Organic Process Research & Development

Highlights from the Literature

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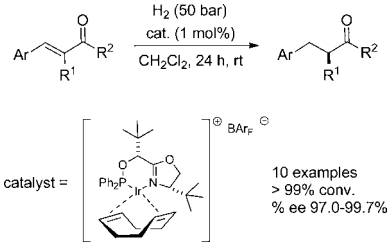
# Some Items of Interest to Process R&D Chemists and Engineers

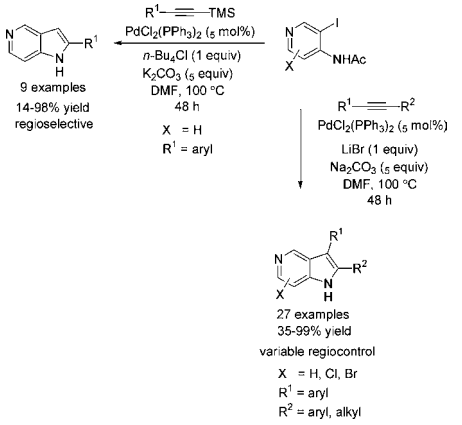
## CATALYSTS FOR STEREOSELECTIVE HYDROGENATION OF $\alpha,\beta$-UNSATURATED KETONES



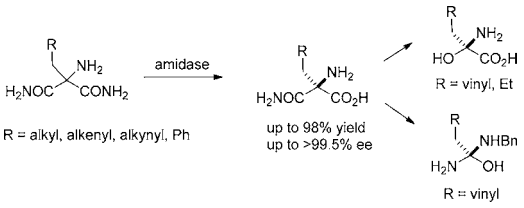

Asymmetric hydrogenations are among the most important catalytic processes for the synthesis of optically active compounds. Their high efficiency, eco-friendliness, and cost/benefit ratio have established them as one of the best utilized methods in the last 40 years. The Kazmaier group in Germany now reports on the development of iridium phosphinitoxazoline complexes that catalyze the asymmetric hydrogenation of arylated $\alpha,\beta$-unsaturated ketones (*J. Org. Chem.* **2012**, *77*, 5139).The best results were obtained with the *tert*-leucine-derived ligand, which gives excellent ee's with linear as well as cyclic substrates, giving selectivities of up to 99.7% ee. By varying the central metal and the substitution pattern, especially at the phosphorus atom, a wide range of comparable complexes and catalysts are accessible, which should be useful for not only asymmetric hydrogenations but also many other transition-metal-catalyzed reactions. Investigations of such complexes are currently in progress.

## Pd-CATALYZED SYNTHESIS OF 2,3-DISUBSTITUTED 5-AZAINDOLES VIA HETEROANNULATION

Many strategies have been developed for the synthesis of indoles including the Madelung reaction, the Fischer synthesis, the Leimgruber–Batcho reaction, the Hemetsberger–Knittel reaction, and the Bartoli reaction. Notably, the palladium-catalyzed heteroannulation reaction reported by Larock allows the straightforward preparation of a broad range of 3- or 2,3-disubstituted indole skeletons from easily accessible starting materials. As part of ongoing research aiming at the evaluation of polysubstituted 5-azaindoles as kinase inhibitors, the Schmidt group describe the preparation of these scaffolds through Pd-catalyzed Larock heteroannulation reaction (*J. Org. Chem.* **2012**, *77*, 5006). The use of unsymmetrical alkynes allowed evaluation of regioselectivity (which was generally poor) and its dependence on electronic and steric effects. An unexpected sila- Sonogashira/5-endocyclization process led to the preparation of 2-monosubstituted 5-azaindoles. Both methods permitted the synthesis of a large scope of 5-azaindoles possessing various substituents on both the pyridine and the pyrrole ring.




## ENANTIO-ENRICHED FUNCTIONALIZED $\alpha$-TETRASUBSTITUTED $\alpha$-AMINO ACIDS FROM BIOCATALYTIC DESYMMETRIZATION OF PROCHIRAL $\alpha$-AMINOMALONAMIDES




Biotransformations using either enzymes or whole cell catalysts have become important and routinely applied preparative methods in asymmetric synthesis. Biocatalytic desymmetrization of prochiral substrates, in particular, constitutes an elegant and powerful strategy for the generation of enantioenriched chiral compounds. Now, the Wang group report a highly efficient and enantioselective biocatalytic desymmetrization reaction using *Rhodococcus erythropolis* AJ270 whole cell catalyst under mild conditions (*J. Org. Chem.* **2012**, *77*, 5584). The amidase-catalyzed hydrolysis of prochiral $\alpha$- substituted $\alpha$-aminomalonamides provides a convenient and straightforward synthetic route to densely functionalized $\alpha$-tetrasubstituted $\alpha$-amino acids in high yields with excellent enantiomeric excesses. The presence of a free $\alpha$-amino ($NH_2$) substituent in the substrates was necessary to ensure high biocatalytic efficiency and enantioselectivity. The resulting enantio-enriched products, which are not readily available by other chemical and biochemical means, are invaluable chiral building blocks in organic synthesis, and their applications have been demonstrated by the practical and expedient preparation of $\alpha$-substituted or functionalized serine analogues and diamino alcohols.

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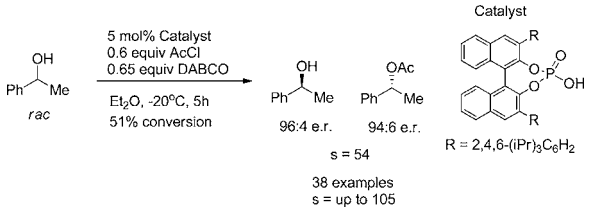
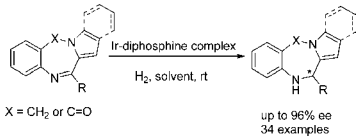
## KINETIC RESOLUTION OF SECONDARY ALCOHOLS BY THE COMBINATION OF A CHIRAL BRØNSTED ACID, DABCO, AND ACETYL CHLORIDE



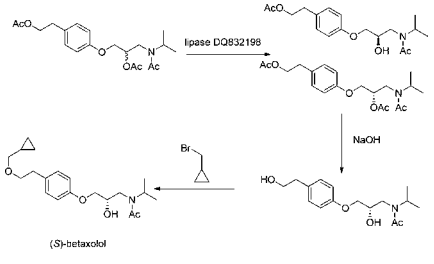

Nonenzymatic kinetic resolutions of secondary alcohols continue to be an active field of research. In a recent article by Mandai et al. (*Org. Lett.* **2012**, *14*, 3486) reported on the successful implementation of kinetic resolution using a chiral acid, DABCO and acetyl chloride. Using Kagan's equation for selectivity(s) they evaluated several catalysts and substrates and found a good efficient and simple system suitable for several aromatic secondary alcohols.

## IRIDIUM-CATALYZED ASYMMETRIC HYDROGENATION OF CYCLIC IMINES OF BENZODIAZEPINONES AND BENZODIAZEPINES



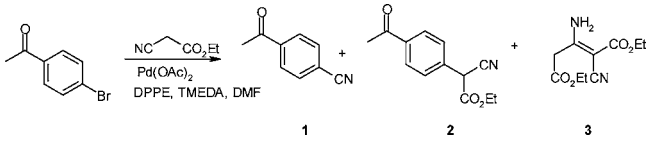

Yong-Gui Zhou et al. recently reported the use of iridium to perform an asymmetric hydrogenation on benzodiazepinone substrates (*Org. Lett.* **2012**, *14*, 3890). The article reports on the authors findings and showcases the results from extensive screening of both ligands and additives. The best system explored was using the [Ir (COD) Cl]$_2$ catalyst with (*S*,*S*,*R*)-Tunephos ligand and the morpholine-TFA additive in DCM/PhMe (1:2) solvent system at room temperature and with moderately high pressure (700 psi) of hydrogen gas. The highest yield was 99% with an enantiomeric excess of 96%.

## APPLICATIONS OF ENZYMATIC AND NONENZYMATIC METHODS TO ACCESS ENANTIOMERICALLY PURE COMPOUNDS USING KINETIC RESOLUTION AND RACEMISATION



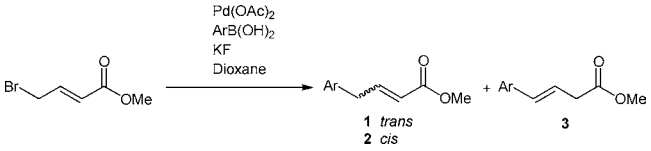

A recent Tetrahedron report by Ghanem et al. (*Tetrahedron* **2012**, *68*, 6781) reviews the use of lipases in kinetic resolution of organic compounds. One example is shown of the use of a lipase from *Rhodotorula mucilaginosa* in the manufacture of (*S*)-betaxolol. The review discusses the theory behind both enzymatic-assisted and nonenzymatic kinetic resolution as well as the theory of deracemization reactions with examples of both published over the last 5 years in the literature.

## ETHYL CYANOACETATE: A NEW AGENT FOR CYANATION OF ARYL HALIDES UNDER PALLADIUM CATALYSIS




Introduction of cyano groups into molecules has been achieved by the Rosenmund von Braun, Sandmeyer, and the ammoxidation reactions plus a range of direct cyanation techniques in more recent times. A novel method for cyanation of aryl halides that has been reported recently (*Org. Lett.* **2012**, *14*, 3644) employs ethyl cyanoacetate as the cyanating agent under palladium catalysis; the reaction works equally well with electron-deficient and electron-rich aryl bromides. There are limited examples of the use of chlorides in the paper. Interestingly, the presence of two or more electron-withdrawing groups completely inhibits the cyanation reaction and yields the corresponding phenylacetonitrile derivative (2) by an aromatic nucleophilic substitution reaction. The authors also comment on the reaction mechanism.

## LIGANDLESS SUZUKI COUPLING OF ARYLBORONIC ACIDS WITH ALLYLIC HALIDES




Recently, the arylation of methyl-4-bromocrotonate (which has been used as a model substrate) has been reported (*Org. Lett.* **2012**, *14*, 3298) which serves to highlight the synthetic potential of the reaction. The arylation of methyl-4-bromocrotonate was initially investigated with phenyl boronic acids with palladium acetate (5 mol %) and the phosphine P(*t*-Bu)$_2$Me (20 mol %). The reaction yielded the expected compound as a mixture of the trans and cis forms (**1** and **2**) along with the styryl compound **3** in a ratio of 74:23:5. Further studies on catalyst and ligand loading established that the reaction worked well in the absence of phosphine ligand, but potassium fluoride was essential. The preferred ligandless conditions also resulted in the desired *trans* allylic adducts (**1**) with none of the styryl product. The group demonstrated the reaction with 13 examples which gave yields in the range of 84−97%.

## ENANTIOSELECTIVE CONJUGATE ADDITION OF ALKYLBORANES UNDER COPPER−N-HETEROCYCLIC CARBENE CATALYSIS

Conjugate additions using organoboron compounds as organometallic reagents have been a focus of attention, given their broad substrate scope and functional group compatibility. However, until now the methodology had not been extended to the use of alkylborons. The article under consideration (*J. Am. Chem. Soc.* **2012**, *134*, 11896) reports the first catalytic enantioselective conjugate addition of an alkylboron (alkyl-9-BBN) compound. The reaction involves the addition of alkyl-9-BBN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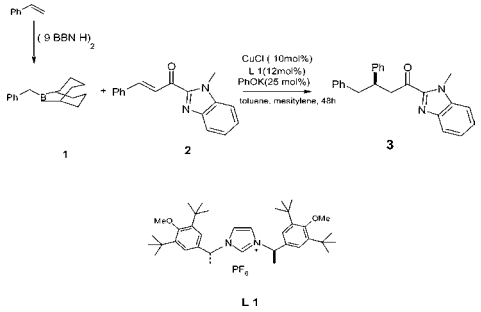
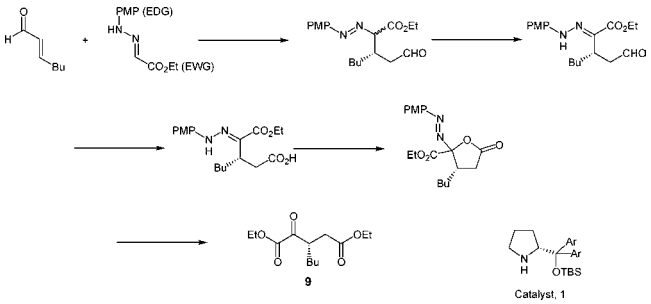



compounds to imidazol-2-yl $\alpha,\beta$-unsaturated ketones catalyzed by a Cu(I) complex with a chiral N-heterocyclic carbene (NHC) ligand. The alkyl boron substrate **1** was prepared by hydroboronation of styrene with 9-BBN. The *trans*-cinnamyl 1-methylimidazol-2-ylketone **2** was used as the other substrate. Following screening for ligands, base, etc., the authors identified the preferred conditions. PhOK was found to be the appropriate base as it yielded the product in 93% yield and 85% ee. Substituent variations of the imidazolyl ketone were also investigated with yields ranging from 64−93% and chirality in the range range 77−93% ee. The enantioselectivities have been rationalized on the basis of transition state models.

## ■ ENANTIOSELECTIVE CONJUGATE ADDITION OF DONOR−ACCEPTOR HYDRAZONES TO $\alpha,\beta$-UNSATURATED ALDEHYDES THROUGH A DIAZA−ENE REACTION: ACCESS TO 1,4-DICARBONYL COMPOUNDS

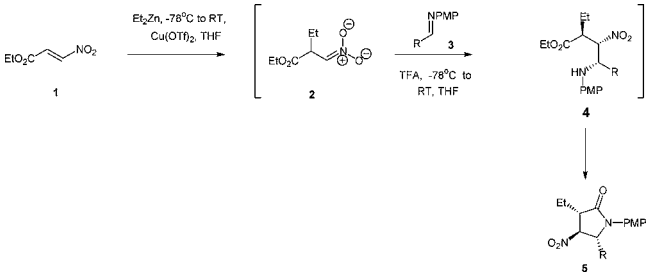
New umpolung transformations have been an important field of research since the introduction of the concept by Corey and




Seebach. In a novel approach (*J. Am. Chem. Soc.* **2012**, *134*, 11872) Vicario and co-workers, have reported the conjugate addition of donor−acceptor hydrazones (hydrazones with an electron-donating group (EDG) at the amino end and an electron-withdrawing group (EWG) at the azomethine end) as acyl anion equivalents to a chiral $\alpha,\beta$-unsaturated iminium ion (generated from an $\alpha,\beta$-unsaturated aldehyde and a chiral secondary amine). The proline-derived catalyst (**1**) was identified as the preferred catalyst giving a 70:30 mixture of diastereomers of the initial adduct with the major isomer having 98% ee and the minor isomer having 86% ee. The adduct was transformed as shown to the tricarbonyl (**9**) which retained high optical purity.

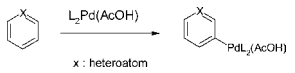
## ■ STEREOSELECTIVE SYNTHESIS OF DENSELY FUNCTIONALIZED PYRROLIDIN-2-ONES BY A CONJUGATE ADDITION/NITRO-MANNICH/ LACTAMIZATION REACTION

The structural unit of pyrrolidin-2-one is common to many complex natural products and pharmaceutical compounds. A novel approach to the enantioselective construction of the same




is described herein (*J. Org. Chem.* **2012**, *77*, 6186). The reaction proceeds via the conjugate addition of a diorgano zinc reagent to nitroacrylate **1** and subsequent trapping of the resultant nitronate anion **2** with an imine **3** that leads to an intermediate $\beta$-nitroamine **4**; in situ cylization of **4** yields the pyrrolidin-2-one **5**. The stereochemical outcome of the reaction was found to be contingent on the solvent employed. A small solvent screen revealed THF and diethyl ether to be the solvents of choice. With respect to substituents, the PMP group was identified as the optimum imine N-protecting group. A range of aryl and heteroaryl groups as well as alkylsubstituted imines are reported to have worked. The lower yields obtained with primary alkyl chains were presumably due to the instability of the imine. A methoxy acetal and an ethyl-ester substituent were also well tolerated. Mechanistic investigations revealed that the initial product, the *syn,anti*-$\beta$-nitroamine, cyclizes in a rate-determining lactamization step to give the densely functionalized pyrrolidin-2-one **5** as a single diastereoisomer. Any alternate acyclic diastereoisomers of the nitroamine formed in the reaction undergo equilibration to allow cyclization to the diastereoisomer **5**.

## ■ REGIOSELECTIVITY IN PALLADIUM ACETATE-MEDIATED C−H BOND ACTIVATION OF HETEROARENES




Functionalisation of arenes is often used in complex synthesis; one of the strategies employed has been catalytic C−H activation. Regioselectivity in arene and heteroarene C−H activation/functionalization is controlled either by a substrate-directing group or alternatively by the intrinsic positional reactivity of C−H bonds. In a recent disclosure (*Org. Lett.* **2012**, *14*, 3680) a method based on the thermodynamic stability of the metal aryl intermediate formed from C−H bond cleavage has been described for predicting C−H bond activation in heteroarenes (pyridines, pyridine *N*-oxides, pyridazines, furans, thiophenes, thiazoles, pyrazoles, imidazoles) and arenes. The activation energies ($\Delta E^{\ddagger}$) for C−H bond cleavage of heteroarenes with (Ph)($PMe_3$)-Pd(OAc) and the reaction energies ($\Delta E_{rxn}$) for the resulting palladium aryl intermediate were derived and the TS activation energy, the TS and Pd−C bond energies were computed. The above analysis provided a quantitative estimate of the relative strengths of developing Pd aryl bonding in the TS. A plot of the $\Delta E^{\ddagger}$ values vs TS bond showed an excellent linear correlation between these values, which provides the possibility for predicting regioselecitivty in new compounds without calculation of the transition states.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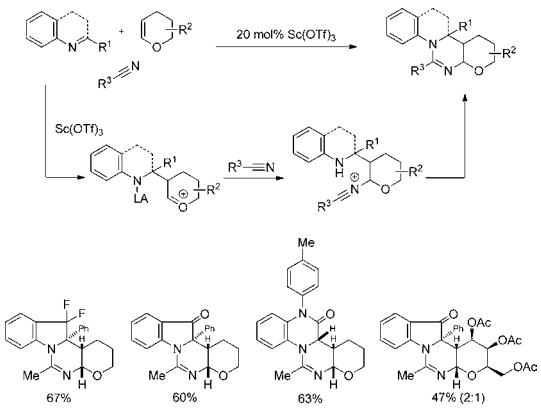
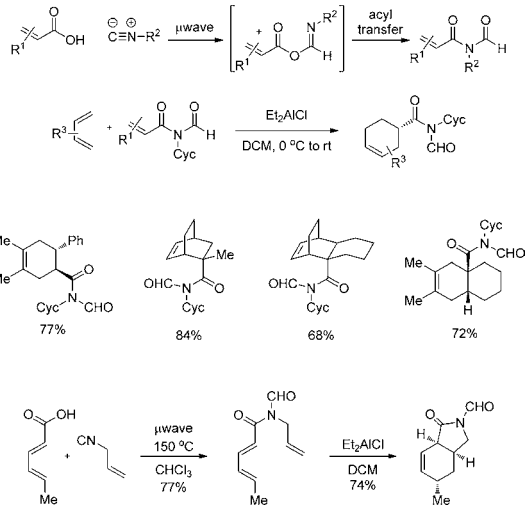
## MULTICOMPONENT MANNICH–RITTER REACTIONS




To the extent that multicomponent reactions (MCRs) continue to pique the interest of medicinal chemists seeking to expedite the generation of molecular diversity, process chemists will be challenged to develop scalable and robust processes involving the simultaneous consumption of several reactants and the formation of multiple bonds in a single step. Lavilla and co-workers from University of Barcelona report a new three-component Mannich-Ritter reaction that generates cyclic amidines in *Angew. Chem., Int. Ed.* **2012**, *51*, 6874. The reaction sequence entails three transformations: (1) condensation of a cyclic *N*-methylene aniline with a 2*H*-dihydropyran catalyzed by $Sc(OTf)_3$, (2) Ritter reaction of the resulting Mannich adduct with a nitrile to afford a nitrilium ion, and (3) formation of the amidine product via intramolecular trapping of the nitrilium by the aniline nitrogen. The authors study the scope of the reaction in detail following a methodical screening of cyclic imines, nitriles, and olefins. For example, $\alpha$-difluorinated indolenines and 3*H*-indol-3-ones afford the final adducts in good yields, whereas sterically or electronically inactivated analogues are unreactive. A variety of enol ethers, including glucal and galactal, yielded the MCR adducts. Moreover, linear, branched, benzyl, and allyl cyanides provided the desired amidines. This report demonstrates an elegant strategy to discover new MCRs—namely, the exposure of reactive intermediates to intermolecular pathways while restricting customary intramolecular processes.

## ENHANCING THE SCOPE OF THE DIELS–ALDER REACTION

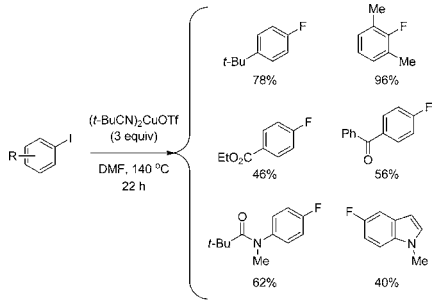
The laboratories of Professor Danishefsky report a new strategy to enhance the efficacy of the Diels–Alder reaction using $\alpha,\beta$-unsaturated *N*-formyl amides as dienophiles (*J. Am. Chem. Soc.* **2012**, *134*, 10659). The unsaturated imides can be prepared in excellent yields through a two-component coupling between a carboxylic acid and an isonitrile. This coupling generates an intermediate formimidate-carboxylate mixed anhydride that undergoes 1,3-O → *N*-acyl migration to afford the desired *N*-formyl amide. Direct competition studies revealed a superior dienophilicity of the *N*-formyl amides relative to ester, acid, amide, and aldehyde-activated cinnamates in the reaction with 1,3-cyclohexanediene. The cycloadditions are promoted by stoichiometric amounts of $Et_2AlCl$, which presumably forms a six-membered chelate with the two carbonyl groups of the *N*-formyl amide. The scope of the methodology was expanded




to $\alpha$- and $\beta$-substituted, unsaturated *N*-formyl amides and tested with a range of dienes. It is important to note that the new strategy enables the synthesis of complex polycyclic systems through normal- or inverse-demand intramolecular cycloadditions of substrates prepared by means of the carboxylic acid–isonitrile coupling. The *N*-formyl moiety present in the cycloaddition product can be easily converted to the corresponding alcohol, amide, or amine with high yields using standard functional group manipulations.

## Cu-MEDIATED FLUORINATION OF ARYL IODIDES

The past few years have seen a growing interest in the development of transition metal-catalyzed methods for the preparation of aryl fluorides. In particular, several procedures for the fluorination of aryl nucleophiles with electrophilic fluoride have been reported. The reactants, however, are often synthesized from their aryl halide cousins. Fier and Hartwig describe the direct




transformation of aryl iodides to the corresponding aryl fluorides using a simple cationic Cu reagent and AgF as the fluoride source (*J. Am. Chem. Soc.* **2012**, *134*, 10795). A successful metal-catalyzed fluorination must overcome the retardation of the reductive elimination step due to formation of stable species bearing strong metal–fluorine bonds. The authors hypothesized that the combination of a noncoordinating counterion and a poorly donating ligand could facilitate the reductive elimination. Indeed, a series of aryl iodides reacted with $(t\text{-BuCN})_2CuOTf$ and AgF to yield the desired aryl fluorides in good yields. The reaction works well with a variety of functional groups, such as ethers, amide, esters, ketones, and aldehydes,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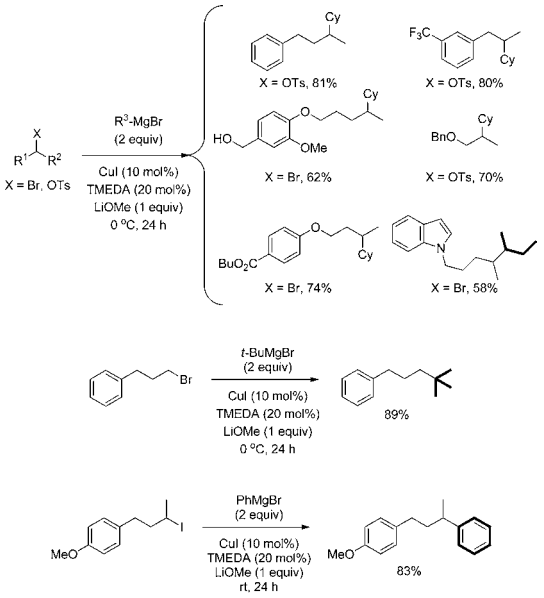
and provides virtually quantitative yields with hindered aryl iodides. A proposed reaction mechanism involves (1) reversible oxidative addition of the aryl iodide to the nitrile-bound CuOTf to give an aryl copper(III) iodide species, (2) transmetalation of AgF with the Cu(III) species, and (3) reductive elimination to form the C−F bond. The greatest challenge in the current process is the separation of the major aryl fluoride from the hydrodehalogenated byproduct generated by adventitious water.

## Cu-CATALYZED CROSS-COUPLING OF SECONDARY ALKYL HALIDES

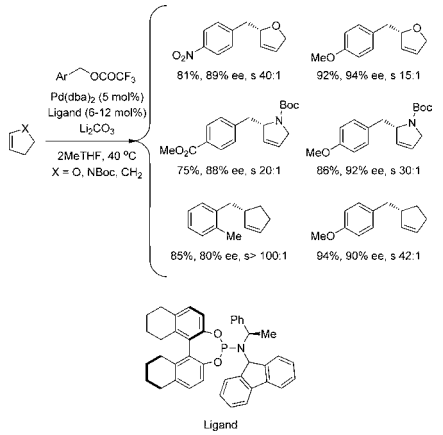
The cross-coupling of nonactivated secondary alkyl halides and pseudohalides with secondary alkyl Grignard reagents remains a challenge. Collaborative research between chemists at Tsinghua and Hefei Universities resulted in the discovery of a Cu-




catalyzed process that addresses the question (*J. Am. Chem. Soc.* **2012**, *134*, 11124). Inspired by the positive effect of Li additives upon the coupling of primary alkyl halides with different Cu catalysts, the authors found that a catalyst containing CuI, TMEDA, and LiOMe promotes the formation of C−C bonds between secondary alkyl bromides and secondary and tertiary alkyl Grignard reagents. The catalyst system also mediates the cross-coupling of secondary alkyl iodides with aryl Grignard reagents. Interestingly, substrates with aryl and alkyl sites prefer to react at the alkyl site opening up the possibility of completing sequential C−C and C−heteroatom cross-couplings catalyzed by Cu catalysts. The reaction of chiral tosylates with primary and secondary Grignard reagents allows for the stereocontrolled formation of C−C bonds from chiral secondary alcohols, which undergo inversion of configuration during the process. This result supports the intervention of an $S_N2$ mechanism. The reaction tolerates a variety of functional groups including esters, amides, olefins, and even unprotected alcohols. Pd and Ni complexes do not mediate the cross-coupling, excluding the participation of Pd or Ni contamination in the process.

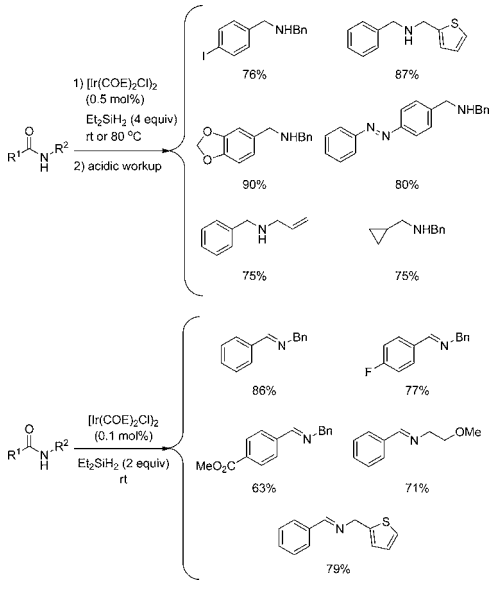
## ASYMMETRIC HECK REACTION OF BENZYLIC ELECTROPHILES

Yang and Zhou from Nanyang Technological University (Singapore) push the limits of the asymmetric Heck reaction to




incorporate benzyl triflates as electrophiles (*J. Am. Chem. Soc.* **2012**, *134*, 11833). Previous to this work, benzylic electrophiles were associated with sluggish oxidative additions, slow olefin insertions into the Pd−C bond, and competing olefin isomerization in the product. A screening of ligands, bases, and solvents led to the effective coupling of benzyl trifluoroacetate and 2,3-dihydrofuran in good yield and excellent stereoselectivity when using a partially saturated phosphoramidite, $Pd(dba)_2$, and $Li_2CO_3$ in 2-MeTHF. Structure−reactivity considerations indicate that the diolate moiety of the phosphoramidates is the key to achieve high enantioselectivities. In addition, the use of $Li_2CO_3$ minimized undesired olefin isomerization in the Heck product. Whereas the reaction works well in polar ethereal solvents, TBME or diethyl ether erode the catalyst turnover, and polar solvents such as DMSO and DMA inhibit the process possibly due to coordination to the active Pd species. An extensive analysis of the reaction scope shows that the procedure is general and tolerates a wide range of functional groups with the exception of those that bind to the Pd intermediates, such as pyridines. Moreover, the screening of a variety of benzylic electrophiles was unsuccessful, highlighting the uniqueness of the triflate group. A mechanistic proposal suggests the intervention of cationic Pd-benzyl species based on the higher reactivity of electron-rich olefins.

## Ir-CATALYZED REDUCTION OF SECONDARY AMIDES





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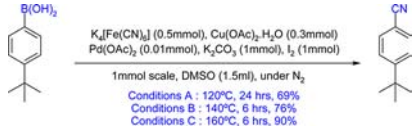
Stoichiometric methods for the reduction of amides suffer from poor functional group tolerance and air and moisture sensitivity. Thus, the discovery of alternative catalytic methods has drawn the attention of numerous research groups attracted by prospects of upgrading the ubiquitous transformation. Whereas the catalytic reduction of tertiary amides has been achieved in different settings, methods for the catalytic reduction of their secondary counterparts lag far behind. Chen and Brookhart describe the reduction of secondary amides to imines or secondary amines (*J. Am. Chem. Soc.* **2012**, *134*, 11304). The use of $Et_2SiH_2$ and the Ir complex $[Ir(COE)_2Cl]_2$ in nonpolar solvents reduces secondary amides to imines and later to the corresponding amines in excellent yields. The significant gap between the rates of the two reactions enables the isolation of the reduction at the stage of imine by using exactly 2 equiv of $Et_2SiH_2$. The method tolerates a variety of functional groups including halides, ethers, amines, and alkenes but is not compatible with nitro compounds and nitriles. Spectroscopic studies indicate that a silylene-bridged Ir dimer mediates the reduction by consecutive hydrosilylations across the C═O and C═N bonds. Interestingly, kinetic studies reveal that substrates bearing an electron-deficient substituent react more slowly than unsubstituted systems, indicating that electrophilic addition of "$Et_2SiH^+$" to the C═O group is an important step in the overall reduction.

## THE FIRST EXAMPLE FOR CYANATION OF ARYLBORONIC ACIDS WITH NONTOXIC AND INEXPENSIVE $K_4[Fe(CN)_6]$

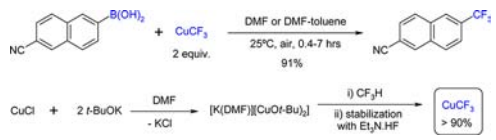
Aromatic nitriles are an important class of compounds, and numerous methods for their formation have been developed.




However, many of these suffer from drawbacks from an environmental and economic perspective owing to the cyanating agents employed. Tian and co-workers have developed a system for the cyanation of aryl boronic acids using nontoxic and inexpensive $K_4[Fe(CN)_6]$ (*Chem. Lett.* **2012**, *41*, 719). The reaction proceeds well in polar, high-boiling solvents at temperatures of 120–160 °C. Screening revealed that a combination of $Cu(OAc)_2 \cdot H_2O$ and $Pd(OAc)_2$ was the most effective catalyst combination. Other copper sources proved to be far less effective even in combination with palladium. The presence of base ($K_2CO_3$ was optimal) was critical, and one equivalent of iodine was added to the reaction. Switching to $K_3[Fe(CN)_6]$ led to a significant decrease in yield, and the presence of oxygen was shown to inhibit the reaction. Aryl and heteroaromatic boronic acids were effectively cyanated under optimal conditions, and the reaction is believed to proceed via a stepwise process with the aryl iodide as the intermediate species, which is cyanated.

## FLUOROFORM-DERIVED $CuCF_3$ FOR LOW-COST, SIMPLE, EFFICIENT, AND SAFE TRIFLUOROMETHYLATION OF ARYL BORONIC ACIDS IN AIR

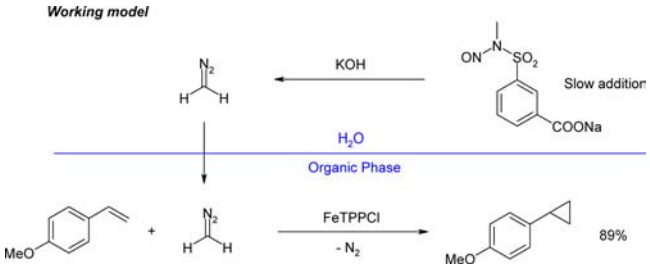
The interest in trifluoromethylated aromatics has stimulated the development of a range of protocols for the introduction of this moiety. Many of the synthetically useful methods focus on the conversion of boronic acids or their esters under copper-mediated conditions, although these become cost-prohibitive on an industrial




scale due to the expense of the $CF_3$ sources utilized. Grushin and co-workers have developed a low-cost, simple, and safe method for the trifluoromethylation of aryl boronic acids using $CuCF_3$ generated in situ through the reaction of CuCl and KO*t*-Bu with fluoroform in DMF (*Angew. Chem., Int. Ed.* **2012**, *51*, 7767). Two equivalents of the reagent stabilized with $Et_3N \cdot HF$ reacts smoothly with a range of aryl and heteroaryl boronic acids at room temperature to directly provide the trifluoromethylated product in excellent yield. Higher temperatures were shown to accelerate the reaction, although the amount of deborylation of the substrate was increased. If this was seen to be an issue for substrates at room temperature (typically <5%), or in cases for volatile products, the reaction can be run at 0 °C. Maintaining strictly anhydrous conditions is not necessary to run the reaction, which displays an impressive breadth of functional group tolerance, including the first examples of substrates containing an aldehyde function. Although, the mechanism is not fully understood, a radical pathway has been ruled out, and the reaction is likely to proceed through a "$Cu(II)CF_3$" electrophilic species.

## IRON-CATALYZED CYCLOPROPANATION IN 6 M KOH WITH IN SITU GENERATION OF DIAZOMETHANE

The utility of diazomethane as a reagent in organic synthesis has long been recognized, though valid concerns regarding its




safe handling due to its explosive and toxic nature have precluded its widespread use. Several solutions to this problem have been presented that involve continuous-flow chemistry, although specialized equipment is often required. Morandi and Carreira have developed a simple alternative approach to safely generate diazomethane under aqueous conditions for the cyclopropanation of olefins (*Science* **2012**, *335*, 1471). The two phase system uses a water-soluble diazald derivative, which releases diazomethane into the organic phase containing the olefin on treatment with 6 M KOH. A number of metal catalysts were screened for activity in the cyclopropanation reaction, and it was found that the air- and water-stable porphyrin FeTPPCl was the most effective. A range of styrenes as well as phenyl-substituted dienes and the corresponding enynes all underwent cyclopropanation in good to excellent yield. Mechanistic studies demonstrated the crucial need to maintain a biphasic system, as use of a water-soluble catalyst or a hydrophilic substrate, or addition of ethanol to generate a homogeneous system all led to a severe deterioration in yield. This method for the generation of diazomethane under aqueous conditions offers important advantages over previous approaches, although the use of strongly basic conditions places a limitation on the substrate scope at this time.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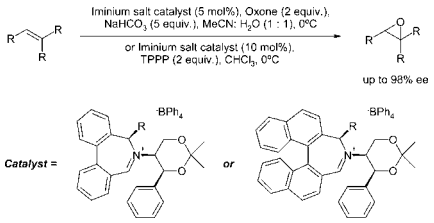
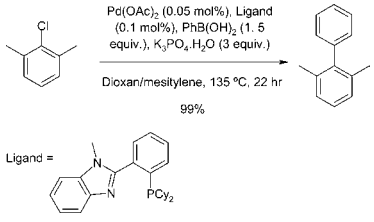
## ASYMMETRIC EPOXIDATION USING IMINIUM SALT ORGANOCATALYSTS FEATURING DYNAMICALLY CONTROLLED ATROPISOMERISM



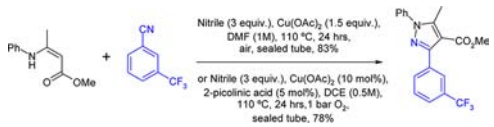

The asymmetric epoxidation of unfunctionalized olefins still represents a challenge within organic synthesis. A range of dioxiranes, oxaziridinium salts, and more recently iminium salts has been developed to address this problem. Bulman Page and co-workers have reported on an extension of their previously reported iminium salt catalysts, featuring the stereoselective introduction of a carbon substituent adjacent to the nitrogen atom in the azepinium ring (*J. Org. Chem.* **2012**, *77*, 6128). The substituents occupy a pseudoaxial position in the catalysts and serve to control both the atropisomerism at the biphenyl axis as well as the regiochemistry of the introduction of the double bond. Catalysts in both the binaphthyl and biphenyl series were evaluated with a range of substituents on the azepinium nitrogen against a series of olefins. Under classical epoxidation conditions utilizing oxone as the stoichiometric oxidant, sodium carbonate as the base, and aqueous acetonitrile as the solvent, the new catalysts (5 mol %) gave excellent yields, and improved enantioselectivities over earlier systems. The catalysts were also shown to perform better under the nonaqueous conditions with the use of tetraphenylphosphonium monoperoxysulfate as the oxidant. Significant studies were carried out on the structure of the active catalysts, and it is rationalized that the enhanced reactivity and enantiocontrol demonstrated by these systems is due to the new methyl ring substituent altering the ratio of $sp^2N-sp^3C$ rotamers.

## AN EFFICIENT CLASS OF P,N-TYPE "PhMezole-phos" LIGANDS: APPLICATIONS IN PALLADIUM-CATALYZED SUZUKI COUPLING OF ARYL CHLORIDES



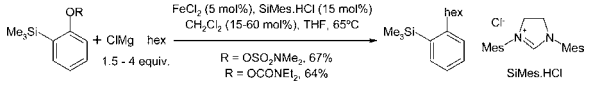

Numerous ligand systems have been developed for the Suzuki–Miyaura cross-coupling in the past decade to broaden the substrate scope of the reaction. Kwong and co-workers have reported on a novel class of hemilabile P,N-type phosphane ligands based on a benzimidazole framework representing an extension of the previously developed 2-phenylindole ligands (*Eur. J. Org. Chem* **2012**, 4172). The new ligands are easy to assemble in a modular manner, and the additional nitrogen atom on the framework provides an additional coordinating site for dynamic interaction, which could increase catalyst longevity. Screening studies determined the optimal conditions with potassium phosphate as base and dioxan as solvent and a metal/ligand ratio of 1:2. Reactions were run at 135 °C, and catalyst loadings as low as 0.0002 mol % were shown still to give excellent yields with mesitylene added as a cosolvent. A wide range of aryl and heteroaryl chlorides were coupled effectively under the optimum conditions. Under very low catalyst-loading conditions, heterocycles with coordinating atoms proved problematic due to competitive coordination to the metal complex. This issue could be easily resolved under these conditions by increasing the metal/ligand ratio slightly to 1:4.

## AN EFFICIENT COPPER-CATALYZED FORMATION OF HIGHLY SUBSTITUTED PYRAZOLES USING MOLECULAR OXYGEN AS THE OXIDANT




The selective synthesis of highly substituted pyrazoles still represents a major challenge. Glorius has recently reported on a novel approach involving the coupling of enamines and nitriles by oxidative C–C/N–N bond formation. However, the method was limited due to the need for large excesses of the nitrile (often employed as solvent), and the use of a stoichiometric amount of $Cu(OAc)_2$ as the Lewis acid and oxidant. Further optimization of this chemistry has enabled good yields to be obtained using 3 equiv of the nitrile and oxygen as the stoichiometric oxidant (*Green Chem.* **2012**, *14*, 2193). Two reaction protocols were developed. One utilizes DMF as the solvent in a sealed system, whilst the second employs DCE under an oxygen atmosphere with 5 mol % of picolinic acid as an additive and allows the copper to be employed in catalytic amounts. It is believed that in this system the additive acts both as a catalytic $H^+$ source to help regeneration of Cu(II) from Cu(I) in the redox cycle and can potentially coordinate to stabilize various intermediates. The authors also note that the reaction displays a degree of product inhibition with the pyrazole competing with the nitrile to coordinate the copper. A wide range of solid, liquid and even gaseous nitriles were demonstrated to be effective coupling partners, and the scope of substituted enamines was good, with neither electronics nor sterics adversely affecting the reaction.

## IRON-CATALYZED ALKYLATIONS OF ARYL SULFAMATES AND CARBAMATES




Iron is widely regarded as the ideal metal for catalytic transformations owing to being abundant, inexpensive and nontoxic. Garg and co-workers have reported on the iron-catalyzed cross-coupling of aryl sulfamates and carbamates with alkyl Grignard reagents to generate new $sp^2-sp^3$ C–C bonds (*Org. Lett.* **2012**, *14*, 3796). Reactions proceed under mild conditions in THF using catalytic iron(II) chloride and an NHC ligand, with substoichiometric quantities of $CH_2Cl_2$ necessary to obtain good yields and consistent results. Only minor amounts of product (<15%) are observed in the absence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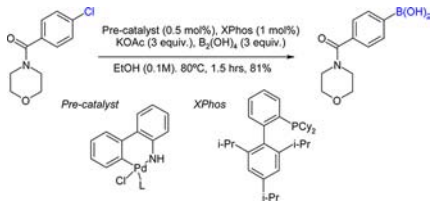
of iron with or without palladium, copper, or nickel salts. The substrate scope is good with a range of aromatic and heteroaromatic moieties performing well in the reaction. For the Grignard partner, branching at either the $\alpha$ or $\beta$ carbon, and heteroatom or heterocycle substitution are well tolerated. The fact that aryl sulfamates and carbamates are easy to prepare, can be used as directing groups, and remain unreacted unless subjected to specific coupling conditions makes this methodology highly valuable for the preparation of polyfunctional aromatic compounds.

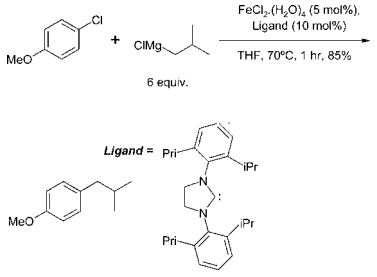
## SCOPE OF THE PALLADIUM-CATALYZED ARYL BORYLATION UTILIZING BIS-BORONIC ACID




Molander at the University of Pennsylvania in collaboration with Merck has reported the scope and an improved protocol for the palladium-catalyzed aryl borylation utilizing bis-boronic acid (BBA) (*J. Am. Chem. Soc.* **2012**, *134*, 11667). The general method now utilizes Buchwald's second-generation XPhos precatalyst. This enables rapid formation of the active Pd(0) species at room temperature, and potassium acetate can be employed as the base. In addition, the yields are higher than with the previously reported procedure. All the reagents employed are commercial and bench stable, and the reactions are typically performed in ethanol or methanol. The reaction is operationally easy to perform with all the reagents simply being combined prior to addition of the solvent. The products are typically obtained as the trifluoroborates for ease of isolation and stability purposes. The reaction can also be performed using $Pd(OAc)_2$, but it is important to preactivate the Pd species prior to addition of BBA to prevent decomposition. Monitoring the reaction is extremely facile as completion of the reaction is indicated by a color change from colorless to yellow for aryl chlorides (orange for the corresponding bromides). Kinetic studies demonstrated the borylation rate to be ArCl > ArBr > ArI. These relative rates are attributed to the electrophilicity of the intermediate organopalladium species, which depends on the electronegativity of the halide. The reaction scope is broad, with only the main limitation being substrates with electron-withdrawing groups in the ortho position. Nitro, aldehyde, and ketone groups are tolerated, but minor amounts of products from these functionalities being reduced are also observed, although this is minimized with methanol as the solvent. A method for the borylation of heterocycles that uses cataCXium A as the catalyst is also disclosed .

## AN UNPRECEDENTED IRON-CATALYZED CROSS-COUPLING OF PRIMARY AND SECONDARY ALKYL GRIGNARD REAGENTS WITH NONACTIVATED ARYL CHLORIDES

Perry and co-workers have demonstrated the iron-catalyzed cross-coupling of nonactivated aryl chlorides with a range of primary and secondary Grignard reagents (*Tetrahedron Lett.* **2012**, *53*, 4436). The reaction proceeds using iron chloride as




the catalyst with an NHC as the ligand. Screening studies demonstrated that a sterically bulky ligand was critical, and interestingly, it was key to have water present for an optimum reaction. With this in mind, the tetrahydrate of iron(II) chloride was employed as the catalyst of choice. The stoichiometry of the Grignard reagent was also shown to be important, and two protocols developed, involving complete addition at the outset of the reaction, or in two distinct batches. Reactions proceeded at 70 °C in THF, and a range of primary Grignard reagents was shown to effectively couple even with the electron-rich 4-chloroanisole. Secondary Grignard reagents also coupled, albeit in slightly depressed yield, and the deshalogenated arene was also observed in these reactions. Branched Grignard reagents such as isopropylmagnesium chloride gave a mixture of the branched and linear products, indicating that the reaction proceeds under an ionic mechanism, as has been demonstrated in previous studies. The branched isomer always predominated, and this ratio could be further optimized by increasing the amount of Grignard reagent used, although at the expense of yield.

## CRYSTAL ENGINEERING OF ISOSTRUCTURAL QUATERNARY MULTICOMPONENT CRYSTAL FORMS OF OLANZAPINE

Because of the expiration of the Lilly 2011 patent for olanzapine (Zyprexa), an atypical antipsychotic drug, this molecule has been the target of several pharmaceutical companies for the development of generic forms. Alkermes, Amgen, and the University of South Florida reported some of their work in this area (Clarke, H. D.; et al. *Cryst. Growth Des.* **2012**, *12*, 4194). Olanzapine, a BCS class II API (low solubility, high permeability) exhibits six anhydrous polymorphs, three polymorphic dehydrates, two polymorphic sesquihydrates, and several mixed solvates and hydrates. Through a systematic analysis of the published crystal structures, the authors were able to crystal engineer and prepare several new isostructural forms. The new forms thus developed are unique because they contain four molecular components, and they could potentially be classified as solvates, hydrates, or cocrystals. The new olanzapine forms were obtained using a cocrystal former, isopropyl acetate, and water. The cocrystal formers employed were nicotinamide, salicylamide, and *p*-hydroxybenzamide. Crystal structures for all the new forms were determined. The newly obtained olanzapine forms join a rather exclusive "club": in the Cambridge Structural Database, where more than 250,000 structures are recorded, and only 152 contain four distinct chemical entities.

## SYMMETRY BREAKING: POLYMORPHIC FORM SELECTION BY ENANTIOMERS OF THE MELATONIN AGONIST AND ITS MISSING POLYMORPH

During drug development, we only wonder if we were able to identify and characterize all the polymorphs of a given API;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however, we are quite concerned when we are unable to isolate the *stable* polymorph of the API at stake. A case of such a "missing polymorph" is reported by a team from Lilly (Stephenson, G. A.; et al. *Cryst. Growth Des.* **2012**, *12*, 3964).

One enantiomer of a melatonin agonist (MA) in development at Lilly (program now discontinued) exhibited biological activity (R-MA), whereas the other enantiomer was inactive. For S-MA both a metastable as well as a stable form were isolated. For the active R-MA only one form could be crystallized, which was calculated to be the metastable form (the estimated Gibbs free energy difference between the forms = 0.7 kcal/mol at room temperature), in spite of the fact that R-MA was synthesized 37 times, including 11 multikilogram campaigns, with over 1000 attempts made to isolate the corresponding stable polymorph. Moreover, of the 40 samples stored for 14 years, none showed conversion to the stable form. Extensive experimental and computational investigations are reported, together with a possible explanation for the absence of the stable form of R-MA. Many conventional, empirical crystallization "rules" were violated by the MA system studied. This article has 73 references.

## A STATISTICAL APPROACH TO MICROKINETIC ANALYSIS

Microkinetic analysis typically refers to the examination of (heterogeneous) catalytic reactions in terms of their elementary steps (mechanism) and their relation with each other during a catalytic cycle. Fortunately, we have a reason why certain chemical processes are incompletely understood after nearly a century since their invention: it is their complexity—chemical, physical, and mathematical. The Fischer−Tropsch process is one such example. A team from Sasol, where the process has been practiced for over 60 years, reports about their microkinetic analysis of the famous methanation reaction (van Helden, P.; et al. *Ind. Eng. Chem. Res*, **2012**, *51*, 6631). The focus of the work is the simplification of the mathematical complexity associated with the model describing heterogeneously catalyzed reactions. Even for relatively simple cases, the corresponding kinetic differential equations "add up", leading to computational challenges. The authors propose the use of space-filling uniform designs for sampling the experimental space, leading to simplified, approximate process models of potential practical value. In the example used, 14 reactions were identified, associated with 56 parameters and 17 responses. Further development of this methodology is expected to lead to its use for several industrial catalytic processes.

## N−H ACTIVATION BY Rh(I) VIA METAL−LIGAND COOPERATION

In the course of the development of homogeneous catalysts, ligand design is often focused on its stereoelectronic properties engineered to assist bond activation via the corresponding oxidative addition to the metal center. In such cases ligands do not participate in the bond-breaking and bond-making processes.

Milstein's group at the Weizmann Institute of Science discovered a new mode of metal−ligand cooperation, based on aromatization−dearomatization of pyridine-based pincer ligands. In continuation of their investigations, the group reports the case of an unusual N−H bond activation by a Rh(I) complex exhibiting a dearomatized pincer ligand (Feller, M.; et al. *Organometallics* **2012**, *31*, 4083). The products of such N−H activation reactions are Rh(I) complexes, wherein the oxidation state of the metal center remains unchanged in the process. In general, such activation of X−H bonds (X = H, C, O, N) formally involves proton transfer from a substrate to a dearomatized ligand, leading to the breaking of the X−H bond, concomitantly accompanied by ligand aromatization. Synthetic details, physical characterization of complexes, mechanistic investigations, and reactivity trends are reported. Spin saturation experiments showed chemical exchange between the pyridylic arm of the pincer ligand and the NH protons of the aniline substrates prior to and after the N−H activation. The reversible process was also observed, with formation of the N−H bond. This article has 67 references.

**Mark McLaughlin**

Merck & Co. Inc., Rahway, New Jersey 07065, United States. E-mail: mark_mclaughlin@merck.com.

**Magnus Widegren**

Almac Sciences, 22 Seagoe Industrial Estate, Portadown, Craigavon, County Armagh, BT63 5QD Northern Ireland, U.K. E-mail: magnus.widegren@almacgroup.com.

**Soumendu Paul**

Consultant, Lucknow, India.
E-mail: spaaul@yahoo.com.

**Antonio Ramirez**

Bristol-Myers Squibb, Chemical Development, One Squibb Drive, New Brunswick, New Jersey 08903, United States. E-mail: antonio.ramirez1@bms.com.

**Paul Richardson**

Pfizer, Chemistry, 10578 Science Center Drive, San Diego, California 09121, United States.
E-mail: paul.f.richardson@pfizer.com.

**Andrei Zlota**

The Zlota Company LLC, 15, Fairbanks Road, Sharon, Massachusetts 02067-2858, United States.
E-mail: andrei.zlota@thezlotacompany.com.

**John Knight***

Scientific Update LLP, Maycroft Place, Stone Cross, Mayfield, East Sussex, TN20 6EW U.K.

## AUTHOR INFORMATION

**Corresponding Author**

*john@scientificupdate.co.uk