Organic Process Research & Development

Highlights from the Literature

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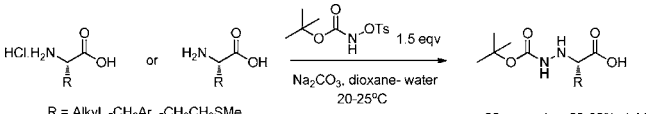
Some Items of Interest to Process R&D Chemists and Engineers

FACILE ELECTROPHILIC N-AMINATION OF AMINO ACIDS

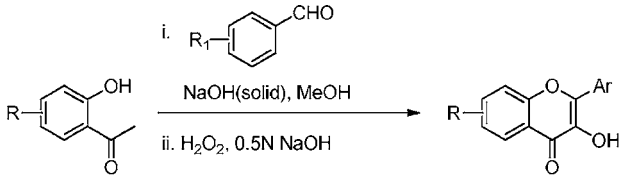
Chiral α-hydrazinoacids can be obtained from the parent α-aminoacids by use of oxaziridines or rearrangement of hydantoins; however, these approaches have drawbacks such as the requirement to prepare the amination reagent and the need for multistep processes. Thambidurai and co-workers of Alagappa University, India (*Tetrahedron Lett.* **2012**, *53*, 2292−2294), present a straightforward approach using *N*-



Boc-*O*-tosyl hydroxylamine as an electrophilic amination reagent which is readily available by tosylation of commercial *N*-Boc-hydroxylamine. Thus, portionwise addition of this reagent to an aminoacid (either free base or hydrochloride salt) in dioxane−water gave higher conversion to the *N*-aminated product. Isolation of the pure *N*-Boc hydrazinoacid was achieved by glycolic acid quench and recrystallisation. The main benefit of this approach is the use of unprotected aminoacid and readily available electrophilic amination reagent.

EFFICIENT SYNTHESIS OF 3-HYDROXYFLAVONES

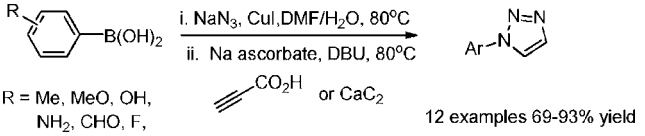
Ozturk et al. (*Org. Lett.* **2012**, *14*, 1576−1579) report a facile one-pot synthesis of 3-hydroxyflavones. Thus, treatment of a



substituted 2-hydroxyacetophenone and arylaldehyde with solid NaOH in methanol followed by addition of hydrogen peroxide/sodium hydroxide afforded the 3-hydroxyflavone in typically modest-to-good yield. The authors claim this one-pot procedure gave higher yields and was more reproducible than earlier methodology. It also avoids the need to isolate the chalcone intermediate or use toxic oxidising agents (e.g., SeO_2).

VERSATILE SYNTHESIS OF *N*-ARYL TRIAZOLES

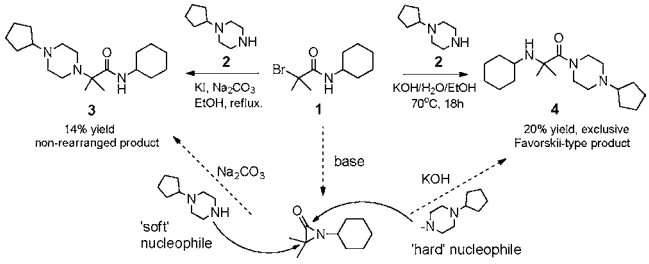
Yang et al. (*Helv. Chim. Acta* **2012**, *95*, 448−454) report an efficient one-pot, two-step conversion of aryl boronic acids to



N-aryl triazoles via Cu-catalysed coupling with sodium azide and 'click' cycloaddition with either calcium carbide or propiolic acid. This approach appears versatile in light of the wide variety of aryl boronic acids available and also gives higher yields than direct aryl boronic acid−triazole Cu-coupling.

FAVORSKII-TYPE REARRANGEMENT OF AN α-BROMO AMIDE

Whilst investigating the synthesis of esaprazole analogues, Kelly et al. (*Synth. Commun.* **2011**, DOI: 10.1080/



00397911.2011.629357) of Nensius Research, Denmark, have demonstrated an interesting orthogonal reactivity of α-bromo amide **1** with the piperazine **2**. Under mild conditions using sodium carbonate as base in the presence of KI in refluxing ethanol, the expected displacement product **3** was obtained. However, under harsher conditions with potassium hydroxide as base in water−ethanol at 70 °C, only the 'Favorskii'-type rearranged amide **4** was formed in modest yield. The authors rationalised this result on the basis of the formation of a hard piperazine nucleophile with KOH attacking the intermediate aziridinone at the carbonyl position. Thus, the protic and softer nucleophile with $NaCO_3$ as base attacked at the sp^3 carbon to yield the nonrearranged product.

COPPER-MEDIATED CYANATION USING AMMONIUM IODIDE AND DMF

Copper-mediated cyanation of aromatic compounds was developed using ammonium iodide and DMF as the source of a nitrogen and a carbon atom, respectively, of the cyano unit (*J. Am. Chem. Soc.* **2012**, *134*, 2528−2531). The reaction proceeds via a two-step process, initial iodination and then cyanation, in which ammonium iodide plays a dual role to provide iodide and the nitrogen atom of the cyano moiety. It has been demonstrated that aryl iodide is the reaction intermediate whose subsequent reaction would provide the desired cyano substituted product. Aryl boronic acids substituted at the para-, meta-, and ortho-position were all smoothly cyanated in good yields. In addition, high product yields were obtained from boronic esters such as pinacolboronates. Furthermore, the procedure was successfully applied to the C−H cyanation of electron-rich arenes.

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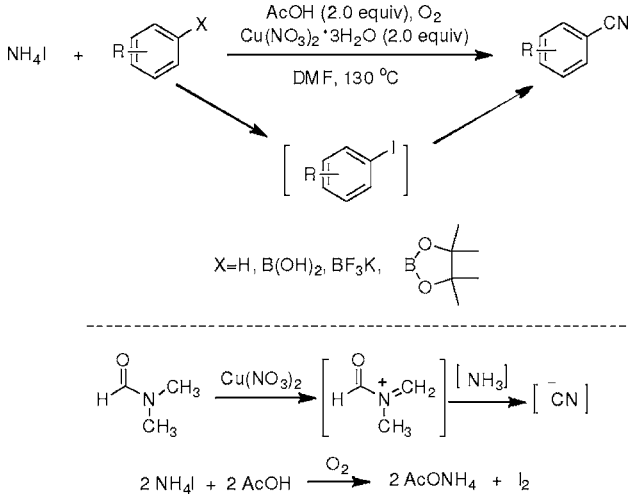
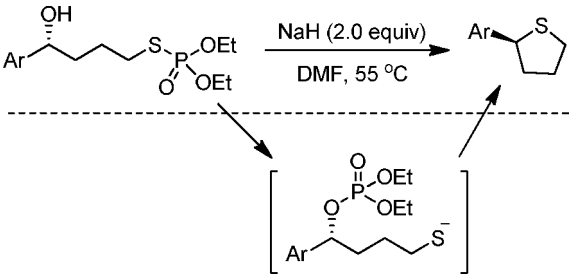


SYNTHESIS OF CHIRAL TETRAHYDROTHIOPHENES USING PHOSPHOROTHIOIC ACIDS AND RELATED COMPOUNDS AS SURROGATES FOR H_2S

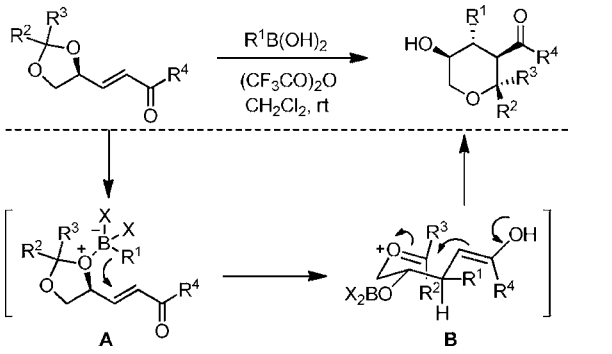
An efficient stereospecific synthesis of enantioenriched tetrahydrothiophenes was realized by utilization of phosphor-



othioic acids and related compounds as hydrogen sulfide (H_2S) surrogates (*J. Am. Chem. Soc.* **2012**, *134*, 2775−2780). The base-promoted transformation involves a double intramolecular S_N2 displacement. Subjecting enantioenriched alcohols to NaH/DMF (Note: This reagent/solvent combination is considered unsafe from a large chemical process perspective.) resulted in the corresponding tetrahydrothiophene products in good yields and enantiopurities. A broad array of functional groups is tolerated including electron-rich and electron-deficient aromatic groups. This methodology is amenable to heteroaromatics as well.

DIASTEREOSELECTIVE SYNTHESIS OF TETRAHYDROPYRANS VIA TRIFLUOROACETIC ANHYDRIDE-PROMOTED CASCADE CONJUGATE ADDITION OF BORONIC ACIDS/ACETAL RING-OPENING

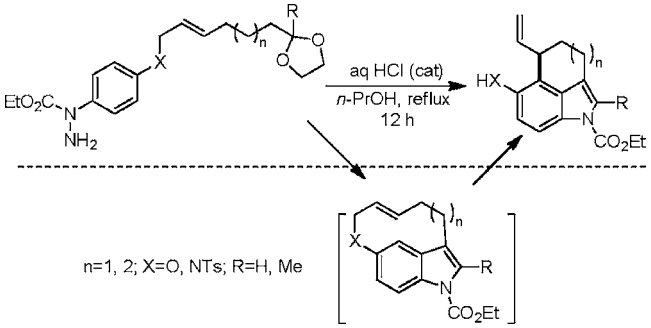
A new stereoselective cascade reaction consisting of the metal-free conjugate addition of boronic acids followed by an intramolecular ring-opening of a cyclic acetal has been disclosed (*Org. Lett.***2012**, *14*, 1187−1189). Exposure of an *α,β*-unsaturated ketone to a mixture of boronic acid (1.2 equiv) and trifluoroacetic anhydride (3.0 equiv) in methylene chloride at room temperature afforded an optically pure polysubstituted tetrahydropyran. Mechanistically, reaction of $(CF_3CO)_2O$ with the boronic acid may give a mono- or diacylboronate, where the Lewis acidity of the boron atom is enhanced. Coordination of this species with the *γ*-oxygen of the acetal gives intermediate



A, whose pseudo-intramolecular 1,4-addition (in *syn*-fashion) will lead to intermediate **B**. Subsequent intramolecular ring-closure finally accounts for the formation of the tetrahydropyran product. Several phenyl ketone substrates performed well, giving the corresponding tetrahydropyrans in good yields with high diastereoselectivity. However, no reaction was observed for the methyl ketone under similar conditions. Reactions of a variety of styrylboronic acids, with the exception of (4-methoxystyryl)boronic acid, with the acetals proceeded smoothly. No reaction was observed when the reaction was carried out with (4-methoxystyryl)boronic acid.

CASCADE INTRAMOLECULAR FISCHER INDOLE SYNTHESIS/[3,3]-SIGMATROPIC REARRANGEMENT

A synthetic approach for the access of tricyclic benzo[*cd*]-indoles was released by Professor Cho and his co-workers in



Korea (*Angew. Chem., Int. Ed.* **2012**, *51*, 2946−2949). Aryl hydrazides, incorporating a C−C double bond within the tether, were subjected to the Fischer indolization conditions (HCl, *n*-PrOH, reflux) affording the corresponding tricyclic benzo[*cd*]indoles in good overall yields. This synthetic method involves a Fischer indolization/[3,3]-sigmatropic rearrangement cascade process. It was presumed that the Fischer indolization occurs prior to the [3,3]-sigmatropic rearrangement.

CASCADE ULLMANN/SMILES/ULLMANN PROCESS CATALYZED BY COPPER IODIDE FOR THE SYNTHESIS OF DIBENZOXAZEPINONES

The synthesis of tricyclic dibenzoxazepinones was realized via a cascade process involving an Ullmann-type reaction/Smiles rearrangement/Ullmann-type reaction sequence (*Angew. Chem., Int. Ed.* **2012**, *51*, 2925−2929). The process employed CuI as a catalyst, dibenzoylmethane (dbm) as a ligand, and K_3PO_4 as a base in DMF. When a polar solvent such as toluene was used, only the Ullmann cross-coupling diaryl ether product

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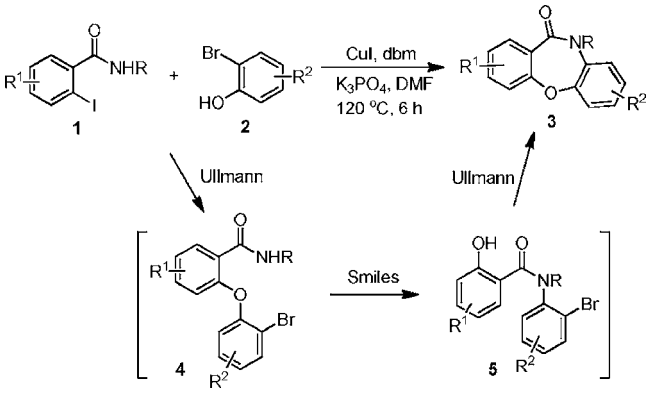
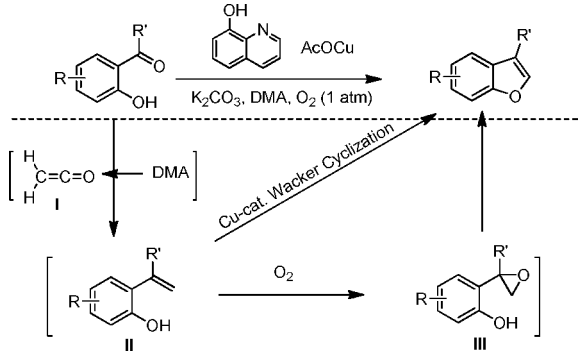


was obtained, and the subsequent Smiles rearrangement was shut down. The reactions of amides with *N*-substituted groups such as *N*-ethyl, benzyl, and 2,4-dimethoxybenzyl functional groups proceeded smoothly. However, introducing a steric hindrance group ortho to the amide proved detrimental to the reaction, resulting in relatively low product yields. Various results were obtained from reactions with bromophenol substrates bearing electron-rich or electron-poor groups.

SYNTHESIS OF BENZOFURANS VIA A COPPER-PROMOTED CASCADE PROCESS

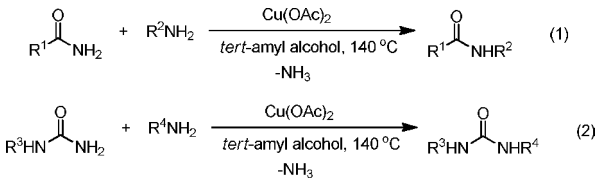
The synthesis of benzofurans, via a copper-promoted cascade process, was realized by treatment of 2-hydroxybenzophenone



derivatives with CuOAc (50 mol %) in the presence of one atmosphere of oxygen, 8-hydroxyquinoline (8-OQ, 40 mol %), and potassium carbonate (1 equiv) in *N*,*N*-dimethylacetamide (DMA) at 140 °C (*Angew. Chem., Int. Ed.* **2012**, *51*, 3220−3224). Under these reaction conditions, diarylketone substrates bearing functional groups such as alkyl, alkoxy, heteroaryl, or halogen are well tolerated. However, the reactions could not be extended to substrates with strong electron-withdrawing groups such as nitro or sulfonic acid. It was demonstrated that DMA participated in the reaction, generating a ketene **I** that would, after interactions with 8-hydroxyquinoline and diarylketone, lead to 2-hydroxy-α-phenylstyrene **II**. Two possible reaction pathways are proposed, including the copper-catalyzed Wacker cyclization of **II** and epoxidation followed by intramolecular cycloaddition/ring-opening/dehydration.

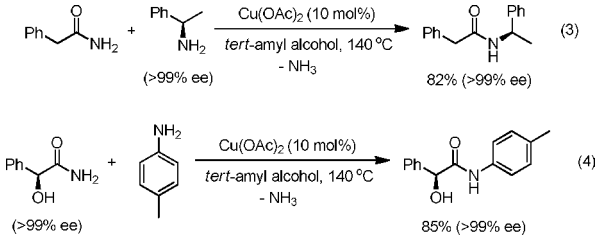
COPPER(II)-CATALYZED TRANSAMIDATION OF NONACTIVATED PRIMARY CARBOXAMIDES AND UREAS WITH AMINES

A copper-catalyzed transamidation protocol was developed for the synthesis of functionalized amides and ureas (eqs 1 and 2)

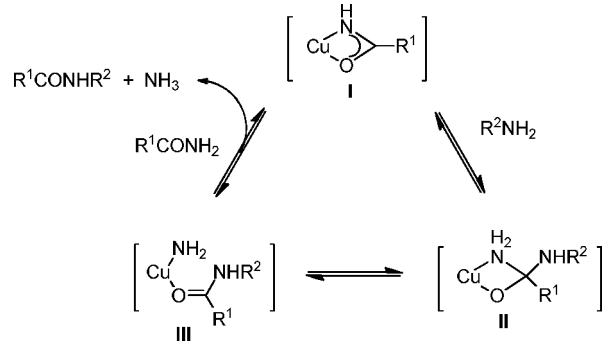


(*Angew. Chem., Int. Ed.* **2012**, *51*, 3905−3909). The transformation was performed by exposure of primary carboxamides or ureas to amines in the presence of $Cu(OAc)_2$ (10 mol %) as a catalyst in *tert*-amyl alcohol at 140 °C. The reaction tolerated electron-withdrawing and electron-donating substituents on the aryl ring of the anilines. In addition, alkyl amines as well as hydrazine exhibited excellent reactivity and yielded full conversion.

The copper-catalyzed transamidation protocol is also applicable for the preparation of chiral amides in good yields and enantiopurities (eqs 3 and 4).



Mechanistically, the reaction proceeds through several intermediates such as **I**−**III**, and the release of ammonia shifts the equilibrium to the desired product.



POLYSTYRENE-SUPPORTED (2*S*)-(−)-3-*exo*-PIPERAZINOISOBORNEOL: AN EFFICIENT CATALYST FOR THE BATCH AND CONTINUOUS FLOW PRODUCTION OF ENANTIOPURE ALCOHOLS

A polystyrene-supported analogue (PS-PIB) of 3-*exo*-morpholinoisoborneol (MIB), designed for increased chemical stability, has been synthesized and used as a ligand in the asymmetric alkylation of aldehydes with Et_2Zn (*Org. Lett.* **2012**, *14*, 1816−1819). According to Pericàs et al. from Spain, the supported ligand turned out to be highly active and enantioselective for a broad scope of substrates (92−99% ee), allowing repeated recycling. A single-pass, continuous flow process implemented with PS-PIB has been operated for over 30 h at consistently high conversion and enantioselectivity.

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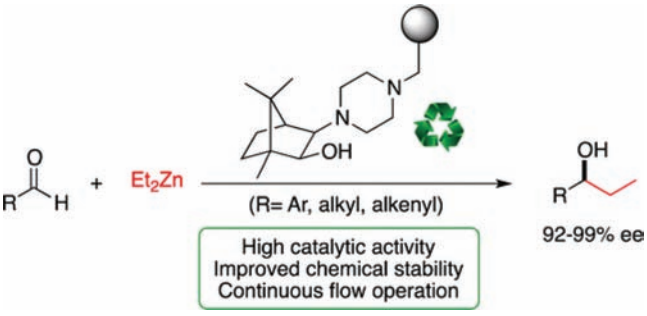
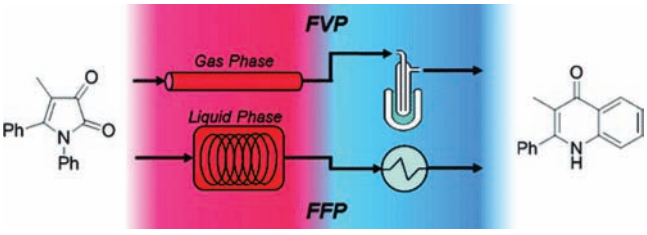


FLASH FLOW PYROLYSIS: MIMICKING FLASH VACUUM PYROLYSIS IN A HIGH-TEMPERATURE/HIGH-PRESSURE LIQUID-PHASE MICROREACTOR ENVIRONMENT

It is demonstrated by Kappe et al. from Karl-Franzens-University Graz that liquid-phase high-temperature/high-pressure (high-T/p) microreactor conditions (160−350 °C, 90−180 bar) employing near- or super-critical fluids as reaction media can mimic the results obtained using preparative gas-phase FVP protocols (*J. Org. Chem.* **2012**, *77*, 2463−2473). The high-T/p liquid-phase "flash flow pyrolysis" (FFP) technique was applied to the thermolysis of Meldrum's acid

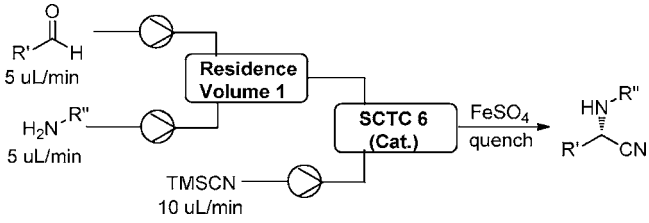


derivatives, pyrrole-2,3-diones, and pyrrole-2-carboxylic esters, producing the expected target heterocycles in high yields with residence times of 10 s to 10 min. Differential scanning calorimetry measurements and extensive DFT calculations provided essential information on pyrolysis energy barriers and the involved reaction mechanisms. The authors also investigated the correlation between computed activation energies and experimental gas-phase FVP (molecule−wall collisions) and liquid-phase FFP (molecule−molecule collisions) pyrolysis temperatures.

Flash vacuum pyrolysis (FVP) is a gas-phase continuous-flow technique where a substrate is sublimed through a hot quartz tube under high vacuum at temperatures of 400−1100 °C. Thermal activation occurs mainly by molecule−wall collisions with contact times in the region of milliseconds. As a preparative method, FVP is used mainly to induce intramolecular high-temperature transformations leading to products that cannot easily be obtained by other methods. The exact control over flow rate (and thus residence time) using the liquid-phase FFP method allows a tuning of reaction selectivities not easily achievable using FVP. Since the solution-phase FFP method does not require the substrate to be volatile any more, the transformations become readily scalable (a major limitation in classical FVP), allowing higher productivities and space−time yields compared with those of gas-phase protocols.

SELF-SUPPORTED CHIRAL TITANIUM CLUSTER (SCTC) AS A ROBUST CATALYST FOR THE ASYMMETRIC CYANATION OF IMINES UNDER BATCH AND CONTINUOUS FLOW AT ROOM TEMPERATURE

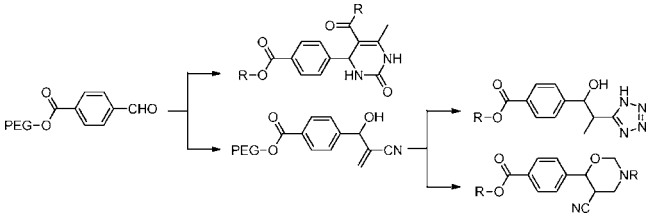
A robust heterogeneous self-supported chiral titanium cluster (SCTC) catalyst and its application in the enantioselective imine-cyanation/Strecker reaction is described under batch and



continuous processes by Seayad, Ramalingam, et al. from the Institute of Chemical and Engineering Sciences in Singapore (*Chem. Eur. J.* **2012**, DOI: 10.1002/chem.201200528). From previous publications, few efficient and reusable heterogeneous catalysts could be applied in this asymmetric catalysis at room temperature. The authors synthesized a self-supported chiral titanium cluster (SCTC) catalyst by the controlled hydrolysis of a preformed chiral titanium-alkoxide complex. The isolated SCTC catalysts were remarkably stable and showed up to 98% enantioselectivity (ee) with complete conversion of the imine within 2 h for a wide variety of imines at room temperature. Moreover, the heterogeneous catalysts were recyclable more than 10 times without any loss in activity or selectivity, which allows them to be integrated in a packed-bed reactor for continuous flow cyanation. In the case of benzhydryl imine, up to 97% ee and quantitative conversion with a throughput of 45 mg/h were achieved under optimized flow conditions at room temperature. Finally, a continuous flow three-component Strecker reaction was performed by using the corresponding aldehydes and amines instead of the preformed imines. A good product distribution was obtained for the formation of amino nitriles with ee values up to 98%.

SOLUBLE POLYMER-SUPPORTED FLOW SYNTHESIS: A GREEN PROCESS FOR THE PREPARATION OF HETEROCYCLES

PEG-supported aqueous flow synthesis coupled with ultrafiltration as the separation technique has been investigated for



the first time by Scherrmann et al. from Université Paris-Sud in France (*Eur. J. Org. Chem.* **2012**, *77*, 2188−2200). The authors applied this strategy to the preparation of new 3,4-dihydropyrimidin-2(1*H*)-ones, tetrazoles, and tetrahydro-1,3-oxazines from the same PEG-linked aldehyde as case studies. Dihydropyrimidinones were prepared by a copper(II)-catalysed Biginelli reaction, whereas a new tetrazole-containing compound was obtained by Baylis−Hillman reaction followed by reduction and 1,3-dipolar cycloaddition. Finally, a four-step

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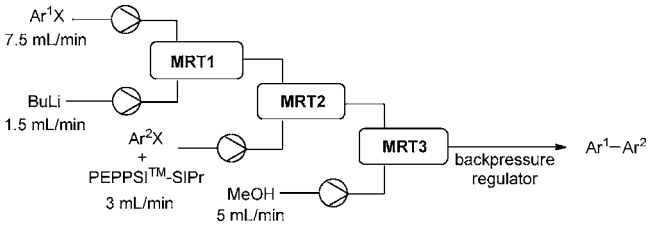
synthesis resulted in various new tetrahydro-1,3-oxazines, including Baylis–Hillman reaction, Michael addition of amines, cyclization with formaldehyde, and hydrolysis of the linkage to PEG. It is worthwhile noting the principles of green chemistry in this paper: (1) the use of water during the synthesis and most of the purification steps and (2) the benefits of the flow process in terms of improved safety and heat transfer.

CROSS-COUPLING OF ARYLLITHIUMS WITH ARYL AND VINYL HALIDES IN FLOW MICROREACTORS

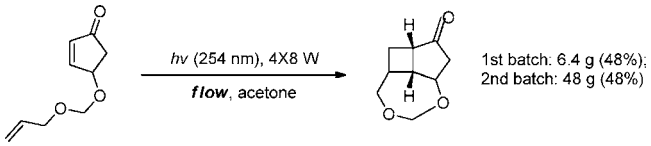
Cross-coupling of aryllithiums with aryl and vinyl halides in flow microreactors has been reported recently by Yoshida et al.



(*Chem. Asian J.* **2012**, DOI: 10.1002/asia.201101019). With the integration by Br/Li exchange of ArBr with BuLi in flow, the Pd catalysts containing a carbene ligand (for example PEPPSI-SIPr) could speed up the Murahashi coupling of ArLi with ArBr to give target products after three continuous flow microreactors (shown in the graphic). Thus, space integration realized the rapid cross-coupling of two different ArBr substrates. However, in the case of vinyl halides, the cross-coupling reaction could not be achieved under similar conditions. Finally, the Murahashi coupling with vinyl halides succeeded by using $Pd(OAc)_2$ as an effective catalyst under the same space integration strategy.

EVALUATION OF A FLOW-PHOTOCHEMISTRY PLATFORM FOR THE SYNTHESIS OF COMPACT MODULES

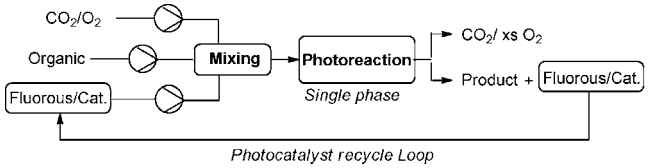
A custom-made mesoscale continuous flow-photochemistry platform towards the synthesis of novel compact modules was



evaluated recently by Nettekoven et al. from F. Hoffmann-La Roche Ltd. in Switzerland (*Tetrahedron Lett.* **2012**, *53*, 1363–1366). By pumping through the single-pass photoreactor, the continuous flow photochemistry occurred with the irradiation of thin layers (20–90 μm) of reactant dissolved in a suitable solvent. The commercially available Ehrfeld Photoreactor XL system was equipped with standard UV lamps (emission maximum at 254 nm) which are cheap, durable, and low in power consumption (8 W). This photochemical transformation could afford a synthetically relevant amount of product (>5 g, with the option of 10–100 g). A known intramolecular [2 + 2] cycloaddition reaction was chosen as a leading study to investigate the influence of flow rate (irradiation time), layer thickness, and reactant concentration. Finally, the system delivered in a first run 6.4 g of tricycle under optimized conditions, which was further successfully scaled up to 48 g, demonstrating the robustness and reliability of this flow-photoreactor platform.

MAXIMISING THE EFFICIENCY OF CONTINUOUS PHOTOOXIDATION WITH SINGLET OXYGEN IN SUPERCRITICAL CO_2 BY THE USE OF FLUOROUS BIPHASIC CATALYSIS

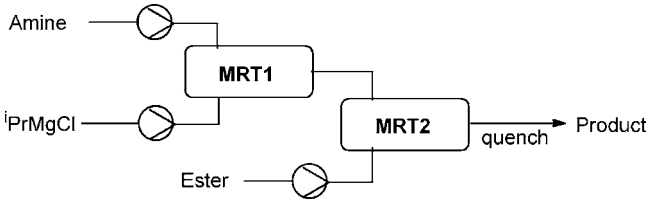
A recyclable fluorous photosensitiser for continuous photooxidation in $scCO_2$ was recently reported by George et al. from



the University of Nottingham (*Chem. Commun.* **2012**, *48*, 3073–3075). The authors have recycled this photocatalyst (fluorous biphasic catalysis) 10 times in $scCO_2$ with $^1O_2$, producing 240 mL of product by using only 12 mL of the photocatalyst solution. Before the amount of photocatalyst in the fluorous phase becomes too low (due to leaching into the organic phase), the process could work very efficiently. By using this continuous fluorous biphasic separation, the productivity could be increased, and the amount of catalyst with a ×20-fold decrease could be realized.

PREPARATION OF AMIDES MEDIATED BY ISOPROPYLMAGNESIUM CHLORIDE UNDER CONTINUOUS FLOW CONDITIONS

Amide formation mediated by isopropyl magnesium chloride is a common transformation in organic and medicinal chemistry.



Alcázar et al. described a safe, green, and functional-group-tolerant flow version of the direct amide bond formation, which was mediated by Grignard reagents, i.e., the Bodroux reaction (*Green Chem.* **2012**, DOI: 10.1039/c2gC35037h). The procedure can be applied to a wide variety of primary and secondary amines and anilines, as well as to aromatic and aliphatic esters. By using two continuous flow microreactors, final products could be obtained (shown in the graphic). This green process provides an efficient alternative to the use of alkylaluminium- and metal-catalyzed procedures.

NITROXIDE-MEDIATED POLYMERIZATION OF STYRENE, BUTYL ACRYLATE, OR METHYL METHACRYLATE BY MICROFLOW REACTOR TECHNOLOGY

A joint research project on nitroxide-mediated polymerization (NMP) in a continuous flow manner was reported by Ryu, Studer, and their co-workers from Osaka Prefecture University and University of Münster recently (*Synthesis* **2012**, DOI: 10.1055/s-0031-1290780). This radical NMP polymerization of styrene and butyl acrylate was examined in microflow tubular reactors. In comparison with polymerizations conducted in a

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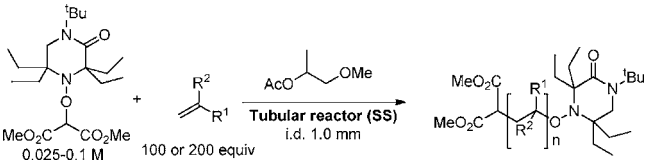
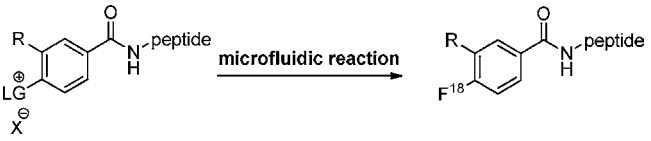


batch reactor under otherwise identical conditions, the microflow setup gave higher conversions and produced polymers with lower polydispersity indices. Block copolymers of the two monomers could be synthesized by connecting two microflow tubular reactors through a T-junction. The NMP of methyl methacrylate in a microflow tubular reactor was investigated as well.

SINGLE-STEP RADIOFLUORINATION OF PEPTIDES USING A CONTINUOUS FLOW MICROREACTOR

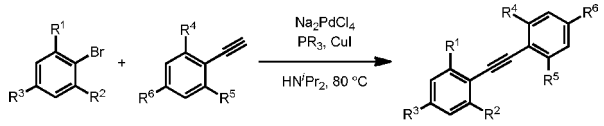
Direct ^{18}F radiolabeling of peptides performed in a continuous flow microreactor was reported recently as a joint research



project by Ametamey, Wadsakand, their co-workers (*Org. Biomol. Chem.* **2012**, DOI: 10.1039/c2Ob00015f). Single-step radiofluorination of peptides using a continuous flow microreactor was successfully accomplished for the first time. The authors found that (1) radiochemical yields were dependent on precursor concentration, reaction temperature, and flow rate; (2) the choice of leaving group had a dramatic influence on the reaction outcome; and (3) rapid reaction optimization was possible.

AN EMPIRICAL GUIDE TO SONOGASHIRA CROSS-COUPLING REACTIONS

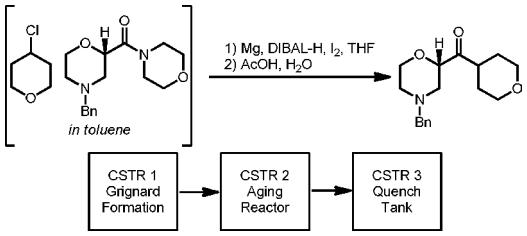
By systematically varying the aryl bromides, aryl acetylenes (and trimethylsilylacetylene), and phosphine ligands in determining the conversion−time data for nearly 200 different Sonogashira reactions, Plenio and co-workers have proposed a set of empirical rules for aiding such cross-coupling reactions (*J.*



Org. Chem. **2012**, *77*, 2798−2807). The steric and electronic properties of the substituents on the aryl bromide and acetylene components are correlated to their performance in the Sonogashira reactions. Guidelines for choosing the best phosphine ligand for a given substrate to obtain the "ideal" substrate/catalyst combination are proposed. Finally, optimized procedures for practical Sonogashira transformations are provided in the Experimental Section.

PRACTICAL CONTINUOUS FLOW BARBIER REACTION

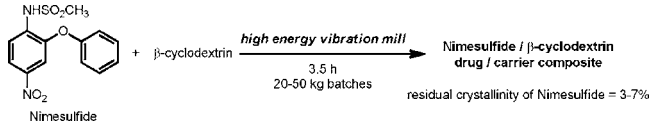
Grignard processes in the chemical industry are traditionally performed in batch mode in a three-vessel setup where the Grignard reagent formation, reaction, and quench are run separately. A simpler version (in principle) of this chemistry is the Barbier reaction where the organohalide and electrophile



are combined in one stream and then added to activated magnesium. Scientists from Eli Lilly and Company have developed and piloted a continuous flow Barbier reaction to prepare a pharmaceutical intermediate (*Green Chem.* **2012**, *14*, 1524−1536). The optimal flow process was demonstrated on a three-vessel CSTR train for a 47-h campaign run over 4 days; the product stream was subjected to continuous extraction, solvent exchange, and crystallization stages to furnish 0.4 kg product in >99% ee. Relative to the batch process, the continuous process reduced process mass intensity and magnesium usage by >30%, the quantity of magnesium to quench by >100×, and the quantity of DIBAL-H required to initiate by >100×. The authors estimate that 22 L would be the maximum scale required to manufacture 15 MT of product from the continuous process, as compared to several 2000 L reactors in series that would be required for the batch process.

POTENTIAL OF MECHANOCHEMISTRY FOR NEW AND SUSTAINABLE SYNTHESIS

Solution-based synthesis is the norm in the chemical industry, and mechanochemistry (i.e., reactions induced by the input of mechanical energy) has historically been sidelined. James and coauthors, after a review of the state-of-art in the field of mechanochemistry, conclude that, with the recently reported



advances, mechanochemistry should be a strong candidate amongst those considered for the development of new and sustainable synthesis (*Chem. Soc. Rev.* **2012**, *41*, 413−447). The major sections in the review include industrial aspects, inorganic materials, organic synthesis, cocrystallization, pharmaceutical aspects, metal complexes, supramolecular aspects, and characterization methods. An overview of the obstacles and inherent limitations to the mainstream adoption of mechanochemistry completes this analysis.

PREDICTING REGIOSELECTIVITY IN NUCLEOPHILIC AROMATIC SUBSTITUTION

Nucleophilic aromatic substitutions feature frequently in manufacturing processes in the chemical industry. Scientists from AstraZeneca have reported methods for the quantitative prediction of regioselectivity in these reactions (*J. Org. Chem.* **2012**, *77*, 3262−3269). Their "σ-complex" approach quantitatively predicts the regioselectivity for anionic nucleophiles with F^- as the leaving group as well as for neutral nucleophiles with HF as the leaving group. Their transition state approach is successful for the same predictions with Cl^-/HCl or Br^-/HBr. The authors conclude that the accuracy obtained with their

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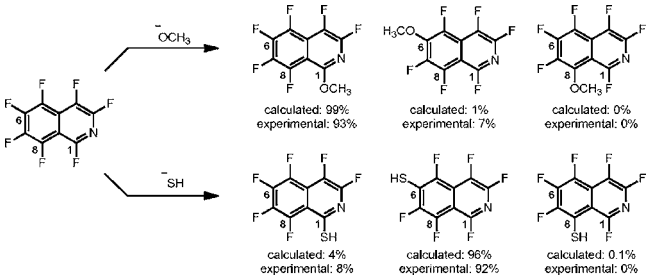
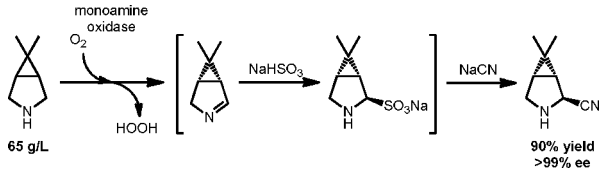


calculations is sufficient to predict whether the reaction under consideration will give predominantly the right isomer, a wrong isomer, or a mixture of isomers.

CHEMOENZYMATIC MANUFACTURING PROCESS BASED ON AN AMINE OXIDASE-CATALYZED DESYMMETRIZATION

Scientists from Merck and Codexis have reported on their collaborative research towards developing a chemoenzymatic manufacturing process for a drug intermediate where the net



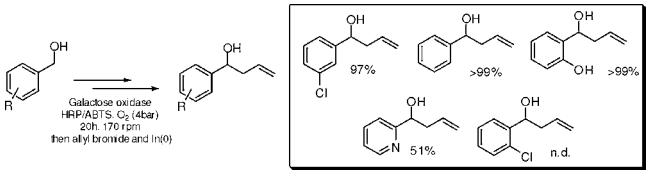
reaction is an oxidative Strecker reaction (*J. Am. Chem. Soc.* **2012**, *134*, 6467−6472). The lead wild-type monoamine oxidase enzyme was subjected to four rounds of targeted and random evolution to identify the variant enzyme optimal for reaction activity, solubility, and thermal stability. Key challenges from a process development perspective were identified (use of molecular oxygen and release of a proton per turnover), and the efforts to address these are also described. Compared to the classical resolution process utilized during the discovery and development stages, the commercial chemoenzymatic process reduced the raw material usage by 60%, the consumption of water by 61%, and the overall process waste by 63%, and increased the product yield by 150% as well.

SOLVATOCHROMIC PARAMETERS FOR SUSTAINABLE SOLVENTS

Although the field of sustainable solvents is still in its nascent stage, these solvents are increasingly being explored in academia as well as in industry as "green" alternatives to conventional organic solvents. Amongst the numerous aspects that need to be addressed before the mainstream acceptance of these solvents is a quantitative understanding of their properties. Jessop and co-workers have tried to address this lacuna by collecting from literature, or newly measuring, the solvatochromic properties of 288 solvents claimed as being "green" (*Green Chem.* **2012**, *14*, 1245−1259). These include conventional "green" solvents, bioderived solvents, liquid polymers, fluorous liquids, switchable solvents, ionic liquids, supercritical CO_2, and CO_2-expanded liquids. The Kamlet−Taft solvatochromic parameters *viz.* α (which quantifies H-bond-donating ability or acidity), β (which quantifies H-bond-accepting ability or basicity), and π^* (which quantifies polarity/polarizability) have been tabulated for these solvents. Other parameters collected include the normalized Reichardt's parameter and the λ_{max} for the dye, Nile red.

ONE-POT CHEMOENZYMATIC OXIDATION−ALLYLATION CASCADE

Faber and co-workers (*Adv. Synth. Catal.* **2011**, *353*, 2354−2358) have recently developed a method for a one-pot chemoenzymatic cascade oxidation−allylation protocol. The



main advantage of this protocol is to expand the scope of the Barbier-type reaction to aldehydes of limited stability. It is important to note that the procedure involves two sequential reactions where the allylation reagents are added after completing the oxidation step due to an incompatibility between the enzyme and other reagents. The authors have proposed and demonstrated by tandem liquid chromatography/mass spectrometry that Tyr495, at the catalytic site, under the reaction conditions studied was allylated on the phenolic moiety by an Ullmann-type aryl ether reaction disabling the active catalytic site. The optimized procedure takes place at room temperature in aqueous buffer solution without the requirement of cosolvents and is tolerant for different kinds of functional groups.

trans-FATTY ACID SELECTIVE LIPASE

At the beginning of 2012 Bornscheuer and co-workers published an interesting paper on the protein engineering of a highly selective lipase for *trans*-fatty acids (*Angew. Chem., Int. Ed.* **2012**, *51*, 412−414). The consumption of *trans*-fatty acids (TFA) is strongly related with coronary heart disease and an important issue for the food industry. Several procedures have been developed during these years to remove TFA, but up to now the most used method remains catalytic hydrogenation. The authors chose CAL-A as a starting point due to the diversity of substrates accepted by this enzyme. Several mutants were produced, and the enzymatic activity was measured by the hydrolysis of *p*-nitrophenyl esters. The best hits were tested on the hydrolysis of partially hydrogenated vegetable oils (PHVO), and the ability to recognize different fatty acids sources was measured, as shown in Table 1.

It is possible to observe from the results of the assay that CAL-A mutants do not differentiate *trans*-fatty acids from saturated fatty acids, probably due to a similarity in linear geometry adopted by both fatty acids. On the other hand, *cis*-fatty acids were not good substrates for the mutant enzymes.

Table 1

		activity		
CAL-A mutant	conv (%)	Σ_{cis} [a]	Σ_{trans} [a]	Σ_{sat} [a]
wild-type	22	883	1203	1076
L305N	14	120	299	239
T221H	5	0	48	47
I301H	12	0	107	87

[a]Volumetric activity of CAL-A variants for released fatty acids (Σ_{cis} = released amount of *cis*-fatty acids, Σ_{trans} = released amount of *trans*-fatty acids, Σ_{sat} = released amount of saturated fatty acids). One unit is defined as the amount of enzyme that releases one millimole of fatty acids per minute under the assay conditions.

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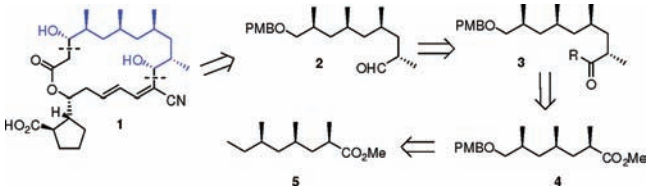
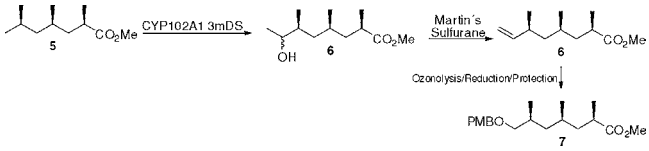
With this approach, novel CAL-A variants were engineered for *trans*-fatty acid selectivity.

CHEMOENZYMATIC SYNTHESIS OF BORRELIDIN FRAGMENT

Borrelidin is a polyketide natural product with a broad biological activity profile against a variety of diseases. Recently, Urlacher, Rauhut, and Laschat reported a chemoenzymatic approach to the synthesis of the C3−C11 fragment of this

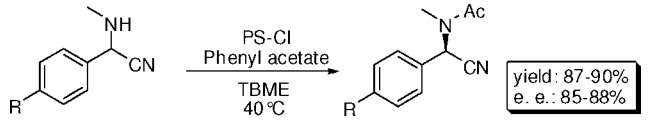


natural product (*Eur. J. Org. Chem.* **2011**, 4241−4249). Two different synthetic routes were designed to achieve the desired target where key steps were performed by enzymes. The first one is not shown here because the lipases/esterases chosen did not succeed in making the kinetic differentiation of the desired substrates and the alternative chemical step lead to epimerization of the chiral center. The second approach is shown in the next graphic, and the enzymatic step is a hydroxylation in the (w-1) position of **5** performed at preparative scale using an NADH-dependent mutated enzyme variant, CYP102A1 3mDS, of the cytochrome P450 monooxygenase from *Bacillus megaterium*, CYP102A1. The reaction was carried out using crude cell extract and afforded, after purification, 34% yield for the intermediate **6**. The next step consisted of an elimination reaction followed by ozonolysis, reduction, and protection, leading to the final intermediate **7** in 92% yield.



B. cepacia LIPASE WITH RACEMASE ACTIVITY

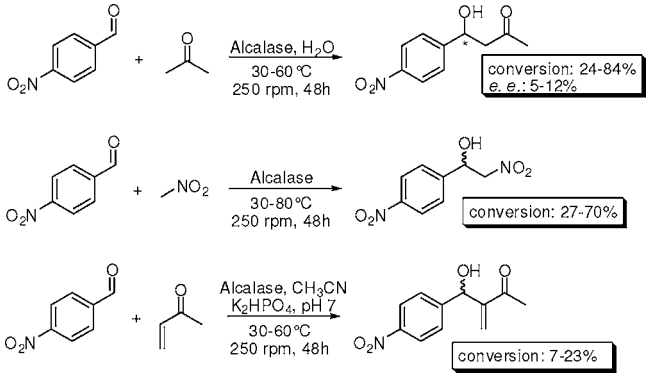
Recently, Ramström and co-workers (*Angew. Chem., Int. Ed.* **2012**, *51*, 6592−6595) found racemase activity for *Bacillus cepacia* lipase and have used this property together with the acylation activity in a dynamic kinetic resolution (DKR) for the asymmetric synthesis of α-aminonitrile amides in good yields



with high enantiomeric purity. It is important to note that these achievements circumvent the need for a chemical catalyst for the racemization step, thus avoiding any kind of incompatibility between chemical and enzymatic reagents. Two hypotheses evaluated were the following: (1) abstraction of the hydrogen atom of the starting *N*-methyl α-aminonitrile by a base and (2) in situ bond cleavage through a retro-Strecker reaction. After several controlled experiments the authors found that the racemase activity emanates from the lipase and is directly related to the retro-Strecker mechanism. Hybrid DFT calculations propose that a racemization mechanism proceeds through a C−C bond-breaking/-forming retro-Strecker/Strecker reaction catalyzed at the hydrolase active site.

PROMISCUOUS CATALYST FROM *Bacillus licheniformis*

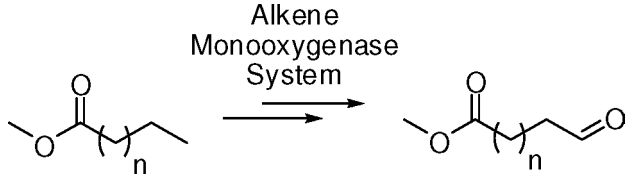
Vicente Gotor and Vicente Gotor-Fernandez in 2011 (*Adv. Synth. Catal.* **2011**, *353*, 2345−2353) published their results on the promiscuity of a protease from *Bacillus licheniformis* for different organic C−C and C−N bond-formation reactions.



The protease from *B. licheniformis* (EC 3.4.21.62) is an extracellular protease, and the authors decided in this work to explore new synthetic possibilities of the commercially available protease, immobilized as cross-linked enzyme aggregates (Alcalase-CLEA), since this type of immobilization improves the stability of the protein towards denaturation by heating, organic solvents, and auto proteolysis. The results presented show that for C−C carbon coupling the protease from *B. licheniformis* can lead to good conversions and significant enantiomeric excess in some cases. Although good results were obtained for the aldol reactions, the Baylis−Hillman reaction did not follow with the same conversion and enantiomeric excess. Excellent results were obtained for the Michael additions, where a great improvement on reaction rates could be achieved by the use of the alcalase-CLEA catalyst.

MONOOXYGENASE-BASED OXYFUNCTIONALIZATION IN FATTY ACID METHYL ESTERS

In the end of 2011, Bühler and co-workers (*Adv. Synth. Catal.* **2011**, *353*, 3485−3495) presented their results on the kinetic analysis of terminal C−H bond oxyfunctionalization in fatty



acid methyl esters by the use of a monooxygenase whole cell biocatalyst. The functionalization of this unactivated C−H bond expands the scope of fatty acid methyl ester utilization mainly by the use of this product as a precursor of biopolymers. The alkane hydroxylase system used in this work (AlkBGT) consists of the monooxygenase (AlkB), a rubredoxin (AlkG), and a rubredoxin reductase (AlkT). The results obtained show that catalyst efficiency is dependent on various parameters not directly related with the enzyme characteristics. The formation of a single product obtained by the functionalization of the

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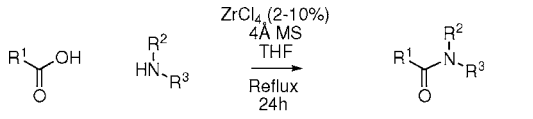
terminal C−H bond was achieved by the use of AlkBGT in vivo. The best conversion was obtained when using nonanoic acid methyl ester where 95% yield for the monofunctionalized product was obtained.

ZIRCONIUM(IV) CHLORIDE-CATALYZED AMIDE BOND FORMATION FROM NONACTIVATED CARBOXYLIC ACIDS

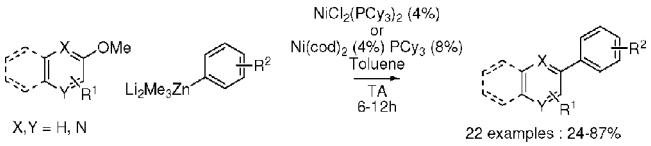
Direct amide bond formation from carboxylic acid and amine under mild conditions remains a great challenge for the synthetic community. A Swedish group described an efficient protocol using zirconium chloride as the Lewis acid promoter for the reaction and molecular sieves as the water scavenger (*Chem. Eur. J.* **2012**, *18*, 3822−3826).



Interestingly, this transformation is tolerant regarding the choice of the solvent and, unlike previously described methods, preserves the integrity of chiral centers present in the carboxylic acid coupling partners. One limitation is that aromatic carboxylic acids do not react under the developed conditions.

ARYL ETHERS AS NEGISHI COUPLING PARTNERS

Methoxyarylethers have been proved to be efficient partners in cross-coupling reactions mediated by nickel. A new example of

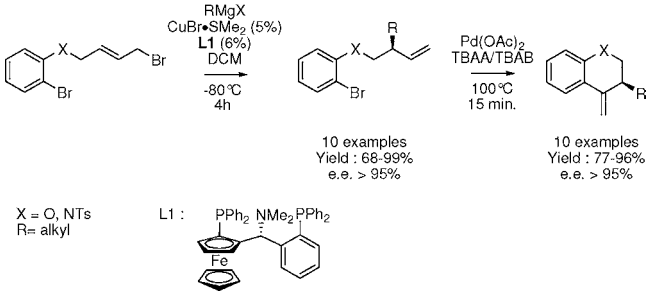


this approach has been described by Uchiyama's group in Japan. The aryl zincates, generated by the reaction of aryl iodides with Me_4ZnLi_2, reacted with various (hetero)aromatic ethers at room temperature in toluene to furnish the corresponding biaryl products in moderate to high yields (*Chem. Eur. J.* **2012**, *18*, 3482−3485).

Many functional groups are tolerated under the reaction conditions which are also mild enough to prevent racemization of the benzylic chiral center of a naproxen amide.

CATALYTIC ASYMMETRIC SYNTHESIS OF CHROMENES AND TETRAHYDROQUINOLINES

Feringa's group in The Netherlands described a sequential asymmetric allylic alkylation (AAA) with a Grignard reagent

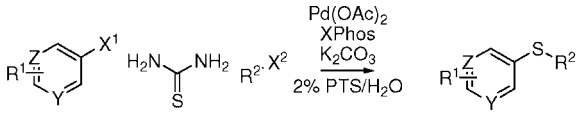


followed by an intramolecular Heck coupling which provides an efficient access to chiral chromenes and tetrahydroquinolines (*Chem. Commun.* **2012**, *48*, 3712−3714). The first step relies on a CuBr/Taniaphos-mediated AAA with different alkyl Grignard reagents. The S_N2' products are obtained in high yields and enantiomeric excess. Exo-selectivity during the Heck coupling, essential in preserving the newly formed chiral center, is assured by the use of palladium acetate in a molten mixture of tetrabutylammonium bromide (TBAB) and tetrabutylammonium acetate (TBAA).

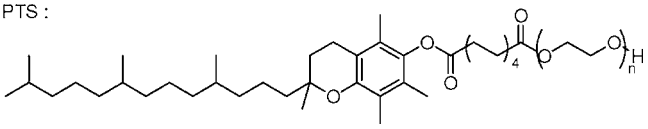
Further transformations such as hydroboration, hydrogenation, or ring-closing metathesis are also described.

PALLADIUM-CATALYZED FORMATION OF ARYL ALKYL THIOETHERS IN WATER

A palladium-catalyzed one-pot synthesis of aryl alkyl thioethers from aryl halides, alkyl bromides, and thiourea in water has



PTS :



been realized (*Adv. Synth. Catal.* **2012**, *354*, 839−845). The optimized conditions use 2% of Lipschutz's polyoxyethanyl-tocopheryl sebacate (PTS) in water, potassium carbonate, and a $Pd(OAc)_2$/XPhos as a catalytic system. Interestingly the reaction can be run at room temperature (or 50 °C in the case of electron-rich aryl chloride) even with tertiary alkyl bromides.

The mechanism is believed to involve the formation of an *S*-alkylthiouronium salt that collapses under the action of the aqueous base to liberate thiolate which enters the palladium catalytic cycle.

NEW APPLICATIONS OF TOSYLHYDRAZONES: METAL-CATALYZED DIRECT ALKYLATION OF AZOLES AND SYNTHESIS OF ALKYLBORONATES

Over the past few years, since Barluenga's report of their palladium-catalyzed cross-coupling with aryl halides, there has been renewed interest in tosylhydrazones. Two new reports highlight the versatility and usefulness of these compounds for organic chemists.

Miura's group reported the direct alkylation of azoles with tosylhydrazones (*Angew. Chem., Int. Ed.* **2012**, *51*, 775−779). The best conditions for the reaction of benzoxazoles use nickel bromide; although for oxazoles, thiazoles, and benzothiazoles cobalt bromide performed better. In all cases phenanthroline was found to be the most efficient ligand. Tosylhydrazones derived from aliphatic or aromatic ketones as well as aliphatic aldehydes react well under the described conditions.

The transition-metal-free synthesis of pinacol alkylboronate from tosylhydrazones has been achieved (*Angew. Chem., Int. Ed.*

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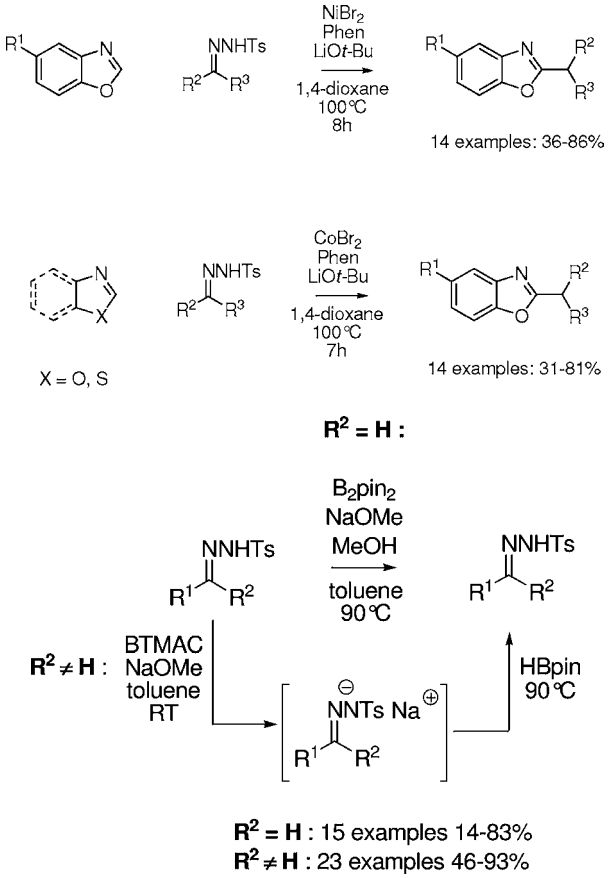

2012, *51*, 2943−2946). The reaction of tosylhydrazones derived from aldehydes is performed at 90 °C in toluene with bis(pinacolato)diboron in the presence of an equimolar amount of sodium methanolate and methanol. A change of the borylating agent to pinacolborane and formation of the sodium salt at room temperature (by the action of sodium methanolate in the presence of a phase transfer catalyst) prior to the reaction are mandatory to achieve high yields in the case of tosylhydrazones derived from ketones. Both reaction conditions tolerate a wide range of functional groups including halogen atoms.

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