Organic Process Research & Development

Highlights from the Literature

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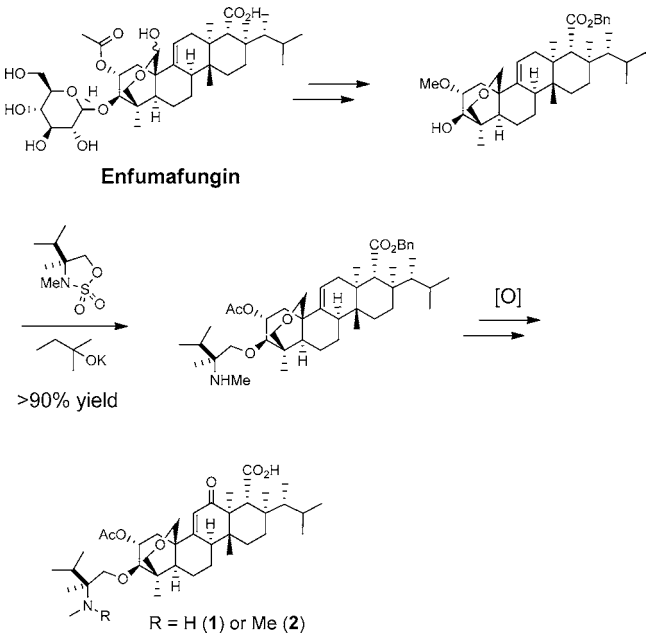
Some Items of Interest to Process R&D Chemists and Engineers

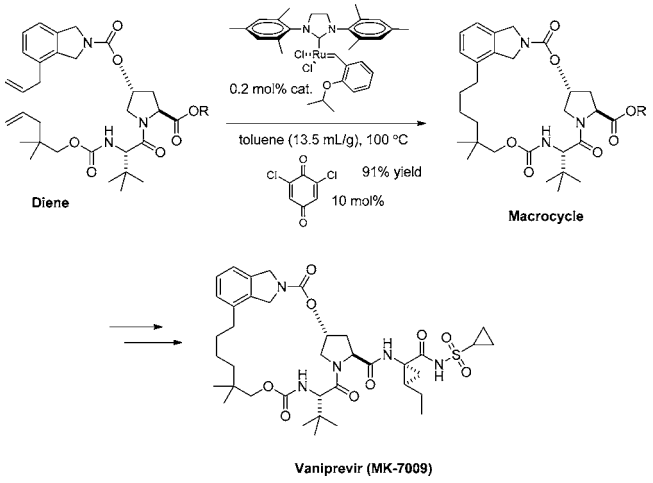
SYNTHESIS OF ANTIFUNGAL GLUCAN SYNTHASE INHIBITORS



The incidence of systemic fungal infections has increased in recent decades. The major antifungal therapeutic reagents for the treatment of systemic fungal infections, including the polyenes, azoles, and echinocandins, are often limited by their side effects, clinical resistance, and a narrow spectrum of antifungal activity. The natural product enfumafungin, isolated from a fermentation of *Hormonema* sp., is capable of inhibiting fungal glucan synthase. As part of an ongoing drug discovery program at Merck Research Laboratories, two novel enfumafungin derivatives, **1** and **2**, were identified as potent glucan synthase inhibitors and selected for further development. Now Zhong and co-workers at Merck Process Research describe an efficient and scalable semisynthesis of glucan synthase inhibitors **1** and **2** starting from the fermentation product enfumafungin (*J. Org. Chem.* **2012**, *77*, 3297). The highlights of the synthesis include a high-yielding ether bond-forming reaction between a sterically demanding sulfamidate and alcohol and a remarkably chemoselective palladium(II)-mediated Corey–Yu allylic oxidation at the highly congested C-12 position of the enfumafungin core. Multihundred gram quantities of these challenging target drug candidates **1** and **2** were prepared, in 12 linear steps with 25% isolated yield and 13 linear steps with 22% isolated yield, respectively.

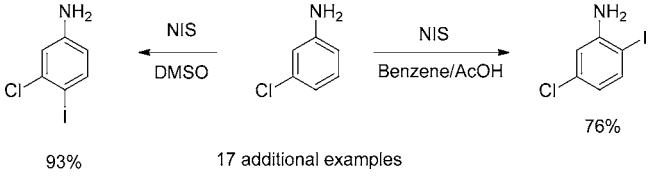
A RING-CLOSING METATHESIS STRATEGY FOR THE SYNTHESIS OF HCV PROTEASE INHIBITOR VANIPREVIR (MK-7009)

Chronic infection with hepatitis C virus (HCV) is a worldwide epidemic, affecting approximately 180 million individuals around the globe. The launch of two new drugs, Boceprevir and Telaprevir, shows promise to improve the success rate in HCV therapy. Despite these tremendous accomplishments, additional improvements in the area of genotype coverage, drug dose, and cure rate are still desired. Vaniprevir (MK-7009) is a potent HCV NS3/4a protease inhibitor that is being evaluated for the treatment of HCV at the late stage of clinical studies. To ensure



the supply of the drug for ongoing clinical studies, a chemical process amenable to production of multikilogram quantities of MK-7009 was required. A highly efficient synthesis of Vaniprevir (MK-7009) is reported by Kong, Chen and co-workers at Merck Process Research has been accomplished in nine linear steps and 55% overall yield (*J. Org. Chem.* **2012**, *77*, 3820). The key features of this synthesis include a cost-effective synthesis of the isoindoline subunit and efficient construction of the 20-membered macrocyclic core of Vaniprevir (MK-7009) utilizing ring-closing metathesis technology. A practical and volume efficient ring-closing metathesis protocol was achieved via simultaneous slow addition of the ruthenium catalyst (0.2 mol % loading) and the diene substrate at a concentration of 0.13 M.

REGIOSELECTIVITY IN THE IODINATION OF ANILINES WITH NIS



The electrophilic iodination of anilines has a long history, featuring a myriad of reagents. Typically, para-substitution dominates, and attempts to change this selectivity have been based primarily on *N*-directed ortho-metalation strategies. However, ortho-iodination can be quite competitive, even in the case of aniline itself, raising the question whether regiocontrol might be attained by simple alteration of reaction conditions. Studies toward this

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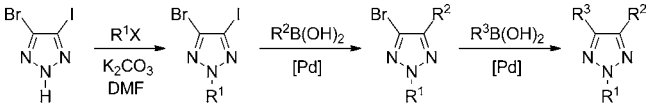
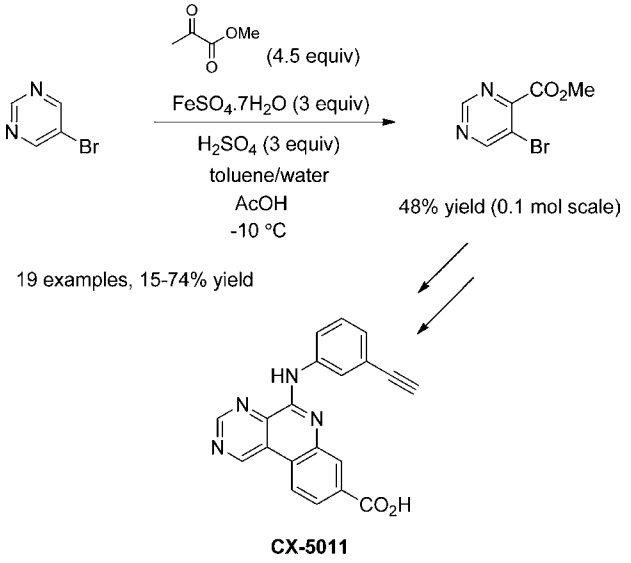
end are described in a recent letter by the Vollhardt group (*Synlett* **2012**, *23*, 208). The direct iodination of anilines by NIS in polar solvents (such as DMSO) affords *p*-iodinated products with up to >99% regioselectivity. Switching to less polar solvents (such as benzene) in the presence of AcOH inverts this outcome toward dramatically increased or preferential generation of the *o*-isomers, also with up to >99% regioselectivity. The scope is examined across 17 substrates with varying selectivities achieved.

REGIOSELECTIVE SYNTHESIS OF POLYSUBSTITUTED 1,2,3-TRIAZOLES



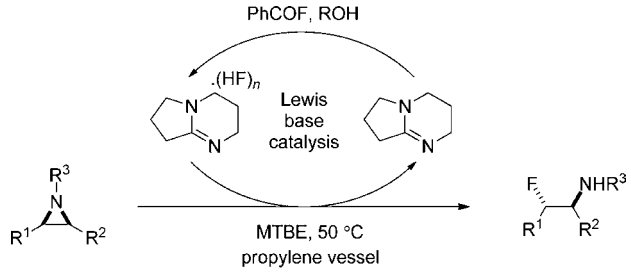
Zhang and co-workers in the Department of Chemical Development at Boehringer Ingelheim describe a regio-controlled approach to polysubstituted 1,2,3-triazoles (*Synlett* **2012**, *23*, 1052). The regioselective N2-substitution of 4-bromo-5-iodo-1,2,3-triazole with alkyl/aryl halides in the presence of K_2CO_3 in DMF produces the desired 2-substituted 4-bromo-5-iodo-1,2,3-triazoles as the major product in good to excellent regioselectivity. Subsequent iterative and chemoselective Suzuki–Miyaura cross-coupling reaction of N2-substituted 4-bromo-5-iodo-1,2,3-triazoles provides polysubstituted 1,2,3-triazoles efficiently.

SYNTHESIS OF 5-HALOPYRIMIDINE-4-CARBOXYLIC ACID ESTERS VIA A MINISCI REACTION



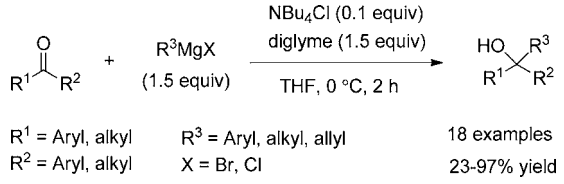
Pyrimidines are ubiquitous heterocycles found across a wide range of biologically active molecules, including various marketed drugs such as Gleevec (oncology), Etravirine (virology), and Trimethoprim (antibacterial), among others. Regan and co-workers at Cylene Pharmaceuticals report on the synthesis of various 5-halopyrimidine-4-carboxylic acid esters via the Minisci homolytic alkoxycarbonylation of 5-halopyrimidines (*Synlett* **2012**, *23*, 442). The reaction was found to be highly regioselective, allowing the one-step synthesis of useful amounts (>10 g) of ethyl 5-bromopyrimidine-4-carboxylate where other methods proved difficult. Ethyl 5-bromopyrimidine-4-carboxylate was used for the preparation of potent inhibitors of protein kinase CK2, including CX-5011. This work represents an interesting application of radical chemistry for the preparation of pharmacologically active molecules.

SYNTHESIS OF β-FLUOROAMINES BY LEWIS BASE-CATALYZED HYDROFLUORINATION OF AZIRIDINES



Lewis base catalysis promotes the in situ generation of amine-HF reagents from benzoyl fluoride and a non-nucleophilic alcohol. The hydrofluorination of aziridines to provide β-fluoroamines using this latent HF source is described by the Doyle group in a recent note (*J. Org. Chem.* **2012**, *77*, 4177). This protocol displays a broad scope with respect to aziridine substitution and *N*-protecting groups. Examples of regio- and diastereoselective ring-opening to access medicinally relevant β-fluoroamine building blocks are presented.

QUATERNARY AMMONIUM SALTS AS ADDITIVES FOR ADDITION OF GRIGNARD REAGENTS TO KETONES



Nucleophilic addition reactions between Grignard reagents and ketones are widely used for synthesizing tertiary alcohols. However, competing β-hydride reduction and enolization are often significant side reactions. The Song group describes the use tetrabutylammonium chloride (NBu_4Cl) as an additive together with diglyme as a cosolvent to increase selectivity for addition over enolization and reduction (*J. Org. Chem.* **2012**, *77*, 4645). The authors suggest that NBu_4Cl shifts the Schlenk equilibrium of Grignard reagents in favor of dimeric species, which in turn promotes addition to ketones via a six-membered transition state to form the desired tertiary alcohols. Additionally, it is proposed that the diglyme cosolvent increases the nucleophilicity of the Grignard reagents by coordination of the magnesium ion. A total of 18 examples are presented, including both alkyl and aryl Grignard reagent additions. Yields range from 23 to 97%.

GENERAL ASYMMETRIC HYDROGENATION OF 2-ALKYL- AND 2-ARYL-SUBSTITUTED QUINOXALINES

Asymmetric hydrogenation of prochiral unsaturated compounds using molecular hydrogen and chiral catalysts is an efficient and

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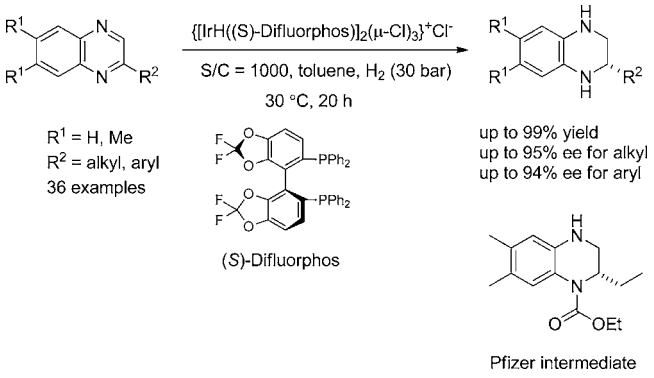
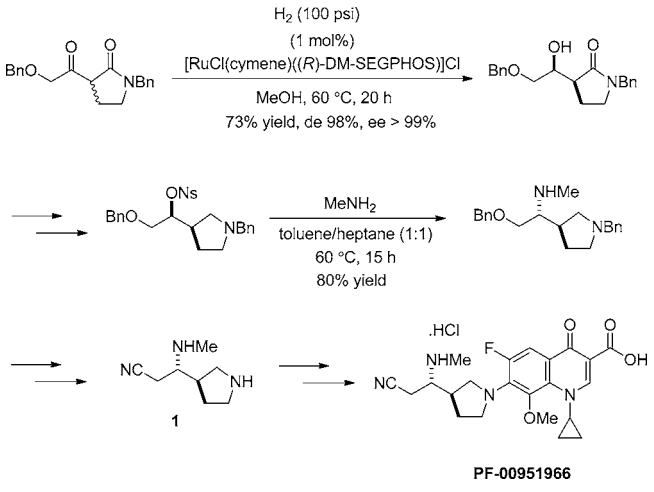
atom economical way to produce a wide range of enantioenriched compounds. A general asymmetric hydrogenation of



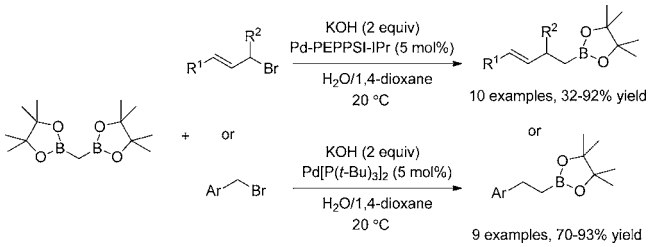
2-alkyl- and 2-aryl-substituted quinoxaline derivatives catalyzed by an iridium−difluorphos complex has been developed by Ohshima, Mashima, Ratovelomanana-Vidal, and co-workers (*J. Org. Chem.* **2012**, *77*, 4544). Under mild reaction conditions, the corresponding biologically relevant 2-substituted-1,2,3,4-tetrahydroquinoxaline units were obtained in high yields and good to excellent enantioselectivities up to 95%. With a catalyst ratio of S/C = 1000 and on a gram scale, the catalytic activity of the Ir−difluorphos complex was maintained. The authors applied this process in the preparation of an intermediate in the synthesis of a Pfizer cholesteryl ester transfer protein (CETP) inhibitor.

STEREOSELECTIVE SYNTHESIS OF (*S*)-3-(METHYLAMINO)-3-((*R*)-PYRROLIDIN-3-YL)-PROPANENITRILE



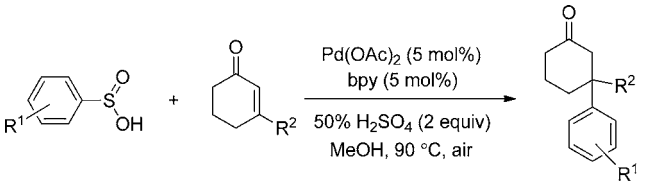
(*S*)-3-(Methylamino)-3-((*R*)-pyrrolidin-3-yl)propanenitrile (**1**) is a key intermediate in the preparation of PF-00951966, a fluoroquinolone antibiotic for use against key pathogens causing community-acquired respiratory tract infections including multidrug resistant organisms. Lall and co-workers at Pfizer Worldwide Research and Development report on the development of a highly efficient and stereoselective synthesis of **1** in 10 steps with an overall yield of 24% from readily available benzyloxyacetyl chloride (*J. Org. Chem.* **2012**, *77*, 4732). Two key transformations in the synthetic sequence involve (a) dynamic kinetic resolution via catalytic asymmetric hydrogenation with chiral DM-SEGPHOS-Ru(II) complex to afford the *β*-hydroxy amide in good yield (73%) and high stereoselectivity (de 98%, ee >99%) after recrystallization and (b) S_N2 substitution reaction with methylamine to provide the diamine with inversion of configuration at the 1′-position in high yield (80%), after efficient purification using a simple acid/base extraction protocol.

ALLYLIC AND BENZYLIC CROSS-COUPLING USING A DIBORYLMETHANE REAGENT



A novel example of the Suzuki−Miyaura cross-coupling reaction between sp^3-carbon and sp^3-carbon is described by Endo, Shibata, and co-workers (*J. Org. Chem.* **2012**, *77*, 4826). The reaction of a diborylmethane derivative with allyl halides or benzyl halides proceeds efficiently in the presence of appropriate Pd-catalysts at room temperature. This approach provides functionalized homoallylboronates and alkylboronates with excellent regio- and chemoselectivities.

PALLADIUM-CATALYZED DESULFITATIVE CONJUGATE ADDITION OF ARYL SULFINIC ACIDS



Transition-metal-catalyzed conjugate addition of organometallic reagents to *α*,*β*-unsaturated carbonyl compound is one of the most useful methods for the construction of C−C bonds. A new and efficient method for palladium(II)-catalyzed desulfitative conjugate addition of arylsulfinic acids with *α*,*β*-unsaturated carbonyl compound has been developed by Li, Duan, and coworkers (*J. Org. Chem.* **2012**, *77*, 4849). Using a catalyst system comprising $Pd(OAc)_2$ and an oxidatively robust bipyridyl ligand, arylsulfinic acids undergo loss of SO_2 and a subsequent 1,4-addition/*β*-hydride elimination sequence in MeOH at 90 °C under an atmosphere of air. The key reacting intermediates, including aryl Pd(II) sulfinic intermediate, aryl Pd(II), and C═O−Pd complexes, were captured by ESIMS/MS, which provide experimental evidence to support the proposed reaction mechanism.

HYDROPHOBIC SUBSTITUENT EFFECTS ON PROLINE CATALYSIS OF ALDOL REACTIONS IN WATER

In a recent article Schafmeister et al. (*J. Org. Chem.* **2012**, *77*, 4784) reported on the use of derivatives of 4-hydroxyprolines as organocatalysts for the aldol reaction. The article covered the synthesis of **1** with different stereochemistry as well as a detailed investigation into substrate, solvent, and temperature effects on the stereochemical outcome of the reaction.

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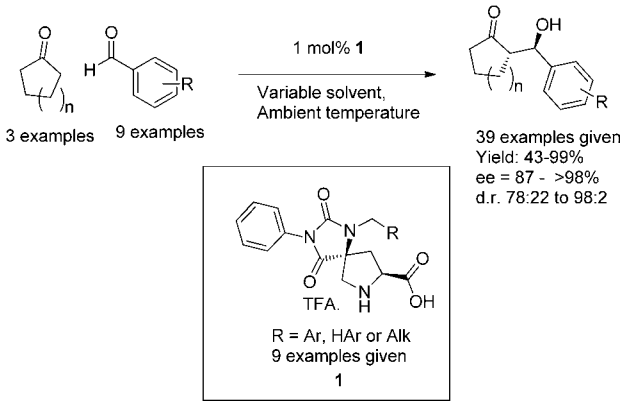
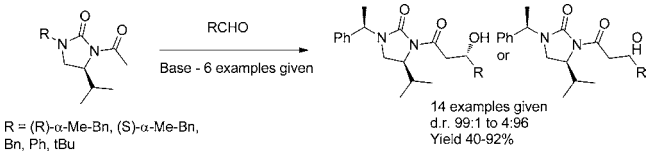


Using cyclohexanone as the substrate they found that the reaction with *p*-nitrobenzaldehyde could be achieved in water with excellent dr and ee. Some discussions around possible transition state models applicable to the reaction were also touched upon.

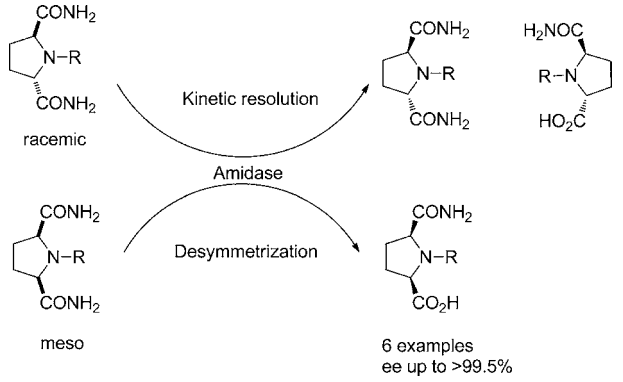
REVERSAL OF SELECTIVITY IN ACETATE ALDOL REACTIONS OF *N*-ACETYL-(*S*)-4-ISOPROPYL-1-[(*R*)-1-PHENYLETHYL]IMIDAZOLIDIN-2-ONES



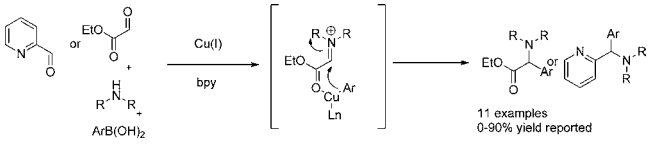
Nair and colleagues from the NIPER Department of Medicinal Chemistry in India recently reported on the potential to reverse the selectivity of the acetate aldol reaction depending on the metal used (*Org. Lett.* **2012**, *14*, 2442). The authors made several imidazolidin-2-ones via a seven-step process which were then tested under cryogenic conditions against several aldehydes using a diverse number of metal bases. They found that using LiHMDS/THF they would predominately get the anti product, whilst if using $TiCl_4$/DIPEA/DCM they reversed the selectivity and achieved mainly the syn product. The authors also discussed the synthesis of either (*S*)- or (*R*)-fluoxetine in excellent yields and ee.

ENANTIOSELECTIVE BIOTRANSFORMATIONS OF RACEMIC AND MESO PYRROLIDINE-2,5-DICARBOXAMIDES AND THEIR APPLICATION IN ORGANIC SYNTHESIS

A recent article by Wang et al. (*J. Org. Chem.* **2012**, *77*, 4063) reported of the use of *Rhodococcus erythropolis* AJ270 as a whole cell catalyst for the kinetic resolution of racemic pyrrolidine-2,5-dicarboxamides and the desymmetrization of meso-pyrrolidine-2,5-dicarboxamides. The authors discuss the evaluation of the whole cell catalyst, substrate scope, and application of the methodology. The article also contains some information on a 20 g scale desymmetrization reaction using a 10 wt % (wet weight) catalyst load under fairly dilute conditions (12−13 mL/g substrate) but reasonable reaction time (12 h).

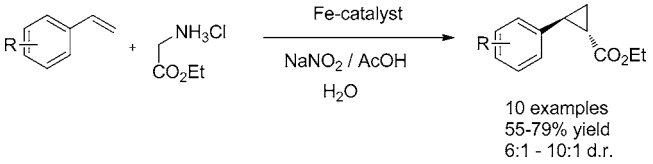


A COPPER-CATALYZED PETASIS REACTION FOR THE SYNTHESIS OF TERTIARY AMINES AND AMINO ESTERS



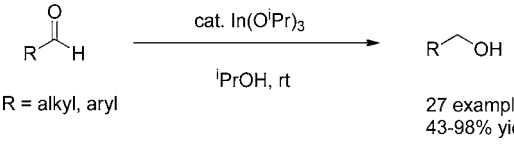
A variation on the Petasis reaction which consists of a three-component coupling of an aldehyde, amine, and boronic acid was recently reported by Bergin et al. (*J. Org. Chem.* **2012**, *77*, 4445). In this paper the authors described the novel use of pyridine-2-carboxaldehyde as starting material for the reaction. The investigation looked at the copper salt used as well as substrate scope for this new application. A mechanistic discussion was also included.

IRON-CATALYZED CYCLOPROPANATION WITH GLYCINE ETHYL ESTER HYDROCHLORIDE IN WATER



Expanding on their work around trifluoromethyl diazomethane chemistry Carreira et al. recently published an article on formation of *trans*-cyclopropyl esters using an iron catalyst and water as the solvent (*Org. Lett.* **2012**, *14*, 2162). After screening several catalysts they found that the catalyst FeTPPCl could be used. The protocol consisted of using 2 equivalents of glycine ethyl ester hydrochloride with 2.4 equivalents of sodium nitrite, 15 mol % acetic acid and 1 mol % of the catalyst in water at 40 °C. The article also looked at substrate scope.

INDIUM TRI-(ISOPROPOXIDE)-CATALYZED SELECTIVE MEERWEIN−PONNDORF−VERLEY REDUCTION OF ALIPHATIC AND AROMATIC ALDEHYDES



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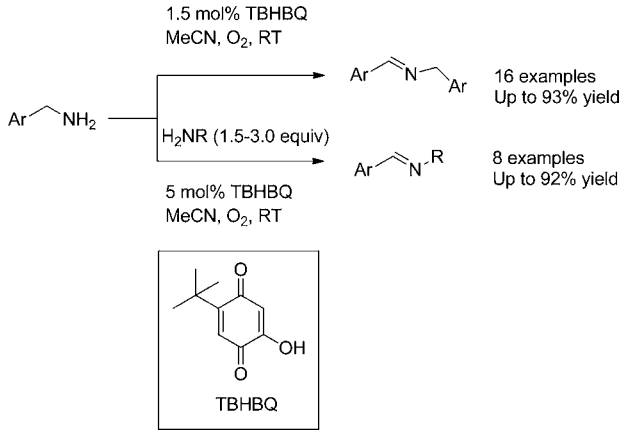
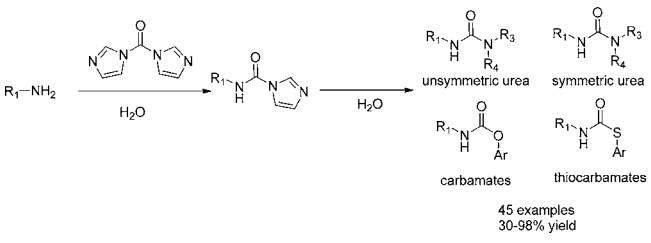
Phil Ho Lee et al. from Kangwon National University recently published an article regarding their work on indium-catalysed Meerwein−Ponndorf−Verley-type reductions of aldehydes (*J. Org. Chem.* **2012**, *77*, 4821). In this work the authors discuss the investigation into the aldehyde reduction looking at the solvent dependency using the indium catalyst. They found that both toluene and isopropanol could be used as solvent and achieved good yields when the catalyst loading approached 20 mol %. The same conditions used for aldehydes worked sluggishly with ketone, nitrile, nitro, ether, alkene, ester, or epoxide groups, indicating selective conditions for aldehydes. The authors also showed the reaction conditions working with a wide range of substrates from aryl to alkyl.

CHEMOSELECTIVE ORGANOCATALYTIC AEROBIC OXIDATION OF PRIMARY AMINES TO SECONDARY IMINES



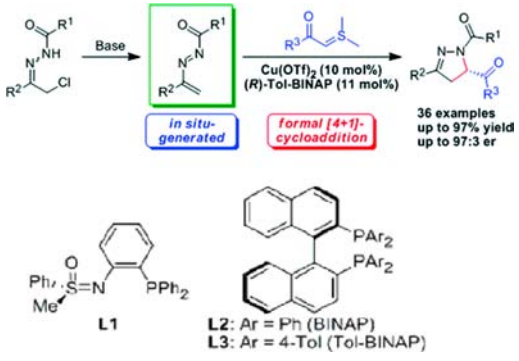
Stahl et al. published an article recently regarding the biomimetic aerobic oxidation of primary amines to secondary imines using a quinone catalyst (TBHBQ) (*Org. Lett.* **2012**, *14*, 2850). They found that by exposing a primary amine with the catalyst in acetonitrile under oxygen they could oxidize the amine to an imine. The imine then condensed with the primary amine substrate forming a secondary imine. By introducing a sterically hindered amine into the reaction mixture the authors found that they could form unsymmetric imines. A proposed mechanism involving the TBHBQ was introduced and discussed as well.

UNPRECEDENTED "In Water" IMIDAZOLE CARBONYLATION: PARADIGM SHIFT FOR PREPARATION OF UREAS AND CARBAMATES



In this paper the authors Padiya et al. describe the first "In Water" imidazole carbonylation of an amine (*Org. Lett.* **2012**, *14*, 2814). They also report the usefulness of this reaction by showing the possibility of trapping said carbonylimidazolide with nucleophiles opening up the formation of ureas, carbamates, and thiocarbamates which would potentially exclude the more common method using anhydrous solvents and inert atmosphere. The products precipitate out from solution and can be easily isolated by filtration in high purity; potentially this reaction could be a simple and scalable method to generate these compounds.

ENANTIOSELECTIVE SYNTHESIS OF FUNCTIONALIZED DIHYDROPYRAZOLES BY FORMAL (4+ 1)CYCLOADDITION



A novel strategy for the enantioselective preparation of highly substituted dihydropyrazoles has been described (*J. Am. Chem. Soc.* **2012**, *134*, 6924). The reaction proceeds via a (4 + 1) cycloaddition of in situ-derived azoalkenes and sulfur ylides catalysed by a chiral copper/Tol-BINAP complex.

The initial reaction of the N-Boc substituted hydrazone (R^1 is O^tBu; R^2 is phenyl) and the phenyl-substituted hydrazone (R^3 is Ph) in the presence of the ligand, **L1**, and cuprous triflate yielded the product in 80% yield, albeit with a poor chiral selectivity (er: 58:42). Subsequent ligand screening revealed that the enantiomeric ratio could be increased to 66:34 with BINAP. The R substituent was varied to induce greater selectivity in the reaction; use of the benzoyl group increased the er to 73:27. Further optimization with the Tol-BINAP system revealed that reaction at −30 °C with 11 mol % of Tol-BINAP ligand (**L3**), 10 mol % of cuprous triflate, and 1.0 equiv of sodium carbonate afforded the product in 83% yield with an enantiomeric ratio of 92:8. Interestingly, the reaction period could be reduced from 36 h to 17 h by conducting the reaction at −20 instead of −30 °C without any significant alteration of the enantiomeric ratio (91:9). The reaction also showed good substrate tolerance with respect to both the components—hydrazones as well as the sulfur ylides. It was also found that, in a scaled-up version (in gram quantities) of the reaction, the catalyst loading could be substantially reduced to 5 mol % of the copper salt and 5.5% of the ligand; the use of these conditions yielded the product in 92% yield with an enantiomeric ratio of 96:4, showing the synthetic potential of the reaction .

STEREOCONTROLLED SYNTHESIS OF HIGHLY FUNCTIONALIZED 1,3-DIENES BY A TANDEM 1,3-PHOSPHATYLOXY AND 1,3-HALOGEN MIGRATION

The paper describes a highly stereocontrolled synthesis of functionalized 1,3-dienes by a double migratory cascade reaction of α-halogen-substituted propargylic phosphates (*J. Am. Chem. Soc.* **2012**, *134*, 6928).

The reaction features a 1,3-phosphatyloxy migration followed by a 1,3-halogen migration (chlorine or bromine; 1,3-iodine migration, a hitherto unknown transformation, has also been observed with cyclic substrates). Copper catalysis of the reaction yielded (*Z*)-1,3-dienes, whereas gold-catalyzed reactions yielded

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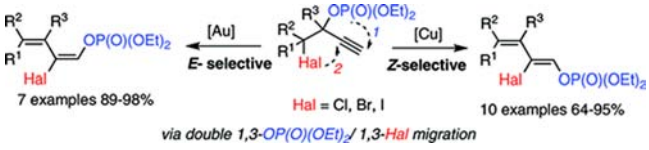
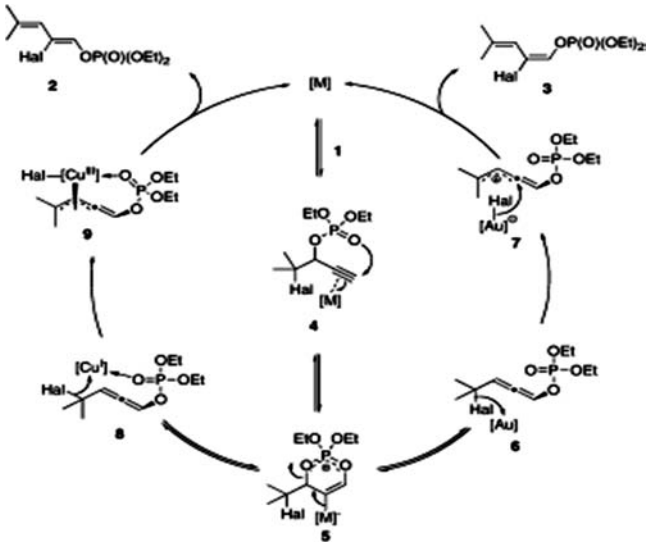
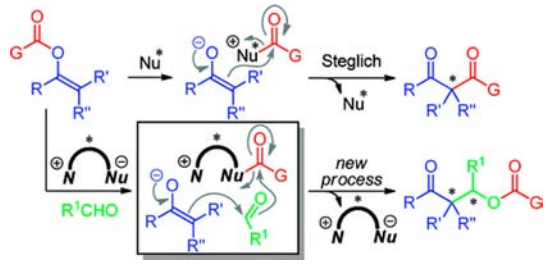


the corresponding (*E*)-dienes. The reaction demonstrated good substrate tolerance with both acyclic as well as cyclic precursors affording products as single stereoisomers with excellent yields under copper- as well as gold-catalyzed conditions. The iodine migration reaction, with cyclohexyl substrates under gold-catalyzed conditions, however, proceeded only with a moderate degree of stereocontrol. The synthetic potential of the dienes was further demonstrated through their participation in Diels–Alder reactions with suitable dienophiles, Suzuki–Miyaura, and Kumada coupling reactions.

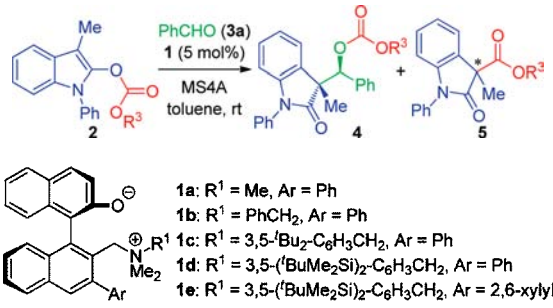


Mechanistically,the reaction is believed to proceed through an initial coordination of the metal to the alkynic π system, followed by coordination with the phosphatyloxy group to yield a cyclic intermediate; elimination of the metal from the cyclic intermediate leads to an allenyl phosphate. Halide abstraction (under Au catalysis) by the metal leads to an allyl cation, which upon anti halide addition yields the (*E*)-diene. Under copper catalysis, metal elimination was followed by coordination of the metal to the phosphatyloxy group, which was followed by halide abstraction and syn attack of the halide to yield the (*Z*)-diene.

STEREOSELECTIVE ALDOL REACTION OF OXINDOLE-DERIVED VINYLIC CARBONATES UNDER IONIC NUCLEOPHILIC CATALYSIS



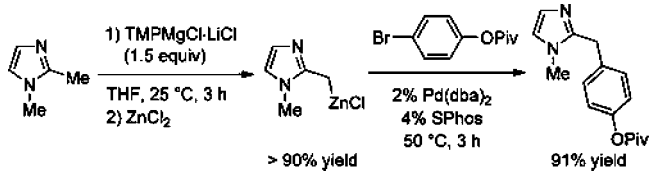
Vinylic carbonates are frequently encountered as structural units in natural products and are reactive synthetic intermediates. While the activated ester functionality of the vinylic esters has been employed as a mild and efficient acylating agent, the olefinic component has found utilization mostly as a monomer in the synthesis of polymers and copolymers. The present paper (*J. Am. Chem. Soc.* **2012**, *134*, 6972) describes a novel approach for the stereoselective aldol reaction of vinylic carbonates with simple aldehydes, by taking advantage of the ionic nucleophilic catalysis of chiral ammonium betaines to utilize vinylic esters as both enolate precursors as well as acylating agents.



The synthetic utility of the concept has been demonstrated by the highly diastereo- and enantioselective aldol reactions of oxindole-derived vinylic carbonates.

Reaction of the *O*-trichloroethoxycarbonyl-substituted vinylic carbonate (R^3: CCl_3CH_2) with benzaldehyde in the presence of the chiral ammonium betaine **1a** in the presence of 4 Å molecular sieves proceeded smoothly to yield the desired aldol compound **4** in 77% yield along with the Stieglich product **5** in an 8:1 ratio. An enantiomeric excess of 34% was achieved in the reaction. With a view to improve the product distribution and the chiral excess of the reaction, the betaine as well as the vinylic carbonate were structurally modified. Extensive optimization studies revealed that use of the 3,5-bis(trifluoromethyl)benzyl-substituted (i.e., R^3) vinylcarbonate in conjunction with the catalyst **1e** led to a 20:1 ratio of **4**:**5** and an ee of 95%. Heteroaromatic aldehydes also proved to be good coupling partners in the reaction.

BENZYLIC ARYLATION OF 2-METHYL FIVE-MEMBERED HETEROCYCLES



Knochel and co-workers have disclosed a novel protocol for the arylation of various 2-methyl five-membered heterocycles (*Org. Lett.* **2012**, *14*, 1951).

The reaction sequence employs the use of TMP bases, TMP·MgCl·LiCl, TMPLi, or TMP·ZnCl·LiCl, for selective metalation at the 2-methyl position, subsequent transmetalation of which yielded the 2-methyl zincated intermediate. Under Negishi cross-coupling conditions this afforded the corresponding arylated heterocycle. Thus, magnesiation of 1,2-dimethyl imidazole with 1.5 equiv of TMP·MgCl·LiCl (0.50 h) and subsequent transmetalation with $ZnCl_2$ generated the zincated intermediate which on cross-coupling with a bromo-aryl derivative in the presence of 2% $Pd(dba)_2$ and 4% SPhos provided the desired arylated heterocycle. The reaction showed good substrate tolerance as arylation with both electron-rich as well as electron-poor aryl bromides proceeded smoothly with

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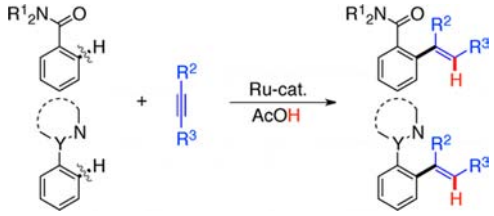
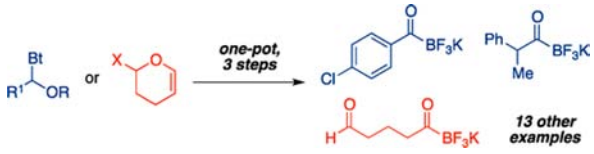
good yields (71−91%). With less acidic substrates such as 2-methyl benzothiophene, TMPLi was employed as the base; lithiation of 2-methyl benzothiophene, followed by transmetalation and subsequent coupling with variously substituted aryl bromides, yielded the corresponding arylated benzothiophenes in moderate to good yields (68−98%). To further demonstrate the generality of the approach, the authors zincated 1-methoxymethyl-2-methyl imidazole with TMP·ZnCl·LiCl, which on arylation with 1-bromo anisole yielded the arylated product in 68% yield. The above protocol acquires significance as it avoids lithiation at the 5-position prior to alkylation of the 2-methyl group as has been reported earlier (*Tetrahedron Lett.* **2005**, *46*, 8315).

RUTHENIUM(II)-CATALYZED REGIO- AND STEREOSELECTIVE HYDROARYLATION OF ALKYNES



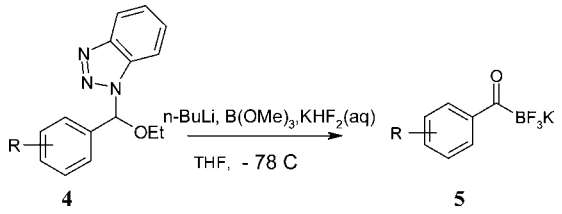
Regio- and stereoselective hydroarylation of alkynes with benzamides involving amide-directed C−H bond cleavage in the presence of a ruthenium/silver catalyst system is described. (*Org. Lett.* **2012**, *14*, 2058). The reaction of *N*,*N*-dimethylformamide with 2.0 equiv of diphenylacetylene was conducted in the presence of 5 mol % [Ru-(*p*-cymene)Cl_2]$_2$ and $AgSbF_6$ in dioxane at 100 °C and yielded the hydroarylated product in 43% yield. In the presence of acetic acid (1 mmol), the yield of the reaction could be increased to 96%; reducing the amount of acetic acid to 0.1 mmol reduced the yield to 55%. Unsymmetrical alkynes such as 1-phenylpropyne and hexyne also reacted smoothly with benzamide under the above conditions to yield the desired products. Mechanistically, it has been proposed that the reaction proceeds through ortho-metalation to form a five-membered ruthenacycle, followed by alkyne insertion into the Ru−C bond and subsequent protonolysis to yield the desired product. Further, it was confirmed, by deuteration studies, that the C−H bond cleavage is the rate-determining step of the reaction.

SYNTHESIS OF ACYLTRIFLUOROBORATES



A novel synthesis of acyltrifluoroborates from benzotriazole (Bt)-based *N*,*O*-acetals has been described (*Org. Lett.* **2012**, *14*, 2138).

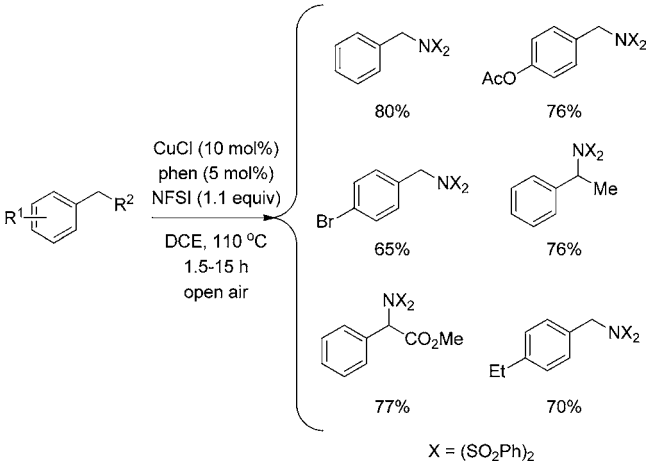
The *N*,*O*-acetals were prepared directly from the corresponding aldehydes. Lithiation of the acetal **4** with *n*-BuLi at −78 C, followed by anion quenching with trimethylborate and subsequent treatment with KHF_2 afforded the benzoylated trifluoroborate **5** in 45% yield. Variously substituted benzoyl trifluoroborates were prepared according to the above procedure



4 **5**

in similar yields. *n*-BuLi was used as the limiting reagent to avoid the formation of trace amounts of $BuBF_3K$ which would be difficult to separate from the desired product. Although the overall yields were modest, the process acquires significance as it comprises a three-step, one-pot sequence and also provides for the isolation of the potassium trifluoroborate salt without any chromatography. In addition to the mixed acetals derived from benzotriazole, the synthesis could be extended to substituted (6-ethoxy) and unsubstituted dihydropyrans, which afforded the corresponding acyclic trifluoroborate salts. Interestingly, the acyl trifluoroborates displayed reactivity similar to that of aldehydes or ketones.

BENZYLIC AMIDATIONS



The selective functionalization of toluene derivatives at the benzylic position is a powerful method to enhance the synthetic value of simple raw materials. Q. Zhang, J. Zhang, and Q. Liu describe a highly selective amidation that, in contrast to literature precedent, does not require a nitrene precursor, a directing group, or the use of a large excess of benzylic substrate (*Angew. Chem., Int. Ed* **2012**, *51*, 1244). In the presence of 10 mol % CuCl and 5 mol % 1,10-phenanthroline (phen), *N*-fluorobenzenesulfonimide (NFSI) reacts with a wide variety of methyl arenes including electron-donating and electron-withdrawing substituents on different positions of the ring. The amidation displays a moderate selectivity for primary C−H bonds relative to their secondary counterparts, possibly due to the steric hindrance of NFSI. A primary kinetic isotope effect found in the reaction of toluene and toluene-d_8 indicates that the rate-limiting step involves the cleavage of the C−H bond. The authors propose a putative catalytic cycle that considers the formation of a benzylic radical.

Alvarez, Muñiz, and co-workers report a related approach for the C−H amidation of benzylic positions in *Angew. Chem., Int. Ed* **2012**, *51*, 2225. Two groups of substrates, 8-methyl quinolines and 2-methylphenyl ethers, were studied to demonstrate a Pd-catalyzed intermolecular amidation that uses NFSI as nitrogen source and oxidant. The reaction of a selection of 8-methyl

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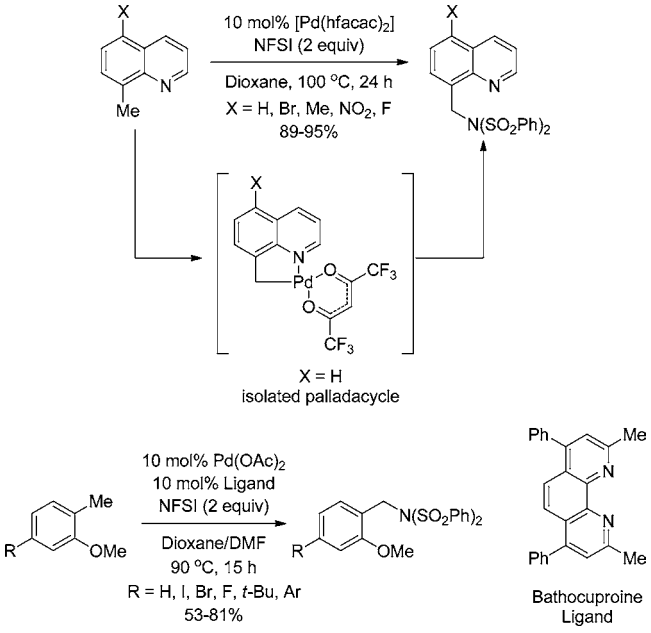
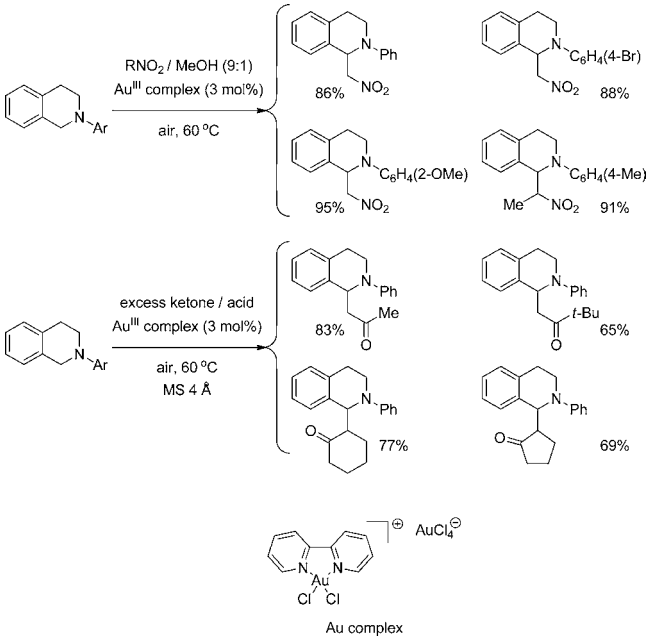


quinolines took place with commercially available $[Pd(hfacac)_2]$ (hfacac = hexafluoroacetylacetonate) to afford the sulfonyl imide products in excellent yields. The corresponding 8-aminomethylquinolines could be readily obtained under acidic hydrolysis. Similarly, 2-methylphenyl ethers underwent C−H amidation in the presence of $Pd(OAc)_2$ and bathocuproine to give the desired sulfonyl imides in good yields. A combination of control experiments and DFT calculations completes a catalytic cycle proposal that incorporates the formation of an intermediate palladacycle Pd^{II}−Pd^{IV} oxidation and C−N bond-formation steps. The transformations constitute an example of C−H amidation mediated by weak metal coordination.

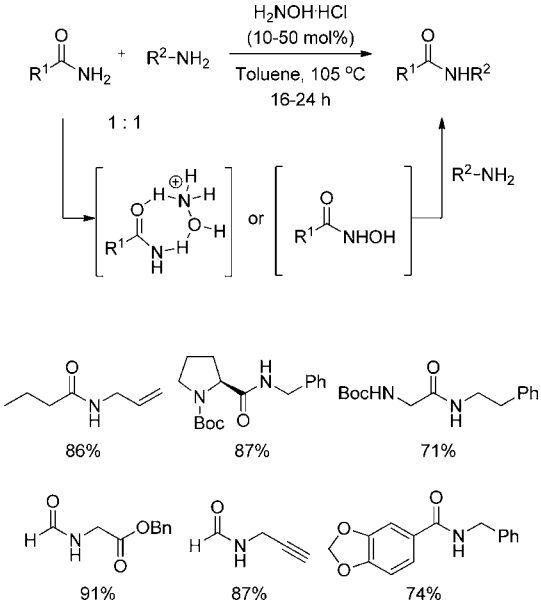
Au-CATALYZED OXIDATIVE C−C COUPLINGS WITH NITROALKANES AND KETONES



Zhu and co-workers at Nanjing University report the Au-catalyzed C−C coupling of *N*-aryltetrahydroisoquinolines with nitroalkanes and ketones (*Angew. Chem., Int. Ed.* **2012**, *51*, 1252).

Following a screening of plausible catalysts and reaction conditions, the authors found that a 2,2′-bipyridine-Au^{III} catalyst promotes the desired C−C coupling in the presence of air as oxidant and the nitroalkane or the ketone reactants as solvent. In general, the couplings are compatible with a variety of aromatic substituents on the isoquinoline nitrogen. However, whereas the reaction with nitroalkanes requires the use of MeOH as an additive, the reaction with ketones benefits from the use of acid (AcOH or MsOH) and molecular sieves. The detection of iminium salt intermediates by mass spectrometry upon addition of the catalyst suggests the formation of fleeting isoquinolinium−Au^{I} complexes that could be trapped by the nitroalkane or the ketone. Reduction of the 2,2′-bipyridine-Au^{III} catalyst to the active Au^{I} species would be promoted by the solvent or the substrates.

TRANSAMIDATION OF PRIMARY CARBOXAMIDES



The discovery of catalytic methods for the transamidation of amides has attracted the attention of numerous research groups undaunted by the stability of the starting materials. Allen and co-workers at University of Bath report the use of catalytic hydroxylamine hydrochloride to activate a range of primary carboxamides and mediate their transamidation (*Angew. Chem., Int. Ed.* **2012**, *51*, 1383). Thus, treatment of a range of primary amides and amines with hydroxylamine hydrochloride in toluene at 105 °C affords good yields of the transamidation products while tolerating a variety of functional groups (e.g., carbamates, esters, ureas). An interesting feature of the reaction is that the resulting secondary amide is highly stable and does not react with other nucleophiles, such as primary amines, under the reaction conditions. Kinetic studies reveal a first-order dependence in hydroxylamine hydrochloride concentrations, consistent with a hydrogen bonding activation of the primary amide or the nucleophilic attack of the hydroxylamine to give a hydroxamic acid intermediate. A series of control experiments indicate that the two routes coexist.

Cu-CATALYZED AMINATION OF ARYLBORONATES

The Cham-Lam coupling of arylboronic acids with amines is a powerful tool to generate C−N bonds. However, under the original coupling conditions, the amination of the aromatic

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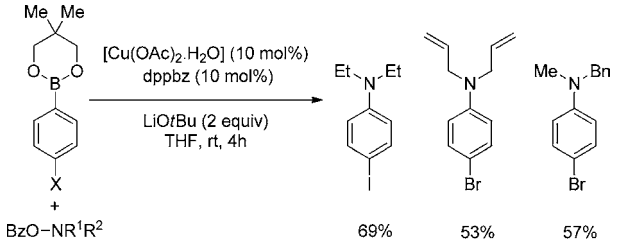
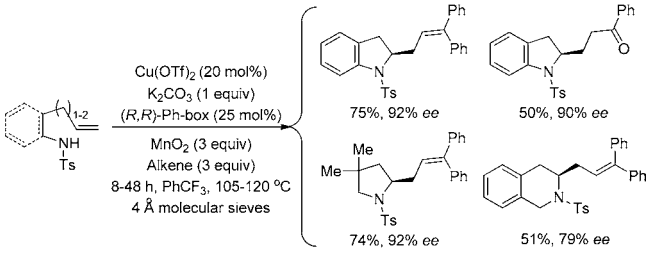


dppbz=1,2-bis(diphenylphosphino)-benzene

substrates with secondary acyclic alkylamines remains a challenge. Hirano and Miura from Osaka University circumvent this problem in *Angew. Chem., Int. Ed.* **2012**, *51*, 3642 where they disclose a Cu-catalyzed amination of phenylboronic acid neopentylglycol esters with hydroxylamines as electrophilic aminating reagents. The optimized reaction conditions promote the amination of different phenylboronic derivatives with a range of *O*-benzoylhydroxylamines. Remarkably, the process is compatible with iodo- and bromo-substituted arylboronates as well as aromatic esters, ketones, and aldehydes. The umpolung amination appears to take place via monoarylcopper species and their diarylcuprate derivatives.

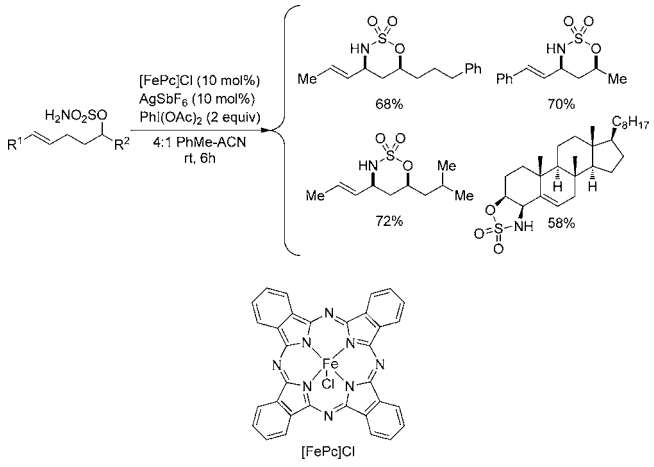
■ ENANTIOSELECTIVE Cu-CATALYZED CYCLIZATION OF ALKENYLSULFONAMIDES



Liwosz and Chemler from The State University of New York at Buffalo describe a Cu-catalyzed coupling cascade that quickly assembles indolines, pyrrolidines, and isoquinolines in an enantioselective manner (*J. Am. Chem. Soc.* **2012**, *134*, 2020). The sequence brings together two transformations: (1) the enantioselective intramolecular aminocupration of a γ-amino-alkene and (2) the intermolecular oxidative Heck-type coupling of the intermediate β-amino alkyl radical. For example, the intramolecular amination of *N*-tosyl-2-allylaniline mediated by $Cu(OTf)_2$ and (*R*,*R*)-Ph-box provides an intermediate indoline that reacts with 1,1-diphenylethylene to give the corresponding coupling product in 75% yield and ~90% ee. The nature of the para substituent of the aniline does not influence yields or enantioselectivities. Moreover, different coupling partners such as styrene, α-methylstyrene, α-acetoxystyrene, α-pivaloxystyrene, benzofuran, and 3-methylbenzofuran react effectively to yield the desired products. A series of mechanistic observations indicate that the stereochemistry-determining step corresponds to the aminocupration and that the addition of an intermediate carbon radical to the vinyl arene is more likely than a carbocupration followed by β-hydride elimination.

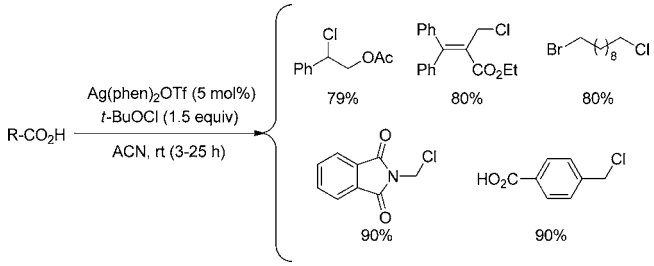
■ Fe-CATALYZED ALLYLIC C–H AMINATION

A recent manuscript by Paradine and White describes the development of a highly chemo- and site-selective allylic C–H amination of sulfamate esters catalyzed by a safe and inexpensive



Fe-phthalocyaninato complex (*J. Am. Chem. Soc.* **2012**, *134*, 2036). The novel procedure minimizes the formation of aziridine byproducts typically observed in metal nitrenoid C–H aminations and shows a strong penchant for the oxidation of allylic C–H bonds over stronger C–H bonds. Thus, the relative reactivities of different C–H centers follow the order: allylic > benzylic > ethereal > tertiary > secondary ≫ primary. The optimized conditions include the use of a noncoordinating silver salt ($AgSbF_6$), a soluble oxidant ($PhI(OPiv)_2$), and a mixed solvent system (4:1 toluene/acetonitrile). The measurement of a small intramolecular kinetic isotope effect and the configurational scrambling of the double bond support a mechanism involving the participation of an allyl radical formed via a homolytic C–H bond abstraction. In contrast, the absence of double bond isomerization during the amination mediated by $Rh_2(OAc)_4$ suggests a different mechanism under rhodium-based catalysis.

■ Ag-CATALYZED CHLORODECARBOXYLATION OF ALIPHATIC CARBOXYLIC ACIDS



On the 70th anniversary of the original report by Hunsdiecker and Hunsdiecker, the decarboxylative halogenation of carboxylic acids is still a subject of active research. Li and co-workers at the Shanghai Institute of Organic Chemistry report the first catalytic decarboxylative chlorination of carboxylic acids (*J. Am. Chem. Soc.* **2012**, *134*, 4258). Following a screening of catalysts, halogenating agents, and solvents, the optimal conditions surfaced when using $Ag(phen)_2OTf$ and *tert*-butyl hypochlorite in acetonitrile. An extensive analysis of the reaction scope shows that the procedure is general and tolerates a wide range of functional groups with the exception of those that can react with *tert*-butyl hypochlorite, such as electron-rich arenes, alcohols, and amines. Moreover, the distinct reactivity of different carboxylic acids enables the successful chemoselective decarboxylation of diacids (benzylic ~ tertiary > secondary > primary ≫ aromatic).

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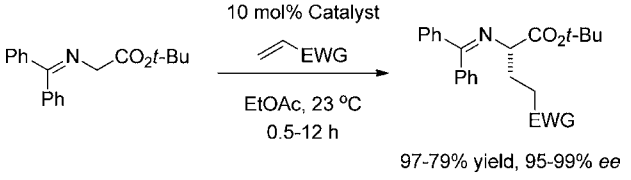
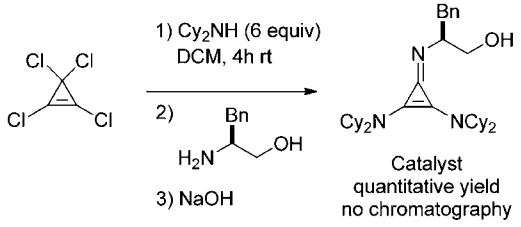
Preliminary mechanistic studies suggest the participation of radical intermediates.

ENANTIOSELECTIVE CYCLOPROPENIMINE-CATALYZED MICHAEL ADDITIONS

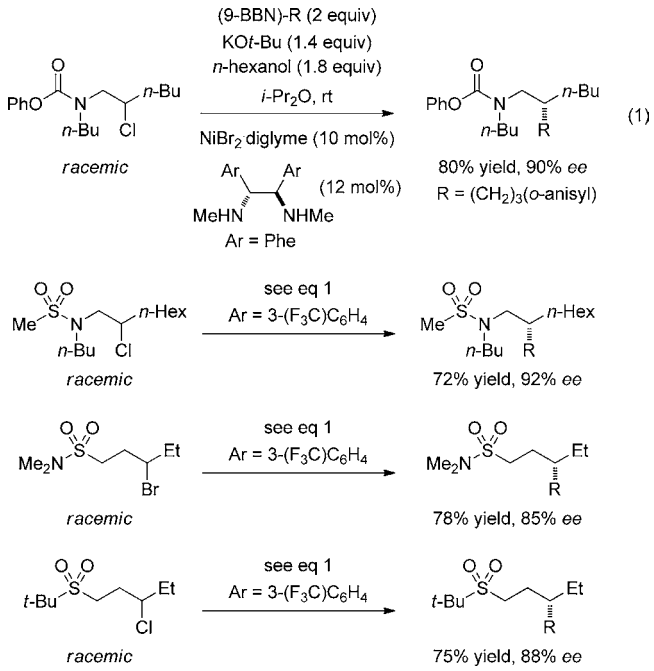




Although the concept of using chiral Brønsted bases in asymmetric synthesis has piqued the interest of numerous groups in recent years, finding strong bases that can promote enantioselective transformations and are easy to prepare remains an intimidating challenge. In a recent communication (*J. Am. Chem. Soc.* **2012**, *134*, 5552) Bandar and Lambert describe the development of 2,3-bis(dialkylamino)cyclopropenimine catalysts that afford high enantioselectivites for a variety of glycine imine conjugate additions. Cyclopropenimines are orders of magnitude more basic than comparable guanidines due to the formation of a resonance-stabilized cyclopropenium cation upon protonation of the imino nitrogen. Moreover, the preparation of these bases is extremely simple by condensation between perchlorocycloprop-1-ene and a chiral amine. Then 1−10 mol % of a phenylalaninol-substituted cyclopropenimine catalyzes the addition of a generic glycine imine to several Michael receptors, including acrylates, methyl vinyl ketone, and chalcones. The reaction occurs under mild conditions to afford the desired Michael adducts in high yields and enantioselectivities. The catalyst's hydroxyl group and the choice of solvent are critical for both reactivity and enantioselectivity, suggesting that the transition states guiding the conjugate addition involve structures that are carefully orchestrated by H-bonding.

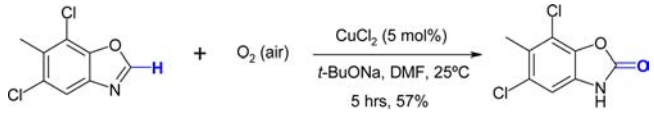
ASYMMETRIC SUZUKI CROSS-COUPLINGS OF RACEMIC ALKYL HALIDES

The first examples of the use of sulfonamides and sulfones as efficient directing groups in metal-catalyzed asymmetric C−C bond-forming reactions are reported by Wilsily, Tramutola, Owston, and Fu in *J. Am. Chem. Soc.* **2012**, *134*, 5974. The breakthrough comes to light in the context of studies on directing groups that promote the asymmetric Ni-catalyzed Suzuki couplings of inactivated alkyl electrophiles. Thus, chiral Ni-diamine catalysts mediate the asymmetric Suzuki couplings of racemic carbamate-protected β-chloro amines with alkylboranes as well as the coupling of tosyl- and mesyl-protected secondary dialkylamines in good yields and enantioselectivities. Interestingly, in the case of sulfonamide substrates, arylations can also be



achieved with excellent results. The sulfonamide oxygen appears to bind the Ni atom since reversing the sulfonamides or using simple sulfones results in stereoconvergent C−C bond formation. A mechanistic probe based on the measurement of coupling-constants and the use of enantiomerically enriched, deuterium-labeled substrates indicates that the transmetalation, which is probably the turnover-limiting step, occurs with retention of configuration at carbon.

ROOM-TEMPERATURE COPPER-CATALYZED OXIDATION OF ELECTRON-DEFICIENT ARENES AND HETEROARENES USING AIR



Lei and co-workers have reported on an impressive copper-catalyzed "oxygenase-type" oxidation of arenes and heteroarenes under extremely mild conditions using air as the stoichiometric oxidant (*Angew. Chem., Int. Ed.* **2012**, *51*, 4666). Although oxidative functionalization has been achieved using both palladium- and copper-based systems, previous studies required forcing reaction conditions, used a limited range of substrates, and often employed high catalyst loadings. Lei's system was optimized using benzothiazole as the model substrate. Choice of the copper source was important, though it is interesting to note that both copper(I) and copper(II) chloride gave similar results. The reaction performed best in polar solvents (DMF), and sodium *tert*-butoxide was the optimum base. Addition of N or O donor ligands inhibited the reaction to some extent. A range of heterocyclic substrates proved effective in the transformation as well as activated arenes, which have previously shown a propensity for C−H activation. A wide range of mechanistic studies were carried out, which suggested that the reaction is not radical based, and is most likely to proceed through a copper-mediated single electron transfer (SET) process, with copper *tert*-butoxide the active catalytic species.

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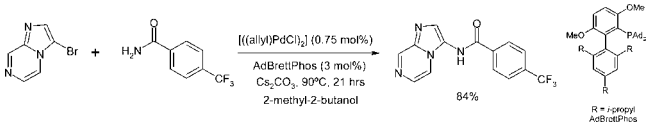
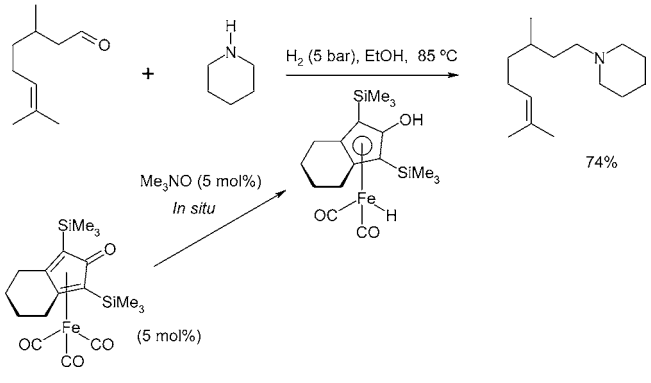
A BULKY BIARYL PHOSPHINE LIGAND ALLOWS FOR PALLADIUM-CATALYZED AMIDATION OF FIVE-MEMBERED HETEROCYCLES AS ELECTROPHILES



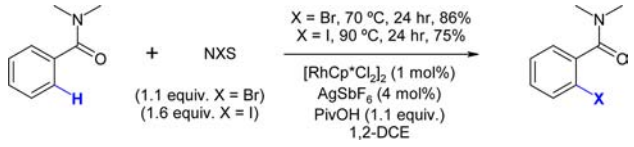
Reliable, robust methods for coupling five-membered heterocyclic compounds in Pd-mediated C−N bond-forming reactions have so far proven elusive. This is in contrast to their six-membered counterparts. One reason provided for the lack of reactivity is the presence of a basic nitrogen, which is able to coordinate to the palladium, and thus deactivate the catalyst. Buchwald and Su have provided a solution in the amidation of five-membered heterocycles employing the sterically hindered ligand AdBrettPhos (*Angew. Chem., Int. Ed.* **2012**, *51*, 4710). The new system is effective for a range of heterocyclic bromides including imidazoles, pyrazoles, thiazoles, pyrroles, and thiophenes. A range of pharmaceutically interesting bicyclic systems were also shown to be efficient coupling partners. However, the reaction of substrates containing free (H)N-bromoimidazoles and (H)N-bromopyrazoles remains problematic. The authors speculate that the success of the new ligands system in this reaction is driven by steric constraints of the ligand restricting free rotation in the intermediate oxidative addition complex, and distorting this towards the desired transition state for reductive elimination.

KNÖLKER'S IRON COMPLEX: AN EFFICIENT IN SITU GENERATED CATALYST FOR REDUCTIVE AMINATION OF ALKYL ALDEHYDES AND AMINES



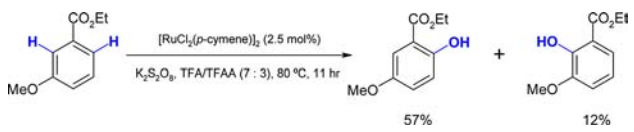
The most appealing reducing agent available to effect reductive amination of aldehydes and amines is molecular hydrogen. Indeed both heterogeneous and homogeneous catalysis has been applied to achieve this goal. However, these systems suffer from drawbacks such as poor chemoselectivity, issues with functional group compatibility, or limited availability and high cost of the catalysts utilized. Renaud and co-workers have reported on the use of an easily accessible and well-defined iron catalyst for the reductive amination of aliphatic amines and aliphatic aldehydes under smooth reaction conditions using molecular hydrogen as the reducing agent (*Angew. Chem., Int. Ed.* **2012**, *51*, 4976). After screening, Knölker's complex was identified as an effective catalyst, and concerns regarding its stability could be alleviated by generating the active 16-electron species in situ by treatment of the tricarbonyl precursor with trimethylamine-*N*-oxide. The optimal conditions used 5 mol % of both the catalyst and the *N*-oxide at 85 °C under 5 bar hydrogen pressure with ethanol as the optimal solvent. A wide range of primary and secondary amines reacted smoothly with alkyl aldehydes to provide the amines in good to excellent yields with impressive functional group selectivity being demonstrated. Addition of a catalytic quantity (10 mol %) of ammonium hexafluorophosphate enabled the reaction scope to be extended to benzaldehydes as well as ketones. The mechanism is believed to proceed through initial imine or enamine formation, which is reduced by an iron(II) hydride species formed in the reaction.

HIGH-YIELDING, VERSATILE, AND PRACTICAL [Rh(III)Cp*]-CATALYZED ORTHO BROMINATION AND IODINATION OF ARENES



Haloarenes are considered to be core building blocks within organic synthesis. With this in mind, methods enabling their preparation in a selective and high-yielding way for a large scope of compounds are of prime synthetic value. Rhodium(III) has been widely utilized as a C−H activation catalyst, though there are no reports of this metal being used for carbon−halogen bond formation. Glorius and co-workers have reported a system using $[RhCp^*Cl_2]_2$ as the catalyst (1 mol %) for this transformation with NBS or NIS as the respective economical halogen sources for bromination or iodination (*J. Am. Chem. Soc.* **2012**, *134*, 8298). Solvent choice is of critical importance with the reaction being run at 60 °C in 1,2-dichloroethane with $AgSbF_6$ (4 mol %), and pivalic acid (10 mol %) as additives. A range of diverse directing groups were able to influence the reaction including tertiary and secondary amides, acetamides, esters, and pyridines. In the case of acetophenones, under the standard conditions, noncatalyzed halogenation of the methyl group takes place. However, switching the additive from pivalic acid to copper acetate enables formation of the desired ortho-halogenated acetophenones. Mechanistic studies using kinetic isotope effects suggest that the C−H activation is the rate-determining step, and two potential pathways involving either a Rh(III) or Rh(V) intermediate rhodacycle are proposed.

RUTHENIUM(II)-CATALYZED SYNTHESIS OF HYDROXYLATED ARENES WITH ESTER AS AN EFFECTIVE DIRECTING GROUP



Direct functionalization of C−H bonds by transition metals continues to be an area of highly active research interest. Although significant progress has been reported, numerous challenges exist such as the need for more applicable directing groups to be developed and extending the range of metals utilized in such processes. Rao and co-workers have reported on a ruthenium(II) catalyzed ortho-hydroxylation of arenes directed by widely accessible ester functional groups (*Org. Lett.* **2012**, *14*, 2874). The products obtained are extremely common molecular

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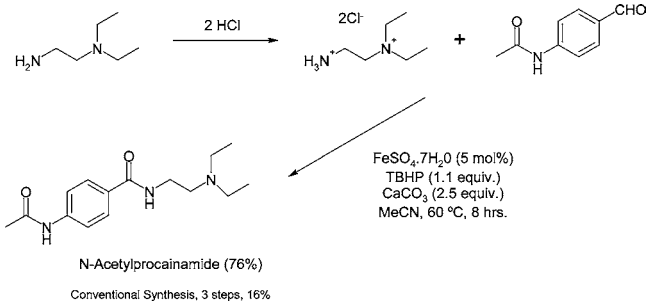
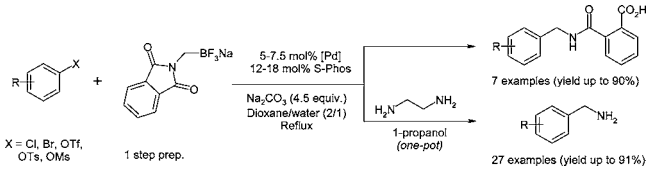
scaffolds in their own right, or can be utilized as versatile reactive intermediates. The optimized reaction conditions use 2.5 mol % of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst with potassium persulfate or Selectfluor as the stoichiometric oxidant at 80 °C. Of critical importance is the use of TFA/TFAA (7:3) as the solvent system. Reaction yields greatly diminished when either the solvent or ratio was varied or if alternative ruthenium catalysts were employed. The scope of mono- and disubstituted ethyl (or methyl) benzoates was found to be very broad, and typically one major product was obtained. Heterocycles were also shown to be suitable substrates for the reaction. Both electron-rich and electron-deficient aryl groups are well tolerated, and satisfactory yields could be obtained even with strongly electron-withdrawing groups if iodic acid was employed as the oxidant. Initial mechanistic studies are not conclusive, but KIE studies suggest that C−H activation is involved in the rate-limiting step.

IRON-CATALYZED EFFICIENT SYNTHESIS OF AMIDES FROM ALDEHYDES AND AMINE HYDROCHLORIDE SALTS



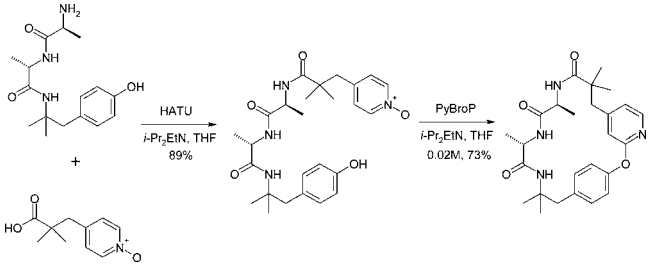
Conventional methods for the preparation of amides either involve the reaction of an amine with a carboxylic acid derivative or by using a coupling reagent. Given that these methods suffer from significant drawbacks (poor atom economy, use of hazardous reagents), a number of alternative methods have been developed for amide synthesis. However, many of these new methods have not been employed in industry due to challenges such as the use of expensive catalysts, limited substrate scope or harsh reaction conditions. Chen and co-workers have developed a promising method describing the oxidative amidation of aldehydes with amine salts using relatively inexpensive and easily accessible iron compounds as catalysts (*Adv. Synth. Catal.* **2012**, *354*, 1407). The optimized conditions utilized iron sulfate as the catalyst (5 mol %), T-Hydro (70% aqueous *tert*-butyl hydroperoxide) as the stoichiometric oxidant, and calcium carbonate as the base with acetonitrile as the solvent. The use of the weak base proved to be critical in slowly releasing the free amine from the salt form. The reactions were carried out at 60 °C with good yields being obtained typically after 6 h reaction times. A wide substrate scope was demonstrated for both secondary and tertiary amides, and amino-acids were shown to couple with no detectable racemization. The in situ formation of amine salts was developed to extend the substrate scope of the reaction. The reaction is proposed to proceed through initial hemi-aminal formation. This species is converted to the desired amides via iron-catalyzed TBHP oxidation occurring through a free radical mechanism.

ONE-POT PRIMARY AMINOMETHYLATION OF ARYL AND HETEROARYL HALIDES WITH SODIUM PHTHALIMIDOMETHYLTRIFLUOROBORATE



The introduction of the pharmaceutically relevant aminomethyl group onto aromatic rings is commonly achieved using starting materials such as aryl aldehydes, cyanides, amides, oximes, methyl halides, and methyl azides. However, accessing these starting materials is often challenging. In contrast, aryl halides, tosylates, and mesylates are widely available. Tanaka and co-workers have developed a general, robust, and high yielding method for the introduction of a primary aminomethyl group into aromatic rings via palladium-catalyzed cross-coupling (*Org. Lett.* **2012**, *14*, 2818). The key reagent for this purpose is the borate, sodium phthalimidoylmethyltrifluoroborate, which is easily accessed in one step. The Suzuki−Miyaura reaction of this substrate was optimized using (*S*)-Phos as the ligand (12 mol %), either $Pd(OAc)_2$ or $Pd(dba)_2$ as the palladium source (5 mol %), sodium carbonate as the base in a dioxan/water (2:1 ratio) solvent system. The optimal palladium source depended on the functionality of the aromatic coupling partner. Application of these conditions led to isolation of the corresponding *N*-(arylmethyl)phthalamic acids. If after the coupling the reaction was diluted with 1-propanol and refluxed with ethylenediamine, it was possible to obtain the desired aminomethyl compounds directly in good yield. A wide range of aryl and heteroaryl substrates participated in the reaction, and the observed functional group compatibility was good with aldehydes, esters, and nitro and cyano groups all being well tolerated.

A NEW AND USEFUL METHOD FOR THE MACROCYCLIZATION OF LINEAR PEPTIDES



Macrocyclic peptides offer the opportunity to have markedly improved properties over their linear counterparts making them attractive targets as peptide-based therapeutics. Despite this, the ring closure of small/medium rings in this class is challenging and often requires either harsh or high-dilution conditions to obtain acceptable reaction yields. Workers at Pfizer have demonstrated a novel macrocyclization reaction employing PyBroP as a general and mind pyridine *N*-oxide activator. This species is subsequently trapped in an intramolecular fashion to form the ring by the side-chains of natural amino-acids (tyrosine, lysine and histidine) acting as tethered nucleophiles (*Org. Lett.* **2012**, *14*, 2890). The reaction is carried out in THF, with a solution of the substrate being added over 15 min to a solution of PyBroP

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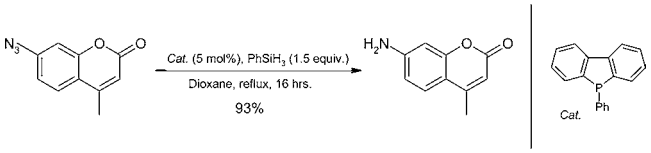
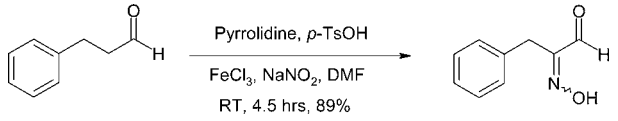
and Hunig's base. Although concentration was demonstrated to be important, it was not necessary to run at such high dilutions (<0.01 M) commonly associated with macrocyclizations. Varying three components of the substrate enabled a range of diverse products to be isolated in modest to excellent yield, with no evidence of epimerization. In certain cases, the cyclization precursors were insoluble and unreactive in THF, but generally this issue could be resolved by tuning the ester moieties in the side chain to achieve moderate solubility, and hence drive the reaction.

■ ORGANOPHOSPHORUS-CATALYSED STAUDINGER REDUCTION



The oxidation of phosphine reactants to phosphine oxides serves as a key driving force for a number of classical organic reactions. However, downstream issues have been realized with this in the production of significant waste and purification problems. Given this, desirable solutions that allow these reactions to proceed with better phosphorus atom economy have been persued. Van Delft and co-workers have reported on a novel variant of the Staudinger reaction, which effects the transformation of alkyl and aryl azides to the corresponding amines (*Adv. Synth. Catal.* **2012**, *354*, 1417). The system utilizes 5−10 mol % of a dibenzophosphole catalyst, which is recycled by reduction of its phosphine oxide using phenylsilane as the reducing agent. It was recognized that the reducing agents employed are incompatible with the typical aqueous conditions of the Staudinger reaction, and thus, refluxing dioxane was used as the reaction solvent, with the N−Si bond formed in the reduction of the iminophosphorane easily hydrolyzed in the reaction workup. A wide variety of azides were capable of being reduced, and the reaction displayed excellent functional group compatibility. The reaction is practical to carry out, and it is simple to recover the unoxidized phosphorus catalyst. P^{31} studies were employed to track the reaction, and a comparison of the current system with triphenylphosphine is provided.

■ A REMARKABLY SIMPLE α-OXIMATION OF ALDEHYDES VIA ORGANO-SOMO CATALYSIS



Synthetically important α-oximinino carbonyl compounds are accessed via the direct α-oximation of aldehydes, ketones, or esters by NOCl. Typically, this is achieved in aqueous acid solution using either an organic nitrosating agent or sodium nitrite, though other methods have been developed. Often though, issues arise when aldehydes are employed as substrates due to purification difficulties or instability of the initial adducts. Organocatalysis has rapidly emerged as a strategy for the effective α-functionalization of aldehydes. Gentili and Pedetti have exploited the SOMO (singly occupied molecular orbital)-enamine activation to develop a simple system for the α-oxyamination of aldehydes (*Chem. Commun.* **2012**, *48*, 5358). The reaction uses 20 mol % of pyrrolidine as the organocatalyst with 10 mol % of *p*-TsOH present to facilitate generation of the initial enamine. The optimum solvent for the reaction is DMF with iron(III) chloride and sodium nitrite added to effect the nitrosation. Aliphatic aldehydes performed well in the reaction regardless of steric hindrance of the substituent on Cα. However, α,β-unsaturated aldehydes gave no reaction. Substrates with remote unactivated olefins also led to byproduct resulting from proposed cyclization of an intermediate radical-cation species. Mechanistically, the initial enamine is proposed to be oxidized by Fe(III) in a single-electron process to generate a three-π-electron SOMO-activated intermediate, which reacts with the NO radical (generated by Fe(II) and nitrite in the presence of H^+). Tautomerization and hydrolysis lead to the desired 2-hydroxyimino-aldehydes.

■ POLYMORPHS, SALTS, AND COCRYSTALS: WHAT'S IN A NAME?

During the past decade, we witnessed an ongoing debate regarding the development of a widely accepted definition of cocrystals. Discovered nearly 170 years ago, cocrystals have "re-emerged" in the pharmaceutical industry due to their ability to modulate API physicochemical properties and to add value to the intellectual property developed by research organizations. The FDA published in December 2011 a new guidance for the regulatory classification of cocrystals (sic). In this document, the FDA provides definitions for cocrystals, polymorphs, and salts. In February 2012, several industrial and academic researchers met to discuss "The Evolving Role of Solid State Chemistry in Pharmaceutical Science". A summary of the discussions held at the meeting regarding the FDA guidance draft on cocrystals was recently published, authored by 47 scientists (Aitipamula, S. et al. *Cryst. Growth Des.* **2012**, *12*, 2147). Most of the authors are from academia, but a few are from the industry (Novartis, Ranbaxy, etc.). The group takes exception with the FDA guidance on two accounts: (1) the actual definition of a cocrystal ("solids that are crystalline materials composed of two or more molecules in the same crystal lattice") and (2) the classification of a cocrystal as a "dissociable API-excipient molecular complex ... that may be treated as a drug product intermediate, rather than a drug". Four (negative) implications of such a definition and nine reasons why cocrystals should not be classified as molecular complexes (but rather should be grouped with salts) are presented. The main justification for the changes proposed by the group is the possible overlap of the forms exhibited by multicomponent solid forms. The group proposes the following broader definition of cocrystals: *"...solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio".*

■ QUALITY BY DESIGN (QbD)-BASED CRYSTALLIZATION PROCESS DEVELOPMENT FOR THE POLYMORPHIC DRUG TOLBUTAMIDE

Uncomfortable with statistical analysis, some chemists prefer the "Royal Road" to design space development, one that is based (exclusively) on first principles. An elegant example of such an accomplishment has been recently published by Prof. Tan's group in Singapore (Thirunahari, S. et al. *Cryst. Growth Des.* **2011**, *11*, 3027). Crystallization of the polymorphic sulfonylurea drug tolbutamide (six polymorphs) was investigated with the aim of developing a crystallization design space for a metastable form (I). Solution-mediated polymorphic transformations were carefully evaluated using orthogonal partial least-squares principal

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component analysis (OPLS-PCA). Solute concentrations were measured using ATR-FTIR, with the necessary calibrations. Solid form detection was accomplished using Raman spectroscopy aided by multivariate statistical process monitoring (statistics cannot be totally avoided, after all). Cooling rate appears to be a critical process parameter, and at the scale discussed, a cooling rate of 0.08 °C/min was practiced for the temperature range 50 °C−25 °C. Notwithstanding the practical challenges for the implementation of the techniques employed, we note that the robustness of the process requires further proof, and future work will address perhaps the details of the seeding technology employed as well as the approach taken to scale up the design space developed at small scale.

A REVIEW OF RECENT ADVANCES IN MASS SPECTROMETRIC METHODS FOR GAS-PHASE CHIRAL ANALYSIS OF PHARMACEUTICAL AND BIOLOGICAL COMPOUNDS

Mass spectrometry (MS) is often thought to be a "chiral blind" method because enantiomers exhibit the same mass spectrum. Over 30 years ago it was shown that MS can be used to execute chiral analysis, and this method has "re-emerged" in the past decade. A review on the topic was recently published by a team from GlaxoSmithKline (Wu, L. et al. *J. Pharm. Biomed. Anal.* **2012**, DOI: 10.1016/j.jpba.2012.04.022). The paper reviews the five categories of chiral MS analysis: kinetic, host−guest diastereomeric adduct formation, ion/molecule reactions, collision-induced dissociation of diastereomeric adducts, and ion mobility spectrometry. MS chiral methods have the unique advantage of allowing for the analysis to be conducted in the absence of solvent. The authors note that MS methods are still in their infancy as a chirality-resolving tool and that routine quantification methods would require further advances of this method.

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