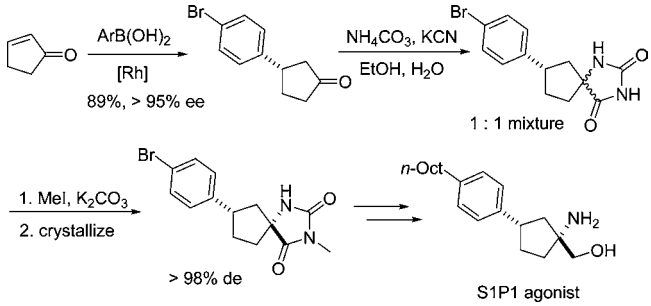
Organic Process Research & Development **2009,** *13,* 1038–1045

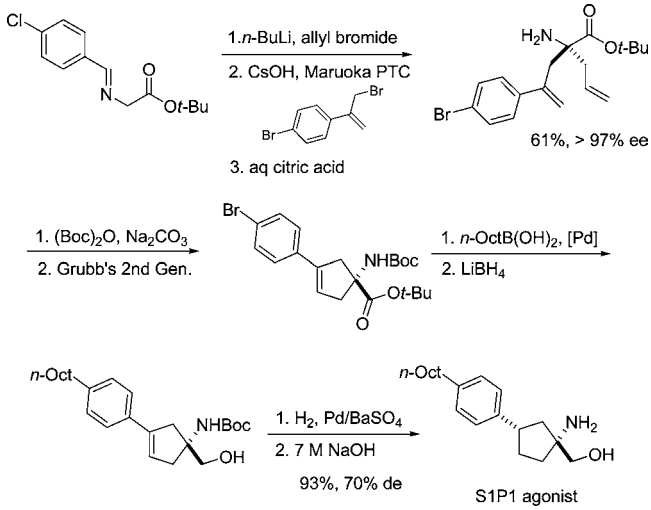
# *Highlights from the Literature*

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

### Synthesis of S1P1 Receptor Agonists

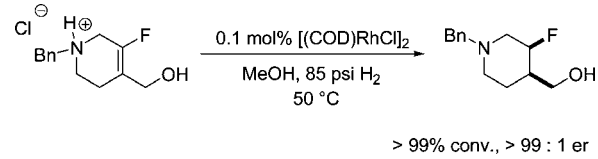



The sphingosine-1-phosphate receptor family is a target for immunomodulation, with potential application in the treatment of multiple sclerosis. Two papers from chemists at Abbott describe different strategies for the synthesis of compounds that behave as agonists of the S1P1 receptor class. Wallace and co-workers report on a stereodivergent approach that allows for construction of each of the four stereoisomers of this compound with >98% ee and de (*J. Org. Chem.* **2009**, *74*, 4886−4889). Key features of this synthesis are control of the benzylic stereocenter via Hayashi−Miyaura 1,4-addition of an arylboronic acid to cyclopenten-2-one and selective crystallization from a mixture of hydantoin diastereomers. The utility of this approach is demonstrated by the chromatography-free synthesis of ((1*R*,3*R*)-1-amino-3-(4-octylphenyl)cyclopentyl) methanol in 7 steps, 11% overall yield, and >98% ee and de.



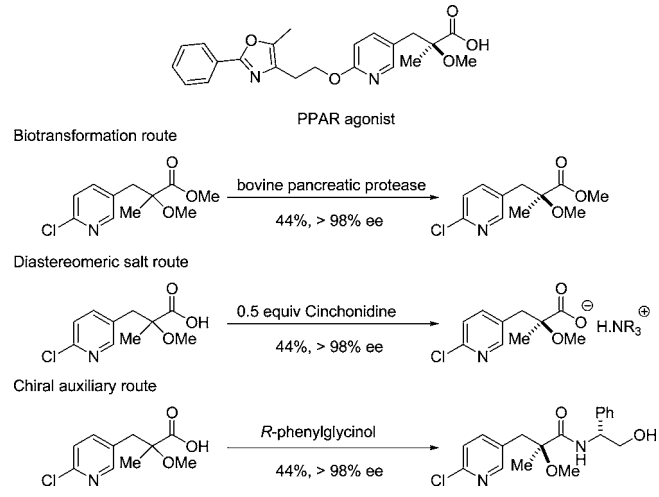

On the other hand, Hayes and co-workers describe an alternative synthesis where control of the quaternary amine-bearing stereocenter is achieved via a robust phase-transfer-catalyzed alkylation reaction employing the Maruoka catalyst (*Tetrahedron Lett.* **2009**, *50*, 4081−4083). This sets the stage for a subsequent substrate-directed hydrogenation to install the second benzylic stereogenic center, although this proceeds with only 70% de. It was necessary to use preparative HPLC to upgrade the de at the end of this synthesis.

### Asymmetric Hydrogenation of a Vinyl Fluoride




The asymmetric synthesis of chiral organofluorine compounds with stereogenic fluorine-bearing carbon atoms remains an active area of research. Now Krska, Nelson and co-workers at Merck report on an asymmetric hydrogenation of a vinyl fluoride derivative that gives efficient access to enantioenriched 1,3,4-trisubstituted piperidine intermediate with a stereogenic alkyl fluoride center (*Tetrahedron* **2009**, *65*, 8987−8994). Extensive catalyst screening across transition metals and chiral ligands identified only one catalyst, a Rh/Walphos complex, that gives high conversion, enantioselectivity and chemoselectivity for olefin reduction over defluorination. An interesting finding was that acid additives exert a significant effect upon the conversion and chemoselectivity of this process, although the enantioselectivity was largely unaffected. Ultimately, it was determined that employing the HCl salt of the hydrogenation substrate gave the best results, and the process was demonstrated on multikilogram scale to provide 99% yield and >99% ee using only 0.1 mol % catalyst loading. Additionally, deuterium-labeling studies identified that significant olefin isomerization accompanies the undesired defluorination side reaction when acid additives are omitted from the process.

### Synthesis of a PPAR Agonist




Peroxisome proliferator-activated receptors (PPARs) are important pharmaceutical targets due to their wide-ranging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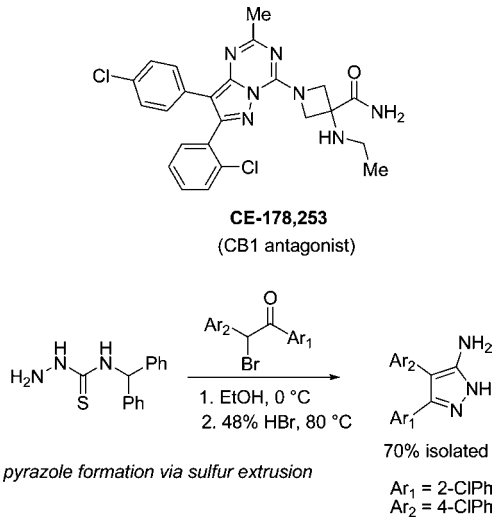
effects on key transcriptional pathways for lipid handling, insulin sensitivity, inflammation, and other functions. Humphries and co-workers describe the development of three approaches used in support of early multigram deliveries of a PPAR agonist of interest at Pfizer (*Tetrahedron Lett.* **2009**, *50*, 1765−1767). The group investigated a biocatalytic resolution, a diastereomeric salt resolution and diastereomer separation after covalent bond formation (amide) using a chiral auxiliary. All three approaches provided acceptable results, but the team elected to use the chiral auxiliary method for their scale-up work.

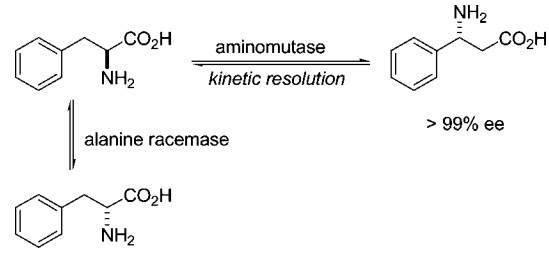
### Synthetic Development of a CB1 Antagonist




CE-178,253 benzenesulfonate (**1**) is a CB1 receptor antagonist discovered by Pfizer medicinal chemists. CB1 receptor antagonists may provide effective therapy options for the management of metabolic disorders, such as obesity. Two syntheses of this compound are described by Ragan and co-workers (*Tetrahedron* **2009**, *65*, 3292−3304). The first, based on the discovery synthesis, involves assembly of an aryl-substituted pyrazolotriazine core onto which the second aryl moiety is installed by a Suzuki coupling; this route has been scaled to provide up to 6 kg of API. A second, more convergent route is also described, which installs the pyrazolotriazine containing both aryl substituents by condensation of a bromoketone with a substituted thiosemicarbazide. This so-called "sulfur extrusion route" was demonstrated on laboratory scale and is viewed as the preferred bond-forming sequence. The paper provides an interesting in-depth discussion of numerous process development issues encountered during optimization and scale-up of the chemistry, and thorough experimental details are given.

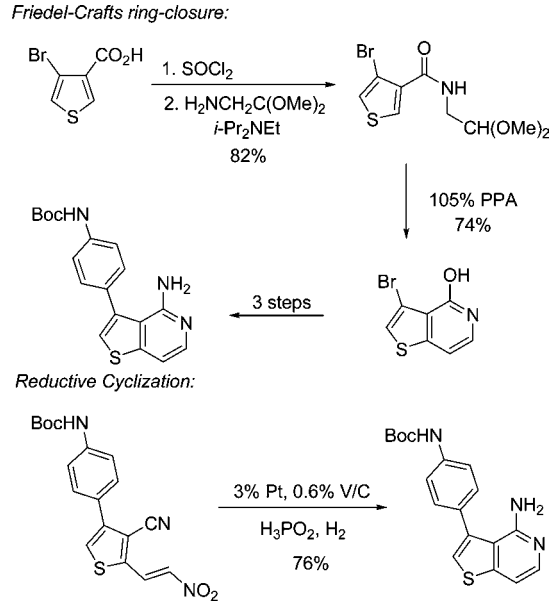
### Biocatalytic Synthesis of $\beta$-Arylalanines

Walker and co-workers at Michigan State University report on the biocatalytic conversion of racemic α-arylalanines into (*R*)-$\beta$-arylalanines with high levels of enantioenrichment (*J. Org. Chem.* **2009**, *74*, 6953−6959). The Taxus phenylalanine aminomutase (PAM) enzyme converts several (*S*)-*R*-arylalanines to their corresponding (*R*)-$\beta$-arylalanines. With racemic starting materials, the ratio of (*R*)-$\beta$-arylalanine product to the (*S*)-α-substrate ranged between 0.4 and 1.8, and the remaining




nonproductive (*R*)-*R*-arylalanine became enriched. To increase efficiency the researchers coupled this system with the catalysis of a promiscuous alanine racemase from *Pseudomonas putida* (KT2440). The inclusion of a biocatalytic racemization along with the PAM-catalyzed reaction moderately increased the overall reaction yield of enantiopure $\beta$-arylalanines between 4 and 19% (depending on the arylalanine), which corresponded to as much as a 63% increase compared to the turnover with the aminomutase reaction alone. The use of these biocatalysts, in tandem, could potentially find application in the production of chiral $\beta$-arylalanine building blocks, particularly as refinements to the process are made that increase reaction flux, such as by selectively removing the desired (*R*)-$\beta$-arylalanine product from the reaction mixture.

### Improved Synthesis of Thienopyridines

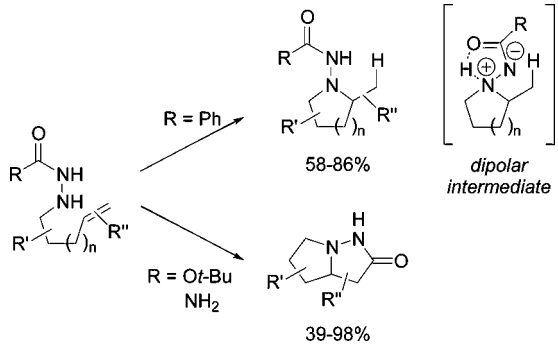



Two syntheses of 3-substituted-4-amino-[3,2-*c*]thienopyridines have been developed by Engstrom and co-workers at Abbott (*J. Org. Chem.* **2009**, *74*, 3849−3855). The first synthesis utilizes a Friedel−Crafts reaction as its key ring-forming step, whereas the second route relies on an unprecedented intramolecular reductive cyclization between a nitroolefin and a nitrile as its key ring-forming step. The development and optimization of each 3-substituted-4-amino-[3,2-*c*]thienopyridine synthesis is discussed, and a comparison of the routes is presented. Although the literature "thermal" route and the Friedel−Crafts route have similar step counts and overall yields, the thermal route has several flaws that make it unattractive for scale-up, including the use of azide and the instability of an

intermediate under the reaction conditions used to make it. While the reductive cyclization route is longer and lower yielding than the thermal route, it also avoids both of these pitfalls. When comparing the Friedel−Crafts and reductive cyclization routes to each other, it is clear that the Friedel−Crafts route is superior in terms of isolations and yield, as well as relative simplicity of the reagents used throughout the sequence. However, the reductive cyclization route is a novel method for accessing 3-substituted-4-amino-[3,2-*c*]-thienopyridine compounds and may prove valuable for targets for which the Friedel−Crafts chemistry fails.

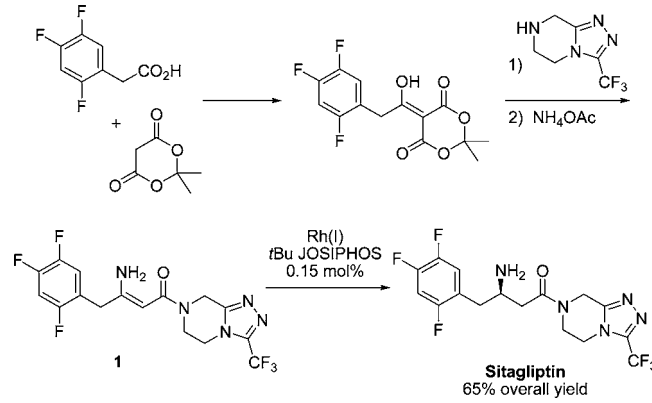
### Alkene Hydroamination and Aminocarbonylation

Beauchemin and co-workers at University of Ottawa reported the use of hydrazides in a metal-free intramolecular hydroamination (*J. Am. Chem. Soc.* **2009**, *131*, 8740−8741). Thus, benzoic hydrazides (R = Ph) cyclize upon heating at 120−200 °C to generate pyrrolidines and piperazines with different substitution patterns. The cyclizations involve an intramolecular hydrohydrazidation followed by proton transfer of the intermediate dipole. Interestingly, carbazates and semicarbazides (R = O*t*-Bu, $NH_2$) undergo a stereospecific alkene aminocarbonylation under similar reaction conditions. The experimental procedures are straightforward and compatible with various solvents (PhMe, dioxane, MeCN, *i*-PrOH, DMF and water), and the products can be purified by chromatography.

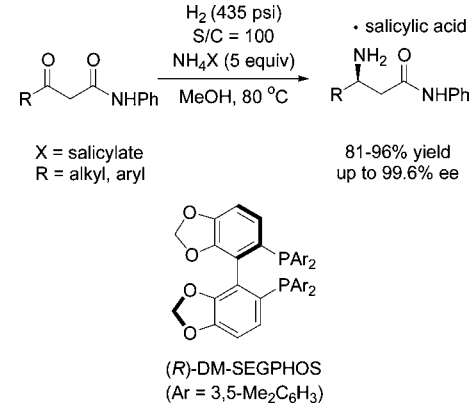



### Highly Efficient Asymmetric Synthesis of Sitagliptin

Process research teams at Merck and Solvias AG disclose full details of a highly efficient synthesis of sitagliptin (Januvia), an orally available DPP-4 inhibitor for the treatment of type-2 diabetes (*J. Am. Chem. Soc.* **2009**, *131*, 8798−8804). Remarkably, the key dehydrositagliptin intermediate **1** was prepared in one pot (82% yield, >99.6 wt % purity over three steps) in a telescoped process that exclusively generated the *Z*-isomer through a simple filtration. Enantioselective hydrogenation of the dehydro precursor was performed using 0.15 mol % Rh(I)*t*-Bu JOSIPHOS following a thorough screening of Ir-, Ru-, and Rh-based catalysts. This transformation, which entailed the unusual asymmetric hydrogenation of a free enamine, was scaled up by generating the active catalyst by in situ mixing the metal precursor $[Rh(COD)Cl]_2$ and the ligand in MeOH under nitrogen atmosphere (98% yield, 95% ee). In the end game, the soluble Rh species were removed from the reaction crude using a solid absorbent (Ecosorb C-941), and the unwanted enantiomer was purged through crystallization. This full paper, which includes thoughtful mechanistic discussions and sustainability analysis, is a must read for pharmaceutical process development practitioners.

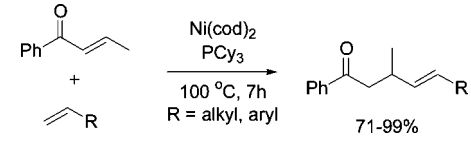



In a related extension of the asymmetric hydrogenation of the enamine intermediate, Steinhuebel, Sun, and Matsumura (Merck and Takasago) report the direct asymmetric reductive amination of $\beta$-keto amides (*J. Am. Chem. Soc.* **2009**, *131*, 11316−11317). The methodology enables a one-pot synthesis of unprotected $\beta$-amino amides using ammonium salicylate as the nitrogen source and $Ru(OAc)_2$((*R*)-dm-segphos)) as the catalyst. The amination, which was demonstrated to produce sitagliptin in 91% yield with unprecedented enantioselectivity levels, is highly chemoselective and nearly completely enantioselective for a variety of substrates.

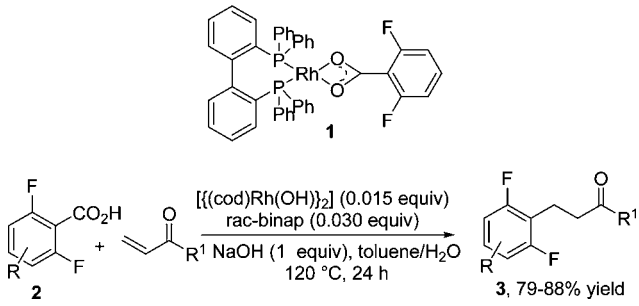



### Metal-Catalyzed Conjugate Additions

The conjugate addition of alkenes to enones constitutes a complex transformation that, before the publication of Ogoshi's work in *J. Am. Chem. Soc.* **2009**, *131*, 10350−10351), required the preparation of an alkenyl metal reactant. In this communication, the authors report the first example of a direct conjugate addition catalyzed by a Ni(0) complex (10 mol % $Ni(cod)_2$, 40 mol % $PCy_3$, 100 °C) to give the desired adducts in excellent yields. A possible mechanism involves the oxidative addition of the enone and the alkene to the Ni(0) complex to generate a $\eta^3$-nickelacycle that, after $\beta$-hydrogen elimination, undergoes reductive elimination to give the conjugate addition products.

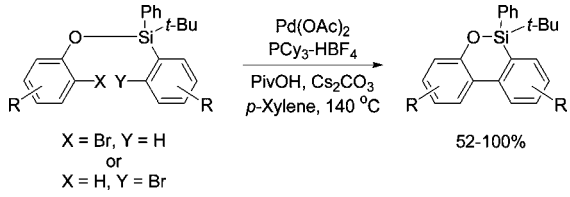


Sun and Zhao recently reported the development of a rhodium-catalyzed decarboxylative conjugate addition of fluorinated benzoic acids (*Angew. Chem. Int. Ed.* **2009**, *48*, 6726−6730). The phosphine-ligated rhodium(I) carboxylato with highest reactivity during development was the bidentate complex [(biphep)Rh{$\kappa^2$-$O_2C(2,6\text{-}F_2C_6H_3)$}] (**1**; biphep = 2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl), which was prepared from 2,6-difluorobenzoic acid and [{(cod)Rh(OH)}$_2$]. Nevertheless, the less expensive racemic binap ligand gave equally good results during screening. Aqueous reaction medium was beneficial for yield and selectivity, and the addition of NaOH was critical for success. Addition of 2,6-difluorobenzoic acids **2** to *n*-butyl acrylate or other electron-poor olefin substrates ($R^1$ = OBu, OEt, $NMe_2$) yielded the desired conjugate-addition products **3** in good yields.



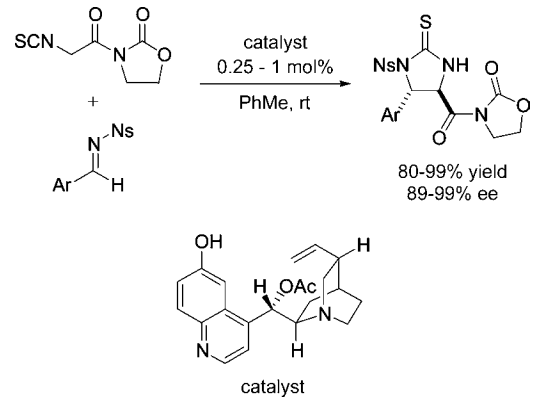

## Pd-Catalyzed Intramolecular Arylations

A temporary silicon tether promotes Pd-catalyzed C−H activations in the TBDPS-mediated arylations developed by Huand, C. and Gevorgyan, V. (*J. Am. Chem. Soc.* **2009**, *131*, 10844−10845). The TBDPS protecting group serves as an excellent aryl group donor for *o*-bromophenols (X = Br, Y = H) via an intramolecular arylation using Fagnou's protocol ($Pd(OAc)_2/PCy_3\text{-}HBF_4$) followed by deprotection (desilylation or oxidation). Iodo- and chlorophenols were less efficient, whereas the triflate analogues were unstable. Similarly, the *o*-Br-TBDPS (X = H, Y = Br) group undergoes intramolecular arylation under the same reaction conditions, enabling a novel entry to *o*-biphenols.



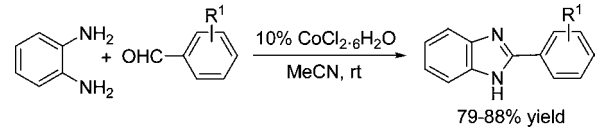

## Enantioselective Synthesis of α,β-Diamino Acids

Ganesh and Seidel at Rutgers University report an expedient method for the enantio- and diastereoselective synthesis of *syn*-α,β-diamino acids in *J. Am. Chem. Soc.* **2009**, *131*, 11648−11649. The procedure involves a Mannich reaction between an *N*-sulfonyl imine and an α-isothiocyanato imide catalyzed by a bifunctional quinidine-based organocatalyst. A variety of electron-rich and electron-poor benzenesulfonyl- and 4-nosyl-protected imines reacted in generally good yields and high selectivities. The authors observed that catalyst turnover is linked to product precipitation and demonstrated that catalyst loadings as low as 0.25 mol % could be used for less soluble *N*-nosyl imines.



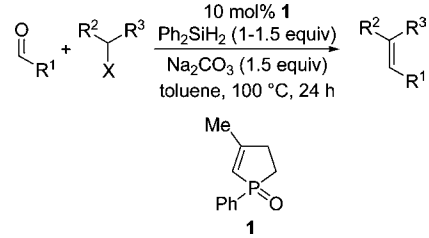

## Mild One-Pot Synthesis of 2-Arylbenzimidazoles

Scientists from the Indian Institute of Technology, Guwahati and Northeastern Hill University, India, described an efficient method for the synthesis of 2-arylbenzimidazole from *o*-phenylenediamine and various aromatic aldehydes using cobalt(II) chloride hexahydrate as a catalyst (*Synth. Commun.* **2009**, *39*, 2339−2346). The best conversion and selectivities were obtained with MeCN as the solvent, which provides products that do not require chromatography. Aromatic aldehydes containing both electron-withdrawing and electron-donating groups underwent oxidative cyclization at room temperature in good yields.



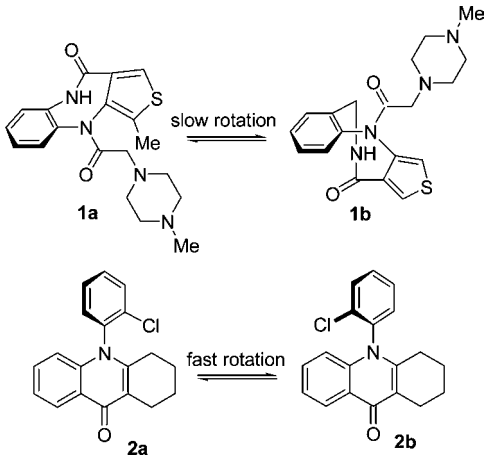

## Development of a Catalytic Wittig Reaction

The Wittig reaction yields alkenes with the concomitant generation of a stoichiometric amount of triphenylphosphine oxide, and complete removal of this byproduct is not always straightforward. Process chemists would immensely benefit from a catalytic Wittig-like transformation, and the pursuit of such endeavor is described in *Angew. Chem. Int. Ed.* **2009**, *48*, 6836−6839. The authors employed 3-methyl-1-phenylphospholane-*N*-oxide (10 mol %) that can be chemoselectively reduced by $Ph_2SiH_2$ (toluene, 100 °C) and can re-enter the catalytic cycle. Theoretical calculations suggest that **1** is easier to reduce than $PPh_3O$ due to the relief of ring strain. Lower temperatures (80 °C) led to a significant amount of the *Z* product, which indicates that isomerization (probably phosphine-mediated) takes place after the olefination. A variety of heteroaryl, aryl and aliphatic aldehydes were converted to the corresponding alkenes in moderate to high yields and high selectivities.



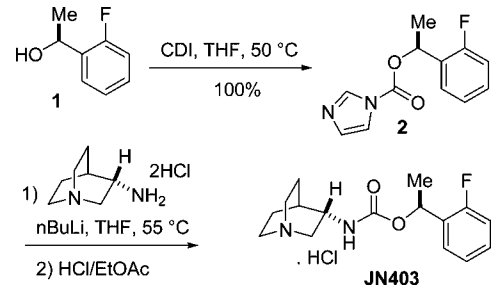
## Atropoisomerism and Regulatory Challenges

In *Angew. Chem., Int. Ed.* **2009**, *48*, 6398−6401 Clayden (University of Manchester), La Plante (Boehringer-Ingelheim, Canada), and co-workers address the pharmaceutical development implications of a largely overlooked source of drug chirality: atropoisomerism. Regulatory agencies have a preference for chiral drugs to be developed as single enantiomers and the FDA policy statement form 1992 emphasizes the importance of understanding therapeutic activities of the isomers through in vivo or in vitro studies. Nevertheless, there are no specific regulations governing conformationally based stereochemistry. Atropoisomerism may give rise to geometrical isomers, diastereomers, or enantiomers, with the distinctive feature that they can be thermally equilibrated. Two main strategies can be adopted for development of a drug candidate: (a) High interconversion barrier: develop the compound as a single, pure, stereochemically stable isomer [telezenpine (**1**), $t_{1/2}^{rac}$ 20 °C = 1000 years]; (b) Low interconversion barrier: develop the drug as a consistent and reproducible mixture [Sch 40120 (**2**), $t_{1/2}^{rac}$ 37 °C = 1.6 min]. With colorful examples peppering the review, the authors strongly advocate the implementation of strategies dealing with atropoisomerism issues at the early stages of drug design.



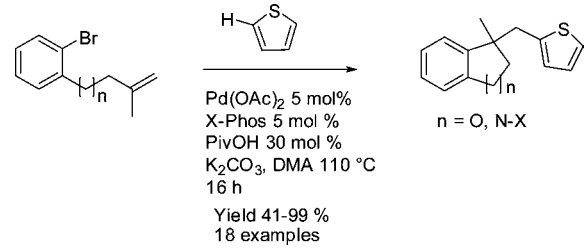

## Concise Synthesis of Schizophrenia Candidate JN403

JN403 is an orally active nicotinic acetylcholine receptor agonist selected at Novartis for further clinical evaluation for schizophrenia. Process chemists at the East Hanover (New Jersey, U.S.A.) facility reported a 3-step synthesis that yielded material in high purity and yield (*Synth. Commun.* **2009**, *39*, 2640−2646). A solution of chiral alcohol **1** was added to a solution of carbonyldiimidazole (1.5 equiv) in THF at 50 °C) to yield carbamate **2** in almost quantitative yield. Due to the insolubility of the dihydrochloride **3**, it was imperative to generate the corresponding amine for the coupling. While the use of aqueous bases led to the hydrolysis of **2**, the problem was circumvented by using BuLi (2 equiv). Treatment of the resulting crude material with HCl in EtOAc yielded the desired product JN403 as a crystalline, easy to handle solid of adequate purity (overall yield: 50%).




## Domino Palladium-Catalyzed Heck-Intermolecular Direct Arylation Reactions

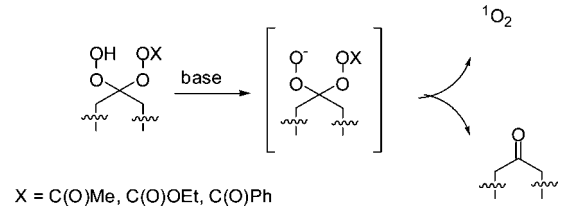
Although the use of aryl halide and organometallic coupling partners is the norm in metal-catalyzed cross-coupling reactions, more efficient processes that can replace the aryl organometallic with a simple arene are emerging as valuable alternatives. The majority of studies done in the past decade have focused on the formation of Csp2−Csp2 bonds. Recently, however, important steps have been made dealing with the formation of Csp3−Csp2 (alkane−arene) bonds. Building on the first reports that validated this reactivity in intramolecular processes, new intermolecular reactions have been realized with aliphatic and benzylic halides with Pd(0) catalysts as well as with aliphatic halides and Pd(II) or Ru(II) catalysts. Fagnou, K. et al. (*Org. Lett.* **2009**, *11*, 4560.) have now developed a domino palladium-catalyzed Heck-intermolecular direct arylation reaction, giving access to a variety of dihydrobenzofurans, indolines, and oxindoles. A variety of sulfur-containing heterocycles such as thiazoles, thiophenes, and benzothiophene can be employed as the direct arylation coupling partner in yields up to 99%.




## A New Peroxide Fragmentation: Efficient Chemical Generation of $^1O_2$ in Organic Media

Singlet molecular oxygen ($^1O_2$), an important oxidant in chemistry, biology, and medicine, is most commonly generated via photosensitized excitation of ground-state ($^3O_2$) dioxygen. The discovery that $^1O_2$ is also produced from reaction of $H_2O_2$ and HOCl led to the discovery of a number of additional methods for chemical generation. However, many of these "dark" oxygenations have significant limitations due to the short half-life of $^1O_2$ in aqueous media.

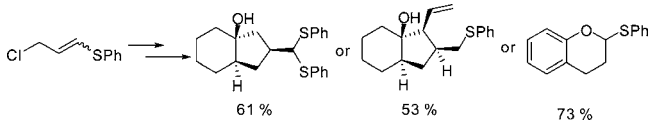
Ghori, P. and Dussalt, P. H. (*Org. Lett.* **2009**, *11*, 4572.) have developed a new heterolytic base-promoted fragmentation that allows efficient and rapid generation of $^1O_2$ in anhydrous organic solvents from readily available monoactivated derivatives of 1,1-dihydroperoxides.




### Readily Prepared 3-Chloro-1-(phenylthio)propene, a Versatile Three-Carbon Annulating Agent

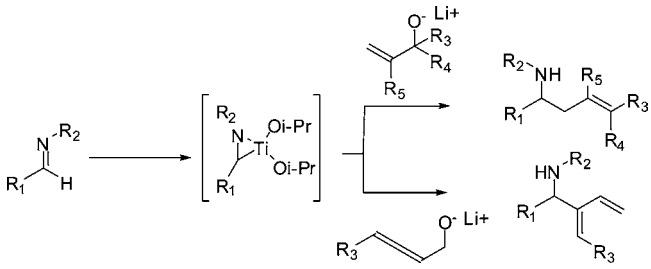
Since vinyl sulfides can be readily converted to aldehydes or ketones, reagents such as 3-chloro-1-(phenylthio)propene behave as synthons of α,β-unsaturated aldehydes or ketones in a Michael sense. In view of the potential versatility of the nucleophilic substitution products such as **1**, it is rather surprising that the only reported uses are as precursors of aldehydes or thioacetals.

Now Cohen, T. et al. (*Org. Lett.* **2009**, *11*, 4576.) have found that 3-chloro-1-(phenylthio)propene, simply generated by chlorination of commercial allyl phenyl sulfide, is a versatile 3-carbon annulating agent for ketones and phenols.




### Aliphatic Imines in Titanium-Mediated Reductive Cross-Coupling: Unique Reactivity of Ti(O-i-Pr)4/n-BuLi

It has long been accepted that alkyl imines are particularly challenging substrates in reductive cross-coupling chemistry. In titanium alkoxide-mediated processes, alkylation of aliphatic imines with the reducing Grignard reagent typically employed in these processes has been cited as the root cause of this limitation. In an attempt to overcome this limitation, Tarselli, M. A. and Micalizio, G. C. (*Org. Lett.* **2009**, *11*, 4596.) initiated empirical studies to probe the structure/activity relationships of a range of reducing organometallic reagents in titanium alkoxide-mediated reduction of aliphatic imines. Initial studies led to the identification of *n*-BuLi as a particularly effective reagent in combination with $Ti(O\text{-}i\text{-}Pr)_4$ for the net reduction of aliphatic imines. A procedure for the coupling of aliphatic imines with allylic and allenic alkoxides has been developed.



### Catalytic Carbene Insertion into C−H Bonds

The breakthrough that brought carbon−hydrogen insertion reactions into the realm of viable synthetic applicability was the report of the Teyssie group of intermolecular carbon−hydrogen insertion reactions of ethyl diazoacetate with alkanes, catalyzed by dirhodium(II) tetraacetate and derivative rhodium carboxylates. Although limited in selectivity, these initial results showed the influence of catalyst ligand on regioselectivity.

The review from Doyle, M. P. et al. (*Chem. Rev.* **2009**, DOI: 10.1021/cr900239n) is intended to provide an overview of metal carbene insertion reactions into carbon−hydrogen bonds that encompasses both intra- and intermolecular transformations and is focused on reaction selectivity.

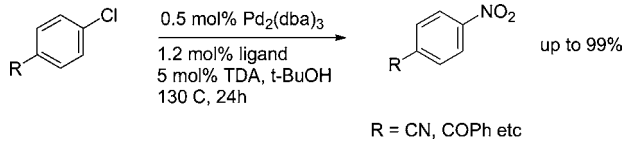
### Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation

Once considered the "holy grail" of organometallic chemistry, synthetically useful reactions employing C−H bond activation have increasingly been developed and applied to natural product and drug syntheses over the past decade (Bergman, R. G. et al. *Chem. Rev.* **2009**, DOI: 10.1021/cr900005n). The ubiquity and relatively low cost of hydrocarbons make C−H bond functionalization an attractive alternative to classical C−C bond-forming reactions such as cross-coupling, which require organohalides and organometallic reagents. In addition to providing an atom economical alternative to standard cross-coupling strategies, C−H bond functionalization also reduces the production of toxic byproducts, thereby contributing to the growing field of reactions with decreased environmental impact. The synthesis of complex molecules from relatively simple precursors has long been a goal for many organic chemists. The ability to selectively functionalize a molecule with minimal preactivation can streamline syntheses and expand the opportunities to explore the utility of complex molecules in areas ranging from the pharmaceutical industry to materials science. Indeed, the issue of selectivity is paramount in the development of all C−H bond functionalization methods. Several groups have developed elegant approaches toward achieving selectivity in molecules that possess many sterically and electronically similar C−H bonds.

### Biocatalysis Reviews

Biocatalysis has been well served by reviews and books in the past, but several new ones have appeared in the last year. Junhua (Alex) Tau, formerly of Pfizer and Bioverdant, has published two reviews and coauthored a book. In the first review (Tao, J. et al. *Curr. Opin. Chem. Biol.* **2009**, *13*, 43−50) biocatalysis in the development of green pharmaceutical processes is reviewed and includes examples such as simvastatin, atorvastatin, pregbalin, paroxetine and leviracetam. In the second paper (Ran, N. et al. *Curr. Pharm. Des.* **2009**, *15*, 124−152), the emphasis is on chemo-enzymatic synthesis of small-molecule therapeutics. In *Expert Opin. Drug Discovery* **2008**, *3*, 187−245, Ramesh Patel of BMS reviewed chemo-enzymatic synthesis of pharmaceutical intermediates.

Along with Guo-Qiang Lin and Andreas Liese, Tao has written a new book, published by Wiley, on *Biocatalysis for the Pharmaceutical Industry; Discovery, Development and Manufacturing*, which will be reviewed in *Org. Process Res. Dev.* soon. Another excellent and recent book on biocatalysis is *Asymmetric Organic Synthesis with Enzymes*, written by Vicente Gotor, Ignacio Alfonso, and Eduardo Garcia-Urdiales, published by Wiley-VCH.




### Conversion of Aryl Chlorides and Triflates to Nitroaromatics

Nitroaromatics are usually accessed by direct nitration methods, but these methods can have scale-up issues; thus, other methods are always welcome. A recent paper from the Buchwald group at MIT reports on the direct replacement of chloride, triflate, and nonaflate groups by sodium nitrite under the influence of palladium catalysis and a phase transfer catalyst, with TDA [tris(3,6-dioxaheptyl)amine] being the best. Interestingly the yield increases as the amount of PTC is increased up to 5% but then falls off. It is suggested that TDA increases the solubility of nitrite in the *tert*-butanol solvent but that too much nitrite may oxidise the Pd(0) or ligand. (Fors, B. R. et al. *J. Am. Chem. Soc.* **2009**, *131*, 12898−12899).

Whilst this reaction is probably not so useful for simple aromatics, it will prove invaluable for heteroaromatics, for introduction of a nitro group in positions which cannot be achieved by nitration, or where the aromatic is deactivated to nitration. I can imagine it being useful for preparation of di- and trinitro- compounds from mononitroaromatics without using nitrating agents, thus minimising hazards, although this was not reported.

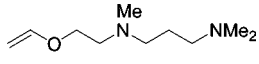
Surprisingly, the reaction with chlorides is much faster than with bromides and iodides, the latter failing to react at all.

### Iron-Catalysed Suzuki Coupling? A Cautionary Tale

Following on from last issue's editorial and a highlight on the contamination of iron by copper leading to spurious results with iron catalysis, a report from Robin Bedford's group at Bristol, U.K. in collaboration with Masaharu Nakamura's group at Kyoto (Bedford, R. B. et al. *Tetrahedron Lett.* **2009**, *50*, 6110−6111) indicates they have failed to reproduce earlier reports (*Tetrahedron Lett.* **2008**, *49*, 6679.) of a Suzuki reaction with iron catalysis. Only once did the workers get a reaction to work reproducibly, but this was followed by 10 successive failures. The earlier 2008 paper has since been retracted.

It is suspected that the reaction worked in the past because of trace contamination by other metals, possibly palladium. Thus, repeating the reaction in the presence of small amounts of palladium gave successful results. Levels as low as a substrate-to-catalyst ratio of a million to one gave quantitative conversion in the reaction of 4-bromoacetophenone with phenylboronic acid.

### An Efficient Deactivating Agent for Olefin Metathesis Catalysts

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Newer olefin metathesis catalysts have allowed the development of ring-closing reactions on scale at relatively low catalyst loadings. The enhanced stability of these catalysts, however, can sometimes lead to problems during work-up, when side reactions occur, owing to the reversibility of the metathesis. In addition, efficient removal of ruthenium residues can sometimes be a problem on large scale. Therefore, there is a need in industry for a reagent that could rapidly deactivate the catalyst and, at the same time, assist with the removal of ruthenium byproducts.

Workers at Array BioPharma in Boulder, Colorado, U.S.A., in collaboration with the local university, have found that inexpensive and commercially available di(ethylene glycol)vinyl ether is more efficient than the volatile vinyl ethers used earlier in the deactivation of RCM catalysts. (Liu, W. et al. *Tetrahedron Lett.* **2009**, *50*, 6103−6105).

Four equivalents (with respect to catalyst) of the ether were required to fully deactivate the Zhan catalyst in 30 min, and these conditions, in a variety of solvents, were used to successfully deactivate all of the other common RCM catalysts (Grela, Hoveyda, Grubbs, Degussa, etc.). Using silica gel to purify the crude material resulted in less than 10 ppm ruthenium in the final product. To avoid chromatography, new amine-based scavengers (e.g., **1**) containing the vinyl ether functionality have been designed, and Ru levels below 15 ppm have been obtained by simple acid washing. A resin-based scavenger was, surprisingly, found not to be effective.

### Phase Behavior and Polymorphism of Organic Crystals Confined within Nanoscale Chambers

High-throughput or high-value (medium-throughput) polymorph screening of organic compounds of pharmaceutical interest typically include manipulation of concentration, solvent, cooling protocols, seeding, and/or the use of capillary crystallization. The same parameters are used to control crystallization processes, specifically polymorph control. Prior to crystal formation, a compound is postulated to exist as crystal nuclei at nanometer scale. Based on this postulate, a reasonable approach for polymorph control could be the "intervention" of crystallization phenomena occurring at nanometer scale. In a contribution from New York University and University of Minnesota (Ha, J.-M. et al. *Cryst. Growth Des.* **2009**, DOI: 10.1021/cg9006185) the authors report results of their work on crystallization control when using nanoscale chambers. Several $\alpha,\omega$-dicarboxylic acids and coumarin were investigated, using nanosized crystallization spaces provided by controlled-pore glass beads and hexagonally ordered cylindrical pores of poly(cyclohexylethylene) monoliths. Using this approach, new polymorphs were discovered for pimelic acid, suberic acid, and coumarin. Moreover, the enantiotropic phase behavior of bulk glutaric acid and suberic acid *switches* from enantiotropic to monotropic when crystallized in nanosize pores. Along with the possible addition of another tool in polymorph screening and control, these results also suggest that nanocrystal formulations must be carefully evaluated with respect to possible polymorphic transformations.

### Process Analysis by Means of Focused Beam Reflectance Measurements

A meaningful implementation of Process Analytical Technology for Quality by Design requires reliable quantitative analysis of the data collected by the sensors used to monitor a

process. For crystallization process monitoring the FBRM is a popular tool, in spite of certain challenges in accomplishing meaningful quantitative analysis of the data. Another paper in a series published by Marquardt and colleagues in Germany (Kail, N. et al. *Ind. Eng. Chem. Res.* **2009**, *48*, 2936.) proposes an approach for a direct chord length distribution (CLD) analysis. The paper reiterates the challenges posed by the classical FBRM model ("the geometric model"), and offers a possible explanation for the unexpected dependence of the FBRM data with solids concentration. The recommendation is to accomplish CLD analysis using several mathematical descriptors, as demonstrated for the case study of the seeded cooling crystallization of α-lactose hydrate. The authors do not attempt to use CLD data in order to reconstruct the corresponding particle size distribution because of an expected low accuracy for such correlations. We must hope that a dialogue between the FBRM manufacturer and this academic group will lead to an improved FBRM experimental protocol and data analysis.

### Thermodynamics and Nucleation Kinetics of *m*-Aminobenzoic Acid Polymorphs

Only one crystal structure was published in 1967 for *m*-aminobenzoic Acid (mABA), with a second zwitterionic form postulated later, based on spectroscopic studies. An industrial−academic collaboration (Abbott−The Royal Institute of Technology in Stockholm: Sward, M. et al. *Cryst. Growth Des*. **2009**, DOI: 10.1021/cg900850u) reports the findings of a very thorough investigation in mABA polymorphism. Two enantiotropical polymorphs were identified, with the metastable form at room temperature being the polymorph initially reported in 1967. A relatively large number of crystallization experiments were carried out in order to better understand the behavior of the mABA polymorphs. Solvent was found to be the dominant factor in determining the type of polymorph obtained. The stable (zwitterionic) form is obtained from crystallization in polar protic solvents such as water and methanol. The two polymorphs were fully characterized using XRPD, FTIR, microscopy, and thermal analysis. The metastable form at room temperature can be obtained form crystallization in polar aprotic solvents such as acetonitrile and ethyl acetate. Interestingly, when 60 *identical* crystallization experiments were executed in saturated acetonitrile at 45 °C, pure form II was obtained only in 83% of the experiments; in 10% of the cases pure form I was obtained, whereas in 7% of the experiments concomitant nucleation of the two forms was observed. These experiments further confirm the stochastic nature of nucleation processes.

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