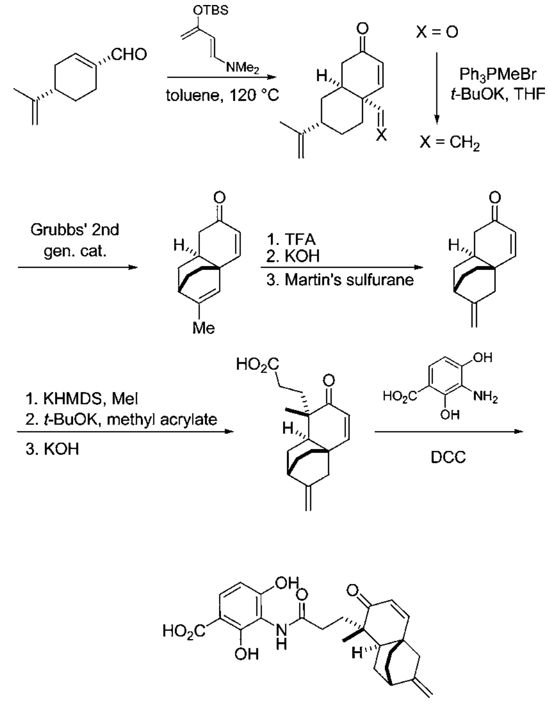
Organic Process Research & Development **2009,** *13,* 660–668

Highlights from the Literature

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

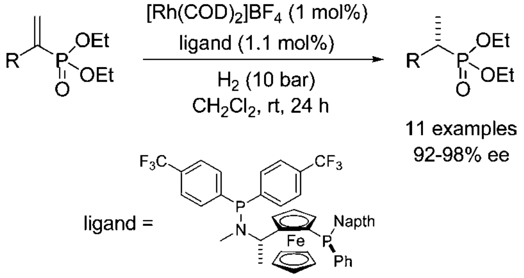
A Nine-Step Total Synthesis of (−)-Platencin



platensin

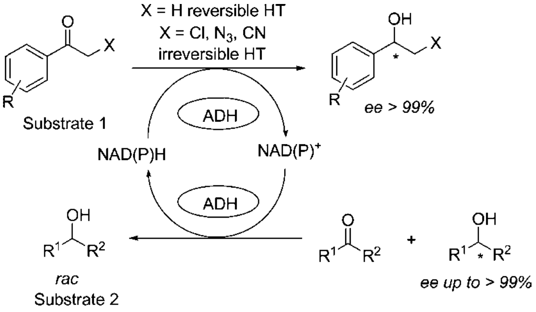
The rise of multiresistant bacteria is a significant problem, especially in hospitals where antibiotics are permanently used and bacteria strains that withstand multiple antibiotic classes can evolve. Due to promising bioactivity and unusual complex molecular architecture, platensin has become a highly competitive synthetic target since it was discovered in 2007. The Mulzer group describes a refined total synthesis (*J. Org. Chem.* **2009**, *74*, 2937−2941) of this molecule that builds upon their previously communicated formal synthesis. Starting from inexpensive perillaldehyde as the raw material, the decalin ring system (containing an all-carbon quaternary center) is constructed via a highly diastereoselective Diels−Alder reaction using Rawal's diene. Aldehyde methylenation followed by ring-closing metathesis generates the strained tricylic skeleton, and then a hydration/dehydration strategy is employed to shift the endocyclic alkene to the exo position. Methylation and then 1,4-addition to methyl acrylate (via enolates) creates the second all-carbon quaternary center. This synthesis achieves an overall yield of 10% and compares favorably with existing literature approaches.

Enantioselective Synthesis of Alkyl/Arylphosphonates



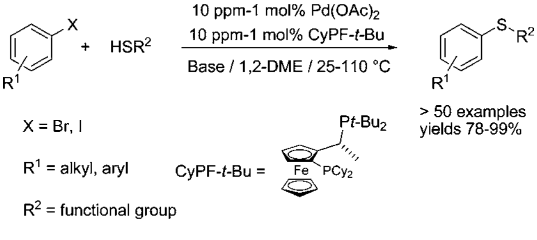
An enantioselective synthesis of optically active 1-aryl- or 1-alkyl-substituted ethylphosphonates is reported by Hu, Zheng and co-workers (*J. Org. Chem.* **2009**, *74*, 4408−4410). The approach is based on Rh-catalyzed asymmetric hydrogenation of corresponding α,*β*-unsaturated precursors in the presence of a *P*-stereogenic BoPhoz-type ligand. A wide range of 1-ary- or 1-alkyl-substituted ethylphosphonates were synthesized in up to 98% ee.

Tandem Concurrent Biocatalytic Processes



A novel one-pot tandem biohydrogen transfer process to concurrently obtain two enantiopure *sec*-alcohols is reported by Gotor and co-workers (*J. Org. Chem.* **2009**, *74*, 2571−2574). Using a suitable single enzyme and a catalytic amount of cofactor, several interesting building blocks can be accessed in an enantiocomplementary fashion, minimizing dramatically the quantity of reagents usually employed in the "coupled-substrate" approach.

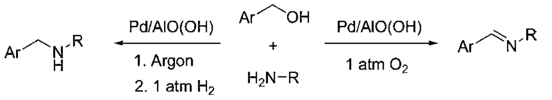
Palladium-Catalyzed Thioetherification of Aryl Bromides and Iodides



10.1021/op9001565 CCC: $40.75

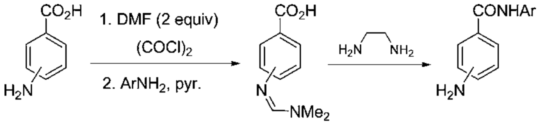
The cross-coupling reaction of aryl bromides and iodides with aliphatic and aromatic thiols catalyzed by palladium complexes of the bisphosphine ligand CyPF-*t*Bu (**1**) is reported by Hartwig and co-workers (*J. Org. Chem.* **2009**, *74*, 1663−1672). Reactions occur in excellent yields, broad scope, high tolerance of functional groups, and with turnover numbers that exceed those of previous catalysts by 2 or 3 orders of magnitude. These couplings of bromo- and iodoarenes are more efficient than the corresponding reactions of chloroarenes and can be conducted with less catalyst loading and/or milder reaction conditions. Consequently, limitations regarding scope and functional group tolerance previously reported in the coupling of aryl chlorides are now overcome.

Pd-Catalyzed Coupling of Benzyl Alcohols and Primary Amines



Imines and secondary amines can be synthesized selectively by controlling reaction conditions for the Pd-catalyzed (heterogeneous Pd/Al(O)OH) one-pot reactions of benzyl alcohols with primary amines, as reported by Park and co-workers (*J. Org. Chem.* **2009**, *74*, 2877−2879). Reactions conducted under an atmosphere of oxygen lead to the formation of imine products, while reactions conducted under an atmosphere of hydrogen lead to the formation of the corresponding reduced amines. The reactions do not require any other additives and were effective for a wide range of alcohols and amines. However, processes requiring a pure oxygen atmosphere present safety concerns for scale-up in batch processes, and the authors do not comment on reaction efficiency under lower concentrations of oxygen.

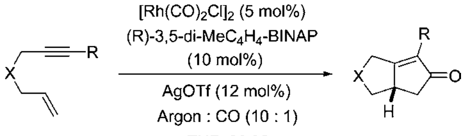
The Use of Formamidine Protection for the Derivatization of Aminobenzoic Acids



one-pot process
31 examples
yields 34-91%

N,*N*-Dimethylformamidine and *N*,*N*-diisopropylformamidine protecting groups can be used to carry out a one-pot conversion of aminobenzoic acids into the corresponding amides, as reported by Zhichkin and co-workers (*J. Org. Chem.* **2008**, *73*, 8954−8959). General conditions for an in situ transformation of aminobenzoic acids and their heterocyclic analogues into the corresponding formamidine-protected acid chlorides are described. These acid chlorides can be used in reactions with amines, including poorly reactive anilines. The protected amides can be deprotected by heating with ethylenediamine derivatives.

Asymmetric Rh-Catalyzed Pauson−Khand-Type Reaction



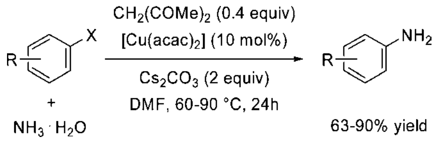
up to 99% yield
99% ee

X = O, Ts-N, $(EtO_2C)C$

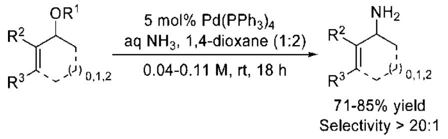
An asymmetric intramolecular PKR catalyzed by a Rh(I) complex at ambient temperature is reported by Ratovelomanana-Vidal, Genêt, Jeong and co-workers (*J. Org. Chem.* **2008**, *73*, 7985−7989). The Rh(I) complex bears a (*R*)-3,5-diMeC_4H_4-BINAP ligand, and loadings of 5 mol % are required. The cyclizations proceed at 18−20 °C under a reduced partial pressure of CO (0.1 atm) and provide bicyclic cyclopentenone products in high chemical yield as well as high enantioselectivity.

Metal-Catalyzed Transformations Using Aqueous Ammonia

The development of organic processes that use ammonia, the most abundant and least expensive synthetic inorganic chemical as feedstock, remains a challenging target. Xia and Taillefer (ENSCM Montpellier) reported the amination of aryl and heteroaryl bromides and iodides with aqueous ammonia using a Cu-based catalytic system (*Angew. Chem., Int. Ed.* **2009**, *48*, 337−339). Optimized conditions include [Cu(acac)$_2$] (10 mol %), Cs_2CO_3 (2 equiv), the ligand 2,4-pentadione (0.4 equiv) and DMF. The desired anilines were obtained in good yields, with no trace of di- or triarylamine byproducts. However, minor amounts (∼5%) of the C−C coupling product resulting from the arylation of the diketone were detected. Two facts are worth noting: (a) the reaction is carried out at 90 °C and 1.3 bar, which allows the use of common glass reactors in lieu of autoclaves, and (b) the biphasic milieu that results upon heating seems crucial for the success of the reaction, which does not work in either neat water or in DMF saturated with ammonia.



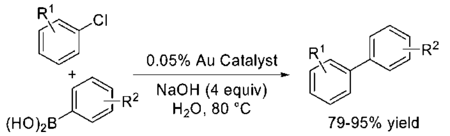
In general, the use of ammonia in metal-catalyzed reactions is challenging because: (a) transition metals react with ammonia to form stable amine complexes; (b) overreaction occurs due to the higher reactivity of the resulting primary amine than that of ammonia itself. Nayano and Kobayashi (The University of Tokyo) revisited the Pd (II)-catalyzed amination of allylic acetates with aqueous ammonia and gratifyingly found that the reaction proceeds to completion at room temperature to give a mixture of primary and secondary amines (*J. Am. Chem. Soc.* **2009**, *131*, 4200−4201). Best selectivities for the primary amine were obtained using Pd(PPh$_3$)$_4$ (5 mol %) in 1,4-dioxane as the solvent, with a 0.11 M concentration of ammonia. Remarkably, ammonia gas did not react under the same conditions, and concentrations of ammonia lower than 0.04 resulted in the deactivation of the catalyst. Cyclic allylic carbonates with a variety of substituents at the vinylic position reacted with excellent selectivities to afford the corresponding primary amines in good yields.



R^1 = Ac, CO_2Me
R^2 = H, Ph, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$

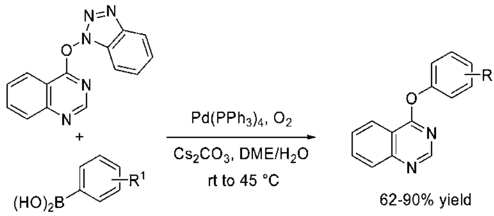
Gold in Water: Nanoparticles for Suzuki–Miyaura Cross-Coupling

Han, Liu, and Guo from Yangzhou University (P.R. China) reported the first gold nanoparticles-catalyzed Suzuki–Miyaura cross-coupling of aryl halides with aryl boronic acids in the presence of water and air (*J. Am. Chem. Soc.* **2009**, *131*, 2060–2061). The nanoparticles were synthesized by redox reaction between $HAuCl_4$ and 2-aminothiophenol. The choice of the reducing agent is based on the efficiency of the polymerized poly(2-aminothiophenol), PATP, to control and stabilize the nanoparticles. Both the size of the nanoparticles as well as the amount of PATP are important for the catalytic activity. By altering the molar ratio between $HAuCl_4$ and 2-aminothiophenol, the size increases from 1 to 2 nm and then to 5 nm, and the yield of the coupling decreases from 87% to 76% to 10%, respectively. The catalyst is stable for at least six months and can be recovered by filtration and reused up to six times without significant loss of activity. As expected, the conversion and isolated yields increase when the halide is a bromide or an iodide.



Palladium Catalysis in S_NAr Reactions: Formation of Heteroaryl Ethers

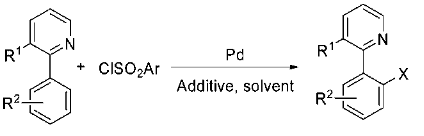
Mansour and co-workers at Wyeth Research (Cambridge) have explored the applications of triazolyl-1-yloxy heterocycles as versatile electrophile intermediates in S_NAr reactions. Pyridotriazolyl-1-yloxy (*O*Pt) quinazolines and thienopyrimidines reacted with aryl boronic acids to yield the corresponding heteroaryl ethers (*J. Am. Chem. Soc.* **2009**, *131*, 4174–4175). Using a Pd catalyst, the methodology exclusively renders the *O*-arylated product, with no C–C or C–N coupling byproducts detected. Isolated yields were high for aryl and heteroaryl boronic acids, whereas 2-indole or 2-furyl boronic acids were refractory to coupling. Studies using $^{18}O_2$ and $H_2{}^{18}O$ suggest that the Pd-mediated pathway involves molecular oxygen from the air to generate $Ar^{18}OH$ from the boronic acid partners. The *O*Pt-heterocycles serve as efficient trapping agents for the phenols *in situ* generated in a S_NAr fashion.



R^1 = 4- or 2-OMe, 4-CF_3, 4-CN, 3-NO_2

Pd-Catalyzed Formation of a C–S Bond: Synthesis of Sulfones

Sulfonyl chlorides can serve as readily available, highly versatile reagents for the Pd-catalyzed formation of sulfones (*J. Am. Chem. Soc.* **2009**, *131*, 3466–3467). Treatment of phenylpyridines **1** with *p*-tolylsulfonyl chloride in the presence of catalytic $Pd(MeCN)_2Cl_2$ and additives (K_2CO_3, 4 Å MS) in 1,4-dioxane at 120 °C provided sulfones **2a** with excellent regioselectivities. As expected, phenylpyridines with *p*- and *m*-substituents yielded the desired products in higher yields than their *o*-substituted counterparts. Whereas the reaction conditions were optimized for a pyridine-directed C–H bond sulfonylation, substrates bearing pyrazole and oxime-directing groups also underwent sulfonylation in good yields (41–78%). The reactivity of sulfonyl chlorides could be dramatically affected by the choice of solvent and additive: the use of DMF as a solvent and $CuCl_2$ as the cocatalyst afforded aryl chlorides **2b** with high selectivities, showcasing the use of arylsulfonylchlorides as chlorinating reagents.



1

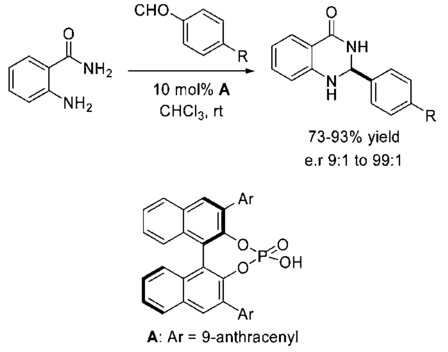
2a: X = SO_2Ar
2b: X = Cl

a = $Pd(MeCN)_2$ (10 mol%) , K_2CO_3 (2 equiv), 1,4-dioxane, 4A MS, 120 °C, 6h

b = $Pd(MeCN)_2$ (10 mol%) , $CuCl_2$ (10 mol%), DMF, 120 °C, 10h

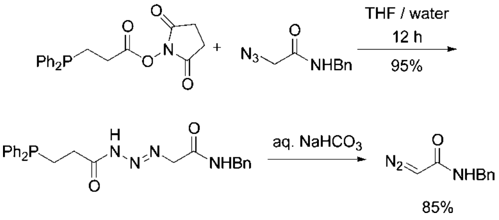
Catalytic Enantioselective Synthesis of Dihydroquinazolinones

2,3-Dihydroquinazolinones are efficient inhibitors of tubulin polymerization, with the *S*-enantiomer showing a remarkably higher activity. Without easy access to these molecules in adequate enantiomeric purity (preparation required a multistep diastereoselective synthesis sequence) investigations on these agents were severely constrained. The group of Magnus Rueping developed an asymmetric, organocatalytic, one-step synthesis of 2,3-dihydroquinazolines using 2-aminobenzamide and a variety of benzaldehydes as starting materials (*Angew. Chem., Int. Ed.* **2009**, *48*, 908–910). In this metal-free process, chiral phosphoric acid diesters (i.e., Brønsted acid **A**) promoted the asymmetric condensation/amine addition sequence. This resulted in a facile access to various enantioenriched 2,3-dihydroquinazolinones (er 90:10 to 99:1), with a preference for the formation of the more active *S*-enantiomer.



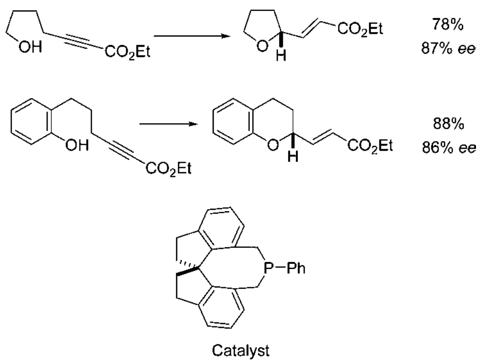
Phosphine-Mediated Conversion of Azides into Diazo Compounds

Myers and Raines at University of Wisconsin reported a mild route to transform azides into diazo compounds via acyl triazenes (*Angew. Chem., Int. Ed.* **2009**, *48*, 2359–2363). A screening of several phosphine initiators revealed that *N*-hydroxy succinimyl phosphinoesters can transform azido glycine derivatives into acyl triazenes. Further conversion into the diazo compounds required the use of wet solvent (THF/water) to prevent secondary reactions between the phosphine reactant and the diazo compound product. The reaction has a general scope, affording the desired diazo derivatives in excellent yields and purities after trivial removal of polar byproducts by a short-path column chromatography. Mechanistic reasoning drives reaction discovery and optimization along the manuscript.



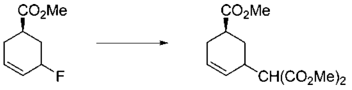
Phosphine-Catalyzed Enantioselective Synthesis of Oxygen Heterocycles

The applications of chiral phosphines as nucleophilic catalysts lag far behind the practical uses of their amine counterparts. In *Angew. Chem., Int. Ed.* **2009**, *48*, 2225–2227, Chung and Fu (at MIT) disclose the preparation of tetrahydrofurans, tetrahydropyrans, and dihydrobenzopyrans from hydroxyl-2-alkynoates catalyzed by a spirophosphepine. Typical reaction conditions involve the use of 10% catalyst, 50% benzoic acid, and an ethereal solvent such as THF or CPME at ~50 °C. Reaction highlights include the air stability of the solid phosphine (>3 days at rt) and the requirement of benzoic acid to achieve good yields and enantioselectivities.



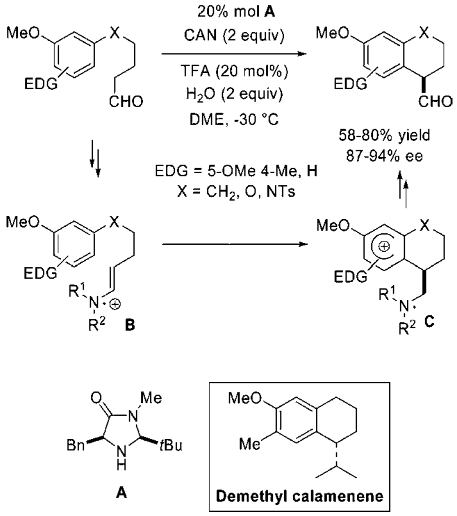
Pd-Catalyzed Substitution of Allylic Fluorides

Hazari, Gouverneur and Brown describe Pd-catalyzed alkylations of allyl fluorides with malonates in *Angew. Chem., Int. Ed.* **2009**, *48*, 1296–1299. Treatment of a fluorocyclohex-3-enecarboxylate with 20 mol % biphep-Pd (biphep = 2,2′-bis(diphenylphosphanyl)biphenyl), 2 equiv $NaCH(CO_2Me)_2$ and 2 equiv 15-crown-5 yields a 1:2 *syn*/*anti* ratio of the alkylated product in acceptable yields. Interestingly, the analogous allyl acetates give the alkylated product with virtual retention of configuration. In addition to convoluted observations beyond the scope of this highlight, kinetic studies reveal: (a) the leaving group propensity of F ($OCO_2Me > OBz \gg F \gg OAc$), (b) that the reaction rates increase with increasing $[F^-]$, and (c) the existence of an unusual stereochemical course.



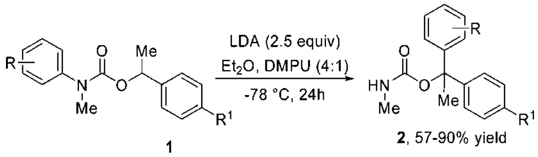
Enantioselective Friedel–Crafts-Type α-Arylation of Aldehydes

Treatment of electron-rich 4-aryl aldehydes with cerium(IV) ammonium nitrate in the presence of a chiral imidazolinone catalyst yielded bicycles resulting from an intramolecular Friedel–Crafts arylation. The methodology was applied by K. C. Nicolaou and co-workers to the synthesis of demethyl calamenene, a potent cytotoxic agent against human adenocarcinoma (*J. Am. Chem. Soc.* **2009**, *131*, 2086–2087). Optimized conditions include the use of the catalyst 2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolinone [(2*R*,5*R*)-**A**, 0.2 equiv], DME as the solvent, and water (2 equiv) and TFA (0.2 equiv) as additives. The absolute (*S*) configuration of the nascent stereogenic center indicates that the intramolecular attack occurs from the Si face of the enamine intermediate. Single-electron transfer oxidation by CAN affords a highly reactive radical cation **C** that collapses into a Wheland- or σ-complex **D**, an intermediate in traditional Friedel–Crafts reactions.



Arylation of Benzylic Alcohols by N-to C Aryl Migration of Lithiated Carbamates

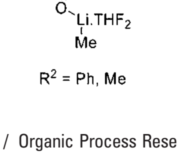
The group of Jonathan Clayden (University of Manchester) reported a novel reaction pathway for lithiated carbamates carrying *N*-aryl substituents (*J. Am. Chem. Soc.* **2009**, *131*, 3410−3411). Upon lithiation of **1**, the *N*-aryl group is cleanly transferred from *N* to *C*, resulting in arylated carbamate **2** that can be easily converted in an α,α-arylated secondary or tertiary alcohol (NaOEt, EtOH, heat). The authors provide mechanistic insight in the rearrangement and the selectivity of the 1,4-aryl transfer versus the 1,2-acyl shift by analyzing the organolithium intermediate species **A** using DFT calculations. The calculated energy barrier for the attack on the aryl is 14.4 kJ mol^{-1} lower than the energy for the attack on the carbonyl. Calculations also shed light on the role of DMPU and excess alkyllithium: during the course of the reaction, one lithium remains close to the carbonyl, whereas other migrates from the carbanion to the adjacent oxygen, freeing the carbanion for nucleophilic attack. Additionally, there was a calculated null energy barrier for the conversion of the intermediate to 2 to product 2 in the absence of THF, Li, and Me species. This suggests that DMPU solvates the Li cation and generates a reactive ion pair.



1

2, 57-90% yield

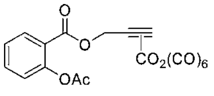
R = H, *p*-Me, *o*-Me, *p*-OMe, *p*-Cl, 2,3- or 3,4- benzo
R^1 = H, Cl



R^2 = Ph, Me

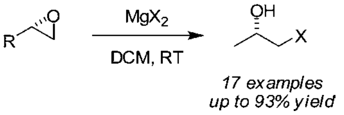
Aspirin Bioorganometallic Complex: Modulation of its Pharmacological Properties

Interest in the development of metal complexes in tumor therapy has been fueled by the tremendous success of cisplatin. In *Angew. Chem., Int. Ed.* **2009**, *48*, 1160−1163, a multi-institutional assembly of scientists reported the modulation of the pharmacological properties of aspirin (ASS) by formation of Co-ASS, a complex of its propynyl derivative with hexacarbonyldicobalt, $Co_2(CO)_6$. Aspirin's mechanism of action is based on the acetylation of a Ser residue in the active site of cyclooxygenases and the blockage of the oxidation of arachidonic acid. The incubation of COX-2 with aspirin showed exclusive acetylation on Ser516, whereas exposure of COX-2 to Co-ASS did not lead to acetylation of this residue, but of various lysine residues. Of these residues (Lys346) is close to the entrance channel of the active site of the enzyme. In addition, the anti-angiogenic effects of Co-Ass and ASS were studied in zebrafish: whereas developing zebrafish embryos treated with Co-ASS displayed defective vascularization, ASS did not show any effect at the same concentration. The different pharmacological properties of the two drugs may be a consequence of an altered interaction with the target enzyme, which is a consequence of the presence of an organometallic fragment.



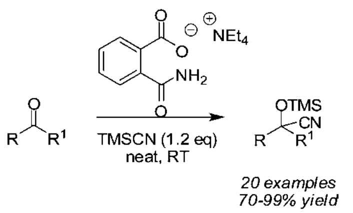
Co-ASS

A Convenient Protocol for Highly Regioselective Cleavage of Terminal Epoxides to *β*-Halohydrins



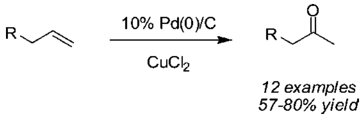
A simple reaction for the conversion of terminal epoxides to *β*-halohydrins with magnesium halides has been described by Zeng and co-workers at the East China University of Science and Technology in Shanghai (*Synlett* **2009**, *9*, 1511−1513). In general, modest to high yields were obtained with reaction times of less than one minute upon addition of freshly prepared $MgBr_2$ or MgI_2 (2.0 equiv, 2 M solution in THF) to a solution of epoxide in DCM. Presumably, the magnesium acts as a Lewis acid, polarizing the C−OMgX bond, which facilitates the S_N2-type attack of the halide ion on the less hindered terminal carbon. The addition of the halide is highly regioselective in the subset of epoxides, the authors report, with the exception of styrene oxide, which produced a mixture of regioisomers. Unfortunately, results for chloride addition with $MgCl_2$ were poor (<20% in most cases), which were attributed to the decreased nucleophilicity of the chloride ion.

An Expeditious Synthesis of Cyanohydrin Trimethylsilyl Ethers Using Tetraethylammonium 2-(Carbamoyl)benzoate as a Bifunctional Organocatalyst



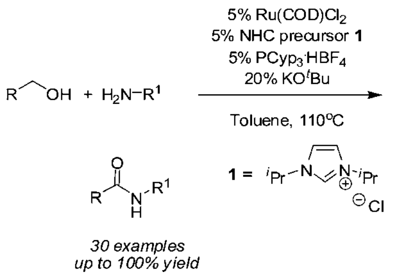
The addition of trimethylsilyl cyanide (TMSCN) catalyzed by tetraethylammonium 2-(carbamoyl)benzoate (TEA-CB) to aldehydes and ketones has been described by Dekamin and co-workers at the Iran University of Science and Technology in Tehran (*Tetrahedron Lett.* **2009**, *50*, 4063−4066). The TEA-CB catalyst is surprisingly prepared in excellent yield from phthalimide and tetraethylammonium hydroxide in ethanol and water, despite the presence of the acidic proton of the phthalimide. Cyanosilation in the presence of 0.5 mol % TEA-CB occurs in high yield with a variety of ketone and aldehydes including aromatic, heteroaromatic, conjugated and aliphatic substrates under solvent-free conditions at room temperature. Reaction times are short for aldehydes (<30 min) and reasonable for ketones (<4 h). The catalyst can be removed from the products using a standard aqueous workup.

Pd(0)/C-Catalyzed Efficient Wacker Oxidation of Functionalized Terminal Olefins



Wacker reactions typically employ soluble Pd(II) catalysts, which leads to the multiple issues including high cost, separation of the catalyst from products, and difficulty in recycling the catalyst. This issue has been addressed by Kulkarni and co-workers at the University of Pune in India (*Tetrahedron Lett.* **2009**, *50*, 2893−2894). Utilizing Pd(0)/C (10 mol %) with a catalytic amount of $CuCl_2$ (10 mol %), a variety of terminal olefins afford the corresponding methyl ketones in good yield under an oxygen atmosphere. After the authors perform an extractive workup, the recovered Pd/C could be recycled without loss of yield after regeneration by drying in the oven at 100 °C and addition of fresh $CuCl_2$.

Amide Synthesis from Alcohols and Amines by the Extrusion of Dihydrogen

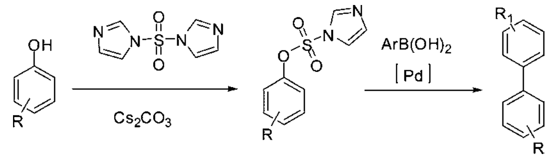


A direct amination from amines and alcohols with extrusion of two molecules of dihydrogen has been reported by Madsen and co-workers at the Center for Sustainable and Green Chemistry at the Technical University of Denmark (*J. Am. Chem. Soc.* **2008**, *130*, 17672−17673). The unexpected reaction was observed while trying to facilitate the alkylation of amines with alcohols. The mechanism is postulated to proceed via dehydrogenation of the alcohol to the aldehyde, condensation of the amine to form a hemiaminal, and further dehydrogenation of the hemiaminal to the amide. The most general catalysts can be generated *in situ* from Ru(COD)Cl_2, tricyclopentylphosphine ($PCyp_3$)·HBF_4, an unsaturated carbene precursor, and KO^{t}Bu, which activates the carbene. In toluene at reflux, primary alcohols and amines afforded the resulting amides in high yields. Steric bulk greatly influences the reaction. In the case of aniline and secondary amines, the temperature had to be raised to 163 °C to achieve modest yields with the major byproduct being self-condensation of the alcohol to the corresponding ether.

Imidazolylsulfonates: Electrophilic Partners in Cross-Coupling Reactions

Triflates have long been used in phenol activation toward cross-coupling reactions due to their superior performance as electrophilic coupling partners. Excellent reactivity, however, comes at the expense of stability, and triflates can often suffer from instability. This problem coupled with the high cost of trifluoromethanesulfonic anhydride and triflimide reagents, from which triflates are made, limits their usefulness on larger scales. Recently, the palladium-catalyzed cross-coupling repertoire has been expanded to include aryl tosylates and aryl mesylates as viable electrophilic partners. Aryl tosylates and mesylates are easily prepared and exhibit better stability than triflates and thus are more easily stored and handled. However, reactivity is diminished in palladium mediated coupling reactions.

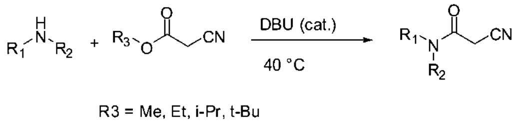
Aryl imidazolylsulfonates participate as electrophilic coupling partners in palladium-mediated cross-coupling reactions (Albaneze-Walker, J.; et al. *Org. Lett.* **2009**, *11*, 1463). The aryl imidazolylsulfonates display good stability while maintaining good reactivity in a variety of palladium-catalyzed coupling reactions. Imidazolylsulfonates are a practical and economic alternative to triflates.



Mild and Efficient DBU-Catalyzed Amidation of Cyanoacetates

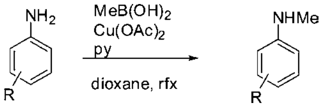
The formation of amide bonds is one of the most common reactions in organic synthesis. Generally, amides are formed either by direct coupling of an amine with a carboxylic acid that is activated in situ or in a two-step process involving activation of the carboxylic acid followed by reaction of the activated intermediate with an amine. Although many amidation strategies have been developed, none of these are universally applicable across substrate classes.

A mild, high-yielding, and practical protocol for the direct amidation of alkyl cyanoacetates using DBU has been reported by Price, K. E.; et al. (*Org. Lett.* **2009**, *11*, 2003). This method eliminates the need for activation of cyanoacetic acid and/or high temperatures.



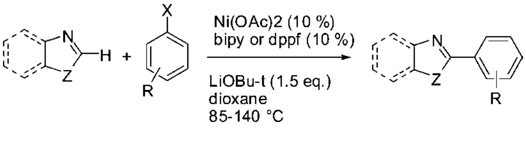
Selective Monomethylation of Anilines by $Cu(OAc)_2$-Promoted Cross-Coupling with $MeB(OH)_2$

Anilines are important compounds found throughout the pharmaceutical and agrochemical industries. In the past few years, C−N bond-forming reactions have become one of the most explored reactions, especially regarding *N*-arylation. Although selective monoarylation of anilines can be easily achieved, aniline monoalkylation (particularly *N*-methylation) represents a challenging task. *N*-Methylanilines are readily synthesized in high yields through the copper(II)-promoted coupling of anilines and methylboronic acid (Gonzalez, I.; et al. *Org. Lett.* **2009**, *11*, 1677). This method represents a new approach for the selective monomethylation of anilines, and it is the first reported example of a Chan−Lam coupling involving the use of methylboronic acid. An incubation period of the substrate with the copper reagent is needed before addition of the methylboronic acid.



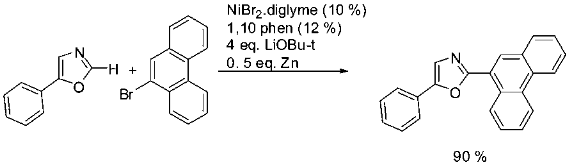
Nickel-Catalyzed Biaryl Coupling of Heteroarenes and Aryl Halides/Triflates

Heterobiaryl species are omnipresent in natural products and pharmaceuticals and are frequently used in organic materials or as ligands for metals. Therefore, the development of efficient methods to connect heteroarene and arene nuclei has been a topic of immense importance in chemical synthesis. Although the Pd-catalyzed cross-coupling reactions of metalated arene/heteroarene and halogenated arene/heteroarene species are undoubtedly among the most important and reliable methods for making heterobiaryls, the C−H bond arylation of heteroarenes holds significant potential to streamline overall synthetic routes. The importance of such processes is also connected with an apparent significance of catalytic C−H bond functionalization in chemical synthesis. Ni-based catalytic systems for the arylation of heteroarenes with aryl halides and triflates have been established (Canivet, J.; et al. *Org. Lett.* **2009**, *11*, 1733). $Ni(OAc)_2$/bipy is a general catalyst for aryl bromides/iodides, and $Ni(OAc)_2$/dppf is effective for aryl chlorides/triflates. Thiazole, benzothiazole, oxazole, benzoxazole, and benzimidazole are applicable as heteroarene coupling partners.



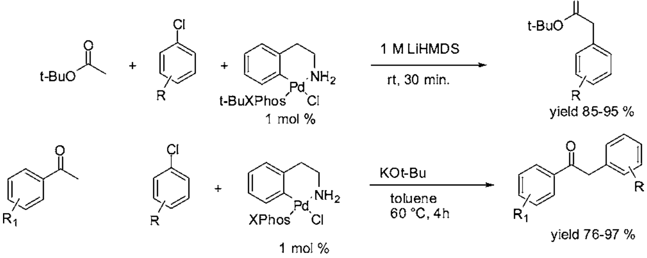
Nickel-Catalyzed Direct Arylation of Azoles with Aryl Bromides

Nickel catalyst systems for the direct C2 arylation of oxazoles and thiazoles have been developed by Miura, M.; et al. (*Org. Lett.* **2009**, *11*, 1737). The catalyst systems are cost-efficient and allow the use of various aryl bromides in the C−H arylation of azoles. The report shows the high potential of nickel catalysts in the direct C−H functionalization of heterocycles.



Selective Monoarylation of Acetate Esters and Aryl Methyl Ketones Using Aryl Chlorides

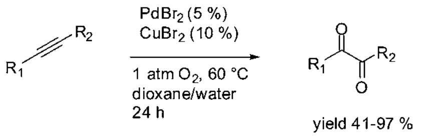
It has been well demonstrated that the use of Pd-catalyzed R-substitution reactions of carbonyl compounds can be an effective strategy to achieve the arylation and vinylation of enolates, often with excellent enantiomeric control. However, there are very few reported examples of the selective monoarylation of enolates from acetate esters and methyl ketones using aryl halides or sulfonates where the enolate is not biased toward monoarylation by the presence of an ortho substituent on the aryl halide or by the presence of a pre-existing R-substituent on the enolate. Such R-arylation reactions are typically unsuccessful, as a result of the instability of alkali ester enolates or the formation of significant amounts of diarylated side products. Simple, efficient procedures for the monoarylation of acetate esters and aryl methyl ketones using aryl chlorides have been presented by Buchwald, S. L.; et al. (*Org. Lett.* **2009**, *11*, 1773). Previously, no general method was available to ensure the highly selective monoarylation of these classes of substrates using aryl chlorides. Using palladium precatalysts recently reported by the Buchwald group, these reactions are easily accomplished under mild conditions that tolerate a wide array of heterocyclic substrates.



Wacker-Type Oxidation of Alkynes into 1,2-Diketones Using Molecular Oxygen

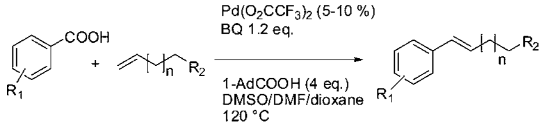
Pd-catalyzed Wacker oxidation of alkenes consists of one of the most important industrial processes employing transition metal catalysts. Owing to its high selectivity and excellent functional group tolerance, this transformation has found widespread application in synthetic chemistry. Compared with the impressive development of alkenes, Wacker-type oxidation of alkyne has not been explored thus far.

A new Wacker-type oxidation of alkynes catalyzed by $PdBr_2$ and $CuBr_2$ has been reported by Ren, W.; et al. (*Org. Lett.* **2009**, *11*, 1841), which opens an efficient access to 1,2-diketones using molecular oxygen. Under the optimized conditions, a variety of alkynes, including diarylalkynes, arylalkylalkynes, and dialkylalkynes, were compatible substrates in this transformation.



$Pd(O_2CCF3)_2$/Benzoquinone: A Versatile Catalyst System for the Decarboxylative Olefination of Arene Carboxylic Acids

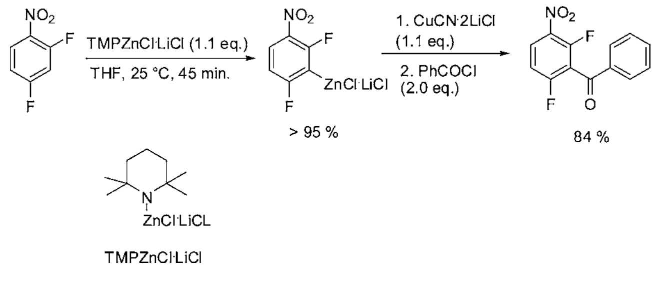
A versatile palladium catalyst system has been developed to effect the decarboxylative Heck coupling of a variety of arenecarboxylic acids with a wide range of olefins (Hu, P.; et al. *Org. Lett.* **2009**, *11*, 2341). The key to obtaining the efficient catalyst system is the use of 1-adamantanecarboxylic acid as additive. Alkyl-substituted olefins with coordinating groups were observed to provide significantly improved regioselectivity compared with other alkyl-substituted olefins lacking coordinating groups, and the acetate group of allylic ester was also tolerated in this reaction.



n=1 R2 = CO_2Et regioselectivity =13:1-63:1, E/Z> 16:1
n=0 R2 = Ph or CO_2Bu 48-99 % yield
n=0 R2 = OAc regioselectivity =8:1-29:1,

TMPZnCl · LiCl: A New Active Selective Base for the Directed Zincation of Sensitive Aromatics and Heteroaromatics

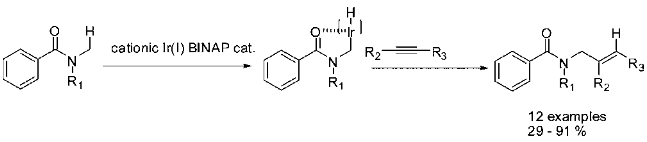
A wide range of polyfunctional aryl and heteroaryl zinc reagents were efficiently prepared in THF via direct zincation using TMPZnCl·LiCl, a new exceptionally mild and efficient base (Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837). Activated arenes and heteroarenes are metalated at room temperature. Remarkably, sensitive functions such as an aldehyde as well as a nitro group are tolerated, expanding significantly the scope of directed metalations.



Cationic Ir(I)-Catalyzed sp3 C−H Bond Alkenylation of Amides with Alkynes

The direct functionalization of unactivated carbon−hydrogen bonds has attracted much attention in both academic and industrial fields over the past decade. Especially, transition metal catalysts have been comprehensively investigated as a powerful tool in C−H activation/carbon−carbon or carbon−heteroatom bond-forming processes. However, transformation at sp3 C−H bonds is still a challenging topic due to the lack of a π-electron system which would facilitate the interaction between catalyst and substrate.

A cationic Ir(I)-BINAP catalyst cleaved sp3 C−H bonds of arylamides rather than sp2 C−H bonds, which was followed by alkenylation with alkynes to give allylamides (Shibata, T.; et al. *Org. Lett.* **2009**, *11*, 1821). Several types of amides and alkynes were suitable as substrates, and the corresponding allylamides have been obtained in moderate to good yield.



Bayesian Framework for Building Kinetic Models of Catalytic Models

For reactor and reaction design, models derived using statistical design of experiments (DoE) are extremely useful. Given the need to execute a relatively small number of experiments, such models are very practical and provide acceptable predictive power. When higher-quality models are needed, such as for cases of molecular design in catalyst development, the quality of DoE models is insufficient. DoE models, like any models derived using linear regression, suffer from the drawbacks of the linearization itself, model bias, experimental error, and point estimates for model parameters. Two teams from Purdue University (Hsu, S.-H., et al. *Ind. Eng. Chem. Res.* **2009**, *48* (10), 4768) report a solution for the development of high quality models: Bayesian statistics. The use of Bayesian statistics does not require linearization, and provides distributions (rather than point estimates) for model parameters. In the past, an important challenge in the use of Bayesian statistical models was the need for significant computational resources. In the case studies reported, linear or classical nonlinear optimization methods were incapable to describe the systems investigated. Existing statistical design of experiments software platforms have not included Bayesian statistics yet, but it is conceivable that in the near future, commercial platforms will include Bayesian modeling too. This paper perhaps qualifies as a mini review, at 24 pages and 57 references.

Effect of Sample Line Characteristics on the Dynamic Monitoring of Fluid Concentrations

Quality by Design (QbD) requires, in addition to statistical design of experiments (DoE) and scale-up science, the use of effective process analytical technologies (PAT). Ideally, sensors are placed in the equipment (reactor) in any suitable position. In reality, only a limited number of analytical methods can accommodate this requirement, and can be truly used "on-line". Other methods, sometimes called "at-line", use a sampling line connecting the point of sampling to the point of analysis.

For many types of processes, concentration monitoring can be a valuable part of a QbD methodology. When sampling lines are used, various experimental errors are expected to impact the quality of the concentration

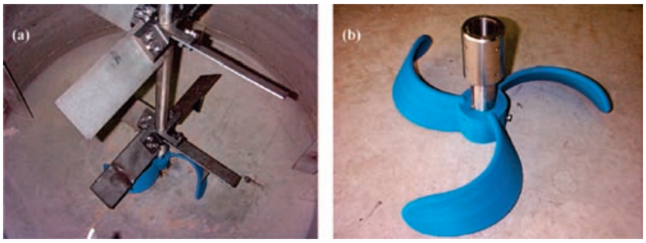


Figure 1. **(a) Patented KT-3 tickler (D_t = 59 cm) mounted in a 152-cm i.d. tank (D_t/T = 0.39), below dual 76-cm PBTs (D/T = 0.50), by means of the shaft extension piece shown in (b).**

measurements, because of fluid/heat transport and adsorption/desorption phenomena occurring in the sampling line. In order to understand and thus quantify such errors, a certain level of modeling of the sampling line is necessary. A group from the University of Arizona (Juneja, H. S.; et al. *Ind. Eng. Chem. Res.* **2009**, *48* (11), 5481) describes such a modeling effort for the case of water and isopropanol concentration measurements. Among the analytical instruments employed were an atmospheric pressure ionization mass spectrometer, a cavity ring down spectrometer, and an electron impact mass spectrometer. Concentration step changes and various profiles were used by the authors to characterize the sampling line. As expected, errors introduced by the sampling line are very significant for fast changing (highly transient) signals. Parameters that were important for the quality of the measurements were temperature and residence time. Such a methodology, modified as needed, can be used for other “at-line” measurements.

KT-3: A Novel Tickler for Solids Removal from Slurry Vessels

For all organic chemical processes that occur in solid−liquid systems, slurry handling must be carefully evaluated during process scale-up. Moreover, for the particular case of high value product crystallization processes, the apparently trivial matter of effective evacuation of the solids, must also be carefully investigated. To quickly remove the solids when the slurry level recedes bellow the main impeller/s, various practical, creative methods are employed, such as liquid sprays. A better solution for effective evacuation of slurry vessels was invented by Dow scientists (Cope, R. F.; et al. *Ind. Eng. Chem. Res.* **2009**, *48* (10), 4990), the KT-3 tickler (see Figure 1). This is a relatively small, curved impeller, installed under the lowest main impeller. The KT-3 edges are rounded to allow for coating, if needed. The KT-3 design was also adopted by mixing equipment manufacturers such as Pfaudler and DeDietrich. The performance of the KT-3 is reported, together with certain nonproprietary design guidelines. Additional applications of the KT-3 may include the handling of sticky, high-viscous media. It is noteworthy that no CFD graphs are included in this report.

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