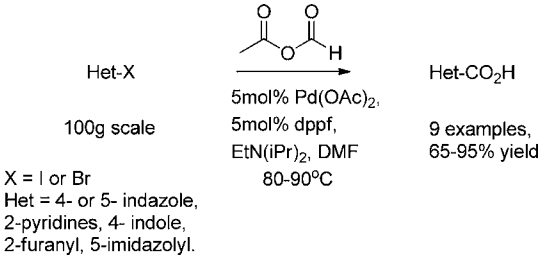
Organic Process Research & Development

Highlights from the Literature

pubs.acs.org/OPRD

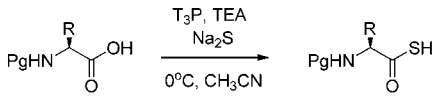
Some Items of Interest to Process R&D Chemists and Engineers

PRACTICAL Pd-CATALYSED CARBOXYLATION OF ARYL HALIDES USING FORMYL ACETATE



Chikanna (Aurigene Discovery Laboratories, India) and academic collaborators have disclosed an optimised procedure for the Pd-catalysed carboxylation of bromoheterocycles using formyl acetate as a nongaseous source of carbon monoxide (*Synth. Commun.* **2012**, *42*, 658−666). Earlier academic protocols employing metal formates failed in the authors hands to provide acceptable purity or yield of the heteroaryl carboxylic acid. Thus, a palladium(II) acetate/diphenylphosphinoferrocene catalyst combination gave optimal results. The conditions proved applicable to a variety of brominated heterocycles and also 2-iodofuran. Notably, chloro groups were reported to be unreactive under these conditions. Whilst other methods exist for the carboxylation of aromatic bromides (e.g., metalation/carbon dioxide quench), this approach benefits from a nongaseous source of carbon monoxide and facile isolation of the product, in most cases by crystallisation.

EFFICIENT SYNTHESIS OF AMINO THIOACIDS USING Na_2S/T_3P



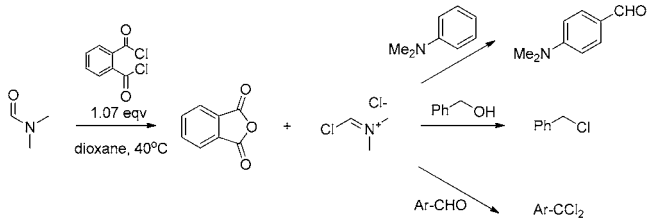
Pg = Boc, Cbz or Fmoc
R = H, Me, Bn, s-Bu, iPr, CH_2OH

10 examples, 74-95% yield

Sureshbabu et al. (*Tetrahedron Lett.* **2012**, *53*, 1406−1409) have reported a straightforward approach to the preparation of amino thioacids from the parent carboxylic acid using propylphosphonic anhydride (T3P) and sodium sulfide. Such thioacids are useful intermediates for peptide ligation. Thus, a variety of carbamate-protected amino acids underwent conversion to the thioacid with no loss of stereochemistry in typically excellent yield. This report further demonstrates the growing utility of T3P as a highly versatile coupling reagent.

ALTERNATIVE SYNTHESIS OF VILSMEIER REAGENT

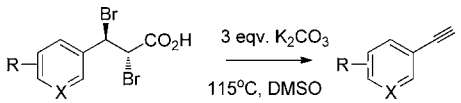
Kimura and co-workers of Iharanikkei Chemicals (Japan) have disclosed an approach for preparation of the Vilsmeier reagent that is more amenable to large-scale synthesis (*Tetrahedron Lett.* **2012**, *53*, 1116−1118). Thus, treatment of *N*,*N*-dimethylformamide



10 examples 82-98% yield

with a slight excess of phthaloyl dichloride in dioxane yielded a white crystalline precipitate of Vilsmeier reagent plus phthalic anhydride as byproduct. The Vilsmeier reagent was used either after filtration or in situ in a number of typical reactions such as aromatic formylation or chlorination of alcohols and aldehydes. The authors claim that, regarding toxicity and environmental issues, this approach is preferential over existing methodology (e.g. use of MsCl, PCl_3, phosgene, etc.).

CONVENIENT SYNTHESIS TERMINAL ALKYNES

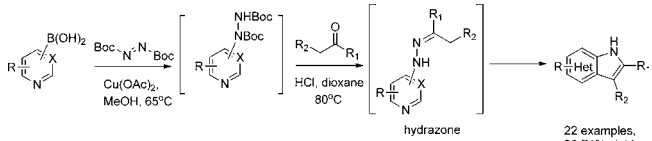


R = alkyl, halo, ester, nitro
X = CH or N

17 examples, 72-94% yield

Terminal alkynes are useful building blocks most commonly employed in metal-catalysed cross-coupling reactions such as the Sonogashira reaction. Chunxiang et al. (*Chin. J. Chem.* **2012**, *29*, 2350−2354) disclose a facile synthesis of such alkynes from aryl 2,3-dibromopropanoic acids on treatment with potassium carbonate in DMSO. The precursor dibromides were readily available from the analogous cinnamic acids by direct bromination.

AZAHETEROCYCLE BORONIC ACID FISCHER INDOLISATION



R = MeO, NH_2
R_1 = H, Me, Et
R_2 = CH_2Ar or cyclohexyl ring with R_1
X = C or N

22 examples,
26-71% yield

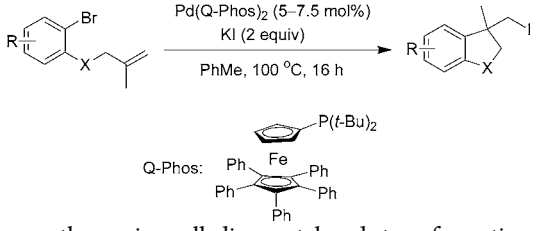
The classic Fisher indole reaction is an established means to prepare such heterocycles. Beveridge et al. (*Tetrahedron Lett.* **2012**, *53*, 564−569) of Pfizer Groton have reported an interesting boronic acid-based variant of this reaction to access a series of pyrrolo-azaheterocycles. For example, treatment of a pyridylboronic acid with DBAD in the presence of catalytic copper(II) acetate leads to the formation in situ of a di-Boc pyridylhydrazine. The indole ring formation was then achieved

Published: April 3, 2012

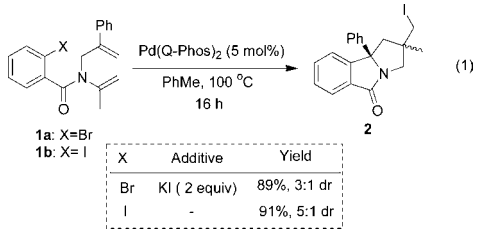
   dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534

by reaction with an enolisable ketone under acidic conditions similar to a standard Fisher indolisation. A number of substituted pyridyl, pyrimidyl, quinoline, and isoquinoline boronic acids successfully underwent this transformation. Only 4- and 8-quinoline boronic acids failed to cyclise, instead yielding the unreacted hydrazone. The commercial availability or easy access to a large number of azaheterocyclic boronic acids makes this approach attractive.

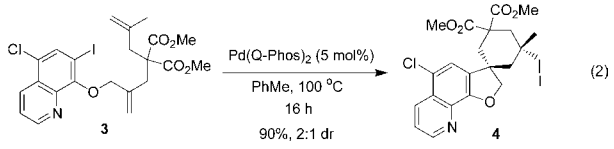
A NEW PATHWAY IN PALLADIUM-CATALYZED TRANSFORMATIONS AND ITS APPLICATION TOWARD SYNTHESIS OF BICYCLIC ALKYL IODIDES



A new pathway in palladium-catalyzed transformations has been developed and utilized to synthesize bicyclic alkyl iodides (*J. Am. Chem. Soc.* **2011**, *133*, 14916−14 919). The protocol involves Pd-catalyzed intramolecular cyclization of an aryl bromide, followed by bromide-to-iodide exchange and subsequent reductive elimination. It was found that the reaction has to be conducted at high dilution (0.05 M) in the presence of 2 equiv of potassium iodide. A range of functionalized dihydrobenzofurans, indolines, and isochromans was prepared in good-to-excellent yields. Polyunsaturated aryl substrates are amenable to the domino carbohalogenation reactions, yielding complex bicyclic alkyl iodides containing multiple stereogenic centers in high yields with good diastereoselectivities.

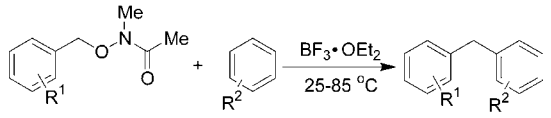


X	Additive	Yield
Br	KI (2 equiv)	89%, 3:1 dr
I	-	91%, 5:1 dr



Equation 1 describes the diastereoselective synthesis of tricyclic alkyl iodide **2** under the reaction conditions. As expected, reaction of aryl bromide **1a** in the presence of 2 equiv of potassium iodide gave **2** in 89% yield with 3:1 dr. In addition, exposure of the aryl iodide **1b** to the typical reaction conditions without external potassium iodide produced a domino cyclization product **2**, obtained in 91% yield as a 5:1 mixture of diastereomers, and no monocyclization product was observed. The domino carbohalogenation reaction was further extended to prepare spirocyclic products such as **4** (shown in eq 2) in 96% yield and 3:1 dr.

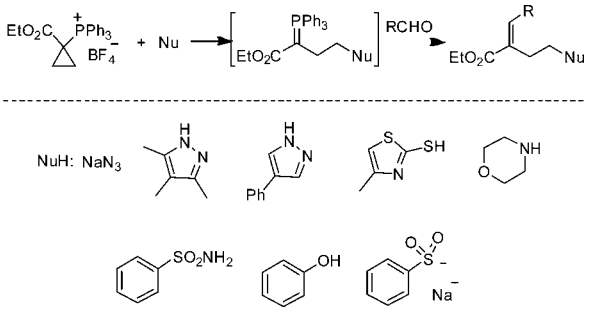
FRIEDEL−CRAFTS BENZYLATION OF ACTIVATED AND DEACTIVATED ARENES



R^1= H, Me, Cl, CF_3, CO_2Me, CN, NO_2
R^2= H, Me, Cl CF_3, CO_2Me, etc

A new Friedel−Crafts alkylation condition was developed by Bode and co-worker of Swiss Federal Institute of Technology for the benzylation of activated and deactivated arenes (*Angew. Chem., Int. Ed.* **2011**, *50*, 10913−10916). The reactions were conducted by mixing benzylic hydroxamate (1 equiv) with aromatic compounds (4 equiv) in the presence of $BF_3{\cdot}OEt_2$ (4 equiv), in which a selective activation of the *N*-methyl hydroxamic acid leaving group with $BF_3{\cdot}OEt_2$ was achieved. Using Lewis acid $BF_3{\cdot}OEt_2$, the Friedel−Crafts alkylation could be executed, easily affording the corresponding product selectively. Under the reaction conditions, various electron-rich arenes were benzylated smoothly to give the monobenzylated products in excellent yield. Deactivated arenes such as 1,3-dichlorobenzene and 1,3-difluorobenzene delivered the corresponding products in moderate yields with excellent regioselectivity.

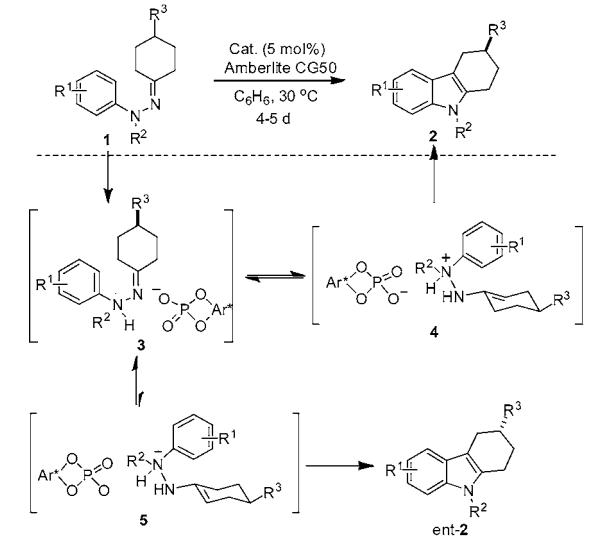
ONE-POT PROCESS INVOLVING CYCLOPROPYL OPENING AND WITTIG REACTION



A one-pot process was designed by a team of scientists of Pfizer to synthesize 2-methylene-4-substituted ethyl butyrates via nucleophilic ring-opening of (1-ethoxycarbonyl-cyclopropyl)-triphenylphosphonium tetrafluoroborate followed by a Wittig reaction (*Org. Lett.* **2011**, *13*, 5338−5341). This two-step tandem sequence was carried out by mixing the commercially available (1-ethoxycarbonylcyclopropyl)triphenylphosphonium tetrafluoroborate with a nucleophile followed by the addition of unhindered aldehyde to provide highly substituted butyrate in moderate isolated yield. Various nucleophiles have been employed to open the ring of the (1-ethoxycarbonylcyclopropyl)triphenylphosphonium salt to form ylide intermediates. Both heterocyclic and aliphatic aldehydes were proved to be good substrates except those with bulky side chains. Ketones failed to react with the ylide intermediates.

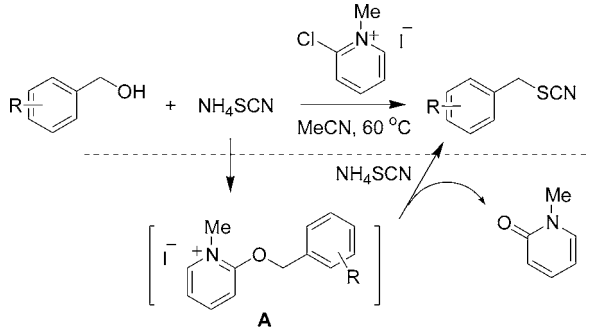
dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534

THE CATALYTIC ASYMMETRIC FISCHER INDOLIZATION



A catalytic asymmetric Fischer indole synthesis was realized with a spirocyclic chiral phosphoric acid as catalyst (5 mol %) in the presence of Amberlite CG50 as an additive (*J. Am. Chem. Soc.* **2011**, *133*, 18534−18537). The reaction features mild reaction conditions (30 °C) wherein 4-substituted cyclohexanone-derived phenylhydrazones **1** undergo Fischer indolization giving various 3-substituted tetrahydrocarbazoles **2** in generally high yields, albeit in 4−5 days in benzene. Another noticeable feature is the involvement of dynamic kinetic resolution via imines **3** and enamines **4** and **5** in a highly enantioselective manner. Amberlite CG50 was required as an additive to scavenge ammonia that otherwise would poison the catalyst. With R^1 = H, R^2 = 4-iodobenzyl, substituent R^3 could range widely from alkyl to various aryl groups. However, substrates bearing a quaternary stereogenic center furnished the corresponding product in poor yield.

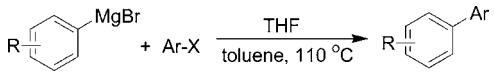
CONVERSION OF ALCOHOLS INTO ALKYL THIOCYANATES MEDIATED BY 2-CHLORO-1-METHYLPYRIDINIUM IODIDE



R=H, 4-MeO, 4-NO_2, 4-Cl, 2-Cl

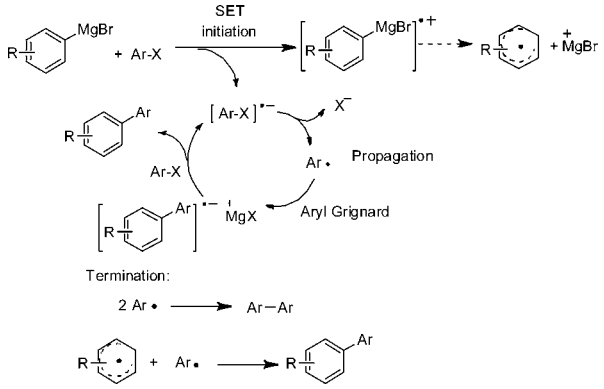
A phosphine-free conversion of alcohols into the corresponding alkyl thiocyanates was realized in the presence of 2-chloro-1-methylpyridinium iodide (*Tetrahedron Lett.* **2012**, *53*, 491−493). This transformation can be achieved either in acetonitrile or under solvent-free conditions, affording the products in good-to-excellent yields. This transformation proceeds through a pyridinium salt **A** intermediate that, in turn, reacts with $^-$SCN to produce the desired alkyl thiocyanate. Under the reaction conditions, substituted benzyl alcohols with electron-rich groups such as a 4-methoxy group performed better than those with electron-withdrawing groups, resulting in the corresponding thiocyanates in excellent yields. Alcohols with bulky groups reacted differently; for example, triphenylcarbinol led to trityl isothiocyanate as the major product.

CROSS-COUPLING OF ARYL GRIGNARD REAGENTS WITH ARYL HALIDES THROUGH $S_{RN}1$ PATHWAY



R=H, 4-Cl, 4-MeO, 3-MeO, 2-Me
X=Br, I

Application of unimolecular radical nucleophilic substitution ($S_{RN}1$) toward the cross-coupling of aryl Grignard reagents with aryl halides has been demonstrated by scientists in Japan (*Angew. Chem., Int. Ed.* **2012**, *51*, 218−221). This transition metal-free cross-coupling reaction involves initiation (to form anion radical $[ArX]^-$), propagation, and termination steps.

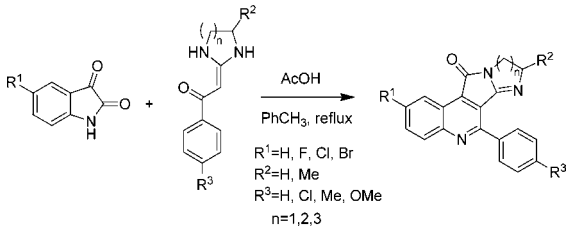


The cross-coupling reaction is applicable to a variety of aryl Grignard reagents and aryl halides. In general, electron-donating substituted arylmagnesium bromides underwent coupling with aryl halides to produce the cross-coupling products in high yields. Interestingly, the reaction of phenylmagnesium bromide with *p*-iodo(trifluoromethyl) benzene gave the coupling product in only 55% yield because of iodo/magnesium exchange side reaction. In contrast, the reaction with *p*-bromo(trifluoromethyl)benzene led to the product in a high yield (92%), where the Br/Mg exchange was sluggish. As expected, the cross-coupling reaction is not sensitive to steric effect, and good-to-excellent yields of cross-coupling products were obtained from reactions of ortho-substituted Grignard reagents and aryl iodides.

SYNTHESIS OF MULTIPLE RING SYSTEMS VIA CASCADE REACTIONS OF ISATINS WITH HETEROCYCLIC KETENE AMINALS

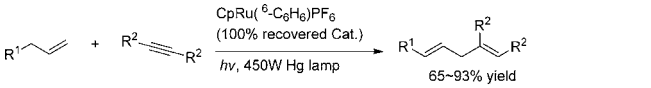
Synthesis of highly substituted imidazopyrroloquinoline derivatives was realized via reactions of isatins with heterocyclic

dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534



ketene aminals (*Org. Lett.* **2011**, *13*, 4782−4785). The process involves a cascade reaction under reflux in toluene in the presence of acetic acid. In terms of environmental impact, this method features atom economy with maximum number of atoms of reactants ending up in the products and the only by-product is water. Reactions of substituted isatins and heterocyclic ketene aminals gave the imidazopyrroloquinoline products in good-to-excellent yields.

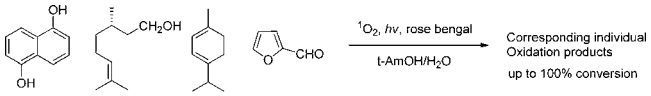
■ CONTINUOUS PHOTOCHEMICAL GENERATION OF CATALYTICALLY ACTIVE [CpRu] COMPLEXES FROM CpRu(η^6-C_6H_6)PF_6



Continuous flow catalytic photoreaction

Jamison and Gutierrez from MIT (*Org. Lett.* **2011**, *13*, 6414−6417) reported a continuous flow, catalytic ene/yne coupling reaction with active [CpRu] complexes, which were in situ generated via photolysis of an inexpensive and shelf-stable complex CpRu(η^6-C_6H_6)PF_6. Various functional groups are tolerated by the reaction to give skipped diene products in high yields (65−93%). It is noteworthy that the catalyst can be recovered quantitatively at the end of the reaction. The authors also foresee more developments for this new type of photocatalytic reactions with [CpRu] species.

■ PHOTOOXYGENATIONS IN A BUBBLE COLUMN REACTOR

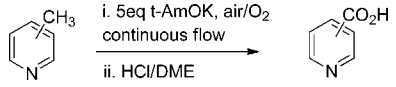


Photoxygenation in a bubble column

Photooxygenations in a bubble column reactor were reported by Oelgemöller et al. from James Cook University (Australia) and Dublin City University (Ireland). A novel, reliable, bubble column reactor was constructed and successfully applied to this dye-sensitized photoreaction in aqueous alcohol solutions (*Green Chem.* **2012**, doi: 10.1039/C2GC16439F. An air slug flow pattern was easily achieved using an appropriate air-inlet capillary for aerating. Altogether four different types of substrates (shown in the scheme) were tested and gave higher conversions and yields, due to an enlarged surface area, improved mass transfer, and superior light penetration within a thin solvent film.The reactions were performed under 'green' conditions in aqueous alcohols using air as a safe oxidant. The simple setup also allowed for a reduction in energy consumption and a complete avoidance of cooling water.

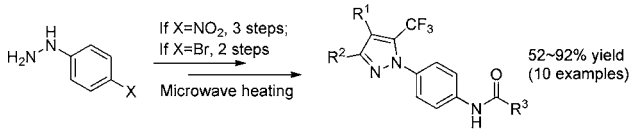
■ CONTINUOUS FLOW METAL-FREE OXIDATION OF PICOLINES USING AIR

The continuous flow, direct oxidations of 2-, 3-, and 4-picoline using either oxygen or air under metal-free conditions have



been reported by Jensen et al. from MIT (*Chem. Commun.* **2012**, *48*, 2086−2088). Complete conversion to the corresponding carboxylic acid for all three substrates was obtained at moderate temperatures and pressures within minutes. The authors also pointed out a couple of possible solutions for practical applications: (1) Automated reactor switching and cleaning protocols using two parallel reactors could ensure the process operation without down time. (2) The high cost of the solvents (if up-scaled to production) can be offset by implementation of recycling and purification schemes.

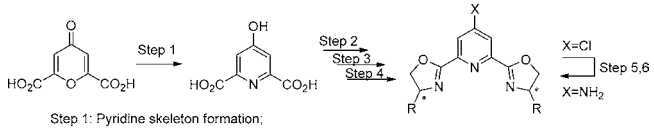
■ MICROWAVE-ASSISTED AND CONTINUOUS FLOW MULTISTEP SYNTHESIS OF 4-(PYRAZOL-1-YL)CARBOXANILIDES



Continuous flow synthesis of TRPC inhibitor

A microwave-assisted and continuous flow, multistep synthesis of 4-(pyrazol-1-yl)carboxanilides as TRPC inhibitors was reported by Glasnov, Kappe, and their co-worker from Karl-Franzens-University Graz (*J. Org. Chem.* **2011**, *76*, 6657−6669). The use of high-temperature/-pressure conditions not only resulted in a dramatic reduction of the required reaction and overall processing times but also provided consistently better product yields than the conventional methods. Two different synthetic protocols have been performed successfully, including a three-step synthesis starting from 4-nitrophenylhydrazine and a two-step synthesis starting from 4-bromophenylhydrazine. In the former protocol, condensation with appropriate 1,3-dicarbonyl building blocks, followed by reduction of the nitro group to the amine, would give the corresponding carboxylic acids after the amidation step. Among those steps, a dramatic reduction in overall processing time from ~2 days to a few minutes was achieved with significantly improved product yields than in the conventional method. In addition, the two-step route was devised involving condensation with appropriate 1,3-dicarbonyl building blocks, followed by a Pd-catalyzed Buchwald−Hartwig amidation.

■ SCALE-UP OF FLOW-ASSISTED SYNTHESIS OF C2-SYMMETRIC CHIRAL PyBox LIGANDS



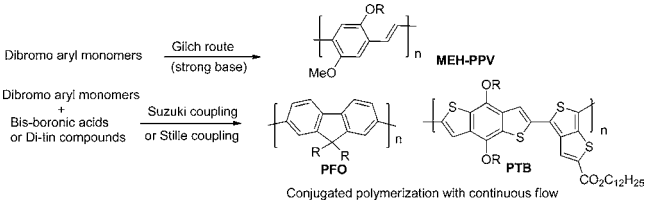
Step 1: Pyridine skeleton formation;
Step 2: Chlorination;
Step 3: Chlorobisamide formation;
Step 4: Cyclodehydration (X=Cl) to chloro-PyBox;
Step 5,6: Amino-PyBox formation (X=NH_2)

Continuous flow synthesis of PyBox ligand

A preparation of a series of PyBox ligands from commercially available chelidonic acid by a multistep flow sequence using mesoreactor technology was reported by Martin, Ley and their co-workers from Roche Ltd. and Cambridge university (*Synthesis* **2012**, *44*, 635−647). As shown in the scheme, a chloro group introduced onto the ligand scaffold was subsequently exploited to give amine derivatives, which are ready for immobilization through microencapsulation technologies.

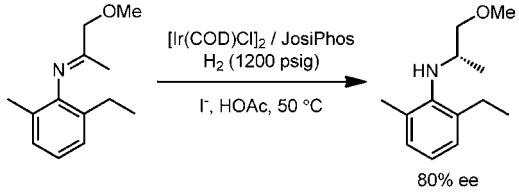
dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534

CONTINUOUS FLOW SYNTHESIS OF CONJUGATED POLYMERS



A continuous flow synthesis of conjugated polymers, widely studied in organic electronics, was recently reported by Hong et al. from the University of Melbourne (*Chem. Commun.* **2012**, *48*, 1598−1600). As shown in the scheme, a selection of different type of polymers, such as MEH-PPV, PFO, PTB, etc. could be generated from the corresponding monomers by Gilch route, Suzuki coupling, or Stille coupling, respectively. Compared to conventional batch reactions, excellent polymer molecular mass distributions were achieved in significantly reduced reaction times due to superior heat transfer and reagent control.

ASYMMETRIC HOMOGENOUS HYDROGENATION AT SCALE

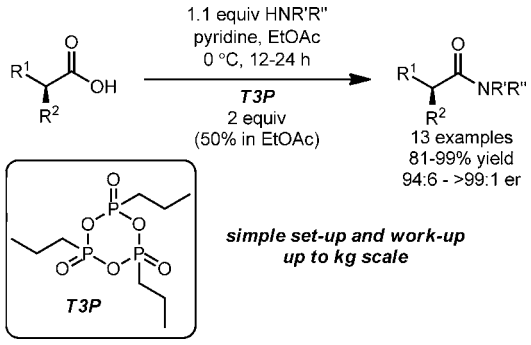


Largest scale asymmetric hydrogenation till date
TON > 600,000 h^{-1}, S/C 2,000,000

The most practiced method to introduce chirality in the pharmaceutical and fine/specialty chemicals industry has remained asymmetric homogeneous hydrogenation. Scientists at DSM Innovative Synthesis have reviewed a variety of aspects associated with practicing these processes at scale in the industry (*Chem. Soc. Rev.* **2012**, doi: 10.1039/c2cs15312b). The review starts with a compilation of select industrial applications of asymmetric homogeneous hydrogenation. This is followed by a discussion over the screening of ligands, catalysts, metals, substrates, and conditions in the development of an asymmetric hydrogenation protocol, supplemented with examples from the literature. Finally, the potential problems that could be encountered during scale up are examined, and the corresponding solutions are exemplified.

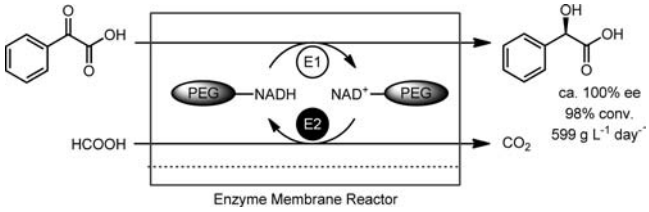
SCALABLE AMIDE BOND FORMATION WITH EPIMERIZATION-PRONE SUBSTRATES

One of the challenges in the ubiquitous amide bond formation is avoiding epimerization for activated carboxylic acid partners at stereogenic α-centers. Other issues associated with the commonly used coupling reagents (e.g., DCC, EDC, HATU, etc.) include chromatographic separation of the reagent byproduct, toxicity and environmental risks, and high cost of the reagents. Scientists from Pfizer Worldwide R&D have reported an amidation protocol utilizing the *n*-propanephosphonic acid anhydride (T3P) reagent which can overcome most of these issues and avoid epimerization of the activated carboxylic acids as well (*Org. Lett.* **2011**, *13*, 5048−5051). The methodology involves straightforward reaction setup and workup, provides



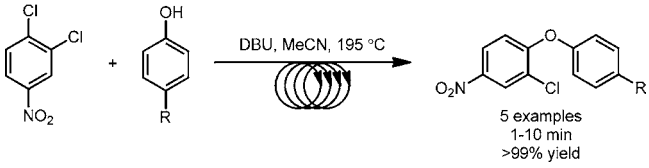
high yield and low epimerization for a range of substrates, and has been successfully demonstrated at the kilogram scale.

COUPLED CHEMO(ENZYMATIC) REACTIONS IN CONTINUOUS FLOW



Biotransformations practiced in academe and industry can be classified into four categories viz. single-reaction processes, single-reaction processes in continuous flow, coupled reaction processes, and coupled reaction processes in continuous flow; these range respectively from the least sophisticated (and most utilized industrially) to highly sophisticated methods resembling the metabolic activity of a living cell. Liese and coworkers have reviewed the state of art in the field of coupled chemo(enzymatic) reactions in flow (*Beilstein J. Org. Chem.* **2011**, *7*, 1449−1467). These processes are further classified in the review into three kinds, viz. single reactor processes in vitro, cascade reactor processes in vitro, and whole cell processes in vivo, and are described with numerous examples. The process exemplified in the scheme is the conversion of benzoyl formate to D-mandelic acid catalyzed by a combination of a D-mandelic acid dehydrogenase (E1) and a formate dehydrogenase (E2) for cofactor regeneration.

TRANSLATION OF MICROWAVE METHODOLOGY TO CONTINUOUS MICROREACTOR METHODOLOGY

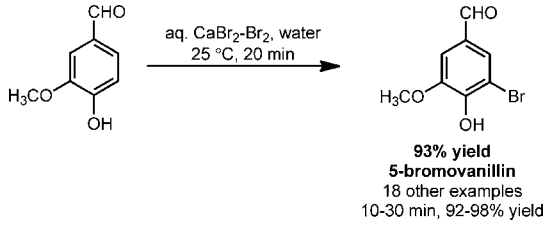


Microwave technology has found tremendous applications at the laboratory scale for rapid reaction screening. However, its implementation at the industrial scale has lagged behind, principally due to the challenges associated with uniform irradiation of large reactor vessels and the high costs associated with microwave heating at production scale. Wiles and Watts report that a methodology developed using microwave technology could be further optimized via microreactor technology, technology which could prove more amenable to industrial scale up (*Beilstein J. Org. Chem.* **2011**, *7*, 1360−1371). This

dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534

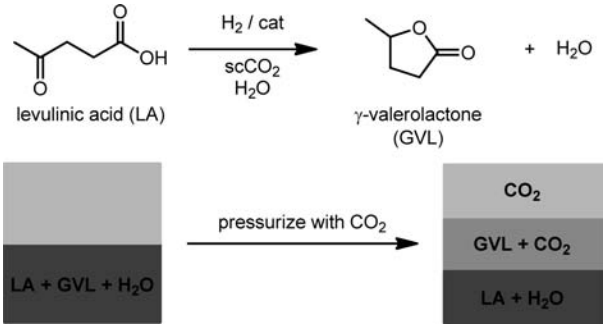
concept was demonstrated by them in their synthesis of diaryl ethers via base-mediated S_NAr reactions using an automated microreaction platform (Labtrix S1).

FACILE AQUEOUS BROMINATION OF INDUSTRIALLY IMPORTANT AROMATIC COMPOUNDS USING RECYCLABLE $CaBr_2$–Br_2 SYSTEM



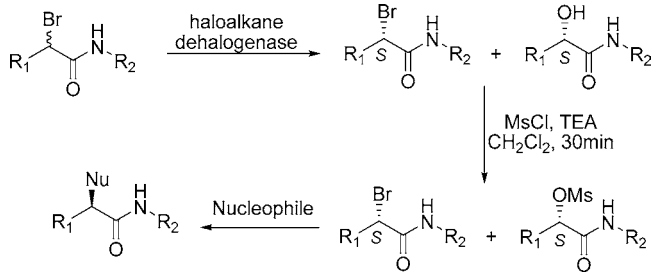
Kumar and co-workers have reported on the development of an instant and facile aqueous bromination of industrially important and structurally diverse phenol and aniline derivatives using $CaBr_2$–Br_2 as a recyclable brominating agent at room temperature (*Green Chem.* **2011**, *13*, 2187–2196). Aqueous conditions were utilized in the workup as well; the insoluble organic products were filtered and obtained in >96% HPLC purity, and $Ca(OH)_2$ was added to the filtrate to neutralize the HBr side product and generate additional $CaBr_2$. Molecular Br_2 can then be added to the filtrate to regenerate the $CaBr_2$–Br_2 reagent which can be recycled in the bromination reaction, thus constituting a "zero" effluent process; this was demonstrated in one example where the reagent was recycled for four batches, affording product with identical yield and purity.

POTENTIAL OF SUPERCRITICAL CARBON DIOXIDE IN THE CHEMICAL INDUSTRY



A number of desirable properties make supercritical carbon dioxide ($scCO_2$) an attractive solvent for use in the chemical industry. However, its use has largely been restricted to the laboratory scale due to the high energy costs associated with compressing CO_2. Methods for mitigating this cost have been reviewed by Poliakoff and co-workers (*Chem. Soc. Rev.* **2012**, *41*, 1428–1436); these include running sequential reactions without intermediate depressurization and using lower pressures of CO_2 to form "gas-expanded liquids". The other half of this review details examples where using $scCO_2$ can offer real processing advantages as compared to conventional solvents, e.g. in controlled phase separations (exemplified in the scheme for separating the product γ-valerolactone from the coproduced water).

CHEMOENZYMATIC ENANTIOCONVERGENT APPROACH FOR α-SUBSTITUTED AMIDES

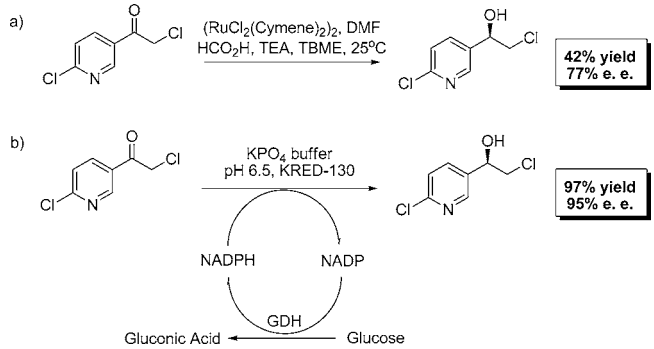


Recently, Janssen and Fering (*Angew. Chem., Int. Ed.* **2011**, *50*, 10712–10715) developed an enantioconvergent process for the synthesis of α-substituted amides where both enantiomers of the racemic substrate are converted to the same enantiomer of the product but with different functionalities. The strategy developed by the authors involves the use of haloalkane dehalogenases as the inverting enzymes in the biocatalytic step followed by synthesis of sulfonyl esters and final displacement reactions (see above). The yields are high (96% after three steps), and the enantiomeric excesses are around 98%.

The enantiopure products obtained after the biocatalytic step are directly related to the mechanism of the haloalkane dehalogenase where the cleavage of the carbon–halide bond is done by an aspartate ion (S_N2 mechanism) leading to an ester intermediate which, after hydrolysis, forms the desired product. The chiral scaffold of an α-substituted amide is an important class of chiral building block in medicinal chemistry.

BIOCATALYSIS AS AN ALTERNATIVE ROUTE TO THE SYNTHESIS OF A β-3 RECEPTOR AGONIST

Researchers from Pfizer have recently shown (*Green Chem.* **2011**, *13*, 2888–2894) that for some specific problems in industry the use of biocatalysis can overcome low yields/low selectivity and the use of difficult-to-handle reagents.



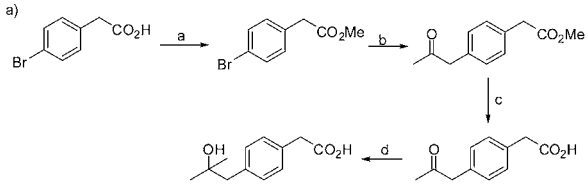
Two examples are shown; in the first one, the reduction of the α-chloroketone was performed using the Noyori asymmetric protocol leading to the desired product in 42% yield and 77% enantiomeric excess. Owing to the low ee, preparative reversed-phase chiral HPLC was required for purification, increasing the ee of the final product to 99.6%. In place of the Noyori asymmetric protocol, the authors also tried a biocatalysis approach using ketoreductases. The use of this class of enzymes leads to a great improvement on reaction yield (97%) and ee (95%), without needing HPLC for increasing enantiomeric purity of the product.

The authors have also calculated the process mass intensity (PMI), which measures the mass of raw materials, reagents,

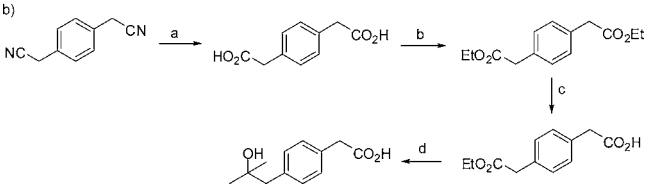
dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526–534

solvents, etc. used to provide the mass of API synthesized, i.e. kg input/kg output. The calculations reveal that the chemical route has a value of 3051 vs 395 of the enzymatic reduction.

The second example involves the undesirable tin chemistry, and the authors were able to change the synthetic route by using a chemoenzymatic approach to overcome the use of this kind of hazardous reagent.



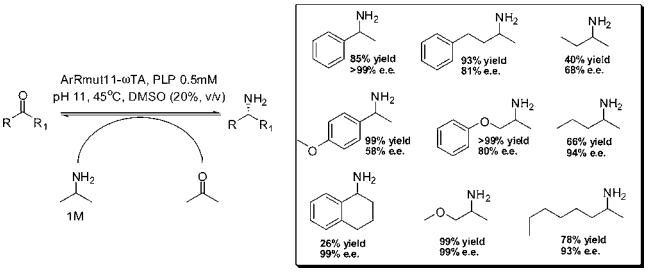
(a) AcCl, MeOH, rt, 16 h, 100%; (b) $(Bu)_3SnOMe$, isoprenyl acetate, $Pd(OAc)_2$, (o-tolyl)$_3$P, PhMe, 100°C, 98%; (c) LiOH (2 M), THF, 0 .C, 89%; (d) MeMgBr, Et_2O, THF, rt,73%.



(a) H_2O, HCl, 100°C, 88%; (b) EtOH, H_2SO_4, 100°C, 99%; (c) Lipozyme TL 100 L, pH 6.0 calcium acetate buffer (0.2 M), MeCN, 35°C, 94%; (d) THF, MeMgBr, 0°C, 54%.

The key step in this approach is the use of an operationally simple enzymatic desymmetrisation of a diester, which can be done on 200-g scale and without any chromatographic purification, in place of working with the Stille coupling early on the second step of the synthetic route. The PMI values were also calculated, but in this case, the chemical route has lower values when compared to those of the enzymatic one, probably due to large amounts of water used on this step.

EFFICIENT (*R*)-SELECTIVE TRANSAMINASES



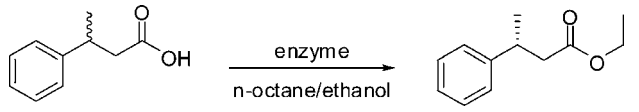
Wolfgang Kroutil and co-workers (*Adv. Synth. Catal.* **2011**, *353*, 3227−3233) have optimized four (*R*)-selective transaminases for the asymmetric reductive amination of several prochiral ketones, which have potential application in the synthesis of APIs.

The ArRmut11-ωTA is a variant of the commercial enzyme ATA-117 obtained after 11 rounds of mutations and designed for sterically demanding ketones. This enzyme presented the best yields/selectivity and was the only biocatalyst capable of transforming α-tetralone with perfect stereoselectivity. It is also important to note that the transaminases studied tolerate DMSO as a cosolvent, leading in some cases to improved yields.

BIOMIMETIC ENCAPSULATION PROMOTES ALTERATION OF ENANTIOSELECTIVITY

Most of the time the use of a biocatalyst is driven by the possible stereoisomer that can be obtained. Sometimes the use of configuration inversion protocols are required since the other stereoisomer is required but the perfect world would be one where, according to the immobilization, we could modify the enzymatic selectivity. Recently, Remaud-Simeon and co-workers (*Chem. Commun.* **2012**, *48*, 1314−1316) showed that this perfect world is not so far away. By using genetic fusion of enzymes with the R5 peptide the authors were able to have a more efficient approach to protein encapsulation based on biomimetic silica mineralization. The results obtained (see Table 1) show that two enzymes were successfully immobilized and their catalytic properties were modified, probably due to unpredictable structural modifications, leading in one case to a complete inversion of enantioselectivity.

Table 1

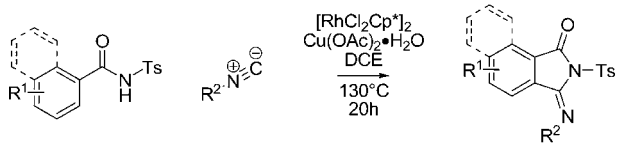


enzyme	ee subst. (%)	ee prod. (%)	conv. (%)	*E* ratio
free Cal-B	1 (*S*)	69 (*R*)	<5	n.d
free Cal-B-R5	2 (*S*)	83 (*R*)	<5	n.d
Cal-B-R5 silica	0	0	0	n.d
free PFE-I	6 (*S*)	76 (*R*)	7	10
free PFE-I-R5	5 (*S*)	79 (*R*)	6	9
PFE-I-R5 silica	23 (*R*)	94 (*S*)	20	40

THE INSERTION OF ISOCYANIDE INTO CARBON−METAL BONDS

In contrast with the many reactions involving carbon monoxide, there are few synthetic applications of the metal-catalyzed insertion of isocyanides. Two reports recently highlighted the usefulness of this kind of reaction for the production of amino-substituted heterocycles.

The group of Prof. Falck from Dallas (*Chem. Eur. J.* **2011**, *17*, 12591) described the rhodium-catalyzed annulation of *N*-benzoylsulfonamide with isocyanide through C−H activation that provides an easy access to 3-(imino)isoindolinone.



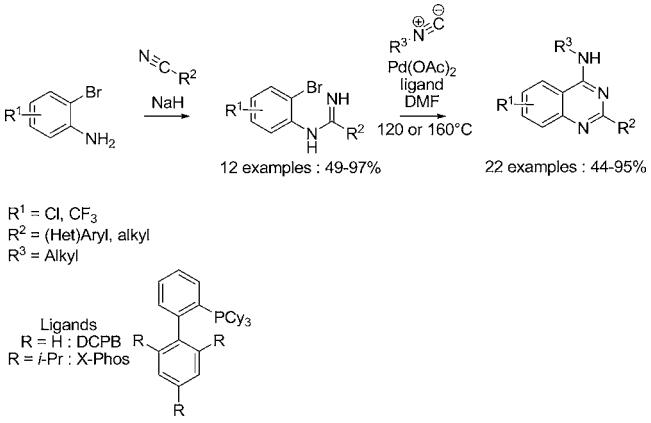
12 examples : 41-81%

The nature of the reoxidant ($Cu(OAc)_2 \cdot H_2O$) as well as the presence of the tosyl group on the amide nitrogen are the key factors for the success of this reaction. The nature of the aromatic ring and its substitution pattern can be varied even if electron-poor aromatics afford better yields. The transformation proceeds readily with both aromatic and aliphatic isocyanide with the exception of phenyl- and methoxyphenyl-isocyanide.

Oru's group from The Netherlands (*Chem. Eur. J.* **2011**, *17*, 15039) described the synthesis of 4-aminoquinoxazoline by palladium-catalyzed imidoylation of *N*-(2-bromoaryl)amidines.

The reaction of different 2-bromoanilines with various nitriles afforded the amidine substrates in fair-to-excellent yields. Subsequently, imidoylation with aliphatic isocyanides, in the presence of palladium acetate in combination with DCPB or X-Phos, furnished the expected heterocycles. The optimization

dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534

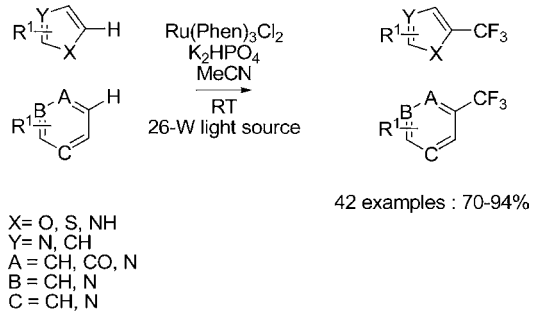


of the temperature, nature, and loading of the catalyst is required to get a high yield. Interestingly, chlorines are tolerated on both aromatic parts as long as the temperature is kept low.

PHOTOREDOX-CATALYZED TRIFLUOROMETHYLATION

As part of their ongoing interest in photoredox catalysis, the group of MacMillan described an efficient protocol for the trifluoromethylation of (hetero)aromatic compounds (*Nature* **2011**, *480*, 224).

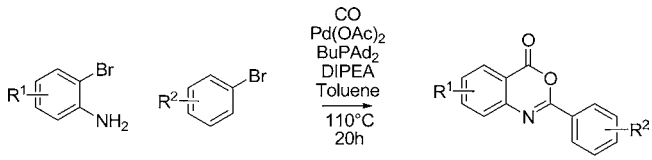
The key improvement compared to the method previously developed for the α-trifluoromethylation of carbonyl compounds is the use of trifluoromethanesulfonyl chloride (trifyl chloride) as the source of CF_3 radicals. Setting up the reaction is quite simple as it involves the irradiation with an ordinary household light bulb of a solution of the substrate, trifyl chloride, K_2HPO_4, and the photocatalyst ($Ru(Phen)_3Cl_2$) in acetonitrile at room temperature.



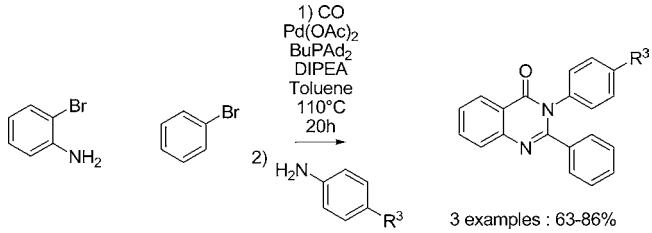
The substrate scope is quite large and includes five- and six-membered heteroaromatic compounds as well as substituted benzene. The yields are uniformly high, the selectivity is, in most cases, impressive, and a wide variety of substituents on the (hetero)aromatic ring is tolerated (alkyl, ether, halogens, thioether, protected amino group). This method has also been applied to more complex substrates such as lidocaine, ibuprofen, or atorvastatin, although with a poor selectivity.

PALLADIUM-CATALYZED CARBONYLATIVE COUPLING FOR THE SYNTHESIS OF 2-ARYLBENZOOXAZINONES

The group of Prof. Matthias Beller (*Chem. Eur. J.* **2011**, *17*, 12246) described the development of an efficient domino synthesis of 2-arylbenzooxazinones from easily available 2-bromoanilines and (hetero)aryl bromides. The reaction is best carried out in toluene with DIPEA as base and a catalytic system consisting of $Pd(OAc)_2$ and the bulky phosphine $BuPAd_2$ under a 5 bar pressure of carbon monoxide.

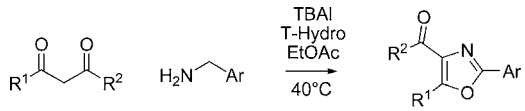


The reaction is quite tolerant regarding the substitution of the aryl bromide as both electron-donating and -withdrawing substituents can be present. Unfortunately, electron-deficient heterocyclic bromides and alkenyl bromides led to low yields. The authors extended their methodology to the one-pot synthesis of 2-arylquinoxalinone by directly adding an aniline at the end of the double carbonylation reaction.



HYPERVALENT IODINE-MEDIATED OXIDATIVE SYNTHESIS OF OXAZOLE DERIVATIVES

Besides traditional metal-catalyzed C−H activation, organocatalytic approaches for the formation of carbon−oxygen or carbon−nitrogen bonds from an sp^3 C−H bond are gaining more importance. Zhu's group from Nanking has disclosed (*Chem. Commun.* **2012**, *48*, 979) an interesting methodology for the synthesis of oxazole derivatives from benzylamines and 1,3-dicarbonyl compounds. The reaction is mediated by a catalytic amount of TBAI and is best conducted with T-hydro as the oxidant in EtOAc as a solvent.



Aliphatic and aromatic 1,3-diketones and β-ketoester are suitable substrates for this transformation which tolerated also electron-rich and -deficient benzylamines. The authors provide a mechanistic study that rules out a possible radical pathway and furnishes evidence of the involvement of ammonium hypoiodite or iodite in the cascade sp^3 C−H activation.

Ian Wilson

Almac Sciences, Almac House, Seagoe Industrial Estate, Craigavon, Northern Ireland, BT63 5QD, United Kingdom

Wenyi Zhao

Jacobus Pharmaceutical Co. Inc., Princeton, New Jersey 08540, United States

Dongbo Zhao

Bayer Technology and Engineering (Shanghai) Co. Ltd., F3 Area, Mu Hua Road, Shanghai Chemical Industry Park, Shanghai 201507, P.R. China

dx.doi.org/10.1021/op300066h | *Org. Process Res. Dev.* 2012, 16, 526−534

Aman A. Desai
Process Science, Core R&D, The Dow Chemical Co., Midland, Michigan 48674, United States
Rodrigo Octavio M. A. de Souza
Chemistry Institute, Federal University of Rio de Janeiro, Athos da Silveira Ramos Street 149, Rio de Janeiro 24230153, Brazil
Sylvain Guizzetti
Structural Biology, Novalix, Building A: Chemistry, Bioparc Boulevard Sébastien Brant BP 30170, F-67405 Illkirch, France
Trevor Laird*
Scientific Update LLP, Maycroft Place, Stone Cross, Mayfield, East Sussex, TN20 6EW United Kingdom

AUTHOR INFORMATION

Corresponding Author
*E-mail: trevor@scientificupdate.co.uk