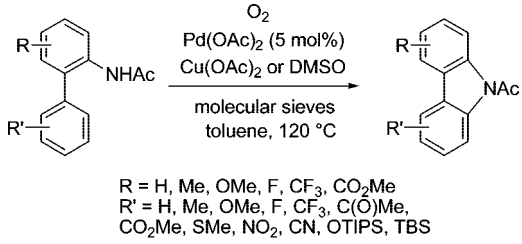
Organic Process Research & Development **2008,** *12,* 1021–1030

Highlights from the Literature

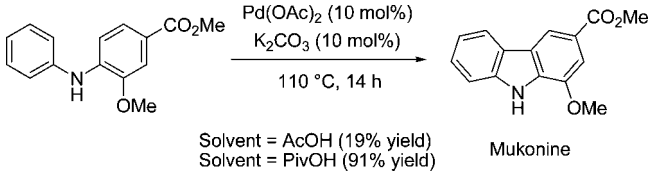
Some Items of Interest to Process R&D Chemists and Engineers

Pd-Catalyzed Synthesis of Carbazoles via C−H Functionalization



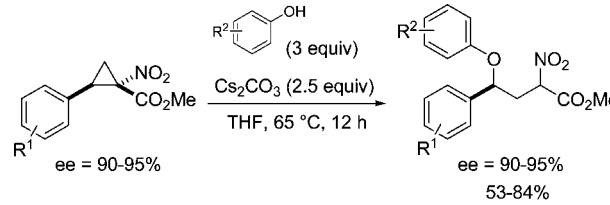
Elaborating on earlier work from within the group, Buchwald and co-workers now present a full account detailing the scope of Pd-catalyzed carbazole synthesis via C−H functionalization (*J. Org. Chem.* **2008**, *73*, 7603−7610). An observation made here is that the overall oxidation can take place in the absence of a Cu source to act as a reoxidant, when DMSO is used as solvent (a tactic frequently employed for processes of this type). The effect of *N*-protecting groups other than acetyl was studied, and although the $PhSO_2$- group gave good results, the use of benzamide, BOC or trifluoroacetamide groups led to low yields of the desired carbazoles. A variety of functional groups can be tolerated on the aryl rings including esters, nitriles, silyl ethers, and an arylsilane. A total of 25 examples with yields ranging from 59−99% are presented along with applications towards the synthesis of three naturally occurring carbazole-based compounds.

Pd-Catalyzed Oxidative Biaryl Synthesis



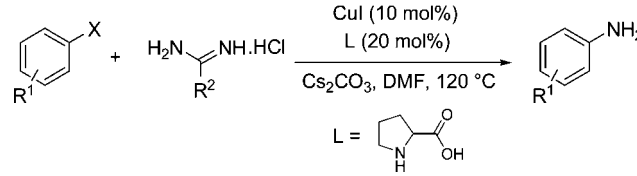
An alternative approach to the synthesis of carbazoles, also based on C−H activation chemistry, is described by the group of Fagnou (*J. Org. Chem.* **2008**, *73*, 5022−5028). Rather than forming a new C−N bond, this process forms a new C−C bond in closing the five-membered ring of the carbazole system. The use of pivalic acid as the reaction solvent (instead of acetic acid) is a key modification that results in greater reproducibility, higher yields, and broader scope. This expanded scope is illustrated by the use of electron-rich diarylamines in the synthesis of three naturally occurring carbazole products: Murrayafoline A, Mukonine, and Clausenine. Additionally, a variety of side products have been characterized, which serve to indicate competing reaction pathways and point the way towards improved efficiency in the future.

Nucleophilic Addition of Phenols to Nitrocyclopropanecarboxylates

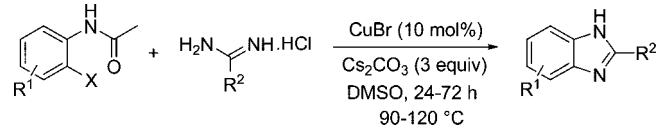


Charette and co-workers in Canada report on a procedure for the synthesis of the 3-aryl-3-aryloxypropane fragment commonly found in pharmaceuticals (*J. Org. Chem.* **2008**, *73*, 6838−6840). Starting from enantio-enriched nitrocyclopropanecarboxylates (substrates themselves obtained via asymmetric cyclopropanation of styrene derivatives) nucleophilic addition of phenols can be achieved using Cs_2CO_3 as the base in THF at 65 °C. In the three enantio-enriched examples studied the additions appeared to proceed via an S_N2 mechanism with preservation of ee and inversion of absolute configuration at the C-4 center. A total of 12 examples are presented along with an extension to the synthesis of the antidepressant atomoxetine in 90% ee.

Cu-Catalyzed Synthesis of Primary Arylamines and Benzimidazoles



Fu, Qiao and co-workers report on the use of amidine hydrochlorides as ammonia surrogates for the synthesis of primary arylamines from aryl halides (*J. Org. Chem.* **2008**, *73*, 6864−6866). Using a CuI/proline catalyst system (10 and 20 mol %, respectively), Cs_2CO_3 as the base, and DMF as the solvent the reaction is assumed to proceed via sequential arylation of the amidine and then hydrolysis of the intermediate to give the target products. This is a convenient, inexpensive, and practical approach to primary arylamines.



In a separate report, the same authors describe more Cu-catalyzed chemistry employing amidines as the nucleophile, this time for the preparation of benzimidazoles (*J. Org. Chem.* **2008**, *73*, 7841−7844). When the aryl halide used for amidine arylation is an *o*-haloacetoanilide derivative, the intermediate undergoes hydrolysis and then cyclization (loss of ammonia) to yield benzimidazoles. A drawback, however, is the need for extended reaction times at elevated temperature in order to

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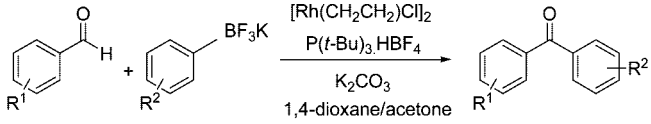
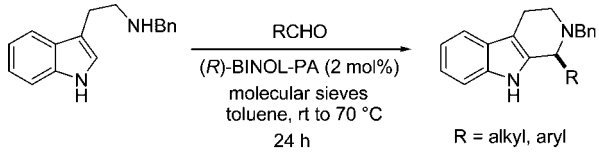
cyclize the intermediate. A total of 14 examples are presented with yields ranging from 45−89%, including some cases where the initial NH-benzimidazole products are further arylated in the same pot by addition of another aryl iodide.

Benzophenones via Rh-Catalyzed Oxidative Arylation of Aldehydes



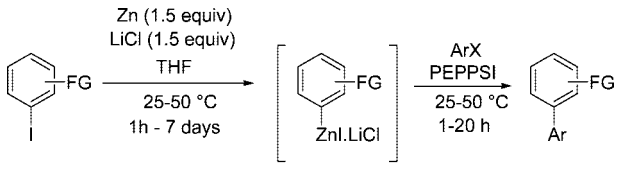
Genet, Darses, and co-workers report on practical improvements to earlier procedures that allow for the synthesis of benzophenones starting from benzaldehydes and potassium aryltrifluoroborates (*J. Org. Chem.* **2008**, *73*, 7800−7802). Stable HBF_4-phosphonium salts (with a catalytic equivalent amount of added K_2CO_3) can be used in place of the easily oxidized tri-*tert*-butylphosphane with comparable or even better results. A notable feature of this process is the use of acetone as a cosolvent and oxidant for the proposed intermediate rhodium-bound alkoxide obtained after reaction with the aldehyde; the acetone is thought to function as a "hydride" trap and appears to be more reactive in this sense than the starting aldehyde. The current work features several sterically hindered examples, including the formation of a tetra-ortho-substituted benzophenone. Typical catalyst loadings are 1.5 mol %.

Enantioselective BINOL-Phosphoric Acid-Catalyzed Pictet−Spengler Reactions



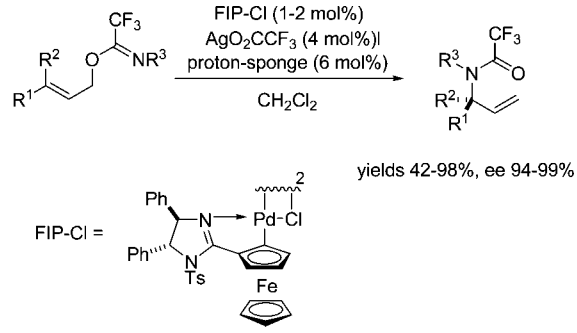
According to a report from the Hiemstra group, optically active tetrahydro-β-carbolines can be synthesized via asymmetric Pictet−Spengler reactions of *N*-benzyltryptamine, using (*R*)-BINOL-phosphoric acids as Brønsted acid catalysts (*J. Org. Chem.* **2008**, *73*, 6405−6408). The tetrahydro-β-carbolines were obtained in yields ranging from 77% to 97% and with ee values up to 87%. The triphenylsilyl-substituted BINOL-phosphoric acid proved optimal for the reaction with aromatic aldehydes. For aliphatic aldehydes, 3,5-bis-trifluoromethylphenyl-substituted BINOL-phosphoric acid was identified as the best catalyst. The paper describes 15 examples with yields ranging from 77 to 97% and ee's from 0 to 87%.

One-Pot Negishi Cross-Coupling Reactions of in Situ Generated Zinc Reagents



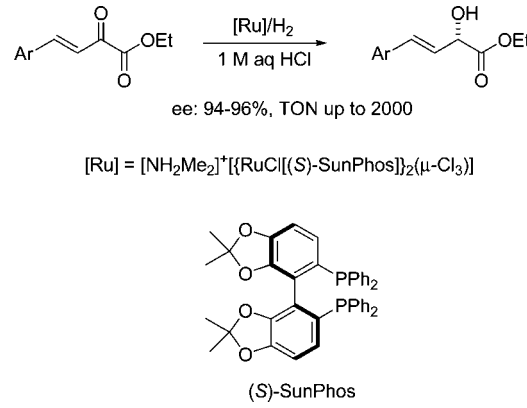
A report from the Knochel group describes their continued expansion of the scope of functionalized organometallic intermediates (*J. Org. Chem.* **2008**, *73*, 7380−7382). In situ generated aryl, heteroaryl, alkyl, or benzylic polyfunctional zinc reagents, obtained by the addition of zinc and LiCl to the corresponding organic iodides, undergo smooth Pd-catalyzed cross-coupling reactions with aryl bromides, chlorides, and triflates in the presence of the Pd-based PEPPSI catalyst system. A wide range of functionalized products were prepared in one-pot processes, demonstrating the utility of this approach.

Catalytic Asymmetric Aza-Claisen Rearrangement of Trifluoroacetimidates



Peters and co-workers at the ETH describe an asymmetric aza-Claisen rearrangement of *N*-aryl- and *N*-alkyl-substituted trifluoroacetimidates that is catalyzed by a ferrocenium imidazoline palladacycle (FIP-Cl) (*Synlett* **2008**, *10*, 1495−1499). Previous reports from this group had focused on the rearrangement of only substrates bearing an *N*-PMB protecting group, from which one can ultimately derive chiral primary allylic amines. The current work has extended the chemistry to include both *N*-alkyl and *N*-aryl groups, which lead to the generation of chiral secondary amine products after reductive or hydrolytic removal of trifluoroacetamide protecting group. The reaction yield (and necessary catalyst loading) is affected by the steric bulk of the substrates while the enantioselectivities are in general very high.

Enantioselective Sequential Hydrogenation of Ethyl 2-Oxo-4-arylbut-3-enoate

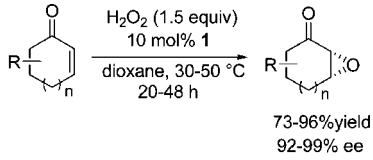


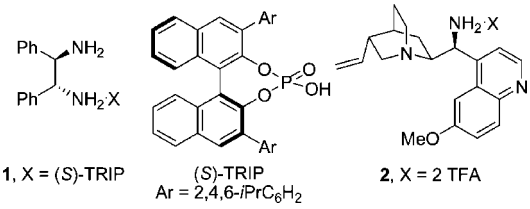
The hydrogenation of (*E*)-ethyl 2-oxo-4-arylbut-3-enoates with $[NH_2Me_2]^+[\{RuCl\ [(S)$-SunPhos$]\}_2(\mu\text{-}Cl_3)]$ can afford ethyl 2-hydroxy-4-arylbutyrates with 94−96% ee according to a report from Zhang and co-workers (*J. Org. Chem.* **2008**, *73*, 7209−7212). The starting materials are conveniently prepared

via base-mediated condensation between substituted benzaldehydes and pyruvic acid. Various ligands were evaluated, and the biaryl diphosphine SunPhos proved optimal. The use of an acid additive was important to achieve high ee, and HCl in particular was better than other Brønsted acids tested. Further investigation of this system uncovered the order of reactivity and established that the carbonyl is reduced first followed by the olefin. Hydrolysis of ethyl 2-hydroxy-4-phenylbutyrate (ee 93%) provided the 2-hydroxy-4-phenylbutyric acid with 81% yield at 99% ee after a single recrystallization from 1,2-DCE.

Catalytic Asymmetric Epoxidation of Cyclic Enones

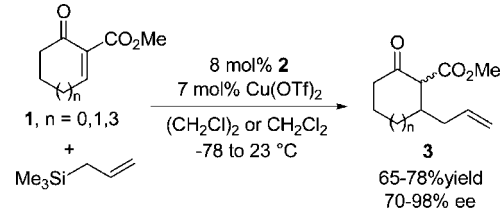
Examples for the enantioselective epoxidation of olefins abound in the literature. In contrast, a highly enantioselective epoxidation of simple cyclic enones remains elusive. Benjamin List and co-workers found that cyclic enones are readily epoxidized with excellent enantioselectivities upon treatment with H_2O_2 in the presence of a catalytic amount of a chiral, primary ammonium salt (*J. Am. Chem. Soc.* **2008**, *130*, 6070−6071). Two useful catalysts were identified: (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (DPEN) mono-TRIP salt **1** and quinine-derived TFA salt **2**. α-Substituted enones were unreactive under the reaction conditions (1.5 equiv H_2O_2, 10 mol % catalyst, dioxane, 30−50 °C). Moreover, catalyst **2** was particularly suitable for the oxidation of β-substituted cyclohexenones. The reaction is proposed to proceed via an iminium ion, with the second basic amine of the catalyst organizing the transition state and directing the attack of the H_2O_2 towards one enantioface of the double bond.

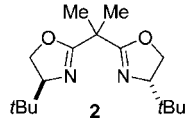




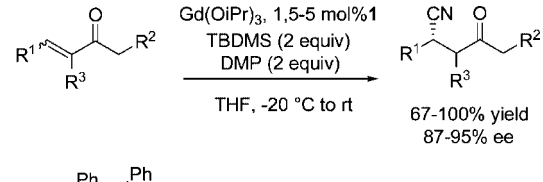
Conjugate Additions to α,β-Unsaturated Carbonyl Compounds

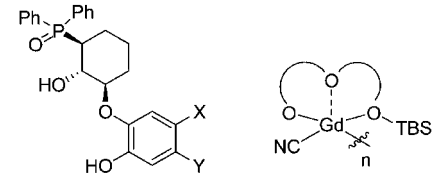
Shizuka and Snapper (Boston College) reported the catalytic enantioselective conjugate addition of allyltrimethylsilane to various activated cyclic enones with selectivities surpassing 98% ee using a commercially available reagent, catalyst, and ligand (*Angew. Chem., Int. Ed.* **2008**, *47*, 5049−5051). The 1,4-addition to unsaturated carbonyl compounds **1** proceeds to >95% conversion in the presence of $Cu(OTf)_2$ (10 mol %) and di(*tert*-butyl)-bis(oxazoline) (box) ligand **2**. Five-, six-, and eight-membered rings reacted effectively with allyltrimethylsilane at low temperatures (0 to −78 °C) to afford the desired 1,4-substituted products **3** in good yields (65−78%) and selectivities (70−98% ee). The conversion of sterically hindered substrates required higher temperatures (23 °C), which in turn led to eroded selectivities. The use of methallyltrimethylsilane resulted in low selectivities presumably due to competitive, background noncatalytic reactions. The optically enriched allylated products can be transformed into diverse building blocks such as decalines and enolphosphates.





The design of an efficient asymmetric conjugate addition of cyanide to enones requires the suppression of the 1,2-addition pathway, as well as enantioselection. Using Gd catalysts, Tanaka, Kanai, and Shibasaki synthesized β-cyano ketones from enones with high enantioselectivities (*J. Am. Chem. Soc.* **2008**, *130*, 6072−6073). The optimized conditions used a catalytic charge of the Gd catalyst derived from ligands **1**, along with TBSCN and 2,6-dimethylphenol (DMP). The active catalysts were defined complexes **2** with higher-order structures (e.g. Gd:**1** = 2:3) generated through modular self-assembly. 1,4-Addition products were exclusively obtained in high to excellent enantioselectivities from linear, branched, aryl, and cyclic enones. Mechanistic studies showed that the Gd catalyst is an O-TBDMS complex, which converts cyanohydrins into their corresponding 1,4-products: the catalyst promotes the retro-cyanation from the cyanohydrin and the subsequent irreversible asymmetric 1,4-addition of cyanide. Interestingly, the conversion of the starting material to the cyanohydrin and then to the1,4-product can be followed by TLC.

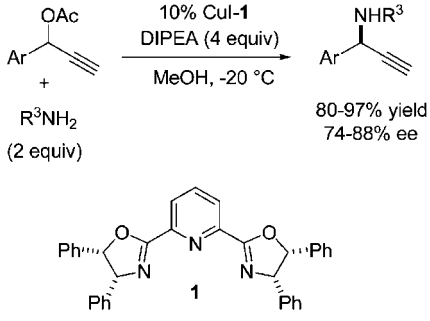




Enantioselective Cu-Catalyzed Propargylic Amination

In contrast to allylic substitution, metal-catalyzed propargylic substitution has been poorly developed. Inspired by the work of Murahashi and co-workers (see *J. Org. Chem.* **1994**, *59*, 2282−2284), the group of Jan H. van Maarseveen at the University of Amsterdam developed an asymmetric version of the Cu-catalyzed amination of propargylic acetates to render versatile propargylic amines (*Angew. Chem., Int. Ed.* **2008**, *47*, 3777−3780). During the screening phase, CuI was selected as the preferred copper salt, and the addition of a base proved

crucial in terms of yield and selectivity, with best results obtained using DIPEA. Substrates with an aromatic substituent at the propargylic position were converted (MeOH, −20 °C) into the corresponding amines in high yields (80−97%) and enantioselectivities (74−88% ee's). In contrast, aliphatic substrates were less reactive and required higher temperatures (40 °C). No reaction occurred with an internal acetylene, which provides evidence for the role of an acetylenic hydrogen in the mechanism. The optical purity of the products was easily increased to >99% ee by high-yielding crystallizations.

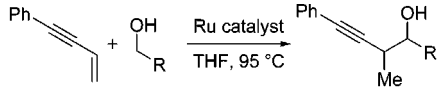


Ar = Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2,4-$Me_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 2-Pyridyl, 1- and 2-Naphthyl

R^3 = 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, Ph

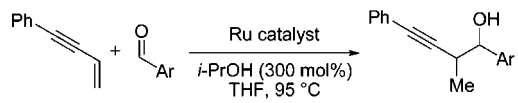
Ru-Catalyzed Carbonyl Propargylations

Krische and co-workers at University of Texas at Austin reported a new Ru-catalyzed C−C bond-forming transfer hydrogenation in *Angew. Chem., Int. Ed.* **2008**, *47*, 5220−5223. The transformation facilitates carbonyl propargylations from alcohols or aldehydes in the absence of allenylmetal reagents by using 1,3-enynes as propargyl donors. Mechanistic studies indicate that the alcohol (added *i*-PrOH in the case of aldehyde propargylation) transfers hydrogen to the Ru catalyst to generate a Ru hydride species that promotes enyne hydrometalation. In the end, the reaction between the nucleophile−electrophile pairs generated in situ affords the product of hydrogenative coupling. Standard reaction conditions employ 1 equiv of alcohol or aldehyde, 2 equiv of enyne, and 5 mol % of an equimolar mixture of [$RuHCl(CO)(PPh_3)_3$] and dppf (dppf = 1,1′-bis(diphenylphosphino)ferrocene) to provide the coupling products in good yields.



R = Ar, alkenyl, alkyl

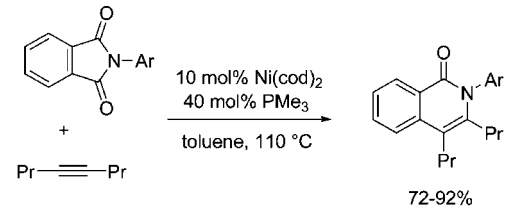
42%-91% yield



61%-91% yield

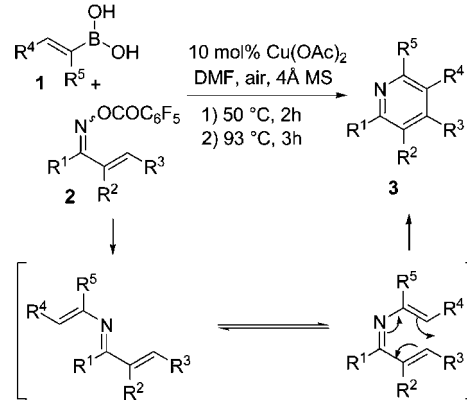
Metal-Catalyzed Synthesis of Isoquinolones and Pyridines

Kashita, Matsubara, and Kurahashi reported a novel Ni-catalyzed reaction of alkynes with electron-deficient *N*-arylphthalimides to provide isoquinolones (*J. Am. Chem. Soc.* **2008**, *130*, 6058−6059). The C−N bonds were susceptible to the nucleophilic attack of the Ni(0) complex, allowing the intermolecular addition to alkynes via decarboxylation. Treatment of *N*-arylphthalimides with 4-octyne using the optimized conditions (10 mol % $Ni(cod)_2$, 40 mol % PMe_3, toluene, 110 °C) afforded the target addition products in good yields. The authors propose a mechanism involving three nickelacycle intermediates: (1) a six-membered nickelacycle arising from the nucleophilic attack of Ni(0) to the C−N amide bond; (2) a five-membered nickelacycle resulting from decarbonylation, and (3) a seven-membered nickelacycle generated from the insertion of the alkyne to the C−Ni bond. Reductive amination of the latter gives the desired isoquinolone and regenerates the Ni(0) complex.



Ar = 2-Py, 3-Py, 4-Py, 2,6-diazine, 1-pyrrol

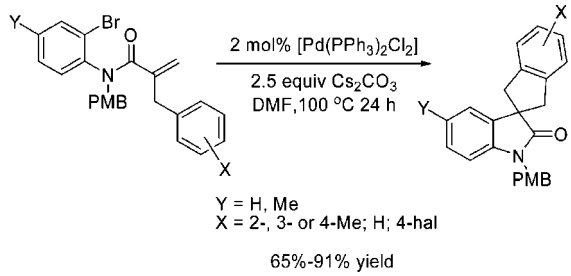
In *J. Am. Chem. Soc.* **2008**, *130*, 6918−6819 the group of Liebeskind at Emory University reported the construction of substituted pyridines by a cascade reaction from readily available starting materials. The process entails (1) the Cu-catalyzed cross-coupling of alkenyl boronic acids **1** and α,β-unsaturated ketoxime-*O*-perfluoroborates **2**;, (2) electrocyclization of the resulting azatriene, and (3) aerobic oxidation to afford highly substituted pyridines **3** in moderate to excellent isolated yields (43−91%). The neutral reaction conditions allow broad functional group tolerance (chloride, bromide, ester, nitrile, nitro), resulting in diversely substituted pyridine cores (aryl, heteroaryl, alkyl). Reaction of the transient 3-azatrienes with water —generated by the boronic acid−boroxine equilibrium—is prevented by the addition of 4 Å molecular sieves. The methodology is orthogonal to classic cross couplings and provides substrates for further elaboration



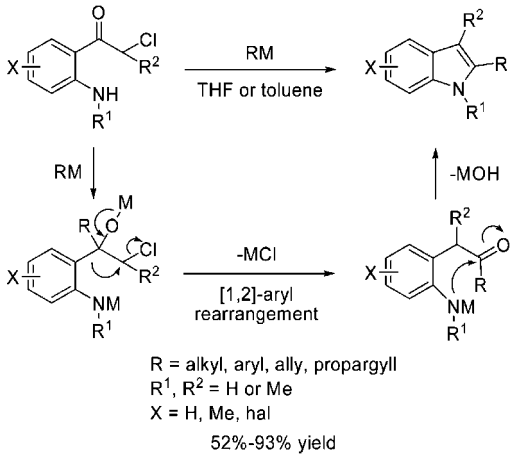
New Methods to Prepare Indoles

The importance of the oxindole scaffold in pharmaceutical chemistry cannot be overstated. Ruck and co-workers at Merck Research Laboratories exploited a tandem Pd-catalyzed Heck/C−H functionalization to prepare spiro-oxindoles from *N*-(2-bromophenyl)acrylamides in excellent yields (*Angew. Chem., Int. Ed.* **2008**, *47*, 4711−4714). Screening studies resulted in the identification of commercially available [$Pd(PPh_3)_2Cl_2$] as the optimal catalyst using Cs_2CO_3 as a base in DMF at 100

°C. The proposed catalytic cycle involves the following sequence: (1) oxidative addition of the Pd catalyst to the C−Br bond, (2) 5-*exo*-trig Heck cyclization to give an alkylpalladium intermediate, (3) aromatic C−H insertion to afford a six-membered palladacycle, and (4) reductive elimination to provide the desired oxindole.

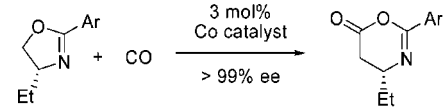


The indole framework is also the subject of synthetic studies by another group at Merck Research Laboratories (Pei, Chen, and co-workers, *Angew. Chem., Int. Ed.* **2008**, *47*, 4231−4233). The authors report the regioselective preparation of 2-substituted indoles from the reaction of chloroacetophenones and organometallic nucleophiles. General experimental conditions involve the treatment of the ketone with 2.5 equiv of nucleophile in either THF or toluene at −10 °C for 15 min, and then at room temperature for 15 min to 2 h. The reaction tolerates a variety of carbon nucleophiles and substituted ketones. Mechanistic studies support the formation of an intermediate alkoxide that undergoes a [1,2]-aryl rearrangement followed by intramolecular condensation to afford the indoles.



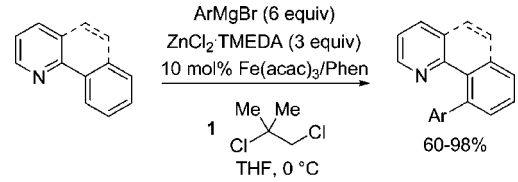
Catalytic Synthesis of β-Amino Acid Derivatives

The importance of β-amino acids in biomedical sciences has stimulated the development of modern synthetic methods for the generation of enantiopure β-amino acid derivatives. The group of Prof. Coates at Cornell University describes the catalytic carbonylation of enantiopure oxazolines to give oxazinones that retain the absolute configuration of their oxazoline precursors (*Angew. Chem., Int. Ed.* **2008**, *47*, 3979−3983). These oxazinones are labile compounds that yield β-amino acid derivatives by reaction with nucleophiles. In a typical experiment, an equimolar mixture of 3−10 mol % [$Ph_3SiCo(CO)_4$] and BnOH promotes the carbonylation of a 0.5 M solution of enantiopure oxazoline in DME using 54 atm CO at 80 °C for 6 h. Isolated oxazinone yields and ee's are excellent (86−99% and >99%, respectively). In situ IR kinetic studies complete the manuscript, affording elegant insights into the reaction mechanism.



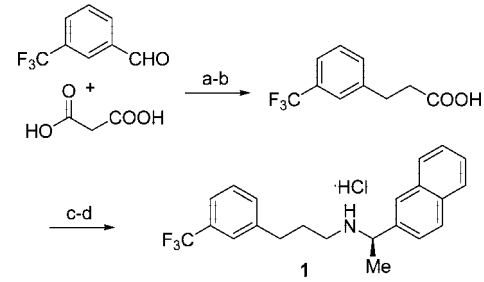
Arylation of 2-Aryl Pyridines

Nakamura and co-workers reported the arylation of 2-arylpyridine derivatives based on a homogeneous, Fe-catalyzed, C−H bond activation (*J. Am. Chem. Soc.* **2008**, *130*, 5858−5859). The formal transformation is the nucleophilic displacement of the ortho hydrogen atom by an arylzinc. A solution of ArMgBr and $ZnCl_2$·TMEDA reacted with 2-arylpyridines in the presence of the catalytic system [Fe(acac)$_3$, 1,10-phenantroline (phen), 1,2-dichloro-2-methyl propane, **1**] at 0 °C to yield the coupled product. The transformation was faster when the aryl component featured electron-withdrawing substituents, whereas sterically hindered aryls (R = Me) exclusively yielded products arylated para to the Me group. The reaction required 2 equiv of PhZnBr; 1 equiv for the reaction and 1 equiv to remove the H atom, as demonstrated by deuterium-labeling experiments. The combination of dihalide **1**-that is converted to the corresponding olefin, with no evidence of the formation of metallic species, Zn, Fe, Mg, and TMEDA, was crucial for the success of the reaction. The authors postulate the complexation of phenantroline to Fe and TMEDA to Zn, and a redox cycle in which the dihalide is the electron acceptor.



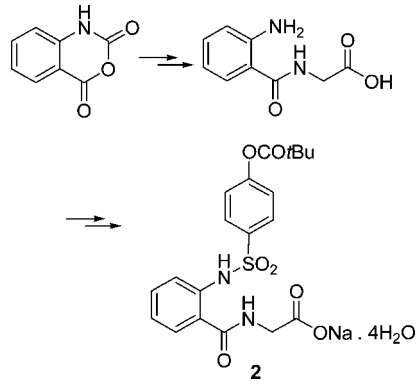
Efficient Synthesis of Sivelistat and Cinacalcet

Scientists at Macleods Pharmaceuticals Ltd. in Mumbai have devised efficient syntheses for two molecules with different indications (*Synth. Commun.* **2008**, *1512−1517* and 1714−1724). Calcimimetics are orally active molecules that decrease the secretion of parathyroid hormone by activating calcium receptors. The first-in-class of these compounds, cinacalcet (**1**) (Sensipar, Amgen) was prepared using the following sequence: (a) Knoevenagel−Doebner condensation of trifluorobenzaldehyde and malonic acid, (b) catalytic hydrogenation, (c) acid chloride formation and condensation with (*R*)-ethyl naphthyl amine, (d) reduction of the resulting amide with sodium borohydride/I_2. **1** could be directly isolated as the hydrochloride salt.



Sivelistat sodium hydrate (Ono-5646, Elaspol) is a selective inhibitor of human neutrophile elastase jointly developed by Lilly and Ono for the treatment of acute lung injury associated with systemic inflammatory response syndrome (SIRS). The molecule

has recently found an application in cosmetic medicine due to its antiwrinkle activity. Starting from isatoic anhydride, sivelistat sodium tetrahydrate was obtained in four steps in 41% overall yield.



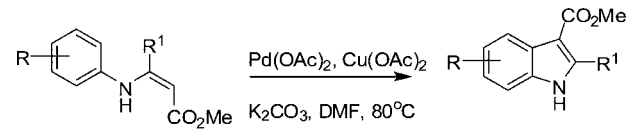
Paclitaxel-Initiated Polymerization of Lactide: Formulation of Nano-encapsulates

Various polymeric nanoencapsulates (NEs) prepared by coprecipitating hydrophobic polymers and drugs have been developed to control the release of Paclitaxel (Ptxl) and reduce its side effects. Tong and Cheng, from the Department of Material Science and Engineering at the University of Illinois at Urbana-Champaign reported the use of drug-initiated living polymerization to facilitate the controlled preparation of Paclitaxel−polylactide (PLA) nanoconjugates at room temperature (*Angew. Chem., Int. Ed.* **2008**, *47*, 4830−4834). Polymerization of DL lactide was initiated by a metal alkoxide formed in situ by reaction of the hydroxyl moieties of Ptxl and 1 equiv of the active metal complex [(BDI)MgN(TMS)$_2$] (BDI = 2-[(2,6-diisopropylphenyl)amino]-4-[(2,6-didsopropylphenyl)imino-2-pentene. Ptxl was quantitatively incorporated into the polyester by reaction of the other OH moieties, with drug loadings controlled by adjusting the LA/Ptxl ratio. Ptxl is gradually released upon cleavage of the ester bond with terminal PLA: 70% of Ptxl was released over 6 days versus 82% in 24 h from Ptxl-PLA NEs, in which the release is controlled by diffusion. PEGylation of the surface of the nanoconjugates by noncovalent interactions yields vehicles with predefined drug loadings, high loading efficiencies, controlled release kinetics without burst release effects, and narrow particle size distribution.

Use of a Table-Top Centrifugal Contact Separator

In *Angew. Chem., Int. Ed.* **2008**, *47*, 3905−3908, scientists from DSM Pharmaceutical Products and the University of Groningen report the use of a table-top centrifugal contact separator (CCS) to separate oil and water in oil spills and for the continuous extraction of products in fermentation. A very didactic cartoon depicts the CCS, which is essentially a centrifuge. The two immiscible phases are sequentially (1) introduced through a small annular mixing zone, (2) mixed fast and efficiently, and (3) centrifuged and gradually separated while moving upwards. The phases leave the device through separate exits. The CCS is used for the preparation of biodiesel from sunflower oil by base-catalyzed methylation (1% NaOMe, MeOH, 60 °C) and for the esterification of oleic acid with 1-butanol catalyzed by a *Rhyzomucor miehei* lipase (heptane/buffer phosphate, pH 5.6). The featured equipment can fit in a fume hood and can produce 100 kg of product in a few days.

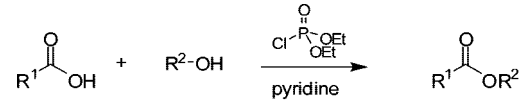
Palladium-Catalyzed Oxidative Cyclization of *N*-Aryl Enamines to Indoles



26 examples
53-85%

A novel synthesis of functionalized indoles utilizing catalytic palladium has been disclosed by Glorius and co-workers (*Angew. Chem., Int. Ed.* **2008**, *27*, 7230−7233). The intramolecular oxidative cyclization exploits selective activation of two C−H bonds, eliminating the need for functionalization of the reaction centers, as normally required in cross-coupling reactions. Optimized reaction conditions using Pd(OAc)$_2$, Cu(OAc)$_2$ as the oxidant, and K_2CO_3 as the base in DMF allow for reactions on a variety substrates, including both electron-donating and electron-withdrawing groups on the aniline moiety and different carbonyl derivatives on the enamine moiety. When various meta-substituted aniline subtrates are employed, products favor 6-substituted indoles over 4-substituted indoles, which are attributed to steric preference. The feasibility of a one-pot synthesis from commercially available anilines is also demonstrated. Aniline and methyl acetoacetate are condensed with $InBr_3$ neat at RT for 20 min prior to subjection to typical reaction conditions to produce the desired indole product in 72% yield.

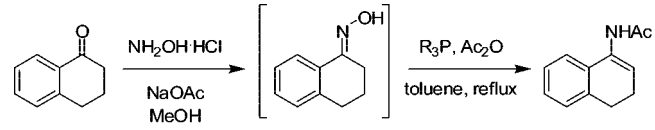
Direct Formation of Esters and Amides with Carboxylic Acids Using Diethyl Chlorophosphate



10 examples
77-91%

Although numerous coupling reagents such are known to facilitate coupling of carboxylic acids to alcohols and amines, byproducts of these reagents can be troublesome to remove efficiently after reaction completion. A recent report by McNulty and co-workers addresses this issue through the use of diethyl chlorophosphate as the activating reagent for coupling reactions in pyridine (*Tetrahedron Lett.* **2008**, *49*, 6344−6347). The mixed carboxyl-phosphate anhydride can be formed in the presence of the alcohols in pyridine and couples in good yields and high purity (>95% in most cases). The phosphate and pyridinium salts formed at the conclusion of the reaction can be removed by simple aqueous workup. Retention of configuration of secondary alcohols and α-amino acids was observed in all cases.

Efficient Synthesis of Enamides from Ketones



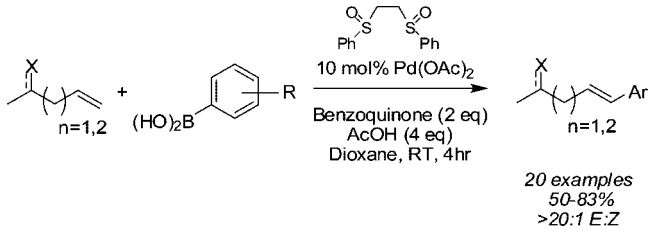
12 examples
54-90%

Synthesis of enamides is desirable as an entry point for chiral acetamides through catalytic asymmetric hydrogenation. A communication detailing the efficient conversion of ketones to enamides through a phosphine-mediated reductive acylation of oximes has been disclosed by Zhao and co-workers at Sepracor (*Org. Lett.* **2008**, *10*, 505−507). The letter builds on work originally

published by Barton in 1975 (*Chem. Commun.* **1975**, 1237.), in which an oxime is converted to an eneamide by refluxing excess acetic anhydride and pyridine, presumably proceeding via a thermal homolytic cleavage of the N−O bond. The authors proposed use of an oxophilic phosphine to allow for more mild reaction conditions. Although a variety of trialkyl and triaryl phosphines lead to desired products, the authors suggest utilizing triethylphosphine as a 50% solution in toluene due to the water solubility of the phosphine oxide byproduct despite its pyrophoric nature. Both benzylic and non-benzylic ketoximes can be converted to enamides in generally reasonable yields.

A Chelate-Controlled Intermolecular Oxidative Heck Reaction

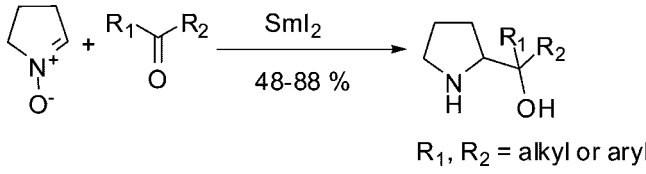
Utilizing a Pd(II)/sulfoxide catalyst, White and co-workers have disclosed a general and highly selective chelate-controlled intramolecular oxidative Heck reaction (*J. Am. Chem. Soc.*, **2008**. *130*, 11270−11271). The methodology utilizes chelation effects from oxygen and nitrogen that allow for good yields and controlled regioselectivity through internal Pd insertion. Functionalities that could effect a five- or six-membered ring chelation ($n = 1$ or 2) include homoallylic carbonyl and bishomoallylic carbonyl, alcohol, and thiol moieties. Substrates gave the desired product in good yields with high regioselectivity ($E:Z$ > 20:1) over a broad range of examples. Remarkably, neither aldehyde nor ketone byproducts, via Pd−H isomerization or erosion of existing stereochemistry, was observed.



A Direct and Versatile Access to α,α-Disubstituted 2-Pyrrolidinylmethanols by SmI_2-Mediated Reductive Coupling

S. Py et al. (*Org. Lett.* **2008**, *10*, 3021.) have found that various α,α-disubstituted 2-pyrrolidinylmethanols are efficiently prepared in a single step from diaryl, monoaryl, or dialkyl ketones using a SmI_2-mediated cross coupling with 1-pyrroline *N*-oxide. The *N*-hydroxy-α,α-diphenylprolinol is also easily prepared and resolved. When prochiral ketones are used, high diastereoselectivities can be attained. Thus, unusual chiral prolinol derivatives are now readily accessible, which should find interesting applications as rigid organocatalysts or, more generally, in enantioselective catalysis.

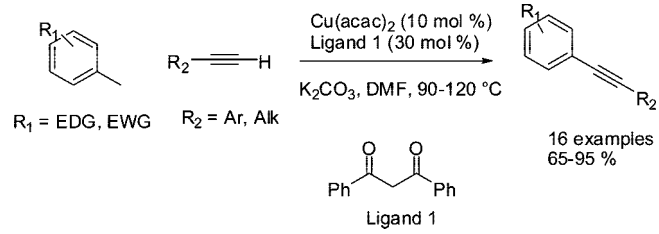
A requisite of this synthesis is an efficient synthesis of 1-pyrroline *N*-oxide by oxidation of pyrrolidine. The authors found that urea hydrogen peroxide complex in combination with methyltrioxorhenium gave the best results.



Copper-Catalyzed Sonogashira-Type Reactions Under Mild Palladium-Free Conditions

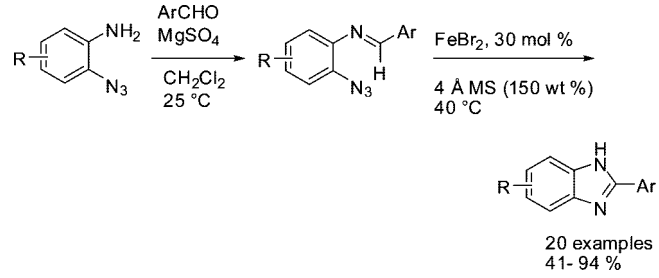
F. Monnier et al. (*Org. Lett.* **2008**, *10*, 3203.) have developed an inexpensive catalytic system using a readily available copper/ligand combination for the Sonogashira-type cross coupling of aryl iodides and phenyl- and hexyl-acetylene which affords disubstituted alkynes in good to excellent yields.

The method is applicable to a wide range of variously substituted aryl iodides for coupling to both alkyl- and aryl-substituted terminal alkynes. This novel catalytic system is tolerant, versatile, and significantly less expensive than "traditional" Pd−Cu-catalyzed cross coupling of terminal alkynes with aryl iodides.



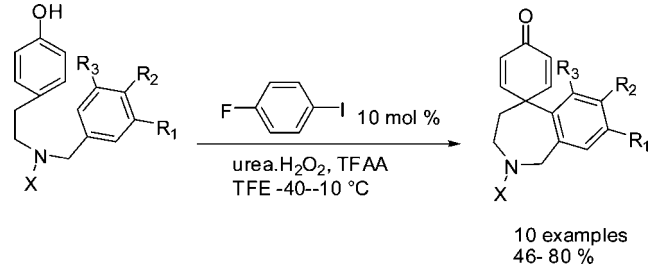
Iron(II) Bromide-Catalyzed Synthesis of Benzimidazoles from Aryl Azides

The identity of the ortho substituent of an aryl azide influences its reactivity toward transition metals. Substitution of a vinyl group with an imine disables rhodium(II)-mediated C−H amination and triggers a Lewis acid mechanism catalyzed by iron(II) bromide to facilitate benzimidazole formation. T. G. Driver and M. Shen (*Org. Lett.* **2008**, *10*, 3367.) have shown that the mode of reactivity of the aryl azide is dependent on the composition of the linker between the aryl azide and the pendant C−H bond. Substitution of the α-carbon atom with a nitrogen atom disables rhodium(II)-catalyzed amination and triggers a Lewis acid mechanism mediated by iron(II) bromide to enable benzimidazole formation from 2-azidoarylimines.



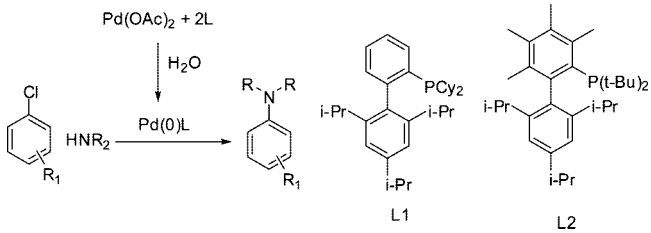
A New H_2O_2/Acid Anhydride System for the Iodoarene-Catalyzed C−C Bond-Forming Reactions of Phenols

T. Dohi et al. (*Org. Lett.* **2008**, *10*, 3559.) have developed versatile iodoarene-catalyzed C−C bond-forming reactions by development of a new reoxidation system at low temperatures using stoichiometric bis(trifluoroacetyl)peroxide in 2,2,2-trifluoroethanol (TFE). The catalytic system supplies a wide range of substrates and functional availabilities sufficient to be used in the key synthetic production of biologically important Amaryllidaceae alkaloids.



Water-Mediated Catalyst Preactivation: An Efficient Protocol for C−N Cross-Coupling Reactions

A protocol for forming a highly active Pd(0) catalyst from $Pd(OAc)_2$, water, and biaryldialkylphosphine ligands has been developed by S. L. Buchwald et al. (*Org. Lett.*, **2008**, *10*, 3505.). This protocol generates a catalyst system, which exhibits excellent reactivity and efficiency in the coupling of a variety of amides and anilines with aryl chlorides.The active catalyst was formed by water-mediated preactivation of readily available $Pd(OAc)_2$ using biaryldialkylphosphine ligands. This new protocol allowed lower catalyst loadings, shorter reactions times, and exclusion of additives, such as Et_3B, in couplings of amides with aryl chlorides. It also gives access to a system that exhibits both high activity and excellent catalyst stability in couplings of electron-deficient anilines and couplings of anilines at low catalyst loadings.



Gold-Catalyzed Organic Transformations

Thanks to its unusual stability, metallic gold has been used for thousands of years in jewelry, currency, chinaware, and so forth. However, gold had not become chemists' "precious metal" until very recently. In the past few years, reports on gold-catalyzed organic transformations have increased substantially. Thanks to gold-based catalysts, various organic transformations have been accessible under facile conditions with both high yields and chemoselectivity (He, C. et al. *Chem. Rev.* **2008**, *108*, 3239.). The review has been organized into several sections; each section contains similar reaction types or reaction mechanisms with discussion.

It is obvious that currently gold catalysis is in a crucial developing stage. The discovery of new reaction categories that could be catalyzed by gold has slowed down, while gold(I)-catalyzed asymmetric organic transformations have accelerated. Satisfactory results have been reported in both yields and ee's. Although currently the reaction scope is limited, the future of gold asymmetric catalysis remains bright.

Ag-Mediated Reactions: Coupling and Heterocyclization Reactions

In the coinage metal series, silver and gold nevertheless exhibit special properties due to the availability of the f orbitals and relativistic contraction of their electron cloud. Both of them thus still present a marked Lewis acid character. The applications of silver salts, mainly AgI, in organic synthesis are indeed mostly driven by this Lewis acidity. However, in several applications, it seems that it is much more the (in)solubility properties of silver salts which actually are driving reactions. Indeed, in many reactions where halogens play a key role, silver salts often activate reactions by specifically interacting with the halogen atom and forming insoluble silver halides, the so-called halogenophilicity of silver. This "effect" has been widely used in organic synthesis, mainly in nucleophilic substitutions including glycosylations, in some eliminations, and in processes involving organometallics (Pale, P. et al, *Chem. Rev.*, **2008**, *108*, 3149.).

The results detailed in this review showed that silver ions are very efficient catalysts for cross-coupling reactions, as well as for heterocyclization reactions. In cross-coupling reactions, silver salts play a dual role. They can abstract halides from organometallic intermediates, rendering the metal more electropositive and opening a vacant site in the coordination sphere. In these cases, the main role is thus to form insoluble silver halides while activating the actual catalytic species. These phenomena have mainly been applied to Heck, Stille, and Suzuki couplings. With some starting materials, especially alkynes, silver salts can form organosilver species, which can either react as such or more often be transmetalated to various metals or organometallics, especially organopalladium intermediates.

Silver-catalyzed heterocyclizations provide a very efficient access to a large variety of substituted *O*- and *N*-heterocycles. From a mechanistic point of view, heterocyclizations correspond to electrophilic additions, the silver ion being the electrophile. They thus usually follow Baldwin's rules and produce the shortest heterocycle possible through *exo*-cyclization, except if steric or electronic effects shift the process toward *endo*-cyclization and thus toward larger rings. More complex mechanisms cannot be ruled out, especially when the nucleophile is a nitrogen atom.

The stereochemical outcome of heterocyclization clearly depends on substitution pattern and ring size. Envelope- and chair-like transition states usually give reasonably correct predictions of the heterocycle stereochemistry.

Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions

Enantioselective copper-catalyzed conjugate addition and allylic substitution are two of the most powerful carbon−carbon bond-forming reactions for construction of enantioenriched synthons for biological active and natural compounds (Alexakis, A. et al. *Chem. Rev.* **2008**, *108*, 2796.).

Significant advantages of these processes are the high compatibility with many functional groups, low cost of the copper salts, and the often high regio- and enantioselectivities.

There is, until now, no review that has discussed the mechanism, catalysis, and application in total synthesis of both Cu-catalyzed conjugate additions reactions and the allylic substitution reactions with the same perspective giving a global view of the research done and the possibilities of future research.

This review covers the literature reports on enantioselective copper-catalyzed conjugate additions and allylic substitution reactions in the most emerging period in these areas of research. Particular emphasis is given to the results published in the last five years (2002−2007).

The review is organized as follows. First the results obtained in the asymmetric conjugate addition reaction are presented. In this part the catalytic data are grouped according to the type of nucleophile. For each nucleophile the authors present an overview of the state of the art and then focus on the catalytic data reported.

In the following part, the results obtained in the asymmetric allylic substitution reaction are covered. For each reaction, mechanistic and practical aspects as well as their application to the synthesis of more complex molecules are discussed.

Biomass

Palm oil has been considered a very good source for biodiesel production not only due to its high productivity (Basiron *Eur. J. Lipid Sci. Technol.* **2007**, *109*, 289.) but also due to the quality of the biodiesel that can be produced. However, glycerol and the biomass are also a potential source of energy. For example, glycerol can be used as a source of synthesis gas and used for hydrocarbon (diesel) production (Dumesic and co-workers *Green Chem.* **2007**, *9*, 1073.). In that area, Chew and Bhatia (*Bioresour. Technol.* **2008**, *99*, 7911.) reviewed the catalytic process towards the production of biofuels using palm biomass as feedstocks. They first listed the advantages of using biofuels over fossil fuels that of course included the CO_2 cycle in the atmosphere, sustainability, and environment-related issues; then they described the advantages of biodiesel and the vast possibilities of using biomass, showing the different processes to be carried out in a biorefinery based on palm feedstocks. Considering the feedstocks produced or coproduced during palm oil production, a biorefinery can involve (catalytic) pyrolysis of biomass (bio-oil and hydrogen production; steam reforming), biomass gasification (Fischer−Tropsch synthesis and bioethanol production), and biodiesel production. They also listed catalytic depolymerization as an alternative way of producing combustibles and catalytic cracking.

On the biodiesel side, Da Silva et al. (*Bioresour. Technol.* **2008**, *99*, 6793.) described the use of Cu(II) and Co(II) for the transesterification of babassu and soy bean oils. The need for renewable energy was emphasized, and biodiesel was claimed to be a solution. In the present process the use of Co(II) and Cu(II) ions adsorbed in chitosan was essayed as a way to overcome soap-related problems (that arose with the use of NaOH) and corrosion problems related to the use of acid catalysis. Of course, the new catalysts are to be used in more friendly conditions avoiding high pressures and temperatures. After optimizing catalysts' preparation, they were tested in biodiesel production. Although conversions were not quantitative, the biodiesel of babassu and soy beans produced were proved to pass Brazilian regulations. The only point to be further explored is how far these catalysts must be recycled.

Much needs to be done to develop a good biodiesel process, and thus, the use of membrane reactors represents an important improvement, perhaps a breakthrough. Cao, Dubé, and Tremblay (*Biomass Bioenergy* **2008**, *32*, 1028.) disclosed that it is possible to have a continuous membrane reactor that can be operated with a very broad range of substrates, including canola, soy bean, and palm, under similar conditions to produce fatty acid methyl esters (FAME). They showed that from virgin soy bean oil and virgin canola oil, FAME pass ASTM specifications even without a water-washing step. A Filtanium ceramic membrane (cutoff 300 kDa, multichannel tubular), operated as a cross-flow filtration device, was used. Recycling the methanol−glycerine-rich phase allowed rich methanol:lipid ratios to be produced compared to commercial batch biodiesel production, but the very high methanol:lipid molar ratio that is maintained in the circulating loop drove the reaction towards completion. The membrane is capable of retaining any emulsions that could be produced due to the NaOH catalyst and any free fatty acid presented. GC analysis according to ASTM D6584 standard confirmed the high purity of the FAME from different sources.

Predictable Disorder versus Polymorphism in the Rationalization of Structural Diversity: A Multidisciplinary Study of Eniluracil

Many crystallization practitioners have been occasionally faced with the challenge of distinguishing between a polymorph (impurity) and a "crystalline disorder". The detailed answer is often complex, and for solid dosage formulations, it must be included in the submissions to the regulatory agencies, together with proof of process robustness for the desired solid form.

Studies conducted at GlaxoWellcome in the late 1990s on the solid-state chemistry of eniluracil (5-ethynyluracil), an oral dihydropyrimidine dehydrogenase (DPD) inhibitor, led to the conclusion that eniluracil exhibits two polymorphs. The team was unable, though, to design a robust process, producing only one of the two polymorphs.

The eniluracil case has been recently reexamined by a team from GlaxoSmithKline and two academic centers (Royston, C. B. C. et al. *Cryst. Growth. Des.* **2008**, *8*, 3474.). It was found that the polymorphic assignments were originally based on several XRPD low-angle weak peaks, some sample-dependent. At that time no single crystal X-ray data were available. Recently, it was possible to grow single crystals under several conditions (using evaporative as well as seeded cooling methods). Four crystals were grown and analyzed by X-ray diffraction. This analysis showed that the eniluracil experimental crystal structures appear intrinsically disordered, and the degree of disorder depends on the crystallization method. When a relatively modern approach was used to assess the similarity between the crystal structures obtained, a very high similarity coefficient was calculated for some of the eniluracil single crystals analyzed.

Furthermore, in spite of the extensive experimental effort invested, the preparation of a fully ordered structure was not possible, and deemed to be an unattainable goal. A computational search for low-energy crystal structures identified several possibilities within a range of a few kJ/mol. On the basis of these calculations, it was postulated that irreversible crystal growth errors are inevitable, leading to the observed disorder.

After careful analysis, it was determined that the structural variations observed with eniluracil are better described as crystalline disorder rather than polymorphism. Several additional examples of computationally predicted disorder are mentioned, such as aspirin, caffeine, and chlorotalonil.

Eniluracil is currently under development by Adherex, entering phase III, with the objective of improving the tolerability and effectiveness of the anticancer agent 5-fluorouracil (5-FU).

Physicochemical Properties of Pharmaceutical Co-Crystals: A Case Study of Ten AMG 517 Co-Crystals

One of the most active fields in crystal engineering is that of co-crystals (cocrystals). Cocrystals are attractive both from a scientific as well as a legal perspective; cocrystals can be used to improve the physical properties of active pharmaceutical ingredients and thus expand the intellectual property of the innovator. An Amgen team published a systematic study for the preparation and

characterization of ten cocrystals of AMG 517, a transient receptor potential vanilloid 1 antagonist developed for chronic pain (Stanton, M. K. et al. *Cryst. Growth. Des.* **2008**, *8*, 3856.). Ten out of fifteen commercially available carboxylic acids (with fewer than nine carbons) screened were successful as cocrystal formers. The acids selected were used before as salt formers and are considered to be pharmaceutically acceptable. Some of the acids used are hydroxy-acids, capable of additional sites for hydrogen bonding, beyond the carboxylic group. It is worth noting that AMG 517 free base, probably due to the presence of an amidic proton, has a rather low calculated pK_a of 0.68. As a result, the ΔpK_a (base-former) is negative, in the −2 to −4 range. Negative ΔpK_a's are indicative of cocrystal, rather than salt formation (for which the ΔpK_a is typically larger than +3). Cocrystal preparation was executed by slow cooling, using sometimes also solvent evaporation. The ten new crystalline solids obtained were fully characterized using ^{1}H NMR, PSD, DSC, TGA, and XRPD. Their fasted simulated intestinal fluid (FaSIF) solubility and stability (40 °C/75% RH) were also evaluated. Linear correlations were found between the melting point of the new solids with the melting point of the cocrystal former, as well as with the solubility of the new solids. Such correlations can form the basis of design for such new molecular materials. Elegant proof of cocrystal formation was the crystallographic data for two single crystals suitable for X-ray analysis (AMG 517-cinnamic acid, AMG 517-hexanoic acid): the difference between the carboxylic C−O bonds was above 0.08 Å; when the C−O bond length difference is below 0.03 Å, such crystals must be considered to be salts. Nine of the cocrystals obtained exhibited excellent stability and lack of hygroscopicity. The maximum solubility of several of the cocrystals prepared was 3−4 times higher than the very low solubility of 5 μg/mL for AMG 517.

Further works is planned, using additional cocrystal formers, not necessarily carboxylic acids used to prepare pharmaceutical salts.

Hydroxypropyl Methylcellulose-Controlled Crystallization of Erythromycin A Dihydrate Crystals with Modified Morphology

Engineering crystal morphology is an important aspect of crystallization process R&D, leading to improved processability of the active pharmaceutical ingredient (API) crystals. Crystal morphology engineering by manipulation of the crystallization conditions such as solvent, seed, and cooling protocol has inherent limitations. Research in the field of tailor-made additives for crystallization has been successfully reported in the last quarter of a century. In spite of this success, perhaps due to the conservative approach of pharmaceutical crystallization process R&D, there are only limited reports on the successful use of additives in API crystallization (adding controlled amounts of impurities as crystallization additives can raise eyebrows).

Successful application of a pharmaceutically acceptable crystallization additive, typically used as a formulation excipient, is reported by an academic team from the Universities of Helsinki and Copenhagen (Mirza, S. et al. *Cryst. Growth. Des.* **2008**, *8*, 3526.). The habit of erythromycin A dihydrate was successfully modified using a polymeric additive, hydroxypropyl methylcellulose (HPMC) at concentrations of approximately 2−4% in the crystallization medium. A thorough solid-state characterization of the new crystals prepared was executed. The morphology of the crystals thus obtained was more regular, with elongated platelike crystals, compared to that of the irregular acicular crystals obtained in the absence of HPMC (under comparable crystallization conditions). Excellent agreement of some of the HPMC-produced crystals with computational predictions was observed. A hypothesis for the mechanism of association of HPMC with erythromycin A dihydrate is proposed. Compaction behavior of the modified erythromycin A dihydrate crystals was also investigated.

Future work will probably also include particle size analysis data.

Mark McLaughlin

Merck & Co. Inc.,
Rahway, New Jersey 07065, U.S.A.
E-mail: mark_mclaughlin@merck.com

Silvina García Rubio

Sapphire Therapeutics, Inc.,
Bridgewater, New Jersey 08807, U.S.A.
E-mail: sgarciarubio@sapphirethera.com

Matthew Pfeiffer

Process R&D, PTD, Exelixis Inc.,
South San Francisco, California 94080, U.S.A.
E-mail: mpfeiffe@exelixis.com

Ulf Tilstam

CMC-Solutions, Belgium,
E-mail: tilstam@skynet.be

Octavio Augusto Ceva Antunes

Departamento de Quimica Inorganica,
Instituto de Quimica, UFRJ, Cidade Universitaria,
Rio de Janeiro, RJ 21949-900, Brazil,
E-mail: octavio@pq.cnpq.br

Andrei A. Zlota

The Zlota Company,
Sharon, Massachusetts 02067-2858, U.S.A.
E-mail: andrei.zlota@thezlotacompany.com

Trevor Laird*
Editor

OP800263S