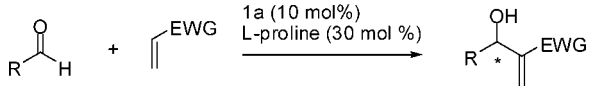
Chiral Tertiary Amine/L-Proline-Cocatalyzed Enantioselective Morita–Baylis–Hillman Reaction

Four types of chiral amines have been synthesized starting from readily available chiral sources. These chiral amines in combination with L-proline have been found to be efficient cocatalysts for the asymmetric Morita–Baylis–Hillman (MBH)

reaction between methyl vinyl ketone (MVK) and aromatic aldehydes (Tang, H.; et al. *Eur. J. Org. Chem.*, **2008**, 126). The corresponding adducts were formed in reasonable chemical yields and with good enantioselectivities (up to 83% ee). Moreover, parallel cocatalytic reactions with the two enantiomers of chiral amine **1** and L-proline revealed that it is the proline stereochemistry that determines the configuration of the newly formed chiral center. In addition, the existence of the free hydroxy group in amine **1a** enhanced the enantioselectivity of the reaction. On the basis of these findings, a plausible mechanism for this cocatalytic MBH reaction has been proposed.

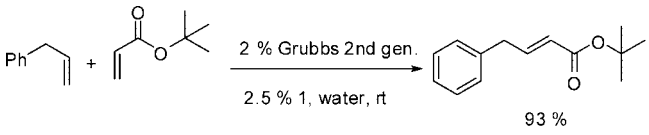


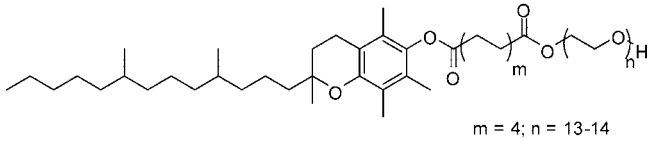
(1R,2R)-(-)- 1a
(1S,2S)-(-)-1b



Olefin Cross-Metathesis Reactions at Room Temperature Using the Nonionic Amphiphile "PTS": Just Add Water

The first examples of unsymmetrical olefin cross-metathesis reactions in water, involving water-insoluble substrates, at room temperature and using commercially available catalysts are reported by Lipschutz, B.H.; et al. (*Org. Lett.*, **2008**, *10*, 1325). The key to success is to include small percentages of the nonionic, vitamin E-based amphiphile "PTS" (**1**). The nanometer micelles formed accommodate water-insoluble substrates, along with a readily available Ru-based metathesis catalyst. Reactions proceed at ambient temperatures with high efficiency and very high *E*-selectivity, and products are easily isolated.





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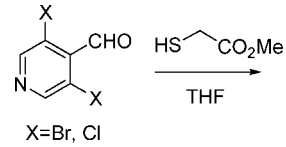
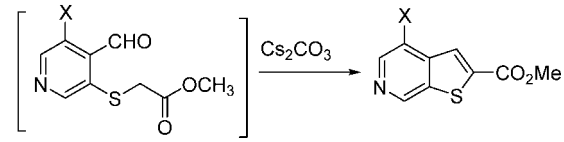
Synthesis of Substituted Thieno[2,3-*c*]pyridines

Thienopyridines are an interesting class of heterocyclic compounds because they contain a π-rich thiophene and π-deficient pyridine. The polarization can be further enhanced by introducing appropriate substituents on this molecule. There are a number of methods available to synthesize unsubstituted thienopyridines. Zhu and co-workers from Abbott Laboratories (*J. Heterocycl. Chem.* **2008**, *45*, 91−96) have reported a general method to synthesize 2,4-di- and 2,4,7-trisubstituted thieno[2,3-*c*]pyridines starting from 3,5-dibromo- (or dichloro-) pyridine-4-carbaldehyde.

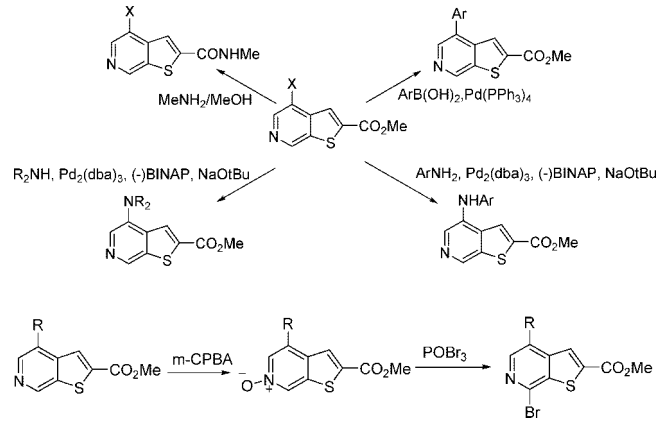
The paper also describes a number of possible transformations with which the molecule can be further functionalized.



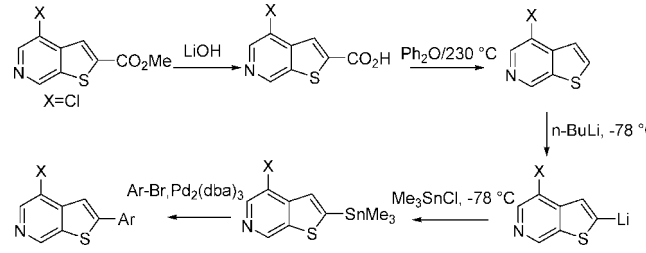
X=Br, Cl



As is evident from the scheme a number of further transformations are possible on these products as well.



Functionalization of the 2-position of 4-chlorothienopyridine-2-carboxylate via a decarboxylation and lithiation is also reported by the authors. The intermediate is also amenable to a number of transformations.

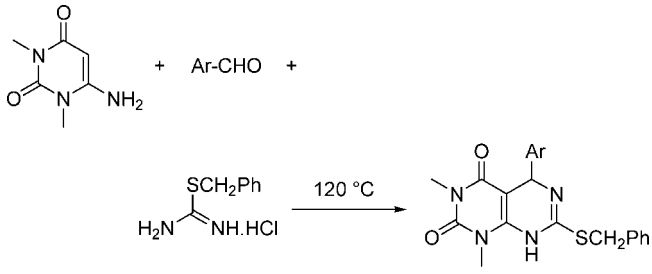


Multicomponent Synthesis of Pyrimidopyrimidine-2,4-diones

Fused pyrimidines have been observed in a number of compounds with interesting biological activities. There are a number of reports available in the literature to synthesize these molecules. However, all of them require either harsh conditions, long reaction time or involves multiple steps. Dabiri and coworkers (Shahid Beheshti University, Iran) have described a three-component one-pot synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-diones (*Heterocycles* **2008**, *75*, 87−93).

Treatment of 6-amino-1,3-dimethyluracil with benzaldehyde and 2-benzylisothiourea in the presence of catalytic *p*-toluenesulfonic acid at 120 °C under solvent-free conditions afforded 1,3-dimethyl-7-(benzylthio)-5-phenylpyrimido[4,5,*d*]pyrimidine-2,4-(1H,3H,5H, H)-dione in 80% yield. After the reaction, a simple water wash and recrystallization afforded the pure material. It should be noted that the neat conditions afforded the best results, whereas the use of solvents (ethanol, acetonitrile, acetic acid, or toluene) resulted in inferior yields. The reaction

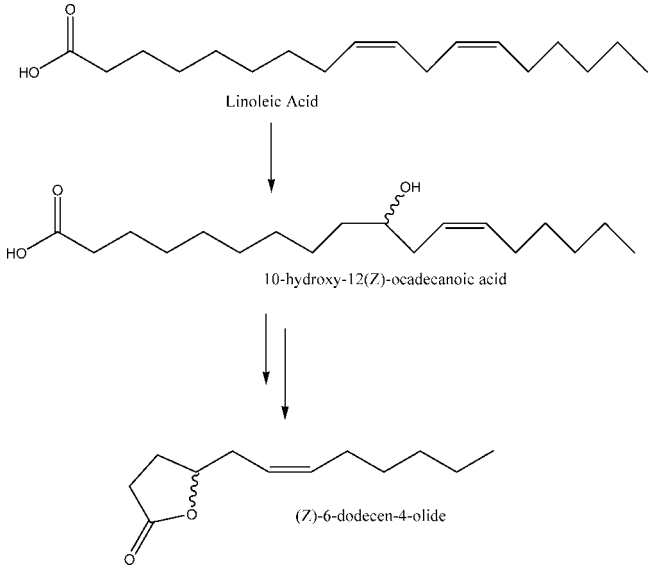
has been found to be general (69−85% yield) with aromatic aldehydes containing both electron-donating and electron-withdrawing groups. The products obtained are amenable to further transformations. This method is useful as it is a one-pot reaction, performed under solvent-free conditions and does not require chromatographic purification.



Tuberose Lactone

Tuberose lactone is the trade name of an important flavor composition containing three lactones, a mixture of (*Z*,*Z*)-6,9-dodecadien-4-olide, (*Z*)-6-dodecandien-4-olide and dodecan-4-olide. Natural tuberose lactone is considered GRAS (generally recognized as safe). The U.S. (Food and Drug Administration) permits the word "natural" to be used with products derived from living or life-derived sources.

10-Hydroxy-12(*Z*)-octadecanoic acid is a known precursor to (*Z*)-6-dodecen-4-olide. Therefore, a process to produce ("naturally") this compound is highly desired. To do that Yu, Kim, and Oh (*Biotechnol. Prog.* **2008**, *24*, 182) used the whole cells of *Stenotrophomonas nitritireducens* to oxidize linoleic acid into 10-hydroxy-12(*Z*)-octadecanoic acid. They achieved a productivity of 15 g/L of this compound, and the cells were able to produce 1.92 g/L of this compound from 2 g/L of linoleic acid.



Biodiesel

In the biocombustible area, recently Muthukumar and co-workers (*Bioresour. Technol.* **2008**, *99*, 3975) published a review on enzymatic production of biodiesel. They listed several sources of raw materials used and discussed different processes. Several lipases (intra- and extracellular) were listed with respective conversions. Continuous systems were also discussed. The fact that glycerol can act as an inhibitor of the process and a process (dialysis) to remove it were reported. A useful comparison of different protocols is found in this article.

Still in this area, but using chemical catalysts, Tittabut and Trakarnpruk (*Ind. Eng. Chem. Res.* **2008**, *47*, 2176) described the use of metal-loaded MgAl oxides for transesterification of palm oil. As is common knowledge, it is highly desirable to have an insoluble catalyst to carry out this transformation. The authors reported that MgAl oxide loaded with 1.5% potassium gave the highest activity. The catalysts were fully characterized. Highest conversions were achieved at above 45:1 methanol:oil molar ratio. Importantly, the catalyst can be regenerated after calcination and reused.

In view of the present economic importance of biodiesel the work of Franceschini and Macchieto (*Ind. Eng. Chem. Res.* **2008**, *47*, 2331) has to be perused due to the fact that it describes a very good model-based experimental design applied to actual rather than simulated biodiesel production. Following the suggested algorithm three experiments of biodiesel production from rapeseed oil were optimized for each of two designed iterations, and statistically, six validated kinetic constants were estimated.

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