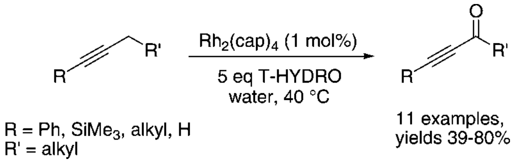
Organic Process Research & Development **2008,** *12,* 548–555

Highlights from the Literature

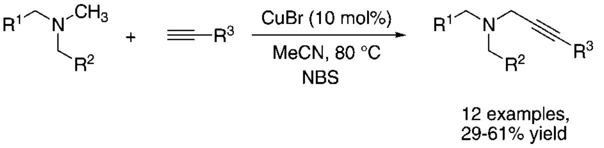
Some Items of Interest to Process R&D Chemists and Engineers

Rh-Catalyzed Propargylic Oxidations in Water



The Doyle group reports (*J. Org. Chem.* **2008**, *73*, 4317−4319) a modified procedure for their Rh-catalyzed C−H oxidation chemistry that uses water as the solvent (replacing the previously used chlorinated hydrocarbon 1,2-DCE). Specifically, propargylic methylene groups can be converted into propargylic ketones via treatment with 1 mol % dirhodium(II) caprolactamate ($Rh_2(cap)_4$) and 70% w/w aqueous *tert*-butyl hydroperoxide (T-HYDRO) at 40 °C. Various salt additives were found not to improve the product yield. The researchers noted that for most substrates the reaction appeared to be two-phase in nature. This fact prompted study of the spent Rh-containing aqueous layer to determine if reuse for a subsequent oxidation was possible. It was found that three oxidations could be conducted with reasonable efficiency using the same aqueous solution of 1 mol % Rh. Conversion of the product ynones into two different heterocycles was also demonstrated.

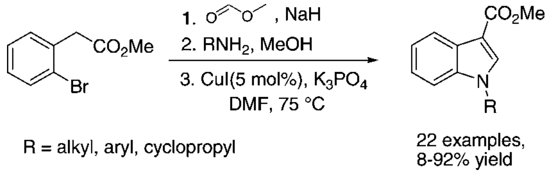
Cu-Catalyzed Preparation of Propargylamines via C−H Activation



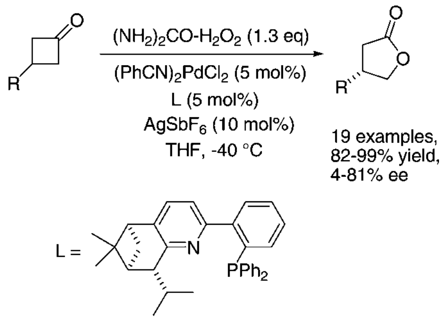
The Fu group in China has developed a method for coupling of tertiary aliphatic amines with terminal alkynes to propargylamines via C−H activation (*J. Org. Chem.* **2008**, *73*, 3961−3963). Building upon earlier work by Li, the current procedure uses CuBr (10 mol %) as the catalyst and NBS as the stoichiometric oxidant in MeCN at 80 °C. For the 12 examples presented, yields are moderate at best, but the method does represent an interesting means for the C−H functionalization of *N*-methyl tertiary amines.

Synthesis of *N*-Substituted Indole-3-carboxylic Acid Derivatives

A variety of *N*-alkylated and *N*-arylated derivatives of methyl 1*H*-indole-3-carboxylate have been prepared by Karchava and co-workers (*J. Org. Chem.* **2008**, *73*, 4275−4278). Starting from methyl 2-(2-bromophenyl)acetate the method comprises two steps, involving initial conversion to methyl 2-(2-bromophenyl)-2-formylacetate followed by condensation with an amine and then Ullmann-type intramolecular arylamination catalyzed by the CuI-K_3PO_4-DMF system. A total of 22 examples are presented with yields ranging from 8−92%. Notable examples include *N*-*tert*-butyl-, *N*-cyclopropyl-, and several hindered *N*-arylindoles.



Pd-Catalyzed Enantioselective Baeyer−Villiger Oxidations



Asymmetric Baeyer−Villiger oxidations of symmetrical cyclobutanones are described by the Kocovsky group (*J. Org. Chem.* **2008**, *73*, 3996−4003). The reported system employs urea-hydrogen peroxide (UHP) as the oxidant in conjunction with $PdCl_2(PhCN)_2$ and a terpene-derived *P*,*N*-ligand. Reactions are conducted at −40 °C in THF. The resulting lactones were generally obtained in high yields and with reasonable enantioselectivity (81% ee). The authors note that their optimized system compares favorably with existing literature methods.

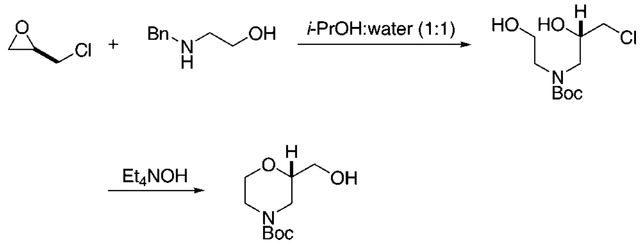
Au-Catalyzed Chemistry

Two recent reports in *Tetrahedron* serve as useful reference sources for the expanding area of Au-catalyzed chemistry. The review by Li and co-workers in Montreal covers various Au-catalyzed reactions of C−H bonds, including C−C, C−O, and C−N bond-forming processes (*Tetrahedron* **2008**, *64*, 4917−4938). The review by Shen focuses on the synthesis of carbo- and heterocycles via hydroarylation of and heteroatom addition to alkynes, alkenes, and allenes (*Tetrahedron* **2008**, *64*, 3885−3903).

Concise Synthesis of (S)-*N*-BOC-2-Hydroxymethylmorpholine

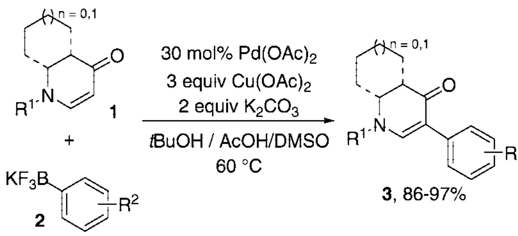
Henegar at Pfizer reports a synthesis of(*S*)-*N*-BOC-2-hydroxymethylmorpholine which starts from epichlorohydrin and *N*-benzylethanolamine (*J. Org. Chem.* **2008**, *73*, 3662−3665).

10.1021/op8001323 CCC: $40.75



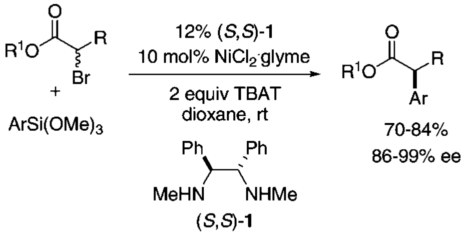
This chiral morpholine derivative is a potentially useful synthon for the preparation of pharmaceutically interesting compounds. No chromatography is required although a high vacuum/high temperature distillation of an intermediate appears necessary.

Direct C−H Functionalization: Miscellaneous Arylation and Alkylation Reactions



R^1 = Me, Bn
R^2 = 4-Me, 4-Br, 4-Cl, 3,4,5-OMe, 3-OH

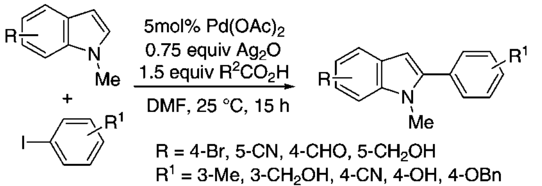
In a recent communication, Ge, Niphakis, and Georg (University of Kansas) described the use of organotrifluoroborates as coupling reagents in a one-pot, palladium-catalyzed C-3 arylation of enaminones (*J. Am. Chem. Soc.* **2007**, *130*, 3708−3709). Organotrifluoroborates rose as apposite reagents for this study upon finding that acidic cosolvents limited the potential of alternative coupling partners such as organoboronic acids, organozinc reagents, or silanes. In a typical experiment, the slow addition of electron-rich trifluoroborates **2** gave the desired arylated products **3** in excellent yields, suppressing homocoupling. The intrinsic instability of substrates **1** imposed the use of a high $Pd(OAc)_2$ loading (30%) to circumvent higher temperatures and long reaction times. Bicyclic diastereomeric enaminones reacted with no observable epimerization under the slightly acidic media. Furthermore, aryl halides were tolerant to the reaction conditions, a unique feature to this reaction compared to Suzuki−Miyaura protocols.



R= alkyl, $CH_2CH_2CO_2Me$, CH_2CH_2OMe, CH_2CHCH_2, CH_2Bn, CH_2CH_2Br
R^1OH = 2,6-di-t-butyl-4-methylphenol

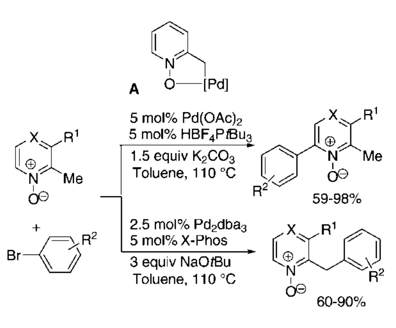
Gregory Fu and co-workers at MIT have developed an asymmetric version of the Hiyama reaction for the cross-coupling of α-bromo esters and aromatic organosilanes to generate enantioenriched α-aryl carboxylic acid derivatives (*J. Am. Chem. Soc.* **2007**, *130*, 3302−3303). Functional groups such as esters, ether, olefins, and inactivated alkyl bromides are compatible with the reaction conditions. In addition, the coupling proceeds at room temperature, and both catalyst components are air stable. The BHT (R^1OCO-) ester can be further reduced with $LiAlH_4$ to access alcohols or oxidatively cleaved with CAN to yield carboxylic acids without erosion of the enantiomeric purity (99% and 95% ee, respectively).

Lebrasseur and Larrosa describe a mild methodology to carry out the ligand-free C-2 arylation of indoles at room temperature (*J. Am. Chem. Soc.* **2008**, *130*, 2926−2927). The key feature of the arylation is the *in situ* generation of a silver carboxylate that promotes the formation of electrophilic Pd(IV) intermediates. The carboxylic acid had a dramatic effect in the efficiency of the reaction, showing an inverse correlation with its pK_a. *o*-NO_2 benzoic acid was found to be the best, affording the C-2 arylation adduct with complete conversion, 58−99% isolated yields, and no C-3 arylation byproducts. The reaction conditions are compatible with *N*-methyl indoles and aryl iodides featuring a variety of functional groups such as bromides and unprotected benzylic alcohols that are rendered available for further transformations. Hindered ortho-substituted aryl iodides react more slowly than their meta- and para-counterparts, and an N1 unsubstituted indole required longer reaction time (38 h) and higher temperature (50 °C) to afford the C-arylated product in 62% yield.

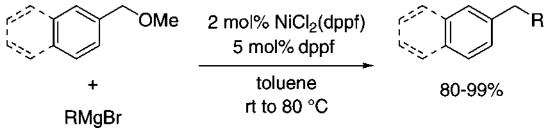


R = 4-Br, 5-CN, 4-CHO, 5-CH_2OH
R^1 = 3-Me, 3-CH_2OH, 4-CN, 4-OH, 4-OBn
R^2 = *o*-$NO_2C_6H_4$

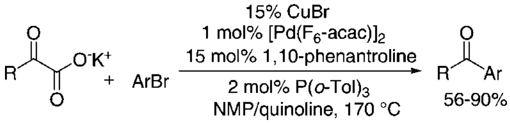
In *J. Am. Chem. Soc.* **2008**, *130*, 3266−3267, the group of Fagnou at the University of Ottawa reported site-selective arylation reactions of both sp^2 and benzylic sp^3 sites on azine and diazine *N*-oxides. Upon noticing lower yields in the sp^2 arylation of pyridine *N*-oxides bearing Me groups adjacent to the *N*-oxide moiety, the authors investigated whether the formation of a palladacycle such as **A** could enable sp^3 arylation. By carefully tuning bases and ligands it became evident that palladium could selectively react at either sp^2 centers [$Pd(OAc)_2$, $HBF_4P^tBu_3$, toluene, 110 °C] or sp^3 centers [Pd_2dba_2, X-Phos, toluene, microwave irradiation, 110 °C] under different reaction conditions. The methodology has been validated in both divergent and sequential sp^2/sp^3 arylations, which are useful tools for the fast derivatization of heterocyclic compounds.



Shi and co-workers reported a benzylic alkylation based on a highly selective C−O bond ether activation (*J. Am. Chem. Soc.* **2008**, *130*, 3268−3869). Only a handful of examples in the literature describe the activation of ether sp^3 C−O bonds, presumably due to their high dissociation energy, as well as the need to discriminate between the two C−O bonds of the ether moiety. The authors circumvented the second problem by choosing substrates bearing a benzylic, more active C−O bond. In the optimized conditions, naphthyl and aryl ethers were reacted with a Grignard reagent (1.5 equiv RMgBr, R = Me, Et) in the presence of catalytic $NiCl_2(dppf)$ to afford the desired alkylation products in good yields. The stereoelectronic properties of the starting materials had little influence in the outcome of the reaction, in that a variety of ethers were transformed into the desired products with high efficiency. By tuning the catalytic system, different C−OMe groups (sp^2 and sp^3) were differentially activated and transformed into Me groups.



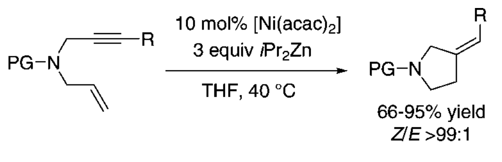
Decarboxylative Coupling of α-Oxoarylcarboxylates and Aryl Bromides

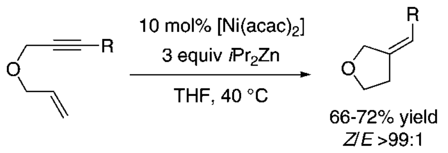


The group of Lukas Goossen developed a strategy for the synthesis of aryl ketones involving the coupling of acyl anion equivalents with carbon electrophiles. In *Angew. Chem., Int. Ed.* **2008**, *47*, 3043−3045, they report the conversion of α-oxocarboxylic acid salts into acyl copper species by decarboxylation promoted by a copper catalyst, followed by arylation with aryl halides. Best results were obtained by using a catalyst system consisting of $[Pd(F_6\text{-acac})]_2$, CuBr, 1,10-phenantroline, and tris(*o*-tolyl)phosphane in NMP/quinoline at 170 °C. The observation that neither copper nor palladium catalysts alone were active rules out alternative Copper- or Ullman-type mechanistic pathways. The system is suitable for the reaction of aryl as well as less-reactive alkyl α-oxocarboxylates, which react with a variety of aryl- and heteroaryl bromides featuring a wide range of functional groups to give the desired aryl ketones in good yields. The limits of the methodology were reached only with thermally labile or sterically hindered substrates. The communication contains a detailed table of examples as well as exhaustive literature on the synthesis of aryl ketones from Friedel−Crafts reactions to advanced cross-coupling approaches.

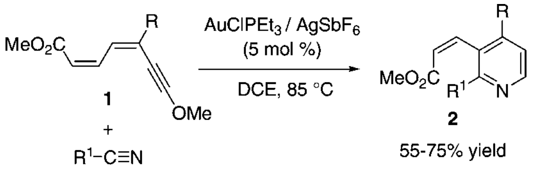
Reductive Cyclization of Inactivated 1,6-Enynes

Transition-metal-catalyzed cyclizations can transform 1,6-enynes into cyclic skeletons in one pot with impressive regio- and stereoselectivity. Few studies have explored the potential of Ni catalysts in direct cyclizations of electronically inactivated enynes, which have been investigated with Pd, Au, Ru, and Rh catalysts. Lei and co-workers at Wuhan University in China developed inexpensive $[Ni(acac)_2]$-catalyzed cyclizations using iPr_2Zn under mild conditions to generate pyrrolidine and tetrahydrofuran derivatives (*Angew. Chem., Int. Ed.* **2008**, *47*, 2279−2282). A variety of *N*- and *O*-tethered enynes were tested under the optimized reaction conditions (10 mol% $[Ni(acac)_2]$, 3 equiv iPr_2Zn, THF, 40 °C) to afford the desired heterocycles with exceedingly high selectivities for the *Z*-alkene. In the cyclization of pyrrolidine precursors the Ts, Boc, and Cbz protecting groups gave comparable results. The configuration of the products, as well as the compounds obtained by quench of the reaction with CD_3CO_2D, are consistent with the formation of a Ni metallacycle intermediate.





Gold-Catalyzed Synthesis of Pyridines

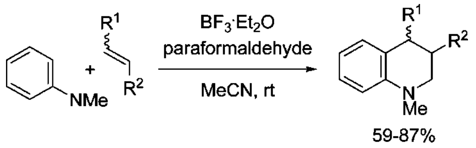


R = Ph, 4-Cl-C_6H_4, 4-OMe-C_6H_4, Bu, *t*Bu
R^1 = Ph, alkyl, 2-furyl, 2-thiophenyl, vinyl

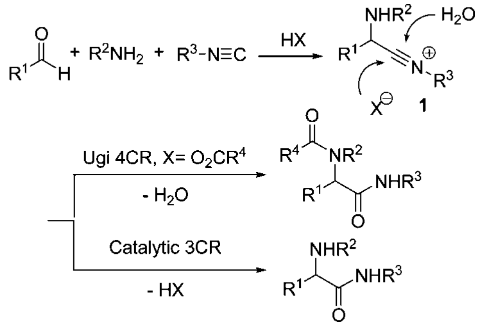
The group of José Barluenga at the Universidad de Oviedo (Spain) reported a Au-catalyzed cycloaddition of dienynes and nonactivated nitriles to yield tetrasubstituted pyridines **2** (*J. Am. Chem. Soc.* **2008**, *130*, 2764−2765). The [4 + 2]-cycloaddition was achieved with a variety of Au catalysts, but the system $AuClPEt_3/AgSbF_6$ exhibited the best results; the yield further improved by using 1,2-dichloroethane as the solvent. A wide variety of dienynes and a set of commercially available nitriles were tested. In all cases, the expected pyridines were obtained as only one regioisomer in good yields (55−75%). A captodative pull−push 1,3-dien-5-yne (e.g., **1**) is crucial for the intermolecular reaction to occur, as electron-deficient, neutral, and electron-rich enynes isomerize, do not react, or polymerize, respectively, under the reaction conditions.

Synthesis of Tetrahydroquinolines via Imino-Diels−Alder Reaction

A variety of tetrahydroquinolines have been investigated as drug candidates against maladies ranging from type II diabetes to cancer. Scientists at Wyeth Research reported a one-pot procedure for the synthesis of the aforementioned compounds starting from *N*-methyl aniline and formaldehyde in the presence of a Lewis acid (*Synth. Commun.* **2008**, 796−802). In a typical experiment, a mixture of a substituted alkene, the aniline, paraformaldehyde, and $BF_3\cdot OEt_2$ were suspended in acetonitrile and stirred at room temperature to afford the desired products in good yields. Mechanistic insight was gained by using *Z*- and *E*-*β*-methylstyrenes as dienophiles. The *Z*-substrate led exclusively to the *trans*-tetrahydroquinoline, whereas the use of *cis*-styrene resulted in a 3:1 mixture of stereoisomers. These observations suggest that the concerted [4 + 2] cycloaddition may be in competition with a stepwise mechanism including cationic species.



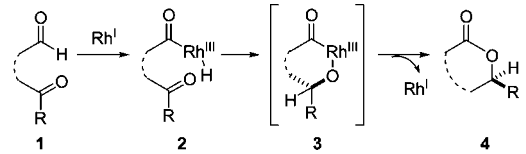
Catalytic Three-Component Ugi Reaction

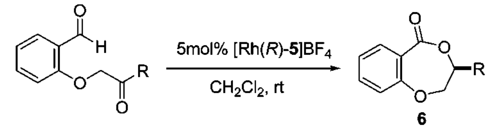


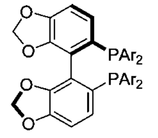
The Ugi four-component reaction is the paramount example in the multicomponent reactions field. A primary amine, a carbonyl compound, a carboxylic acid, and an isocyanide react to give α-amino amides in a model case of atom efficiency. A catalytic, three-component version has been recently developed by List at Max Planck-Institute in Mülheim an der Ruhr (*Angew. Chem., Int. Ed.* **2008**, *47*, 3622–3625). By intercepting the nitrilium intermediate **1** not with the carboxylate but with the water molecule generated in the imine formation and using strong acids, the authors performed the first example of a three-component Ugi reaction. An equimolar mixture of acid, amine, and isocyanate was heated in toluene at 80 °C in the presence of 10% phenyl phosphinic acid to yield the desired products. Particularly high yields were obtained with aromatic aldehydes and aromatic amines. In addition, *tert*-butyl isocyanate can be substituted with longer-chain or functionalized isocyanates (R^3 = EtO_2CCH_2, *p*-$TsCH_2$) without detriment in yield. In addition to the preparation of α-amino acids, the reaction may find use in diversity-oriented synthesis.

Rh-Catalyzed Carbonyl Hydroacylation: Synthesis of Lactones

The vast majority of synthetic approaches to lactones involve the activation of carboxylic acids. On the basis of the ability of Rh(I) complexes to activate C–H bonds of aldehydes, Dong and co-workers reported a novel strategy for transforming keto-aldehydes into chiral lactones: the synthesis features an unprecedented regio-and enantioselective carbonyl hydroacylation (*J. Am. Chem. Soc.* **2008**, *130*, 2916–2917). Rh(I) complexes react with aldehydes **1** to form acyl-Rh(III) intermediates **2**, which in turn undergo a “Tishchenko-type” hydroacylation of the ketone moiety (for a review, see *Curr. Org. Chem.* **2003**, *7*, 1713–1725). Reductive elimination of the organorhodium intermediate **3** yields target chiral lactone **4**. The formation of intermediates **3** containing the R–O–Rh moiety minimizes the competitive Rh-promoted decarbonylation. In addition, the basicity of the phosphine ligand is crucial to promote the hydroacylation vs decarbonylation pathway. The use of the catalyst [Rh(*R*)-DTBM-SEGPHOS]BF_4 in dichloromethane at room temperature afforded lactone **6** in 85–98% yields and 99% ee with negligible formation of the decarbonylated byproduct.

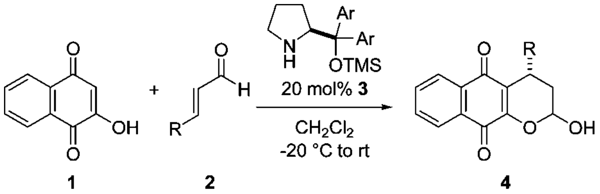




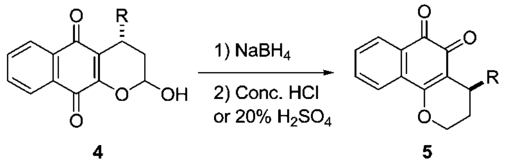


(*R*)-DTBM-SEGPHOS, **5**
Ar = 3,5-*t*-Bu-4-MeOC$_6$H$_2$

Synthesis of Pyranonaphthoquinones and Lapachones



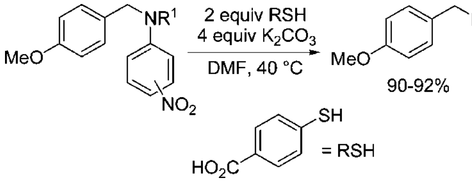
R= alkyl, Ph
2- and 4-ClC$_6$H$_4$, 2-, 3-, and 4-BrC$_6$H$_4$
2-and 4-MeC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 4-OMeC$_6$H$_4$



Based on their biological and structural properties, 1,2- and 1,4-naphthoquinones are considered privileged structures in medicinal chemistry. Magnus Rueping and co-workers have developed a Lewis base-catalyzed enantioselective addition/cyclization cascade that results in the title structures (*Angew. Chem., Int. Ed.* **2008**, *47*, 3046–3049). In this efficient transformation, aliphatic and aromatic α,*β*-unsaturated aldehydes **2** were reacted with quinone **1** in the presence of catalytic diarylprolinol ether **3** (Ar = 3,5-(CF_3)$_2$-C_6H_3) to provide 1,4-pyranonaphthoquinones **4** in good yields and with excellent enantioselectivities. The best results were obtained when the reaction was carried out in dichloromethane at −20 °C to rt. Products **4** were further transformed in 1,2-pyranonaphthoquinones via a simple protocol (reaction with $NaBH_4$ followed by acid treatment) to afford the *β*-lapachone derivatives **5** without loss of enantiopurity.

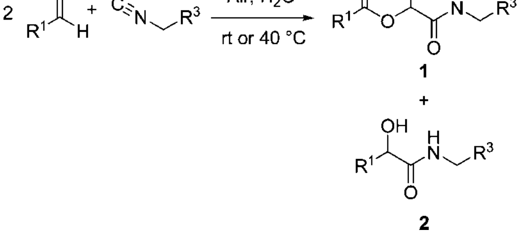
Odorless Thiols for the Cleavage of 2- and 4-Nitrobenzenesulfonamides

o- and *p*-Nitrobenzenesulfonyl (nosyl) groups, used for the protection and activation of amines, remain intact under conditions that remove *N*-protecting carbamate groups but are selectively cleaved by thiols. Nevertheless, the notorious stench and handling issues associated with thiols has hampered the widespread exploitation of the nosyl groups in large-scale synthesis. In *Synth. Commun.* **2008**, 1194−1200, Node and colleagues from Kyoto Pharmaceutical University reported the use of odorless or faint-smelling thiols for the cleavage of nosyl group. The combination of *p*-mercaptobenzoic acid and potassium carbonate in DMF at 40 °C was found to be the best in terms of reaction times, purification of the product, and isolated yields. The resulting sulfide byproducts were removed by washes of the organic phase with aqueous base.



"On Water" Oxidation of Aldehydes and "In/On Water" Passerini Reaction

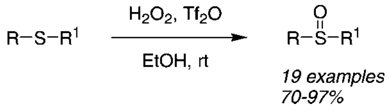
Industrial aldehyde oxidations are carried out by passing a stream of gas through the liquid phase, either in bulk aldehyde or solvents. Surface interactions between oxygen and the substrate can be increased by mixing the aldehyde with water in the presence of oxygen. Shapiro and Vigalok from Tel Aviv University (Israel) found that hydrophobic aliphatic and aromatic aldehydes undergo facile oxidation upon stirring their aqueous emulsions in air to give the corresponding carboxylic acids in high yields (*Angew. Chem., Int. Ed.* **2008**, *47*, 2849−2852). The products are insoluble in water and can be precipitated or separated from the aqueous phase at the end of the reaction. The methodology was further explored by using an aldehyde as the source of both the carbonyl and the ester (generated *in situ*) in three-component Passerini-type reactions (carboxylic acid + carbonyl compound + isocyanide). Using hydrophobic aldehydes, the reaction took place "on water" in 3−4 h at room temperature or 40 °C to give the expected α-acyloxycarboxamide **1**, whereas water-soluble aldehydes gave a mixture of **1** with the α-hydroxamide **2**, product of the "in-water" reaction.



Iron Nanoparticles and Ammonia Borane = Chemical Hydrogen Storage

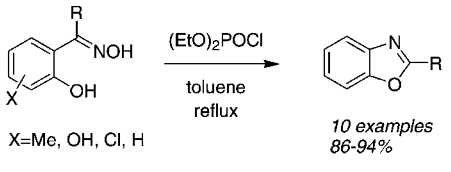
Quiang Xu and co-workers reported a novel method for preparing amorphous iron nanoparticles with high catalytic activity for the generation for hydrogen from ammonia borane (*Angew. Chem., Int. Ed.* **2008**, *47*, 2287−2289). Ammonia borane (AB, NH_3BH_3) is an attractive candidate for on-board chemical hydrogen storage applications due to its high hydrogen content (19.6%). In order to be useful, the storage candidate unit has to be paired with an economical and efficient catalyst for the dehydrogenation. Such transformation proceeds smoothly when Fe nanoparticles were used as the catalyst. The catalytic activity is 20 times higher when the nanoparticles are synthesized *in situ* (instead of presynthesized) by reducing $FeSO_4$ with $NaBH_4$ in the presence of aqueous AB (AB:$FeSO_4$/$NaBH_4$ 1.0:0.12:0.16). Two facts could account for the different reactivity: (1) the X-ray diffraction pattern of the presynthesized particles showed an orderly disposition, whereas the particles prepared *in situ* are amorphous; (2) the presynthesized particles agglomerate in absence of a surfactant, whereas the amorphous particles form a perfect suspension in aqueous solution. The amorphous nanoparticles have a catalytic activity similar to Pt-based materials, they are active in aqueous solution and in aerobic conditions, and can be recycled by magnetic decantation and reused up to 20 times with no loss of activity in air. Are we on the right path towards a hydrogen-powered society?

Selective Oxidation of Sulfanes to Sulfoxides



Although many reagents are currently known for oxidation of sulfanes to sulfoxides, many remain unsatisfactory for large scale use due to factors such as high cost, environmental considerations, or overoxidation of the desired sulfoxides to sulfones. A novel, selective oxidation of sulfanes to sulfoxides utilizing hydrogen peroxide and triflic anhydride in ethanol addresses this issue and has been recently reported by Khodaei and co-workers at Razi University in Iran (*Synthesis* **2008**, *11*, 1682−1684). Employing the new conditions, a variety of diaryl, dibenzyl, aryl benzyl, dialkyl and heterocyclic sulfanes can be oxidized with high yields often in under 20 min. Remarkably, in competition experiments the sulfur is oxidized cleanly in the presence of esters, aldehyde, amines, alcohols, and oximes.

Efficient Synthesis of 2-Substituted Benzoxazoles via Beckmann Rearrangement

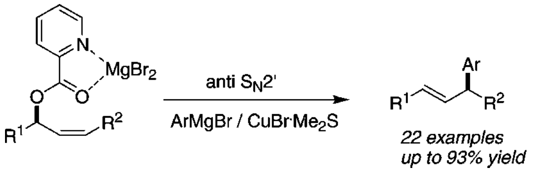


Although the synthesis of 2-substituted benzoxazoles via Beckmann rearrangement has been well documented in previous literature using formic acid, hydrochloric and acetic acids, zinc chloride under MW conditions, and zeolites as ketoxime activators, these methods all suffer poor yields of desired products (44−57%). A new method, reported by Sardarian and co-worker, utilizes diethyl chlorophosphate as the activating reagent and results in greatly improved yields with shortened reaction times (*Synlett* **2008**, *9*, 1391). Generally done in less than 10 min, this method circumvents the need for either strong acids or harsh conditions and allows for substitution at the 2-position by both alkyl and aryl groups. Electron-withdrawing groups were tolerated on the newly formed benzoxazole ring; however, no examples using strongly electron-donating groups were mentioned.

Hydration of Organonitriles to Amides under Ambient Conditions

A major concern with hydrolysis of nitriles to amides has been preventing the unwanted conversion of the amide to the corresponding carboxylic acid. To address this problem, a new catalyst for the conversion of organonitriles to amides without overhydrolysis under ambient conditions in neutral conditions has been described by Saito and co-workers (*Angew. Chem., Int. Ed.* **2008**, *47*, 3607−3609). The low-valent rhodium (I) species, Rh(I)OMe/2PCy$_3$ can be prepared in one step by the treatment of commercially available [{RhCl(OMe)(cod)}$_2$] with PCy$_3$. High yields are obtained when reactions are performed at a catalyst loading of 1 mol % on aliphatic, aromatic, heteroaromatic, and α,β-unsaturated species with 20−40 equiv of water at room temperature in isopropanol.

The Picolinoxy Group: A New Leaving Group for *anti*-S$_N$2′ Selective Allylic Substitution Reactions with Aryl Anions



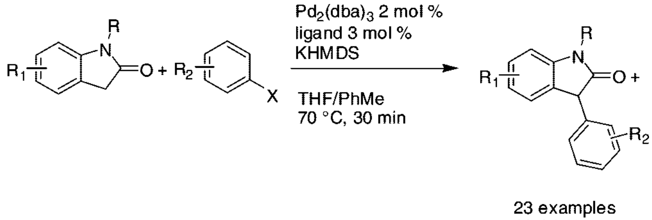
Stereoselective and regioselective transferral of aryl groups in *anti*-S$_N$2′ selective allylic substitution reactions based on copper-promoted Grignard reagents has proven difficult due to the lower nucleophilicity of the sp^2 carbon in relation to their sp^3 carbon counterparts. A new leaving group for these reactions, the picolinoxy group, has been described by Kobayashi and co-workers (*Org. Lett.* **2008**, *10*, 1719−1722). The group, based on the inexpensive and commercially available pinolinic acid, reacts favorably in these systems due to its ability to be doubly activated for substitution by both the electron-withdrawing nature of the pyridyl group and by bidentate magnesium chelation of the carbonyl oxygen and the pyridyl nitrogen. Reagents are derived from ArMgBr and CuBr·Me$_2$S typically added with high regioselectivity (99:1) and yield at 0 °C, although most substrates required lower temperatures (−60 to −40 °C) for the reactions to proceed with good chirality transfer.

The Dehydro-Diels−Alder Reaction

In this review (Weissig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051−2063) both the history and current trends of the dehydro-Diels−Alder (DDA) reaction have been presented in detail. The term "DDA reaction" should be defined as a [4 + 2] cycloaddition whereby at least one of the multiple bonds of the four-atom component is a triple bond, independent from the mechanism underlying the reaction. In contrast to the Diels−Alder reaction itself, DDA reactions can be performed in different ways, and the authors have structured the review according to these conditions. The simplest way to perform a DDA reaction is to heat the reactants, but the required temperatures vary over a broad area including often rather harsh conditions. On the other hand, DDA reactions are known to take place at room temperature and below. The *photochemically* initiated DDA reaction (PDDA reaction) presents new capabilities with reactants inaccessible to the thermal DDA reaction, and a remarkable structural diversity has been developed by now. The treatment of DDA reactants with strong bases may cause an isomerization of alkynes to allenes, mostly driven by acquisition of conjugation energy. These allenes can now undergo "normal" Diels−Alder reactions followed by hydrogen migrations. Catalysis with transition metals is the fourth option to initiate DDA reactions, but there are very few examples for Rh- and Pt-catalyzed DDA reactions, and the intensively investigated Pd(0)-catalyzed DDA reactions are, unfortunately, limited to enynes as four-atom components. The hitherto known DDA reactions regularly provided diaryls as products which may be axially chiral if the rotation around the central aryl−aryl single bond is hindered by steric reasons. In the future it may be possible to do asymmetric DDA reactions to obtain enantiomerically pure diaryls, but for the moment when needed the enantiomers need to be separated.

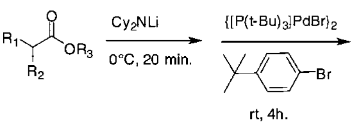
Palladium-Catalyzed α-Arylation of Oxindoles

Durbin, M. J. and Willis, M. C. (*Org. Lett.* **2008**, *10*, 1413) have found that a catalyst generated from Pd$_2$(dba)$_3$ and the bulky electron-rich phosphine ligand 2-(dicyclohexylphosphino)-2′,4′,6′-tri-i-propyl-1-1′-biphenyl is effective for the α-arylation of oxindoles. Generation of the potassium enolates of a range of oxindoles allows coupling with aryl chlorides, bromides, and triflates. Significant variation of the substitution pattern on both the oxindole and aryl halide is possible.



23 examples
60-91 %

α-Arylation of Esters with Bromoarenes Catalyzed by the Pd(I) Dimer {[P(t-Bu)$_3$]PdBr}$_2$

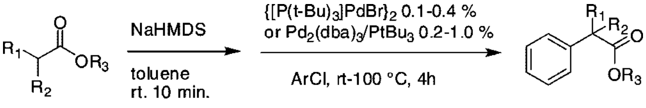


R$_1$ + H; R$_2$ = H; R$_3$ = ^{t}Bu 79 % (0.2 % cat.)
R$_1$ + Me R$_2$ = H; R$_3$ = ^{t}Bu 87 % (0.04% cat.)
R$_1$ + Me; R$_2$ = Me; R$_3$ = Me 86 % (0.05 % cat.)

Hartwig, J. F.; et al. (*Org. Lett.* **2008**, *10*, 1545) have found conditions for the coupling of bromoarenes with esters using a single base and catalyst with improved turnover numbers. These general conditions were made possible by using the Pd(I) catalyst $\{[P(t\text{-}Bu)_3]PdBr\}_2$. Reactions of acetates, propionates, and isobutyrates occur at the methyl, methylene, and methine positions with a variety of bromoarenes. Examples of the reaction have been described for all three classes of esters on a 10-g scale.

Palladium-Catalyzed α-Arylation of Esters with Chloroarenes

Palladium-catalyzed α-arylations of esters with chloroarenes have been reported (Hartwig, J. F.; et al. *Org. Lett.* **2008**, *10*, 1549). The reactions of chloroarenes with the sodium enolates of tert-butyl propionate and methyl isobutyrate occur in high yields with 0.2−1 mol % of $\{[P(t\text{-}Bu)_3]PdBr\}_2$ as with the bromoarenes or the combination of $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ as catalyst. In this case the coupling with *tert*-butyl acetate failed. Instead the reactions of chloroarenes with the Reformatsky reagent of *tert*-butyl acetate occurred in high yields for chlorobenzene and electron-poor chloroarenes catalyzed by 1 mol % of $Pd(dba)_2$ and pentaphenylferrocenyl di-*tert*-butylphosphine (Q-phos).

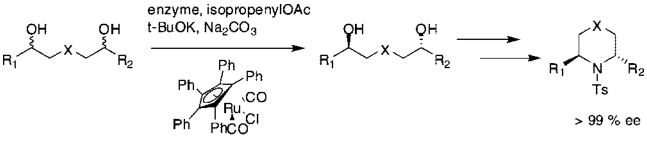


Hydroformylation in Room Temperature Ionic Liquids (RTILs): Catalyst and Process Developments

Over the past few years, ionic liquids have successfully been applied as alternative solvents for homogeneous biphasic catalysis. Many transition metal complexes dissolve readily in ionic liquids, which enables their use as solvents for transition metal catalysis. Sufficient solubility for a wide range of catalyst complexes is an obvious, but not trivial, prerequisite for a versatile solvent for homogeneous catalysis. Obviously, there are many other good reasons to apply ionic liquids as alternative solvents in transition metal-catalyzed reactions. Besides their very low vapor pressure and their good thermal stability, an important advantage is the possibility to tune their solubility and acidity/coordination properties by varying the nature of the anions and cations systematically. The possibility of adjusting solubility properties is of particular importance for liquid−liquid biphasic catalysis. Liquid−liquid catalysis can be realized when one liquid is able to dissolve the catalyst and displays a partial solubility with the substrates and a poor solubility with the reaction products. Under these conditions, the product phase, containing also the unconverted reactants, is removed by simple phase decantation, and the liquid containing the catalyst can be recycled. In hydroformylation, this concept has been successfully applied for reactions of short alkenes in the Ruhrchemie/Rhoñe-Poulenc Process (RCH/RP). Haumann, M. and Riisager, A. (*Chem. Rev.* **2008**, *108*, 1474) have reviewed this interesting topic for hydroformylation reactions.

Enantiopure 1,5-Diols from Dynamic Kinetic Asymmetric Transformation

Dynamic kinetic asymmetric transformation (DYKAT) of a series of 1,5-diols has been performed by Bäckvall, J.-E.; et al. (*Org. Lett.* **2008**, *10*, 2027) in the presence of *Candida antarctica* lipase B (CALB), *Pseudomonas cepacia* lipase II (PS-C II), and ruthenium catalyst **1**. The resulting optically pure 1,5-diacetates are useful synthetic intermediates, and this was demonstrated by the syntheses of both an enantiopure 2,6-disubstituted piperidine and an enantiopure 3,5-disubstituted morpholine.



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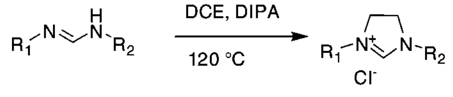
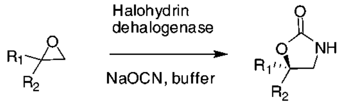
A Facile Preparation of Imidazolinium Chlorides



6 examples 42-92 %

A process for the preparation of symmetric and unsymmetric imidazolinium chlorides that involves reaction of a formamidine with dichloroethane and a base has been described by Grubbs, R. H.; et al. (*Org. Lett.* **2008**, *10*, 2075). This method makes it possible to obtain numerous imidazolinium chlorides under solvent-free reaction conditions and in excellent yields with purification by simple filtration. Alternatively, symmetric imidazolinium chlorides can be prepared directly in moderate yields from substituted anilines by utilizing half of the formamidine intermediate as sacrificial base.

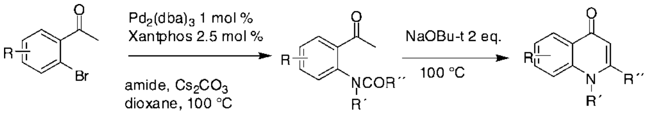
Formation of Enantiopure 5-Substituted Oxazolidinones through Enzyme-Catalysed Kinetic Resolution of Epoxides



up to 47 % yield
up to 98 % ee

Halohydrin dehalogenase from *Agrobacterium radiobacter* catalyzed the enantioselective ring opening of terminal epoxides with cyanate as a nucleophile, yielding 5-substituted oxazolidinones in high yields and with high enantiopurity (69−98% ee). This is the first example of the biocatalytic conversion of a range of epoxides to the corresponding oxazolidinones (Janssen, D. B.; et al. *Org. Lett.* **2008**, *19*). Preparative-scale syntheses could be performed at 15−20 g/L substrate concentrations due to the high substrate concentration tolerance and good enzyme stability This highly promiscuous halohydrin dehalogenase proves to be a valuable new tool for biocatalysis.

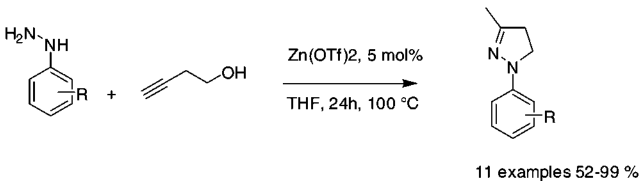
A Mild, One-Pot Synthesis of 4-Quinolones via Sequential Pd-Catalyzed Amidation and Base-Promoted Cyclization



14 examples
29-96 %
over two steps

A mild, one-pot synthesis of 4-quinolones has been described (Faul, M. M.; et al. *Org. Lett.* **2008**, *19*). Under the optimal conditions, a variety of 2-substituted 4-quinolones were synthesized via sequential palladium-catalyzed amidation of 2-bromoacetophenones followed by base-promoted intramolecular cyclization.

Zinc-Catalyzed Synthesis of Pyrazolines and Pyrazoles via Hydrohydrazination



A novel regioselective synthesis of aryl-substituted pyrazolines and pyrazoles has been developed (Beller, M.; et al. *Org. Lett.* **2008**, *19*), . Substituted phenylhydrazines react with 3-butynol in the presence of a catalytic amount of zinc triflate to give pyrazoline derivatives. The resulting products are easily oxidized in a one-pot procedure to the corresponding pyrazoles.

Calorimetric and Spatial Characterization of Polymorphic Transitions in Caffeine Using Quasi-isothermal MTDSC and Localized Thermomechanical Analysis

One of the holy grails of pharmaceutical process R&D remains the prediction of polymorphic behavior for any given organic compound. In addition to computational efforts, increasingly sophisticated analytical methods are developed in order to further the understanding of polymorph transformations. One such report comes from a team from the University of East Anglia, Queen's University Belfast and Astra Zeneca (Menduva, R.; et al. *J. Pharm. Sci.* **2008**, *97* (3), 1285). This work describes encouraging results related to polymorphic transitions using caffeine as a drug model. Caffeine exhibits two enantiotopic polymorphs, forms I and II, with form II being the stable polymorph below the transition temperature of 140 °C. The authors discuss the use of two novel approaches for the study of polymorphic transformations: quasi-isothermal modulated temperature differential scanning calorimetry (QI-MTDSC), and, local thermomechanical analysis (L-TMA). QI-MTDSC was used to measure the heat capacity of the system, allowing for its thermodynamic characterization. L-TMA was used to spatially differentiate between the two polymorphs in caffeine tablets. The kinetics of the polymorphic transformations were analyzed, indicating an Arrhenius behavior. Further refinement of the kinetic analysis may lead to stability predictions. It is hoped that additional work will contribute to improved prediction capabilities for the behavior of polymorphic systems. An appendix includes a novel heat transfer model for the calculation of thermal gradients within a hermetically sealed DSC pan.

Characterization of the "Hygroscopic" Properties of Active Pharmaceutical Ingredients

Hygroscopicity evaluation is an obligatory step executed in the screening of API forms. A minireview from a distinguished group of authors from SSCI, Eli Lilly, and the University of Wisconsin-Madison (Newman, A. W.; Reutzel-Edens, S. M.; Zografi, G. *J. Pharm. Sci.* **2008**, *97* (3), 1047) discusses the state-of-the-art of hygroscopicity assessment for pharmaceutical solids, and proposes a more systematic approach that takes into account the mechanisms of water sorption. The most important mode of water vapor sorption for small organic molecule pharmaceutical solids is absorption by penetration into the bulk. A flow chart is provided as guidance for characterizing the water uptake of pharmaceutical solids. Justification is provided for the selection of the decision-points recommended: 0.5% w/v may represent either three water monolayers of adsorbed water on a pharmaceutical solid surface or absorbed water by amorphous material, and 2% which may represent formation of a (hemi) hydrate. Recommendations are made for sample pretreatment and equilibration times.

Gas−Liquid Mass Transfer in Unbaffled Dual-Impeller Mixers

Some of the most challenging processes to scale up are heterogeneous gas−liquid processes. Frequently, such processes exhibit three phases, for example when solid catalysts are used (solid−gas−liquid systems), further complicating the scale-up. In many cases, the process performance is highly dependent on the effectiveness of the gas−liquid mass transfer, which in turn is mixing-sensitive. Creative solutions for the improvement of gas−liquid mass transfer are reported in a paper from P. Tanguy′s group at the Ecole Polytechnique in Montreal (Cabaret, F.; et al. *Chem. Eng. Sci. 63*, **2008**, 1636−1647). The authors investigated the behavior of both Newtonian and non-Newtonian systems in unbaffled dual-impeller systems. Water, aqueous glucose, and sodium carboxymethyl cellulose (NaCMC), (shear-thinning) solutions were investigated, using dissolved oxygen probes to quantify the amount of gas transferred. The typical approach for the mixing of low-viscosity systems is to use baffled systems with relatively small turbines operating at high shear. When dual impellers are selected, a combination of radial (bottom) and axial (top) impellers can be used. A better approach was found to be the use of a dual-shaft mixer, with two off-centered shafts, allowing for improved gas−liquid transfer in Newtonian fluids of low and high viscosity. Interestingly, in the case of non-Newtonian systems, the centered shaft option is better than the other configurations investigated. Presumably, equipment manufacturers will be interested in evaluating the possibility of including such options in commercial equipment.

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: ulf.tilstam@cmcsol.com

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

Trevor Laird*
Editor

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