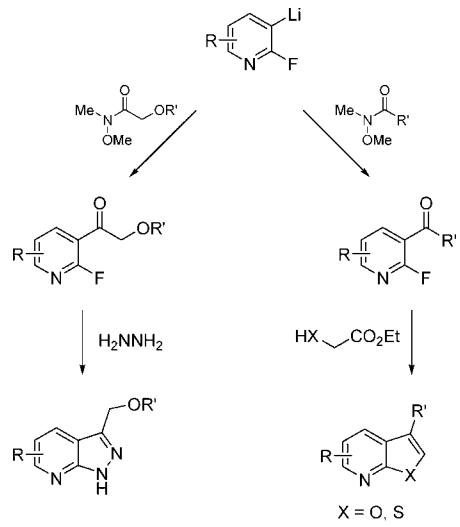
Organic Process Research & Development **2009,** *13,* 364–370

Highlights from the Literature

Some Items of Interest to Process Chemists and Engineers

Synthesis of Fused Heterocycles via 2-Fluoropyridines

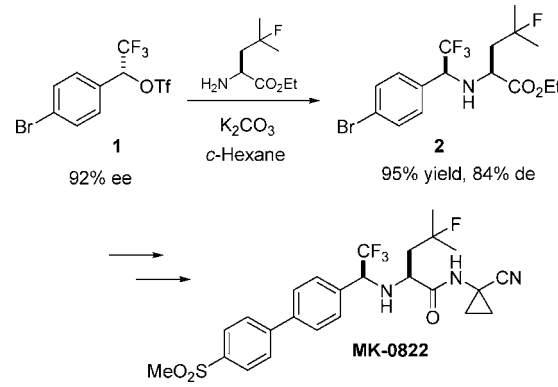


Methods for the synthesis of two different classes of pharmaceutically relevant heterocycles are described in publications from Beutner and co-workers at Merck. In the first paper (*J. Org. Chem.* **2009**, *74*, 789−794), a strategy for the preparation of 3-alkoxymethyl-pyrazolo[3,4-*b*]pyridines (azaindazoles) is presented. Starting from 2-fluoropyridine (and substituted derivatives), directed metalation adjacent to the fluorine followed by quenching with a glycolic acid-derived Weinreb amide affords a ketone intermediate. Treatment of this ketone with hydrazine leads to cyclization to the azaindazole product, although choice of protecting group on the glycolic acid-derived hydroxyl group is crucial in determining the reaction pathway. If the hydroxyl is activated as a leaving group, it will eliminate and give a vinyl azine intermediate that is not productive in the desired sense. In contrast, the use of ether-type protecting groups avoids elimination and leads to the desired cyclization.

In a separate paper, the same researchers present an extension of the azaindazole chemistry towards the preparation of fused furano- and thienopyridines (*Tetrahedron Lett.* **2009**, *50*, 781−784). In this case, ketones derived from metalated 2-fluoropyridine are subjected to glycolate esters or thioglycolate esters under basic conditions leading to a two-step sequence of fluoride displacement and then condensation to the fused furan or thiophene.

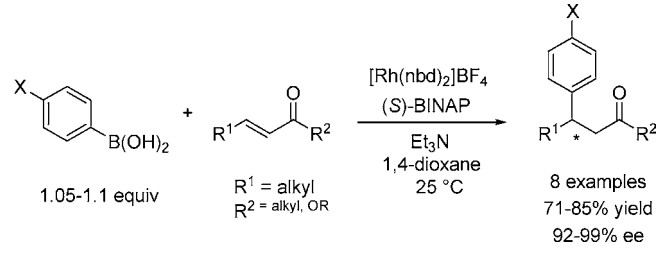
Enantioselective Synthesis of a Potent Cathepsin K Inhibitor

An enantioselective synthesis of the cathepsin K inhibitor odanacatib (MK-0822) is described by O'Shea and co-workers at Merck (*J. Org. Chem.* **2009**, *74*, 1605−1610). The key step involves the novel stereospecific S_N2 triflate displacement of a



chiral α-trifluoromethylbenzyl triflate **1** with (*S*)-γ-fluoroleucine ethyl ester to generate the required α-trifluoromethylbenzyl amino stereocenter. Under optimized conditions, the triflate displacement can be achieved in high yield (95%) and with minimal loss of stereochemical integrity (84% de after coupling). Important findings from this study were that switching the 4-substituent on the phenyl ring from bromo to another aryl ring (present in the target structure) led to decreased performance. Also the use of dipolar aprotic solvents typically employed for S_N2-type displacements led to decomposition of the triflate. The chiral center in the benzylic alcohol is obtained via OAB chemistry, and the 84% de observed after coupling can be upgraded to >98.5% de later in the synthesis via crystallization. The overall synthesis of MK-0822 is completed in six steps in 61% overall yield.

Asymmetric Michael Addition of Arylboronic Acids



A new practical method for the asymmetric Michael addition of arylboronic acids to α,β-unsaturated carbonyl compounds utilizing in situ generated chiral rhodium-binap-based catalyst has been developed by Lukin and co-workers at Abbott (*J. Org. Chem.* **2009**, *74*, 929−931). The main thrust of this paper is to address the lack of commercial availability of more active "second generation" preformed catalysts by developing a reliable procedure for in situ catalyst preparation. A key finding is that in situ chiral catalyst preparation using achiral Rh-cyclooctadiene precursors always leaves some residual achiral material in the system, which then leads to a background

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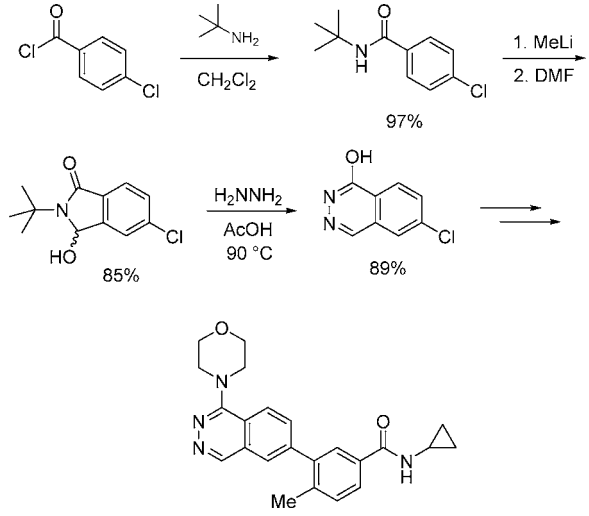
reaction and erosion of enantiocontrol. By substituting with a Rh-norbornadiene precursor, residual achiral species are less catalytically active in the Michael process and enantiocontrol is maintained at a high level. Additionally, high catalyst activity allows these reactions to proceed at room temperature, which aids in minimizing protodeboronation of the arylboronic acids used. Consequently, relatively low charges of both arylboronic acid and catalyst are required for efficient reactions.

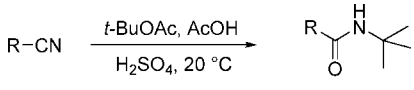
Practical Synthesis of a p38 MAP Kinase Inhibitor



p38 MAP Kinase Inhibitor

p38 MAP Kinase inhibitors have attracted considerable interest as potential agents for the treatment of inflammatory diseases. Achmatowicz and co-workers at Amgen describe a concise and efficient synthesis of one such inhibitor that is based on a phthalazine scaffold (*J. Org. Chem.* **2009**, *74*, 795−809). Highlights of this work include a practical synthesis of a 1,6-disubstituted phthalazine building block via ortho-metalation of a simple benzamide starting material. Treatment of *N*-*tert*-butyl 4-chlorobenzamide with 2 equiv of MeLi followed by quenching with DMF afforded a hydroxyisoindolinone intermediate that was then transformed into the desired phthalazine via heating in the presence of hydrazine. The paper also describes in detail the various possible end-game sequences explored and the relative merits of each. Overall, the group delivered a short (six steps) and practical synthesis of the API with an overall yield of 31%. Multikilogram-scale experimental details are provided.

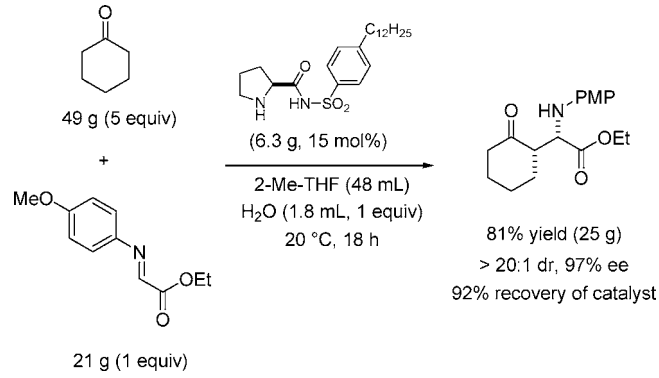
Scalable Ritter Reaction for the Synthesis of *N*-*tert*-Butyl Amides



R = alkyl, benzyl, aryl, vinyl
16 examples, 80-98% yield

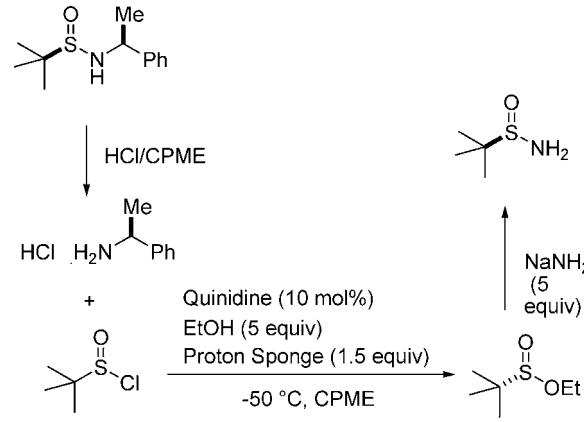
In another paper from the Amgen process group, Milne and co-workers describe a scalable procedure for the conversion of nitriles to *N*-*tert*-butyl amides via the Ritter reaction (*J. Org. Chem.* **2009**, *74*, 2207−2209). The authors note that using *tert*-butyl acetate as the source of *tert*-butyl cation offers several advantages over alternatives such as isobutylene or *tert*-butanol. Additionally, when the reactions are run in the presence of acetic acid this can serve as a (reversible) trap for the *tert*-butyl cation, thereby limiting proton loss and generation of isobutylene gas. Consequently, the process is made safer by the presence of acetic acid. The reaction has a broad scope for aromatic, alkyl, and α, β-unsaturated nitriles.

Enantioselective Organocatalytic Mannich Reactions



A highly enantioselective and diastereoselective protocol for performing Mannich reactions has been developed by the Carter group (*J. Org. Chem.* **2009**, *74*, 2246−2249). using a *p*-dodecylphenylsulfonamide-based proline catalyst. The authors note that this catalyst facilitates the use of common, nonpolar solvents and increased concentrations as compared to alternative methods. A series of *syn*-selective Mannich reactions is reported, including those giving access to α- and β-amino acid derivatives. Examples where the protecting/activating group on the imine nitrogen is something other than *p*-methoxyphenyl (PMP) are also reported (e.g., *N*-Boc). Aldehydes can also be used as the carbonyl component. In the example shown, the process was demonstrated on multigram scale although product isolation was via standard flash chromatography.

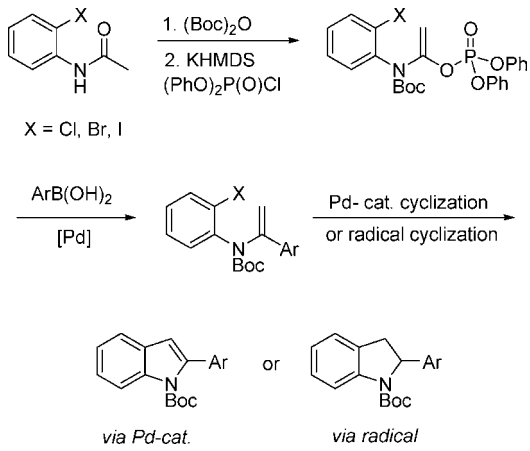
Recycling Procedure for the Ellman *tert*-Butanesulfinamide



A practical process for recycling the *tert*-butanesulfinyl group upon deprotection of *N*-*tert*-butanesulfinyl amines is reported by the Ellman group (*J. Org. Chem.* **2009**, *74*, 2646−2650). Treatment of *N*-*tert*-butanesulfinyl amines with HCl in CPME

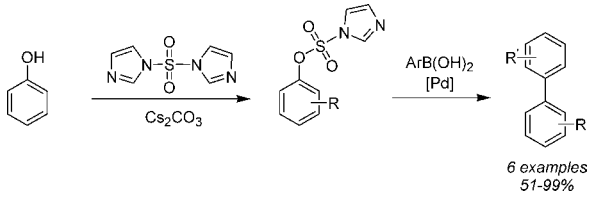
results in complete conversion to *tert*-butanesulfinyl chloride and the corresponding amine hydrochloride salt, which can be isolated by filtration. The filtrate then contains *tert*-butylsulfinyl chloride, which upon treatment with aqueous ammonia affords high-purity racemic *tert*-butanesulfinamide in 97% yield. Alternatively, the *tert*-butanesulfinyl chloride solution can be treated with ethanol and catalytic quinidine as a sulfinyl transfer catalyst to provide a CPME solution of ethyl *tert*-butanesulfinate with 88% ee. Addition of $NaNH_2$ in ammonia followed by simple trituration of the product with octane provides *tert*-butanesulfinamide with 99% ee and in 67% overall isolated yield based upon the starting *N*-*tert*-butanesulfinyl amine.

Synthesis of 2-Substituted Indoles and Indolines



New strategies for the synthesis of 2-substituted indoles and indolines are reported by Fuwa and Sasaki (*J. Org. Chem.* **2009**, *74*, 212−221). Readily available *o*-haloanilides can be acylated and then converted into enol phosphates, which are substrates for Suzuki−Miyaura coupling−cyclization sequences. After cross-coupling, the resultant substrates are precursors for 5-*endo*-*trig* Heck or 5-*endo*-*trig* aryl radical cyclizations to furnish 2-substituted indoles or indolines, respectively. Furthermore, a one-pot Suzuki−Miyaura coupling−cyclization cascade starting from enol phosphates was demonstrated and applied to the synthesis of an indol-2-yl-1*H*-quinolin-2-one KDR inhibitor.

Imadazolylsulfonates: Electrophilic Partners in Cross-Coupling Reactions

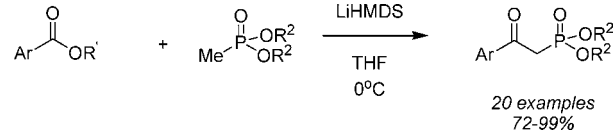


Aryl triflates generally exhibit outstanding reactivity as electrophiles in metal-catalyzed cross-coupling reactions. However, their appeal for larger-scale use is often diminished due to their cost of preparation, limited shelf life, and handling difficulties. Recently, aryl mesylates and aryl tosylates have been employed as more stable alternatives in these types of reactions, but often their reactivity is greatly diminished. A new cross-coupling strategy utilizing aryl imidazoylsulfonates has been reported by Albaneze-Walker and co-workers (*Org. Lett.*, **2009**, *11*, 1463−1466), which is designed to retain high reactivity while maintaining suitable stability and cost characteristics.

The aryl imidazoylsulfonates can be prepared in good yields (85−91%, 7 examples) from commercially available 1,1′-sulfonyldiimidazole and cesium carbonate in THF. A variety of cross-coupling reactions including Suzuki--Miyaura, Negishi-type, hydrogenolysis, and CO insertion reactions are showcased using common Pd catalysts in different solvents.

In order to compare the relative reactivity of these new electrophiles, a Suzuki--Miyaura reaction of 2-naphthyl imidazoylsulfonate and its corresponding triflate and tosylate with 4-methyl phenylboronic acid was investigated. The conversion of the imidazoylsulfonate was somewhat slower than the triflate (2.5 h for >98% completion vs 30 min), but much faster than the tosylate analogue, which was inert under the same conditions. The stability of the new imidazoylsulfonates is excellent; yields are not diminished when using compounds that had been stored at room temperature for up to 7 months. Additionally, the byproduct imidazolesulfonic acid hydrolyzes in water to produce imidazole and sulfuric acid, which circumvent the potential formation of tosic, methanesulfonic, and triflic acids sulfonates which are often flagged as potential genotoxic impurities.

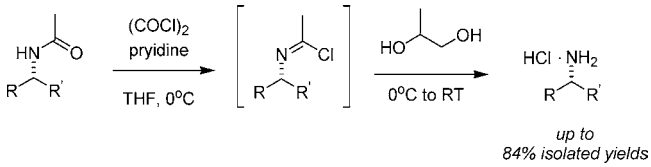
A Practical Preparation of Aryl β-Ketophosphonates



Ketophosphonates for use in Horner−Wadsworth−Emmons reactions are typically synthesized by the deprotonation of methyl dialkylphosphonates with a strong base (*n*-BuLi, LDA, etc.) followed by reaction of the ensuing anion with esters, anhydrides or acid chlorides. Unfortunately, most of these procedures require cryogenic temperatures for high yielding transformations. In order to circumvent cryogenic temperatures, a new protocol for synthesis of aryl β-ketophosphonates at 0 °C under Barbier type conditions has been reported by Milburn and co-workers at Amgen (*Tetrahedron Letters*, **2009**, *50*, 870−872). The reaction takes advantage of the remarkable stability of the $LiCH_2PO(OMe)_3$ anion generated by LiHMDS in THF at 0 °C in which the background decomposition ($t_{1/2}$ = 8 h) is much slower than in similar systems employing either LDA or *n*-BuLi.

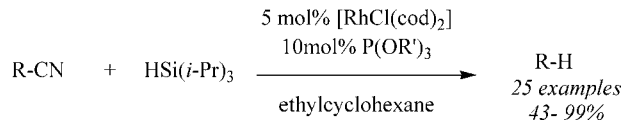
The procedure calls for deprotonation of the dialkylphosphonate (1.1 equiv) with LiHMDS (2.2 equiv) at 0 °C, followed by dropwise addition of an aryl ester. The second equivalent of LiHMDS is required to deprotonate the subsequent acidic ketophosphonate product, and in some cases advantageously allows for the direct precipitation of the lithio-ketophosphonate salt. The reaction is general and high yielding and can be utilized with most electronically activated and deactivated esters as well tolerate steric hindrance in the dialkyl portion of the $MePO(OR)_2$ or the alkyl portion of the aryl ester. The scope of the reaction is limited to aryl β-ketophosphonates, due to the propensity of esters with active α-protons to undergo Claisen condensations.

A Facile Deprotection of Secondary Acetamides



An alternative for deprotection conditions of secondary acetamides without epimerization has been described by Koenig and co-workers at Sepracor (*Org. Lett.*, **2009**, *11*, 433−436). The methodology utilizes a one pot, two-step method in which an imidoyl chloride is generated with oxalyl chloride and liberated by a diol to the amine, which is isolated as the hydrochloride salt. The authors note that the reaction proceeded well in a wide variety of solvents, but the type and equivalents of base and quenching agents play a significant role. The two bases that proved viable for the reaction were 2,6-lutidine and pyridine, while the best quenching reagent was either ethylene or propylene glycol. A variety of secondary acetamides can be deprotected in moderate to good yields. The corresponding secondary benzamides and tertiary acetamides do not react with the described system, which should allow for the selective removal of secondary acetamides in the presence of these moieties.

A Catalytic Protocol for Removal of Cyano Groups

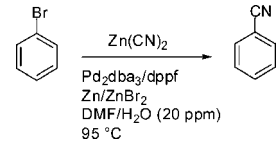


A rhodium-catalyzed reductive cleavage of carbon-cyano bonds of aryl, benzylic and alkyl cyanides has been recently described by Tobisu, Chatani and co-workers at the Osaka University in Japan (*J. Am. Chem. Soc.*, **2009**, *131*, 3174−3175). This general method employs triisopropylsilane as the reducing reagent (2 equiv) and the catalytic complex of either $[RhCl(cod)]_2$, and $P(OBu)_3$ or $P(O\text{-}i\text{-}Pr)_3$ in ethylcyclohexane. In the case of aromatic cyanides, both electron-withdrawing and electron-donating reagents are reduced in good yield while alkyl cyanides as well as primary, secondary, and tertiary benzylic cyanides are also reduced, but require higher temperatures (160 °C) at similarly long reaction times (15 h). The utility of the method might be diminished due to the high temperatures and long reaction times, but the shift from reductions with strong reducing reagents or dissolving metal reductions represents a fundamental advance for this transformation.

Insights Into Palladium-Catalyzed Cyanation of Bromobenzene: Additive Effects on the Rate-Limiting Step

Over the past few years, the metal-catalyzed cyanation of aryl halides has received much attention as a broad synthetic method for the preparation of substituted benzonitriles. Benzonitriles are important building blocks of natural products, agrochemicals, and pharmaceutical products with interesting biological properties. Prior studies of palladium-catalyzed cyanation reactions revealed that catalyst deactivation was dependent on the concentration of dissolved cyanide species, which can form unreactive complexes.

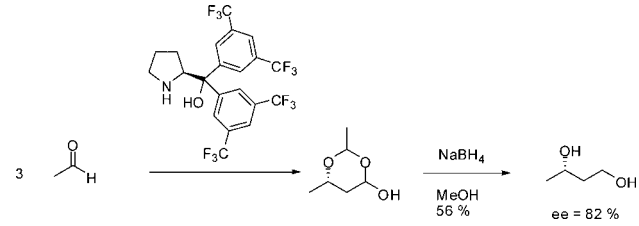
Kinetic studies using reaction calorimetry were conducted (Buono, F. G.; et al. *Org. Lett*, **2008**, *10*, 5325.) under synthetically relevant conditions to study the effect of additives in the cyanation of bromobenzene catalyzed by palladium complexes. This work demonstrates that the addition of a catalytic amount of $ZnBr_2$ facilitates the reaction with an elimination of the induction period observed without additive. This study afforded also a qualitative assessment of the effect of water on the rate-limiting step and the apparent reaction order in bromobenzene.



Asymmetric, Catalytic, and Direct Self-Aldol Reaction of Acetaldehyde Catalyzed by Diarylprolinol

The aldol reaction is one of the most important synthetic transformations in organic synthesis, and several asymmetric and catalytic versions have been developed. The direct aldol reaction of acetaldehyde, which affords synthetically useful α,α-unsubstituted β-hydroxy aldehyde, is regarded as a difficult transformation because the generated aldehyde acts both as a reactive electrophile and as a nucleophile, causing overreactions.

An asymmetric, catalytic, and direct self-aldol reaction of acetaldehyde catalyzed by diarylprolinol in NMP afforded the trimer acetal, generated by the reaction of the self-aldol product with another acetaldehyde molecule in a moderate yield with good enantioselectivity (Hayashi, Y. *Org. Lett*, **2008**, *10*, 5581.). Acetal **1** is the synthetic equivalent of the self-aldol product, which can be converted into other synthetically useful compounds in one pot without compromising the enantioselectivity.

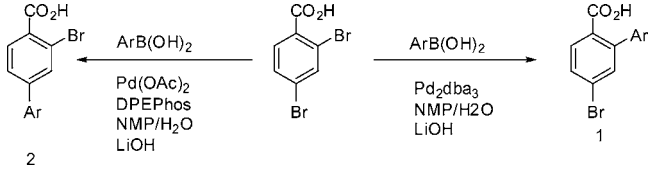


Carboxylate-Directed Cross-Coupling Reactions in the Synthesis of Trisubstituted Benzoic Acids

Directed processes, i.e., the use of neighboring groups to control either the face or regioselectivity of organic transformations, have been an indispensable tool for synthetic organic chemists. More recently, this strategy has been used to provide elegant solutions to the problem of selective C−H activation. A significant number of seminal papers has detailed the use of nitrogen groups to direct the insertion of transition metals to the C−H bond followed by other transformations. Surprisingly, the more synthetically versatile carboxylate function had been under-represented in these processes until J.-Q. Yu published a series of innovative papers demonstrating the powerful directing effect of the carboxylate in cross-coupling and directed

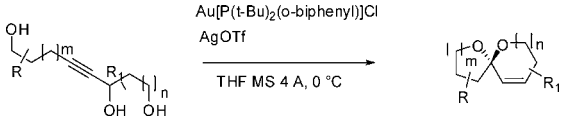
halogenation reactions (Yu, J. Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215.).

The carboxylate anion has been used (Houpis, I. N.; et al. *Org. Lett*, **2008**, *10*, 5601.) as a directing group to effect selective ortho-substituted derivatives **1** (>99:1 selectivity 50−80% yield). The solvent, base, and equivalents of base are the determining factors for the success of this reaction. The directing effect can be reversed by the appropriate use of phosphine ligands to prepare the para-substituted **2** selectively (~12:1 selectivity).



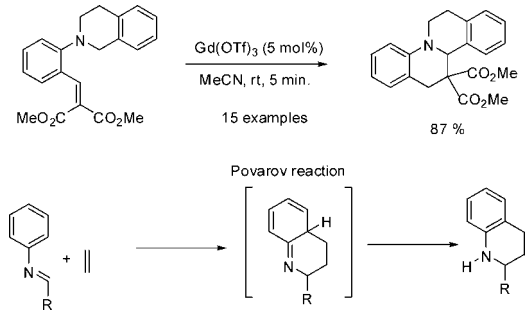
Au-Catalyzed Cyclization of Monopropargylic Triols: An Expedient Synthesis of Mono-unsaturated Spiroketals

Spiroketals are a common motif found in many structurally interesting and biologically significant natural products. In addition to the fully saturated analogues, numerous families of natural products with olefin-containing spiroketals have been reported The gold-catalyzed cyclization of monopropargylic triols to form olefin-containing spiroketals has been reported by Aponick, A.; et al. (*Org. Lett*, **2009**, *11*, 121.). The reactions are rapid and high yielding when 2 mol % of the catalyst, generated in situ from Au[P(*t*-Bu)2(*o*-biphenyl)]Cl and AgOTf is employed in THF at 0 °C. A range of differentially substituted triols leading to substituted 5- and 6-membered ring spiroketals were prepared through the reaction.



Lewis Acid-Catalyzed Formation of Tetrahydroquinolines via an Intramolecular Redox Process

Tetrahydroquinolines have attracted considerable attention due to their diverse array of biological activities. Common methods for the synthesis of tetrahydroquinolines include the Povarov reaction (see scheme). For a recent review on the Povarov reaction, see: Glushkov, V. A.; Tolstikov, A. G. (*Russ. Chem. Rev.* **2008**, *77*, 137−159) and various reductions of quinolines.



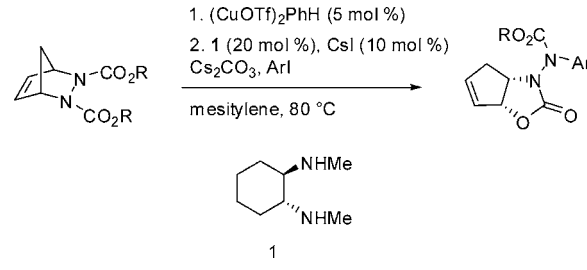
Polycyclic tetrahydroquinolines were prepared by an efficient Lewis acid-catalyzed 1,5-hydride shift, ring-closure sequence (Seidel, D.; et al. *Org. Lett*, **2009**, *11*, 129.). Gadolinium triflate was identified as a catalyst that is superior to scandium triflate as well as other Lewis acids. An approach toward a catalytic enantioselective variant has also been described giving the product in 74% yield with an ee of 30%.

Hydrophilic Ligands and Their Application in Aqueous-Phase Metal-Catalyzed Reactions

Water is the solvent of life, but the majority of synthetic organic chemistry carried out in research laboratories or industrial processes utilizes organic solvents. Organic solvents have a number of attractive features: they will dissolve a wide range of organic compounds, they come with a variety of properties, and they are often volatile and easily removed. Unfortunately, organic solvents are often toxic, flammable, and nonrenewable and have low heat capacities. In contrast, water is nontoxic and nonflammable, has a high heat capacity, and is relatively inexpensive. Of course water has some significant drawbacks as a solvent: it is a poor solvent for most organic molecules, and it is highly reactive with many classes of reagents. Because of these drawbacks, water is rarely used as a primary solvent in synthetic organic chemistry, although there is a growing body of work related to organic chemistry in water. Shaughnessy, K. H. (*Chem. Rev.* **2009**, *109*, 643.) has reviewed the design of water-soluble ligands and their properties, and how these properties affect aqueous-phase, metal-catalyzed reactions. Because the focus of this review is the design and application of water-soluble ligands, aqueous-phase catalysis using hydrophobic ligands, solid-supported catalysts, complexes that are soluble due to the metal center being ionic, and ligand-free catalysts were not covered.

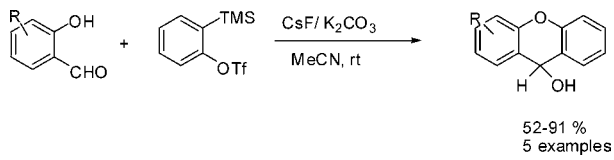
Bifunctional Reactivity of CuI: Sequential Ring-Opening/N-Arylation

The design and development of sequential processes using cheap and abundant metals is a valuable goal in modern catalysis. Low-cost metals such as copper are particularly desirable, as several oxidation states are catalysts for both Lewis acid and/or carbon−heteroatom bond-forming reactions. Copper(I) complexes in particular are highly effective Lewis acids and catalysts for N-arylation/vinylation reactions. Lautens, M.; et al. (*Org. Lett*, **2009**, *11*, 181.) report a process that exploits the Lewis acid and N-arylation activity of CuI in a sequential manner, leading to the structural revision of the ring-opening products of bicyclic hydrazines. The sequential use of a single CuI catalyst enables the one-pot synthesis of *N*′-arylaminooxazolidinones through a Lewis acid-catalyzed rearrangement followed by an *N*-arylation reaction.



Reaction of Benzyne with Salicylaldehydes: General Synthesis of Xanthenes, Xanthones, and Xanthols

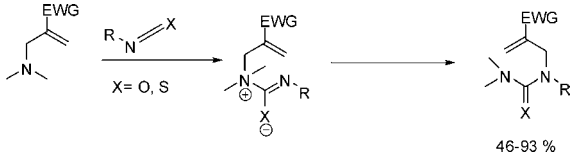
Arynes are highly reactive intermediates that have found numerous applications in organic synthesis. The reaction of salicylaldehydes with benzyne prepared from *o*-trimethylsilylphenyl triflate and CsF gave xanthenes and xanthones (Okuma, K.; et al. *Org. Lett*, **2009**, *11*, 169.). When the reaction was carried out under basic conditions, 9-hydroxyxanthenes (xanthols) were obtained in good yields.



52-91 %
5 examples

Facile 1,3-diaza-Claisen Rearrangements of Tertiary Allylic Amines Bearing an Electron-Deficient Alkene

Tertiary allylic amines with an electron-deficient alkene react with isocyanates and isothiocyanates to give highly substituted ureas and thioureas arising from formal 1,3-diaza-Claisen rearrangements (Aranha, R. M.; et al. *Org. Lett*, **2009**, *11*, 575.). Isocyanates and isothiocyanates with strong electron-withdrawing groups are more reactive. Similarly, the data suggest that a stronger electron-withdrawing substituent on the alkene favors a faster reaction, but this may be offset by sterics in the cyclic transition state.

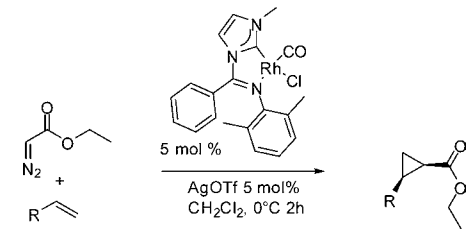


46-93 %

Highly *cis*-Selective Cyclopropanations with Ethyl Diazoacetate Using a Novel Rh(I) Catalyst with a Chelating N-Heterocyclic Iminocarbene Ligand

Cyclopropanes are important substructures in many biologically active compounds. Metal-catalyzed cyclopropanation reactions of substituted styrenes with ethyl diazoacetate are well-known. In such a reaction, two new stereogenic centers are formed, leading to two diastereomeric products. One challenge in intermolecular cyclopropanation reactions can be to control which diastereomer is formed. Many catalysts have been developed that are selective for formation of the thermodynamically favored *trans*-isomer. There are, however, only few reports on *cis*-selective catalysts for this type of reaction. Among these is a Cu(I) homoscorpionate catalyst that gives very good yields and high *cis*-selectivity in the reaction between ethyl diazoacetate and styrene.

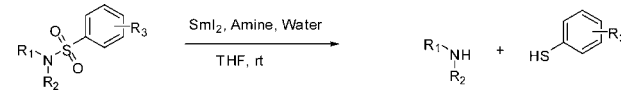
A structurally characterized Rh(I) iminocarbene complex (N,C)Rh(CO)Cl has been reported by Tilset, M.; et al. (*Org. Lett*, **2009**, *11*, 547.). The complex is activated with AgOTf to act as a highly *cis*-selective catalyst for the cyclopropanation of substituted styrenes and other alkenes with ethyl diazoacetate (11 examples, 10−99% yield, up to >99% *cis*-selectivity).



Instantaneous Deprotection of Tosylamides and Esters with SmI_2/ Amine/Water

Protection and subsequent deprotection of amines and alcohols is a routine procedure employed in almost any multistep synthesis, and one of the most versatile protecting groups for amines and alcohols is based on sulfonamide/ester formation. The sulfone amides and sulfone esters display desirable properties such as stability under a range of reaction conditions and ease of purification. However, the robustness, especially for the tosyl amides derived from alkylamines, can be a major disadvantage since it can be notoriously difficult to efficiently deprotect the amines.

SmI_2/amine/water mediates instantaneous cleavage of tosyl amides and tosyl esters (Ankner, T.; Hilmersson, G. *Org. Lett*, **2009**, *11*, 503.). Highly hindered, sensitive, and functionalized substrates were successfully deprotected in near quantitative yield. Mainly pyrrolidine or triethylamine were used as the amine. The method appears to be general and give high yields with all substrates tested including sterically hindered aliphatic tosyl amides as well as highly sensitive ones like the tosylated aziridines.



"Microencapsulated" and Related Catalysts for Organic Chemistry and Organic Synthesis

As a new method for immobilizing metal catalysts onto polymers, the microencapsulation method was first introduced in 1998. Before that, microcapsules had been used for coating and isolating substances until their activity is needed. Their application to medicine and pharmacy was extensively studied. The idea of the new method is to apply the microencapsulation technique for immobilization of catalysts onto polymers. The catalysts were new types of heterogeneous catalysts and were named as "microencapsulated (MC) catalysts". Microcapsules in these catalysts are backbones of immobilized catalysts such as cross-linked polymers and inorganic materials such as silica gel and alumina, and thus are completely different from conventional microcapsules that are used for protection. After that, polymer incarcerated (PI) catalysts, which are more robust against many solvents, were developed based on the MC technique.

In a review Akiyama, R.; Kobayashi, S. (*Chem. Rev.* **2009**, *109*, 594.) have described such unprecedented polymer-supported catalysts as MC catalysts and PI catalysts, which can create recoverable, reusable, and highly active heterogeneous metal catalysts for several organic reactions. While MC and PI catalysts are heterogeneous catalysts, they are very different from conventional heterogeneous catalysts in many aspects.

Therefore, more details of these catalysts have been described in the review.

Characterization, Selection, and Development of an Orally Dosed Drug Polymorph from an Enantiotropically Related System

Polymorph selection in drug development is complicated in enantiotropic systems, especially when the transition temperature is close to room temperature. An extensive report describing such an effort was published by a team from GlaxoSmithKline (Katrincic, L.M.; et al. *Int. J. Pharm.* **2009**, 366, 1). The molecule investigated was {4-(4-chloro-3-fluorophenyl)-2-[4-(methyloxy)phenyl]-1,3-thiazol-5-yl}acetic acid, considered for treatment of overactive bladder by opening "big potassium channels". The team faced further challenges as a result of the decision to pursue the metatstable form at room temperature (form 2). Form 1 converts to form 2 at temperatures above 37 °C (such as accelerated stability conditions at 40 °C/75% RH). Similarly, dry milling of form 1, in the presence of lactose monohydrate excipient, led to the conversion to form 2. Interestingly, no solid-state transformation of form 2 to form 1 was observed. In addition to the need to develop a robust process to produce form 2 free of form 1, suitable analytical methods had to be developed in order to prove polymorphic purity. The team found that ^{13}C- and ^{19}F solid-state NMR methods were capable of providing the necessary accuracy (the formulation designed contains 8.3% w/w active ingredient).

Drug Delivery Technologies: The Way Forward in the New Decade

A useful review (with 103 references) describing the state-of-the-art in drug delivery technologies was published by an academic team from Spain and the United States (Martín del Valle, E. M.; et al. *Ind. Eng. Chem. Res.*, **2009**, *48*, 2475.). Because of their complexity, drug delivery methods cannot be developed using "first principles" and a straightforward sequential approach. Deliveries for different administration routes are presented, and delivery technologies addressing new challenges are discussed. An interesting summary is presented, describing the criteria for the physicochemical properties of drug administered for different routes. Six such criteria are mentioned: molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors sites, polar surface area, number of rotatable bonds, and the calculated octanol/water partition coefficient. The delivery routes analyzed are: oral, transdermal, buccal/sublingual, nasal and vaginal. Among the objectives of future work in the field, the authors mention the development of smart materials, that are stimuli-sensitive, and can respond to subtle changes in the local cellular environment.

In Situ Measurement of Solution Concentration during the Batch Cooling Crystallization of L-Glutamic Acid using ATR-FTIR Spectroscopy Coupled with Chemometrics

After more than a decade of rather intensive research for the development of concentration measurements and predictions using ATR-FTIR one might expect that this technology is well established and, where appropriate, used routinely. The reality is more complicated, as can be seen from an academic−corporate report (Borissova, A.; et al. *Cryst. Growth Design*, **2009**, *9*, 692.). In this work, ATR-FTIR was used to measure the metastable zone width for L-glutamic acid solutions, at two scales: 500 mL and 20 L. Both seeded and unseeded batch cooling crystallization processes were investigated. L-Glutamic acid exhibits polymorphism, and the identities of the polymorphs had to be monitored during crystallizations. As expected, a challenge in routine implementation of in-process FT-IR technology is the need to develop suitable calibration models. The calibration matrix included 45 experiments, at 13 concentrations, and 6 temperatures, to cover a range of 0.02−0.42 M concentrations. The calibration model was developed using a chemometric approach (PLS). Even though the work did not focus on scale-up per se, because the investigations were carried at two different scales, the authors executed suitable chemical engineering calculations to ensure that the hydrodynamic conditions at 50 mL and 20 L can be compared meaningfully. Whereas at 50 mL scale the agitation speed employed was 300 RPM, leading to a Reynolds number of 16,539 and a tip speed of the impeller of 0.85 m/s, at 20 L scale the conditions produced by the impeller operated at 100 RPM led to a Reynolds number of 61,256, with a suitable impeller tip speed of 0.94 m/s. In unseeded experiments, probe fouling prevented the use of the AT-FTIR model for concentration predictions. Results using the same methodology were previously reported for crystallization experiments executed at 250 L scale. Future reports will describe model improvement by taking into account temperature dependency.

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