Organic Process Research & Development

Highlights from the Literature

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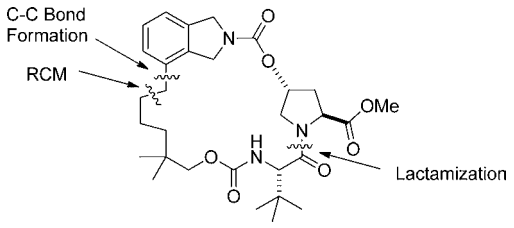
Some Items of Interest to Process R&D Chemists and Engineers

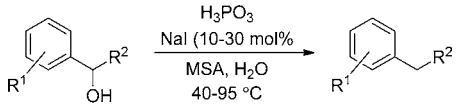
SYNTHESIS OF VANIPREVIR (MK-7009): LACTAMIZATION TO PREPARE A 20-MEMBERED MACROCYCLE



Vaniprevir (MK-7009)

Hepatitis C virus (HCV) affects an estimated 170 million people worldwide and is the leading cause for liver transplants. Vaniprevir (MK-7009) is a HCV NS3/4a protease inhibitor in late-stage clinical development that potentially has significant advantages over existing treatments for HCV. The development of a practical synthesis of this 20-membered macrocycle is described by Song, Tellers, and co-workers at Merck (*J. Org. Chem.* **2011**, *76*, 7804). A variety of ring-closing strategies were evaluated, including ring-closing metathesis, intermolecular palladium-catalyzed cross-couplings, and macrolactamization. Ring closure via macrolactamization was found to give the highest yields under relatively high reaction concentrations. Optimization of the ring-formation step and the synthesis of key intermediates en route to MK-7009 are reported in detail in this full paper.

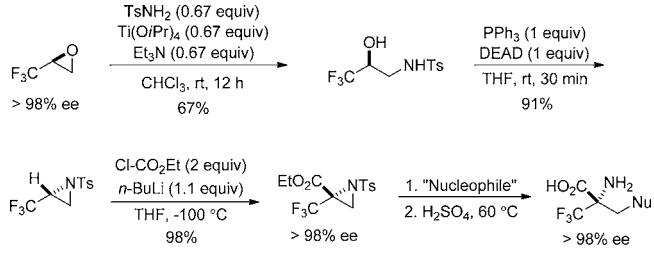
IODIDE-CATALYZED REDUCTIONS: SYNTHESIS OF PHENYLACETIC ACIDS



8 examples, 69-96% yield

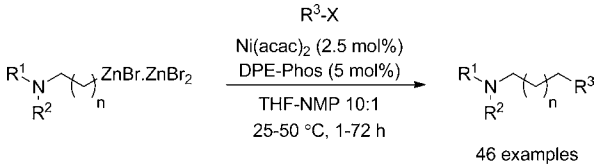
Phenylacetic acids are an important class of compounds prevalent in both pharmaceutical and natural products. Milne and co-workers at Amgen report on a new convenient and scalable synthesis of phenylacetic acids via the iodide-catalyzed reduction of mandelic acids (*J. Org. Chem.* **2011**, *76*, 9519). Building on earlier literature describing similar reductions using fuming HI as both the reagent and solvent for this reaction, the current work sought to increase practicality by introducing a more readily handled stoichiometric reductant. The final procedure relies on in situ generation of hydroiodic acid from catalytic sodium iodide, methanesulfonic acid, and inexpensive phosphorus acid as the stoichiometric reductant. Notably, aryl halides survive these reaction conditions. The procedure was demonstrated on multikilogram scale as part of the synthesis of a development candidate at Amgen.

PREPARATION OF OPTICALLY PURE α-TRIFLUOROMETHYL-α-AMINO ACIDS



The preparation of optically pure α-trifluoromethyl-α-amino acids from *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonylaziridine is described by the Katagiri group in Japan (*J. Org. Chem.* **2011**, *76*, 9305). The requisite optically pure aziridine was prepared in 60% yield via three steps from optically pure 2,3-epoxy-1,1,1-trifluoropropane (TFPO). Ring-opening reactions of the aziridine with a variety of nucleophiles and subsequent deprotection of the *N*-tosyl moieties gave the optically pure β-substituted-α-trifluoromethyl-α-amino acids in moderate to good yields (up to 85%) without racemization at the quaternary stereogenic center of the amino acid. Notably it was possible to remove the *N*-tosyl group in these substrates via hydrolysis in sulfuric acid.

DIRECT AMINOALKYLATION OF ARENES, HETEROARENES, AND ALKENES VIA Ni-CATALYZED NEGISHI CROSS-COUPLING REACTIONS



One of the most frequently occurring functionalities in biologically or pharmacologically active compounds is the aminoalkyl moiety. Consequently, methods for the direct introduction of these aminoalkyl residues into funtionalized compounds are of great interest. Following up on an earlier communication, the Knochel group now provides a full account of the development and scope of Negishi cross-couplings as a means for aminoalkylation of functionalized compounds (*J. Org. Chem.* **2011**, *76*, 8891). The requisite organozinc intermediates are readily obtained from the corresponding Grignard reagents, and the cross-couplings are catalyzed using a $Ni(acac)_2$/DPE-Phos system, typically at or around room temperature. The reaction allows a convenient one-step preparation of various aminoalkyl products, including piperidine and tropane derivatives.

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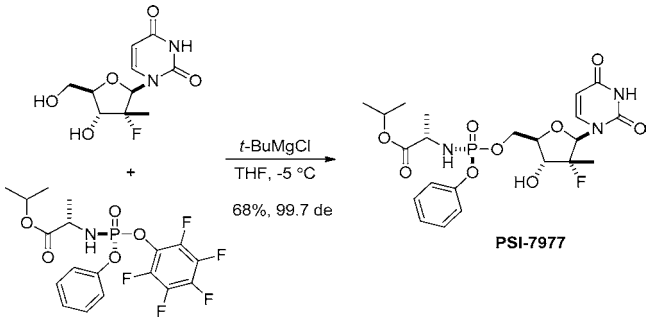
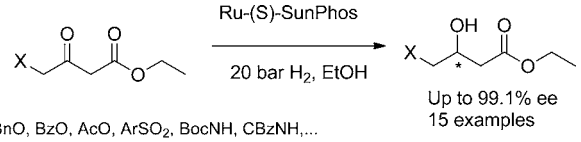
Aryl, heteroaryl, and alkenyl iodides, bromides, chlorides, and triflates are suitable electrophiles. A short total synthesis of two natural products, (±)-galipinine and (±)-cusparine, is also described.

SYNTHESIS OF DIASTEREOMERICALLY PURE NUCLEOTIDE PHOSPHORAMIDATES

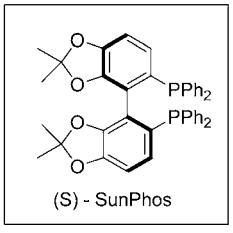


Prodrugs of therapeutic nucleoside monophosphates masked as phosphoramidate derivatives have become an increasingly important class of antiviral drugs in pharmaceutical research for delivering nucleotides in vitro and in vivo. Conventionally, phosphoramidate derivatives are prepared as a mixture of two diastereomers. Now Ross and co-workers at Pharmasset report (*J. Org. Chem.* **2011**, *76*, 8311) on a class of stable phosphoramidating reagents containing an amino acid ester and two phenolic groups, one unsubstituted and the other with electron-withdrawing substituents (e.g pentafluorophenol). These reagents can be isolated as single diastereomers (via simple crystallization) and reacted with the 5′-hydroxyl group of nucleosides through selective nucleophilic displacement of the substituted phenol to prepare single diastereomer phosphoramidate products. The reaction proceeds with inversion of the chiral center at phosphorus. This method has been used to prepare the HCV clinical candidate PSI-7977 in high yield and high diastereomeric purity. The method can likely be applied to the preparation of a variety of stable phosphoramidation reagents and may find great utility in pharmaceutical exploration of nucleotide phosphoramidates.

Ru-CATALYZED ASYMMETRIC HYDROGENATION OF γ-HETEROATOM SUBSTITUTED β-KETO ESTERS

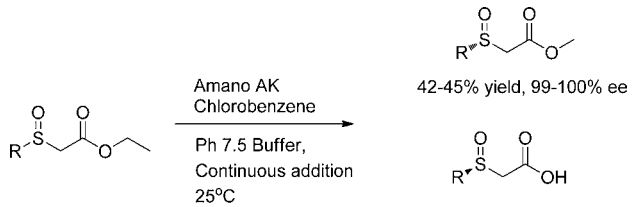


X = Cl, BnO, BzO, AcO, $ArSO_2$, BocNH, CBzNH,...



Asymmetric hydrogenation remains a powerful tool for synthesising chiral molecules. Chiral β-hydroxy acids and esters are in many biological and pharmaceutical building blocks. An example of such a building block is the well-known atorvastatin side chain. Zhang et al. (*J. Org. Chem.* **2011**, *76*, 9444−9451) describes the screening of several catalysts in the synthesis of γ-heteroatom substituted β-hydroxy esters. They found that (*S*)-SunPhos gave ee up to 99.1%. The group also present a general protocol for highly enantioselective synthesis of γ-heteroatom substituted β-hydroxy esters.

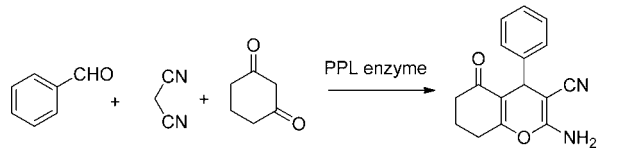
CONTINUOUS FLOW BIOCATALYTIC RESOLUTIONS OF METHYL SULFINYLACETATES



7 examples given

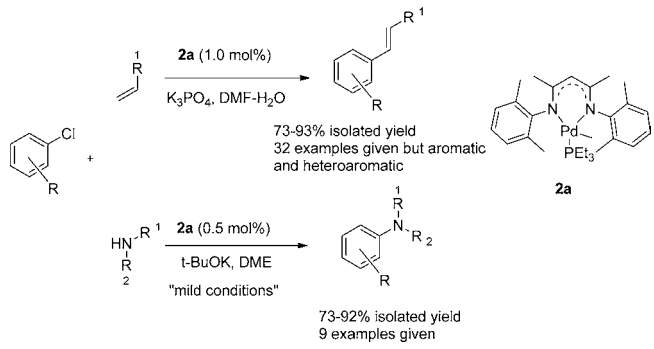
Lipase-assisted resolution of racemic esters is a powerful tool for the organic chemist. Common problems with enzymatic reactions are either substrate and/or product inhibition. This problem was encountered by Burgess et al. (*Tetrahedron Lett.* **2011**, *52*, 6325−6327). The group solved the problem of product inhibition by introducing a continuous extraction step into the synthesis using chlorobenzene as the extraction solvent. By using this simple method they managed to resolve several different sulfoxides with high enantiodifferentiation.

ONE-POT SYNTHESIS OF TETRAHYDROCHROMENE DERIVATIVES CATALYZED BY LIPASE



Enzyme promiscuity has attracted significant attention from chemists recently, with several examples published in the literature over the years. In a recent paper by Zhang et al. (*Tetrahedron* **2011**, *67*, 9582−9587) the group describes the discovery of a lipase from porcine pancreas (PPL) that showed excellent catalytic activity in the synthesis of tetrahydrochromene derivatives. Further investigation showed that the enzyme was most active in ethanol and water and could be used to generate several tetrahydrochromenes in high yields.

AN EFFICIENT AND GENERAL METHOD FOR THE HECK AND BUCHWALD−HARTWIG COUPLING REACTIONS OF ARYL CHLORIDES



A new powerful catalyst for Heck and Buchwald−Hartwig couplings was recently published by Jin et al. (*Org. Lett.* **2011**, *13*,

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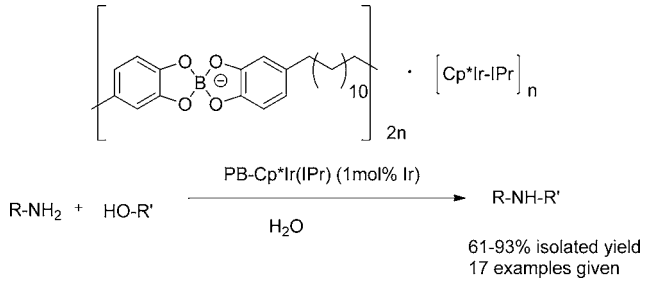
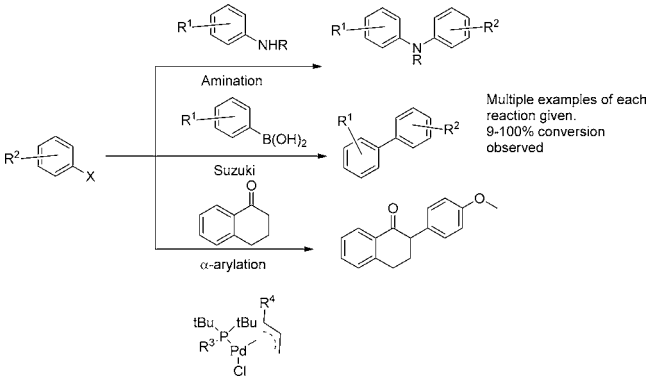
5540−5543). The article describes the synthesis of the catalysts and gives several examples on the versatility of this system for the Heck coupling of both aromatic and heteroaromatic compounds. The authors also described the use of the catalyst in the Buchwald−Hartwig reaction and showed several examples of the coupling between sterically hindered aryl chlorides and various amines. The catalyst was active enough to be able to catalyse the Buchwald−Hartwig reaction at room temperature.

IN-WATER DEHYDRATIVE ALKYLATION OF AMMONIA AND AMINES WITH ALCOHOLS BY A POLYMERIC BIMETALLIC CATALYST



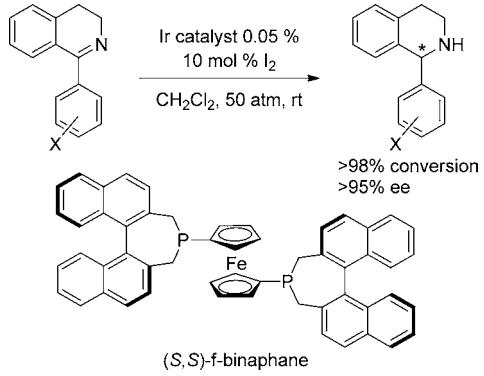
Red−ox-neutral alkylation of amines using alcohols either as neat or in organic solvents is a well established procedure these days. Yamada et al. recently published an article discussing the use of a polymeric bimetallic catalyst to perform an in-water dehydration reaction (*Org. Lett.* **2011**, *13*, 3892−3895). The authors described the synthesis of the polymeric catalyst and evaluated it against several substrates with moderate to excellent yields using water as the solvent and aerobic conditions. The catalyst itself could be recovered from the reaction mixture and reused twice.

AIR-STABLE Pd (R-ALLYL)LCl (L= Q-Phos, P(*t*-Bu)$_3$, etc.) SYSTEMS FOR C−C/N COUPLINGS: INSIGHT INTO THE STRUCTURE−ACTIVITY RELATIONSHIP AND CATALYST ACTIVATION PATHWAY



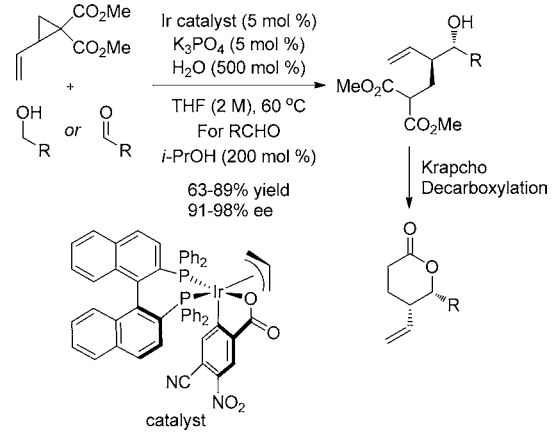
Colacot et al. from Johnson Matthey Catalyst and Chiral Technologies recently published an extensive article regarding catalyst screening for C−C and C−N bond formation (*J. Org. Chem.* **2011**, *76*, 7918−7932). This fascinating article describes the synthesis of 11 different air-stable catalysts and the result from the screening of said catalysts in C−C and C−N bond-forming reactions. One of the catalysts Pd(Crotyl) Q-PhosCl was found to be superior to the other Q-Phos catalysts investigated. The authors go on to investigate the findings that crotyl Pd complexes were more active than the traditional allyl Pd complexes using X-ray crystallography and NMR spectroscopic studies. They came to the conclusion that the difference in activity was due to the formation of different reaction intermediates.

Ir-CATALYZED ASYMMETRIC HYDROGENATION



The first asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinolines was reported by Chang, Li, and Zhang (*Angew. Chem., Int. Ed.* **2011**, *50*, 10679−10681). The perennial complexity of this transformation has been attributed to the rigidity and steric demands of the imine substructure. The team at Rutgers University investigated the ability of Ir−diphosphine complexes to reduce the imines by screening a series of Ir precursors, ligands, additives, and solvents, and discovered that an iodine-bridged dimeric iridium complex of (*S,S*)-f-binaphane gives excellent yields and enantioselectivities. The catalyst $[\{Ir(H)[(S,S)\text{-f-binaphane}]\}_2(\mu\text{-I})_3]^+\Gamma$ was prepared by mixing $[\{Ir(cod)Cl\}_2]$ and 2.2. equiv (*S,S*)-f-binaphane in toluene at rt for 2 h followed by (1) addition of an excess of HI, (2) overnight stirring, (3) evaporation under reduced pressure, and (4) redissolution in CH_2Cl_2 and hexanes to precipitate the desired complex. Optimal hydrogenation conditions involved the use of Ir-complex/I_2/substrate 0.05:10:100 ratios at 50 atm of H_2 and rt during 24 h.

DISUBSTITUTED *δ*-LACTONES VIA ENANTIOSELECTIVE Ir CATALYSIS



The treatment of cyclopropanes incorporating the malonic ester substructure with (*S*)-BINAP complexes of cyclometalated iridium catalysts triggers the umpolung of the donor−acceptor cyclopropanes (Johnson, Krische, and coworkers in *J. Am. Chem. Soc.* **2011**, *133*, 18618−18621). Thus, the electrophilic trapping of nucleophilic *π*-allyls generated from donor−acceptor cyclopropanes with aldehydes leads to diastereo- and enantioselective C−C couplings to afford allyl alcohols. These adducts can be transformed in a subsequent step into *cis*-4,5-disubstituted *δ*-lactones via Krapcho decarboxylation. The Ir-catalyzed reductive couplings use alcohols as terminal reductants (e.g. *i*-PrOH 200 mol %), allowing formal carbonyl trapping from the alcohol or the aldehyde in the

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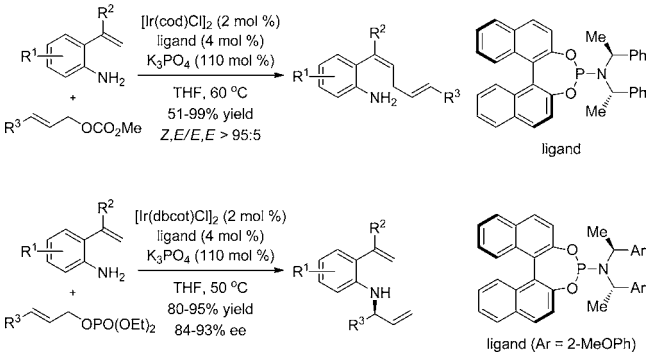
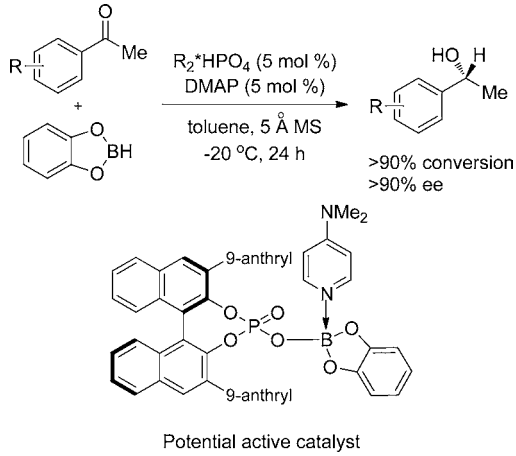
absence of stoichiometric metallic reagents. The vinylcyclopropane reactant can be prepared from commercially available (*E*)-1,4-dibromobut-2-ene and dimethyl malonate.

Ir-CATALYZED ALLYLIC VINYLATION AND AMINATION REACTIONS WITH *O*-AMINOSTYRENES



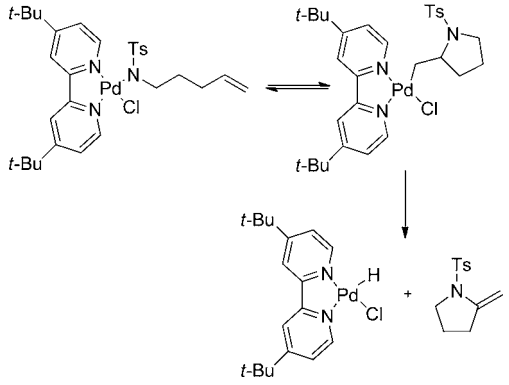
You and co-workers at the Shanghai Institute of Organic Chemistry describe allylic substitution reactions with *o*-aminostyrene derivatives in *J. Am. Chem. Soc.* **2011**, *133*, 19006−19014. The transformations include allylic vinylations and asymmetric allylic aminations catalyzed by phosphoramidite-Ir complexes. The reaction of *o*-aminostyrenes with allylic carbonates as electrophiles provides skipped (*Z*,*E*)-dienes with good yields, chemo- and stereoselectivities. Optimal conditions for the allylic vinylations include the use of 4 mol % $[Ir(cod)Cl]_2$, 8 mol % ligand, and 2.6 equiv of DABCO in THF at 60 °C. The nature of the leaving group of the allylic precursors influences the chemoselectivity of the allylation. Thus, the reaction between cinnamyl diethyl phosphate and substituted *o*-aminostyrenes affords allylic amination products that can be readily transformed into enantioenriched 1,2-dihydroquinolines by subsequent RCM reactions. Typical conditions for the allylic amination involve the use of 2 mol % $[Ir(dbcot)Cl]_2$, 4 mol % ligand, and 110 mol % K_3PO_4 in THF or dioxane at 50 °C.

ASYMMETRIC REDUCTION OF KETONES BY PHOSPHORIC ACID CATALYSTS



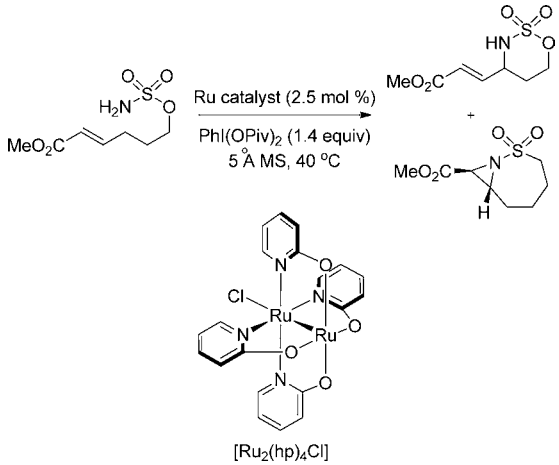
The applications of chiral phosphoric acids continue to expand. Antilla and co-workers at University of South Florida developed a catalyst system for the asymmetric reduction of aryl ketones using catecholborane as the reducing agent (*Angew. Chem. Int. Ed.* **2011**, *50*, 10961 −10964). Thus, a variety of chiral secondary alcohols could be obtained with high enantioselectivities by treating the ketone precursors with a binol-derived phosphoric acid (5 mol %), 4-(dimethylamino)pyridine (5 mol %), catecholborane (1.6 equiv) and molecular sieves in toluene at −20 °C. The methodology tolerates diverse functional groups on the aromatic ring, such as nitrile, nitro, ester, iodide, and bromide. ^{11}B NMR studies indicate that catecholborane reacts with the phosphoric acid and 4-(dimethylamino)pyridine to generate hydrogen and form a phosphoryl catechol borate as the active catalyst.

REVERSIBLE ALKENE INSERTION INTO THE Pd−N BOND OF Pd(II)−SULFONAMIDATES



White and Stahl describe mechanistic studies on the insertion of alkenes into Pd−N bonds, a key step in the Pd-catalyzed oxidative amidation of olefins (*J. Am. Chem. Soc.* **2011**, *133*, 18594−18597). A model Pd(II)−sulfonamidate chloride complex was prepared and crystallographically characterized. The *cis*-aminopalladation of this complex occurred in polar solvents (e.g., DMSO) and was strongly inhibited by the addition of chloride to the reaction mixture, in agreement with a mechanism involving dissociation of chloride prior to the insertion. Notably, the regeneration of the original complex from the intermediate alkyl-Pd species indicated that the alkene insertion is reversible under anaerobic conditions. Electron-rich amidates accelerate the alkene insertion into the Pd−N bond, endorsing a mechanism that involves the intramolecular nucleophilic attack of the amidate to the Pd-coordinated alkene.

Ru-CATALYZED INTRAMOLECULAR ALLYLIC C−H AMINATION



Tetrakis-(2-oxypyridinato)diruthenium chloride, $[Ru_2(hp)_4Cl]$, catalyzes the intramolecular allylic C−H amination of unsaturated sulfamate esters under oxidative conditions. In contrast to the related Rh dimeric catalyst $[Rh_2(esp)_2]$, the Ru system displays high selectivity for the C−H amination relative to the competing aziridination. Typical reactions are performed with 2.5 mol %

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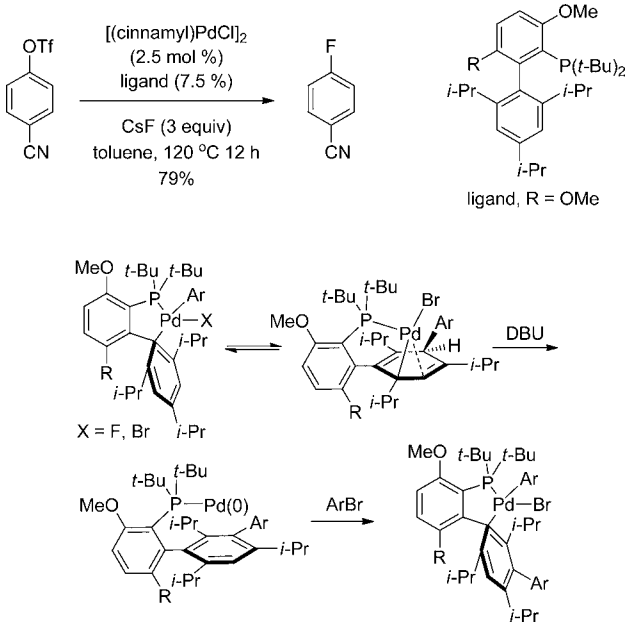
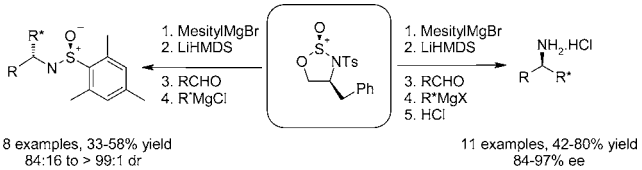
$[Ru_2(hp)_4Cl]$, 1.4 equiv of $PhI(O_2Ct\text{-}Bu)_2$, and powdered 5 Å molecular sieves in CH_2Cl_2 at 40 °C to afford product mixtures with insertion-to-aziridination ratios larger than 20:1. A comprehensive combination of mechanistic and DFT computational studies reveals the prevalence of a stepwise mechanism involving initial H-atom abstraction followed by diradical recombination instead of a closed-shell singlet nitrene concerted insertion (Harvey, Musaev, Du Bois in *J. Am. Chem. Soc.* **2011**, *133*, 17207−17216).

Pd-CATALYZED CONVERSION OF ARYL TRIFLATES TO ARYL FLUORIDES



Buchwald and co-workers described the conversion of aryl triflates to aryl fluorides catalyzed by Pd complexes with bulky biaryl phosphines in *Angew. Chem., Int. Ed.* **2011**, *50*, 8900−8903. More recently, the team reported additional studies revealing that the actual ligand is an arylated form of the original phosphine generated during the reaction (*J. Am. Chem. Soc.* **2011**, *133*, 18106−18109). L-Pd(Ar)F oxidative addition complexes believed to be intermediates in the fluorination and their L-Pd(Ar)Br analogues were independently prepared, isolated, and characterized by X-ray crystallography. In the Br series, the original L-Pd(Ar)Br species was found to be in equilibrium with a dearomatized Pd(II) complex that could also be crystallized. Rearomatization of the Pd(II) complex took place in the presence of DBU and aryl bromide with concurrent oxidative addition. The terarylphosphine ligand of the resulting complex could be detected as a byproduct of the fluorination reactions and was found to be catalytically active in the fluorination of 4-*n*-BuPhOTf. The formation of terarylphosphine ligands may influence the outcome of the reactions mediated by their biaryl phosphine precursors.

ONE-POT SYNTHESIS OF CHIRAL NONRACEMIC AMINES

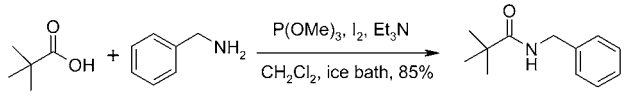


18 examples, 33-58% yield
84:16 to > 99:1 dr

11 examples, 42-80% yield
84-97% ee

Chiral amines are found in numerous natural products and pharmaceutical ingredients, and often serve as both auxiliaries and ligands in homogeneous catalysis. As such, new efficient methods for the asymmetric synthesis of this functionality are of great value. Stockman and co-workers (*J. Org. Chem.* **2011**, *76*, 9452) have reported a practical one-pot five-component reaction affording either chiral nonracemic amines or sulfinamides in good yield, and with high stereoselectivity. The route utilizes a chiral oxathiazolidine oxide as the template, which can be easily accessed from readily available starting materials in >90% yield. The whole process involves the formation of four new bonds and two stereogenic centers, and is complementary to other chiral amine syntheses. The reaction is carried out in 2-methyltetrahydrofuran, and it is key to exclude all tetrahydrofuran to maximize stereoselectivity. Diastereomeric ratios are very high except for lipophilic and sterically encumbered Grignard reagents. The one-pot synthesis also affords greatly enhanced diastereoselectivities over the single-step reaction. The amines are simply isolated by filtration of the precipitated hydrochloride salts formed during removal of the auxiliary.

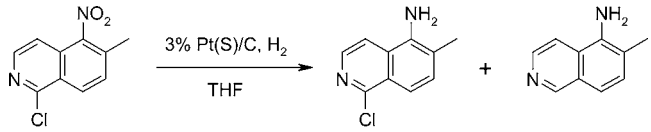
AN EFFICIENT PROTOCOL FOR THE AMIDATION OF CARBOXYLIC ACIDS PROMOTED BY TRIMETHYL PHOSPHITE AND IODINE



27 examples, yield > 70%

There are numerous methods for the synthesis of amide bonds from amines and carboxylic acids, though many suffer from significant drawbacks, such as reagent cost or difficulties in purification of the desired amide from the reagent byproduct. Hui, Luo, and co-workers have reported a simple and efficient protocol utilizing trimethylphosphite and iodine in the presence of an organic base, which overcomes many of these limitations (*Eur. J. Org. Chem.* **2011**, 6916). The reaction shows excellent substrate scope leading to high yields of the desired amides, can be carried out in a number of solvents (though not DMF) without the need for rigorous exclusion of air or moisture, and the byproducts are easily removed by aqueous extraction. In addition, the authors note that this protocol is extremely chemoselective in that the amide bond formation proceeds even in the presence of potentially competing oxygen or sulfur nucleophiles. ^{31}P NMR spectroscopy was utilized to elucidate the pathway for the trimethyl phosphite-mediated amidation process.

SELECTIVE CATALYTIC HYDROGENATION OF NITRO GROUPS IN THE PRESENCE OF ACTIVATED HETEROARYL HALIDES



Selectivity > 99%
11 other examples

(not observed)

The reduction of heteroaromatic nitro groups to the corresponding anilines represents an important transformation in the pharmaceutical industry. Although there are a range of methods available to achieve this, those utilizing hydrogenation typically involve the addition of various additives and are optimized by trial and error on a substrate-by-substrate basis. Workers at Amgen have demonstrated that it is possible to chemoselectively reduce nitro groups in the presence of activated heteroaryl halides using low loadings (<0.1 mol %) of a commercially available sulfided platinum catalyst

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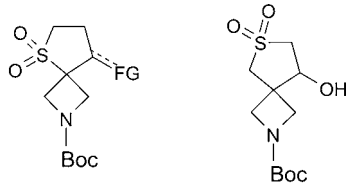
(*J. Org. Chem.* **2011**, *76*, 9841). A range of examples are provided with a combination of high yield and minimal hydrodehalogenation being observed. The reactions take place in THF at low temperature and pressure. The high chemoselectivity of the process is attributed to the poisoning effects of the sulfur, which occupies the most active sites on the platinum surface.

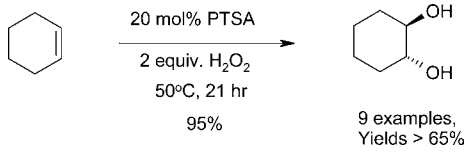
SYNTHESIS OF NOVEL AZASPIRO[3.4]OCTANES AS MULTIFUNCTIONAL MODULES IN DRUG DISCOVERY



FG = CO_2H, NH_2, OH, O

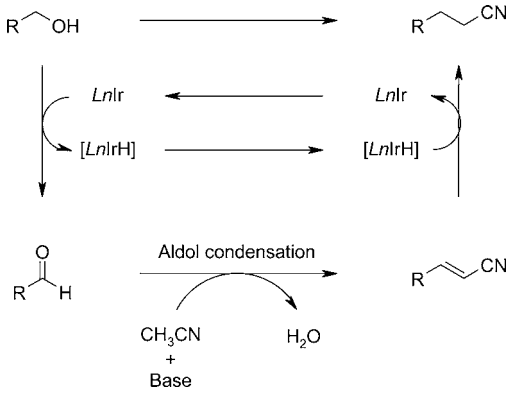
The introduction of novel building blocks allows access to expanded chemical, pharmacological, and proprietary space within drug discovery programs. However, of equal importance in the design of these druglike scaffolds is to have efficient and scalable syntheses in order to access these molecules. Carreira's group have recently disclosed a series of spirocyclic molecules and developed their synthesis (*Org. Lett.* **2011**, *13*, 6134). Key features in the syntheses of these compounds were a methanol-triggered opening of a thiolactone followed by an intramolecular conjugate addition onto an unsaturated ester to form the spirocyclic system in the case of the 5-thia-2-azaspiro[3.4]-octanes, and the development of a modestly efficient sulfenylation procedure for methyl-1-*N*-Boc-azetidinecarboxylate (note unlike the related 1-*N*-Boc-azetidinone, the chemistry of this compound is not well-documented). In general, the yields are good, and the syntheses are 5−6 steps, with the chemistry being performed on gram scale.

BRØNSTED ACID-CATALYZED DIHYDROXYLATION OF OLEFINS IN AQUEOUS MEDIUM



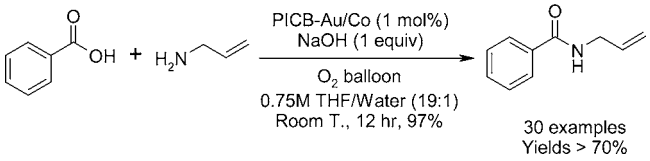
Methods for the *syn*-dihydroxylation of olefins are well established and typically rely on metal catalysis. *anti*-Dihydroxylation is usually achieved by epoxidation and subsequent hydrolysis. Afonso and Rosatella (*Adv. Synth. Catal.* **2011**, *353*, 2920) have reported on a simple, robust, and metal-free dihydroxylation method in aqueous media. The procedure typically uses 20 mol % of *p*-toluenesulfonic acid (PTSA) to promote the reaction with 30% hydrogen peroxide (2 equiv) as the oxidant. A range of olefins are converted to the *trans*-1,2-diols in high yields with cyclic substrates performing better than their acyclic counterparts. Work-up and isolation is facile, and for poorly soluble substrates, 1-propanol can be added as a cosolvent. A wide range of functional group tolerance is also demonstrated, and catalyst can be recycled through eight cycles with continued high efficiency. Experimental observations and labeling studies support a mechanism via epoxidation by the corresponding peroxysulfonic acid followed by acid-catalyzed ring-opening, though the epoxide is never observed. The reactions are carried out at 50 °C, and the authors do highlight the need for caution using 30% hydrogen peroxide at this elevated temperature.

IRIDIUM-CATALYZED α-ALKYLATION OF ACETONITRILE WITH PRIMARY AND SECONDARY ALCOHOLS



Linear nitriles represent an important class of industrial compounds. Often, these can be prepared from the nucleophilic subsitution of alkyl halides, though this method has a significant disadvantage with the generation of undesirable waste salts. Acetonitrile is an important readily available feedstock (coproduced during the production of acrylonitrile) and the one carbon elongation of alkyl chains of alcohols with acetonitrile represents an alternative highly beneficial methodology to access aliphatic nitriles. Obora has demonstrated that it is possible to promote this reaction utilizing iridium catalysis (*Chem. Lett.* **2011**, *40*, 1055). After significant screening studies, the optimum conditions identified use 5 mol % of $[Ir(OH)(cod)]_2$ with 15 mol % of PPh_3 and 10 mol % of *t*-BuOK in 1,4-dioxane at 130 °C. Yields are generally good, and both primary and secondary alcohols are substrates for the reaction. The mechanism is proposed to be three steps with initial oxidation of the alcohol to the aldehyde through hydrogen transfer to an Ir complex, followed by base-catalyzed Aldol condensation to generate the α,β-unsaturated nitrile, which is subsequently hydrogenated by the Ir−hydride complex to yield the desired product.

POWERFUL AMIDE SYNTHESIS FROM ALCOHOLS AND AMINES UNDER AEROBIC CONDITIONS CATALYZED BY GOLD OR GOLD/IRON, -NICKEL, OR -COBALT NANOPARTICLES



Amide bond formation is fundamentally one of the key reactions in organic synthesis, and new widely applicable, cost-effective, and atom-economical approaches to achieve this represent an important challenge. The group of Kobayashi have developed an alternative pathway (*J. Am. Chem. Soc.* **2011**, *133*, 18550) for amide synthesis from alcohols and amines through a tandem oxidative process (TOP) using their polymer-incarcerated (carbon black) catalysts (PICB catalysts). The reactions proceed in a THF/water system with the addition of one equivalent of sodium hydroxide using either a balloon of oxygen or air as the oxidant. The authors found that the most effective catalysts for the transformation were a combination of gold and cobalt (PICB-Au/Co) and rationalize that the cobalt has the dual benefit of stabilizing the intermediate carbinolamine, whilst also tempering the reactivity of the gold nanoparticles in the initial oxidation step. Reactions were conducted

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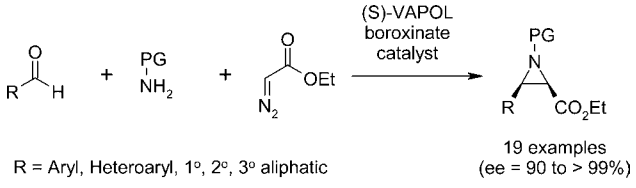
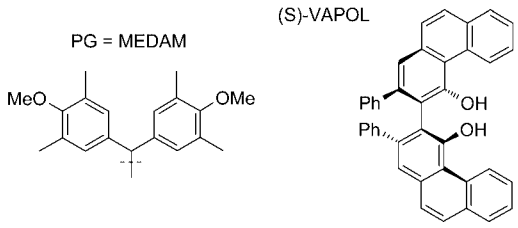
with 1−1.5 mol % of the catalyst either at 25 or 40 °C. Good substrate scope was demonstrated for both the amine (including the use of aqueous ammonia to generate a primary amide) and the alcohol component, and the catalysts could easily be recycled.

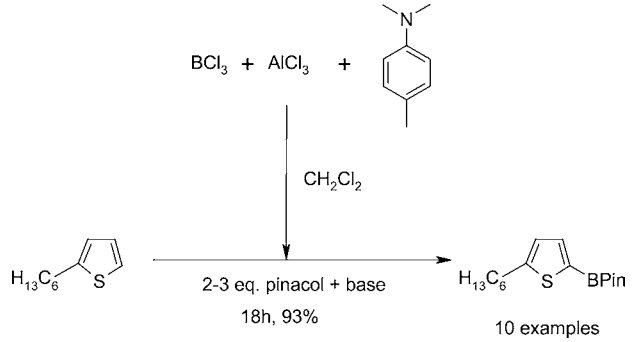
MULTICOMPONENT CATALYTIC ASYMMETRIC AZIRIDINATION OF ALDEHYDES





Wulff and co-workers have developed a simple and robust multicomponent reaction for the asymmetric synthesis of aziridines (*Org. Lett.* **2011**, *13*, 5866) starting from aldehydes. This procedure is mediated by chiral Bronsted acid catalysts, which are generated from the VANOL and VAPOL ligands, enabling high levels of enantio- and diasteroselectivity to be obtained. The major breakthrough in the current study involved the in situ generation of the bis(dimethylanisyl) methyl (MEDAM) imine from the aldehyde and MEDAM amine prior to treatment with ethyl diazoacetate to effect the aziridination. The procedure is simple, and it is key to have equimolar amounts of the aldehyde and MEDAM amine to prevent excess amine killing the catalyst. The reaction works with a range of both alkyl (including unbranched aliphatic aldehydes, which had previously proved problematic) and aryl aldehydes, and further synthetic elaboration of the final chiral aziridines is described.

SIMPLE INEXPENSIVE BORON ELECTROPHILES FOR DIRECT ARENE BORYLATION



The recently reported electrophilic borylation is the boron equivalent of the classical Friedel−Crafts reaction allowing simple access to aryl boronate esters, which are essential synthetic building blocks. Furthermore, the regioselectivity of the new methodology is dictated by electronic effects, which is complementary to the highly effective iridium catalysis where regioselectivity is controlled chiefly by steric factors or heteroatom direction. However, for the electrophilic borylation to be widely adopted, a simple, inexpensive and scalable system that offers expanded substrate scope is required. Ingleson and co-workers have reported a system using a combination of BCl_3/$AlCl_3$/base to achieve this (*Chem. Commun.* **2011**, *47*, 12459). Choice of the base is crucial, and selection of *N*,*N*-4-trimethylaniline (Me_2Ntol) generates a highly active borylation agent, which has been utilized on multigram scale. A range of substrates have been successfully borylated, and a number of experiments demonstrating how the borylating power can be modulated by judicious base selection have been carried out.

A QUALITY BY DESIGN (QbD) CASE STUDY ON LIPOSOMES CONTAINING HYDROPHILIC API:I FORMULATION, PROCESSING, DESIGN, AND RISK ASSESSMENT

Quality by design (QbD) implementation in the drug product area is somehow more advanced than in the drug substance (API) area, and FDA case studies are scarce. The QbD principles are the same, so when the FDA publishes a case study, we all take notice. An example discussing QbD practice for drug product was recently published based on a collaboration between the FDA and the University of Connecticut (Xu, X.; et al. *Intl. J. Pharm.* **2011**, *419*, 52). The API used as a model compound was tenofovir, a nucleoside reverse transcriptase inhibitor. Tenofovir exhibits a polar hydrophilic structure that is difficult to formulate to deliver suitable efficacy. The authors developed alternate formulations using liposomes, while employing a QbD methodology. This paper covers part I of the work, describing the process development efforts up to the DoE investigations step. Using Ishikawa diagrams, two "major" (critical) quality attributes were identified: liposome particle size and drug encapsulation efficiency. Further analysis, using correlation matrixes, determined that there were eight factors of potential high risk (potential critical process parameters): lipid, drug, cholesterol, and buffer concentrations, hydration and sonication times, and extrusion pressure. Pre-DoE experimentation and the corresponding one-variable at a time analysis are presented in detail. The difficulty in developing liposome-based formulations is described by the relatively small number of such commercialized products; only 12 reported in 2005. However, in the past 44 years more than 114,000 scientific publications address this topic.

RACEMIC NAPROXEN: A MULTIDISCIPLINARY STRUCTURAL AND THERMODYNAMIC COMPARISON WITH THE ENANTIOPURE FORM

A very popular method to obtain enantiopure API's is chiral crystallization; development of such resolution processes is often conducted empirically, or semiempirically. Ideally, a complete thermodynamic characterization of all possible solid phases for a given system should be available. Such comprehensive data is rarely available, both because of technical reasons, as well as because of resource limitations for the necessary speed of process development. Thermodynamic computations of suitable accuracy have been sought to provide an additional tool in the effective development of chiral crystallization processes. A collaboration between several academic groups in the United Kingdom led to a detailed report for the interdisciplinary analysis of racemic and (*S*)-naproxen (Braun D. E.; et al. *Cryst. Growth Des.* **2011**, DOI 10.1021/cg 201203u), focused on the thermodynamic comparison between the two compounds. A common experimental challenge of this straightforward solid phase system was the unavailability of (*RS*)-naproxen crystals

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suitable for single crystal X-ray analysis. The structure of this racemate has been solved using powder X-ray diffraction. Calculations predicted the racemate to be more stable than the (*S*)-isomer by a few kilojoules per mole. This prediction is supported by certain thermal and solubility analysis. The report indicates that the measured solubilities are considerably lower than ideal, implying significant solute−solvent interactions. The assumptions made in the calculations are presented, emphasizing that in some cases these computational assumptions can be of the order of magnitude of the energy differences computed. The thermodynamic driving force for a process designed to separate (*S*)-naproxen from racemic-naproxen is thus very low. This account has 84 references.

INTERDEPENDENCE OF DRUG SUBSTANCE PHYSICAL PROPERTIES AND CORRESPONDING QUALITY CONTROL STRATEGY

Whereas the design space proposed by the sponsor must be approved by regulators, the FDA has indicated that in the Quality by Design (QbD) paradigm, another key entity that is also very carefully scrutinized and which must also be approved is the control strategy. The control strategy for the production of a drug product includes the specifications for the drug substance. Because in the QbD methodology multivariate analysis is employed to define the design space, it is expected that the API specifications are described using multivariate models. Control strategies based on multivariate models can be more challenging than those based on univariate models. In the case of high intercorrelation between the API specifications (such as different particle size statistics, surface area, and density), it can be shown that a univariate specification may suffice. A report from Genentech (Cui, Y.; et al. *J. Pharm. Sci.* **2012**, *101*, 312) discusses a case study for a small-molecule API (BCS class II compound) formulated as an immediate release hard capsule. Nonstructured data from 16 batches of API and drug product were analyzed. This analysis is based on the Duchesne−MacGregor method published earlier. The Genentech case study is also an example where a univariate specification is sufficient.

EFFECT OF OPERATING PARAMETERS ON THE MIXING PERFORMANCE OF THE SUPERBLEND COAXIAL MIXER

Scale-up of mixing processes occurring in viscous media remains to be a challenge even for the relatively simpler case of Newtonian fluids. In the quest to avoid stagnancy, segregation, and caverns, mixer manufacturers have developed advanced mixing technologies, such as coaxial mixers. These agitators are dual mixers that combine two different mixers mounted coaxially in a reactor. One such novel coaxial mixer is the Superblend from the SHI Mechanical Equipment Company in Japan. The Superblend combines a Maxblend and a helical ribbon mixer; the Maxblend was also introduced by SHI several years ago, and it is a special type of a frame mixer. Public data available for such novel mixing systems are limited, and a report discussing the mixing performance of the Superblend was published based on a collaboration from SHI and Ecole Polytechnique of Montreal (Wang, X.; et al. *Ind. Eng. Chem. Res.* **2012**, DOI 10.1021/ie200707n). The model media were aqueous solutions of glucose. Power measurements were executed using torque-meters, and mixing times were determined using a decoloration technique based on a fast acid−base indicator reaction. The impact of speed ratios, pumping direction, and rotating modes (co-rotating or counter-rotating) were carefully examined. Characteristic Reynolds numbers were calculated using a suitably defined impeller rotation speed. As expected, the correlations identified were strongly dependent on the flow regime (laminar, transitional, or turbulent). This finding is an additional confirmation of the general observation that, when scaling-up, it is preferable to investigate the process at small scale under the same flow regime as that expected to be practiced at large scale.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on January 11, 2012. The errors have been corrected in the scheme for the SYNTHESIS OF DIASTEREOMERICALLY PURE NUCLEOTIDE PHOSPHORAMIDATES from *J. Org. Chem.* **2011**, *76*, 8311 in the version posted January 20, 2012.