Organic Process Research & Development

HIGHLIGHTS FROM THE LITERATURE

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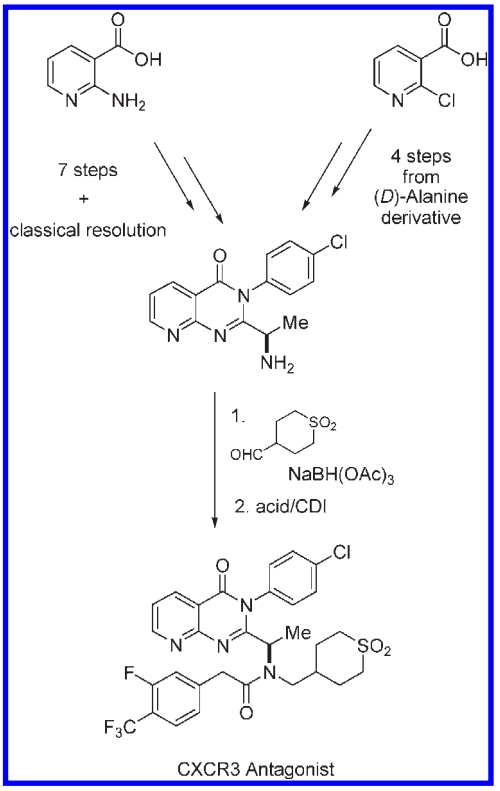
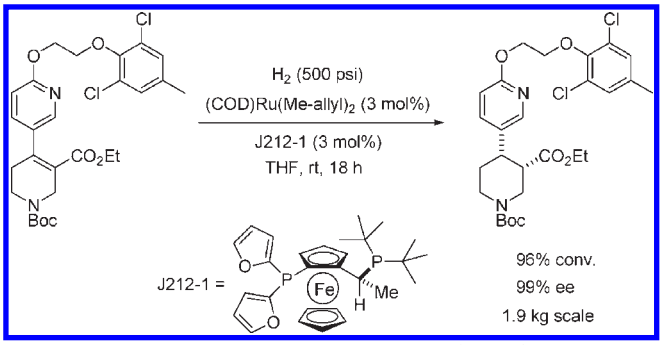
Some Items of Interest to Process R&D Chemists and Engineers

PRACTICAL SYNTHESES OF A CXCR3 ANTAGONIST



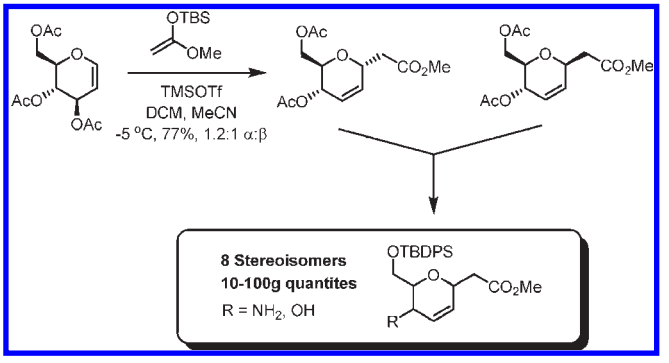
Overexpression of the chemokine CXCR3 receptor has been linked to several autoimmune disorders including psoriasis, rheumatoid arthritis and multiple sclerosis. Two practical synthetic routes to a pyrido[2,3-*d*]-pyrimidine-based inhibitor of the CXCR3 receptor are described by Chan, Burke, and co-workers at Amgen (*J. Org. Chem.* **2011**, *76*, 1767−1774). The first synthesis, which begins with racemic starting materials, constructs the pyrido[2,3-*d*]pyrimidine cores from a 2-amino nicotinamide and triethyl orthopropionate. Selective functionalization (chlorination) of an ethyl moiety of pyrido[2,3-*d*]pyrimidine provided access to the requisite primary amine in four steps and 72% overall yield. Furthermore, a classical resolution of this primary amine using a tartaric acid derivative was developed and implemented at 5 kg scale. The sulfone-containing aldehyde used for end-game reductive amination was secured in practical fashion via a crystalline bisulfite adduct. Lastly, a CDI-mediated coupling to form the final amide bond afforded the API and replaced the existing EDC HCl conditions. In an alternative scheme the amine-bearing stereocenter is derived from the readily available enantiopure building block D-alanine. This approach makes use of a challenging C−N coupling reaction that allowed use of 2-chloronicotinic acid as a cheaper alternative to 2-aminonicotinic acid. By preserving the stereocenter through the isopropylmagnesium chloride-mediated amide bond formation with 4-chloroaniline and the subsequent dehydrative cyclization and Boc group cleavage, the key amine intermediate was accessed in enantioenriched form without the need for a resolution. This second synthesis, thus far performed at gram scale, intersects the former route at a common intermediate and demonstrates a potentially more effective route for future API deliveries.

PRACTICAL SYNTHESIS OF A RENIN INHIBITOR



The renin−angiotensin aldosterone system (RAAS) is known to play a key role in the regulation of blood pressure, and antagonists of the RAAS pathway are potential treatments for hypertension. A practical enantioselective synthesis of a renin inhibitor compound is described by Molinaro and co-workers at Merck (*J. Org. Chem.* **2011**, *76*, 1062−1071). The developed route employs inexpensive and readily available starting materials, *p*-cresol and 2,5-dibromopyridine. The highlight of this synthesis is an enantioselective Ru-catalyzed hydrogenation of a tetrasubstituted ene−ester to generate a *cis*-3,4-disubstituted piperidine (shown in the scheme). A highly efficient epimerization/saponification sequence allowed conversion to the desired *trans*-3,4-disubstituted piperidine that was taken on through an amide formation to yield the final API. The overall synthesis was chromatography-free and was used to prepare approximately 3 kg of API in nine steps and 29% overall yield.

ACCESS ALL STEREOISOMERS



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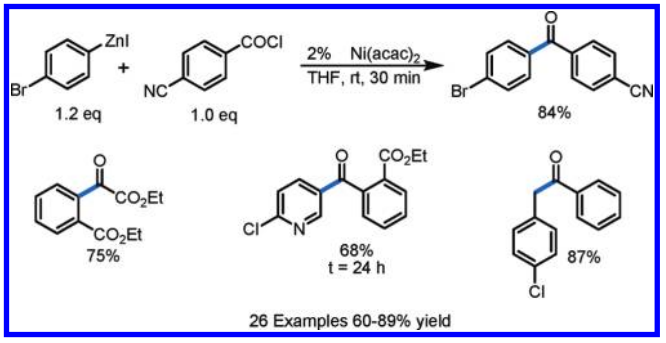
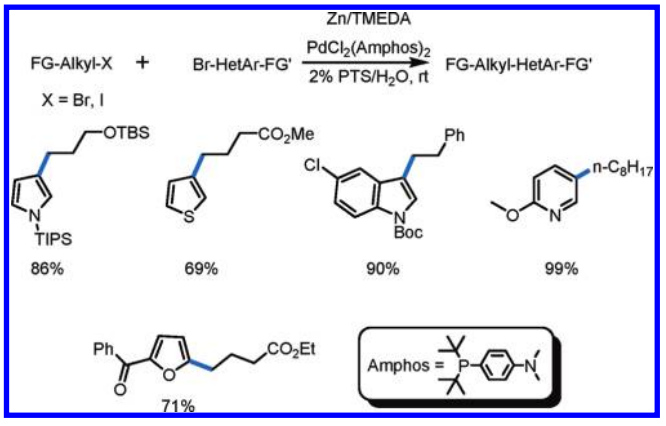
Due to their synthetic versatility and high level of stereochemical diversity, carbohydrates have served as useful building blocks for generating molecular diversity. With the need of large quantities of each stereoisomer of 2,3-unsaturated C-glycoside, a team lead by Marcauelle from the Broad Institute of MIT and Harvard has developed a protocol for the synthesis of all eight stereoisomers of their required template (*J. Org. Chem.* **2011**, *76*, 1898−1901). The initial step, a type-I Ferrier reaction, was performed on 200 g of tri-*O*-acetyl-D-glucal, giving a near 1:1 mix of anomers. Pleasingly, however, these were readily separated by flash chromatography; further elaboration of the templates via Mitsinobu inversions and amine synthesis gave rise to the remaining templates in quantities greater than 10 g. This paper shows that it is possible to generate all stereochemical permutations on large scale from a common starting material using simple flash chromatography to separate the initial anomers formed.

■ ACID CHLORIDE NEGISHI COUPLINGS



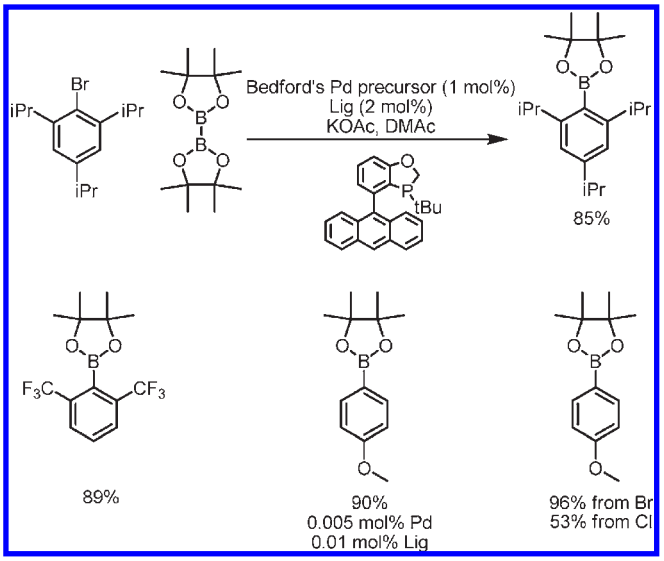
With the plethora of new and efficient C−C bond-forming reactions available to the organic chemists growing on a monthly basis, one area that suffers is the substrate scope for previously reported examples. In this case Kim and Reike (*Tetrahedron Lett.* **2011**, *52*, 1523−1526) reinvestigate work originally reported by Rovis. Initially Kim performs a small catalyst screen using various commercially available catalysts, resulting in $Ni(acac)_2$ being chosen for the remaining coupling reactions due to the rate of reaction and the isolated yield it facilitated. With a large selection of organozinc reagents via direct insertion developed by Reike, they then apply the developed conditions to 26 examples, all of which gave isolated product in good to excellent yields on gram scale.

■ AQUEOUS NEGISHI COUPLINGS



The area of C−C bond formation of heteroaryl halides and alkyl halides has been intensely studied by many groups, and more recently it has been translated to the field of green chemistry. Recently Lipshutz has shown the use of water as reaction medium for Suzuki−Miyaura and Aryl Negishi couplings. In this paper Lipshutz presents the scope and limitations of this approach on heteroaromatic bromides together with various alkyl bromides and iodides (*Tetrahedron Lett.* **2011**, *52*, 2203−2205). As a model reaction *n*-octyliodide and 2-methoxy-5-bromopyridine were coupled using Zn*/TMEDA/$PdCl_2$ $(Amphos)_2$ in the presence of various surfactants. Intriguingly the rate of reaction and conversion was altered dramatically depending on surfactant used, pleasingly the author found the use of polyoxyethanyl α-tocopheryl sebecate (PTS) gave quantitative conversion. Applying these conditions to various sulphur- and nitrogen-based heterocycles facilitated high-yielding reactions with various alkyl groups. However, the application of the chemistry to furans required the addition of 2 equiv of dodecane to facilitate the reaction.

■ BORYLATION OF HINDERED AROMATICS



Arylboronic acids or esters are key building blocks in modern synthetic chemistry that have been utilized in a variety of chemical transformations. Over the years the palladium-catalyzed Miyaura borylation has become an important alternative for the synthesis of boronic esters. However, the main drawback with this technique has been the synthesis of sterically hindered boronic esters. To overcome this, Tang et al. of Boehringer Ingelheim has further developed a family of conformationally hindered biaryl monophosphorus ligands (*Org. Lett.* **2011**, *13*, 1366−1369). After an initial condition screen, it was found that the initial catalyst, Pd_2dba_3, suffered from rapid deactivation. To overcome this issue Tang turned to the Bedford Pd precursor, a phosphite-ligated palladacycle complex. By placing an anthracene portion as the lower aryl ring of the ligand following a ligand screen, Tang discovered the reaction proceeds in higher yield. It is postulated that this ligand does not increase the rate of reaction but rather plays a role in increasing the longevity of the Pd catalyst. Tang applies this methodology to a wide range of hindered aryl groups, thus generating the borylated products in good to excellent yields. To further exemplify this methodology Tang performs comparison reactions of the coupling of hindered aryl chlorides and bromides, showing that the ligand outperforms known methodology in relation to Miyaura borylation.

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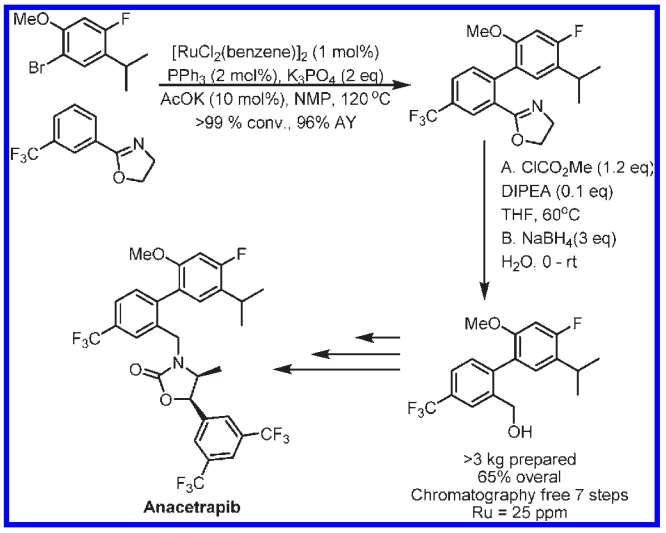
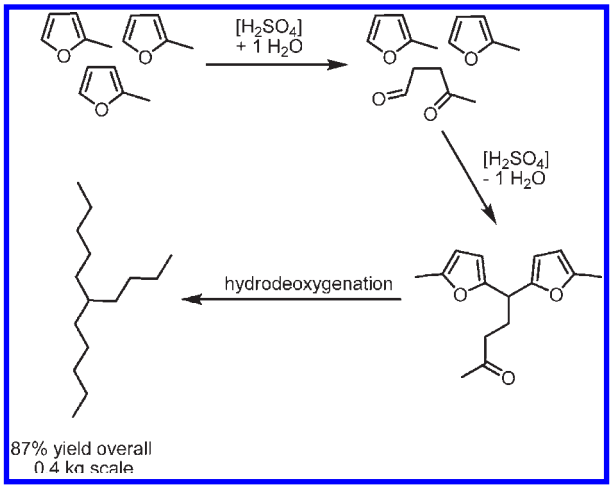
KILOSCALE DIRECT ARYLATION



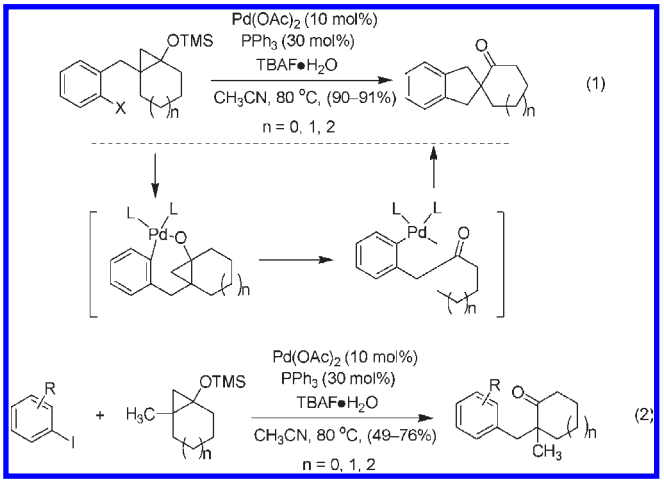
As part of the development campaign of anacetrapib on behalf of Merck, Ouellet et al. took the novel approach to synthesise the compound core using an unprecedented ruthenium-catalysed direct arylation reaction (*J. Org. Chem.* **2011**, *76*, 1436−1439). This was envisaged as a viable route as it contains minimal functional group manipulations prior to cross coupling. Importantly, this strategy not only is advantageous because of its economical and ecological benefits but also allows for streamlining organic synthesis. The initial segment of the paper discusses the synthesis of both aryl halves of the core, and with these in hand conditions developed by Oi et al. were investigated and pleasingly gave good conversion and a clean reaction profile. Upon further investigation of the reaction parameters, in particular the solvent, they noticed varying yields for similar solvents; as a result they discovered that a low-level impurity of γ-butyrolactone was being hydrolysed by the base present, and the resulting carboxylate was helping to facilitate the reaction. This was further proven by the addition of 30 mol % of potassium acetate to the reaction mixture, resulting in clean conversion to the diaryl compound. Ouellet then transferred the optimised reaction conditions to a 4.4 kg synthesis of the oxazoline biaryl to complete the core synthesis. They then developed a one-pot procedure for the conversion of the oxazoline to the benzylic alcohol in good yield, giving over 3 kg of the desired core compound.

PRODUCTION OF HIGH-QUALITY DIESEL FROM BIOMASS WASTE PRODUCTS



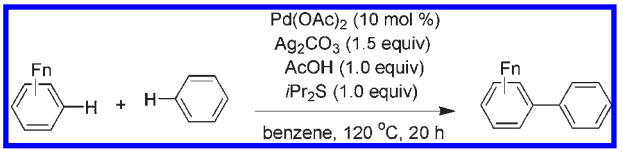
The use of biodiesel has been promoted for the past decade as a substitute for fossil-based diesel fuel. However, it has become evident that its production competes with food production by engrossing cropland. To overcome this Corma has developed a process that uses 2-methylfuran which currently is isolated (280×10^3 tonnes per year) from nonedible biomass (*Angew. Chem., Int. Ed.* **2011**, *50*, 2375−2378). The first step is the trimerization of 2-methylfuran which takes place in water mediated by sulfuric acid in 94% yield. The trimer is then subjected to hydrodeoxygenation using a mixture of Pt/C and Pt/TiO_2 and 5 MPa of hydrogen in 97% yield. Of particular note was the use of no organic solvent in the process. This route opens new routes for the production of high-quality diesel from waste biomass.

SYNTHESIS OF CYCLIC KETONES VIA PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS



Synthesis of cyclic ketones was achieved via intra- or intermolecular palladium-catalyzed cross-coupling of cyclopropanols with aryl halides under mild conditions (*Org. Lett.* **2011**, *13*, 110−113). The intramolecular reactions for the preparation of spiro-ketones were conducted at 80 °C in acetonitrile in the presence of palladium acetate as catalyst and triphenylphosphine as ligand, affording excellent product yields (90−91%). Reactions of aryl bromides work equally as well as aryl iodides. Analogously, the intermolecular cross-coupling reactions proceeded under the same reaction conditions, giving the corresponding cyclic ketones in moderate yields.

PALLADIUM-CATALYZED CROSS-COUPLING OF POLYFLUOROARENES WITH SIMPLE ARENES



A palladium-catalyzed cross-coupling reaction to construct biaryls containing polyfluoroarene moiety was developed via C−H bond functionalization (*Org. Lett.* **2011**, *13*, 276−279). Compared with reactions using aryl halides or aryl organometallic reagents, this dehydrogenative cross-coupling does not require prefunctionalization of both arene partners. Benzene could react with a variety of polyfluoroarenes including

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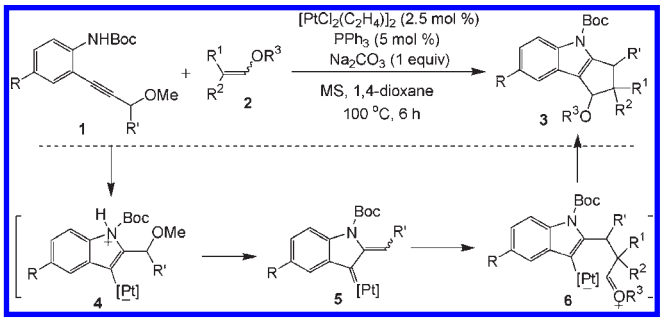
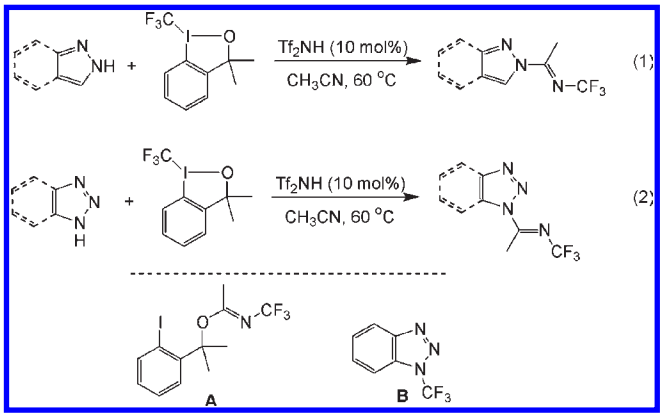
tetrafluoro-, trifluoro-, and even difluorobenzene, affording the corresponding cross-coupling biaryl products in good yields. In addition, tetrafluoropyridines were also found to be suitable for the coupling reactions with benzene. These reactions were extremely sensitive to steric hindrance. For example, *o*-xylene and *m*-xylene reacted at the less hindered positions to generate single-coupling products with good efficiency.

■ SYNTHESIS OF POLYCYCLIC COMPOUNDS VIA PT-(II)-CATALYZED FORMATION OF α,*B*-UNSATURATED CARBENE COMPLEX AND [3 + 2]-CYCLOADDITION REACTION



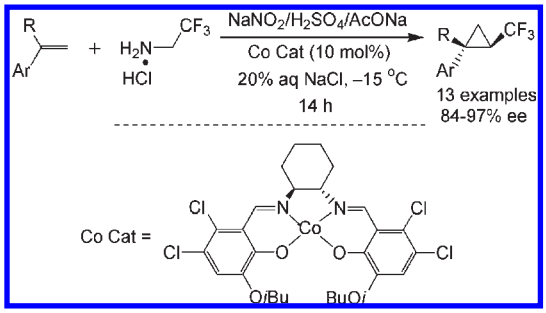
A new approach for the synthesis of polycyclic compounds was developed (*J. Am. Chem. Soc.* **2011**, *133*, 689−691). The tandem process occurred through zwitterionic intermediates **4**, unsaturated carbene complexes **5**, and alkenyl metallic intermediates **6** whose intramolecular nucleophilic cyclization afforded the final products **3**. Various alkyl vinyl ethers, such as *tert*-butyl and *p*-methoxybenzyl vinyl ethers and di- and trisubstituted vinyl ethers, reacted smoothly to afford the corresponding substituted tricyclic indoles in good yields. Aniline derivatives having an electron-donating or -withdrawing group on the aromatic ring could also be employed as substrates to give the corresponding tricyclic indoles.

■ ELECTROPHILIC *N*-TRIFLUOROMETHYLATION USING HYPERVALENT IODINE REAGENTS



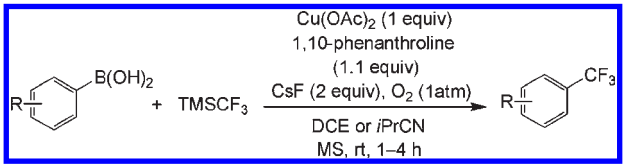
Direct electrophilic trifluoromethylation of heteroarenes using hypervalent iodine reagent and catalytic amounts of bis-(trifluoromethanesulfonyl)imide ($HNTf_2$) in acetonitrile afforded the corresponding *N*-substituted *N*-trifluoroimidoyl derivatives (*Angew. Chem., Int. Ed.* **2011**, *50*, 1059−1063). For the reaction of benzotriazole, two side products, **A** and **B**, were also observed. Their formation was influenced by the ratio between substrate and reagent. When the hypervalent iodine reagent was used in excess, more side product **A** was formed, whereas an excess of substrate led to **B** to a greater extent. The best results in terms of product yield and suppression of side products were obtained using the hypervalent iodine reagent as the limiting species and 1.5 equiv of benzotriazole. Accordingly, general reaction conditions were set up by addition of $HNTf_2$ (10 mol %) in CH_2Cl_2 to a solution of hypervalent iodine reagent (1.0 equiv) and heteroarenes (1.5 equiv) in CH_3CN, and the resulting reaction mixture was allowed to stir for 3.5 h at 60 °C.

■ ENANTIOSELECTIVE COBALT-CATALYZED PREPARATION OF TRIFLUOROMETHYL-SUBSTITUTED CYCLOPROPANES



A mild and environmentally benign approach for the preparation of trifluoromethyl-substituted cyclopropanes was reported (*Angew. Chem., Int. Ed.* **2011**, *50*, 1101−1104). The reactions proceeded smoothly in aqueous media with the alkenes as limiting reagents in the presence of cobalt catalyst. This tandem sequence comprises the generation of reactive F_3CCHN_2 in situ from 2,2,2-trifluoroethylamine hydrochloride and concomitant cyclopropanation in water, which avoids preparation, purification, and handling of the diazoalkane. The use of 20% aqueous NaCl solution as solvent was necessary to prevent freezing of the aqueous reaction media. The method is widely applicable to a range of styrenes, including electron-rich and -poor as well as ortho-substituted substrates. Reactions with electron-rich substrates generally led to excellent results, affording cyclopropanes in high enantioselectivities (up to 94% ee), diastereoselectivities (up to 180:1 dr), and yields (up to 95%).

■ ARYL TRIFLUOROMETHYLATION VIA COPPER-MEDIATED OXIDATIVE CROSS-COUPLING



Buchwald's group at MIT revealed a method for the room-temperature copper-mediated trifluoromethylation of aryl and heteroaryl boronic acids (*J. Org. Chem* **2011**, *76*, 1174−1176). This protocol tolerated a range of functional groups in aryl boronic acids, such as alkyl, alkoxy, chloro, bromo, and carbonyl groups, allowing access to a variety of trifluoromethyl arenes. Thus, electron-rich and -deficient aryl boronic acids can be

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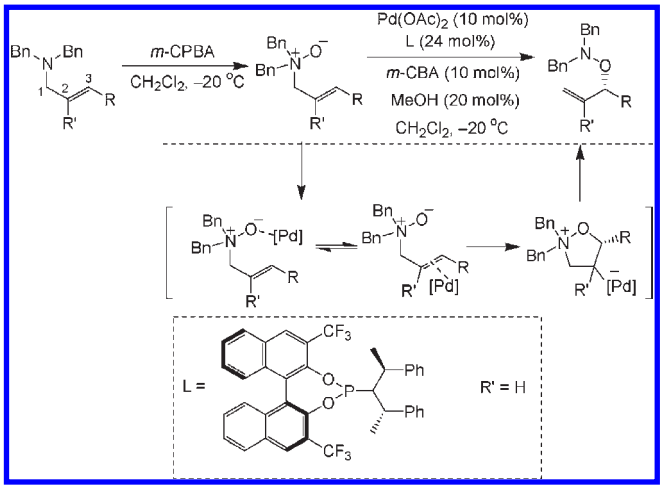
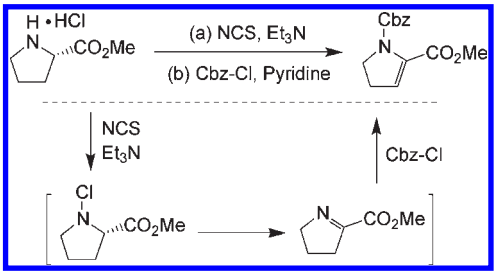
trifluoromethylated in moderate to good yields. While boronic acids bearing chloro or bromo groups are acceptable, aromatic iodides are not compatible with the method. Due to their tendency to undergo competitive 1,2-addition, substrates containing aldehydes or ketones are problematic when applying the trifluoromethylation methods.

■ CATALYTIC ENANTIOSELECTIVE [2,3]-REARRANGEMENTS OF AMINE *N*-OXIDES



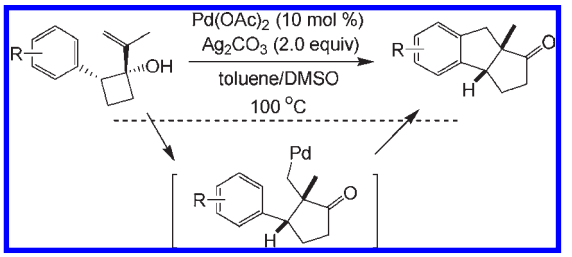
A catalytic enantioselective [2,3]-rearrangement of allylic amine *N*-oxides was realized under mild conditions by Tambar and co-workers of the University of Texas Southwestern Medical Center at Dallas, Texas (*J. Am. Chem. Soc.* **2011**, *133*, 1206−1208). The approach is applicable for the access to chiral secondary alcohols via cleavage of the N−O bond in the rearrangement products. A mechanistic hypothesis involves the formation of an oxide-bound complex or an olefin-bound complex, followed by cyclization and subsequent Grob-type fragmentation. The reaction tolerated a wide range of alkyl substituents at C3 of the allylic system, furnishing aliphatic allylic alcohol derivatives in good yields and enantioselectivities, while a substrate branching at the C2 position ($R' \neq H$) was not reactive under the reaction conditions due to the steric hindrance.

■ ONE-POT SYNTHESIS OF DEHYDROPROLINE DERIVATIVE



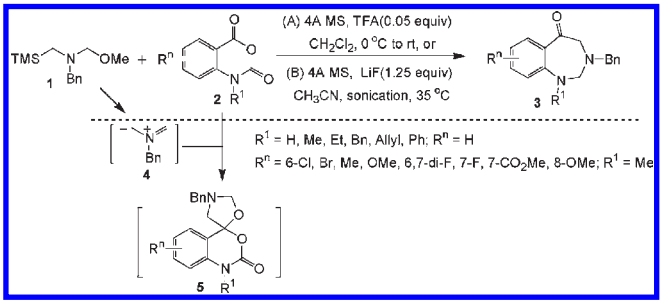
The preparation of dehydroprolines was achieved via a one-pot process by Schmalz and co-workers in Germany (*Org. Lett.* **2011**, *13*, 216−219). The experimental procedure includes the treatment of the hydrochloride salt with triethylamine (2 equiv) in methylene chloride, followed by the portionwise addition of *N*-chlorosuccinimide (NCS). The initially generated *N*-chloroproline would lose HCl, leading to an imine that was then converted to the *N*-protected enamine simply by addition of Cbz-Cl (2 equiv) and pyridine. A 2-fold excess of both Cbz-Cl and the base (pyridine) was required because the succinimide (generated from NCS) also consumed one equivalent of the Cbz-Cl. The one-pot protocol could be performed in the air using technical grade solvents and reagents, furnishing the dehydroprolines in overall yield of 77%.

■ TANDEM PALLADIUM-CATALYZED SEMIPINACOL REARRANGEMENT AND DIRECT ARYLATION



A palladium-catalyzed tandem semipinacol rearrangement/direct arylation reaction using α-aryl isopropenyl-*tert*-cyclobutanols was described (*Org. Lett.* **2011**, *13*, 232−235). This transformation tolerated alkyl-, alkoxy-, and halogen-substituted aryl groups, giving an access to benzodiquinanes in moderate to good yields. Substrates bearing *p*-fluorophenyl, *p*-chlorophenyl, and *o*,*p*-dichlorophenyl groups provided the benzodiquinane products in 45%, 48%, and 56% yields, respectively, while a significantly lower yield was obtained with substrates bearing the *p*-bromophenyl substituent, presumably due to an undesired oxidative addition to the aryl bromide. The mechanistic hypothesis involves a palladium homoenolate intermediate, formed presumably via semipinacol rearrangement, followed by a direct arylation reaction to furnish the benzodiquinane products.

■ SYNTHESIS OF BENZODIAZEPINONES VIA 1,3-DIPOLAR CYCLOADDITION/DECARBOXYLATION OF ISATOIC ANHYDRIDES

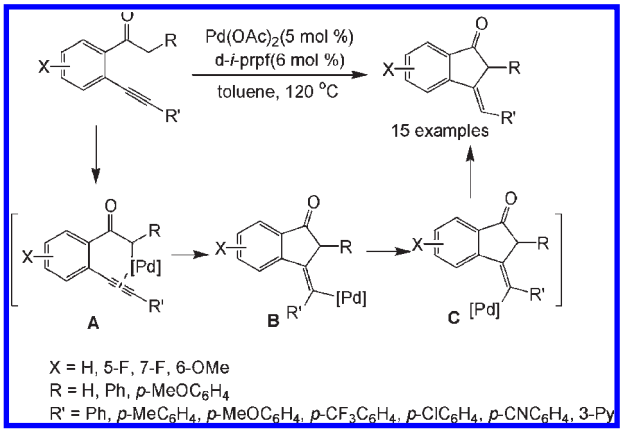


A one-pot cascade reaction was developed for an access to 1,3-benzodiazepin-5-one derivatives **3** (*Org. Lett.* **2011**, *13*, 486−489). The reaction sequence begins with 1,3-dipolar cycloaddition of isatoic anhydride **2** with azomethine ylide **4**, generated in situ from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **1**, to afford spiro-oxazolidine intermediate **5**, followed by ring-opening/decarboxylation/ring closing to yield **3**. The transformation could occur under two sets of reaction conditions: in the presence of 0.05 equiv of trifluoroacetic acid (TFA) and 4 Å molecular sieves in methylene chloride (A) or in the presence of LiF (1.25 equiv) and 4

dx.doi.org/10.1021/op2000942 |*Org. Process Res. Dev.* 2011, 15, 484–490

Å molecular sieves with sonication at 35 °C in acetonitrile (B). A wide range of substituted isatoic anhydrides **2** was proved to be a suitable substrate to afford the novel 1,3-benzodiazepin-5-one derivatives **3** in high yields.

PALLADIUM-CATALYZED CARBOCYCLIZATION OF ALKYNYL KETONES



A Pd-catalyzed regio- and stereoselective carbocyclization of *o*-alkynyl ketones was developed for the synthesis of alkylidene indanones (*Angew. Chem., Int. Ed.* **2011**, *50*, 2342−2345). Treatment of *o*-alkynyl ketones with $Pd(OAc)_2$ in the presence of 1,1′-bis(diisopropylphosphino)ferrocene (d-*i*-prpf) under reflux in toluene afforded alkylidene indanone derivatives as single E stereoisomers in good to excellent yields. Reactions tolerated various functional groups, such as F, Cl, CN, and OMe in the alkynyl ketones. DFT calculations suggest that the reactions would proceed through intermediates (**A**−**C**), wherein the alkyne-coordinated Pd enolate **A**, upon intramolecular carbopalladation of the triple bond, leads to a vinylpalladium species **B**. Upon Z−E isomerization of the double bond, **B** transforms into thermodynamically more favorable Z isomer **C**. Protodepalladation from the latter produces indanones with E geometry of the methylene double bond.

NEW IMPELLER FOR VISCOUS FERMENTATION: POWER INPUT AND MASS TRANSFER COEFFICIENTS

Effective gas−liquid mass transfer in high-viscosity media can still be a challenge to achieve. Non-Newtonian, highly viscous fermentation broths that are rheologically dynamic are one example of such challenging media. A group from the University of Ottawa (Lin, Y.; et al. *Ind. Eng. Chem. Res* **2011**, *50*, 3510), proposes the use of a new impeller for the mixing of such systems. The newly designed rotational reciprocating plate impeller (RRPI) is compared with a classical three-stage Rushton and an axial reciprocating plate impeller (ARPI). The RRPI exhibits a three-arm linkage system, and two hubs with six blades on each hub, somehow resembling the profile of a Rushton turbine. Two of the blades on the upper hub are cut to accommodate fermentation probes. In highly viscous media, the mass transfer performance of the RRPI is better than that of a three-stage Rushton because of the presence of stagnant zones in the latter. The RRPI is more practical than the ARPI which, during operation, moves in and out of the reactor. The RRPI is designed with a unique, back-and-forth movement inspired by clothes washers. Power draw and mass transfer coefficients were measured for the impellers investigated in water and CMC aqueous solutions of high viscosity.

PHYSICAL STABILITY OF SALTS OF WEAK BASES IN THE SOLID STATE

Selection of a drug form for development is a complex task; traditionally, due to bioavailability needs, highly water-soluble salts are typically sought. Stability in the solid state is also an important form selection criterion. Solid-state chemistry is less well understood than solution chemistry, in particular with respect to disproportionation reactions (such as salt decomposition to the corresponding free base and counterion-forming acid). Due to the typically much lower solubility of the free base, the driving force of such disproportionation reactions is strong. A review on the issue of salt stability in the solid state was recently published by a team from Lilly (Stephenson, G.A.; et al. *J. Pharm. Sci.* **2011**, *100*(5), 1607). A detailed description of the impact of the microenvironmental pH created by the formulation excipients is provided. An analysis of 302 commonly prescribed drugs provided a practical observation regarding the lowest acceptable pK_a of the salt to be developed (which apparently must be higher than 4.6). Several specific examples are discussed in more detail. In one case, the loss of potency was explained by solid-state disproportionation followed by the sublimation of the free base thus formed. The recommendation is to consider both the solubility as well as the pK_a in the process of form selection, understanding the impact of the microenvironment on the solid-state stability of the form.

WHAT'S IN A DROP? CORRELATING OBSERVATIONS AND OUTCOMES TO GUIDE MACROMOLECULAR CRYSTALLIZATION EXPERIMENTS

Unfortunately, we are still unable to predict optimal crystallization conditions for either small or large molecules, and crystallization process development remains largely an empirical endeavor. A team from SUNY Buffalo and the Hauptman-Woodward Medical Research Institute (Luft, J. R.; et al. *Cryst. Growth Des.* **2011**, *11*, 651−663) has published a summary of their trend findings from 10 years of high-throughput macromolecular crystallization Twenty million experiments were conducted on 12,500 compounds. The most common crystallization approach used was the microbatch under-oil method, in fractional factorial experimental designs, with automated imaging employed to assess the outcome. Even though there are 23 process parameters likely to impact the outcome of a macromolecular crystallization, some crystallization processes were still found "recalcitrant to optimization". In spite of the value of two-dimensional crystallization phase diagrams, the authors remind us that such diagrams are only "slices" in a multidimensional experimental space; small changes in the "unlisted" process parameters can explain the observed variability in crystallization outcome. This article has 75 references.

FUTURE TRENDS IN ORGANOMETALLIC CHEMISTRY: ORGANOMETALLIC APPROACHES TO WATER SPLITTING

In a "perspective" article (Piers, W. E. *Organometallics* **2011**, *30*(1), 13) the "formidable organometallic tool box" is discussed

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in the context of manipulation of the O−H bond of water with the goal of producing environmentally benign solar fuels. Two recent accounts from the Milstein group at the Weizmann Institute of Science (in *Science* and in *Nature*) are reviewed in some detail. While exploring reactions with water of certain late transition metal complexes designed with pincer, highly tunable ligands, the Milstein group was able to accomplish an unprecedented transformation (oxygen−oxygen bond formation in a reductive elimination) as well as the isolation of a previously considered impossible oxo-platinum(II) complex. This article has 45 references.

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