Organic Process Research & Development

HIGHLIGHTS FROM THE LITERATURE

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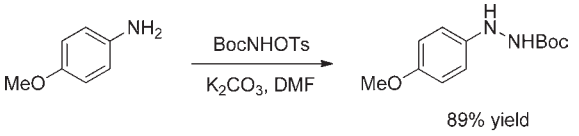
Some Items of Interest to Process R&D Chemists and Engineers

■ *N*-AMINATION USING *N*-BOC-*O*-TOSYL HYDROXYLAMINE

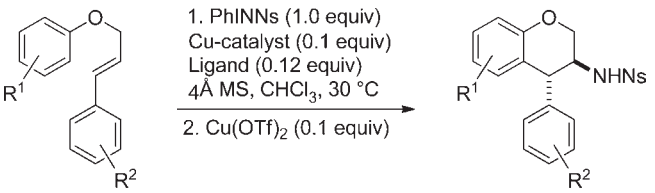


24 examples, 68-92% yield

aryl- and alkylamines

The group of Thambidurai in India reports on the use of *N*-Boc-*O*-Tosyl hydroxylamine as an effective reagent for the amination of aniline and alkylamines (*Synlett* **2011**, 1993). The reagent is readily prepared from aqueous hydroxylamine using $(Boc)_2O$ and tosyl chloride sequentially. Moreover, results from differential scanning calorimetry suggest this reagent is substantially less energetic than other commonly used electrophilic amination reagents (e.g., oxaziridines, *O*-arylhydroxylamines etc). The group applied this reagent in the amination of 12 anilines and twelve primary and secondary alkylamines and typically observed good to excellent yields.

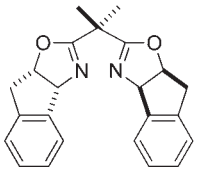
■ CATALYTIC ENANTIOSELECTIVE AZIDOARYLATION OF ARYL CINNAMYL ETHERS



Yield = 25-55%, dr > 99 : 1, ee% up to 95%

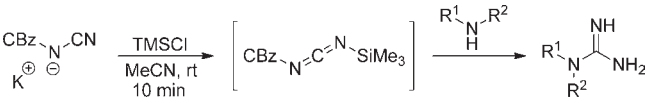
Cu-catalyst = $Cu(OTf)_2$ or $Cu(ClO_4)_2.6H_2O$

Ligand =



Also based in India, the group of Hajra reports on a catalytic enantioselective one-pot aziridoarylation reaction of aryl cinnamyl ethers (*J. Org. Chem.* **2011**, *76*, 7334). The combination of suitable copper catalysts ($Cu(OTf)_2$ or $Cu(ClO_4)_2 \cdot 6H_2O$) and chiral BOX ligands was found to promote an asymmetric aziridination/intramolecular arylation (Friedel–Crafts) sequence. Overall this chemistry provides a general and direct method for the synthesis of *trans*-3-amino- 4-arylchromans with high regio-, diastereo- (dr > 99:1), and enantioselectivity (up to 95% ee). Unfortunately, the yields are currently quite low, and the authors do not discuss this aspect to any significant extent (there is no data on conversion of starting material). Nevertheless, this is a potentially useful catalytic asymmetric transformation if the yield could be improved. The authors demonstrate the utility of this chemistry in the preparation of a *trans*-3-amino-4-arylchroman intermediate in the synthesis of doxanthrine, an agonist for the dopamine-D1 receptor developed at GSK.

■ SYNTHESIS OF MONO-*N*-ACYLGUANIDINES

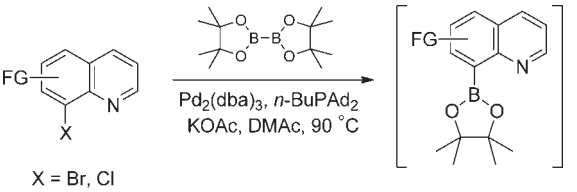


12 examples, 63-92% yield

R = alkyl, aryl

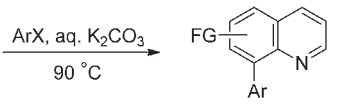
A large number of synthetic methods have been developed to introduce the guanidine group. A simple and efficient one-pot method for the synthesis of monoprotected guanidines is reported by the Looper group at the University of Utah (*J. Org. Chem.* **2011**, *76*, 6967). Treatment of an acylcyanamide with chlorotrimethylsilane generates a reactive *N*-silylcarbodiimide capable of guanylating a variety of amines. Typically the reaction is complete in 15 min at room temperature for primary and secondary aliphatic amines. Hindered amines and anilines are also competent nucleophiles but require extended reaction times. A total of 12 examples are presented with yields moderate to excellent. Deprotection of the product mono-Cbz protected guanidines can be carried out under standard hydrogenolysis conditions to provide the free guanidines or their HCl salts.

■ SYNTHESIS OF 8-ARYLQUINOLINES VIA ONE-POT BORYLATION/SUZUKI–MIYAURA CROSS-COUPLING



X = Br, Cl

FG = F, MeO, CO_2Me, Me, ketone



15 examples, 73-98% yield

8-Arylquinolines are pharmaceutically important scaffolds present in many molecules with biological activity. Zhang and

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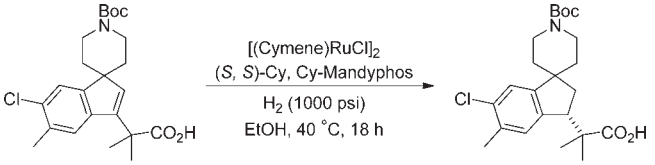
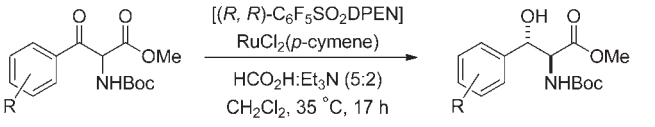
co-workers at Boehringer Ingelheim report on a one-pot process for the synthesis of 8-arylquinolines via Pd-catalyzed borylation of quinoline-8-yl halides and subsequent Suzuki−Miyaura cross-coupling with aryl halides (*J. Org. Chem.* **2011**, *76*, 6394). The process uses the typical bis(pinacolato)diboron for the borylation, which is catalyzed by a $Pd_2(dba)_3$/*n*-BuPAd$_2$ system. The same catalyst system is effective for the cross-coupling with aryl halides, and yields of 73−98% were observed across 15 examples.

CATALYTIC ASYMMETRIC HYDROGENATION TO ACCESS SPIROINDANE DIMETHYL ACETIC ACID



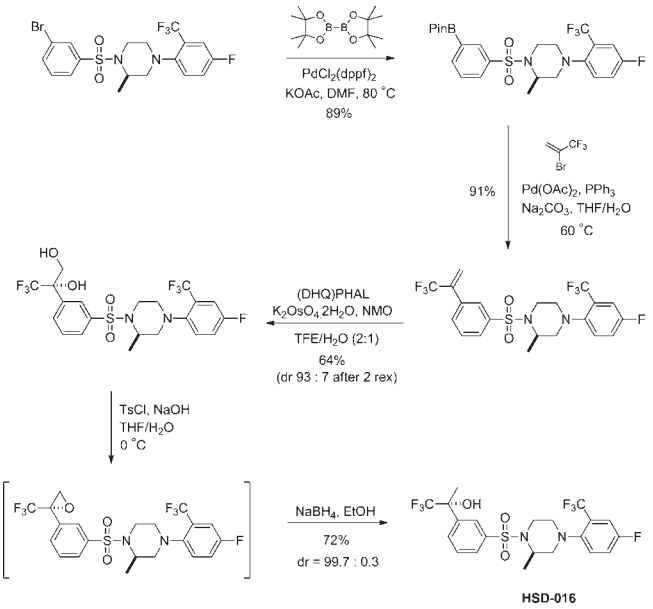
The melanocortin receptor subtype 4 (MC4R) system plays an important role in many physiological processes and MC4R agonists have potential as treatments for obesity and erectile dysfunction. A recent collaboration between the Medicinal and Process chemistry departments at Merck applied high-throughput screening technologies for the development of a catalytic asymmetric hydrogenation of a key synthetic intermediate critical for SAR studies. The report by He and co-workers describes the successful demonstration of an enantioselective synthesis of an (*S*)-spiroindane dimethyl acetic (*Tetrahedron Lett.* **2011**, *52*, 3621). Catalyst screening identified a Mandyphos-ruthenium catalyst which produced the (*S*)-acid in 88% yield and 93% ee with 4 mol % catalyst loading. Hydrogenation of α,β-unsaturated carboxylic acids are ubiquitous in the literature; however, β,γ-unsaturated examples containing geminal α-substitution (which block the ability of the double bond to migrate) have not been previously reported.

ENANTIOSELECTIVE SYNTHESIS OF *ANTI*-ARYL β-HYDROXY α-AMINO ESTERS VIA DKR TRANSFER HYDROGENATION



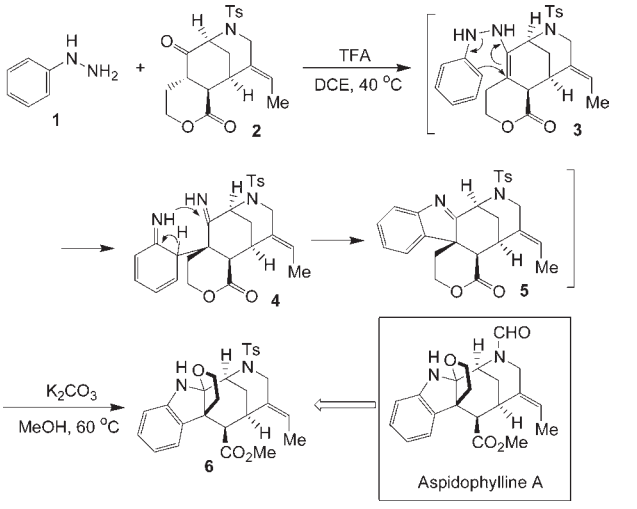
An efficient preparation of highly enantiomerically enriched aryl β-hydroxy α-amino esters via dynamic kinetic resolution (DKR), asymmetric transfer hydrogenation of α-amino β-keto esters, is described by Liu, Shultz, and co-workers at Merck (*Tetrahedron Lett.* **2011**, *52*, 1685). The *anti*-β-hydroxyl α-amino esters were obtained both in high yield and high diasteroselectivity using various Ru-diamine-based catalysts typically employed for this type of reaction. The observed high anti selectivity in this case is inconsistent with previous results in the literature. The absolute stereochemistry of the aryl β-hydroxy α-amino esters was unambiguously confirmed via chemical derivatization as well as vibrational circular dichroism (VCD) techniques.

SYNTHESIS OF AN 11β-HYDROXYSTEROID DEHYDROGENASE TYPE 1 INHIBITOR HSD-016



Cortisol and the glucocorticoid receptor signaling pathway has been linked to the development of diabetes and metabolic syndrome. In vivo, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the conversion of inactive cortisone to its active form, cortisol. Existing clinical data have supported 11β-HSD1 as a valid therapeutic target for type 2 diabetes. As part of a research program at Pfizer, compound HSD-016 was discovered to be a potent, selective, and efficacious 11β-HSD1 inhibitor. In this report, Wan and co-workers describe a reliable and scalable synthesis of HSD-016 (*J. Org, Chem.* **2011**, *76*, 7048). Key transformations include an asymmetric synthesis of a chiral tertiary alcohol via Sharpless dihydroxylation, epoxide formation, and subsequent mild reduction using $NaBH_4$. This route ensured multikilogram quantities of HSD-016 necessary for clinical studies.

EFFICIENT ASSEMBLY OF THREE-RING SYSTEM VIA ONE-POT PROCESS IN THE SYNTHESIS OF ASPIDOPHYLLINE A



A one-pot process is an economically favorable operation by condensing a number of bond-formation steps involving creation of rings and stereogenic centers into a single transformation without

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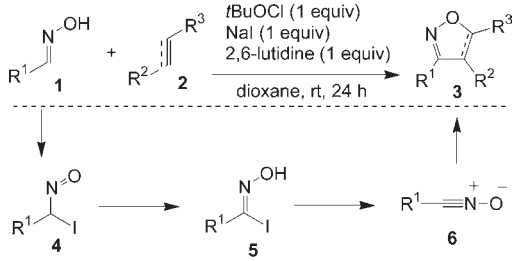
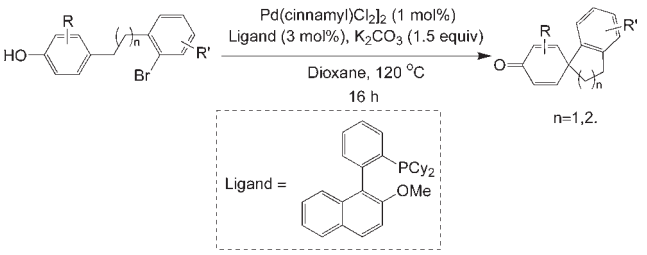
isolation of intermediates. Applying the one-pot approach towards the total synthesis of (±)-aspidophylline A, Garg and his co-workers of University of California, Los Angeles (*J. Am. Chem. Soc.* **2011**, *133*, 8877) constructed efficiently a three-ring system of aspidophylline A. This one-pot process involves a 3,3-sigmatropic rearrangement and subsequent ring rearrangement. The initial nucleophilic addition was realized via reaction of cyclic ketone **2** with phenylhydrazine in the presence of TFA in dichloroethane, leading to **3**. The thermal 3,3-sigmatropic rearrangement of **3** was followed by a base-mediated ring rearrangement of **5** in methanol to afford the methyl ester **6** in 70% overall yield. This base-catalyzed rearrangement involves lactone methanolysis followed by cycloaddition. Thus, the one-pot sequence led to the introduction of three rings by assembly of one C−C bond and two C−heteroatom bonds, all with complete diastereoselectivity.

■ SYNTHESIS OF ISOXAZOLINES OR ISOXAZOLES VIA CYCLOADDITION OF OXIMES WITH ALKENES (OR ALKYNES)

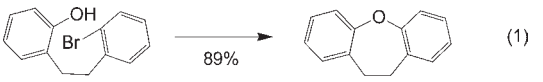


A [3 + 2] oxidative cycloaddition was developed for access to isoxazolines and isoxazoles via reactions of oximes and alkenes/alkynes (*Org. Lett.* **2011**, *13*, 2966). The reactions proceeded readily at room temperature in the presence of *t*-BuOI, generated in situ by reaction of *tert*-BuOCl with NaI and a base, affording the desired products in good to excellent yields. Under these conditions, a variety of electron-deficient olefins and alkynes was transformed into the corresponding isoxazolines and isoxazoles with complete regioselectivity except that methyl propiolate gave a mixture of regioisomers. The reaction tolerates a wide diversity of substituents at the para position of benzaldoximes including both electron-donating and -withdrawing groups. The scope of the reactions was also extended to various aldoximes bearing alkyl groups derived from acetaldehyde, butanal, and cyclohexyl carbaldehyde. Although the detailed reaction pathway is unclear, the reaction was hypothesized to proceed through three intermediates, α-iodonitroso intermediate **4**, oxime derivative **5**, and nitrile oxide **6**.

■ PALLADIUM(0)-CATALYZED ARYLATIVE DEARO-MATIZATION OF PHENOLS



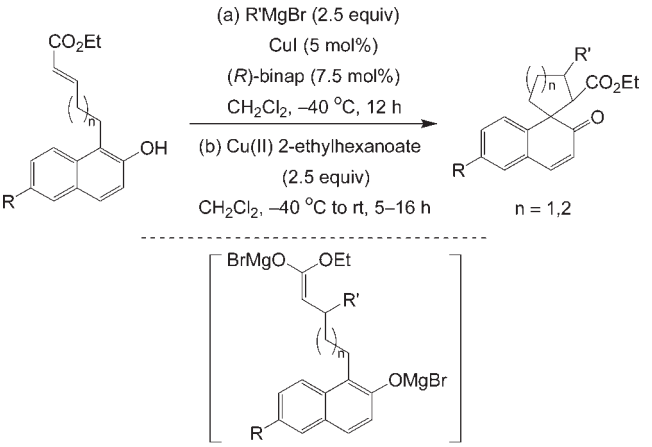
An approach for preparation of spirocyclohexadienone derivatives was developed by Buchwald and his co-workers of Massachusetts Institute of Technology via palladium-catalyzed arylative dearomatization of phenols (*J. Am. Chem. Soc.* **2011**, *133*, 9282). The conversion of phenols was accomplished in the presence of a palladium catalyst (generated in situ) (1 mol %), ligand (3 mol %), and potassium carbonate (1.5 equiv) in dioxane solvent at 120 °C to furnish the spirocyclohexadienone products in good to excellent yields with high levels of enantiocontrol (up to 91% ee). The success of this dearomatization strategy relies on the ability of the catalyst system that is inefficient for C−O bond cross-coupling in order to avoid competitive intermolecular diaryl ether formation. Both R (on phenol ring) and R′ (on aryl bromide moiety) substituents are limited to electron-neutral or -donating groups.



(1)

In addition, the tethered bromoaryl phenol is limited to the para position, or a cyclic diaryl ether could result from intramolecular C−O cross-coupling of the ortho tethered bromoaryl phenol (eq 1).

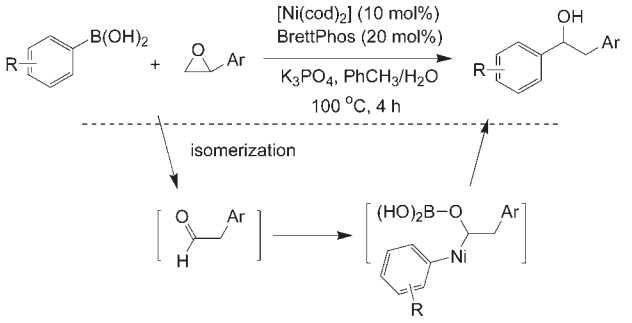
■ CATALYTIC ASYMMETRIC CONJUGATE ADDITION/OXIDATIVE DEAROMATIZATION



In contrast to Buchwald's work, ortho-substituted tethered naphthol compounds underwent a sequential asymmetric conjugate addition/oxidative cyclization affording highly functionalized benzo-fused spirocyclic cyclohexenones containing three contiguous stereocenters with high diastereoselectivity (*Angew. Chem. Int. Ed.* **2011**, *50*, 5834). The transformation was done by treatment of naphthols in CH_2Cl_2 with a solution of CuI (5 mol %), (*R*)-binap (7.5 mol %), and Grignard reagent (2.5 equiv) at −40 °C for 4−12 h, followed by addition of solid copper(II) 2-ethylhexanoate (2.5 equiv) in one-pot fashion. Generally, linear alkyl Grignard reagents performed well, giving the desired products in good to excellent yields with good ee, albeit reaction with isopropylmagnesium bromide resulted in low enantioselectivity. Reactions of Grignard reagents, such as MeMgBr, PhMgBr, and reagent with a terminal olefin, behaved poorly. The reactions tolerated naphthols with electron-withdrawing or -donating groups in the 6 position, providing the corresponding cyclized products in good yields and enantioselectivities. Another observation is that the six-membered spirocyclic

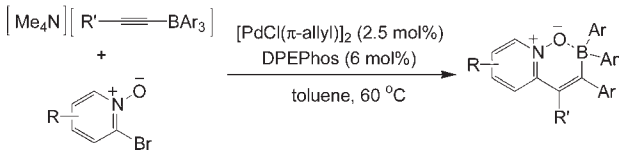
product was obtained from substrate with $n = 2$ in lower yield than the corresponding five-membered ring ($n = 1$).

NICKEL-CATALYZED CROSS-COUPLING OF STYRENYL EPOXIDES WITH BORONIC ACIDS



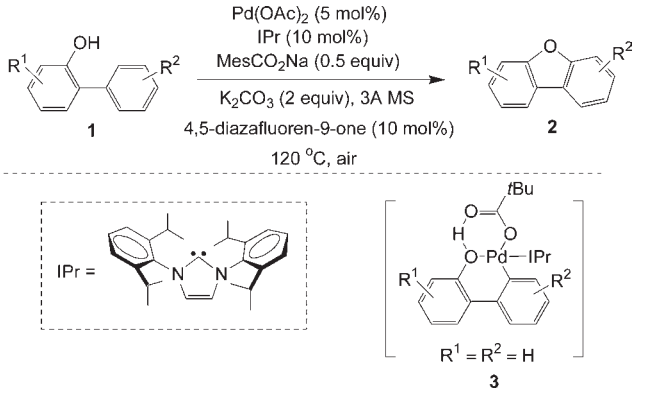
A one-pot method for the transformation of terminal epoxides into secondary alcohols was developed by Doyle and her coworker of Princeton University (*Angew. Chem. Int. Ed.* **2011**, *50*, 6056). The nickel-mediated process involved tandem isomerization/arylation reactions, which were performed in toluene/water in the presence of bis(cyclooctadiene)nickel [$Ni(cod)_2$] catalyst, BrettPhos ligand, and K_3PO_4 as base. Generally, styrenyl epoxides containing *p*- and *m*-substituents performed well under the reaction conditions. Reactions of *o*-tolyl styrene oxide and *o*-fluoro styrene oxide gave the corresponding alcohols in slightly depressed yields. Epoxides bearing *p*-methoxyphenyl group, however, performed poorly, giving no product. The reaction tolerated both electron-rich and electron-poor aryl boronic acids.

SYNTHESIS OF PYRIDINE-*N*-OXIDE–BORANE INTRAMOLECULAR COMPLEXES VIA PALLADIUM-CATALYZED REACTION OF 2-BROMOPYRIDINE–*N*-OXIDES WITH ALKYNYLTRIARYLBORATES



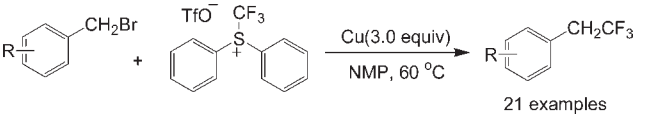
Pyridine-*N*-oxide–borane intramolecular complexes having an aza-stilbene π-framework were synthesized via a palladium-catalyzed reaction of 2-bromopyridine-*N*-oxides with alkynylborates (*Org. Lett.* **2011**, *13*, 3008). These pyridine-*N*-oxide–borane complexes exhibited some unique properties such as higher electron affinities than the corresponding pyridine–borane complexes and considerably more stability toward air than ordinary triorganoboranes. Reactions of both the electron-donating methoxy group and electron-withdrawing trifluoromethyl group on the 5-position of the pyridine moiety resulted in the formation of the corresponding pyridine-*N*-oxide–borane complexes in 79 and 80% yield, respectively. The reaction tolerated an unprotected hydroxyl group at the 6-position of the pyridine–*N*-oxide producing the pyridine–*N*-oxide–borane complex in 76% yield. Various ethynyltriaryl borates (R′ = H, Me, Et; Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4) were shown to be good substrates for these transformations.

SYNTHESIS OF DIBENZOFURANS VIA PALLADIUM-CATALYZED PHENOL-DIRECTED C–H ACTIVATION/C–O CYCLIZATION



A synthetic method for access to dibenzofuran derivatives was developed by Professor Liu and co-workers of Tsinghua University, Beijing, P.R. China (*J. Am. Chem. Soc.* **2011**, *133*, 9250). The approach involves a palladium-catalyzed intramolecular cyclization through C–H bond activation and subsequent C–O bond formation. The reaction proceeded through an isolable palladium complex **3**, whose structure was identified with certainty by X-ray diffraction analysis. It was hypothesized that phenol acted as a directing group for the C–H bond activation leading to **3** in which the hydroxy group coordinated with Pd(II) as a neutral σ donor. This paper reported that several reaction parameters were generated, including temperature, rate-determining step (reductive elimination), base, anhydrous reaction conditions, etc. The reaction tolerated a wide range of substituents on the aromatic rings from electron-rich groups such as methoxy (for R^1 and R^2), ketal, silyl, and phenoxy (for R^2) to electron-deficient groups such as trifluoromethyl (for R^1), cyano, ketone, nitro, amide, ester, sulfonamide, fluoride, and chloride (for R^2).

Cu-MEDIATED TRIFLUOROMETHYLATION OF BENZYL BROMIDES

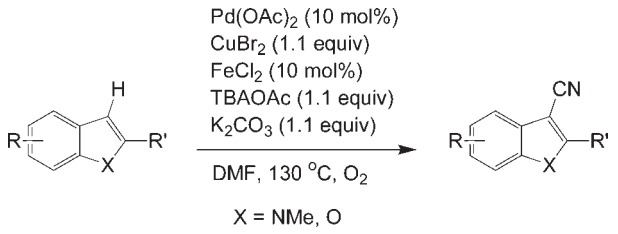


A method (*Org. Lett.* **2011**, *13*, 3596) was developed for a copper-mediated chemoselective trifluoromethylation of benzyl bromides with electrophilic trifluoromethylating reagents affording the corresponding trifluoromethyl products in good to high yields. This reaction proceeds presumably through in situ-generated [$CuCF_3$] species from a single electron-transfer process between the electrophilic trifluoromethylating reagents and copper. Nitrobenzyl bromides (2-, 3-, or 4-) and dinitro-substituted benzyl bromide were converted smoothly into their corresponding trifluoromethyl compounds in 56–81% yields. Other electron-withdrawing groups in benzyl bromides such as cyano, ester, and acetyl and electron-donating groups including *tert*-butyl and methoxy are also tolerated. This method tolerated the coexistence of both a fluorine atom and a nitro group on the aromatic ring. For example, reaction of 2-fluoro-6-nitrobenzyl bromide afforded trifluoromethyl product in 61% yield, without

dx.doi.org/10.1021/op200276n |*Org. Process Res. Dev.* 2011, 15, 1216–1221

any aromatic trifluoromethylation product. Furthermore, bis(bromomethyl)-substituted naphthalene was also a suitable substrate that afforded double trifluoromethylated product in 83% yield.

Pd-CATALYZED C−C BOND FORMATION FOR THE SYNTHESIS OF NITRILES USING DIMETHYLFORMAMIDE AS CYANO SOURCE



A Pd-catalyzed cyanation of indoles and benzofurans was developed by Jiao and co-worker of Peking University to furnish the corresponding aryl nitrile products via C−H bond functionalization with DMF as the cyano source (*J. Am. Chem. Soc.* **2011**, *133*, 12374). The reaction was conducted under an oxygen atmosphere in the presence of both palladium and copper along with $FeCl_2$, TBAOAc, and K_2CO_3 in DMF. Under these optimized reaction conditions, indole substrates bearing either electron-donating (para-, meta-, or ortho-substituted) or -withdrawing substituents could be smoothly functionalized into the desired 3-cyano-substituted products in moderate to good yields (51−79%). The reaction is selective, and exposure of the dimer of 1-methyl-1*H*-indole to the reaction conditions gave only the monocyano product (45%) without the observation of the dicycano product. In addition, 3-phenylindole afforded 2-cyano-3-phenylindole albeit in poor yield (38%). Under the same conditions, cyanation of benzofuran derivatives such as 2-phenylbenzofuran and 3-phenylbenzofuran gave the corresponding cyano products in moderate yields.

POLYMORPHISM AND DESMOTROPY IN HETEROCYCLIC CRYSTAL STRUCTURES

Whereas the concept of polymorphism is reasonably well understood (with a few ongoing debates), probably not the same can be said about desmotropy (in spite of the fact that the concept was coined over 120 years ago); the same is true for tautomerism and tautomeric polymorphism. In a recent perspective (review) these concepts are reviewed in detail, with examples of heterocyclic compounds being given for each definition (Elguero, J.; et al. *Cryst. Growth Des.* **2011**, DOI 10.1021/cg200970t). For polymorphs, an updated definition is proposed: "crystal structures that are different but lead to identical liquid and vapor states, with the condition that no bonds are broken or created". Work reporting the examples mentioned is reviewed and organized according to the "preferred" definition. Another ongoing debate focuses on whether tautomeric polymorphism or desmotropy should be the term of choice. The author recommends the use of "desmotrope" for the case where each tautomer can exist in each crystal. If two tautomers exist in one crystal then this would be deemed a cocrystal. In support of selecting one definition or another, the author recommends using the crystallographic information available: (i) localizing the relevant X−H bond, (ii) inspecting the bond lengths of non-hydrogen atoms that change considerably between tautomers; (iii) using CPMAS NMR in combination with predicted chemical shifts. This perspective has 98 references.

PHASE TRANSFORMATION OF SULFAMERAZINE USING A TAYLOR VORTEX

The impact of mixing on crystallization is complex, this being one reason why crystallization processes can be challenging to scale-up successfully. Sometimes special effort is dedicated to designing processes to produce suitable seed for the production of the desired stable polymorph. A novel method to accomplish solution-mediated phase transformations was developed by researchers at Kyung Hee University and MIT (Lee, S.; et al. *Cryst. Growth Des.* **2011**, DOI 10.1021/cg 200925v). This method uses the unique fluid dynamic properties that can be accomplished in a Couette−Taylor (CT) crystallizer.

A CT reactor is built with two annular cylinders, with the inner cylinder rotating (300−1,000 RPM) and the outer cylinder stationary. The CT used also had temperature control on both cylinders. The CT device was compared with a standard jacketed Rushton crystallizer (operating at 2,000−3,000 RPM). The model compound used in this study was sulfamerazine. The conversion from the metastable to the stable sulfamerazine polymorph was accomplished approximately 10 times faster in the CT crystallizer compared to the standard reactor. The authors postulate that this acceleration of the phase transformation is possible due to the uniquely periodic turbulent motion of Taylor vortices in the CT crystallizer. The unique fluid dynamics provide a strong alignment of the molecules, promoting the nucleation of the stable form. The random turbulent eddies in the standard crystallizer are inadequate to facilitate the nucleation of the stable polymorph. The impact of solvent composition, temperature, and seeding were carefully investigated. A theoretical description of the phase transformation is provided, examining its two consecutive steps: the nucleation of stable crystals and the reconstruction of metastable crystals into stable crystals by dissolution and growth. Coincidentally, the reconstruction times in both crystallizers can be estimated to depend on $\varepsilon^{0.21}$ (ε = energy dissipation of the turbulent flow).

DRAWDOWN OF FLOATING SOLIDS IN STIRRED TANKS: SCALE-UP STUDY USING CFD MODELING

Computational fluid dynamics (CFD) calculations are perceived to be complex and of limited practical value; CFD software developers are working hard to make these calculations more user-friendly and of more practical relevance. A collaboration between Pfizer and Bend Research provides such an example of a practical application of CFD (Waghmare, Y.; et al. *Int. J. Pharm.* **2011**, *418*, 243). In this work, the challenge of scaling up heterogeneous processes involving floating particles is tackled. The model particle used in the experimental work was 100 μm fumed silica particles of high true density (2.2 g/cm^3) but of low bulk density (0.05 g/cm^3). For computational purposes, an important assumption had to be made regarding the solids density, and this was set at 0.92 g/cm^3. Four reactor/agitator configurations were investigated at 2-L scale, including tilted and offset agitators. The CFD calculations were executed using *Fluent* ver. 6.3.26. The authors found that the rate of particle drawdown (experimentally measured) correlated well with the computationally determined average liquid velocity (at the free liquid surface). As expected, the correlation is solid specific. The first experimental

validation was conducted at 10 L, and experiments at commercial scale (40−40,000 L) are planned. An experimental limitation was identified: the correlation does not work for unbaffled systems (where strong vortex formation is possible).

NEW BOOK ON PHARMACEUTICAL PROCESS DEVELOPMENT

The Royal Society of Chemistry have recently published an excellent new book entitled *Pharmaceutical Process Development; Current Chemical and Engineering Challenges* , edited by John Blacker of IPRD, Leeds University, and Mike Williams, formerly of Pfizer U.K. The book is aimed at chemistry, engineering, and pharmacy undergraduate and postgraduate students but will clearly be read by process R&D chemists and engineers in industry. Hopefully the book will also be read by teachers of chemistry in universities who will be able to gain a better appreciation of the skills involved in the industry. The book covers each aspect of process R&D including synthesis and route design (especially green chemistry, for which there is a separate chapter, emphasising its importance), kinetic approaches and physicochemical data requirements for process design, liquid−liquid extraction, enabling technologies (including automation), the analytical interface, solid form design and crystallisation process development, and technology transfer. At over 340 pages there is a lot of useful information and many case studies which will enlighten the reader (ISBN 978-1-84973-146-1; available from http://www.rsc.org/shop/books/2011/9781849731461.asp).

Mark McLaughlin

Merck & Co., Process Research, Rahway, New Jersey 07065, United States; E-mail: mark_mclaughlin@merck.com

Wenyi Zhao

Jacobus Pharmaceutical Co. Inc., Princeton, New Jersey 08540, United States; E-mail: Wenyi38@hotmail.com

Andrei Zlota

The Zlota Company LLC, 15, Fairbanks Road, Sharon, Massachusetts 02067-2858, United States; E-mail: andrei.zlota@thezlotacompany.com

Trevor Laird

Scientific Update LLP, Maycroft Place, Stone Cross, Mayfield, East Sussex TN20 6EW, U.K.*

AUTHOR INFORMATION

Corresponding Author

trevor@scientificupdate.co.uk.