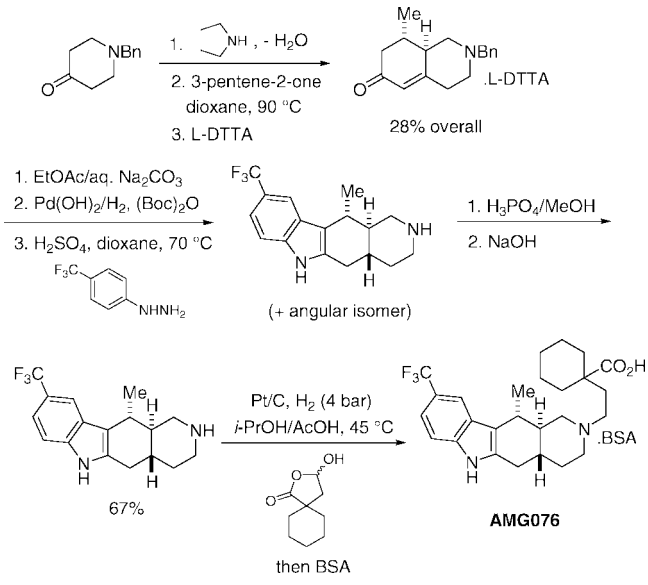
Highlights from the Literature

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

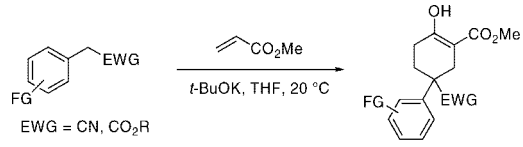
Synthesis of a MCHr1 Antagonist

Antagonism of the melanin-concentrating hormone (MCH) receptor could provide a means to control overeating/obesity in people since this hormone is implicated in the feeding behavior of mammals. Andersen and co-workers at Amgen describe their efforts towards a scalable synthesis of AMG076, a compound that was identified as a potent MCHr1 antagonist (*J. Org. Chem.* **2007**, *72*, 9648–9655). A Robinson annulation between *N*-benzyl-4-piperidone (pyrrolidine enamine) and 3-pentene-2-one in 1,4-dioxane at 90 °C gave the annulated product as a mixture of diastereomers, from which the desired compound was separated using a tartrate salt resolution (28% overall yield from *N*-benzyl-4-piperidone). Hydrogenation of the desired enone yielded the ketone fragment necessary for coupling with an arylhydrazine in a Fischer indole synthesis. The indole synthesis afforded an 8:1 mixture of regioisomers, from which the desired (linear) product could be separated via a H_3PO_4 salt formation/salt break sequence in 67% overall yield from the starting ketone. The optimal end game featured a reductive amination of a lactol under heterogeneous catalytic hydrogenation conditions. Multikilogram experimental details are provided.



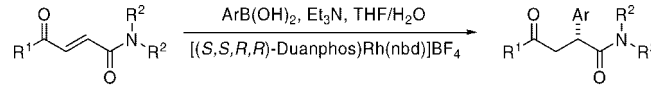
Synthesis of 4,4-Disubstituted Cyclohexane β-Keto Esters

A one-pot method for the synthesis of 4,4-disubstituted cyclohexane β-keto esters from benzylic nitriles or esters is described by Julian, Powers, and co-workers at Amgen (*J. Org. Chem.* **2007**, *72*, 7455–7458). The process relies on a tandem double Michael addition−Dieckmann condensation reaction sequence between the ester or nitrile substrates and 2 equiv of methyl acrylate, which results in the formation of three discrete carbon−carbon bonds in a single pot, including a quaternary center. Although similar chemistry is described in the literature, the authors note that the existing procedures suffered from reproducibility problems and safety issues (95% NaH used as base). By substituting KO*t*-Bu as the base the authors were able to conduct the double Michael−Dieckmann sequence in one pot in good overall yield.



34 examples, 66-92% yield

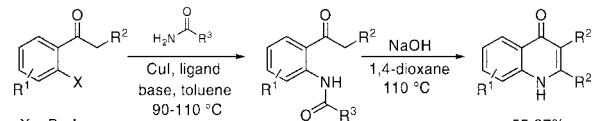
Rh-Catalyzed Conjugate Addition Reactions of 4-Oxobutenamides



18 examples, 54-99% yield
(> 98:2 regioselectivity, > 95% ee)

A variety of 4-oxobutenamides were shown to undergo Rh-catalyzed conjugate addition with arylboronic acids in a recent report from Tedrow and co-workers at Amgen (*J. Org. Chem.* **2007**, *72*, 8870–8876). These reactions generally provided high regio- and enantioselectivity (97:3 to >99:1, >95% ee) and moderate to excellent yields (54–99%). The key to high selectivity is the use of sterically demanding *P*-chiral diphosphines, such as Tangphos or Duanphos. The product oxobutanamides were converted to alternate targets by selective derivatization of either the amide or ketone functional group. A stereochemical model was proposed, predicting the absolute sense of induction based on single-crystal X-ray structures of the product and precatalyst.

Sequential Cu-Catalyzed Amidation/Base-Mediated Camps Cyclization



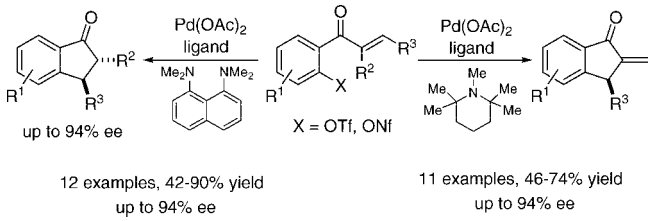
16 examples

A two-step method for the preparation of 2-aryl- and 2-vinyl-4-quinolones that utilizes a Cu-catalyzed amidation of *o*-halophenones followed by a base-promoted Camps cyclization of the resulting *N*-(2-ketoaryl)amides is described by the Buchwald group (*J. Org. Chem.* **2007**, *72*, 7968–7973). In the presence of a base (usually K_2CO_3 or K_3PO_4) and with CuI/

Published on Web 01/18/2008
10.1021/op700278r CCC: $40.75

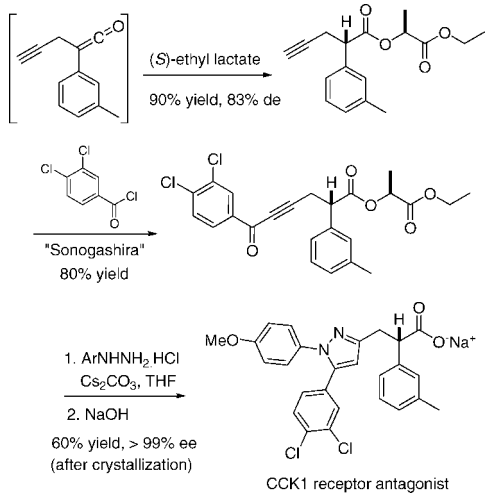
diamine ligand as the catalyst system, the amidation reactions afforded good yields for a range of aryl, heteroaryl, and vinyl amides. For the subsequent Camps cyclization, treatment with NaOH in 1,4-dioxane at 110 °C (sealed tube) efficiently provided the desired 4-quinolones, which were isolated directly from the reaction mixtures following dilution with water.

Chiral Indanones via Enantioselective Reductive-Heck Reactions



In another report from the Buchwald group, the development of an intramolecular Pd-catalyzed, asymmetric reductive-Heck reaction is described (*J. Org. Chem.* **2007**, *72*, 9253–9258). Treatment of various chalcone substrates with a chiral catalyst system composed of $Pd(OAc)_2$ and (*R*)-3,5-XylMeOBIPHEP can provide either 3-aryl-substituted indanones or α-*exo*-methylene indanones depending upon the exact conditions used. Specifically, the use of a proton sponge as the base leads exclusively to 3-aryl-substituted products, whereas the use of 1,2,2,6,6-pentamethylpiperidine leads to incorporation of an additional carbon atom in the form of an *exo*-methylene group. Enantiomeric excess was highest when a substituent was present ortho to the triflate/nonaflate group in the starting material.

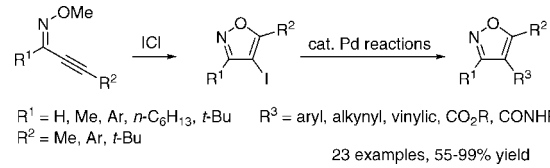
Scalable Route to a Cholecystokinin 1 (CCK 1) Receptor Antagonist



The development of efficient and scalable routes for the synthesis of a selective cholecystokinin 1 (CCK 1) receptor antagonist is described by Mani and co-workers at Johnson and Johnson (*J. Org. Chem.* **2007**, *72*, 8243–8250). A key feature of the scale-up route is the construction of the pyrazole in a single step via reaction of an aryl hydrazine with an elaborated acetylenic ketone. The ratio of regioisomers obtained from this step was 3:1 in favor of the desired isomer, but the undesired isomer could be completely rejected through ester hydrolysis/salt formation and crystallization. In the optimal route, the stereocenter was set early in the synthesis via diastereoselective addition of (*S*)-(−)-ethyl lactate to an alkylaryl ketene.

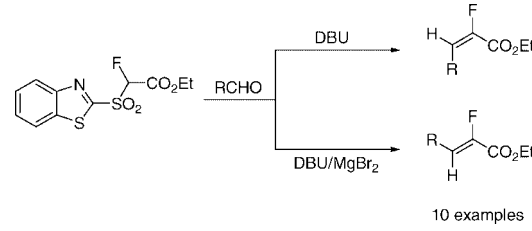
Synthesis of Isoxazoles by Electrophilic Cyclization

A variety of functionalized 2-alkyn-1-one *O*-methyl oximes have been cyclized under mild reaction conditions, as reported by Larock and co-workers (*J. Org. Chem.* **2007**, *72*, 9643–9647). In the presence of electrophilic activators such as ICl or I_2, alkynyl oximes undergo cyclization at room temperature to give the corresponding 4-iodoisoxazoles in moderate to excellent yields. The resulting 4-iodoisoxazoles are amenable to the usual array of Pd-catalyzed reactions to yield 3,4,5-trisubstituted isoxazoles, including the COX-2 inhibitor valdecoxib.

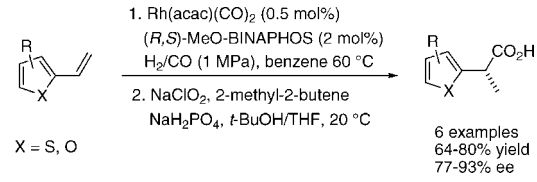


Modified Julia Fluoroolefination

A modified Julia olefination reaction was applied by Lequeux and co-workers to a stereoselective synthesis of fluoroalkenoate derivatives (*J. Org. Chem.* **2007**, *72*, 7871–7877). Depending on the base and the additive used to perform the reaction, it was possible to prepare selectively both the (*Z*)- and the (*E*)-alkenoates, using a single reagent, in good yields from aromatic and aliphatic aldehydes. In most cases chelation with $MgBr_2$ allowed the (*Z*)-alkenoates to be obtained from either aromatic or aliphatic aldehydes. In the absence of $MgBr_2$, the reaction was selective with aromatic aldehydes to afford the (*E*)-alkenoates. The method was extended to a ketone and appeared to be limited to aliphatic ketones under the developed conditions.



Synthesis of α-Heteroarylpropanoic Acids via Asymmetric Hydroformylation

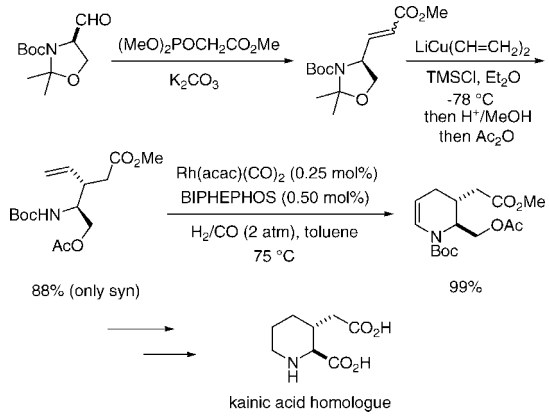


Access to enantioenriched α-hetereoarylpropanoic acids is of significance for the synthesis of pharmaceuticals. The Nozaki group reports on the asymmetric hydroformylation of vinyl heteroarenes (vinylfurans and vinylthiophenes) as one route into this class of useful building blocks (*J. Org. Chem.* **2007**, *72*, 8671–8676). Using a catalyst system comprising Rh(acac)(CO)2 and (*R*,*S*)-MeO-BINAPHOS, the asymmetric hydroformylation

of various substrates was investigated. The hydroformylation of vinylthiophenes gave the corresponding branched aldehydes with high enantiopurities as major products (branched:linear product ratios in the range 84:16 to 95:5). Oxidation of the aldehydes successfully afforded α-heteroarylpropanoic acids in good yields. In addition, the aldehydes could be reduced to alcohols without loss of enantiomeric excess using $NaBH_4$.

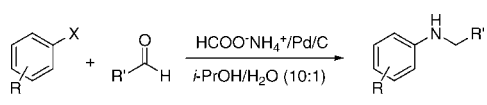
Rh-Catalyzed Cyclohydrocarbonylation

Homologues of kainic acid, a naturally occurring glutamate receptor agonist, were designed and prepared by the Ojima group (*J. Org. Chem.* **2007**, *72*, 9418–9425). These novel homokainoids were synthesized in enantiomerically enriched form starting from (*R*)- or (*S*)-Garner's aldehyde. In one key step, a diastereoselective addition of an alkenylcuprate to a substituted acrylate intermediate is used to set one of the stereocenters. Perhaps more interesting is the use of a Rh-catalyzed cyclohydrocarbonylation reaction to complete the construction of the heavily functionalized piperidine ring. Treatment of the homoallylic amine intermediate with 0.25 mol % $Rh(acac)(CO)_2$ and 0.50 mol % BIPHEPHOS under a mixture of H_2 (2 atm) and CO (2 atm) at 75 °C in toluene affords near quantitative conversion to the desired piperidine. Similar chemistry was also applied to the synthesis of various more substituted analogs.



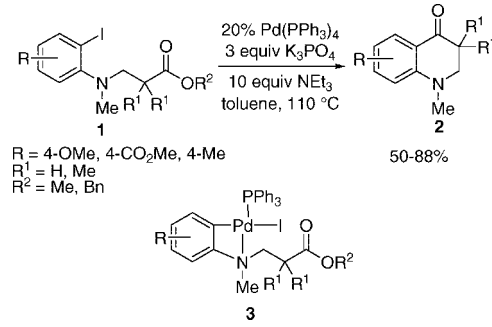
Reductive Mono-N-alkylation of Anilines and Nitroarenes

A one-pot reductive mono-N-alkylation of aniline and nitroarene derivatives using various aldehydes is reported by the Rhee group (*J. Org. Chem.* **2007**, *72*, 9815–9817). These heterogeneous (Pd/C) reactions proceed under neutral conditions in aqueous alcoholic solvent, using ammonium formate as the reductant. Demonstration of the one-pot nitro-reduction/reductive amination sequence with 14 different nitroarene substrates expands the potential utility of this method.



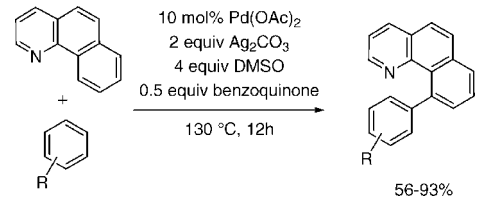
Novel Palladium-Catalyzed Acylation of Aryl-iodides

Solé and Serrano at the Universitat de Barcelona reported the Pd-catalyzed nucleophilic addition of N-tethered esters to 2-iodoanilines to yield dihydroquinolin-4-ones (*Angew. Chem., Int. Ed.* **2007**, *46*, 7270–7272). In a typical experiment, the starting material is heated in toluene at 110 °C in the presence of $Pd(PPh_3)_4$ (20%), K_3PO_4 (3 equiv), and Et_3N (10 equiv) to afford the desired acylated products in good yields. Reduced conversion in some cases is due to reduction of the starting material via the competitive retro-Michael fragmentation of the β-amino ester. Substrates in which the coordinating ability of the nitrogen has been hampered (R = CO_2Me, Ts) failed to undergo the transformation. This fact suggests the intermediacy of a four-membered azapalladacycle **3** with increased electron density on the Pd center that enables the otherwise unfavorable carbopalladation.



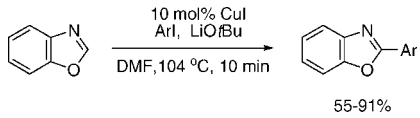
Direct Cross-Coupling of Arenes

Several research groups have recently reported the development of new methods for the direct formation of aryl-aryl bonds in a practical and selective manner. Hull and Sandford at the University of Michigan studied the Pd-catalyzed oxidative cross-coupling of aromatic C-H substrates (*J. Am. Chem. Soc.* **2007**, *129*, 11904–11905). Thus, 2 equiv of Ag_2CO_3, 0.5 equiv of benzoquinone, and 10 mol % of $Pd(OAc)_2$ successfully couple a directing heterocycle with excess arene in good to excellent yields with no homocoupled products observed. The transformation is believed to happen via two consecutive C-H activation steps controlled by the proximity of the directing group in the heterocycle and the steric effects around the oxidized arene C-H bond. Moreover, the screening of benzoquinones with different degrees of substitution suggests that the benzoquinone coordinates the Pd species during the arene C-H activation.



In *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405, Do and Daugulis (University of Houston) report a direct catalytic arylation of heterocyclic C-H bonds. Under optimized conditions, treatment of 1 equiv of heterocycle with 10 mol % CuI, 2 equiv of lithium *tert*-butoxide, and 3 equiv of aryl iodide affords the desired aryl heterocycles in 56–93% yields. The reaction is successful for a variety of substituted aryl iodides, whereas the scope with respect to heterocycles is limited to azoles and pyridine oxides. Preliminary mechanistic studies reveal that, using lithium *tert*-butoxide as base, a plausible lithium-copper transmetalation follows the initial lithiation. In

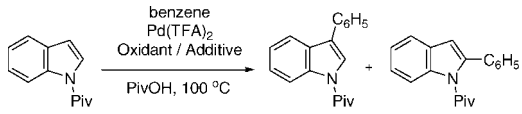
contrast, deprotonation using potassium *tert*-butoxide appears to mediate a copper-assisted benzyne-type mechanism. This new methodology is of potential interest to synthesize aryl heterocycles that are ubiquitous in pharmaceutical chemistry, since the methods currently used to complete this transformation involve expensive palladium or rhodium catalysts.



55-91%

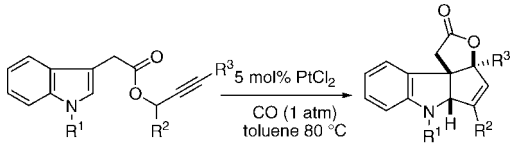
Pd(II)-Catalyzed Arylation of Heterocycles

Stuart, Villemure, and Fagnou (University of Ottawa) describe ways to successfully control the regiochemical outcome in arene cross-couplings catalyzed by Pd (*J. Am. Chem. Soc.* **2007**, *129*, 12072–12073). For example, whereas the indole-benzene cross-coupling shown below can be achieved in a 87% conversion with C2 > C3 ratios using 2 mol % $Pd(TFA)_2$ and 3 equiv of AgOAc, the same coupling with 300 mol % $Pd(TFA)_2$ and no oxidant affords 100% conversion with C3 > C2 ratios. The regioselectivity can also occur at substituted benzene components, and benzene homocoupling appears at indole conversions >90%. The authors rationalize the observed regiocontrol, invoking alternate pathways that are dependent on the structures of the Pd aggregates in solution, which in turn rely on the total Pd concentration and carboxylate-induced deaggregation of the Pd clusters.



2 mol% Pd, 3 equiv AgOAc 1 : 14
300mol% Pd, 0 equiv AgOAc 99 : 1

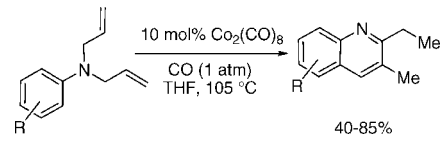
Pt(II)-Catalyzed Synthesis of 2,3-Indolines



50-95%

The group of Zhang at University of Nevada reported a $PtCl_2$-catalyzed regioselective formation of 2,3-indoline-fused cyclopentenes from propargylic 3-indole acetates (*J. Am. Chem. Soc.* **2007**, *129*, 11358–11359). The efficiency of this transformation improves when CO is used as additive with 5 mol % $PtCl_2$ in refluxing toluene; Brønsted acids do not catalyze the process. An intricate matrix of arrow pushes rationalize the reaction mechanism—a [3,3]-rearrangement followed by [3 + 2] cycloaddition that occurs via a Pt carbenoid—and explains the different regioselectivities observed in Au(I)-catalyzed transformations (*J. Am. Chem. Soc.* **2005**, *127*, 16804–16805). Overall, the propargyl moiety in the starting material acts as a three-carbon unit for the formal [3 + 2] cycloaddition. The synthetic utility of this method is shown in the synthesis of the tetracyclic substructure of indole alkaloid vindolinine.

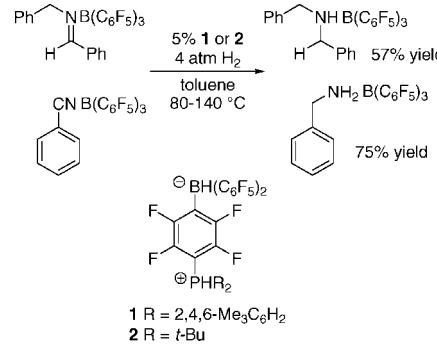
Co-Catalyzed Synthesis of Quinolines



40-85%

Quinolines are important components in pharmaceuticals, industrial oxidants, and dyes. Li and Jones at University of Rochester recently described the development of a catalytic method to prepare 2,3-substituted quinolines (*J. Am. Chem. Soc.* **2007**, *129*, 10707–10713). Catalytic amounts of $Co_2(CO)_8$ (10 mol %) in THF under 1 atm CO convert diallylanilines to quinolines in yields that depend on steric and electronic effects. Steric effects appear to predominate over electronic effects. Ortho-substitutions inhibit the reactions by preventing ring closure. In contrast, electron-donating groups favor the reactions by facilitating the C-N and C-H activations required to achieve the ring closure. An elegant mechanistic study based on deuterium labeling experiments is reported in detail in the second part of the full paper.

Metal-Free Catalytic Hydrogenation

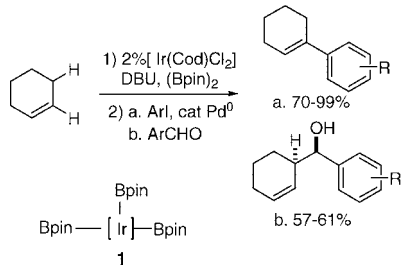


1 R = 2,4,6-$Me_3C_6H_2$
2 R = *t*-Bu

"Hydrogen is the cleanest reducing agent and hydrogenation is arguably the most important catalytic method in synthetic organic chemistry both on the laboratory and the production scale" (*Adv. Synth. Catal.* **2003**, *345*, 103–151). Process chemists are constantly longing for methods that use cheaper reagents, provide products in higher yields, and minimize waste generation. The group of Stephan at the University of Windsor (Canada) introduced the air- and moisture-stable phosphonium borates **1** and **2** as active catalysts for the hydrogenation of C-N multiple bonds with hydrogen (*Angew. Chem., Int. Ed.* **2007**, *46*, 8050–8053). The system provides the first metal-free catalysts that effect the addition of molecular hydrogen to imines, nitriles, and aziridines. The compounds are reduced in toluene at 80–140 °C using moderate hydrogen pressures (1–5 atm), with the resulting amines are separated from the catalyst by filtration. In the case of nitriles and imines that bind to the B center of the catalyst, there was no catalyst turnover observed, and the problem was circumvented by coordinating the nitrogen lone pair to $B(C_6F_5)_3$. Therefore, stoichiometric reductions mediated by Li and Na hydrides can be performed in a catalytic fashion, reducing waste production. The approach can also replace expensive precious-metal catalysts, diminishing costs and reducing the environmental impact from heavy-metal pollutants.

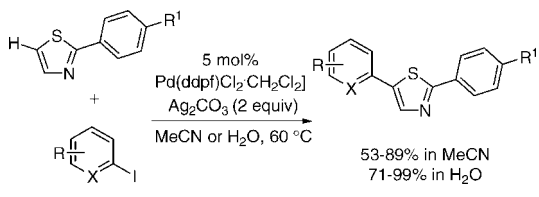
Catalytic Boronation of Unactivated Cycloalkenes

Szabó and Olsson have found that selective C-C bond formation can be achieved via the Ir-catalyzed C-H activation/borylation reaction of unactivated alkenes. The intermediate organoboranes can react with aryl iodides or aldehydes in a one-pot sequence (*Angew. Chem., Int. Ed.* **2007**, *46*, 6891–6893). The allylation reaction proceeds with excellent stereoselectivity, providing a single diastereomer of the corresponding vinyl alcohols. The special features of the Ir-catalyzed C-H activation/boronation arise from the formation of a tris(boryl)Ir complex **1**. The double bond of cyclohexene undergoes insertion into the Ir-B bond of the active catalyst, and subsequent β-hydride elimination gives vinyl boronates that are amenable to undergo C-C bond formation.



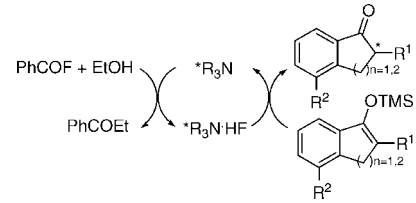
Direct Arylation of Thiazoles on Water

Arylated and alkenylated thiazoles have been popular substrates in direct arylation studies. Turner, Morris, and Greaney reported a general methodology for the arylation of 2-substituted thiazoles under mild conditions (*Angew. Chem., Int. Ed.* **2007**, *46*, 7996–8000). A combination of [Pd(ddpf)Cl_2·CH_2Cl_2] and PPh_3 worked as an effective catalyst system in the presence of Ag_2CO_3. The reaction was successful for a wide spectrum of electrophiles, with thiazoles effectively coupling with electron-rich (R = OMe, Me) and electron-poor (R = F, Cl, CF_3, CN, CO_2Et, COMe, NO_2) partners in good yields. Certain heterocyclic iodides (iodopyridines, pyrimidines, and thiazoles were viable for direct arylation. Surprisingly, higher yields were obtained when the reaction was carried out using water as a solvent. Given the lack of solubility of reagents, products, and catalysts, the system is an example of what Sharpless termed an "on-water" reaction. With mechanistic investigations pending, the authors suggest a substantial increase in the effective concentration as the driving force for acceleration using "on-water" conditions.

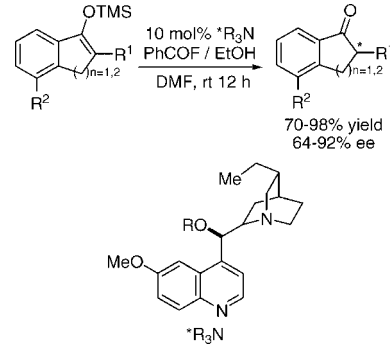


Enantioselective Protonation of Silyl Enolates

The group of Levacher at INSA-Universite de Rouen reported the first organocatalytic enantioselective protonation of silyl enolates by hydrogen fluoride salts of tertiary amine derived from cinchona alkaloids (*Angew. Chem., Int. Ed.* **2007**, *46*, 7090–7093). The technique overrides the difficulties of preparing and storing dry HF salts: the reaction of an acid fluoride as PhCOF and an alcohol (EtOH) in the presence of a chiral amine generate catalytic amounts of the salt *R_3N·HF.

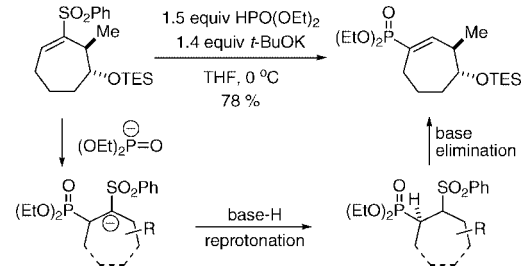


By taking advantage of the affinity of silicon towards fluoride, the activated silyl ethers and the salts were in close proximity, and the proton transfer was facilitated. In the optimized conditions, silyl enol ethers reacted with PhCOF (1.05 equiv) and EtOH (1.05 equiv) in the presence of catalytic amounts of a cinchona alkaloid to afford the target ketones in good yields with ee's up to 92%.



Conversion of Vinyl Sulfones to Vinyl Phosphonates

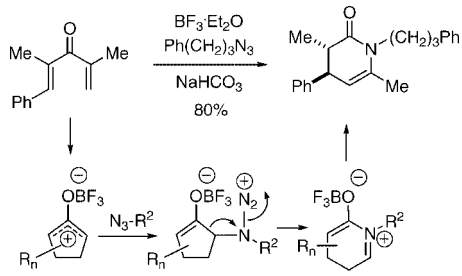
In the context of the study of six- and seven-membered cyclic dienyl sulfones as precursors of chiral substituted acyclic arrays, the group of Fuchs at Purdue University discovered the conversion of cyclic vinyl sulfones to transposed vinyl phosphonates (*J. Am. Chem. Soc.* **2007**, *129*, 11242–11247). In a typical one-pot experiment, the reaction of diethyl phosphite with an alkali base and the corresponding vinyl sulfone in THF at room temperature affords the desired vinyl phosphonate in good yields. A mechanistic proposal involves the conjugate attachment of the phosphite anion to the vinyl sulfone followed by reprotonation of the resulting sulfone anion and final irreversible elimination of phenylsulfinate. The transformation tolerates many functional groups and has been successfully implemented in the synthesis of natural products.



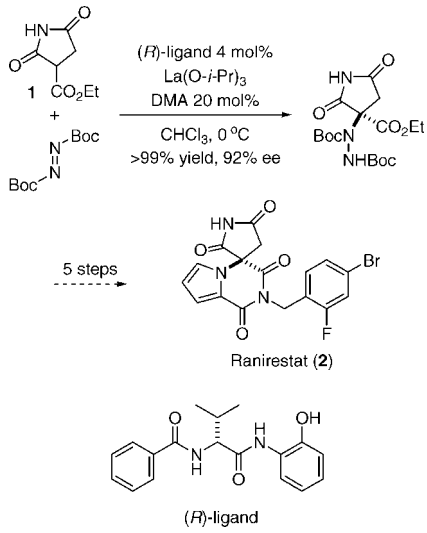
One-Pot Synthesis of Dihydropyridones

West and co-workers at University of Alberta describe the direct synthesis of dihydropyridones from simple building blocks in *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022. Upon treatment with BF_3·Et_2O, 1,4-dien-3-ones undergo Nazarov

cyclization to give transient cyclopentenyl cations that can be trapped by various azides to afford 3,4-dihydropyridin-2-ones in moderate to good yields. In a representative procedure, a solution of dienone is mixed with the azide of choice and $BF_3 \cdot Et_2O$ in dichloromethane at −78 °C during 10 min. From a mechanistic perspective, the electrocyclization and azide capture is followed by a Schmidt-type rearrangement. Overall, the process involves insertion of the internal azide nitrogen atom between the dienone carbonyl and the neighboring α carbon.



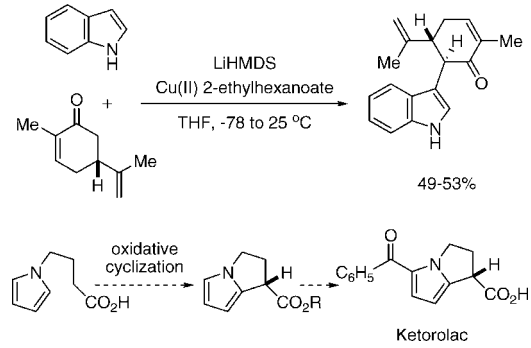
Catalytic Asymmetric Amination of a Succinimide



Succinimide **1** is a key intermediate in the synthesis of ranirestat (**2**), an aldose reductase inhibitor under phase III clinical development in the U.S.A. and Canada for the treatment of diabetic complications. The unique coordinating abilities of **1** pose a challenge to develop a practical metal-catalyzed amination suitable for multigram scale up. As a result of collaboration with Sumitomo, Shibasaki (University of Tokyo) and co-workers achieved a catalytic asymmetric amination promoted by a new lanthanide-amide complex (*J. Am. Chem. Soc.* **2007**, *129*, 11342–11343). Following extensive lanthanide, solvent and amide catalyst screenings the highest enantiomeric excess was observed in chloroform with 2 mol % catalyst and di-*tert*-butyl azodicarboxylate as the source of electrophilic nitrogen. Laboratory scale experiments could be performed under air.

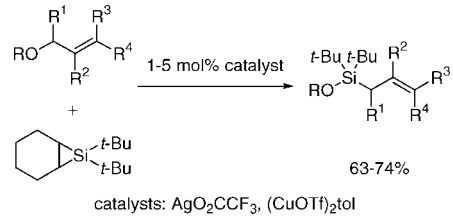
Direct Indole and Pyrrole Couplings

The group of Baran at Scripps published a 13-page manuscript reporting advances in the scope and mechanism of direct indole and pyrrole couplings adjacent to carbonyl compounds (*J. Am. Chem. Soc.* **2007**, *129*, 12857–12869). The key step of these transformations involves an oxidative enolate coupling. The indole-carvone reaction below illustrates the remarkable ability of the intermolecular reaction to quickly generate complexity with superb selectivities. An intramolecular version of the oxidative pyrrole coupling was brilliantly applied to the total synthesis of Ketorolac. Mechanistic observations suggest that the process occurs via oxidation of the carbonyl compound, which reacts with the heterocycle anion to provide a radical anion intermediate that could be further oxidized by the remaining copper species. The authors discuss the optimization and scope of the reaction in detail and give an instructive review of the literature of oxidative couplings.



Silylene Insertions of Allylic Ethers

Chiral nonracemic allylsilanes are valuable synthons. Their preparation, however, still remains a synthetic challenge. Woerpel and co-workers at University of California, Irvine, disclose the elaboration of allylic silanes by silylene insertion into optically active allylic C-O bonds using silacyclopropane as the silylene source (*J. Am. Chem. Soc.* **2007**, *129*, 12602–12603). Silylenes (SiR_2) are reactive intermediates capable of inserting into activated σ bonds to afford silanes (SiR_4). A study of substrate scope shows that the reaction tolerates 1,2-disubstituted and trisubstituted alkenes (R^2, R^3, R^4), as well as substitution at the allylic position (R^1) and different protecting groups on the hydroxyl group (R). Ag- and Cu-based catalysts promote the insertion. The reaction is intramolecular with respect to the allylic ether as shown by crossover experiments and occurs with retention of facial selectivity on the same face as the C-O bond that is broken.

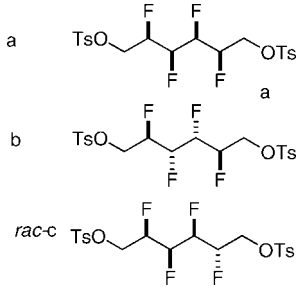


Synthesis and Conformation of Fluoroalkane Diastereomers

Partially fluorinated compounds have been less studied than their perfluorinated counterparts, owing to the lack of good synthetic methods and control in multiple fluorine introduction. Vicinal fluorines originate stereochemical complexity, a key feature that sets multivicinal fluoroalkanes apart from hydrocarbon analogs. Kirsh, Hagan, and co-workers report the preparation of three different diastereomers of a four-vicinal-fluorine motif and the evaluation of their relative conformations

in the solid and solution states (*Angew. Chem., Int. Ed.* **2007**, *46*, 8036–8038). The three compounds are crystalline with structures confirmed by single-crystal X-ray analyses.

The "all-*syn*" compound adopts a C_2-symmetric *bent* conformation that preserves *gauche* alignments. Compound **b** has an extended zigzag conformation and shows $^3J_{HF}$ values that reflect *gauche* and *anti* alignments. The conformation of **rac-C** in solution does not match the conformation in the X-ray crystal: in the former, the fluoroalkyl chain foregoes one fluorine *gauche* interaction so a longer section of the carbon chain can adopt a zigzag conformation. In the solid state, the three pairs of vicinal fluorines are approximately *gauche*, but the dihedral angles deviate from 60°. It appears that the tosyl groups, essential for the crystallinity, dominate the crystal packing interactions and may obscure the conformational preferences of the fluoroalkyl chain themselves. The avoidance of 1,3-repulsive interaction rises as the dominant conformational consideration, with a more subtle influence by the fluorine *gauche* effect.

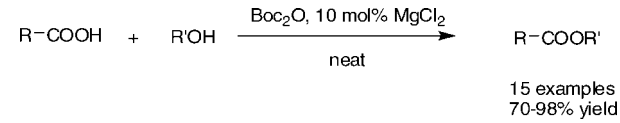


Characterization of Active Pharmaceutical Ingredients by Solid-State NMR Spectroscopy

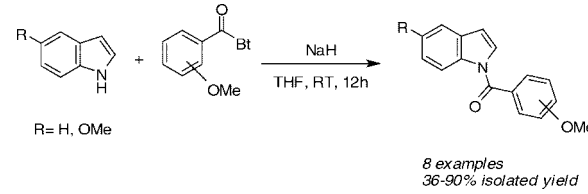
Polymorphic or pseudopolymorphic changes (e.g., the formation of hydrates) in active pharmaceutical ingredients can have significant effects on bioavailability. The characterization and identification of solid forms is essential in all steps of pharmaceutical development. Of great importance is the form adapted by an API in a tablet subjected to accelerated stability studies, where the active ingredient is combined with fillers (excipients) and compressed. Although ^{13}C solid-state NMR is used routinely to examine physical forms of APIs in drug substance and drug products, the application of ^1H solid-state NMR has been limited because of large anisotropic effects due to extensive dipolar-coupled proton networks. ^1H DQ (double quantum) CRAMPS (combined rotation and multiple-pulse spectroscopy) NMR was used to characterize the solid from of an API that contains about 20 carbon atoms (*Angew. Chem., Int. Ed.* **2007**, *46*, 8036–8038). The experiment required small amounts of each form of API (30 mg, anhydrous and monohydrate) to fingerprint the species. Spectra were acquired on a crushed tablet stored at regular conditions and a tablet stressed for 1 week at 40 °C/75% RH. Whereas the NMR of the tablets showed signals corresponding to excipients, the signals from the API were unique and easily recognizable. The technique conclusively demonstrated the presence of a single pseudopolymorph, the anhydrous API, in the stressed tablet.

Improved Method for Reaction Esterification of Carboxylic Acids with Dicarbonates

Building on the research of Takeda and co-workers (*Synthesis*, **1994,** 1063) and Goossen and Döhring (*Adv. Synth. Catal.* **2003**, *345*, 943), Bartoli and co-workers have developed a general esterification method for the coupling of carboxylic acids with primary, secondary, and aromatic alcohols in the presense of Boc_2O employing a nontoxic, mild Lewis acid catalyst (*Synthesis,* **2007**, *22*, 3489). In previous reports, ester formation was dictated by the choice of dicarbonate (e.g., dimethyl dicarbonate produced methyl esters). After forming the mixed anhydride from the initial reaction of the carboxylic acid and Boc-anhydride, the rate difference of addition of a primary or secondary alcohol over the addition of the liberated ^{t}BuOH now allows for a variety of esters to be synthesized. This method substantially reduces the amount of dicarbonate reagents, eliminates the need for extensive fine-tuning of individual reactions, and creates more environmentally friendly waste streams. The protocol, usually done under solvent-free conditions, shows a wide range of functional group tolerance, including esters and amide that would normally be cleaved under standard esterification conditions.

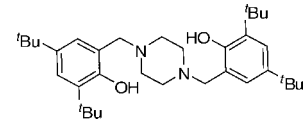


Efficient N-Aroylation of Substituted Indoles with *N*-Aroylbenzotriazoles



Although many methods for direct N-aroylation of indoles are known, few are synthetically useful when either the aroylating agent or the indole contain an electron-donating moiety. This issue has been recently addressed by Katritzky and co-workers (*Synthesis*, **2007**, *23*, 3673) utilizing *N*-acylbenzotriazoles as activated carboxylic acids. The *N*-aroylbenzotriazoles, derived from the corresponding carboxylic acids and 1*H*-benzotriazole in good yields, coupled efficiently with both indole and 5-methoxyindole, improving upon the existing literature yields by up to 72%.

An Inexpensive, Air-Stable Ligand for Low Temperature Suzuki Cross-Coupling and Heck Reactions



A new bulky, bidentate ligand, 1,4-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine, for Suzuki−Miyura and Heck cross-coupling reactions has been synthesized by Balakrishna and co-workers (*Tetrahedron,* **2008**, *64*, 240). Especially attractive is the ligand's ability to affect Pd-catalyzed transformations under aerobic conditions, which is seldom possible when phosphine or *N*-heterocyclic carbene ligands are employed. Ligand syn-

thesis is easily accomplished in one pot from piperazine, formaldehyde, and 2,4-di-*tert*-butylphenol in 65% yield. When combined in a 1:1 molar ratio with $Pd(COD)Cl_2$, coupling reactions of aryl bromides and phenylboronic acids proceed in good to excellent conversions (up to 100%) at room temperature or 60 °C with 0.5 mol % of catalyst, although lowered catalyst loaded should be viable as TONs of up to 128,100 have been observed. Aryl chlorides also participated in couplings; however, elevated temperatures were needed (110 °C) and modest yields (32–81%) were observed. The new ligand also proved viable in a small array of Heck cross-coupling reactions.

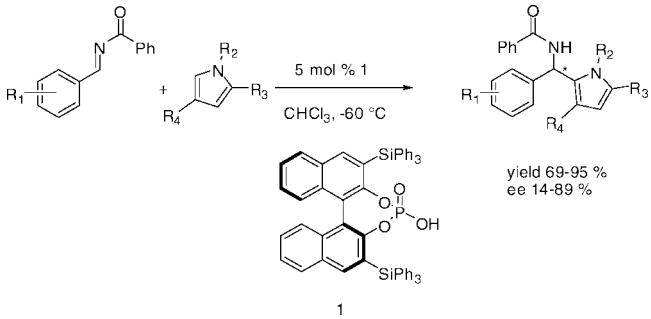
N-Heterocyclic Carbene and Phosphine Ruthenium Indenylidene Precatalysts: A Comparative Study in Olefin Metathesis

Clavier and Nolan (*Chem. Eur. J.* **2007**, *13*, 8029) have carried out kinetic studies on ring-closing metathesis of unhindered and hindered substrates using phosphine and N-heterocyclic carbene (NHC)- containing ruthenium-indenylidene complexes (first and second generation precatalysts, respectively). These studies have revealed an appealing difference between the phosphine and NHC-containing catalysts, associated with a distinctive rate determining step in the reaction mechanism. These catalysts have been compared with the benzylidene generation catalysts and their respective representative substrates.

The two most interesting precatalysts that contain tricyclohexylphosphine and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (SIMes) were thereafter investigated in more detail for their scope of the reaction on a larger range of olefins. As a result of their high thermal stability, the SIMes-based catalysts were more efficient than their benzylidene analogues in the ring-closing metathesis of tetrasubstituted dienes. Importantly though it was found that none of the indenylidene precatalysts were the most efficient for all of the substrates.

Organocatalytic Enantioselective Friedel–Crafts Reaction of Pyrrole Derivatives with Imines

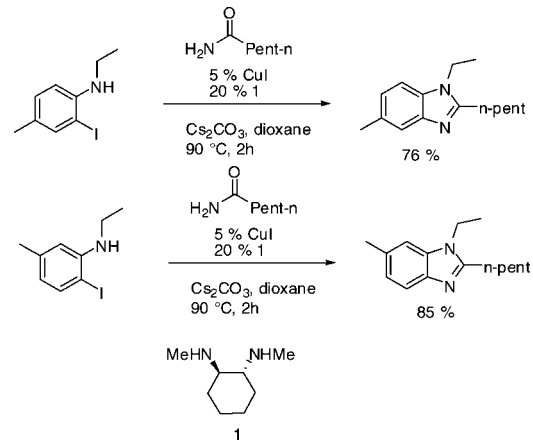
A highly enantioselective Friedel–Crafts reaction of N-alkyl pyrroles with N-acyl imines catalyzed by chiral phosphoric acid has been developed (Li et al. *Org. Lett.* **2007**, *9*, 4065). The reaction produces the pyrrole derivatives in high yields and enantioselectivity. An especially good substrate is *N*-methyl pyrrole. The best catalyst for the reaction was the phosphoric acid **1**. Eight examples were investigated with good to high yields and low to high enantioselectivities.



1

Copper-Catalyzed Regiospecific Synthesis of *N*-Alkylbenzimidazoles

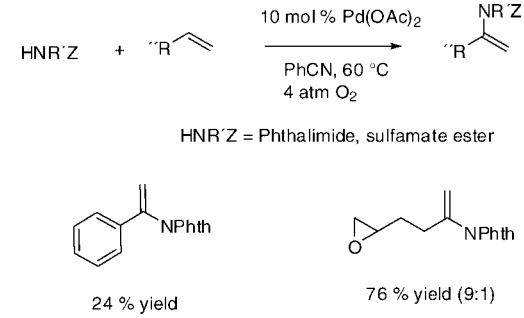
Benzimidazoles are an important class of heterocycles with a wide range of applications. Although numerous methods for their synthesis have been disclosed it remains difficult to access regioisomerically pure N-substituted benzimidazoles. Zheng and Buchwald (*Org. Lett.* **2007**, *9*, 4065) have developed a copper-catalyzed method for the preparation of *N*-alkylbenzimidazoles in regioisomerically pure form starting from *o*-haloanilines. The method utilizing CuI and *trans-N,N*-1,2-cyclohexanediamine allows the preparation of *N*-alkylbenzimidazoles in good to excellent yield.



1

Palladium-Catalyzed Oxidative Amination of Alkenes: Improved Catalyst Reoxidation Enables the Use of Alkene as Limiting Reagent

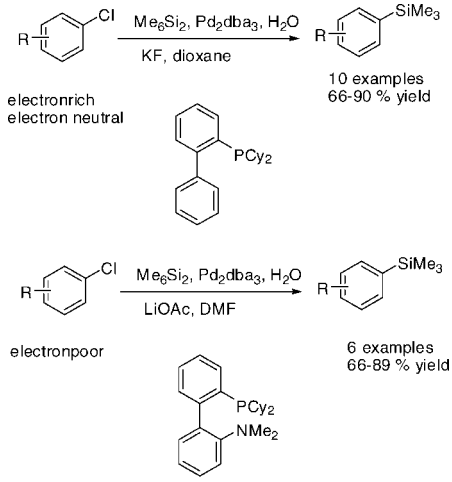
Stahl et al. (*Org. Lett.* **2007**, *9*, 4331) have found new methods for the palladium-catalyzed intermolecular aerobic oxidative amination of alkenes that are compatible with the use of the alkene as the limiting agent. These procedures, which enhance the utility of this reaction with alkenes that are not commercially available, have been demonstrated with substrates bearing dialkyl ether, carboxyester, epoxide, and silyl ether groups. The identified reactions are among the most effective catalytic methods to date for intermolecular aza-Wacker reactions, and the ability to employ alkenes as the limiting reagents should significantly enhance their utility. The authors describe 19 examples with yields from low (13%, 17%) to good (77%, 83%).



Palladium-Catalyzed Silylation of Aryl Chlorides with Hexamethyldisilane

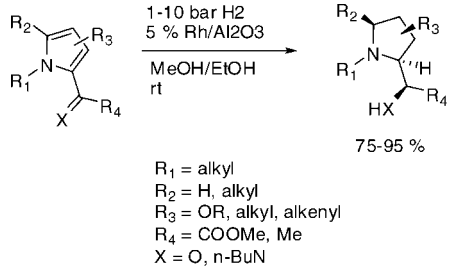
Buchwald et al. (*Org. Lett.* **2007**, *9*, 3785) have developed a method for the palladium-catalyzed silylation of aryl chlorides.

The method affords the product in good yield, is tolerant of a variety of functional groups, and provides access to a variety of aryltrimethylsilanes from commercially available aryl chlorides. The method functions for electron-poor, -neutral, and -rich aryl chlorides. From the aryltrimethylsilanes aryl iodides can be obtained in a telescoped process.



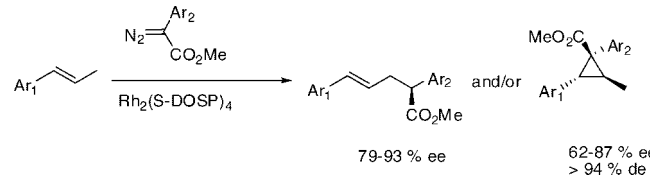
Stereoselective Synthesis of Pyrrolidine Derivatives via Reduction of Substituted Pyrroles

The heterogeneous catalytic hydrogenation of highly substituted pyrrole systems has been studied by Frontier et al. (*Org. Lett.* **2007**, *9*, 4939). It is known that heterogeneous catalytic hydrogenation delivers the hydrogen to one side of 2,5-substituted pyrroles. These aromatic systems could be fully reduced with excellent diastereoselectivity to afford functionalized pyrrolidines with up to four new stereocenters. It is likely that the process is a two-step sequence, and the initial reduction of the C=X bond provides a stereocenter that directs the subsequent hydrogenation of the aromatic ring.



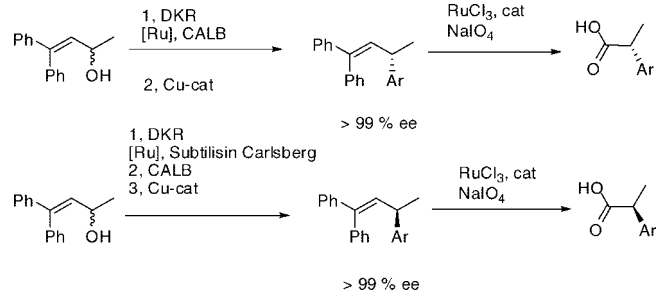
Balance between Allylic C-H Activation and Cyclopropanation in the Reactions of Donor/Acceptor-Substituted Rhodium Carbenoids with *trans*-Alkenes

Donor/Acceptor-substituted rhodium carbenoids are capable of a wide range of highly selective intermolecular reactions. As a result of the donor group, typically aryl or vinyl, these carbenoids are more stabilized than the conventional carbenoids derived from ethyldiazoacetate. When the reactions are catalyzed by the dirhodium tetraprolinate, Rh_2(S-DOSP)$_4$, high enantioinduction is possible. The cyclopropanation can be conducted on a wide range of unsaturated substrates. A more recent development is intermolecular C-H functionalization by these carbenoids through a C-H insertion process. This reaction is especially effective for allylic C-H bonds. Considering that both the intermolecular C-H insertion and the cyclopropanation are very important reactions, it becomes important to define which factors control the balance between the two processes. Davies et al. (*Org. Lett.* **2007**, *9*, 4971) have studied this balance for *trans*-substituted alkenes and have been able to demonstrate that *trans*-substituted alkenes are capable of intermolecular C-H insertions as well as cyclopropanations. The product distribution in these reactions depends not only on the steric and electronic nature of the alkene but also on the electronics of the donor/acceptor carbenoid as well as the catalyst structure.



An Enantioselective Route to α-Methyl Carboxylic Acids via Metal and Enzyme Catalysis

Dynamic kinetic resolution (DKR) has become an active area



of research and is of importance in organic synthesis as a powerful tool to prepare enantiomerically enriched compounds in high yields. Dynamic kinetic resolution of allylic alcohols to allylic acetates followed by copper-catalyzed allylic substitution gives alkenes in high yields and optical purity (Bäckvall et al. *Org. Lett.* **2007**, *9*, 4971). Subsequent oxidative C-C double bond cleavage affords pharmaceutically important α-methyl-substituted aryl carboxylic acids in high ee.

Mannitol Production

Mannitol is a naturally occurring polyol directly used in pharmaceutical, food, and other chemical industries. It is also a raw material for a variety of chemicals. Its production has increasing importance, and the need for a cleaner process for its manufacture is urgent, not only because of the drastic conditions required for the reduction of a fructose/glucose mixture, the most common process, but also because in this process mannitol is obtained in about 25% selectivity. Recently, Racine and Saha (*Process Biochem.* **2007**, *42*, 1609) from the National Center for Agricultural Utilization Research, USDA, reported the production of mannitol by *Lactobacillus intermedius* NRRL B-3693 in fed-batch and continuous cell-recycle fermentations.

Mannitol at 180 $g \cdot L^{-1}$ concentration can be easily recovered from the fermentation broth by cooling crystallization, but to obtain such production very high levels of fructose are needed and result normally in long lags in production. In addition, as the authors stated, to produce mannitol cost-effectively on an

industrial scale by fermentation, more economical nutrient sources are required to replace the expensive Bacto-peptone and Bacto-yeast extract, and they succeeded in using cheaper soy peptone, corn steep liquor, and manganese sulfate in batch fermentation processes.

For cell recycling, fermentations were conducted in a batch mode for 14 h to build cell mass. After incubation, a continuous feed was started (100–160 $g \cdot L^{-1}$ fructose). A series of fermentations, each lasting 48–96 h, were run at various substrate concentrations, dilution rates, and corn steep liquor concentrations.

The fed-batch process resulted in 176 g of mannitol from 184 g of fructose and 92 g of glucose per liter of final fermentation (5.9 $g \cdot L^{-1} \cdot h^{-1}$ volumetric productivity, in 30 h).

Further improvements were obtained in a continuous cell-recycle fermentation process that reached more than 40 $g \cdot L^{-1} \cdot h^{-1}$ volumetric productivity.

Lipase-Catalyzed Fructose Esters

Fatty acid sugar esters are nonionic surfactants use in the pharmaceutical and food industries. Although their chemical production is feasible, normally enzymatic processes afforded a better product.

Fructose esters (Sabeder et al. *J. Food Eng.* **2006**, *77*, 880) were obtained using different lipases in organic solvents in batch reactors. Novozyme 435 proved to be the best choice. Best yields (about 80%) were obtained in methylethylketone as solvent using molecular sieves at 12.1% w/w. Other enzymes and solvents also showed good performances.

Glucosamine Production

Glucosamine, 2-amino-2-deoxy-D-glucose, can be obtained from the hydrolysis of chitin and chitosan and has growing importance in the pharmaceutical industry. Hsieh et al. (*Biotechnol. Prog.* **2007**, *23*, 1009) described a convenient protocol for the production of this compound using three different wild-type fungi, *Aspergillus* sp. BCRC31742, *Monascus pilosus* BCRC31527, and *Rhizopus oligosorus* BCRC 31996. It has been made possible to obtain 3430 mg/L by using *Aspergillus* sp. BCRC31742 in glucose and peptone medium.

The experimental design and the analytical protocol disclosed proved to be very useful in optimizing (and detecting) glucosamine production, and the process can be scaled up.

Statistical Cluster Analysis of Pharmaceutical Solvents

Attempts to quantify chemical intuition can be met with some resistance, because systematic methods are viewed as interfering with creativity. However, when we can save money, there is a chance to succeed in such quantification efforts. High confidence pharmaceutical solid state screening studies are expensive, often because of the large number of solvents included in such investigations. A report from Procter and Gamble and San Diego State University (Xu, D. et al. *Int. J. Pharm.* **2007**, *339*, 175) describes an improved statistical methodology for solvent classification. One of the main challenges in such an analysis is the case of missing data. To solve this problem, the authors used a QSPR strategy based on the average data for similar compounds. The work focused on 57 ICH class 2 and 3 solvents; 231 physical properties were found in the literature, and 17 calculated molecular descriptors were discovered to be relevant in the solvent classification. The PCA-cluster analysis revealed that the 57 solvents belong to 20 clusters; some of those clusters have only one or two members, whereas others can have up to nine solvents. The proposed value for this analysis method is the possibility of more efficient solid-state screening studies, by reducing the number of solvents included. Thus, the selection of one solvent from each cluster is expected to be sufficient. Following the same methodology, users can customize the analysis, perhaps also including solvent mixtures.

An Experimental and CFD Study of Liquid Jet Injection into a Partially Baffled Mixing Vessel: A Contribution to Process Safety by Improving the Quenching of Runaway Reactions

Computational Fluid Dynamics (CFD) applications in pharmaceutical process R&D are increasingly reported in the literature. A recent report from a French-Australian team (Torre et al. *Chem. Eng. Sci.* **2007**, published online: http://dx.doi.org/10.1016/j.ces.2007.10.031) discusses the use of CFD in the analysis of runaway reaction quenching. Because of the inherent experimental challenges, runaway reactions are an ideal case for process modeling applications, with potential value for process safety management. In addition, the intuitive approach of injecting a stream of the quenching reagent, at high velocity, at the media surface, is not often practiced because of the incomplete understanding of the mixing of such a stream in the reactor. The investigation was executed in a partially baffled reactor, fitted with a custom designed Retreat Curve Impeller (Pfaudler), both features of practical relevance for pharmaceutical manufacturing. The liquid jet was tracked in water using Fluorescein, UV lighting, and a high resolution camera. CFD calculations were executed using ANSYS-CFX 11.0. Several parameters were varied such as jet velocity, location and time of injection, and agitation speed. Because the common mixing quality indexes are not useful in such a study, new ones were defined: t_{50} and t_{90}, the times required for quenching 50% and 90% of the reactor volume, respectively. Among the expected experimental challenges encountered were air-entrapment, and the nonreproducibility of the experiments due to the chaotic nature of the mixing process. Surprisingly, the most effective quenching method did not involve the use of the highest velocity jet; it was the optimized trajectory of the jet that accomplished the fastest quenching. There was good agreement between the numerical predictions and the experimental results, and the value of the CFD visualization tools is demonstrated in the graphs presented.

Measurement and Enhancement of Gas–Liquid Mass Transfer in Milliliter-Scale Slurry Reactors

Catalyst screening is an important step in the development of many chemical processes, such as catalytic hydrogenations. Frequently, because of the high cost of the catalysts, such screening experiments are conducted at milliliter-scale, in reactors that often do not have suitable mixing. Under those conditions, catalyst comparison is not straightforward, because the reactions are not necessarily executed under kinetically controlled conditions.

A team from Pfizer and the University of California (Fan et al. *Chem. Eng. Sci.* **2007**, *62*, 5940) proposed a new magnetic agitation system for a milliliter reactor (15 mL), capable of achieving a gas–liquid mass transfer performance comparable to that of efficient large-scale reactors (mass transfer coefficient $k_l a = 0.50\ s^{-1}$). The authors report the first measurements of gas–liquid mass transfer coefficients in milliliter-scale reactors. Creative solutions were found for the expected challenges of the small amount of gas absorbed in a very short period of time. Using the proposed agitation system, the gas–liquid mass transfer coefficients in milliliter reactors can be doubled when compared to the commercially available agitation systems (such as the Endeavor or the ChemScan). The authors report some unexpected observations that may offer the opportunity for further studies, such as the nonmonotonous dependence of the mass transfer coefficient ($k_l a$) with agitation speed, as well as the $k_l a$ dependence on the volume of the media. The impact of baffling can also be addressed.

Mark McLaughlin

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

Silvina García Rubio

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

Matthew Pfeiffer

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

Ulf Tilstam

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

Octavio Augusto Ceva Antunes

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

Trevor Laird*
Editor

Andrei A. Zlota

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

OP700278R