Organic Process Research & Development

Highlights from the Literature

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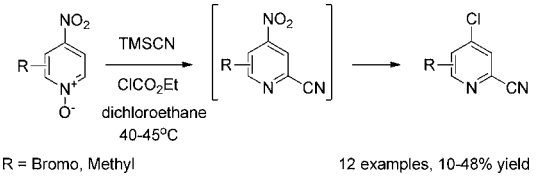
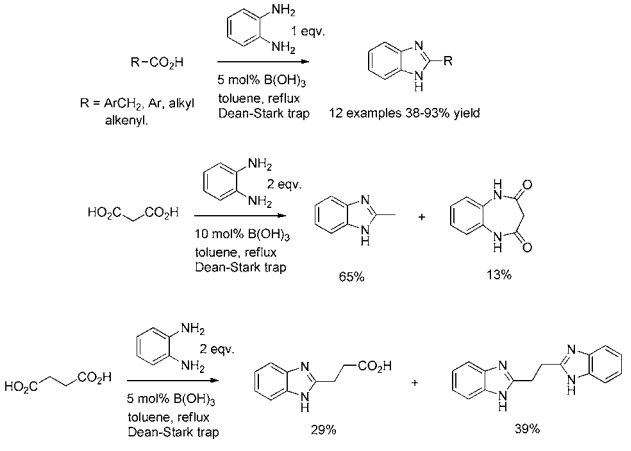
Some Items of Interest to Process R&D Chemists and Engineers

SYNTHESIS OF 2-CYANO-4-CHLOROPYRIDINES



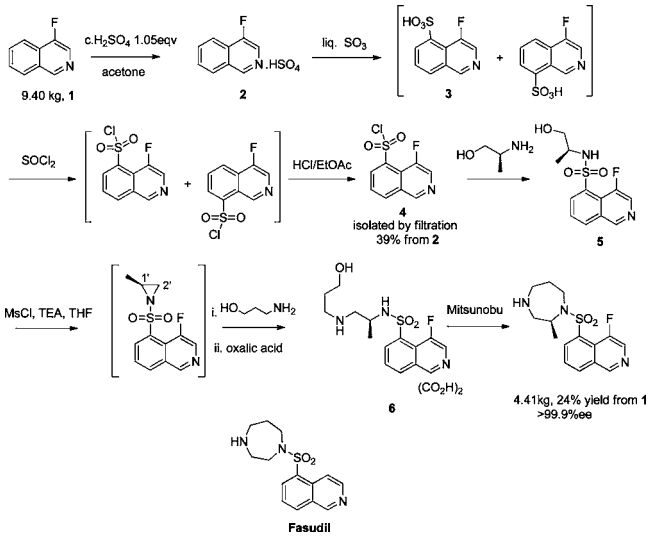
Veerareddy and co-workers of Suven Life Sciences have reported (*J. Heterocycl. Chem.* **2011**, *48*, 961) an improved procedure for the synthesis of 2-cyano 4-chloropyridines. Such products are useful building blocks en route to more elaborate pyridines, e.g. via SnAr of the 4-chloro group or manipulation of the 2-cyano group. Thus, direct conversion of 4-nitropyridine *N*-oxides into 2-cyano-4-chloropyridines was achieved via sequential addition of trimethylsilylcyanide and ethyl chloroformate in dichloromethane under mild conditions. Whilst most yields were modest (10−48%), this chemistry provides an advantage over other approaches that are restricted to 2-methyl 4-nitropyridine-*N*-oxides or that use highly toxic dimethylcarbamyl chloride.

GENERAL DIRECT SYNTHESIS OF BENZIMIDAZOLES FROM CARBOXYLIC ACIDS



The boric acid-catalysed condensation of a carboxylic acid and an amine is an efficient method for the synthesis of amides (see *Organic Syntheses*; 2005, Vol. 81, p.262). Kocevar and Maras (*Helv. Chim. Acta* **2011**, *94*(10), 1860−1874) have extended this methodology to the preparation of benzimidazoles. Thus, treatment of 1,2-benzenediamine with a range of monocarboxylic acids in the presence of catalytic boric acid afforded the benzimidazole derivatives in typically good yield. Extension of the methodology to dicarboxylic acids such as malonic acid lead to both a decarboxylation benzimidazole product (65%) and cyclisation to the benzodiazepinedione (13%). Succinic acid reacted with 2 equiv of the diamine to yield a mixture of the mono- and bis- benzimidazoles.

PRACTICAL SYNTHESIS OF RHO-KINASE INHIBITOR



Shibuya of Kowa Research laboratories and collaborators from Fuji Chemical (*Heterocycles* **2011**, *83*(8), 1771−1781) report a scaleable approach to a novel chiral analogue of the known kinase inhibitor Fasudil. Initial attempts to prepare chlorosulfonyl isoquinoline **4** via direct sulfonyation ($c.H_2SO_4/SO_3$) proved problematic due to handling issues with **1** (m.pt 20−25 °C) and the need to neutralise large volumes of excess H_2SO_4. Acceptable yields in the sulfonation step were achieved by conversion of preformed sulfate salt **2** in neat sulfur trioxide without additional sulfuric acid. One-pot sequential addition of SO_3 and $SOCl_2$ to **2** yielded a mixture of sulfonyl chloride isomers. The desired isomer **4** was then isolated after crystallisation. Subsequent reaction with L-alaninol installed the chiral side chain. Mesylation of **5** afforded an intermediate *N*-sulfonylaziridine which underwent ring-opening with aminopropanol. Recrystallisation of the oxalate salt **6** removed the isomer resulting from 1′ aziridine ring-opening. Ring closure under Mitsunobu conditions completed the synthesis in overall 24% yield and >99.9 ee.

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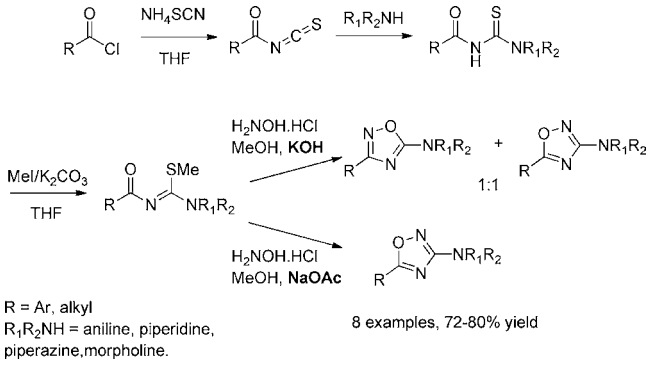
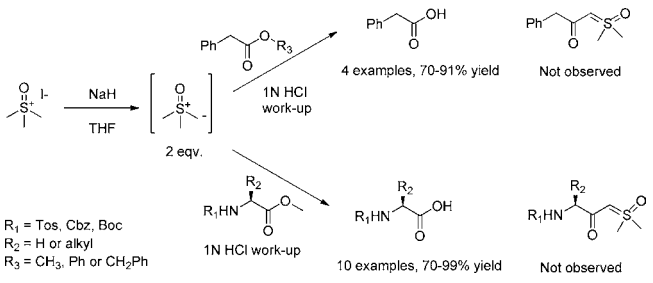
FACILE SYNTHESIS OF 3-AMINO 5-SUBSTITUTED 1,2,4-OXADIAZOLES

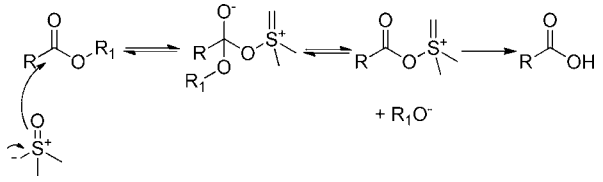


Manjunatha et al. of AstraZeneca Bangalore (*Tetrahedron Lett.* **2011**, *52*(46), 6170−6173) report an approach for the regioselective synthesis of 3-aryl/alkylamino 5-aryl/alkyl 1,2,4 oxadiazoles. Existing chemistry to construct these heterocycles relies on the use of toxic cyanogen bromide. The intermediate acylthioureas above were prepared via reaction of acid chlorides with ammonium isothiocyanate and a secondary amine. The selectivity of final hydroxylamine cyclisation was controlled by choice of base. The stronger base, potassium hydroxide, afforded a 1:1 mixture of isomeric oxadiazoles, possibly due to competitive reaction of NH_2O^- aminoxide ion and hydroxylamine, whilst a milder base, sodium acetate, provided a single oxadiazole regioisomer, typically in good yield. This approach was applied to both aryl and alkyl acid chlorides, although displacement of the thiomethyl group was only reported for cyclic secondary amines and aniline. Note the release of methanethiol (stench!) is a drawback to scale-up of this procedure.

DEPROTECTION OF CARBOXYLIC ESTERS WITH DIMETHYLSULFOXONIUM METHYLIDE

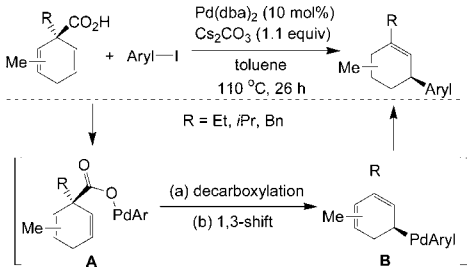


The conversion of carboxylic esters to β-keto dimethylsulfoxonium ylides with dimethylsulfoxonium methylide has been reported in the literature as an alternative to diazomethane in the synthesis of α-chloroketones (see BMS process development group *J.Org. Chem.* **2004**, *69*, 1629−1633). In an attempt to repeat this work, Leggio et al. (*Eur. J. Org. Chem.* **2012**, 114−118), found instead that this reagent deprotected methyl, benzyl, ethyl *and* phenyl esters to the parent carboxylic acid in good yield and without racemisation of chiral amino acid substrates. No β-keto dimethylsulfoxonium ylides were obtained. Highest yields were achieved using 2 equivalents of the ylide derived from trimethylsulfoxonium iodide and sodium hydride at room temperature in THF followed by acidic work up. Phenyl phenylacetate (i.e., R_3 = Ph) was successful cleaved to phenylacetic acid thus the reaction was presumed not to involve nucleophilic attack of the ylide on the alcohol moiety. Evidence for the reaction mechanism was obtained by a series of labelling experiments. Reaction of methyl phenylacetate with the ylide followed by hydrolytic workup with $H_2{}^{18}O$ gave unlabeled phenylacetic acid. The authors speculate the reaction mechanism to proceed via nucleophilic addition to the ester carbonyl by the ylide oxygen atom followed by release of the alkoxide and final hydrolysis of the sulfur-containing adduct on workup to the carboxylic acid.



Whilst numerous methodologies exist for the deprotection of carboxylic acids this approach may be favorable for chiral substrates such as peptides.

STEREOSPECIFIC PALLADIUM-CATALYZED DECARBOXYLATIVE C−C BOND FORMATION



German scientists described (*Angew. Chem., Int. Ed.* **2011**, *50*, 8614−8617) a highly stereospecific Pd-catalyzed decarboxylative arylation of 2,5-cyclohexadiene-1-carboxylic acids with aryl iodides. The reaction was conducted with $Pd(dba)_2$ as catalyst and Cs_2CO_3 as base in the absence of external ligand in toluene at 110 °C. The carboxylate anion plays important roles in the transformation servicing as internal ligand to form intermediate **A** and to facilitate the intramolecular 1,3-palladium shift to **B**. The study showed that the reaction was sensitive to steric effect in the carboxylic acids and no coupling product was detected for 2,5-dimethyl carboxylic acid derivative. In contrast, the reaction tolerated ortho-substituted aryl iodides including sterically hindered 2,6-disubstituted aryl iodides. The reaction is effective to a broad range of substitutents in the para position in the aryl iodides such as methoxy, methyl, amino, ethoxycarbonyl, trifluoromethyl, fluoro, and acyl groups, albeit lower yields for electron-deficient groups. Due to the competitive aromatization, reactions of aryl iodides with electron-rich groups favored the desired reductive elimination, affording good yields of the coupling products. Furthermore, the stereospecific chemistry was demonstrated from the cross-coupling of optically active 1,2-dimethyl-2,5-cyclohexadiene-1-carboxylic acid (93% ee) with iodobenzene to give the corresponding diene in 62% yield with 93% ee, indicating that decarboxylation/1,3-shift occurred with perfect stereospecificity.

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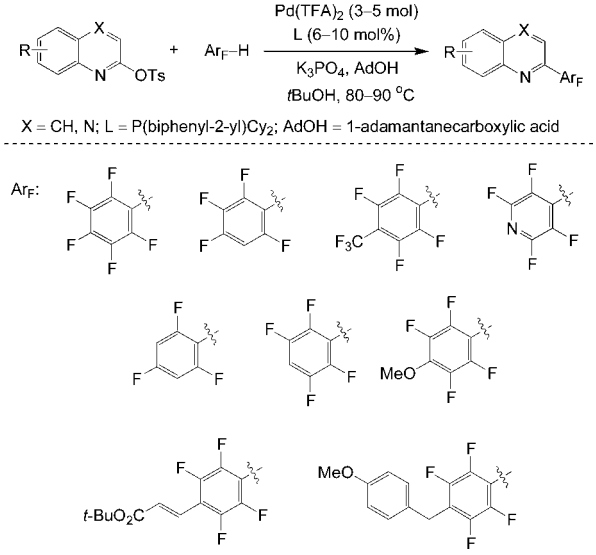
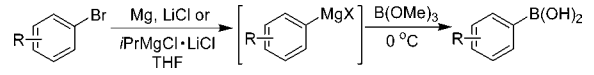
Pd-CATALYZED CROSS-COUPLING OF ELECTRON-DEFICIENT POLYFLUOROARENES WITH HETEROAROMATIC TOSYLATES



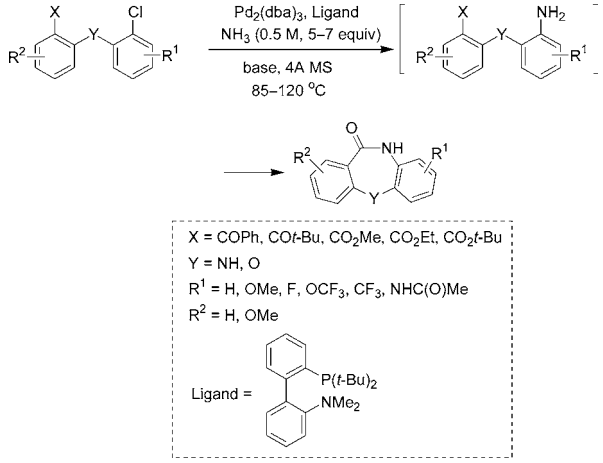
A Pd-catalyzed C−C bond cross-coupling reaction of heteroaromatic tosylates with electron-deficient polyfluoroarenes was developed by Zhang and co-workers of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (*Org. Lett.* **2011**, *13*, 4374−4377). Upon optimization the reaction could be carried out in the presence of 3 mol % of $Pd(TFA)_2$, 6 mol % of ligand, and K_3PO_4 (1.2 equiv) with 1.2 equiv of 1-adamantanecarboxylic acid (AdOH) as an additive at 90 °C, producing the cross-coupling products in good to excellent yields. Employing this protocol, a variety of pentafluorophenylated azine and diazine compounds were prepared. Good yields were achieved for substrates of 2-quinaxolinyl tosylates bearing electron-donating groups, while diminished yields were obtained for substrates with electron-withdrawing groups. In contrast, the reaction was less sensitive to the electronic nature of the substituents on the fluoroarenes, and good yields were observed with fluoroarenes bearing either electron-rich or electron-poor groups. This reaction methodology provides an alternative way in access of polyfluoroaryl azine and diazine derivatives.

HIGHLY EFFICIENT ONE-POT SYNTHESIS OF FUNCTIONALIZED ARYLBORONIC ACIDS



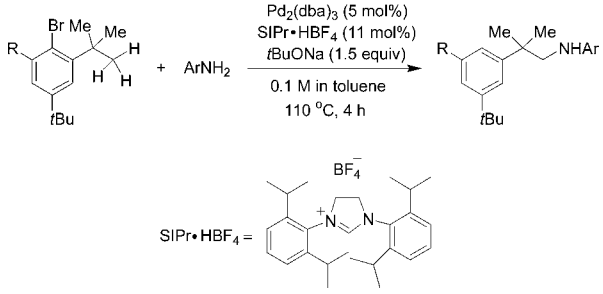
A general and convenient one-pot protocol for the synthesis of arylboronic acids was disclosed by Colobert and co-workers from France (*Org. Lett.* **2011**, *13*, 4479−4481). The two-step preparation was done by Grignard formation from a reaction of arylbromides with Mg in the presence of LiCl or by Mg/Br exchange with *i*PrMgCl·LiCl followed by the treatment of the resulting arylmagnesium compounds with trimethylborate at 0 °C. Both electron-donating and -withdrawing groups are tolerated under the reaction conditions. It is noteworthy that sterically crowded and electron-rich Grignard reagents were very efficiently prepared and transformed into the corresponding boronic acids which are otherwise difficult to prepare because of the hydrolytic deborylation during acidic aqueous workup.

CONCISE PALLADIUM-CATALYZED SYNTHESIS OF DIBENZODIAZEPINES AND STRUCTURAL ANALOGUES



A general and highly efficient protocol for the synthesis of dibenzodiazepines and their structural analogues was reported by Buchwald and co-worker of Massachusetts Institute of Technology (*J. Am. Chem. Soc.* **2011**, *133*, 14228−14231). This one-pot protocol involves a Pd-catalyzed C−N bond formation of aryl chloride with ammonia spontaneously followed by an intramolecular condensation to form the corresponding dibenzodiazepines. Upon application of the protocol, a wide variety of dibenzoheterocycles, such as dibenzodiazepines, dibenzooxazepines, and dibenzodiazepinones with electron-rich or electron-deficient substituents, was synthesized efficiently. Under these conditions, heterocycles such as diaxoles, thiols, and pyridines as well as various functional groups were tolerated. Notably, substrates bearing ester groups including methyl, ethyl, and *tert*-butyl esters reacted smoothly to afford dibenzodiazepinones and dibenzooxazepinone in good yields.

PALLADIUM-CATALYZED INTERMOLECULAR AMINATION OF UNACTIVATED C_{SP^3}–H BONDS



Inspired by the great importance of nitrogen-containing compounds among biologically active molecules, Buchwald and co-workers developed a novel approach for an intermolecular amination of C_{sp^3}–H bond (*Angew. Chem., Int. Ed.* **2011**, *50*, 8647−8651). This protocol involves a Pd-promoted tandem C−H bond activation and a successive C−N bond cross-coupling sequence, in which both steps shared the same palladium source, making the process cost efficient. The combination of $Pd_2(dba)_3$ as palladium source with *N*-heterocyclic carbene ligand ($SIPr{\cdot}HBF_4$) provided the desired aminated products in good yields. One of the competing reactions is the direct C−N cross-coupling, and the installation of a sterically hindered R group

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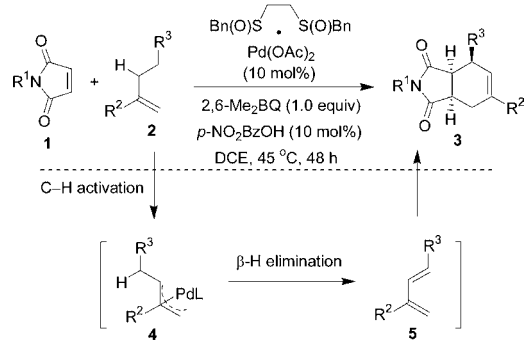
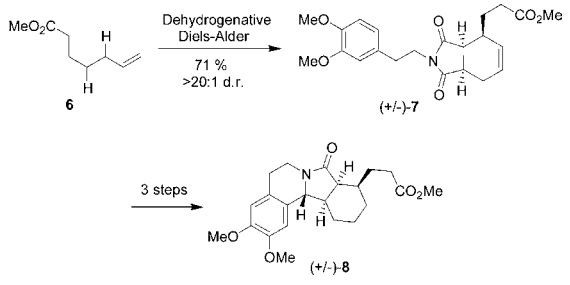
helps to suppress this side reaction. Aryl amines bearing electron-rich or electron-deficient functional groups gave the expected products in good to excellent yield. *N*-Substituted anilines and alkyl amines, however, do not work under the current reaction conditions.

ATOM-ECONOMIC PROCESS: Pd-CATALYZED DEHYDROGENATION/DIELS–ALDER REACTION

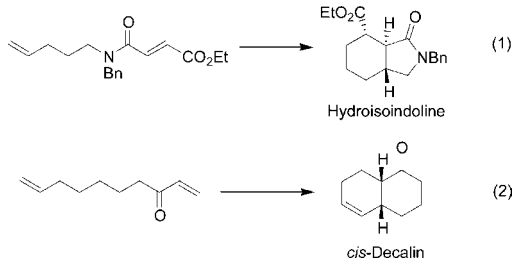


R^1 = Ph, *p*-$OMeC_6H_4$, *p*-AcC_6H_4, *p*-FC_6H_4, *p*-BrC_6H_4, etc.
R^2 = H, Me,
R^3 = CH_2OTBS, CH_2NPhth, $(CH_2)_4NO_2$, etc.

A challenging tandem reaction was developed (*J. Am. Chem.* **2011**, *133*, 14892–14895) by White and her co-worker of the University of Illinois, Urbana, which would enable the rapid construction of diverse molecular skeletons from simple starting materials. The tandem sequence involves a dehydrogenation via palladium-catalyzed C–H bond activation and subsequent *β*-hydride elimination followed by Diels–Alder reaction. The unique C–H bond activation was achieved with Pd(II)/bis-sulfoxide catalyst to lead to *π*-allyl palladium complex **4**, which sets the stage for the successive transformation of **4** into 1,3-butadiene intermediate **5** through *β*-hydride elimination. Key success for the catalytic process is the combination of bulky 2,6-dimethyl-1,4-benzoquinone (2,6-Me_2BQ) (1.0 equiv) with *p*-NO_2BzOH (10 mol %). Since the 1,3-butadiene thus formed was unstable under the reaction conditions, the Diels–Alder (DA) reaction was required to proceed promptly. Maleimides proved to be superior dienophiles for effective trapping of the reactive 1,3-diene intermediates. The dehydrogenative Diels–Alder reactions tolerated a wide range of functional groups in the terminal olefins such as nitro group, amides, acid-sensitive acetals, and *α,β*-unsaturated enones. Maleimide dienophiles with both electron-donating and -withdrawing *N*-aryl substituents are suitable substrates.

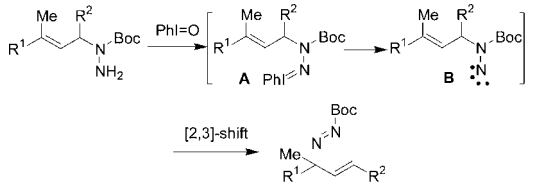


Furthermore, the versatility of the tandem reaction enables rapid access of complex skeletons found in biologically active molecules. For example, an isoindoloquinoline polycycle **8** was synthesized in four steps including the key tandem dehydrogenation/DA reaction. This isoindoloquinoline skeleton is found in several alkaloids, such as jamtine that exhibits significant antihyperglycemic activity.



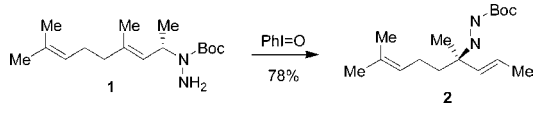
The tandem dehydrogenation/DA cycloaddition was extended to intramolecular reaction with tethering terminal olefin substrates to furnish the corresponding cycloadducts (eqs 1 and 2).

AN OXIDATIVE [2,3]-SIGMATROPIC REARRANGEMENT OF ALLYLIC HYDRAZIDES



R^1 = $(CH_2)_7Me$, CH_2CH_2OBn, CH_2CH_2OTBS, CH_2CH_2Ph, $CH_2CH_2CH{=}CMe_2$, cyclohexyl, Ph
R^2 = H, Me, *i*-Pr

An efficient and high-yielding transformation of allylic hydrazides into diazene products was realized through an oxidative [2,3]-sigmatropic rearrangement with iodosobenzene as the oxidant in THF (*J. Am. Chem. Soc.* **2011**, *133*, 14252–14255). The reaction includes two stages: oxidation of hydrazides to aminoiodinane **A** followed by loss of iodobenzene to produce the corresponding singlet *N*-nitrene **B** and [2,3]-sigmatropic rearrangement. A range of acyclic allylic hydrazides produced the desired allylic diazene products in good yields. Analogously, cyclic hydrazides underwent the oxidative rearrangement smoothly under the reaction conditions giving the diazenes in good yields, albeit in variable levels of diastereoselectivity.



On the contrary, the oxidative rearrangement of acyclic allylic hydrazides proceeded in a highly stereoselective manner, e.g., a complete stereochemical transfer was observed during the transformation of an enantioenriched hydrazide **1** to diazene **2**.

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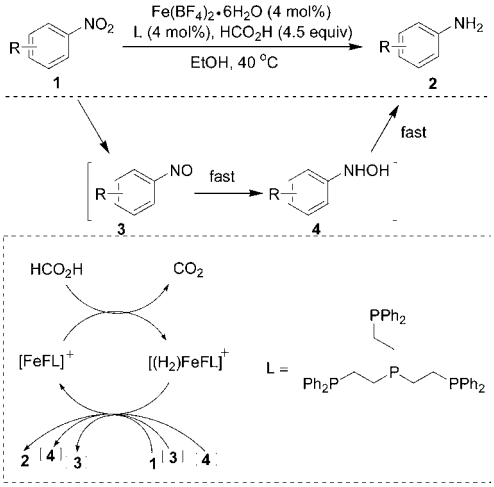
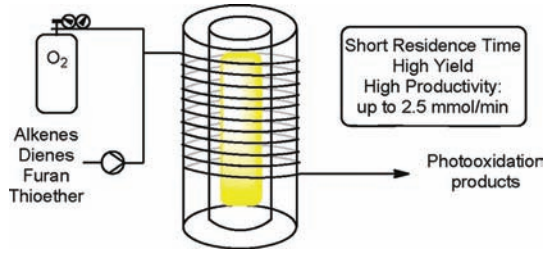
A GENERAL AND SELECTIVE IRON-CATALYZED TRANSFER HYDROGENATION OF NITROARENES



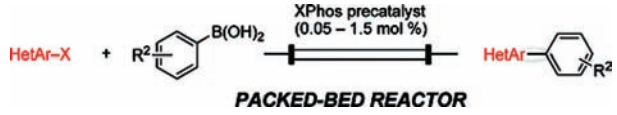
An iron-based catalyst system for the transfer hydrogenation of nitroarenes to anilines was developed (*J. Am. Chem. Soc.* **2011**, *133*, 12875−12879). The reduction was conducted at 40 °C in the presence of $Fe(BF_4)_2$ (4 mol %) and tetraphos ligand (4 mol %) with 4.5 equiv of formic acid as reducing agent in EtOH. Thus, these reaction conditions will draw great attention from industrial chemists in terms of cost (inexpensive biorelevant catalytic system), green solvent (EtOH), and mild conditions (40 °C). This reaction is applicable to a wide range of substituted nitroarenes affording the corresponding anilines in excellent yields. Functional groups, such as ketones, esters, ethers, thioethers, and amino groups, are well tolerated. More importantly, for halogenated nitrobenzenes, full conversions were achieved with no dehalogenation products being observed. Similar to other methods, the Fe-catalyzed nitro reduction went through two intermediates, nitrosoarenes **3** and hydroxylamines **4**. Hydroxylamines are known carcinogens and potentially explosive at higher concentration due to their thermal instability. Using the reaction protocol, no hydroxylamines were observed in the reaction mixture, indicating that the reductions of **3**→**4** and **4**→**2** proceed promptly.

HIGHLY EFFICIENT CONTINUOUS FLOW REACTIONS USING SINGLET OXYGEN AS A "GREEN" REAGENT



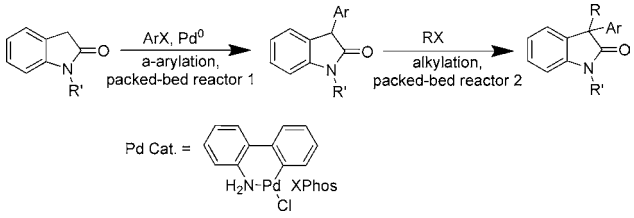
Seeberger and his co-worker from Max Planck Institute of Colloids and Interfaces, Department of Biomolecular Systems, described a new method for the efficient in situ production of singlet oxygen in a simple and inexpensive continuous flow photochemical reactor (*Org. Lett.*, **2011**, *13*, 5008−5011). The extremely large interfacial area generated by running the biphasic mixture in a narrow channel at a high flow rate ensures high throughput as well as fast and efficient oxidation of various alkenes, 1,3-dienes, and thioethers on a preparative scale. For example, the reactions produce up to 2.5 mmol of product per min and hold great potential for the acceleration of biphasic reactions involving oxygen and other gases.

SUZUKI−MIYAURA CROSS-COUPLING OF HETEROARYL HALIDES AND ARYLBORONIC ACIDS IN CONTINUOUS FLOW



A general continuous flow process for the Suzuki−Miyaura cross-coupling of heteroaryl halides and (hetero)arylboronic acids (*Org. Lett.*, **2011**, *13*, 5180−5183), was developed recently by Noël and his co-worker from the Department of Chemistry, Massachusetts Institute of Technology. A wide range of heterobiaryl components could be obtained in good to excellent yields (20 examples). Noteworthy are the use of low catalyst loadings (0.05−1.5 mol % Pd), unstable 2-heteroarylboronic acids, and the possibility to scale up the reaction very efficiently. The authors also pointed out the key factors to success in this paper: (i) the use of an XPhos precatalyst which guarantees fast activation of the catalytically active species; (ii) the use of a biphasic solvent system, which ensures good solubility of both organic and inorganic solids; and (iii) the use of a packed-bed reactor, which improves the contact between the immiscible phases.

CONTINUOUS-FLOW SYNTHESIS OF 3,3-DISUBSTITUTED OXINDOLES BY A PALLADIUM-CATALYZED α-ARYLATION/ALKYLATION SEQUENCE



A method for the palladium-catalyzed α-arylation of oxindoles in a continuous-flow manner has been successfully developed (*Angew. Chem. Int. Ed.* **2011**, *50*, 6396−6400). by Buchwald and Li from Department of Chemistry, Massachusetts Institute of Technology. The authors believe that the implementation of a biphasic system with KOH as the base, palladacycle as the rapidly activated precatalyst, and a packed bed as the microreactor is key to the success of this process. Furthermore, this facilitating chemistry was further extended to a two-step continuous-flow α-arylation/alkylation sequence for rapid, modular, and efficient syntheses of 3,3-disubstituted oxindoles, providing access to pharmaceutically interesting heterocyclic structures.

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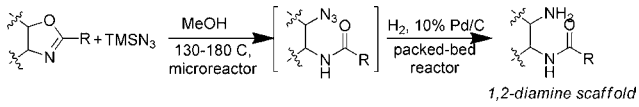
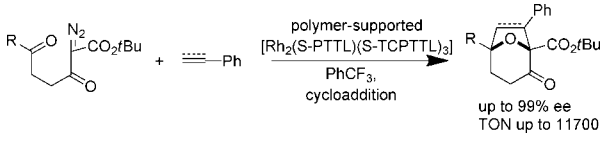
A TWO-STEP CONTINUOUS-FLOW SYNTHESIS OF *N*-(2-AMINOETHYL)ACYLAMIDES THROUGH RING-OPENING/HYDROGENATION OF OXAZOLINES



Kappe et al. from Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University, and Roberge et al. from Microreactor Technology, Lonza AG, jointly developed a ring-opening of 2-oxazolines in a very efficient manner by treatment with in situ generated hydrazoic acid (*Chem. Eur. J.*,**2011**, 13146−13150). Despite the toxic and explosive nature of hydrazoic acid, this process can be conducted safely in a continuous-flow high-temperature/pressure format (see scheme above).

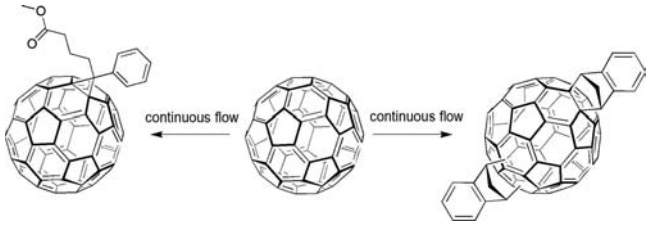
Key to the success of this protocol is the in situ generation of toxic and explosive HN_3 within the microreactor environment from $TMSN_3$ and MeOH. The resulting *N*-(2-azido-ethyl)acylamides can be further reduced directly to *N*-(2- aminoethyl)acylamides by using a continuous-flow hydrogenation protocol. The selectively protected 1,2-diamine scaffold prepared by this method constitutes an important structural moiety in several pharmaceutical products.

CONTINUOUS-FLOW SYSTEM WITH A POLYMER-SUPPORTED DIRHODIUM(II) CATALYST: APPLICATION TO ENANTIOSELECTIVE CARBONYL YLIDE CYCLOADDITION REACTIONS



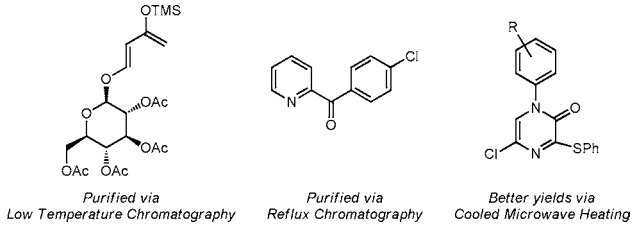
The first example of a continuous-flow system with immobilized dirhodium(II) complexes was reported recently (*Chem. Eur. J.* **2011**, 13992−13998) by Hashimoto et al. from Faculty of Pharmaceutical Sciences, Hokkaido University, who described a successful tandem carbonyl ylide formation−cycloaddition intermolecular reaction. The immobilization of $[Rh_2(S\text{-PTTL})(S\text{-TCPTTL})_3]$ (PTTL = *N*-phthaloyl-*tert*-leucinate, TCPTTL = *N*-tetrachlorophthaloyl-*tert*-leucinate) has been accomplished by copolymerization of the RhII-complex-containing monomer with 2-(trifluoromethyl)-styrene and a flexible cross-linker. Under those continuous-flow conditions, high yields as well as high levels of enantioselectivity (up to 99% ee) and turnover number were achieved. The robust nature of the flow reactor was demonstrated by the retention of full activity and enantioselectivity for a number of hours (up to 60 h) with a low leaching level (2.1 ppm). Moreover, this flow system exhibited exceptionally high turnover numbers (up to 11700) relative to that of the homogeneous catalyst system.

CONTINUOUS-FLOW SYNTHESIS OF FULLERENE DERIVATIVES



The 1,3-dipolar cycloaddition of the tosylhydrazone precursor and the Diels−Alder cycloaddition of indene to either C60 or C70 under conventional batch reaction conditions were translated to the continuous-flow process (*J. Org. Chem.* **2011**, 76, 3551−3556) recently by Wong, Jones, and their co-workers from Bio21 Institute, School of Chemistry, University of Melbourne. By varying the residence time, temperature, and equivalents of cycloaddition reagent, significant improvements in yields and reaction times were achieved over conventional batch processes, providing various fullerene-based electron-acceptor materials for organic photovoltaic applications via [3 + 2] and [4 + 2] cycloadditions, such as PC61BM, PC71BM, IC60BA, and IC70BA. For example, a production of up to approximately 15 g/day could be realized in the case of PC61BM, with one benchtop continuous-flow reactor.

LESSER KNOWN ENABLING TECHNOLOGIES FOR ORGANIC SYNTHESIS



Ley and co-workers have compiled a list of lesser used tools and techniques for aiding organic synthesis which are either newly emerging in the community or just simply overlooked (*Synthesis* **2011**, 1157−1192). These are divided in the review into two categories: separation methods (including low-temperature chromatography, reflux chromatography, and phase-switching methods) and synthesis methods (including cooled microwave heating, ball-milling, and design of experiments). Numerous examples are given along with description and pictures of the respective apparatus involved; three are highlighted here in the scheme above. The silyl enol ether-containing sugar, which under normal circumstances would decompose instantaneously on silica gel, could be purified by chromatography on silica gel at −78 °C. A medicinal chemistry application of reflux chromatography was for the purification of the pyridyl aryl ketone shown. Externally cooling while simultaneously microwave heating copper-mediated Chan−Lam reactions of arylboronic acids and pyrazinones gave improved yields for the *N*-arylated products.

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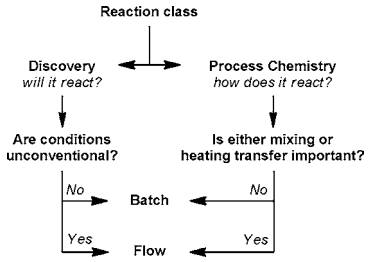
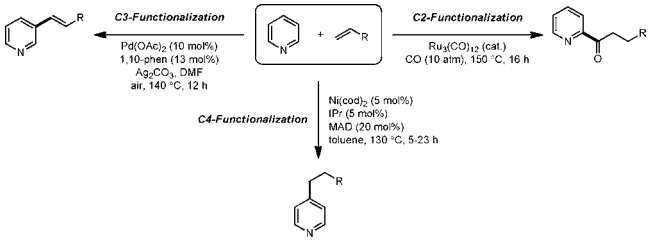
EVALUATING THE MERITS OF FLOW REACTORS FOR SYNTHESIS



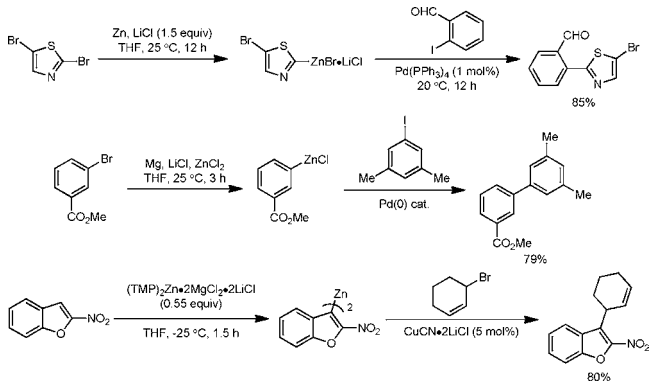
The use of flow reactors, especially microreactors, for intensified organic synthesis has gained tremendous traction in both academia and industry. Jensen and co-workers have authored a timely report discussing the relative merits of batch and microflow reactors for organic synthesis in laboratory environments (*Angew. Chem., Int. Ed.* **2011**, *50*, 7502−7519). The reaction engineering and heat and mass transfer concepts governing both batch and micro-chemical systems are discussed at length. Examples are offered from the organic synthesis literature where enhanced mixing or heat transfer due to microreaction technology has directly influenced the reaction outcome. Finally, the authors propose a decision roadmap (vide supra) for deciding whether a reaction should be performed in a flask or a flow reactor.

TRANSITION METAL-CATALYZED C−H FUNCTIONALIZATION FOR SUBSTITUTED PYRIDINES



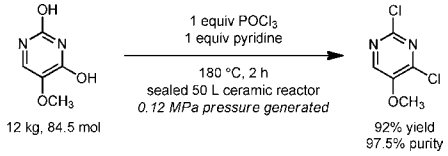
Pyridines are arguably amongst the most important heterocyclic motifs in organic synthesis. Nakao has reviewed the direct functionalization of pyridines through carbon−carbon bond-forming reactions, with a focus on reactions that introduce alkyl, alkenyl, aryl, and acyl groups directly to the pyridine core (*Synthesis* **2011**, 3209−3219). The review is organized according to C2-selective, C3-selective, and C4-selective functionalizations, and reviews the state-of-art in the field until mid-2011. That the field has already seen tremendous progress is apparent from the fact that the reactions of unsubstituted pyridine and monosubstituted olefins can be fine-tuned to afford either C2-, C3-, or C4-selective functionalizations (vide supra).

PREPARATION OF POLYFUNCTIONAL ARYL AND HETEROARYL MAGNESIUM AND ZINC DERIVATIVES



Knochel and co-workers have compiled the most important procedures, predominantly from their own laboratories, for the preparation of functionalized organozinc and organomagnesium derivatives (*Beilstein J. Org. Chem.* **2011**, *7*, 1261−1277). Three methods are illustrated for the preparation of aryl and heteroaryl zinc derivatives viz: (1) direction insertion of Zn, (2) direction insertion of Mg in the presence of Zn(II) salts, and (3) metalation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (vide supra). Also three methods are illustrated for the preparation of aryl and heteroaryl magnesium reagents, viz. (1) Br (or I)−Mg exchange, (2) direct insertion of Mg turnings in the presence of LiCl, and (3) direct magnesiation using TMPMgCl·LiCl. Typical experimental procedures for the most important methods are made available in the Supporting Information.

SOLVENT-FREE OR LOW-SOLVENT, LARGE-SCALE PREPARATION OF CHLOROPYRIMIDINES AND ANALOGUES



Chlorinated pyrimidines are important synthetic intermediates for agrochemicals and pharmaceutical drugs, traditionally prepared via methods involving excess solvents/reagents. Sun and co-workers have reported a large-scale (33 g to 12 kg) protocol for the chlorination of hydroxypyrimidines and other similar N-containing heterocycles with stoichiometric amounts of $POCl_3$ and a base (pyridine or triethylamine) and little or no solvent (*J. Org. Chem.* **2011**, *76*, 4149−4153). To mitigate the use of stoichiometric reagents, the reactions were carried out at temperatures higher than refluxing conditions in sealed Teflon-lined stainless steel reactors or ceramic reactors; a maximum of 0.12 MPa of pressure was reached during the heating. The workup and purifications also involved minimal solvents, and good to excellent yields and purities were obtained for a number of examples.

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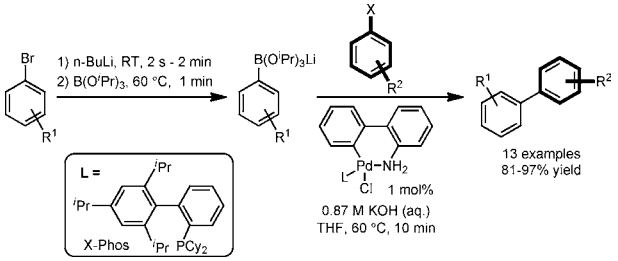
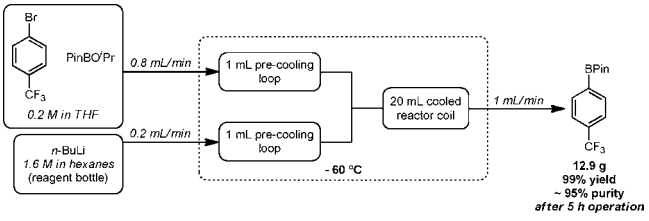
LITHIATION/BORYLATION/SUZUKI–MIYAURA CROSS-COUPLING SEQUENCE VIA CONTINUOUS-FLOW TECHNOLOGY



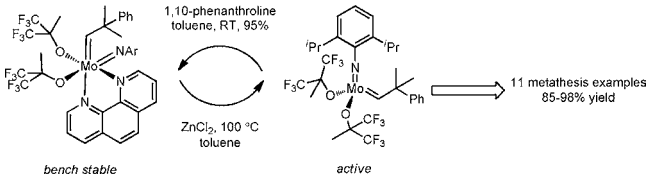
A common method of forming the organoboron reagents for Suzuki–Miyaura coupling reactions is via Li–H or Li–X exchange to form an organolithium intermediate which is quenched with a boron source. The lithiation processes are carried out under cryogenic conditions and involve hazardous reagents; these are often difficult to scale up in batch mode. Buchwald and co-workers have reported a three-step synthesis of biaryls involving lithiation of aryl halides/heteroarenes followed by borylation and Suzuki–Miyaura coupling under continuous-flow conditions (*Angew. Chem., Int. Ed.* **2011**, *50*, 10665–10669). A major challenge in the development of multistep syntheses under flow conditions, especially that involving organolithiation chemistry, is the possibility of precipitation of solids which leads to irreversible clogging. This was overcome by the Buchwald group with the use of acoustic irradiation (ultrasonication), which also enabled good mixing for the three-phase Suzuki–Miyaura coupling reaction. In addition to the scope shown in the scheme, the protocol was also extended to the reactions of heteroarenes (via Li–H exchange) with aryl halides.

ENABLING TECHNOLOGY FOR CONTINUOUS-FLOW PROCESSING AT LOW TEMPERATURES



Conducting cryogenic reactions under flow conditions poses problems such as solvent freezing, water ingress, and accurate temperature control. Ley and co-workers have reported a new cryogenic mesoscale flow reactor which overcomes these problems on a laboratory scale (*Org. Lett.* **2011**, *13*, 3312–3315). Lithium–halogen exchange chemistry was showcased to generate a number of (hetero)aromatic boronic esters under segmented flow synthesis on a small scale. Continuous processing at −60 °C for 5 h enabled scale-up to 13 g of product in excellent yield and purity without chromatography (vide supra). No frosting of the flow cell device was observed even after the reactor was kept at −60 °C for 12 days.

SCHROCK-TYPE Mo ALKYLIDENE COMPLEXES FROM AIR-STABLE PRECATALYSTS FOR ALKENE METATHESIS



Although the molybdenum alkylidene complexes developed by Schrock and co-workers are amongst the most versatile alkene metathesis catalysts until now, their use is limited due to high sensitivity towards air and moisture. Fürstner and co-workers have rendered these catalysts air stable by complexation with bidentate N ligands (*Angew. Chem., Int. Ed.* **2011**, *50*, 7829–7832). While the ligated complexes are devoid of catalytic activity, the ligands can be readily and in situ pulled off by treatment with $ZnCl_2$ in toluene. This generates the intact parent tetracoordinate molybdenum alkylidene complex in solution which demonstrates uncompromised catalytic activity for a range of alkene metathesis examples.

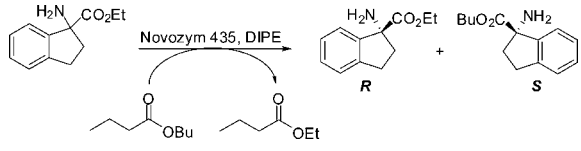
BIOCATALYTIC ALKANE ACTIVATION

Recently, Drone and co-workers from the Institute Charles Gerhardt Montpellier (*Angew. Chem., Int. Ed.* **2011**, *50*, 2075–2079) published a proof of concept and evidence that CYP153A13a fused to RhFred could be an alternative biocatalyst to alkane activation. The biocatalyst developed by this group is self-sufficient, soluble, and efficient which performs the alkane activation in an aqueous medium at low temperature and with oxygen. The results presented show that regio- and chemoselectivities are much higher than those for the existing enzymes, thus showing the exclusive formation of primary alcohol or monohydroxylated products.

ASYMMETRIC BIOREDUCTION USING ENE REDUCTASES

Bommarius and co-workers (*Org. Lett.* **2011**, *13*, 2540–2543) presented their results on the catalytic efficiency of YersER and KYE1 on reducing α,β-alkyl-substituted cyclic enones, enol ethers, carboxylic esters, nitrostyrenes, and maleimide-type compounds in aqueous/organic solvent systems. It is important to note that when using two-phase systems with toluene or hexane the results obtained do not show any decrease even at 50% of organic solvent concentration. DMSO and ethylene glycol do not show the same behavior since the catalytic activity decreases when concentrations reach values around 25 and 40% respectively.

KINETIC RESOLUTION OF QUATERNARY α-AMINO ESTERS



The present work published by Liisa T. Kanerva and co-workers (*Eur. J. Org. Chem.* **2011**, 1755–1762) with the title "*Candida antarctica* Lipase B in a Chemoenzymatic Route to Cyclic α-Quaternary α-Amino Acid Enantiomers" shows the results on

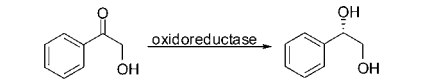
dx.doi.org/10.1021/op300014y | *Org. ProcessRes. Dev.* 2012, 16, 174–183

the kinetic resolution of quaternary α-amino esters by transesterification with butyl butanoate in DIPE as solvent (scheme above) leading to high enantiomeric ratios (>200) and conversions with long reaction times.

MINIATURIZING BIOCATALYSIS

In this work (*Adv. Synth. Cat.* **2011**, 2511−2521), authors address the importance of several parameters (capillary diameter, flow velocity, phase ratio, enzyme and substrate concentrations) for performing biocatalysis on segmented flow microreactors. The comparison between the results obtained in different reaction conditions shows that segmented flow systems can be a promising tool for the development of biocatalytic reactions which are strongly affected by mass transfer issues.

ANTI-PRELOG CARBONYL REDUCTASES



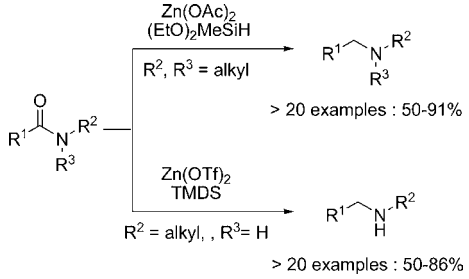
2-hydroxyacetophenone (*S*)-1-phenyl-1,2-ethanediol

The results presented by Montelione and Xu and co-workers (*Org. Biomol. Chem.* **2011**, *9*, 4070−4078) show a new gene cluster of oxidoreductases in *Candida parapsilosis* with unusual anti-Prelog stereospecificity for reduction of prochiral ketones such as 2-hydroxyacetophenone and demonstrates the diversity of oxidoreductases present in microorganisms. The product obtained (*S*)-1-phenyl-1,2-ethanediol (PED) is an important and versatile building block for the synthesis of pharmaceuticals, agrochemicals, liquid crystals, and chiral biphosphines.

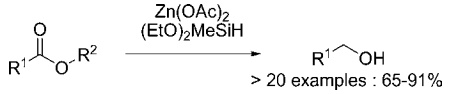
ZINC-CATALYZED REDUCTION OF CARBOXYLIC ACID DERIVATIVES

The group of Prof. Matthias Beller in Rostock reported in 2010 an efficient zinc-catalyzed reduction of tertiary amide to amine (*J. Am. Chem. Soc.*, **2010**, *132*, 1770). Triethoxysilane was used as the stoichiometric reductant. They have now improved their method by replacing triethoxysilane, which presents potential safety issues, by methyldiethoxysilane (*Chem. Eur. J.*, **2011**, *17*, 12186). Treatment of the tertiary amides with zinc acetate and methyldiethoxysilane in refluxing THF affords the amines in good to very good yield. Almost all functional groups (halogen, nitro, cyano, diazo) are tolerated with the exception of thioether, ketone, and to a certain extent ester.

In the same paper the authors described an efficient zinc trifluoromethanesulfonate reduction of secondary amide to amine using tetramethyldisiloxane as the reducing reagent. In this case also, exceptional functional group tolerance is reported as ester, alkene, nitro, cyano, diazo are tolerated.

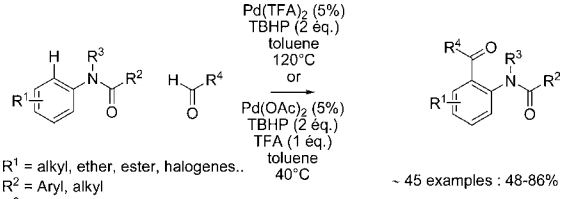


The same group reported earlier this year a similar system for the reduction of ester to alcohol (*Chem. Eur. J.* **2011**, *17*, 7414). In the presence of zinc acetate and methyldiethoxysilane, esters are easily reduced to alcohol. Functional group tolerance is also very high as alkynes, alkenes (both conjugated and nonconjugated), nitro, or cyano can be present in the substrate.



PALLADIUM-CATALYZED ORTHO ACYLATION OF ANILIDES WITH ALDEHYDES

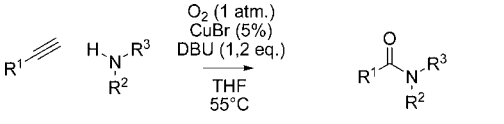
2-Aminobenzophenones are important intermediates in the synthesis of a number of heterocycles. Two groups from Shanghai and Hong Kong described independently their synthesis by palladium-catalyzed ortho acylation of anilides with aldehydes (*Chem. Eur. J.* **2011**, *17*, 10208 and *Adv. Synth. Catal.* **2011**, 2099). In both cases, the oxidant is *tert*-butylhydroperoxide (TBHP). The key finding is that the electrophilic cyclopalladation step occurred only in the presence of $Pd(TFA)_2$, directly introduced or generated in situ from palladium acetate and trifluoroacetic acid.



Interestingly, both aromatic (as well as heteroaromatic) and aliphatic aldehydes are tolerated under the reaction conditions and provide the 2-aminobenzophenones in moderate to good yields.

COPPER-CATALYZED OXIDATIVE SYNTHESIS OF AMIDE WITH DIOXYGEN AS THE OXYGEN SOURCE

Amides remain one of the most frequently encountered functionalities in bioactive molecules. Ji and co-workers in China report a catalytic oxidative synthesis of this functionality from amine and terminal alkyne, using dioxygen as the oxygen source (*Chem. Commun.* **2012**, 305−307). The catalytic system is composed of a copper salt and a base, copper bromide and DBU being the best combination. One drawback of the described method is that excess alkyne should be employed, as Glaser coupling also takes place under the reaction conditions.



This oxidative amination allows access to both secondary and tertiary amides. Electron-neutral and electron-rich aromatic alkynes perform best under the reaction condition, while electron-poor aromatic and aliphatic alkynes provide the desired product, albeit in lower yields.

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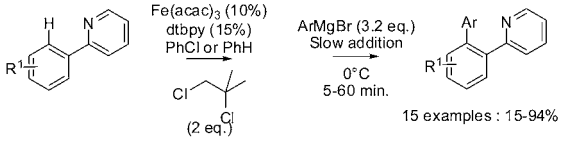
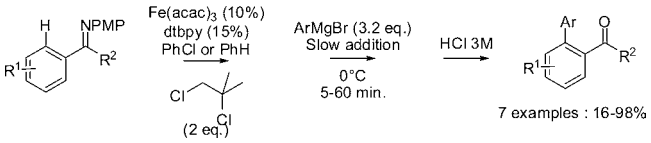
IRON-CATALYZED ORTHO ARYLATION OF ARYL PYRIDINE OR ARYL IMINE WITH GRIGNARD REAGENT

C−H activation chemistry is often limited to the use of expensive transition metal catalysts. The group of Nakamura in Japan described a procedure for ortho arylation of aryl pyridine or aryl imine with a Grignard reagent using iron as the catalyst (*Chem. Asian J.*, **2011**, *17*, 3059). High efficiency of the reaction is ensured by using 1,2-dichloro-2-methylpropane as the oxidant, benzene or chlorobenzene as the cosolvent. Homo-coupling of the Grignard reagent is suppressed by slow addition. The reaction is very fast at 0 °C and complete at the end of the addition.





Interestingly, halogens or pseudohalogens are tolerated under the reaction conditions. The authors also gave insight into the reaction mechanism that would proceed via a stable ortho-metalated intermediate that reacts only in the presence of the dichloroalkane to generate an arylated product.

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