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

ARTICLE *in* ORGANIC PROCESS RESEARCH & DEVELOPMENT · SEPTEMBER 2010

Impact Factor: 2.53 · DOI: 10.1021/op100229b

6 AUTHORS, INCLUDING:

Wenyi Zhao

Jacobus pharmaceutical company

20 PUBLICATIONS **82** CITATIONS

SEE PROFILE

Trevor Laird

Scientific Update LLC

106 PUBLICATIONS **338** CITATIONS

SEE PROFILE

Andrei Zlota

The Zlota Co., LLC

33 PUBLICATIONS **37** CITATIONS

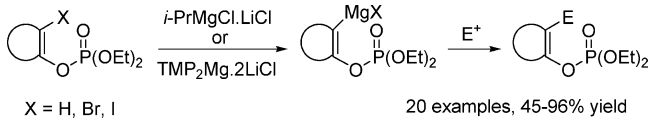
SEE PROFILE

Organic Process Research & Development **2010,** *14,* 1052–1060

Highlights from the Literature

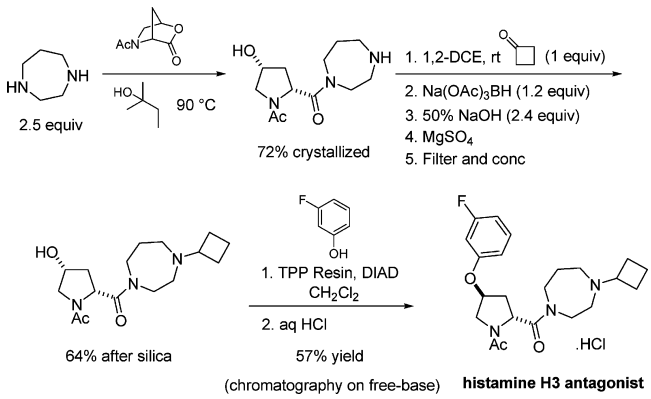
Some Items of Interest to Process R&D Chemists and Engineers

Directed Deprotonation of Cyclic Enol Phosphates



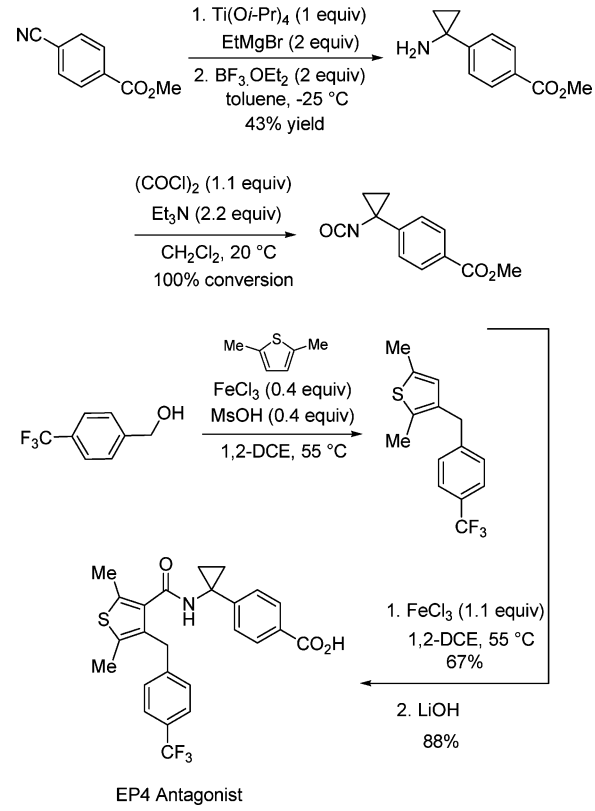
Enol phosphates have found applications as insecticides and phosphatase inactivators. Additionally, they are versatile intermediates for the regioselective preparation of substituted double bonds. Several methods have been developed allowing efficient transition-metal-catalyzed cross-coupling reactions with these electrophiles. In fact, enol phosphates are a useful synthetic alternative to the corresponding triflates since they are generally less expensive and more stable. The Knochel group reports a new method for the elaboration of enol phosphates via organomagnesium intermediates (*J. Org. Chem.* **2010**, *75*, 4365−4375). Cyclic enol phosphates can be magnesiated by a halogen/magnesium exchange reaction or by direct deprotonation using TMP-derived magnesium amide bases. The resulting magnesium reagents react readily with a wide range of electrophiles such as allyl bromides and acid chlorides or can be used in Pd-catalyzed cross-coupling reactions. Several optically pure enol phosphates were prepared, starting from readily available D-(+)-camphor derivatives.

Synthesis of a Histamine H3 Antagonist



Histamine H3 antagonists have the potential to play a therapeutic role in a range of CNS disorders, including narcolepsy, cognition, attention-deficit hyperactivity disorder, and suppression of food intake. Pippel and co-workers at Johnson and Johnson describe their efforts to develop a synthetic route suitable for the preparation of multigram quantities of active pharmaceutical ingredient (API) required to support early preclinical toleration studies (*J. Org. Chem.* **2010**, *75*, 4463−4471). The new synthesis consists of four steps and starts from the inexpensive naturally occurring trans-4-hydroxy-L-proline. This choice of raw material necessitates stereochemical inversions at two centers, accomplished via La Rosa's lactone and a late-stage Mitsonobu reaction. As is common for routes used for early small-scale deliveries, chromatographic purification was needed to obtain one particular intermediate in adequate purity. Nevertheless, this route clearly satisfied the requirements of preclinical development for an expedient entry into the target compound, enabling key animal studies. A first-generation synthesis that employed *N*-Boc-diazepine was improved in a second-generation approach wherein diazepine was directly desymmetrized. Finally, the water solubility of a key intermediate necessitated the development of a nonextractive workup for the sodium triacetoxyborohydride reduction.

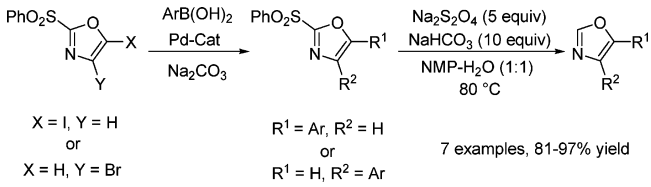
Synthesis of a Prostaglandin EP4 Receptor Antagonist



Prostaglandin EP4 inhibitors have potential as treatments for conditions associated with arachidonic acid metabolism (e.g., inflammation and atherosclerosis). The evolution of scalable, economically viable synthetic approaches to a selective prostaglandin EP4 antagonist is reported by Gauvreau and co-workers at Merck (*J. Org. Chem.* **2010**, *75*, 4078−4085). Initially the group developed a chromatography-free synthesis comprising a seven-step sequence. Subsequently, the approach was further modified in an effort to identify a long-term manufacturing route. The final synthesis avoids cryogenic (<−25 °C) conditions, comprises a total of four steps (only three of which are in the longest linear synthesis), and features the use of two consecutive iron-catalyzed Friedel−Crafts substitutions.

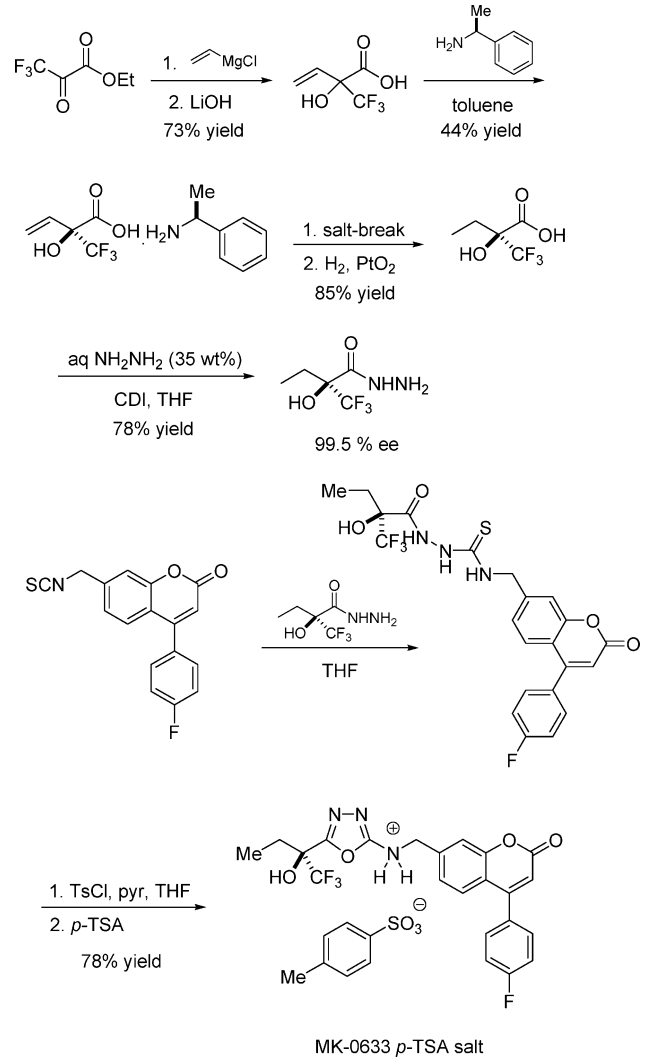
Published on Web 09/01/2010
10.1021/op100229b

Regioselective Oxazole Synthesis and Mild Desulfonylation Procedure



Oxazoles represent an important class of five-membered heterocycles that find frequent use in pharmaceutical development. The Williams group describes a method for elaboration of 2-phenylsulfonyloxazoles via established metalation/halogenation/cross-coupling strategies that are facilitated by incorporation of a blocking group at the 2-position (*Synlett* **2010**, 1641−1646). The procedure to desulfonylate the cross-coupled products is of note since it avoids the use of dissolving metal conditions typically employed to remove arylsulfonyl groups. In the case of these oxazole substrates, the researchers found that heating aqueous NMP in the presence of buffered sodium hydrosulfite (sodium dithionite $Na_2S_2O_4$) as a mild reductant was sufficient to cleave the sulfonyl group and afford high yields of the desired 2-H oxazoles.

Synthesis of a 5-Lipoxygenase Inhibitor



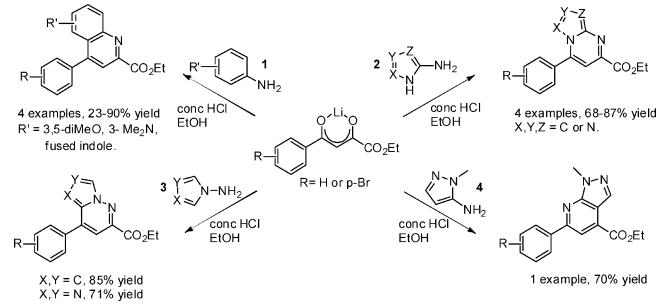
MK-0633 *p*-TSA salt

Leukotriene metabolism plays a central role in inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and atherosclerosis. In particular, the activation of the enzyme 5-lipoxygenase (5-LO) and its associated protein, 5-LO activating protein (FLAP), initiates a cascade that transforms arachidonic acid into inflammatory leukotrienes. Consequently, compounds that can inhibit 5-LO have potential as new treatments for the conditions listed above. Gosselin and coworkers at Merck describe two routes towards one such compound (MK-0633) brought forward as a development candidate at Merck (*J. Org. Chem.* **2010**, *75*, 4154−4160). The first route used an asymmetric zincate addition to ethyl 2,2,2-trifluoropyruvate followed by 1,3,4-oxadiazole formation and reductive amination as key steps. An improved second route (shown here) featured an inexpensive diastereomeric salt resolution of a vinyl hydroxy-acid followed by a through-process hydrazide acylation/1,3,4-oxadiazole ring-closure/salt-formation sequence to afford MK-0633 as the *p*-toluenesulfonate salt.

Review of Synthetic Approaches to DPP4 Inhibitors

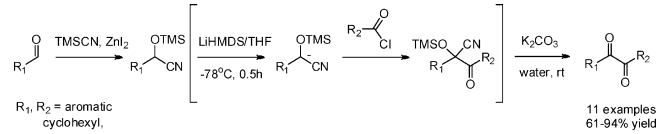
Iqbal and Pal at the University of Hyderabad in India present a Tetrahedron Report that provides an overview of DPP4 inhibitors that are currently marketed as treatments for type 2 diabetes mellitus, alongside compounds still in clinical development for the same indication (*Tetrahedron* **2010**, *66*, 4919−4938).

Lithio-benzoylpyruvates as Useful Heterocycle Precursors



Weigelt et al. (*J. Heterocycl. Chem.* **2010**, *47*, 878,) at AstraZeneca Sodertalje have demonstrated that lithiated benzoylpyruvates when quenched *in situ* with 2 equiv of conc. HCl in the presence of suitable nitrogen/nitrogen or nitrogen/carbon 1,3-bis-nucleophile yield an array of fused, substituted pyridines and pyridazines in good yield and as single regioisomers after recrystallisation. Amino-substituted indazole, pyrazole, tetrazole, and triazole gave good yields, whilst only anilines (**1**) with electron-rich substituents performed satisfactorily. In most instances the regioisomer was formed, resulting from condensation of the primary amine with the keto group α to CO_2Et. The reaction of *N*-methylpyrazole (**4**) was anomalous, yielding the fused pyridine with ring nitrogen distal to the CO_2Et group. The authors speculate that intramolecular hydrogen bonding by the carboxyethyl group and not just its electron-withdrawing properties account for the observed selectivities.

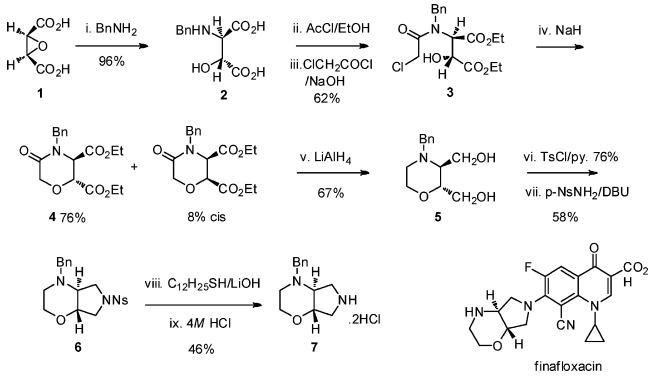
Facile Preparation of 1,2-Diketones



Nowak et al. (*Synth. Commun.* **2010**, *40*, 2164−2171) at Pfizer's (formerly Wyeth's) Pearl River facility have reported

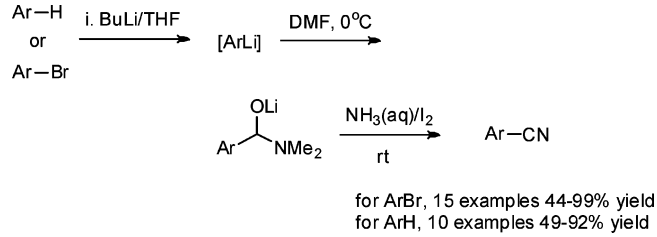
a straightforward synthesis of unsymmetrical 1,2-diketones. Existing methods such as the benzoin condensation (followed by oxidation), alkyne oxidation using NBS/wet DMSO, or permanganate alkene oxidation possess drawbacks such as availability of precursors or the potential of the cross-benzoin condensation to yield homocoupled products. With these limitations in mind the authors developed a two-step protocol to convert readily available aldehydes to unsymmetrical 1,2-diketones. TMS-protected cyanohydrins were prepared in excellent yield using TMSCN in the presence of ZnI_2. The reaction failed to proceed in the absence of this additive. Best yields in the subsequent acylation step were obtained by the use of LiHMDS as base followed by acid chloride addition. Attempts to regenerate the keto group with TBAF failed; however, simple workup with aqueous K_2CO_3 afforded the desired 1,2-diketones. Examples include both aliphatic, aromatic aldehydes and acid chlorides. 4-Pyridyl substrates were incompatible with these conditions and failed to yield any diketones.

Practical Synthesis of an Orthogonally Protected Finafloxacin Intermediate



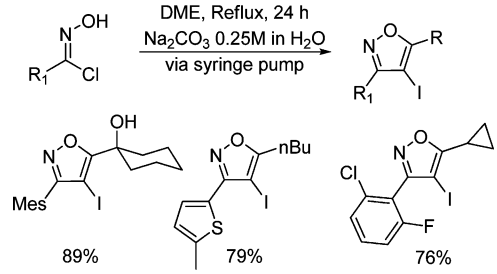
Walker et al. (*J. Heterocycl. Chem.* **2010**, *132. Prepress.*) of Pfizer (Chesterfield, U.S.A.) describe a synthesis of key finafloxacin intermediate **7** in nine steps and 6% overall yield. Thus, commercially available epoxy-succinic acid **1** was treated with benzylamine to afford *trans*-acid **2**. Subsequent esterification and acylation yielded **3** as expected. Ring closure under basic conditions lead to a mixture of *trans*- and unwanted *cis*-diesters. The authors demonstrated that a pure sample of *trans*-**4** subjected to the reaction conditions lead to epimerization as seen. Fortunately, the minor *cis*-stereoisomer could be removed by simple trituration in hexane/ether. Reduction with excess $LiAlH_4$ afforded diol **5**; this material was then bis-tosylated under standard conditions. To introduce a second orthogonally protected amine the authors employed Fukuyama's 4-nitrobenzenesulfonamide methodology to yield **6** in modest 58% yield (2-$NsNH_2$ performed less well in this cyclisation giving 20% cyclisation product). Cleavage of the Ns-group was achieved using dodecanethiol in presence of LiOH, however ~15% of the byproduct from thiol displacement of the 4-nitro group was also isolated. Subsequent hydrogen chloride salt formation completed the synthesis of desired intermediate **7**.

One-Pot Conversion of Aryl Halides and Aromatics to Nitriles

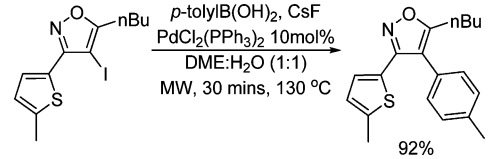


Togo et al. (*Synlett* **2010**, *10*, 1562−1566) report an efficient one-pot conversion of aromatics or aryl bromides to aromatic nitriles. The reaction proceeds via lithiation (or metal−halogen exchange in the case of the halides), trapping of the aryllithium with DMF followed by in situ quench with ammonia and iodine-mediated oxidation to the nitrile. Products were isolated by silica gel chromatography. This methodology appears general to most aryllithiums whether prepared by directed metalation or metal−halogen exchange.

Synthesis of Iodoisoxazoles from Iodoalkynes

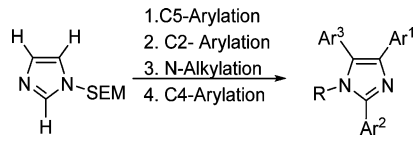


In recent years the thermal cycloaddition of alkynyl boronates utilized by Harrity has increased in use for synthesis of novel aromatic and heteroaromatic boronic esters. Herein, we find a new substrate synthesis to similar heterocycles by Browne using alkynyl iodides to synthesise heavily substituted iodoisoxazoles (*J. Org. Chem.* **2010**, *75*, 5414−5416).

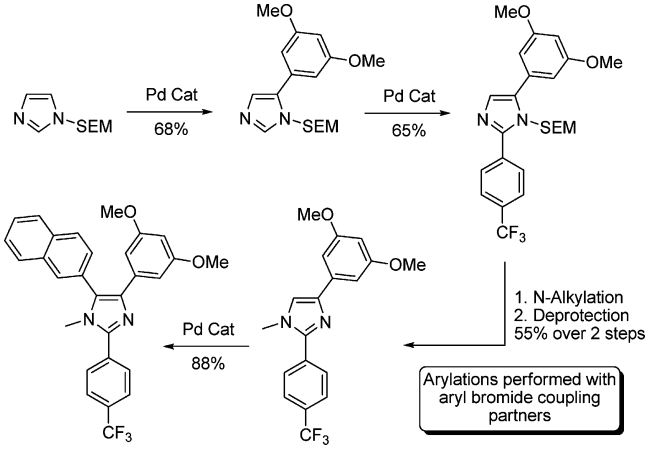


In relation to the cycloaddition step high levels of regioselectivity are observed for R_1 = ortho-substituted aromatic and heteroaromatic groups. With a range of iodoisoxazoles in hand Browne then turned his hand to the Suzuki−Miyaura coupling reaction and found that previously reported conditions for the coupling of 4-halo-isoxazoles were not compatible with his system. Instead, more forcing conditions were utilized for the coupling of *p*-tolyl boronic acid, giving rise to products with varying pendant motifs. The only question raised is to the thermal stability of alkynyl iodides and perhaps a thermal hazards study on the reaction may need to be performed if this technique were to be scaled up to deliver multiple grams of the iodoisoxazoles.

A General Approach to Complex Arylated Imidazoles

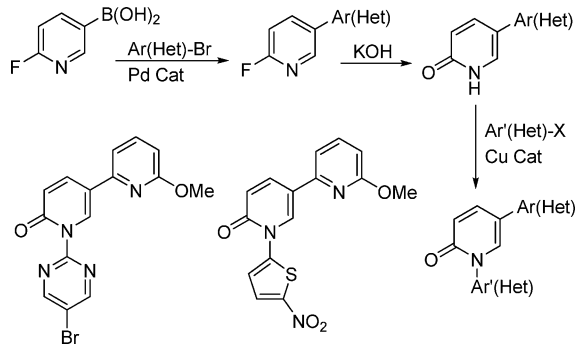


In this paper Sames describes a general and comprehensive approach for the synthesis of complex aryl imidazoles, where all three C−H bonds of the imidazole core can be arylated in a regioselective and sequential manner (*J. Org. Chem.* **2010**, *75*, 4911−4920). The particular strength of this strategy is the flexibility with which the *N*-alkyl groups can be introduced in a regioselective manner at various stages of the arylation sequence. Another important advance this paper brings is that both C5- and C2-arylation reactions can be carried out with low-cost and readily available aryl chloride donors. Of particular note is that the use of aryl iodide donors for the C5- and C2-arylation give poor conversion. The pivotal key to the regioselective construction of the substituted imidazoles is the use of the SEM protecting group and its transposition across the molecule to generate a substitution pattern that is often prevented due to the steric control that normally governs imidazole alkylation.



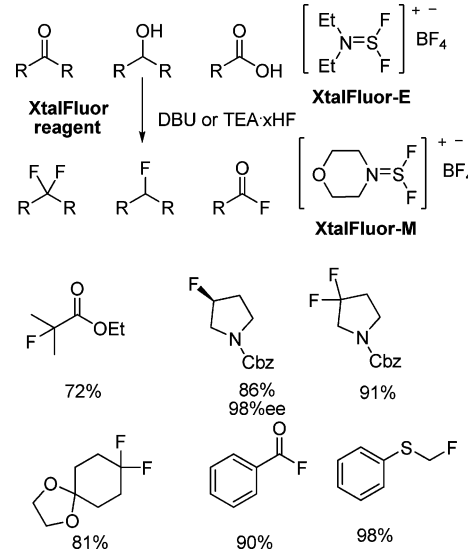
To demonstrate the ability to build complex molecules and the potential use in library synthesis Sames constructs a triaryl imidazole using sequential palladium couplings.

Divergent Synthesis of Arylated Pyridin-2(1*H*)-ones



Recently, Bryce and co-workers have been developing routes to triheteroaryl systems due to their wide usage in pharmaceuticals, agrochemicals, and coordination chemistry (*Tetrahedron* **2010**, *66*, 6138−6149). With a wide range of methods available for their synthesis generally showing low-yielding reactions and poor functional group tolerance, Bryce decided to devise a route starting with the commercially available 2-fluoro-5-pyridylboronic acid. Pleasingly, Bryce et al. found that the starting boronic acid coupled to a wide range of aryl and heteroaryl bromides in yields greater than 80%. With the material in hand a simple KOH hydrolysis of the fluoropyridine gave rise to the pyridone. They then turned their attention to the selective *N*-alkylation; initial attempts gave a mix of *O*- and *N*-alkylation. After screening a number of conditions Buchwald's *N,N*′-dimethylcyclohexane-1,2-diamine ligand with copper iodide and potassium carbonate in toluene was found to give a 95% ratio of *N*- vs *O*-alkylation. What Bryce et al. have shown in this paper is an efficient and flexible procedure to triheteroaryl systems.

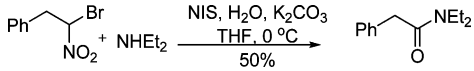
Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling



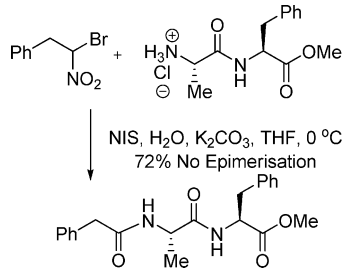
In a joint collaboration lead by Couturier of Omegachem two new fluorinating agents that have enhanced thermal stability and ease of handling over and above the previous standards set by Deoxo-Fluor, Dast and their analogues (*J. Org. Chem.* **2010**, *75*, 3401−3411) have been discovered and commercialized. This group had previously reported the use of dialkylaminodifluorosulfinium salts for deoxyfluorination reactions. However, they had found these to be very hygroscopic. This problem was elevated by a recrystallisation from dichloroethane which gave rise to more stable polymorphs of the reagents. Moreover, the type-two polymorphs are less moisture sensitive, exhibit superior handling properties, and are storage stable. With the materials in hand a thermal hazards study was performed, and it was shown that the XtalFluor reagents had a higher decomposition temperature and a lower exothermic heat generated during decomposition than the Deoxo-Fluor and DAST. With the safety data in place the reagents were then reacted with a range of alcohols, ketones, and carboxylic acids to give a range of fluoro, gem difluoro, and acid fluoride compounds. The authors found during their studies that to promote the reactions an additive such as triethylamine trihydrofluoride is

required; this is beneficial as no free HF is generated which means that, unlike Olah's with reagent, the reaction can be carried out in borosilicate glassware.

New Route to Amide Formation



A new reaction developed by Johnston that uses an atypical starting material to create amide linkages could make it easier to prepare peptides and other amide-containing compounds that have been difficult to make until now. The reaction works completely differently from conventional amide syntheses and provides better enantioselectivities in some cases (*Nature* **2010**, *465*, 1027).



The researchers demonstrated the capabilities of the umpolung approach by reacting aryl glycine (acyl source) with amino acids (amine sources) to form amides enantioselectively. Aryl glycine is prone to base-promoted epimerization (enantiomeric conversion) in traditional amide synthesis, making it difficult to control chirality. But the new reaction does not allow epimerization and thus creates aryl glycine-based amides enantioselectively. This approach could be envisaged in the synthesis of enantiopure polypeptides and complements the current arsenal of coupling procedures available to chemists.

NMR Chemical Shifts of Trace Impurities

NMR Data for Common Contaminants in Frequently Used Deuterated Solvents

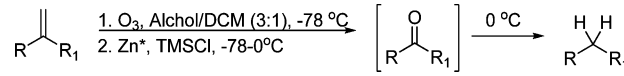
contaminant	proton	mult	THF-d_8	CD_2Cl_2	toluene-d_8	C_6D_5Cl	TFE-d_3
n-hexane	CH_3	t	0.89	0.89	0.88	0.85	0.91
	CH_2	m	1.29	1.27	1.22	1.19	1.31
hydrogen	H_2	s	4.55	4.59	4.50	4.49	4.53
imidazole	CH(2)	s	7.48	7.63	7.30	7.53	7.61
	CH(4,5)	s	6.94	7.07	6.86	7.01	7.03
methane	CH_4	s	0.19	0.21	0.17	0.15	0.18

On the desk of almost every chemist whose work heavily relies upon using NMR spectroscopy lies NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities from *J. Org. Chem.* **1997**, *62*, 7512. However, despite the utility of the work of Gottileb et al.'s work, the chemical shift values of impurities in a number of NMR solvents more commonly used by chemists today are not included. THF-d_8, CD_2Cl_2, C_6D_5Cl, and TFE-d_3 are now commonplace in multidisciplinary laboratories.

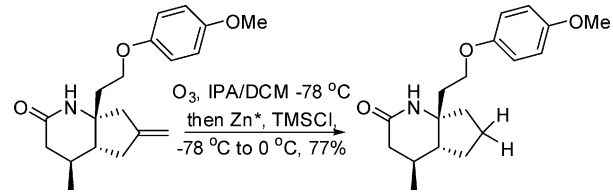
As a result of this Fulmer et al. have expanded the spectral data compilation with the inclusion of chemical shifts of common impurities recorded in deuterated solvents (*Organometallics* **2010**, *29*, 2176).

The author also reports the chemical shift values of various gases (hydrogen, methane, ethane, propane, ethylene, propylene, and carbon dioxide) often encountered in organometallic chemistry. Of note is that physically larger tables, containing all of the ^1H and $^{13}C\{^1H\}$ NMR spectral data of all substrates is available in the Supporting Information.

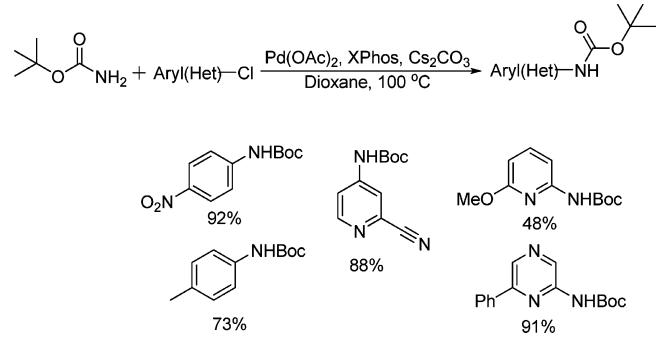
One-Pot Reductive Cleavage of *exo*-Olefin to Methylene



The reductive cleavage of an *exo*-olefin to methylene is an important transformation and so far it can only be achieved by multiple-step operations. With the current major trend in organic synthesis of step and atom economy, Arimoto has applied this principle to steroidal and heavily functionalised molecules (*Tetrahedron Lett.* **2010**, *51*, 4534−4537). Initial work was performed on the Clemmensen reduction under mild conditions where classically the transformation is performed with conc. HCl and zinc powder. The developed procedure was optimised to 10 equiv of TMSCl with 10 equiv of zinc powder. The author then turned his attention to the one-pot reductive cleavage which was performed on both simple and complex systems.



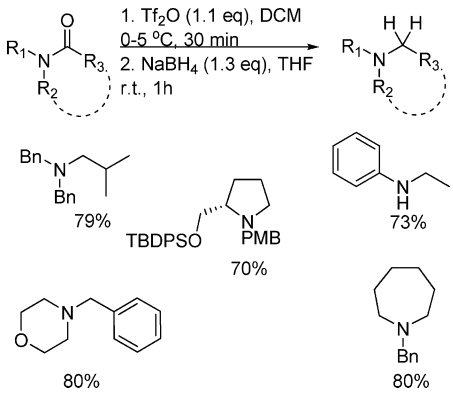
Pd-Catalyzed Amidation of Aryl(het) Halides with *tert*-Butyl Carbamate



Over the last 10 years only a number of examples of the palladium-catalyzed couplings of aryl bromides to *tert*-butyl carbamate have been reported by Hartwig and Hornberger. However, the use of aryl chlorides has not been reported until now. This work by Wu (*Tetrahedron Lett.* **2010**, *51*, 4445−4448) investigates the use of various ligands initially on aryl bromides once optimized to yields in the region of 80−97%. With the methodology developed for the aryl(het) bromides, it was then transferred to the aryl(het) chlorides. In general the yields are

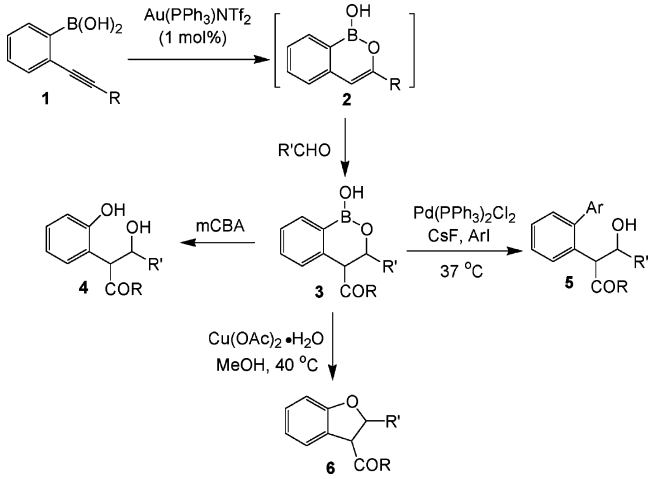
lower in the case of more sterically hindered aryl(het) chlorides and the reaction times slower than that of the bromides. However, this coupling system has been shown to work well for both electron-deficient and -rich systems.

Reduction of Amides by $NaBH_4$ under Mild Conditions



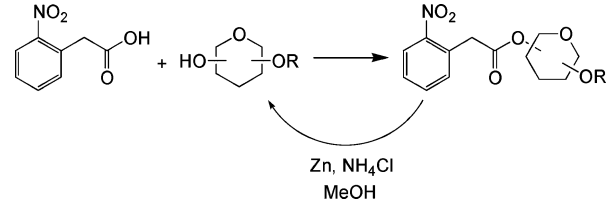
The direct reduction of amides constitutes one of the main entries into amines. Lithium aluminium hydride and diborane or borane complex are, among others, the most widely used reducing agents for amide reduction. The drawbacks to these reagents are the harsh reaction conditions and often the formation of amine complexes with the reducing agents. To circumvent this problem Huang et al. (*Synlett* **2010**, *12*, 1829−1832) have developed an amide activation protocol that can be used with commonly available reducing agents. Treatment of the amide with triflic anhydride gave rise to an activated intermediate which was subjected to a screening of reducing agents. This showed $NaBH_4$ to give the highest conversion to amine, and was followed by reaction optimization which showed, when carried out in THF, even tertiary amides can be reduced to the tertiary amine. This has proved difficult to perform using Hantzch ester reduction of the activated intermediate developed by Charette. In total Huang gives 22 examples of the reduction with yields between 70−91%.

Alternative Approach to Aldol Reaction



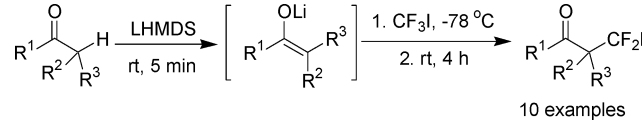
The aldol reaction is one of the most well-known methods for the formation of C−C bonds. However, the enolate often needs to be generated at low temperature in a separate flask as the enolation reaction usually lacks selectivity. In addition, the enolate thus formed is often sensitive to moisture. An elegant method was developed to conduct the aldol reaction under extremely mild conditions (*J. Am. Chem. Soc.* **2010**, *132*, 5968−5969). Treatment of **1** with PPh_3AuNTf_2 (1 mol %) led to the rapid formation of isolable boron enolates **2**. The subsequent aldol reaction of boron enolates **2** with aldehydes at room temperature gave the cyclic boronates **3** as a mixture of separable diastereoisomers. Notably, this two-step procedure can be telescoped into a one-pot process where the boron enolate **2** (R = Bu) was generated in the presence of the aldehyde (R′ = Pr), the aldol product **3** being obtained in 87% overall isolated yield (80:20 dr). Further transformations of the cyclic boronates **3** furnished phenols **4**, biaryls **5**, or 2,3-dihydrobenzofurans **6** via oxidation, Suzuki−Miyaura coupling, or Chan−Lam coupling, respectively.

(2-Nitrophenyl)acetyl: A New Hydroxyl Protecting Group



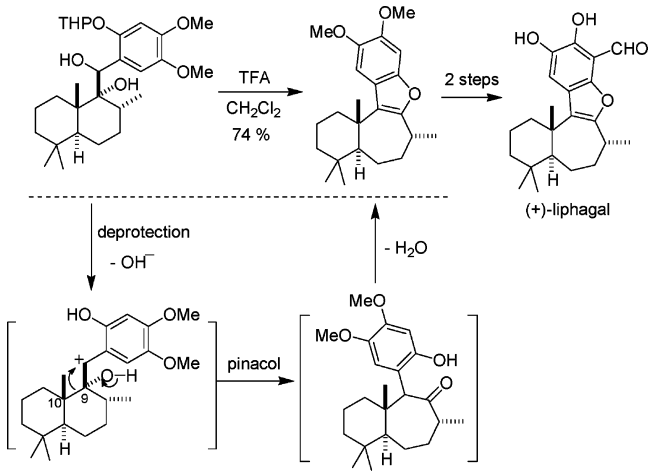
Protecting groups play an important role in organic synthesis. A good protecting group should meet the following criteria: easy installation, high selectivity, and stability under a wide range of conditions. Although an enormous number of protecting groups have been reported, only a small set meets the above criteria and are used routinely. Accordingly, the discovery of new protecting groups is welcome by synthetic chemists. (2-Nitrophenyl)acetyl (NPAc) group was demonstrated as a selectively removable hydroxyl protecting group (*Org. Lett.* **2010**, *12*, 2076−2079). The NPAc group is stable under most of the commonly used carbohydrate transformation conditions. Selective removal of the NPAc group with Zn-NH_4Cl can be accomplished in the presence of other carbohydrate protecting groups. The NPAc group is orthogonal with other hydroxyl-protecting groups, such as TBS, levulinoyl (Lev), and 9-fluorenylmethoxycarbonyl (Fmoc). Due to its advantageous properties, such as low cost, easy installation, and selective removal, NPAc group is anticipated to become a valuable tool for the protection of hydroxyl groups.

Difluoromethylation of Lithium Enolates with Trifluoromethyl Iodide



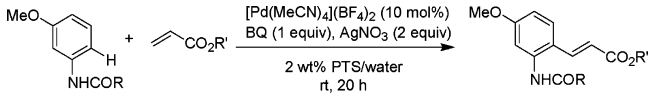
Compounds with difluoromethyl functional groups are biologically important. The synthesis of difluoroiodomethyl-substituted organic compounds was accomplished by Mikami and co-workers in Japan (*Angew. Chem., Int. Ed.* **2010**, *49*, 3819−3822) by the reactions of lithium enolates, generated in situ from ketones, esters, or amides, with trifluoromethyl iodide. Both acyclic and cyclic carbonyl substrates gave the α-difluoromethyl products in moderate to good yields.

Seven-Membered Ring Formation via Biomimetic Ring Expansion



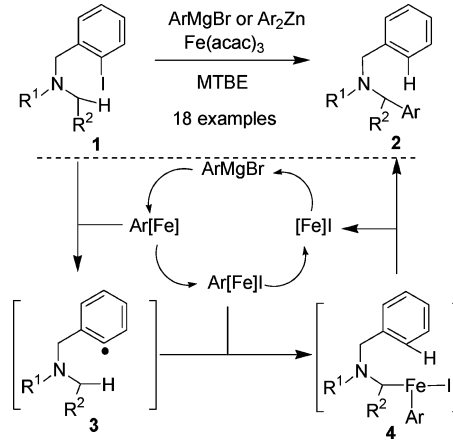
Pinacol rearrangements are frequently employed in the construction of complex molecular skeletons under acidic conditions. For example, a pinacol rearrangement has been incorporated into a 13-step synthesis of (+)-liphagal. The key step of biomimetic ring expansion furnished the desired tetracyclic ring system (*Org. Lett.* **2010**, *12*, 2394−2397). Mechanistically, this reaction presumably proceeds via initial removal of the labile phenolic THP group, followed by a facile dehydration to generate a benzylic carbocation. A subsequent pinacol rearrangement of this transient intermediate via selective cleavage of the C(9)−C(10) bond gives the cycloheptanone which, in turn, undergoes addition and dehydration to form the benzofuran.

A Mild Pd(II)-Catalyzed Fujiwara−Moritani Reaction in Water



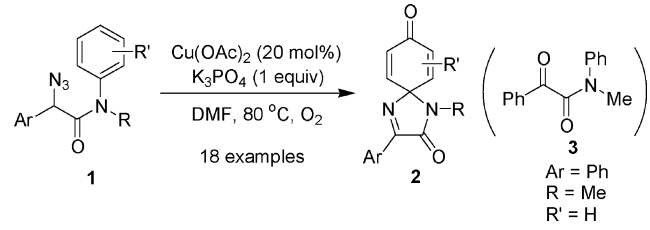
Fujiwara−Moritani reactions are usually carried out at elevated temperature (80−160 °C) under anhydrous acidic conditions. A new development, released by Nishikata and Lipshutz at the University of California, Santa Barbara (*Org. Lett.* **2010**, *12*, 1972−1975), demonstrated that the Fujiwara−Moritani reactions could be run at room temperature without addition of external acid. Additionally, water was used as reaction solvent in the presence of surfactant polyoxyethanyl α-tocopheryl sebacate (PTS). 1,4-Benzoquinone (BQ) and a silver salt ($AgNO_3$) were employed to oxidize Pd(0) back to Pd(II), notwithstanding the potential for BQ to competitively ligate Pd(II).

Iron-Catalyzed α-Arylation of Aliphatic Amines



Nakamura's group in Japan has reported a novel α-arylation reaction of aliphatic amines **1** to give products **2** (*J. Am. Chem. Soc.* **2010**, *132*, 5568−5569). The formation of products **2** occurred through an iron-mediated 1,5-hydrogen atom shift of radical intermediates **3** to generate iron complexes **4**, followed by $C(sp^3)-C(sp^2)$ bond formation. The reaction is applicable to a variety of aliphatic amines such as six- and seven-membered cyclic amines as well as acyclic aliphatic amines. This reaction proceeds under simple and mild conditions in the presence of a catalytic amount of an iron salt.

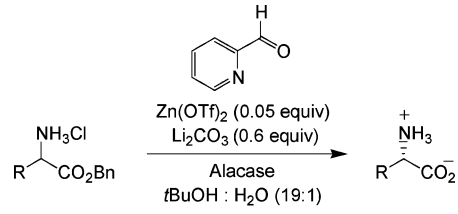
Copper(II)-Catalyzed Oxidative Cyclization



The most common method to construct spirodienone structures involves oxidative treatment of phenol derivatives. Chiba and co-workers in Singapore developed a copper-catalyzed synthesis for azaspirocyclohexadienones from α-azido-*N*-arylamides under an oxygen atmosphere (*J. Am. Chem. Soc.* **2010**, *132*, 7266−7267). This transformation favors substrates with electron-donating substituents (R′) on the aromatic ring. Good yields were obtained for both electron-rich and deficient aromatic groups (Ar). Although mechanistic details are unclear, an experiment using of $^{18}O_2$ showed that the oxygen atoms in the carbonyl group of the cyclohexadienone ring originated from O_2. Interestingly, no azaspirocyclohexadienone **2** was observed when a reaction was carried out with 1 equiv of $Cu(OAc)_2$ under an argon atmosphere; instead α-keto amide **3** (Ar = Ph, R = Me, and R′ = H) was exclusively obtained.

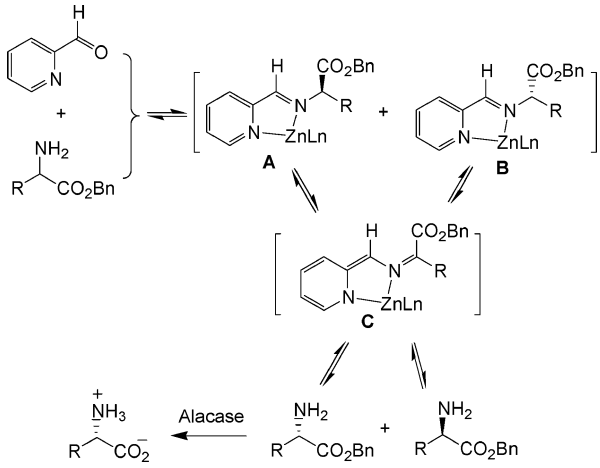
Dynamic Kinetic Resolution of Amino Acids

The use of biomimetic catalysts is considered an attractive technology for dynamic kinetic resolutions because of low cost



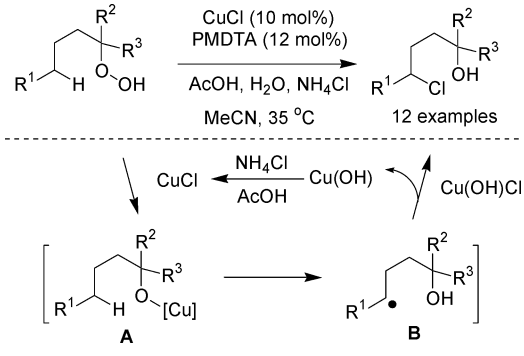
R	Yield of amino acid, %	ee %
$C_6H_5CH_2$	79	>98
4-$HOC_6H_4CH_2$	63	>98
$(CH_3)_2CHCH_2$	77	>98
$CH_3CH_2CH_2$	89	64
$CH_3(CH_2)_2CH_2$	75	>98

and environmentally benign conditions. Dynamic kinetic resolution of amino acids was reported by Aron and co-workers at Indiana University (*Org. Lett.* **2010**, *12*, 1916−1919). Reactions were carried out at room temperature in the presence of 0.6 equiv of Li_2CO_3, aldehyde (0.1 equiv), and $Zn(OTf)_2$ (0.05 equiv), furnishing the desired amino acids in fairly good yield with high chiral purity. The in situ formed Zn−picolinaldehyde complex was identified as a low cost and environmentally benign catalyst, providing high reaction rates and turnovers for the racemization of amino acids.



Mechanistically, the dynamic kinetic resolution was presumably realized by an equilibrium between **A** (or **B**) and **C** wherein the metal binding would facilitate Schiff base formation.

Copper-Catalyzed Chlorination of Remote C(sp^3)−H Bonds in Alkyl Hydroperoxides



A copper-catalyzed chlorination of remote sp^3 C−H bonds in alkyl hydroperoxides was reported by Ball and co-worker at Rice University, Houston, Texas (*Org. Lett.* **2010**, *12*, 2460−2463). This transformation involves an internal redox process wherein ammonium chloride was employed as the chlorine source without external redox reagents. The combination of CuCl and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) as ligand in the presence of acetic acid provided the chloro alcohols in moderate to good yields. Mechanistically, the catalytic process was hypothesized to occur via an alkoxy copper(III) **A** whose 1,5-hydrogen atom abstraction then provides intermediate radicals **B**. The following radical reaction with copper(II) species [Cu(OH)Cl] furnishes the observed products. Acetic acid is essential to facilitate the regeneration of CuCl via a reaction of the initially formed copper(I) hydroxide with ammonium chloride.

The Utility of Sulfonate Salts in Drug Development

Potential genotoxic impurities have been scrutinized very carefully in the last several years, with sulfonate esters amongst the compounds that led to considerable debate. A diverse group from several pharmaceutical companies published a review updating the status of our knowledge regarding sulfonate salts in drug development: (Elder, D. P.; et al. *J. Pharm. Sci.*, **2010**, *99* (7), 2948). One of the triggers for intensified studies of sulfonate salts was the European Medicines Agency suspension of the marketing authorization in 2007 for Viracept (nelfinavir mesylate). The conservative approach of avoiding sulfonate salts in drug development altogether proves to be quite impractical, especially for the cases of very low solubility APIs. Careful mechanistic studies also showed that the elevated levels of ethyl methanesulfonate found in the Viracept drug product were the result of (atypical) ethanol contamination of the starting methanesulfonic acid. This paper reviews in detail the advantages of sulfonate salts compared to other salts used in drug development. The authors comment that the number of sulfonates used in the development of new chemical entities has doubled during 1993−2006 compared to the period up to 1993. Sulfonates have the advantage of originating from strong acids, exhibiting high melting points (relative high stability), and having a lower propensity for polymorph and hydrate formation. Given the possibility to manipulate the side chains, the solubility of sulfonate salts can be designed to meet various targets (both high and low). Several surprising cases where a sulfonate salt was selected in preference to a halide salt are mentioned. Five strategies aimed at the minimization of sulfonate ester formation are discussed. One of the main conclusions that the group reached is the sulfonate salts should not be eliminated from the list of potential salts to be investigated. The decision of which salt must be selected for a new chemical entity will continue to be a difficult one, depending on the specific molecule investigated, and often based on conflicting criteria. This review has 64 references.

Isomorphism, Disorder, and Hydration in the Crystal Structure of Racemic and Single Enantiomer Carvedilol Phosphate

Because of the impact on bioavailability, stability, and manufacturing performance, extensive understanding of the solid phases present in a solid dosage form is needed. A rather

complex example of such an understanding is described by a team from Glaxo and Academia (Vogt, F. G.; et al. *Cryst. Growth Des.* **2010**, *10*, 2713−2733) discussing racemic carvedilol phosphate, a cardiovascular drug in the market. Surprisingly, this compound exists as a solid solution of its enantiomers, a rather infrequent occurrence with organic molecular crystals. Because of twinning, in order to understand the crystal structure of the racemate, the pure enantiomers had to be prepared and analyzed. Using several analytical methods, the authors concluded that the racemate was isomorphous with the single enantiomers, also a rather infrequent occurrence. The crystal structure of the *R*-enantiomer was successfully solved. Both the racemate and the *R*-enantiomer are nonstoichiometric, hemihydrates. The mechanisms of water incorporation and dehydration were probed.

A Comparative Study of ATR-FTIR and FT-NIR Spectroscopy for In Situ Concentration Monitoring during Batch Cooling Crystallization Processes

In the quality by design (QbD) paradigm, the desired state requires real time release of the API and drug product; for API crystallization processes, this could be accomplished, among others, by using supersaturation control. A key component of such a process control scheme are the sensors (PAT tools). A study from Delft University, Albermarle, and Bruker (Kadam, S. S.; et al. *Cryst. Growth Des.* **2010**, *10*, 2629−2640) compares the value of the ATR-FTIR, MIR (medium infra-red), and FT-NIR spectroscopic methods for concentration monitoring during batch cooling crystallizations. Four systems were investigated: α-lactose/water, ammonium sulfate/water, ibuprofen/hexane, and L-glutamic acid in water. The group concluded that MIR should be the method of choice. The biggest difference identified between the two technologies is in the solubility estimation; whereas with MIR the average relative error was approximately 2%, with NIR the same error was much higher, up to 11%. An important advantage of MIR is the distinct spectral peaks, allowing for the definition of suitable regions in the development of PLS models. The team concluded that the implementation of either method is "not an easy task". Suitable preprocessing techniques are needed to compensate for spectral shifts due to temperature changes and to stress in the fiber optics. Both types of probes can exhibit fouling. The authors also included an overview of all other relevant methods for concentration monitoring.

Mark McLaughlin

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

Ian Wilson

Almac Sciences, Craigavon, Northern Ireland, BT63 5QD, U.K. E-mail: ian.wilson@almacgroup.com

Patrick Delaney

Peakdale Molecular Ltd., Peakdale Science Park, High Peak SK23 0PG, U.K. E-mail: patrick.delaney@peakdale.co.uk

Wenyi Zhao

Jacobus Pharmaceutical Company, Inc., P.O. Box 5290, Princeton, New Jersey 08540, U.S.A. E-mail: Wenyi38@hotmail.com

Trevor Laird*

Editor

Andrei Zlota

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

OP100229B