Organic Process Research & Development

Highlights from the Literature

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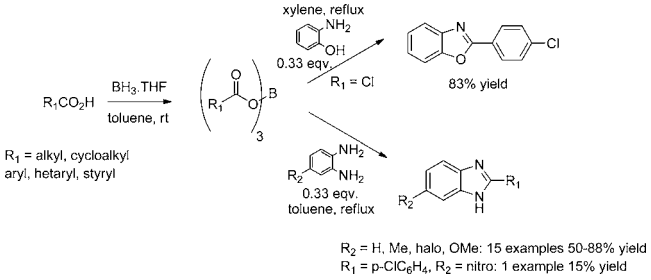
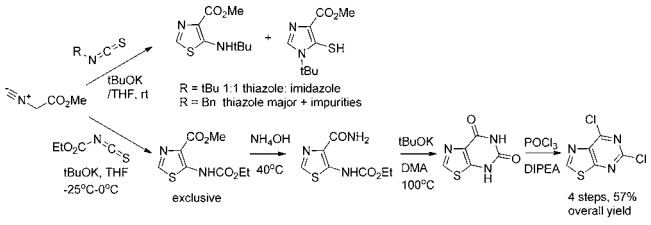
Some Items of Interest to Process R&D Chemists and Engineers

SYNTHESIS OF BENZIMIDAZOLES AND BENZOXAZOLES USING TRIACYLOXYBORANES



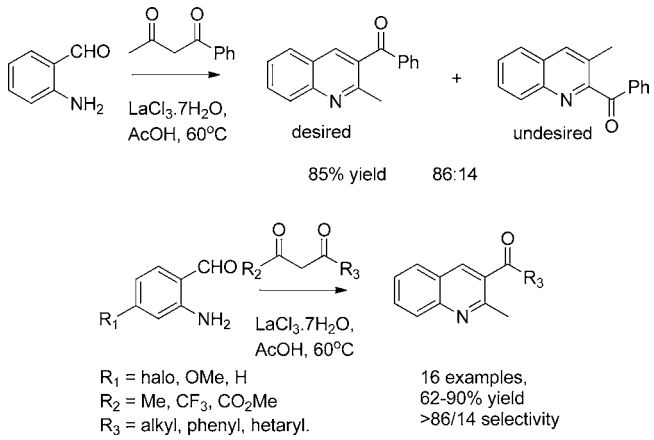
Cui et al. of AMRI have developed (*Synlett* **2012**, *23*, 247−250) an efficient synthesis of benzimidazoles and benzoxazoles by condensation of triacyloxyboranes with aromatic diamines and 2-aminophenol, respectively. In most instances the benzimidazole products were obtained in modest-to-good yield irrespective of the carboxylic acid used. However, the deactivated 4-nitrobenz-2,3-diamine (R_2 = nitro) afforded the corresponding benzimidazole in low yield. This methodology was also extended to aminophenol which yields, under more forcing conditions, the benzoxazole in good yield. Notably, acid-sensitive functional groups (e.g., Boc) were inert under these conditions.

CONVENIENT SYNTHESIS OF A DICHLOROTHIAZOLOPYRIMIDINE



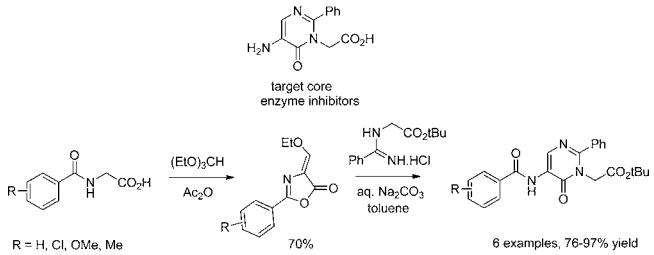
Shu and co-workers at Roche Nutley have disclosed (*Heterocycles* **2012**, *85*, 1721−1726) an improved process to 5,7-dichlorothiazolo[5,4-*d*]pyrimidine, an important building block in a drug discovery programme. Earlier syntheses in the academic and patent literature starting from uric acid proved unsuitable to scale up. The key stage to this new approach proved to be the regioselective condensation of ethoxycarbonyl isothiocyanate with methyl isocyanoacetate to yield exclusively the thiazole product. Earlier attempts with *tert*-butyl or benzyl isothiocyanate gave imidazole−thiazole mixtures or decomposition. The authors attributed the observed selectivity to lower reaction temperature and/or a stabilization effect of the electron-withdrawing ethoxycarbonyl group. Subsequent cyclization and chlorination steps concluded the synthesis in overall good yield.

REGIOSELECTIVE FRIEDLANDER REACTION USING LANTHANUM CHLORIDE



The Friedlander reaction is an established protocol for the preparation of quinolines by the condensation of a 2-aminobenzaldehyde and a 1,3-dicarbonyl compound. Chen and coworkers at Amgen (*Tetrahedron Lett.* **2012**, *53*, 3237−3241) have addressed the regioselectivity of the reaction where an unsymmetrical 1,3-dicarbonyl is used. From a screen of various Lewis acids (lanthanide triflates and chlorides), $LaCl_3$ heptahydrate (commercially available, nonhygroscopic) gave optimal results with highest yield and selectivity. High regioselectivity was observed with a range of 2-aminobenzaldehydes and 1,3-dicarbonyls. Notably, trifluoromethyl 1,3-diketones (up to 100:0 desired/undesired) gave higher selectivity than their nonfluorinated analogues.

STRAIGHFORWARD SYNTHESIS OF A PYRIMIDONE FROM HIPPURIC ACID



Takahashi and co-workers from Ajinomoto (*Heterocycles* **2012**, *85*, 1089−1103) have reported a straightforward synthesis of 5-amino-6-oxo-2-phenyl-1-pyrimidineacetic acid, an important core molecule for the preparation of nonpeptidic enzyme inhibitors. Thus, treatment of hippuric acid (R = H) with triethyl orthoformate afforded the intermediate oxazolone in good yield; subsequent treatment with an *N*-(carboxy

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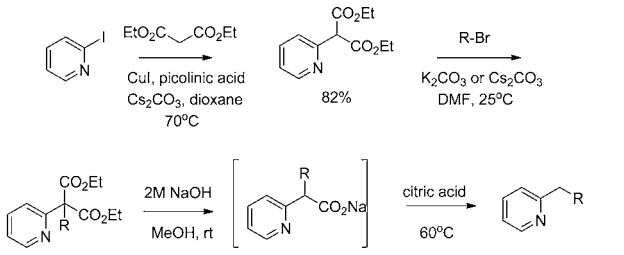
tert-butyl)benzamidine afforded the *N*-benzoyl,*tert*-butyl protected pyrimidinone in good yield. This approach provides an advantage over earlier syntheses which require Curtius or Lossen-type rearrangements to introduce the 5-amino group.

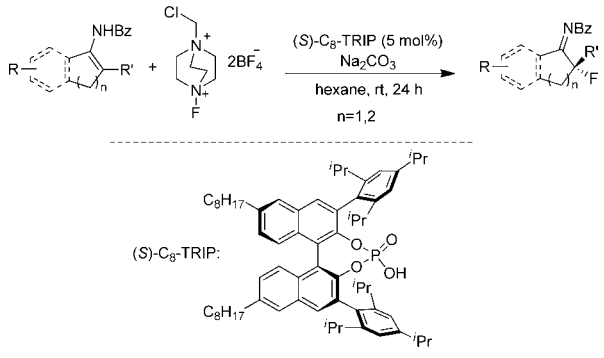
SYNTHESIS OF 2-ALKYLPYRIDINE VIA DOUBLE DECARBOXYLATION



R = allyl, benzyl, cinnamoyl, -$CH_2CH_2OTBDMS$, -CH_2CH_2OMe, -CH_2CO(cyclopropyl).

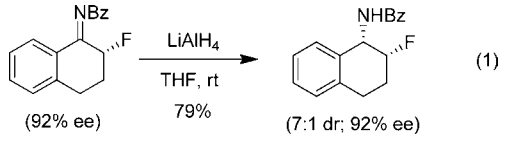
Donald and Boyd of AstraZeneca, Alderley Park, report (*Tetrahedron Lett.* **2012**, *53*, 3853−3856) an efficient approach to the preparation of a wide range of 2-alkylpyridines from 2-iodopyridine. Thus copper(I)-catalyzed coupling of diethylmalonate and 2-iodopyridine afford the desired 2-pyridylmalonate in good yield using a known established procedure. Alkylation of the malonate was performed with a range of allyl, alkyl, benzyl, and propargylic bromides to afford the disubstituted malonate in modest-to-excellent yield. Monodecarboxylation to the pyridineacetic acid proved facile using sodium hydroxide methanol. Initial attempts to effect the second decarboxylation with HCl at pH 1 failed, even with prolonged heating, but was achieved by quenching the pyridineacetic acid with citric acid at pH 4−5 and heating to 60 °C.

SYNTHESIS OF α-FLUOROIMINES VIA ASYMMETRIC FLUORINATION OF ENAMIDES USING AN ANIONIC CHIRAL PHASE-TRANSFER CATALYST

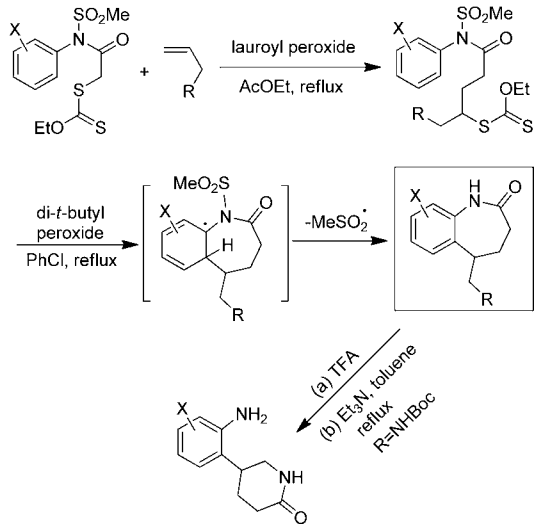


An enantioselective fluorination of enamides using Selectfluor as the fluorinating reagent was accomplished in the presence of a BINOL-derived phosphate as a chiral anionic phase-transfer catalyst to afford α-fluoroimines (*J. Am. Chem. Soc.* **2012**, *134*, 8376−8379). Reactions of indanone-derived enamides bearing 5-chloro, 5-fluoro, and 5-methoxy functional groups proceeded well under the reaction conditions. Substituents (R′) such as chloro, bromo, methyl, allyl, phenyl, and benzyl groups on the cyclic enamides were tolerated, giving the desired products in high enantiopurity.

Furthermore, it was demonstrated that the α-fluoroimines could be readily converted into the corresponding stereodefined β-fluoroamines with lithium aluminum hydride without any loss of stereochemical integrity (eq 1).



SYNTHESIS OF BENZAZEPIN-2-ONES VIA DESULFONYLATIVE RADICAL RING CLOSURE



A radical approach to benzazepin-2-ones was developed. This approach involves an intermolecular radical addition of *N*-xanthylacetyl-*N*-methanesulfanilides to allylamine followed by radical ring closure with loss of a methanesulfonyl radical (*Org. Lett* **2012**, *14*, 2018−2021). It is necessary to have a methanesulfonamide substituent as a blocking group on the nitrogen for the radical cycloaddition on the aromatic ring to occur. During the radical ring closure, the loss of the sulfonamide group eliminated the need for a subsequent deprotection step and had otherwise no deleterious effect on the rest of the sequence. The approach tolerates a wide range of substituents on the aromatic ring including both electron-donating and electron-withdrawing groups such as methoxy and trifluoromethoxy functional groups. Of particular note is the tolerance of the process to the presence of chlorine, bromine, and iodine, which opens up further avenues for diversification through numerous powerful cross-coupling reactions. Furthermore, upon deprotection of the radical cycloaddition products (R = NHBoc) and exposure to triethylamine, these compounds rearrange into 5-aryl-2-piperidones.

AN EFFICIENT SYNTHESIS OF BENZOFURO[3,2-*d*]PYRIMIDINES VIA A COPPER(I)-MEDIATED CASCADE PROCESS

A cascade reaction was developed to synthesize benzofuro[3,2-*d*]pyrimidine derivatives (*Org. Lett* **2012**, *14*, 2398−2401). The process was operated in the presence of CuBr (1.0 equiv) and DBU (2.0 equiv) in DMF at 90 °C, utilizing readily prepared 3-chlorochromenones and various commercially available amidines as starting materials. The electron-property of the

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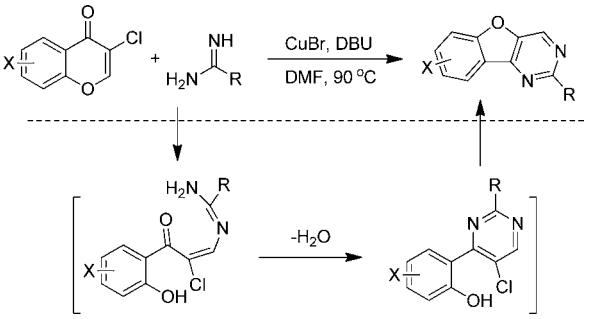
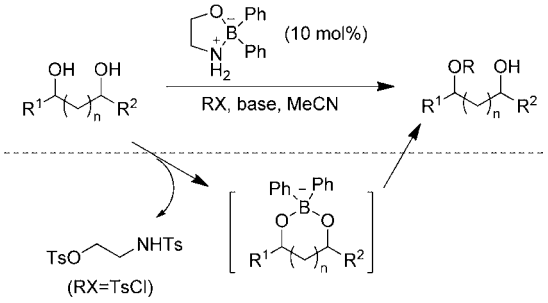


substituents on the aromatic ring of 3-chlorochromones has little effect on the reaction. For instance, substrates bearing either electron-withdrawing or electron-donating groups on the aromatic ring react equally well to form the corresponding benzofuropyrimidines in moderate to good yields. Reactions of amidines with the R substituent being an alkyl group or variously substituted aryl groups furnished the desired products in good-to-excellent yields. In contrast, changes in the R amidine substituent from alkyl (or aryl) to R = H, NH_2, or MeO resulted in low yields (27−41%).

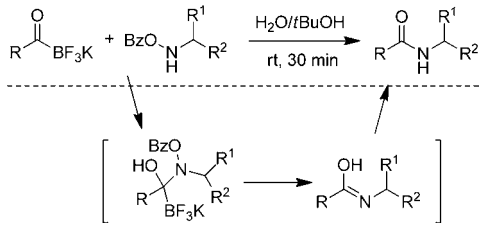
REGIOSELECTIVE, BORINIC ACID-CATALYZED MONOACYLATION, SULFONYLATION, AND ALKYLATION OF DIOLS AND CARBOHYDRATES



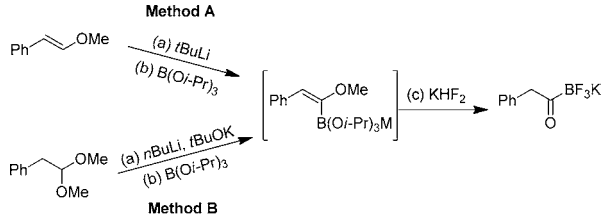
Protocols for regioselective monofunctionalization of 1,2- and 1,3-diols were developed (*J. Am. Chem. Soc* **2012**, *134*, 8260−8267). Two sets of experimental conditions were established for acylation/sulfonylation and alkylation, respectively. Using aminoethyl diphenylborinate as the precatalyst, acylation and sulfonylation were conducted in the presence Pr_2NEt as base in acetonitrile at 23 °C, while benzylation was achieved with K_2CO_3 as base and KI as additive at 60 °C. Mechanistically, the entry of aminoethyl diphenylborinate into the catalytic cycle in the sulfonylation is triggered by irreversible bis-sulfonylation of the ethanolamine ligand and binding of the diol to form an activated 'ate' complex. Using the diarylborinic acid precatalyst, various 1,2-diols including acyclic and cyclic alkanediols were monoacylated and -tosylated efficiently in high yields. Sterically hindered (−)-pinanediol was monotosylated at the secondary over the tertiary OH group. Analogously, a wide range of diols were alkylated with benzyl, 4-methoxybenzyl, and 2-naphthylmethyl groups under the optimized conditions.

AMIDE SYNTHESIS VIA CROSS-COUPLING BETWEEN ACYLTRIFLUOROBORATES AND HYDROXYLAMINES

A mild protocol for amide synthesis was developed (*Angew. Chem., Int. Ed.* **2012**, *51*, 5683−5686). The reaction was performed simply by mixing acyltrifluoroborates with *O*-benzoyl hydroxylamines in a mixture of water and *tert*-butanol

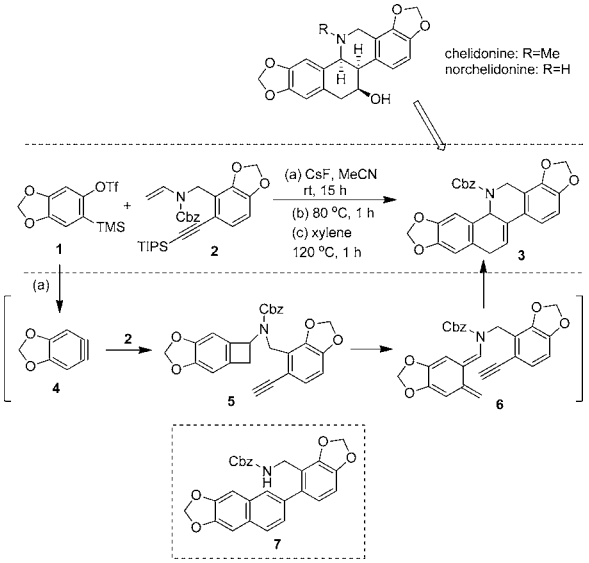


(1:1) at room temperature for 30 min, affording the amides in good to excellent yields. The reaction is compatible with various functional groups in the acyltrifluoroborates including hydroxyl group, aldehydes, carbamates, and alkyl chlorides. Analogously, the reaction was also general with respect to *O*-benzoyl hydroxylamine substrates.



The acyltrifluoroborates could be prepared through either method A or method B described in their previous publication (*J. Org. Chem* **2010**, *75*, 4304−4306).

APPLICATION OF A CYCLOADDITION TANDEM PROCESS TOWARD TOTAL SYNTHESES OF CHELIDONINE AND NORCHELIDONINE



A cycloaddition tandem approach was successfully applied toward total syntheses of chelidonine and norchelidonine, which features an intermolecular [2 + 2] enamide−benzyne cycloaddition followed by pericyclic ring-opening and subsequent intramolecular Diels−Alder reactions (*Org. Lett* **2012**, *14*, 2742−2745). Treatment of the mixture of silylaryl triflate **1** and enamide **2** with CsF at room temperature in acetonitrile followed by heating at 80 °C and subsequently at 120 °C in xylene led to **3** in 65% overall yield. Removal of acetonitrile appeared to be critical in the Diels−Alder reaction, or a ring-opened product such as **7** is generated during the heating in xylene in the presence of acetonitrile.

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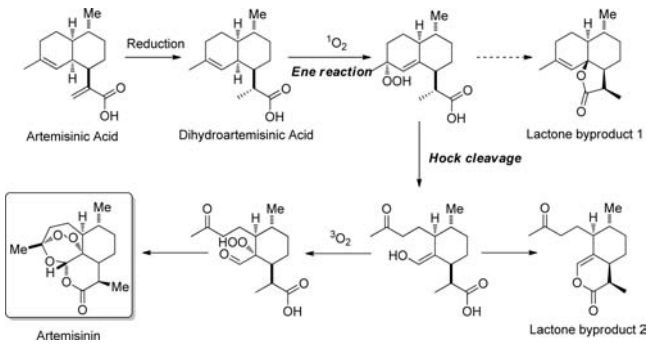
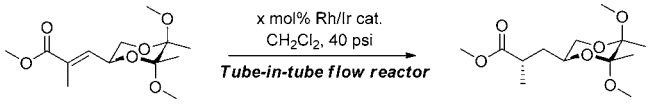
CONTINUOUS-FLOW SYNTHESIS OF THE ANTI-MALARIA DRUG ARTEMISININ



A continuous-flow synthesis of anti-malaria drug artemisinin (*Angew. Chem., Int. Ed.* **2012**, *51*, 1706−1709) reported recently by Seeberger et al. from Department for Biomolecular Systems, Max-Planck Institute for Colloids and Interfaces, was proven to be a high-yielding, scalable, and low-cost process starting from artemisinic acid. Since dihydroartemisinic acid could be conveniently derived from artemisinic acid by hydrogenation or produced by fermentation in engineered yeast, challenges for this semisynthesis are the three-step reaction sequence of photochemically induced ene reaction with singlet oxygen, acid-mediated cleavage of the O−O bond (Hock cleavage), and oxidation with triplet oxygen. This technically simple, efficient, and inexpensive synthesis is readily scalable by virtue of the continuous-flow process and does not require isolation and purification of intermediates.

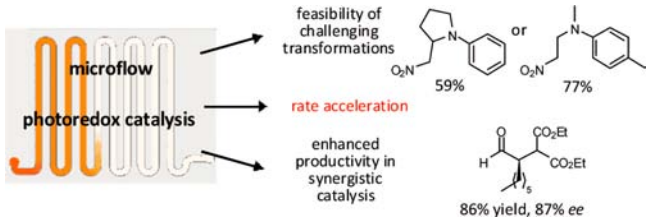
Combined with the production of artemisinic acid in engineered yeast, access to the much needed malaria drug is now possible by semisynthesis rather than isolation from plants, ensuring a steady supply of artemisinin at greatly reduced cost. The authors also estimated that approximately 1500 efficient, simple, and productive photoreactors could meet current demand of ACT treatment, with a basis of 200 g of artemisinin per day capacity from this particular setup.

ASYMMETRIC HOMOGENEOUS HYDROGENATION IN FLOW USING A TUBE-IN-TUBE REACTOR



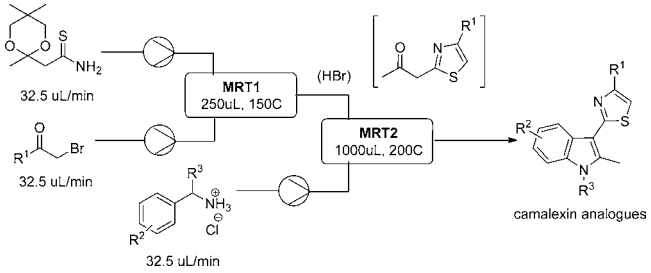
Asymmetric homogeneous hydrogenation of a number of trisubstituted olefins in a tube-in-tube gas−liquid flow reactor (*Adv. Synth. Catal.* **2012**, *354*, 1805−1812), was reported recently by Newton and Ley from University of Cambridge and their co-workers from Johnson−Matthey Catalysis and Chiral Technology. A number of chiral iridium- and rhodium-based catalysts have been tested for this asymmetric transformation. The merits of this flow setup also afford rapid screening and optimization of other reaction parameters, such as pressure, solvent, temperature, and catalyst loading. Furthermore, a comparative study using batch conditions aided in the optimization of the flow reaction setup. The authors further modified this flow setup to recycle the catalyst and prolonged the catalytic activity.

APPLICATION OF MICROFLOW CONDITIONS TO VISIBLE LIGHT PHOTOREDOX CATALYSIS



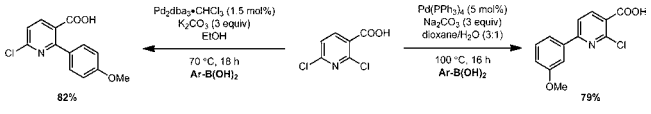
Zeitler et al. from the university of Regensburg (Germany) have successfully developed visible light photoredox catalysis under microflow conditions (*Org. Lett* **2012**, *14*, 2658−2661). By using different photocatalysts such as $[Ru(bpy)_3]^{2+}$ and Eosin Y, significant improvement of several photoredox reactions could be realized with an operationally simple microreactor and fluorinated ethylene propylene copolymer (FEP) tube reactor systems. Besides rate acceleration, this approach also facilitates previously challenging transformations of nonstabilized intermediates. Furthermore, this synergistic, catalytic enantioselective, photoredox α-alkylation of aldehydes can be easily scaled up with an increased productivity by 2 orders of magnitude, generating useful enantiopure products (up to 87% ee).

AUTOMATED MULTISTEP CONTINUOUS FLOW SYNTHESIS OF 2-(1*H*-INDOL-3-YL)THIAZOLE DERIVATIVES



Due to a broad spectrum of therapeutic areas, methodology for high-throughput synthesis of indolylthiazoles, such as tadalafil, camalexin, and BE 10988, is of significant interest. Cosford et al. from Sanford-Burnham Medical Research Institute (United States) recently reported an automated multistep continuous flow synthesis of 2-(1*H*-indol-3-yl)thiazole derivatives (*Synthesis* **2012**, *44*, DOI: 10.1055/s-0031-1290953). Sequential Hantzsch thiazole synthesis, deketalization, and Fischer indole synthesis provides rapid and efficient access to highly functionalized camalexin analogues. These complex druglike small molecules are generated within less than 15 min and in high yields (38−82% over three chemical steps without isolation of intermediates). Apart from this facile synthesis of libraries of biologically active analogues, the authors also developed an efficient one-pot (batch) procedure for the synthesis of related 2-*H*-indolylthiazoles.

CHEMO- AND SITE- SELECTIVE SUZUKI−MIYAURA COUPLING REACTIONS OF POLYHALOGENATED HETEROARENES



Selective Suzuki−Miyaura coupling reactions of polyhalogenated heteroarenes are of indispensible value to the pharmaceutical,

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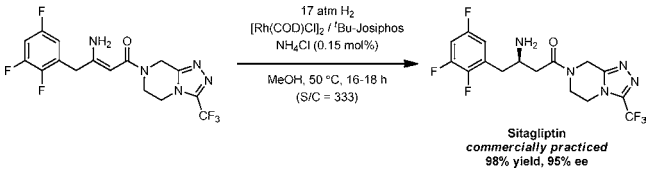
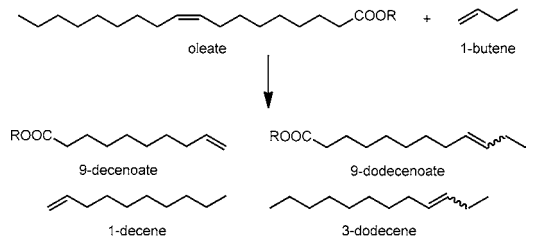
agrochemical, and electronic materials industries. The challenges faced for the development of successful examples increase exponentially in going from heteroarene substrates with different halogens to asymmetrically substituted heteroarenes with identical halogens and finally to symmetrically substituted heteroarenes with identical halogens. This field has been comprehensively reviewed by Rossi, Bellina, and Lessi (*Adv. Synth. Catal.* **2012**, *354*, 1181−1255). The review is divided into cross-coupling reactions of polyhalogenated five-membered heteroarenes, six-membered heteroarenes, and heterocycle-annulated heteroarenes; an emphasis is placed on the synthesis of polysubstituted heteroarenes via consecutive monocoupling reactions or one-pot polycoupling reactions.

TRANSITION METAL-CATALYZED ENANTIOSELECTIVE HYDROGENATION OF UNPROTECTED ENAMINES



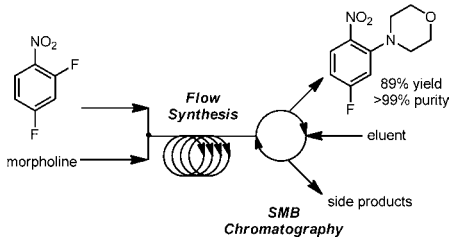
Transition metal-catalyzed enantioselective hydrogenation of *N*-acyl enamines has historically been a *tour de force* for the preparation of chiral amines. The acyl protecting group was long thought to be a prerequisite for good asymmetric inductions due to its ability to form a beneficial chelate complex with the metal of the catalyst; this strategy is inherently disadvantaged due to the protection/deprotection steps that are necessitated. A large body of research in the past decade has established several asymmetric hydrogenation protocols that successfully accept unprotected enamines as substrates; this field has been recently reviewed by Xie, Zhu, and Zhou (*Chem. Soc. Rev.* **2012**, *41*, 4126−4139). The review details successful chiral rhodium, ruthenium, and iridium catalyst systems that have been developed for unprotected *β*-enamine esters/amides and those developed for *N*-substituted enamines. A similar review has subsequently been published by Yu and co-workers as well (*Angew. Chem., Int. Ed.* **2012**, *51*, 6060−6072).

REFINING OF PLANT OILS TO CHEMICALS BY OLEFIN METATHESIS



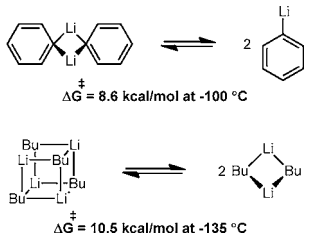
Olefin metathesis of plant oils has emerged as a potential alternative approach for the manufacture of a variety of products in the chemical industry. Two obstacles exist for application of this technology at scale: requirement of high catalyst activities as well as that technical grade plant oil is a mixture of different fatty acids which would provide a range of metathesis products thus necessitating inventive separation solutions. This emerging field has been reviewed by Mecking and Chikkali (*Angew. Chem., Int. Ed.* **2012**, *51*, 5802−5808). The review begins with various methathesis reactions of unsaturated fatty acids such as self-metathesis, ethenolysis, and alkenolysis. A major section of the review is a discussion on the large-scale industrial scenario of this technology; this includes a detailed look at a potential industrial process involving metathesis of purified plant oil with 1-butene (see scheme).

COMBINING A FLOW REACTOR AND SIMULATED MOVING BED (SMB) CHROMATOGRAPHY FOR CONTINUOUS SYNTHESIS AND PURIFICATION



Key to the development of a truly continuous process is coupling a continuous reaction with continuous downstream processing (unit operations such as workup, extraction, and purification). The benefits of a continuous reaction are quickly negated if the downstream processing is time-consuming in batch mode. Seeberger and co-workers have reported such successful coupling of flow synthesis and SMB chromatography for purification (*Angew. Chem., Int. Ed.* **2012**, *51*, 7028−7030). Nucleophilic aromatic substitution which provided a complex mixture of products was studied using a 10-mL SS loop reactor and a six-column SMB configuration; pure product in 89% yield was obtained at the steady state with a flow rate of 5 mL/min.

WHAT'S GOING ON WITH THESE LITHIUM REAGENTS?



Practicing chemistry with lithium reagents is a complex undertaking; they exist as mixtures of aggregates and frequently form new mixed aggregates during their reactions with electrophiles. The Reich group has conducted substantial research towards understanding the behavior of lithium reagents, and this work has been put in perspective by Reich (*J. Org. Chem.* **2012**, *77*, 5471−5491). They have consistently utilized multinuclear NMR experiments, using both classical as well as rapid injection NMR techniques, to understand and define solution structures and to conduct dynamic and kinetic studies. One of the many "take-home lessons" provided by Reich is that the rate-limiting step in most common reactions involving *n*-BuLi in THF is dissociation of the tetramer/hexamer mixture of *n*-BuLi in the commercial hexane solution to the active dimer; this occurs at −78 °C in under 10 min and thus makes redundant and often counter-productive the hour-long

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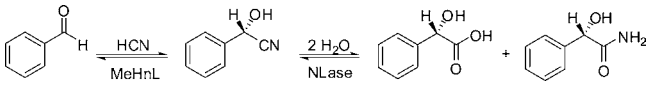
reaction times and warmup to 0 °C that most practitioners employ.

ORGANIC SOLVENT NANOFILTRATION AS A POTENTIAL ALTERNATIVE TO DISTILLATION FOR SOLVENT RECOVERY FROM CRYSTALLIZATION MOTHER LIQUORS

Distillation is the current method of choice for solvent recovery from crystallization mother liquors; however, it can be energy intensive, and for instances where thermal degradation of the active in the mother liquor or appropriate azeotrope formation are concerns, a less energy-intensive and nonthermal separation technique based on steric differences rather than volatilities can be an attractive alternate. Pink and co-workers have investigated the feasibility of organic solvent nanofiltration (OSN) for recovering isopropyl acetate from crystallization mother liquors containing the desired API as well as a complex mixture of other components (*Green Chem.* **2012**, DOI: 10.1039/c2gc35216h). Lab-scale optimization led to a pilot-scale proof of concept demonstration using a 1.8" × 12" spiral-wound Puramem280 module with a total membrane area of 0.11 m^2. To demonstrate that the purity of recovered solvent was acceptable for subsequent use, crystallizations and solvent recycles were performed for four subsequent crystallization batches, with successful results. Considering the lower volume of solvent recovery from OSN as compared to that from distillation, a hybrid design involving both OSN and distillation was proposed; calculations indicated that the energy requirement for such a hybrid process was 9 times lower than that for the use of distillation alone.

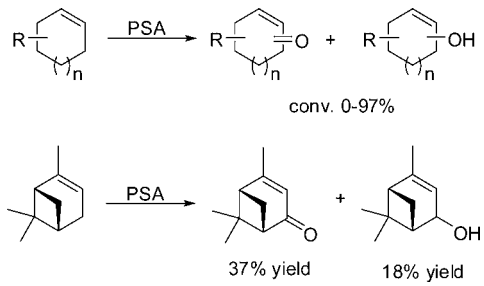
HYDROXYNITRILE LYASE AND NITRILASE ACTIVITIES FOR THE PRODUCTION OF (*S*)-MANDELIC ACID AND (*S*)-MANDEOLAMIDE



Chiral α-hydroxynitriles and the corresponding carboxylic acids and amides are very interesting building blocks for the chemical industry, but the chemical synthesis of this kind of molecular skeleton is not simple. Recently, Stolz and co-workers (*Adv. Synth. Catal.* **2012**, *354*, 113−122) reported their results on the production of mandelic acid and mandeolamide by the reaction between benzaldehyde and cyanide catalyzed by a recombinant *Escherichia coli* strain which express an oxynitrilase from *Manihot esculenta* and also an aryl-acetonitrilase from *Pseudomonas fluorescens*.

Due to the fact that the nitrilase was sensitive to the increase in substrate concentration (benzaldehyde), the use of a biphasic system was studied, and the use of ionic liquids was evaluated. The main idea was to use the ionic liquids as a reservoir of substrate in order to avoid enzyme inhibition. BMpl NTf_2 and BMim PF_6 were the best ionic liquids tested, leading to the desired products in 87−100% yield and 94% of ee. It is important to note that the use of ionic liquids allows the use of highly concentrated media (700 mM), and the recombinant microorganism was more effective in the presence of BMpl NTf_2 than in the presence of BMim PF_6.

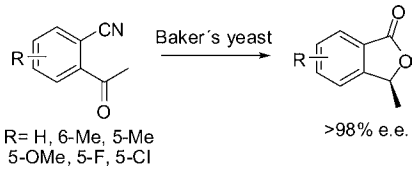
ALLYLIC OXIDATIONS CATALYZED BY THE FUNGUS *Pleurotus sapidus*



Recently, Maison and Zorn published their work on the enzymatic allylic oxidation of a variety of substrates, including terpenoids and related cycloalkenes, achieving the desired products in high yields and moderate selectivities (*Green Chem.* **2012**, *14*, 639). The functionalizations of the C−H bond are particularly attractive with a high impact on the synthesis of multifunctional molecules; however, the traditional methods in general are not environmentally friendly, and the need for a biocatalyzed process still persists.

In this work, authors have used a lyophilizate from the fungus *Pleurotus sapidus* (PSA), and in general, different types of oxidized products were obtained such as ketones, alcohols, and epoxides. When working on benzylic oxidations the major product obtained was the corresponding ketone but with other related cycloalkenes chemo- and regioselectivity depend on the nature of the starting material, and no stereoselectivity was observed. Despite the excellent results the reaction times are still long, and the use of diluted media compromises the productivity for industrial applications.

CHEMOENZYMATIC PROCESS FOR 3-METHYLPHTHALIDES



Gotor and Gotor-Fernández have recently (*Org. Lett.* **2012**, *14*, 1444 published their work on the chemoenzymatic synthesis of substituted 3-methylphthalides in moderate to good yields and high enantiomeric excess. This five-membered ring lactone can be found in several bioactive molecules and fragrances.

The authors started working with alcohol dehydrogenases in Tris-HCl buffer solution; however, at pH lower than 7 the starting material, 2-acetylbenzonitrile, led to the undesirable 3-hydroxy-3-methyl-2-benzofuran-1(3*H*)-imine as the unique final product. The formation of this product can be explained by the formation of the hemiacetal followed by intramolecular cyclization and imidate formation.

The use of other oxidoreductases was evaluated, and Baker's yeast was chosen as a catalyst for the reduction of 2-acetylbenzonitrile. The reaction was performed in aqueous media, and the reduction led to the (*S*) product in high yields and selectivity after 16 h (>97% and >97%, respectively). Different substitutions on the aromatic ring were also evaluated for this bioreduction. Substitution of the aromatic ring with halogens increases the reaction time and decreases the selectivity without loss of yield.

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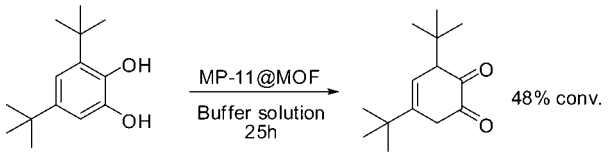
ENZYME IMMOBILIZATION ON METAL ORGANIC FRAMEWORKS

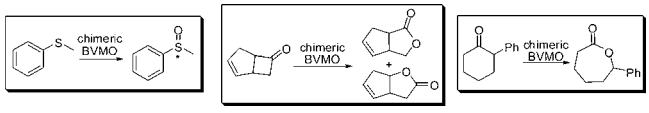


Metal organic frameworks (MOF) have emerged in recent years as new types of porous materials with wide applicability in chemistry. Despite that, the use of these materials as supports for enzyme immobilization is still at an early stage. In this work, Ma and Ming (*J. Am. Chem. Soc.* **2011**, *133*, 10382−10385) have reported the immobilization of microperoxidase-11 (MP-11) on to a mesoporous MOF consisting of nanoscopic cages.

The choice of a mesoporous MOF to be used as a support for enzymatic immobilization was done on the basis of the pore sizes being Tb-mesoMOF chosen due to the predominance of 3.0 and 4.1 mesopores. The immobilization procedure leads to a final loading of 19 μmol/g after 50 h and further characterization of the MP-11@MOF showed a decrease in BET surface area and decrease in pore size. A comparison of catalytic activities of immobilized MP-11 into Tb-mesoMOF was compared with the immobilization into MCM-41, a mesoporous molecular sieves (Mobil Composition of Matter No. 41).

The results obtained shows that MP-11@Tb-mesoMOF leads to the oxidation of substituted catechol in the presence of 10 mM of H_2O_2 in 48.7% of conversion with an initial rate of 7.58×10^{-5} mM/s and MP-11@MCM-41 gave just 17% of conversion with a lower initial rate (3.57×10^{-5} mM/s). It is important to note that the catalytic activity of MP-11@Tb-mesoMOF fluctuates in first six cycles, while the MP-11@MCM-41 shows a decrease in more than 60% of activity after the first cycle which is strongly related with the leaching of MP-11. In summary, the encapsulation of MP-11 in Tb-mesoMOF can lead to greater improvements on oxidation of catechol derivatives.

CREATING CHIMERIC ENZYMES WITH NOVEL CATALYTIC PROPERTIES

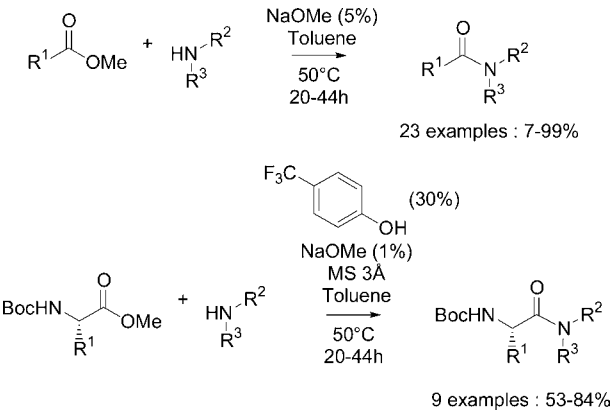


In the beginning of 2012, Fraaije and co-workers (*Chem. Commun.* **2012**, *48*, 3288−3290) reported their results on the introduction of novel selectivities from other Baeyer−Villiger monooxygenases (BVMO) into phenylacetone monooxygenase (PAMO) by structured inspired subdomain exchanges. PAMO was due to be one of the most robust BVMOs employed, showing thermostability, broad pH range, and toleration of various organic solvents.

In order to improve the substrate specificity of PAMO, subdomains were exchanged by introducing a suitable restriction site in the PAMO gene and homologous regions of steroid monooxygenase (STMO) or cyclohexanone monooxygenase (CHMO) were introduced to create two new chimeric enzymes named as PASTMO and PACHMO, respectively.

The results obtained shows that all chimeric enzymes show catalytic behavior different from that of their origin, especially concerning enantioselectivity. The best example was obtained using PASTMO where higher conversions and enantioselectivity were shown when compared with those of the parent enzyme.

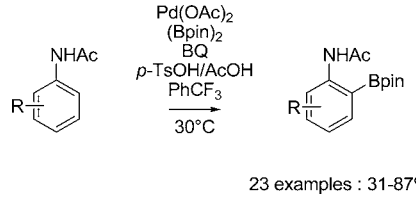
DIRECT AMIDATION OF ESTERS CATALYZED BY SODIUM METHOXIDE



A Japanese group has discovered that sodium methoxide efficiently catalyzes the direct amidation of esters and lactones under mild conditions (*Chem. Commun.* **2012**, *48*, 5434−5436). At 50 °C, 5−10% of the catalyst in toluene is enough to promote the amide formation from various esters and amines. The addition of molecular sieves as a water scavenger allows the amount of catalyst to be reduced to 1%. One limitation is that anilines performed poorly under the developed conditions.

Noteworthy is that the addition of 30% of 4-trifluoromethylphenol prevents the racemization of N-Boc-protected aminoesters and allows their coupling with different nucleophilic amines including H-Ala-O*t*-Bu.

SELECTIVE MONOBORYLATION OF ACETANILIDES VIA C−H ACTIVATION



A Chinese group has described an efficient method for the ortho C−H borylation of acetanilides (*Chem. Commun.* **2012**, *48*, 4854−4856). Conducting the reaction in acidic media was found to be key to avoiding further coupling reactions of the boronate esters. Moreover, it was demonstrated that the boron atom in the product is coordinated to the oxygen atom of acetanilide, thus preventing bis-borylation. Substrate scope is very large with halogens, sulfonates, and esters being well tolerated under the reaction conditions. Interestingly, the isolation procedure only involved recrystallization.

Further transformation of the obtained boronate esters into *o*-trifluoromethylacetanilide is also described.

RHODIUM-CATALYZED *Z*-SELECTIVE DEHYDROGENATIVE ALKENE−ARENE COUPLING

Glorius' group has described an original protocol for the highly *Z*-selective synthesis of substituted alkenes by chelate-assisted olefin C−H activation (*Chem. Asian. J.* **2012**, *7*, 1208−1212). The reaction takes place between various bromoarenes and vinylic substrates bearing a directing group, in most cases a diisopropylamide moiety, in the presence of an electrophilic Rh-species, pivalic acid, catalytic cesium pivalate, and excess copper

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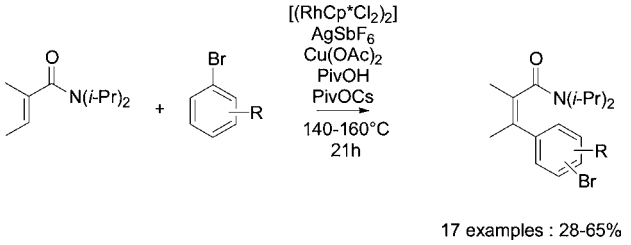
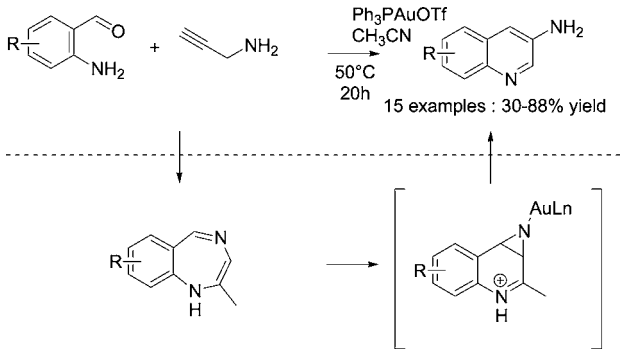


acetate. Whereas bromobenzene furnishes a mixture of meta and para isomers of the olefins, 1,2- and 1,3-substituted bromenzenes afford only one isomer as long as the second substituent is more sterically demanding than fluorine. Yields are modest especially for β-substituted vinylic substrates, but this methodology offers a new strategy for the generation of tri- or tetra-substituted alkenes, which otherwise are often difficult to access.

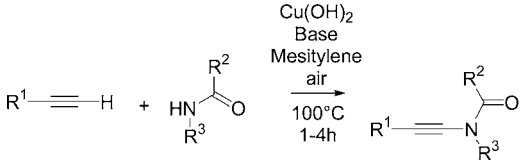
GOLD-CATALYZED SYNTHESIS OF 3-AMINOQUINOLINES



An Indian group from Hyderabad has discovered a new synthesis of 3-aminoquinoline by the reaction of various 2-aminobenzaldehydes and propargylamine (*Chem. Eur. J.* **2012**, *18*, 5530−5535). The reaction setup is quite simple as it only involves heating the two reactants in acetonitrile in the presence of the gold catalyst ($Ph_3PAuOtf$). A handful of functional groups are tolerated including iodine, bromine, and esters.

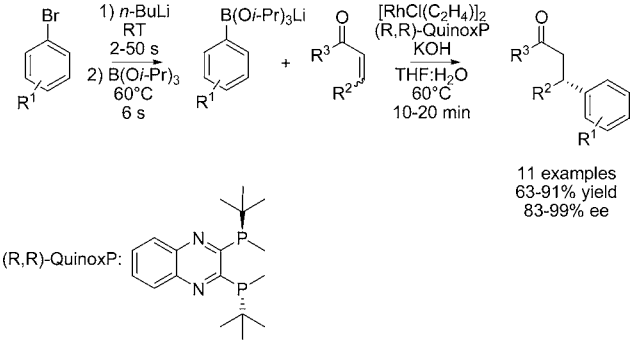
Quantum chemical calculations performed to unravel the mechanistic aspect of this transformation led the authors to suggest a pathway involving the formation of a benzodiazepine intermediate that rearranges to Au-coordinated azirinoquinoline which finally affords the product.

OXIDATIVE CROSS-COUPLING OF ALKYNES AND AMIDES



With the development of (mainly gold-catalyzed) alkyne chemistry, ynamides are gaining more importance as synthetic intermediates. Mizumo and co-workers from Tokyo have described an efficient and green synthesis of this class of compounds by reaction of terminal alkynes and amides catalyzed by copper(II) hydroxide, with air as the terminal oxidant (*Chem. Commun.* **2012**, *48*, 4974−4976). The chief advantages of the developed method is the reduced excess of amides used (compared to previous state-of-the-art methods, unless 3 equiv are still needed) and the heterogeneous nature of the catalyst under the ligand-free conditions. The substrate scope is large, regarding the alkyne coupling partners, as both aromatic and aliphatic ones are tolerated, but only lactams (and one example of sulfonamide) have been used as nitrogen nucleophiles.

ENANTIOSELECTIVE MULTISTEP SYNTHESIS OF β-ARYLATED KETONES IN CONTINUOUS FLOW



The development of asymmetric catalysis under continuous flow conditions still remains a major challenge. Buchwald's group has described an efficient three-step synthesis of enantioenriched β-arylated ketones from bromoarene and $\alpha-\beta$ unsaturated ketones (*Angew. Chem., Int. Ed.* **2012**, *51*, 5355−5358). The developed sequence begins with the lithiation of bromoarene at room temperature with *n*-BuLi which, within minutes, is followed by the formation of lithium aryltriisopropylborate. After quenching the stream with aqueous potassium hydroxide, the generated boronic acid is engaged in a rhodium-catalyzed 1,4-addition. Careful optimization of the reaction parameters is required, including the choice of the ligand ((*R*,*R*)-QuinoxP) and the recourse to sonication during the two last steps to prevent clogging. Starting from various bromoarenes, and cyclic as well as acyclic ketones (and one aldehyde), the desired products are obtained in very good yield and enantiomeric excess.

INFLUENCE OF DISSOLVED GASES ON ORGANIC MATERIAL CRYSTALLIZATION

This contribution (*Cryst. Growth Design* **2011**, *11*, 2463−2470) reports the influence of the dissolved gases on the growth of the ciclopirox crystals. The investigation results have shown that for experiments performed in stagnant and isothermal conditions the gases containing oxygen atoms (air, dioxygen, nitrous oxide, and carbon dioxide) lead to high crystal growth rates and promote the formation of liquid inclusions. Other gases that are free from oxygen (nitrogen, helium, argon, dihydrogen), as well as degassing treatments, cause a decrease in growth rates and give rise to crystals deprived of liquid inclusions.

EFFECT OF AIR BUBBLES ON IN SITU PARTICLE SIZE MEASUREMENTS

In situ particle size measurement sensors can be influenced by the presence of bubbles; thus crystallization process control robustness can be significantly affected. This work (*Chem. Eng. Technol.* **2012**, *35*(6), 1017−1023) presents a comparison between the ultrasound sensor, the Lasentec/Mettler Toledo

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FBRM, the 2D ORM from Sequip S&E GmbH, Germany, and the 3D ORM, Messtechnik Schwartz, Germany. The authors conclude that, indeed, the chord length measurements recorded by reflectance sensors are sensitive to the presence of bubbles, and the measurement errors can be as high as 44%.

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