Organic Process Research & Development

Highlights from the Literature

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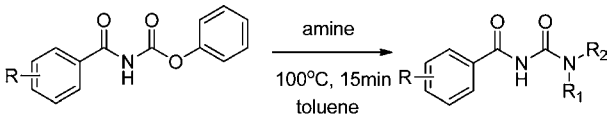
Some Items of Interest to Process R&D Chemists and Engineers

SYNTHESIS OF *N*-BENZOYL UREAS

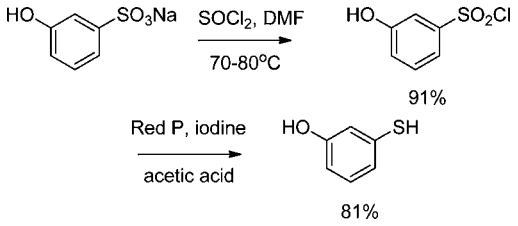


R = halo or heterocycle
R_1/R_2 = H, alkyl or Heterocycle

20 examples, 56-95%

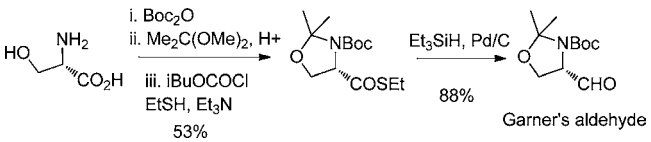
Martin and co-workers at AstraZeneca Alderley Edge (*Tetrahedron Letters* **2012**, *53*, 4802−4804) have disclosed an efficient protocol for the synthesis of *N*-benzoyl ureas by heating *N*-benzoyl carbamate with the appropiate amine or aniline in toluene. The reaction appears tolerant to a variety of functional groups and was applicable to both anilines, primary and secondary amines. Only the hindered secondary amine, 2,2,6,6-tetramethylpiperazine, failed to react. The ready availability of the precursor carbamate makes this approach attractive over existing methods such as the reaction of *N*-acylisocyanates with amines or amides with isocyanates.

CONVENIENT 3-HYDROXYTHIOPHENOL SYNTHESIS



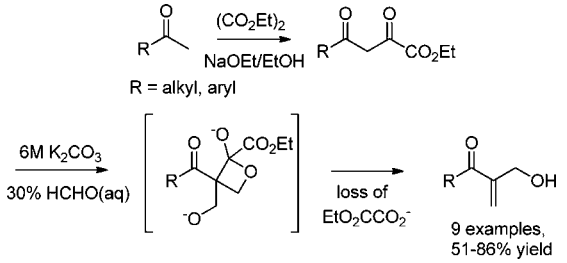
Biggs et al. of INDSPEC Chemical Corporation (*Synth. Commun.* DOI:10.1080/00397911.2011.611921) have reported an industrially viable synthesis of 3-hydroxythiophenol from commercially available 3-hydroxybenzene sulfonic acid sodium salt. Thus the sulfonic acid sodium salt was converted to the sulfonyl chloride with thionyl chloride in good yield. Reduction to the thiol was achieved using red phosphorus (recyclable) in acetic acid with a catalytic amount of iodine.

EFFICIENT SYNTHESIS OF GARNER'S ALDEHYDE



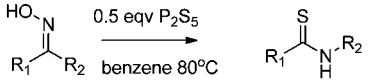
The chiral aldehyde known as Garner's aldehyde is a ubiquitous building block for the synthesis of a wide variety of amines and non-natural amino acids. It is available from serine by a N-bocylation, oxazolidine sequence followed by reduction of the Weinreb amide or a two-step reduction/oxidation of the primary alcohol. Ferjancic and Saicic and co-workers at the University of Belgrade (*Tetrahedron: Asymmetry* **2012**, *23*, 602−604) have developed an efficient gram scale synthesis of this compound via thioester reduction. Thus L-serine was converted to the thioester intermediate and subject to reduction using triethylsilane in the presence of catalytic Pd/C. The authors emphasized the efficiency of this approach compared to use of the Weinreb amide or the two-step reduction/oxidation to obtain this aldehyde.

SYNTHESIS OF α-HYDROXYMETHYL VINYL KETONES



Ameri et al. (*Synth. Commun* **2013**, *43*, 110−117) report an interesting conversion of 2,4-diketoesters to hydroxymethyl vinyl ketones by a base catalyzed reaction with formaldehyde. The precursor ketoester was readily available from the reaction of aryl or alkyl methyl ketone with diethyl oxalate. A subsequent reaction with 6−10 M potassium carbonate with aqueous formaldehyde afforded the target compounds in good yield. This approach compares favorably with alternatives such as the Bayliss−Hillmann reaction which often suffers from long reaction times.

DIRECT CONVERSION OF KETOXIMES TO THIOAMIDES



R1 = Me, H
R2 = aryl, napthyl.
R1/R2 = C5 or C11 ring.

18 examples, 65-90% yield

Thioamides are useful compounds both in their own right and as intermediates for heterocycle synthesis. Typically these compounds are prepared from the precursor amide, e.g., by treatment with Lawesson's reagent or from the nitrile, e.g., with thioacetic acid. More obscure methods such as the Willergodt reaction can be employed. Jiangsheng et al. (*Chin. J . Chem.* **2012**, *30*, 1687−1689) report the conversion of a variety of aldoximes and ketoximes with phosphorus pentasulfide via a Beckmann rearrangement to primary and secondary thioamides respectively. For example, acetophenone ketoxime yielded thioacetanilide in 90% yield.

SYNTHESIS OF 4-OXO-2-ARYL-4*H*-CHROMENE-3-CARBOXYLATE DERIVATIVES FROM 4-HYDROXYCOUMARINS

The synthesis of 4-oxo-2-aryl-4*H*-chromene-3-carboxylate (flavone-3-carboxylate) derivatives from 4-hydroxycoumarins and β-nitroalkenes in an alcoholic medium is described (*J. Org.*

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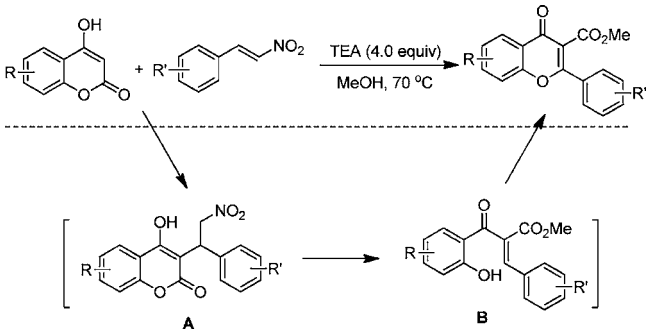
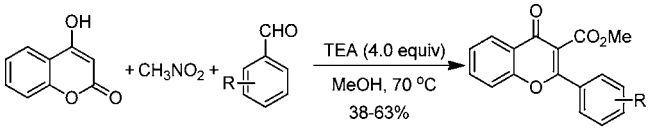


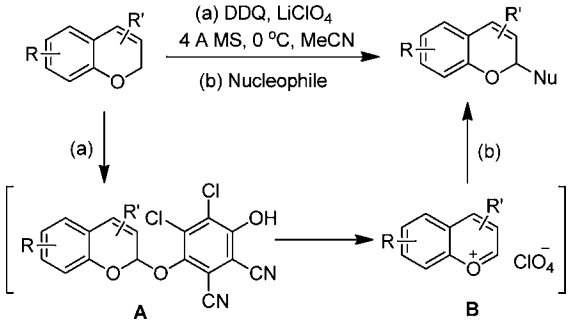
Chem. **2012**, *77*, 6495−6504). The transformation involves two stages: Michael addition (taking place at room temperature) giving adducts **A**, followed by ring-opening/ring-closing rearrangement (occurring at 70 °C). The yields of the desired products were found to be dependent on the electronic nature of the substituents on the phenyl moiety of (*E*)-(2-nitrovinyl)-benzenes. Yields ranged from moderate to good for substrates with electron-donating groups and were poor for substrates with electron-withdrawing groups (such as a nitro group). Reactions with halide substituted (*E*)-(2-nitrovinyl)benzenes also produced lower product yields. Interestingly, *o*-substituted (*E*)-(2-nitrovinyl)benzenes provided the products in good to excellent yields, indicating that the ring opening of the adducts **A** could be the rate-determining step. No desired products were observed for reactions with heterocyclic nitroalkenes, such as pyridine, pyrrole, indole, and furan.



R=4-Me, 4-Cl, 2-Br, 2-OMe

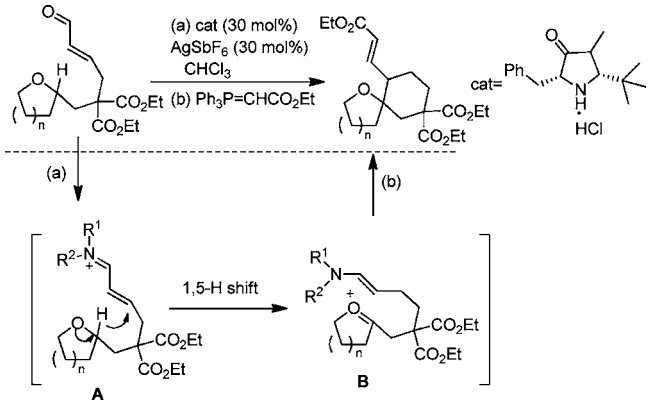
Furthermore, the nitroalkenes could be replaced with aldehydes and nitromethane, which, in turn, led to the development of a three-component protocol. Therefore, treatment of 4-hydroxycoumarin and nitromethane with different aromatic aldehydes in the presence of TEA in methanol afforded the products in moderate yields.

C−C BOND FORMATION BETWEEN AROMATIC CATIONS AND NUCLEOPHILES



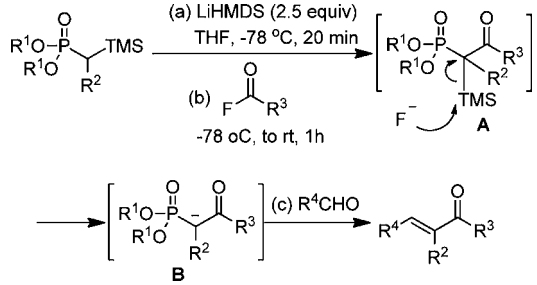
A coupling reaction of aromatic oxocarbenium ions, being generated in situ via oxidative carbon−hydrogen cleavage of chromenes and isochromenes with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was developed by Professor Floreancig and co-workers of the University of Pittsburgh, United States (*J. Org. Chem.* **2012**, *77*, 6574−6582). This protocol involves two reaction stages in which the formation of aromatic cations in the first stage with sufficient lifetimes is critical for the subsequent nucleophilic reaction. Exposure of the substrates to DDQ in acetonitrile at 0 °C in the presence of 4 Å MS resulted in intermediates **A** within 30 min. $LiClO_4$ was incorporated in this step to promote the conversion of **A** to ion pairs **B**. This process is tolerant of both electron-donating and -withdrawing groups on the benzene ring and additional substitution on the pyran ring. A variety of nucleophiles could be used in the subsequent bimolecular reaction. Prochiral substituted allylic silanes proved to be useful nucleophiles and provided the products in good to excellent levels of diastereocontrol. The reaction is not sensitive to the nature of solvents and can also be conducted in other solvents, such as CH_2Cl_2 or toluene.

APPROACH TO CHIRAL SPIROETHERS VIA ORGANOCATALYTIC 1,5-HYDRIDE MIGRATION−INTRAMOLECULAR CYCLOADDITION



An approach to access chiral spiroethers was developed via an organocatalytic enantioselective C_{sp^3}−H functionalization and cycloaddition process (*Angew. Chem., Int. Ed.* **2012**, *51*, 8811−8815). The formation of iminium ion **A** through the reaction between a cyclic ether containing an *α,β*-unsaturated aldehyde group and a chiral organocatalyst would initiate a 1,5-hydride shift to lead to oxocarbenium **B** followed by intramolecular cycloaddition to give chiral spiroethers. The initial aldehyde products were converted in situ into their corresponding unsaturated ethyl esters via Wittig reactions. The presence of a counterion (SbF_6^-) is essential in stabilizing and enhancing the electrophilicity of the ionic intermediates **A** and **B**. By employing the reaction protocol, a series of chiral spiroethers with various substituents and ring sizes were prepared from racemic ethers with good to high levels of enantioselectivity.

SYNTHESIS OF *α,β*-UNSATURATED KETONES VIA ONE-POT THREE-COMPONENT PROCESS



An approach to access *α,β*-unsaturated ketones was developed via a three-component coupling between trimethylsilylmethyl-phosphonate, acyl fluoride, and aldehyde (*Org. Lett.* **2012**, *16*,

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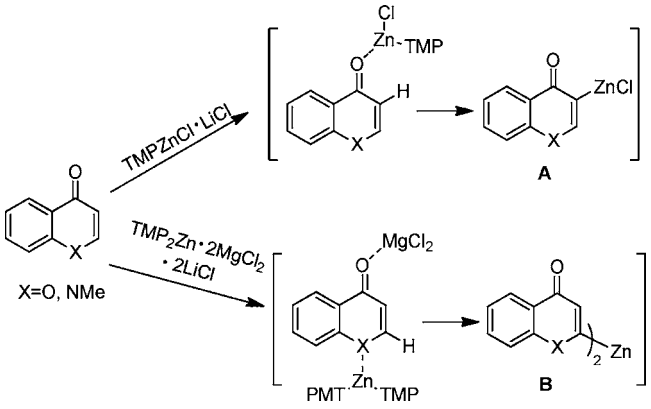
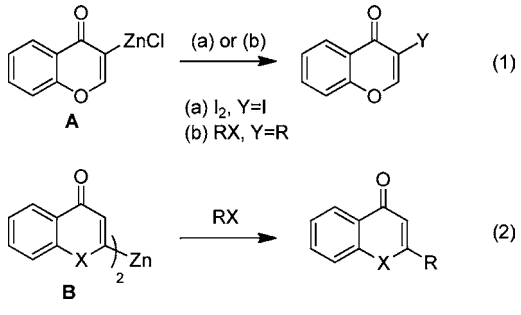
4206−4209). Exposure of trimethylsilylmethylphosphonates to LiHMDS in THF at −78 °C, followed by sequential addition of a solution of acyl fluorides, generated intermediates **A**, whose in situ desilylation led to enolates **B**. A subsequent Horner−Wadsworth−Emmons reaction with aldehydes afforded the desired α,β-unsaturated ketones in high yields. Various *E*- and *Z*-enones were obtained with high stereoselectivities by this one-pot procedure. A wide variety of aldehydes and acyl fluorides participated in the one-pot procedure, providing the *E*-enones as the sole stereoisomers in high yields. Aromatic aldehydes with electron-donating or -withdrawing groups afforded the *E*-enones in high yields, although longer reaction times were needed with the electron-donating aldehydes and sterically demanding aldehydes. Alkyl aldehydes were also converted into the *E*-enones in good to excellent yields. Various acyl fluorides bearing benzyl ether, acetate, and olefin groups were also good substrates for the present reaction.

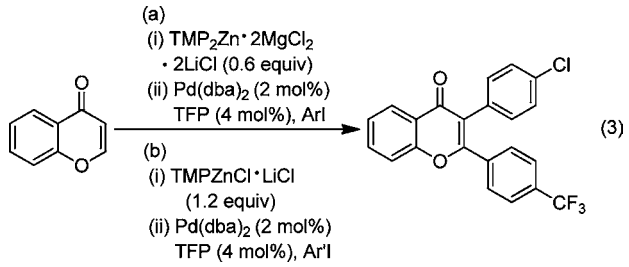
REGIOSELECTIVE ZINCATION OF CHROMONES, QUINOLONES, AND THIOCHROMONES



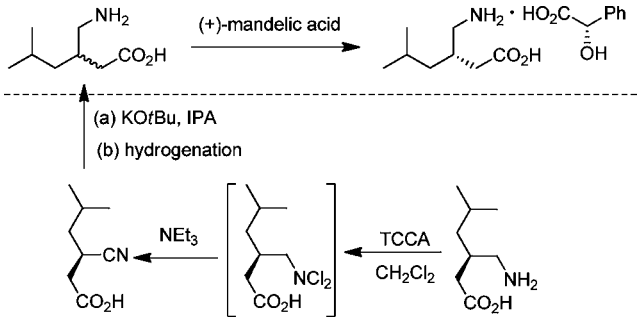
An approach to the regioselective zincation of chromone, *N*-methyl-4-quinolone, and thiochromones was developed by Knochel and co-workers of Ludwig-Maximilians-Universität München, Germany (*J. Am. Chem. Soc.* **2012**, *134*, 13584−13587). Depending on the reaction conditions, the zincation can occur with TMPZn·LiCl or $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at either C(2) or C(3) of chromone and *N*-methyl-4-quinolone to afford zincated intermediate **A** or **B**.



The resulting intermediate **A** was trapped by electrophiles such as iodine to lead to 3-iodo-chromone (eq 1). Cross-coupling reactions of **A** (or **B**) with various other electrophiles mediated by either copper or palladium led to a range of products (eq 2). Additionally, 2,3-disubstituted chromones can be readily prepared by two successive metalation/cross-coupling sequences (eq 3).

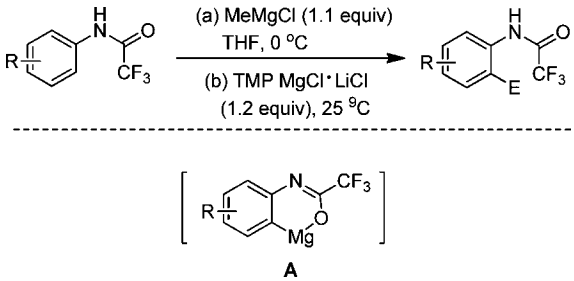


RACEMIZATION OF (*R*)-3-AMINOMETHYL-5-METHYLHEXANOIC ACID VIA (*R*)-3-CYANO-5-METHYLHEXANOIC ACID



(*S*)-(+)-3-Aminomethyl-5-methylhexanoic acid (pregabalin), a GABA (γ-aminobutyric acid) analogue, was developed for the treatment of epilepsy, neuropathic pain, anxiety, and social phobia in the early 1990s. The preparation of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid was realized through classic resolution of the racemic 3-aminomethyl-5-methylhexanoic acid with (+)-mandelic acid. An approach (*Tetrahedron Lett.* **2012**, *53*, 6075−6077) was developed for recycling the undesired *R*-enantiomer of pregabalin by converting the *R*-enantiomer to (*R*)-(−)-3-cyano-5-methylhexanoic acid, followed by base-induced racemization and hydrogenation. Thus, treatment of (*R*)-(−)-3-aminomethyl-5-methylhexanoic acid with trichloroisocyanuric acid (TCCA) gave a *N*,*N*-dichloroamino intermediate whose dehydrochlorination with triethylamine in situ afforded (*R*)-(−)-3-cyano-5-methylhexanoic acid. The subsequent racemization was accomplished with potassium *tert*-butoxide by heating in IPA at 80 °C for 4 h.

MAGNESIATION REACTION AT ORTHO AND META OF FUNCTIONALIZED ANILINES



A practical approach was developed (*Angew. Chem., Int. Ed.* **2012**, *51*, 10624−10627) for the magnesiation of trifluoroacetamides of anilines, aminopyridines, and aminopyrazines. The method can be used at room temperature and is compatible with several functional groups, such as fluorine, chlorine, bromine, carbonyl, and cyano groups. Typically, trifluoroacetamides are readily deprotonated with MeMgCl (1.1 equiv), followed by ring metalation at room temperature with TMPMgCl·LiCl (1.2 equiv), leading to magnesiated intermediates **A**. The resulting magnesiated

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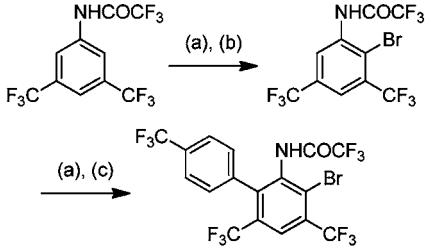
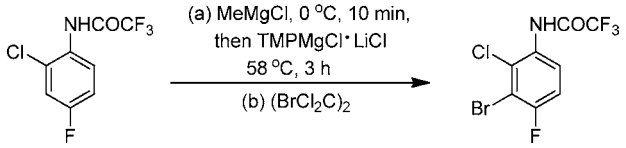
intermediates may be trapped by a range of electrophiles (E) including iodine, aryl, heteroaryl, and allylic halides, to afford substituted anilides with satisfactory yields. Both ortho and ortho′ positions to the $NHCOCF_3$ group can be functionalized stepwise using this method.

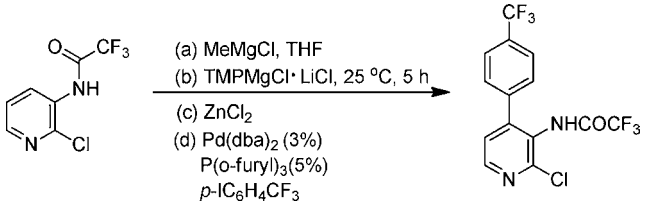


(a) MeMgCl, 0 °C, 10 min, then TMPMgCl·LiCl, 25 °C, 4 h
(b) $(BrCl_2C)_2$
(c) $ZnCl_2$ (1.2 equiv), 0 °C, 10 min, then $Pd(dba)_2$ (3%), P(*o*-furyl)$_3$ (5%) *p*-$IC_6H_4CF_3$ (1.1 equiv), 50 °C, 3 h

This double ortho,ortho′ functionalization allows a versatile preparation of pentasubstituted aniline derivatives. Thus, bis-(trifluoromethyl) trifluoroacetamide was metalated, leading, after bromination, to the *ortho*-bromoanilide in 74% yield. Further magnesiation with MeMgCl and TMPMgCl·LiCl, followed by transmetalation with $ZnCl_2$ (1.2 equiv) and subsequent Negishi cross-coupling, provided the biphenyl in 78% yield.

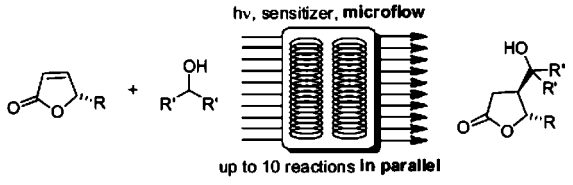


The high kinetic activity of TMPMgCl·LiCl also allows the performance of meta magnesiation. Thus, the chlorofluoroanilide was regioselectively metalated at position 3 with TMPMgCl·LiCl followed by bromination leading to the 1,2,3,4-tetrasubstituted anilide.



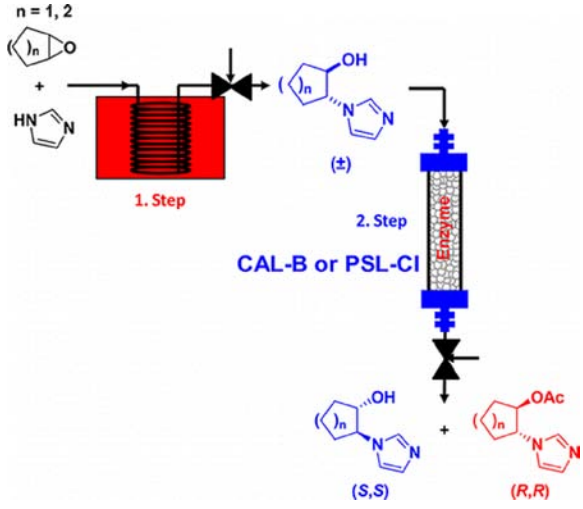
Utilization of the metalation sequence allowed a smooth regioselective magnesiation of amino-pyridine furnishing the 4-pyridylmagnesium derivative whose subsequent Pd-catalyzed cross-coupling under standard conditions provided the 2,3,4-trisubstituted pyridine in 80% yield.

PARALLEL MICROFLOW PHOTOCHEMISTRY: PROCESS OPTIMIZATION, SCALE-UP, AND LIBRARY SYNTHESIS



The Oelgemoeller group from James Cook University (Australia) and other cowokers recently reported a series of sensitized photoadditions involving 2(5*H*)-furanones, by using a novel, multimicrocapillary flow reactor (MμCFR, *Org. Lett.* **2012**, *14*, 4342−4345). Compared to in-series operations with a single-capillary reactor, the MμCFR reactor allowed for process optimization, scale-up, and library synthesis with energy-, time-, and space-efficient sensitizer screening (see the scheme). For example, the microreactor consumed ∼30% less energy than a conventional chamber reactor in one of the photosyntheses on a scale of 1 kg, and cooling water was not required with this MμCFR setup. However, the usage of a single multisyringe pump with identical flow rates for all capillaries was the current disadvantage of this microflow photochemistry. The authors expected a rapid transfer of this resource-efficient and green technology to chemical R&D processes after integrating automated pump systems in parallel with individual flow rate settings.

STEREOSELECTIVE CHEMOENZYMATIC SYNTHESIS OF ENANTIOPURE 2-(1*H*-IMIDAZOL-YL)CYCLO-ALKANOLS UNDER CONTINUOUS FLOW CONDITIONS



Santiago V. Luis et al. from Universitaet Jaume (Spain) and their co-workers (*ACS Catal.* **2012**, *2*, 1976−1983) developed an efficient multistep continuous flow process for the synthesis of chiral enantiopure 1-(2-hydroxycycloalkyl)imidazoles. For the first step of the ring-opening reaction, a continuous flow system gave an obviously improved productivity compared with microwave batch processes, although similar conversions were obtained in both cases. Also for the second step of the lipase-catalyzed kinetic resolution of the racemic 2-(1*H*- imidazol-yl)cycloalkanols, the continuous flow reactor demonstrated a much higher efficiency than the corresponding batch processes, with either immobilized CAL-B or PSL-C catalysts. The continuous flow biotransformations facilitated the production scale-up of these chiral imidazoles towards the synthesis of chiral ionic liquids.

RAPID ACCESS TO COMPOUND LIBRARIES THROUGH FLOW TECHNOLOGY: FULLY AUTOMATED SYNTHESIS OF A 3-AMINOINDOLIZINE LIBRARY VIA ORTHOGONAL DIVERSIFICATION

The James group from the Scripps Research Institute demonstrated a novel methodology for the synthesis of druglike heterocycle libraries by using flow reactor technology (*ACS Comb. Sci.* **2012**, *14*, 570−578). A diverse 25-membered library of druglike 3-amino-indolizines was generated in situ with orthogonal modification, which could be further extended to a 100-member virtual library through variation of the amino-substituted heteroaryl bromide

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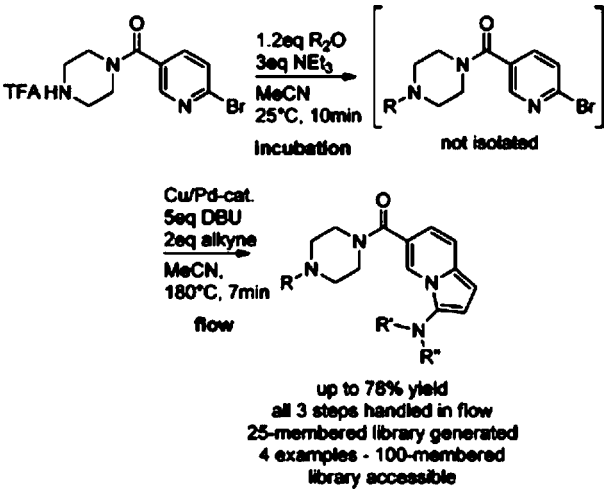
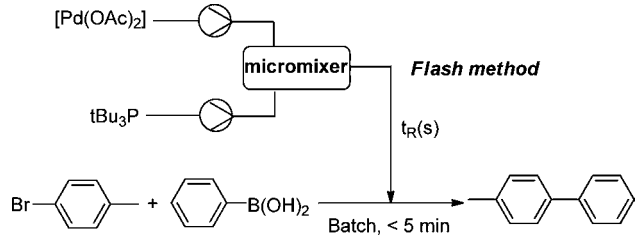


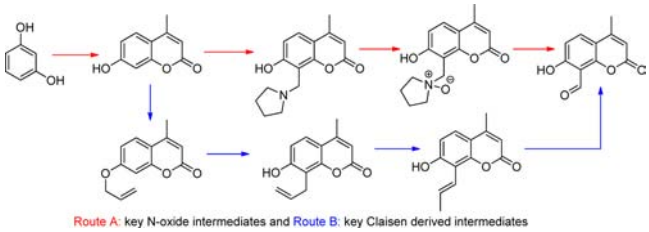
core fragment (see the scheme). The general protocol is a three-step flow synthesis under full automation in the flow reactor, including a broad range of acylation, alkylation, and sulfonamidation reactions followed by a tandem Sonogashira coupling/cycloisomerization sequence. As part of a lead discovery strategy or within a lead optimization program, this approach opens the way to the highly efficient generation of druglike heterocyclic systems. First, the size and diversity of the virtual library accessible are substantial, since it affords a variety of N-modifications of the first step in a short time. Second, a broad range of propargyl amines and amides with either aromatic or aliphatic groups of varying polarities could be applied in the second step coupling within minutes. And further extension to the three variants of thecore fragment could afford a total of 100 3-amino-indolizines within several days. Moreover, the option of combining the flow reactor employed in this program with an automated purification system has the potential to achieve the highly efficient production of large libraries of druglike heterocycles.

FLASH GENERATION OF A HIGHLY REACTIVE Pd CATALYST FOR SUZUKI–MIYAURA COUPLING BY USING A FLOW MICROREACTOR



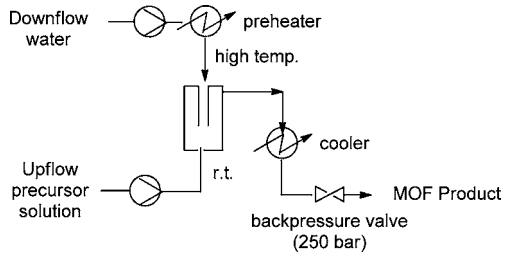
J.-i. Yoshida et al. from Kyoto University (Japan) demonstrated an application of flash generation of a highly reactive Pd catalyst for a Suzuki–Miyaura reaction (*Chem.—Eur. J.* **2012**, *18*, 11871–11875). Compared with batchwise catalyst preparation methods (via the kinetic study of the coupling reaction), this flash method could generate a much more reactive Pd catalyst precursor by using a flow microreactor in the absence of substrates. The fast 1:1 micromixing of $[Pd(OAc)_2]$ and tBu_3P in flow and its quick transfer to the reaction vessel could bring the coupling reactions to an end within 5 min even at room temperature. Moreover, aryl- or heteroarylboronic acids, which quickly deboronate under basic conditions, could be also used as coupling partners, because the reactions can be conducted at lower temperatures and in a short time. This flash chemistry opens a new possibility for not only Suzuki–Miyaura coupling but also other catalytic reactions, which greatly enhance the possibility of catalytic reactions with on-site on-demand generation of a catalyst or its precursor.

ESTABLISHING A FLOW PROCESS TO COUMARIN-8-CARBALDEHYDES AS IMPORTANT SYNTHETIC SCAFFOLDS



The Riva group from the University of Cambridge and their co-workers have established a flow process to coumarin-8-carbaldehydes as important synthetic scaffolds and fluorophores (*Chem.—Eur. J.* **2012**, *18*, 9901–9910). In this continuous flow synthesis, a target aldehyde product (7-hydroxy-4-methyl-2-oxo-2*H*-chromene-8-carbaldehyde) could be produced in high yield on a gram scale without manual intermediate purification or workup. Two complementary flow syntheses via key *N*-oxide or Claisen derived intermediates have been developed. In the former synthetic route, a four-step telescoped sequence with a single filtration was applied, which could be easily scaled and also readily applied to the synthesis of various analogues. The latter flow synthesis also allowed an efficient four-step process (starting from preprepared 7-hydroxycoumarin) as an alternative Claisen based sequence, which afforded a high yield and purity with automated reagent delivery by in-line monitoring and "catch-and-release" purification.

INSTANT MOFs: CONTINUOUS SYNTHESIS OF METAL–ORGANIC FRAMEWORKS BY RAPID SOLVENT MIXING



The Lester group from the University of Nottingham, the Walton group from the University of Warwick and other co-workers (*Chem. Commun.* **2012**, *48*, 10642–10644) recently reported a continuous synthesis of metal–organic frameworks (MOFs) by rapid solvent mixing. This strategy allowed the preparation of porous MOF material with crystallite sizes from nano- to micrometer scale in high volume production (132 g h^{-1}). The rapid mixing of preheated water and reagent solutions in organic solvent gave the corresponding porous CPO-27(Ni) with comparable textural properties to conventional synthesis, which showed a typical Type I isotherm with a slight mesopore character by high relative pressure BET nitrogen sorption analysis. Also a CO_2 uptake of 19.57 wt % was measured. The authors believe that this synthetic method has the potential for fine-tuning of the crystal morphology for scalable production and can also be

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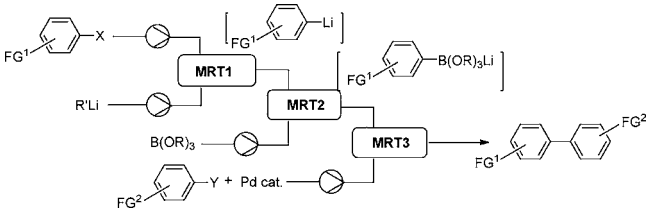
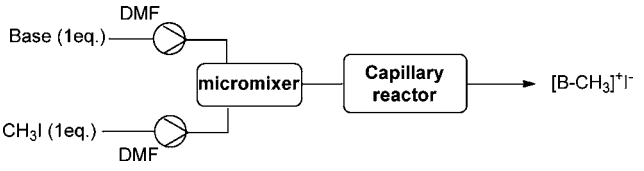
extended to a wide range of MOF syntheses, by varying solvent or solvent mixtures, organic linkers, and metal precursors.

FLOW SYNTHESIS OF ARYLBORONIC ESTERS BEARING ELECTROPHILIC FUNCTIONAL GROUPS AND SPACE INTEGRATION WITH SUZUKI–MIYAURA COUPLING WITHOUT INTENTIONALLY ADDED BASE



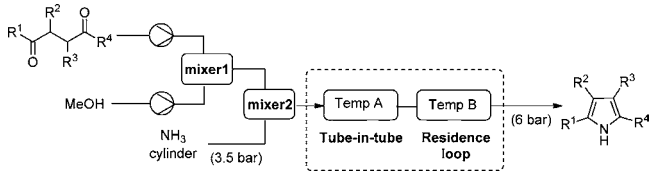
The Jun-ichi Yoshida group from Kyoto University (Japan) demonstrated a flow synthesis of arylboronic esters bearing electrophilic functional groups, followed by Suzuki–Miyaura coupling without intentionally added base (*Chem. Commun.* **2012**, *48*, DOI: 10.1039/c2cc36197c). Based on this method, the cross-coupling of two aryl halides bearing electrophilic functional groups was achieved to obtain the corresponding biaryl compounds in one flow (see the scheme). In the first step, various arylboronic esters bearing electrophilic functional groups could be prepared by halogen–lithium exchange followed by borylation. It is worth noting that the second step Suzuki–Miyaura cross-coupling could proceed without intentionally added base by space integration. The authors hope the extension of this transformation to a full scope would enhance the synthetic utility of aryllithium compounds and add a new dimension to the chemistry of cross-coupling.

KINETICS SCREENING OF THE N-ALKYLATION OF ORGANIC SUPERBASES USING A CONTINUOUS FLOW MICROFLUIDIC DEVICE: BASICITY VERSUS NUCLEOPHILICITY



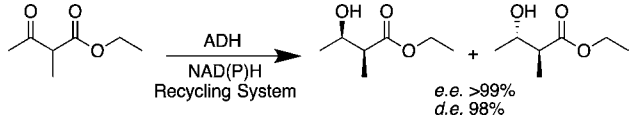
The Rolando group from Université de Lille 1 (France) described the determination of the alkylation rate of a set of organic superbases by iodomethane in DMF using a microfluidic continuous flow reactor (*Org. Biomol. Chem.* **2012**, *10*, 8059–8063). The organic bases in this study included a set of the most used organic bases, such as guanidine, 1,8-diaminonaphthalene and guanidine based proton sponges, bicyclic guanidines, amidines, and phosphazenes. The alkylation of the base was ascertained and followed by ESI mass spectrometry. The determined rate constants cover 6 orders of magnitude and are well fitted by Mayr's equation. The authors found that the base nucleophilicity decreases unusually when its basicity increases except for the phosphazene P_2Et. From a synthetic point of view, the crowded bis-guanidine TMGN and the phosphazene BEMP are the best choices of base due to their low alkylation rates. The extension of this method to other alkylating agents and to other solvents will be an interesting topic.

FLOW SYNTHESIS USING GASEOUS AMMONIA IN A TEFLON AF-2400 TUBE-IN-TUBE REACTOR: PAAL–KNORR PYRROLE FORMATION AND GAS CONCENTRATION MEASUREMENT BY INLINE FLOW TITRATION



The Steven V. Ley group from the University of Cambridge reported the Paal–Knorr reaction of 1,4-diketones with gaseous ammonia in flow by using a simple and accessible Teflon AF-2400 based tube-in-tube reactor (*Org. Biomol. Chem.* **2012**, *10*, 5774–5779). The tube-in-tube configuration that has the gas in the central tube and the liquid on the outside facilitates efficient thermal contact and allows the liquid to be heated or cooled as appropriate. Moreover, this inexpensive and operationally simple flow system also integrated a simple colourimetric inline flow titration technique, which allowed measurement of the ammonia concentration and its relationship to residence time and temperature. The concentrations varied approximately linearly with residence time and could not approach saturation, while lower temperatures led to higher rates of gas uptake. Finally, the authors found that the optimal flow setup included a gas injection in the tube-in-tube device at a lower temperature and the subsequent reaction in a residence loop proceeding at a higher temperature (see the scheme).

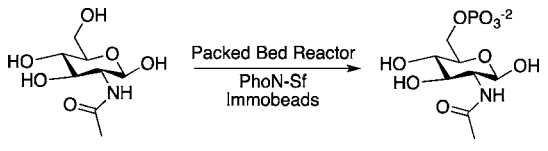
ALCOHOL DEHYDROGENASES MEDIATE DYNAMIC KINETIC RESOLUTION OF α-ALKYL-β-HYDROXY ESTERS



Methodologies that could afford highly enantio- or diastereoisomeric pure compounds are of great importance in synthetic organic chemistry, and several efforts have been made during the recent years to expand the toolbox of such a transformation. The most successful example is the combination of lipases and a metal catalyst for the dynamic resolution of alcohols and amines. But recently, Gotor and co-workers (*Adv. Synth. Catal.* **2012**, *354*, 1743–1749) have shown that ADH enzyme could also be used for a dynamic protocol for the resolution of α-alkyl-β-hydroxy esters.

The substrate studied in this work is particular because the high acidity of the α-proton leads to a fast racemization at neutral pH. Different steric demanding substrates were tested, and the results presented by the author shows that the use of purified or lyophilized *E. coli* containing overexpressed ADHs can lead to excellent conversions and stereoselectivities, depending in general on the ADH source used.

CONTINUOUS FLOW ENZYMATIC PHOSPHORYLATION



Phosphorylation is considered a key reaction in API synthesis, but this is not an easy task under conventional organic synthesis

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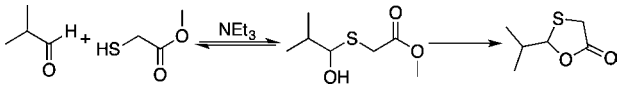
methodologies. The synthesis of phosphorylated derivatives can increase the stability of some molecules in biological media and also improve the delivery capability (prodrugs). The use of enzymatic phosphorylation procedures is preferred to chemical methods since the use of enzymes requires mild conditions and affords the desired product with high regio- and stereoselectivities. Wever and co-workers (*Chem.—Eur. J.* **2012**, *18*, 6604−6609) developed a continuous method for the phosphorylation of alcohols on large scale.

The phosphorylation reaction was carried out using the acid phosphatase enzyme from *Shigella flexneri* (PhoN-Sf) and pyrophosphate as the phosphate donor. The PhoN-Sf enzyme was covalent bounded to two different polymethacrylate porous beads (Immobeads-150 and Sepabeads EC-EP) by the use of epoxy linkers and charged to a packed bed continuous reactor. The system developed by the authors presented a high dependence on the pH used for the reaction, but high yields (82%) could be obtained for the phosphorylation of *N*-acetyl-D-glucosamine and the continuous flow system was stable for 16 days. Other starting materials were tested such as glucose, dihydroxyacetone, glycerol, allyl alcohol, and inosine leading to moderate to good yields of the desired phosphorylated product.

ONE-POT HEMITHIOACETAL TRANSFORMATION AND LIPASE CATALYZED γ-LACTONIZATION

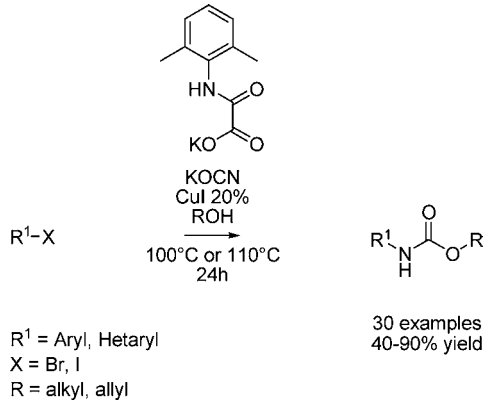


The 1,3-oxathiolan-5-one moiety is an important scaffold in the synthesis of molecules such as emtricitabine and lamivudine, especially due to the control needed at the 2-position. Ramstrom's group has performed interesting work (*Chem.—Eur. J.* **2012**, *18*, 6129−6132) on the tandem hemithioacetal formation followed by lipase-catalyzed γ-lactonization. The main idea is, first, to carry out the hemithioacetal reaction mediated by triethylamine leading to a racemic intermediate, which has a secondary hydroxyl group that can be used by the lipase for a γ-lactonization resolution. Since the first step is reversible, in theory, all γ-hydroxyesters could be transformed into an enantiomerically pure lactone.

The best results were obtained with γ-hydroxyesters, but δ-hydroxyesters were also tested, yet without any observation of lactonization catalyzed by lipases. Several commercial lipases were tested, and Novozyme 435 gave the best results. Depending on the substrate, as the one shown above, moderate conversions (55%) and moderate enantiomeric excesses (89%) could be obtained. When a heteroaromatic aldehyde is used, the enantiomeric excess is high (>99%) but the conversions are extremely low (1.6%).

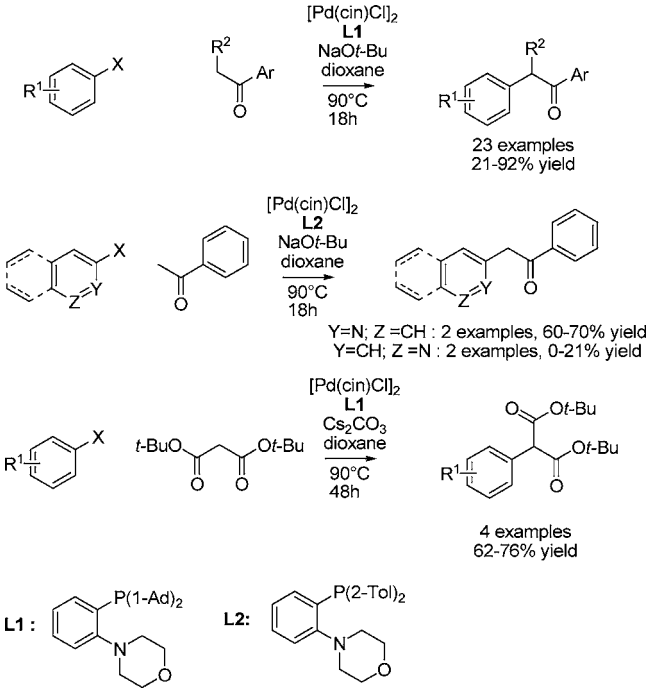
COPPER-CATALYZED SYNTHESIS OF CARBAMATES FROM ARYL HALIDES

Metal-catalyzed carbon−nitrogen bond formation is arguably one of the prominent reactions of the modern synthetic arsenal, and new nitrogen sources continue to be actively sought after. Dawei Ma and co-workers have reported an efficient synthesis of carbamates by reaction of aryl halides with potassium cyanate (*Adv. Synth. Catal.* **2012**, *354*, 2243−2246). The best conditions involve the use of copper(I) iodide with 2-(2,6-dimethylphenylamino)-2-oxoacetic acid (DMPAO) potassium salt as the ligand in the corresponding alcohol as the solvent. A number of functional groups are tolerated as long as the ortho positions are free. It is interesting to note that arylbromides react



as well as aryliodides in the transformation. Regarding the alcohol partner, only sterically hindered *tert*-butanol failed to provide the desired product.

PALLADIUM-CATALYZED α-ARYLATION OF CARBONYL-CONTAINING COMPOUNDS USING DalPhos LIGANDS



Despite significant advances, α-arylation of carbonyl compounds is one of the less mature palladium catalyzed C−C bond forming reactions. In their full paper, Prof. Stradiotto's group describes the scope and limitations of the catalytic system based on the DalPhos ligand developed in their laboratory for the mono-α-arylation of carbonyl compounds (*Eur. J. Org. Chem.* **2012**, 6042−6050). By optimizing the solvent and temperature, the authors were able to demonstrate that their catalytic system allows the successful reactions of arylmethylketones, heteroarylmethylketones, propopiophenone, malonates, and methoxyacetone. Noteworthy is that only a slight excess of the carbonyl compounds is used (1.05 equiv). Moreover, the main limitations of the developed protocol are also highlighted: low yields for the reactions of electron-poor arylhalides, 3-bromopyridine, and 3-bromoquinoline with acetophenone; the requirement of an excess of alkylketones; and the impossibility to arylate acetates or amides.

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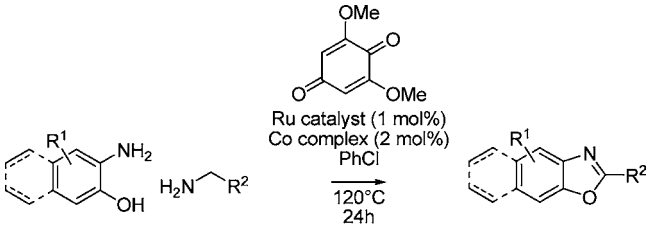
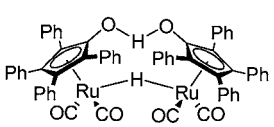
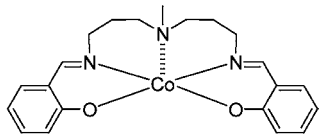
BIOMIMETIC RUTHENIUM AND COBALT COCATALYZED SYNTHESIS OF BENZOXAZOLES

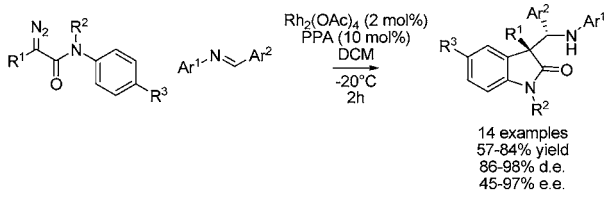


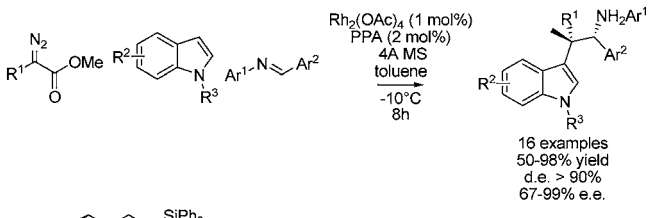

Ru catalyst

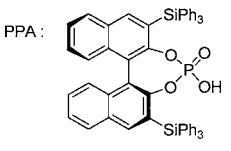

Co complex

Pursuing his successful work on biomimetic coupled reaction systems for the aerobic oxidation of different classes of substrates, Bäckwall's group has described an interesting synthesis of benzoxazoles from the coupling of benzylamines and 2-aminophenols (*Chem.—Eur. J.* **2012**, , 13609−13613). Based on their ruthenium and cobalt catalytic system, they investigated the effect of the 2-aminophenol coupling partner (benzylamine or benzaldehyde), the nature of the electron-transfer mediator, solvent, and temperature to set up the best conditions. The substrate scope includes alkyl and halogen substituents for the 2-aminophenol part, but strong electron-withdrawing groups (such as fluorine) prevent the reaction from taking place. Regarding the amine part, a number of substituted benzylamines are tolerated, but simple alkylamines failed to provide the desired products. Interestingly, one example of the synthesis of benzimidazole and benzothiazole is also described, and a higher yield in these cases is obtained when using benzaldehyde instead of benzylamine as the coupling partner of respectively the *o*-phenylenediamine and 2-aminothiophenol.

RHODIUM AND CHIRAL PHOSPHORIC ACID CATALYZED ASYMMETRIC TRAPPING OF ZWITTERIONNIC INTERMEDIATES BY IMINES

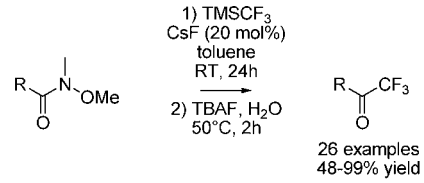


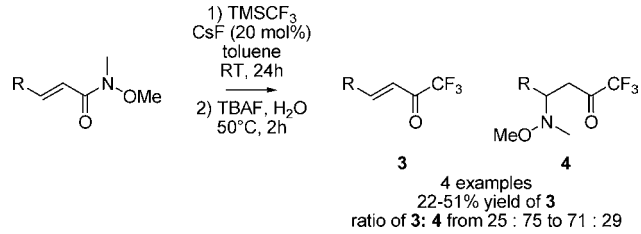




Cocatalysis by a transition metal and an organocatalyst offers the possibility of achieving otherwise impossible reactions. Hu's group from Shanghai has reported the highly enantioselective trapping of *in situ* generated zwitterionic species with imines (*Nat. Chem.* **2012**, *4*, 733−738). The reaction of diazoacetamide with imines in the presence of rhodium acetate and a chiral phosphoric acid allows the rapid synthesis of substituted oxindoles, presenting two newly generated chiral centers in high yields as well as diastereo- and enantiomeric excesses in most cases. With slight variations (solvent and temperature), the same conditions were applied to a three-component reaction between indoles, α-diazoacetate, and imines to prepare densely substituted tryptamines in high yields as well as high diastereo- and enantiomeric excesses. In both cases, alkenes and halogens were tolerated in the different coupling partners allowing further opportunities for derivatisation.

TRIFLUOROMETHYLKETONES SYNTHESIS FROM WEINREB AMIDES





Trifluoromethylketones are highly valuable building blocks whose synthesis mainly relies on the alkylation of trifluoroacetic acid derivatives or the oxidation of α-trifluoromethylcarbinols. Leadbeater's group from Connecticut has described an efficient approach to this moiety from Weinreb amides (*Chem. Commun.* **2012**, *48*, 9610−9612). The one-pot, two-step procedure begins with the addition of Ruppert's reagent ($TMSCF_3$) to the Weinreb amide mediated by a catalytic amount of cesium fluoride in toluene followed by desilylation of the tetrahedral intermediate by a stoichiometric amount of TBAF in water. The substrate scope includes alkyl as well as aryl and heteroaryl based Weinreb amides. The main limitation of the present method is that sterically crowded (ortho substituted aryl or α-disubstituted alkyl) Weinreb amides fail to react. In addition, α−β-unsaturated Weinreb amides furnish a mixture of the expected trifluoromethylketone and the trifluomethylketone resulting from Michael addition of *N,O*-dimethyl-hydroxylamine.

NATURAL EMULSION STABILIZERS FOR PHARMACEUTICAL APPLICATIONS

The topic of this recent review (*Int. J. Pharm.* **2012**, *436*, 359−378) is on the potential use of natural emulsion stabilizers for pharmaceutical applications. The article presents an extended survey of the recent research on biopolymer-based emulsion stabilizers and also discusses the comparison between small molecule surfactants and biopolymers. The main classes of addressed biostabilisers are proteins (caseins, whey proteins, gelatin, pea proteins), polysaccharides (xanthan gum, alginates, carrageenans, hyaluronan, chitosan, gum arabic, hydroxypropyl-methylcellulose, galactomannans, pectin), and the protein−polysaccharide combinations. Additionally, the following hurdles related to the application in the pharmaceutical industry are

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raised by the authors: biopolymer composition variability depending on the natural source, appearance of allergies, bacteriological and storage issues.

SOLID SUPPORTED EVAPORATION OF DISSOLVED COMPOUNDS

The subject of investigation in this contribution (*Ind. Eng. Chem. Res.* **2012**, *51*, 13445−13453) is related to the separation of dissolved compounds as solids using the solid supported evaporation (SSE) method. According to this report, the solution to be evaporated is put in contact with granular porous polymer beads so that the dissolved compounds can deposit on these. This method could be advantageous when the solid forms a sticking and/or dusting powder and when the increase of concentration may cause side reactions that raise quality or safety concerns.

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