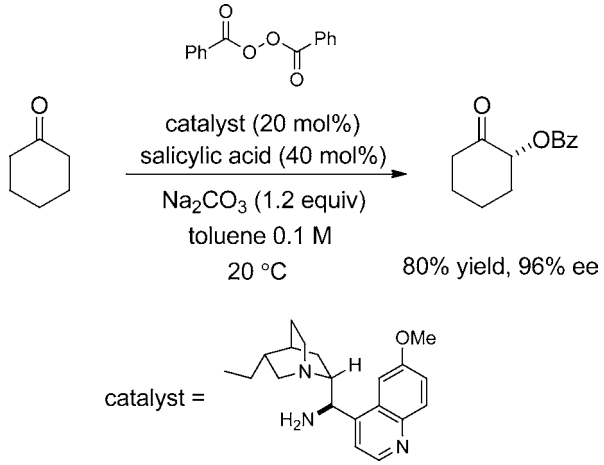
Organic Process Research & Development

Highlights from the Literature

pubs.acs.org/OPRD

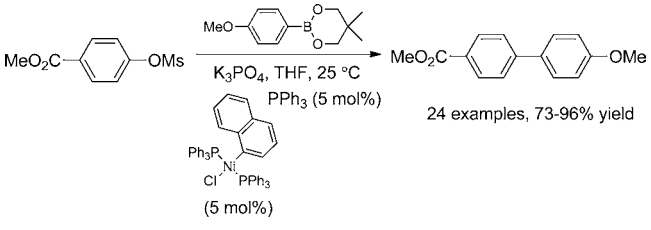
Some Items of Interest to Process R&D Chemists and Engineers

ENANTIOSELECTIVE α-BENZOYLOXYLATION OF KETONES



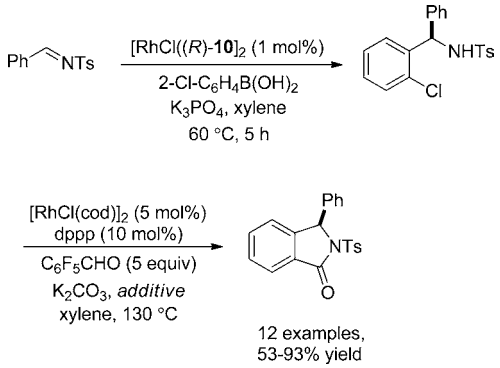
Catalytic methods for the enantioselective α-functionalization of carbonyl compounds are of significant interest in organic synthesis. The Bencivenni group reports on the development of a cinchona alkaloid system for the direct α-benzoylation of ketones (*J. Org. Chem.* **2012**, *77*, 2667). A mixture of 9-amino(9-deoxy)epi-dihydroquinidine and salicylic acid was able to promote the direct reaction of various cyclohexanones with dibenzoyl peroxide, thus affording the corresponding protected α-hydroxy carbonyl compounds in high yield and enantioselectivity. Interestingly, the same catalytic salt was found to be active when 1-indanone derivatives were directly employed in the reaction with dibenzoyl peroxide, furnishing chiral 1-oxo-2,3-dihydro-1*H*-inden-2-yl benzoates in high yields and enantioselectivity. Furthermore, treatment with $NaBH_4$ gives easy access to the corresponding enantioenriched 1,2-diols in high yields and without impact on stereochemical integrity. Typical reaction conditions for the oxidation step involve multiday reaction times at 0−20 °C.

Ni-CATALYZED ROOM-TEMPERATURE CROSS-COUPLING OF ARYL MESYLATES AND SULFAMATES



Phenol derivatives can function as alternative electrophiles for the Suzuki−Miyaura cross-coupling reaction since these electrophiles are inexpensive and widely available, even though they are less reactive than aryl halides due to the stronger C−O bond. To overcome this issue, Ni catalysts can be used since Ni(0) is more reactive in oxidative addition processes than the more frequently encountered Pd(0). The Percec group reports that the bench-stable and readily available transchloro(1-naphthyl)-bis(triphenylphosphine)Ni(II) complex is an efficient pre-catalyst for the cross-coupling of electron-rich and electron-deficient aryl and heteroaryl mesylates and sulfamates with aryl and heteroaryl neopentylglycolboronates (*J. Org. Chem.* **2012**, *77*, 2885). The reaction is carried out in THF at room temperature (without added reducing agents) and tolerates a variety of functional groups. The ability of transchloro(1-naphthyl)bis(triphenylphosphine)Ni(II) complex to catalyze the Suzuki−Miyaura cross-coupling of aryl and heteroaryl neopentylglycolboronates provides support for the Ni(0)/Ni(II) catalytic cycle mechanism for this nickel-catalyzed cross-coupling reaction.

ISOINDOLINONES VIA CO GAS-FREE AMINOCARBONYLATION

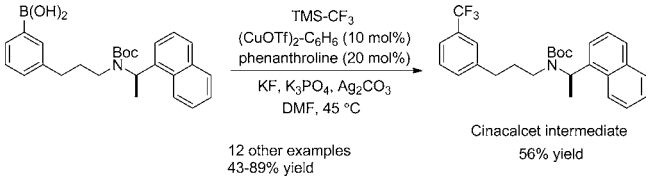


A method for the synthesis of chiral 3-substituted isoindolinone frameworks is described by the Morimoto group (*J. Org. Chem.* **2012**, *77*, 2911). The method involves Rh(I)-catalyzed asymmetric addition of arylboronic acids to 2-halobenzaldimines and a subsequent Rh(I)-catalyzed intramolecular aminocarbonylation of the resulting 2-halobenzylamines. Notably, the procedure uses an aldehyde as the carbonyl source rather than gaseous carbon monoxide. The method tolerates a variety of functional groups, yielding isoindolinone derivatives in moderate to high yields with high ee values. In addition, both of the Rh(I)-catalyzed transformations can be efficiently accomplished in one-pot fashion to give chiral isoindolinones by the simple addition of a ligand and an aldehyde after the Rh(I)-catalyzed asymmetric arylation.

Published: May 11, 2012

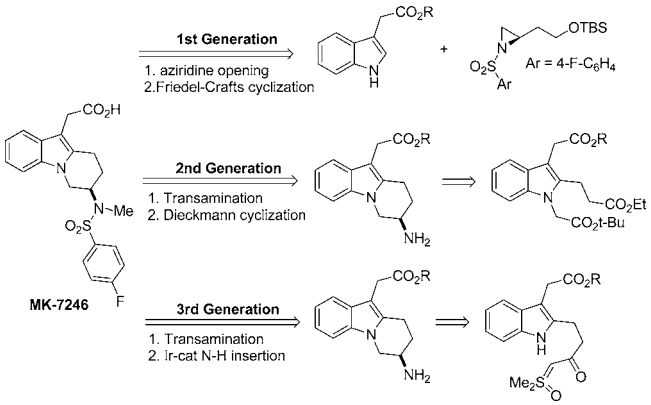
   dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

Cu-CATALYZED OXIDATIVE TRIFLUOROMETHYLATION OF TERMINAL ALKYNES AND ARYL BORONIC ACIDS USING (TRIFLUOROMETHYL)TRIMETHYLSILANE



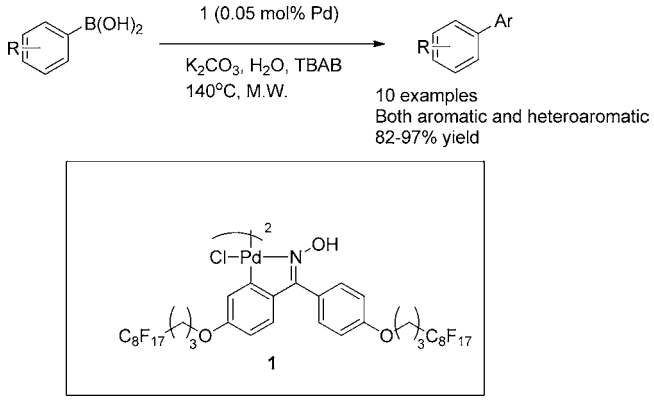
The introduction of trifluoromethyl (CF_3) groups into organic molecules can substantially alter their chemical and metabolic stability, lipophilicity, and binding selectivity because of the strongly electron-withdrawing nature and large hydrophobic domain of trifluoromethyl groups. Many biologically active compounds, including the antidepressant Prozac and the herbicide Fusilade, contain the CF_3 groups as the essential motif. As a result, much attention has been paid to the development of new synthetic methods for the introduction of the CF_3 groups into diverse organic compounds. The Qing group describes an efficient Cu-catalyzed oxidative trifluoromethylation of terminal alkynes and aryl boronic acids (*J. Org. Chem.* **2012**, *77*, 1251). The success of this catalytic method is dependent on a simultaneous syringe-pump addition of both the substrate and reagent (CF_3TMS) to the reaction mixture. Yields are moderate to good across a range of simple substrates, and the authors also present an application of this method to the synthesis of Cinacalcet.

SYNTHETIC DEVELOPMENT OF A CRTH2 ANTAGONIST MK-7246



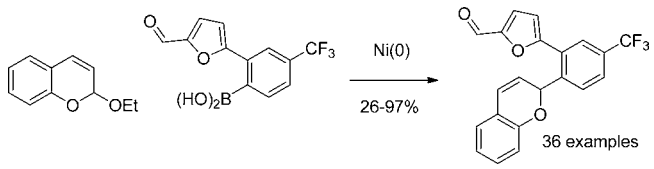
CRTH2 (chemo-attractant receptor expressed on Th2 cells) is one of the two high-affinity transmembrane receptors for prostaglandin D2 (PGD2) that have been identified to date. PGD2 has been implicated as a mediator of allergic inflammation and diseases including asthma, allergic rhinitis, and atopic dermatitis. The hypothesis that blockade of the CRTH2 receptor could provide a novel mechanism for treatment of chronic allergic disease is being aggressively pursued by the pharmaceutical industry. In a full paper, Molinaro, Bulger, and co-workers at Merck describe the development of different synthetic routes to MK-7246 (*J. Org. Chem.* **2012**, *77*, 2299). The initial aziridine opening/cyclodehydration strategy was also directly amenable to the first GMP deliveries of MK-7246, streamlining the transition from milligram- to kilogram-scale production needed to support early preclinical and clinical evaluation of this compound. Subsequently, a more scalable and cost-effective manufacturing route to MK-7246 was engineered. Highlights from the second- and third-generation routes include a highly enantioselective conversion of a cyclohexanone derivative into a cyclohexylamine via a transaminase process and an Ir-catalyzed intramolecular N−H insertion of a sulfoxonium ylide. Reactions such as these illustrate the enabling impact and efficiency gains that innovative developments in chemo- and biocatalysis can have on the synthesis of pharmaceutically relevant target molecules.

FLUOROUS OXIME PALLADACYCLE: A PRECATALYST FOR CARBON−CARBON COUPLING REACTIONS IN AQUEOUS AND ORGANIC MEDIUM



The research groups of Yulin Lam and Lee-Chiang Lo recently described the synthesis and investigation of an oxime-derived fluorous-tagged palladacycle (**1**) and its use in a number of carbon−carbon-coupling reactions using microwaves (*J. Org. Chem.* **2012**, *77*, 2729). The groups report the successful use of the catalyst in Sonogashira, Stille, Suzuki, and Heck reactions using a wide variety of substrates. They also show the successful recycle of the catalyst five times with minimum leaching and loss in yield.

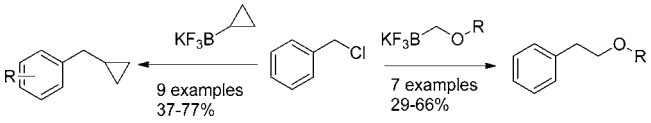
NICKEL-CATALYZED CROSS-COUPLING OF CHROMENE ACETALS AND BORONIC ACIDS



In a recent paper Doyle, A. G., et al. (*Org. Lett.* **2012**, *14*, 1616) showed the practical use of nickel-catalyzed cross-coupling of chromene acetals and boronic acids. The paper has several examples of different boronic acid substrates that they successfully used in the cross-coupling reaction including two examples of pharmaceuticals (loratidine and indomethacin methyl ester). The catalyst used was $Ni(cod)_2$ or PPh_3, respectively, at 10−30 mol % loading with reasonable yields in most cases.

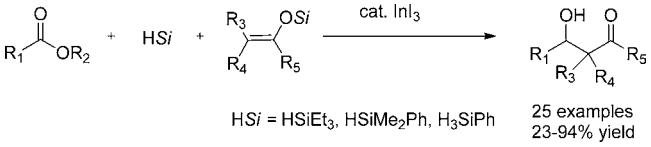
dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

SUZUKI COUPLING OF POTASSIUM CYCLOPROPYL- AND ALKOXYMETHYLTRIFLUOROBORATES WITH BENZYL CHLORIDES



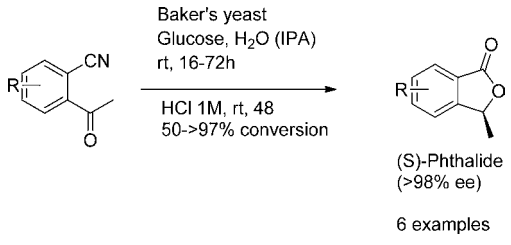
Gary A. Molander et al. recently published a paper continuing their investigation into the use of trifluoroborates in Suzuki-coupling chemistry (*J. Org. Chem.* **2012**, *77*, 2966). In this paper the authors investigate the formation of C_{sp3}–C_{sp3} bonds from cyclopropyl or alkoxymethyl potassium trifluoroborates with benzyl chlorides. The authors also touch upon the use of several different ligands (e.g., SPhos, XantPhos, and PEPPSI) as well as the Pd source itself ($Pd(OAc)_2$ and $Pd_2(dba)_3$) and their impact on the results of their investigation. Several examples are given, and the yields vary from poor to good.

DIRECT USE OF ESTERS IN THE MUKAIYAMA ALDOL REACTION: A POWERFUL AND CONVENIENT ALTERNATIVE TO ALDEHYDES



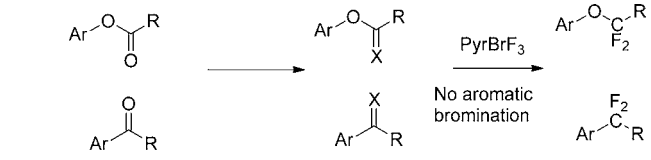
A fascinating paper by Aiko Baba et al. (*Org. Lett.* **2012**, *14* , 1168) discusses the combined use of a silane reducing agent in the Mukaiyama aldol reaction catalyzed by indium(III) iodide. This combination makes it possible to use esters as aldehyde equivalents in this reaction potentially broadening its substrate scope and versatility. The authors investigated several different substrates and silanes for this reaction and also propose a reaction mechanism. The paper touches a bit on the stereoselectivity using these reaction conditions, but no in-depth investigation was reported.

HIGHLY STEREOSELECTIVE CHEMOENZYMATIC SYNTHESIS OF THE 3*H*-ISOBENZOFURAN SKELETON. ACCESS TO ENANTIOPURE 3-METHYLPHTHALIDES



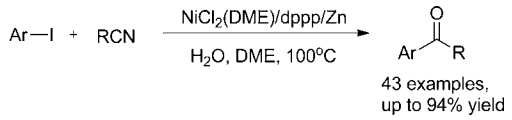
Using baker's yeast Gotor et al. (*Org. Lett.* **2012**, *14*, 1444) developed a synthesis for the production of several (*S*)-phthalide derivatives. The yields varied from good to excellent with high stereoselectivity achieved. The authors found that pH was important for the transformation with neutral to slightly acidic being preferred. They also discuss the road travelled to identify the best conditions and also the isolation of the cyclic imidate intermediate that could have further uses in, for example, asymmetric catalysis.

PYRIDINE–BROMINE TRIFLUORIDE, THE MISSING LINK FOR CLEAN FLUORINATIONS OF AROMATIC DERIVATIVES



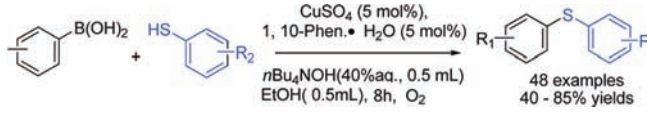
Fluorination of organic compounds is an important tool in organic chemistry. A recent paper from Rozen et al. (*Org. Lett.* **2012**, *14*, 1114) described the use of pyridine–bromine trifluoride to generate *gem*-difluoro compounds from aromatic esters and ketones. The first transformation involves the formation of a thioester, xanthate, or imine from the ester or ketone followed by clean selective fluorination of the intermediate to the *gem*-difluoride compound. The article covers a few examples using this methodology and looks at aromatics with both electron-withdrawing and electron-donating substituents

NICKEL-CATALYZED INTERMOLECULAR INSERTION OF ARYL IODIDES TO NITRILES: A NOVEL METHOD OF SYNTHESIZING ARYLKETONES



The importance of arylketones in organic synthesis cannot be overstated. The common methods of introducing a ketone functionality such as the Friedel–Craft acylation and Grignard chemistry can often be restrictive in its application due to substrate vulnerability. In a paper by Hsieh, J.-C. et al. (*Org. Lett.* **2012**, *14*, 1282) an alternative method using transition metal chemistry is discussed. The authors have found a method of introducing the ketone functionality by reacting an aryl iodide with a nitrile using a nickel catalyst and Zn. Several examples of using this methodology are discussed as well as a possible mechanism. The procedure calls for 10 mol % nickel catalyst, 10% ligand, and 2 equiv of Zn.

S-ARYLATION OF THIOLS

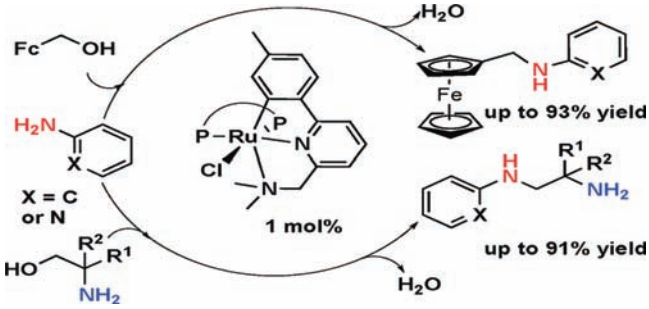


Aryl sulfides are known to have broad significance in the realms of pharmaceutical and material sciences and as intermediates in organic synthesis. The paper, *J. Org. Chem* **2012**, *77*, 2878, reports an efficient Chan–Lam type method for the construction of aryl C–S bonds. The synthetic protocol involves the coupling of aryl and heteroaryl boronic acids with thiols and disulfides in the presence of a catalytic amount of copper sulfate (5 mol %) and 1,10-phenanthroline (as ligand)with tetrabutyl-ammonium hydroxide as a base in ethanol. The ratio of the base to solvent was found to impact the yield of the reaction with the highest yields being achieved with a 1:1 ratio of TBAH

dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716–726

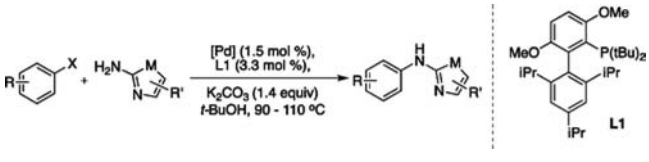
(40% aq) and ethanol. The reaction was found to be inert to electronic influences as alkylation of both electron-withdrawing and electron-releasing sulfides proceeded with equal ease. Steric hindrance, as seen with 2,6-dimethyl benzenethiol and 2-mercaptobenzoic acid, was found to be obstructive and resulted in poor yields (40 and 41%, respectively).The presence of a free hydroxy group was also well tolerated as the coupling of 4-hydroxy thiophenol proceeded efficiently without any C−O coupling product. Mechanistically, it has been proposed that $CuSO_4$ reacts with phenanthroline to form a Cu(II) species, which undergoes transmetalation with arylboronic acid to form a metalated intermediate that reacts with the aryl sulfide in the presence of tetrabutylammonium hydroxide with subsequent elimination of a cuprous specie to yield the coupled product. Oxygen, which is used as a oxidant, regenerates the Cu(II) intermediate.

RUTHENIUM PINCER COMPLEX CATALYZED MONOALKYLATION OF AROMATIC/HETEROAROMATIC AMINES WITH ALCOHOLS



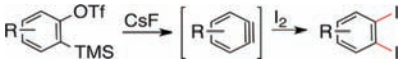
Matute et al. from The Arrhenius Laboratory, University of Stockholm, have reported (*Org. Lett.* **2012**, *14*, 1456) a novel method for the alkylation of amines with alcohols in presence of the readily available Ru(II)−CNN Pincer complex and potassium *tert*-butoxide as a base. A low catalyst loading (1 mol %) and alkylation with a wide range of alcohols such as pyridine, furan, and thienyl- and ferrocenyl-substituted alcohols to afford monoalkylated amines are the key features of the reaction. It needs to be emphasized that even alkylation of diamines proceeded efficiently to yield the *N*,*N*-trialkylated compounds. Alkylation of benzylamine and hexylamine, and amines incapable of forming imines, however, were unsuccessful, which underlines the fact that the corresponding amino alcohols could be used as alkylating agents. Mechanistically, the reaction is believed to proceed through imine formation, the reduction of which affords the alkylated product.

N-ARYLATION OF 2-AMINO THIAZOLES



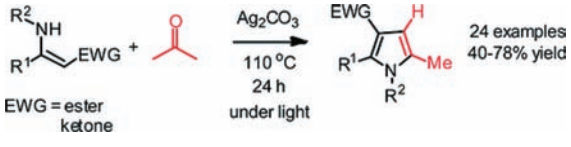
Buchwald and co-workers have disclosed (*Org. Lett.* **2012**, *14*, 1432) a novel procedure for the N-arylation of 2-aminothiazoles with aryl bromides and triflates in the presence of $Pd(OAc)_2$ using *tert*-butyl Brettphos (**L1**) as a ligand. The reaction exhibited a broad substrate scope with the arylation of substituted and unsubstituted aminothiazoles, 2-amino-1,3,4-thiadiazoles, 2-aminobenzimidazoles, and benzoxazoles proceeding efficiently with electron-rich and electron-deficient aryl bromides and triflates. Aryl chlorides, however, proved to be incompatible with the reaction conditions and failed to yield the desired products. It is notable that the addition of a catalytic amount of acetic acid (3 mol %) to the reaction mixture led to a significant enhancement of the catalytic activity. The exact role of acetic acid in the catalytic cycle, however, is presently under investigation.

SYNTHESIS OF *o*-DIIODOARENES



o-Diiodoarenes are known to be valuable synthetic intermediates, the majority of which are not available commercially. The above fact coupled with the lack of efficient, general methods of synthesis of *o*-diidoarenes, makes them important synthetic targets. The communication, *Org. Lett.* **2012**, *14*, 1363, reports a new method of diiodination which involves the direct insertion of arynes into the I−I σ-bond. This method is applicable to arynes bearing electron-donating or -withdrawing substituents, and also to polycyclic arynes. Kobayashi's method (*Chem. Lett.* **1983**, 1211), i.e. the treatment of *o*-(trimethylsilyl)aryl triflates with fluoride, has been used for aryne generation, subsequent iodination of which yielded the diiodo compound. Anhydrous conditions were found to be central to the success of the reaction as inclusion of moisture led to the formation of the monoiodinated compound. Optimization studies revealed that the best yields were obtained in acetonitrile with 1:2.5:5 molar ratio of the *o*-(trimethylsilyl)aryl triflate, iodine, and an anhydrous fluoride source (CsF or $BnMe_3NF$). Mechanistically, it has been proposed that initially the fluoride reacts with iodine to generate the iodide, excess fluoride reacts with the *o*-(trimethylsilyl)aryl triflate to form the aryne, and nucleophilic attack of iodine yields a monoiodinated phenyl carbanion, that on further iodination yields the diiodo compound. In the presence of a proton source the phenyl carbanion gets protonated to yield the monoiodinated compound.

TETRASUBSTITUTED PYRROLES BY A CDC REACTION

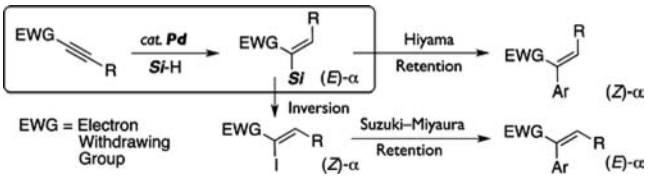


In a novel approach to the construction of densely substituted pyrrole rings, Li and co-workers have reported (*Org. Lett.* **2012**, *14*, 1412) a CDC (cross-dehydrogenative coupling) reaction of enamino esters (with *N*-aryl substituents) and ketones. in the presence of an oxidant. Silver carbonate was identified as the oxidant after optimization studies. Substrates with varying N-substituents were examined. Electron donating, -withdrawing, and halogen substituents across the aryl group were well tolerated In addition to aryl substituents, *N*-benzyl and substituted *N*-benzyls, also

dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

reacted smoothly. Apart from acetone, acetyl acetone and β-ketoesters reacted smoothly to afford the corresponding pyrroles. On the basis of deuteration and radical inhibition studies, it has been proposed that the reaction proceeds by the single electron oxidation of of the anion of the β-imino-ester tautomer, followed by the nucleophilic addition of acetone and subsequent condensation of the amino with the carbonyl group.

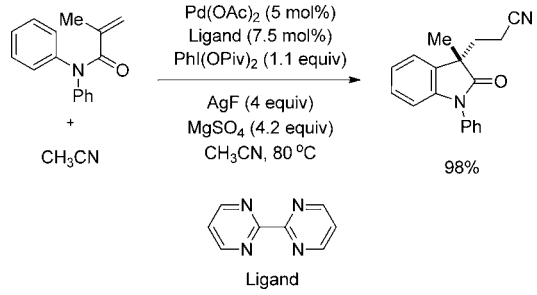
REGIO- AND STEREOSELECTIVE HYDROSILYLATION OF ELECTRON-DEFICIENT ALKYNES



Silylalkenes are versatile building blocks in organic synthesis owing to their participation in a diverse range of transformations such as protodesilylation for olefin generation, Tamao Fleming oxidation and Hiyama coupling reactions. The present communication, *Org. Lett.* **2012**, *14*, 1552, details a novel method for the regio- and stereoselective generation of silylalkenes from electron deficient alkynes and their subsequent transformation to functionalized alkenes (substituted at the carbon α to the EWG) by Hiyama coupling. Catalyst screening experiments performed with methyl-2-hexanoate and phenyl dimethylsilane ($PhMe_2SiH$) revealed a combination of Pd $(dba)_2$ and PCy_3 to be ideal for the formation of the desired (E)-α-isomer. Use of $PhMe_2SiD$ led to deuteration at the β carbon, which confirmed that the reaction had proceeded in accordance with the Chalk–Harrod mechanism (*J. Am. Chem. Soc.* **1965**, *87*, 16; *J. Am. Chem. Soc.* **1965**, *87*, 1133). The optimized conditions could be extended to a wide range of trialkyl and dialkyl silanes to yield α-silylated alkenes with an E/Z ratio of 99:1 Silanes substituted with 2-pyridyl or alkoxy groups exhibited a faster reaction rate. The reaction was, however, found to be sensitive to steric influences as shown by the poor reactivity of triisopropyl silane. The reaction also exhibited a tolerance for a wide range of alkynes as not only β-alkylated ynoates but also β-aryl, trimethylsilyl-substituted compounds, ynals, and ynamides reacted smoothly to yield the desired products with the anticipated yields and selectivity Further functionalization to afford the α-arylated compounds without any alteration of the E/Z ratio was achieved by Hiyama coupling using $PdCl_2(PPh_3)_2$, AgF, and K_2CO_3 in acetonitrile. 4-Iodoanisole, 2-iodonitrobenzene, and phenyl acetylene were used as alkylating agents. Protodesilylation of the silylalkenes yielded the corresponding cinnamates. Iododesilylation of the (E)-α silylalkene led to inversion of geometry to yield the corresponding (Z)-α-iodoenoates, (E/Z-3/97)which could be employed to furnish the (Z)-α-arylenoates via a Suzuki –Miyaura reaction.

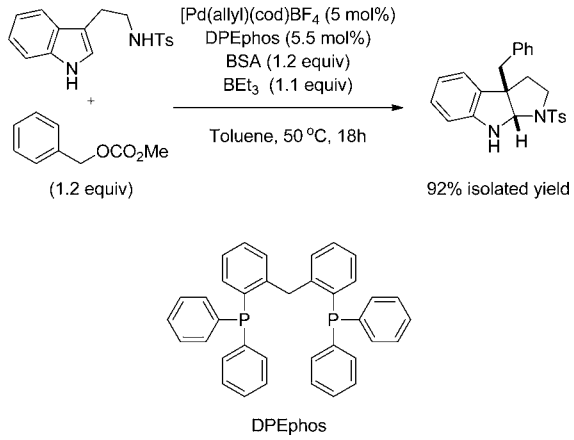
Pd-CATALYZED ARYLALKYLATION OF ACTIVATED ALKENES

Wu, Mu, and Liu describe a Pd-catalyzed oxidative arylalkylation of *N*-phenylmethacrylamides with acetonitrile that generates nitrile-bearing indolinones in excellent yields



(*Angew. Chem., Int. Ed.* **2012**, *51*, 12578). The transformation, which involves the cleavage of two C–H bonds (Ar–H and H–CH_2CN) and the formation of two C–C bonds, requires a Pd catalyst, $PhI(OPiv)_2$ as an oxidant, AgF as a potential C–H activator, and 2,2′-bipyrimidine as a bidentate ligand. The authors propose a Pd^{II}/Pd^{IV} catalytic cycle that is in agreement with (1) the compatibility of the conditions with halide substituents on the aromatic ring (i.e., Br or I), and (2) the mandatory presence of an oxidant. Moreover, the insensitivity of the reaction rates to the electronic nature of the substituents on the aromatic ring and a series of deuterium kinetic isotope effects support an aromatic substitution-type mechanism in which the cleavage of the H–CH_2CN bond is rate determining.

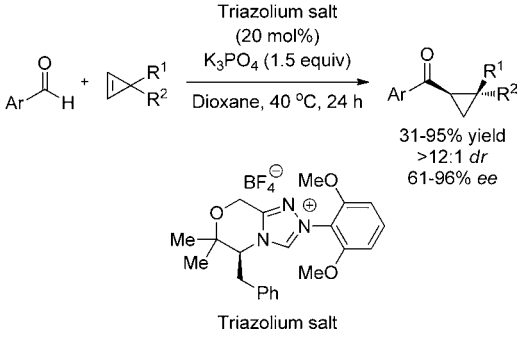
Pd-CATALYZED C3-BENZYLATION OF INDOLES



The development of new methods to modify the indole ring has become very important due to the numerous bioactive molecules that contain this heterocycle. In *J. Am. Chem. Soc.* **2012**, *134*, 111, Zhu and Rawal report a mild and high-yielding Pd-catalyzed procedure for the regioselective C3-benzylation of 2,3-disubstituted indoles. An extensive screening of the reaction parameters led to optimal conditions that involve the use of benzyl carbonate as benzyl group donor, a ligand with large bite angle such as DPEphos, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and triethylborane as additives. BSA and triethylborane facilitate the formation of the intermediate π-benzyl–Pd complex, while BSA silylates the MeO group of benzyl carbonate, triethylborane coordinates the carbonyl group of the carbonate. Remarkably, the benzylation works well for 3-substituted indoles to give the corresponding 3-alkyl-3-benzylindolenines. The latter do not rearrange to 3-alkyl-2-benzylindoles despite the high migratory aptitude of the benzyl group and can be effectively trapped by an intramolecular nucleophile.

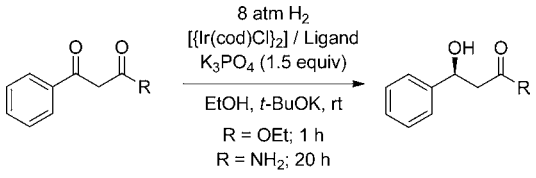
dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716–726

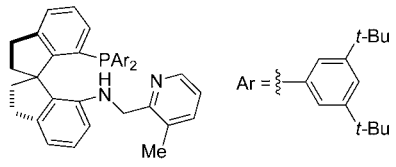
ASYMMETRIC HYDROACYLATION OF CYCLOPROPENES



N-Heterocyclic carbenes (NHCs) derived from chiral triazolium salts catalyze the enantioselective hydroacylation of cyclopropenes. Liu and co-workers at the University of Münster report a mechanistic approach to design NHC catalysts that promote the enantioselective hydroacylations of 3,3-disubstituted cyclopropenes (*Angew. Chem., Int. Ed.* **2012**, *51*, 12626). A combination of experimental and theoretical studies indicated that electron-donating substituents at the ortho positions of the aryl substituent on N1 were essential to trigger the reaction and led to the discovery of a highly effective 2,6-dimethoxyphenyl-substituted NHC. Thus, 20 mol % of the optimal triazolium salt catalyzes the reaction between a series of aromatic aldehydes (1 equiv) and 3,3-disubstituted cyclopropenes (1.5 equiv) to give the corresponding cyclopropyl aryl ketones in high yields and enantioselectivities. The triazolium salt can be prepared in five steps from readily available starting materials.

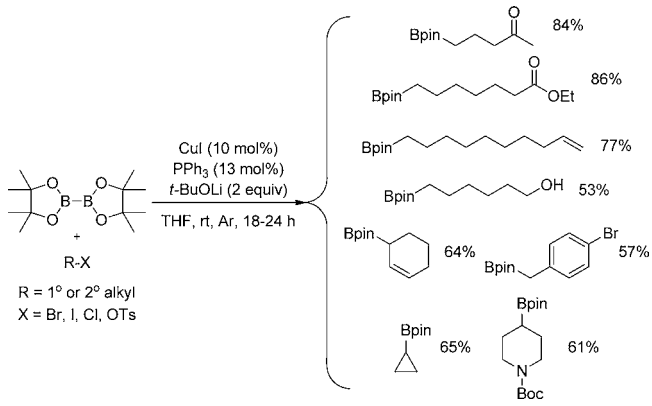
ASYMMETRIC HYDROGENATION OF β-KETOESTERS AND β-KETOAMIDES BY Ir CATALYSTS





Researchers led by Jian-Hua Xie and Qi-Lin Zhou of Nankai University disclose the use of chiral Ir catalysts bearing pyridine-aminophosphine (SpiroPAP) ligands to achieve a highly efficient asymmetric hydrogenation of β-aryl β-ketoesters and β-ketoamides in *Angew. Chem., Int. Ed.* **2012**, *51*, 201. Typical reaction conditions involve the use of very low catalyst loadings (S/C = 1000) at room temperature to afford β-hydroxyesters and β-hydroxyamides in excellent yields and enantioselectivities. Interestingly, the SpiroPAP-based catalyst appears to undergo activation by the enolate salt of the ketoacid derivative. This is in contrast to the inert behavior of [$RuCl_2$(diphosphine)-(diamine)] complexes toward the hydrogenation of the β-ketoesters complexes, which require a strong base to generate the active form of the catalyst that promotes the hydrogenation of simple ketones.

Cu-CATALYZED BORYLATION OF HALIDES AND PSEUDOHALIDES

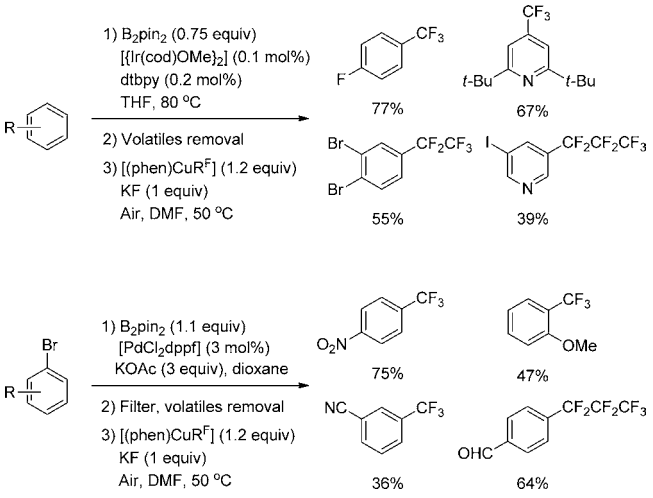


Common methods for the preparation of alkylboronic esters require the reaction of alkyllithiums or alkylmagnesium reagents with boron compounds, the hydroboration of alkenes, the C−H activation and borylation of alkanes catalyzed by transition metals, or the β-boration of unsaturated carbonyls. Steel, Marder, and Liu report the results of a research program carried out jointly by their groups at Durham University and University of Science and Technology of China Hefei on the Cu-catalyzed borylation of alkyl halides and pseudohalides (*Angew. Chem., Int. Ed.* **2012**, *51*, 528). The unprecedented direct cross-couplings between primary or secondary alkyl halides and B_2pin_2 were executed at rt using 10 mol % of CuI and 2 equiv of LiOMe to yield primary and secondary alkylboronic esters with diverse functional groups. A plausible mechanism might include the formation of a Cu(I)−boryl complex that could interact with the halide via an S_N2-type substitution or, alternatively, through an oxidatively added transition state.

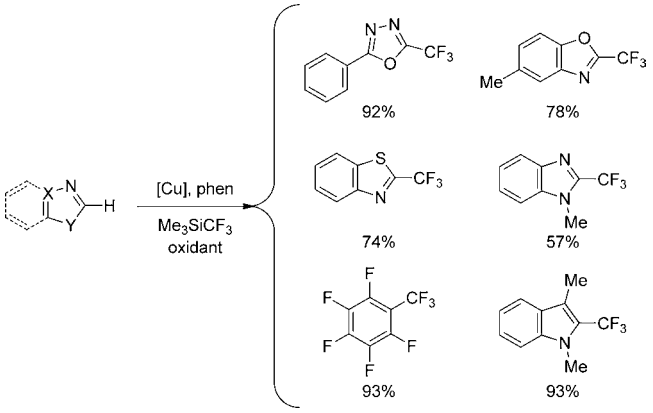
PERFLUOROALKYLATION OF ARENES AND ARYLBROMIDES

The increasing importance of trifluoromethylarene derivatives in the pharmaceutical industry has fueled the interest of the method development community in the preparation of perfluoroalkylarenes. Litvinas, Fier, and Hartwig report two general strategies for the perfluoroalkylation of arenes and arylbromides that takes place via arylboronate esters and uses perfluoroalkyl (phen)Cu(I) complexes ([(phen)CuR^F]) as the source of the perfluoroalkyl group (*Angew. Chem., Int. Ed.* **2012**, *51*, 536). In the first approach, the Ir-catalyzed C−H borylation of an arene is followed by a Cu-mediated perfluoroalkylation. Since steric effects direct the regioselectivity of the borylation, 1,3-disubstituted arenes afford 1,3,5-trisubstituted products, and 1,2-disubstituted arenes give 1,2,4-trisubstituted arenes. A second approach involves the Pd-catalyzed borylation of an aryl bromide followed by the Cu-mediated perfluoroalkylation. This method complements the substitution patterns observed for the Ir-catalyzed process, yielding 1,2-, 1,3-, and 1,4-disubstituted arenes.

dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726



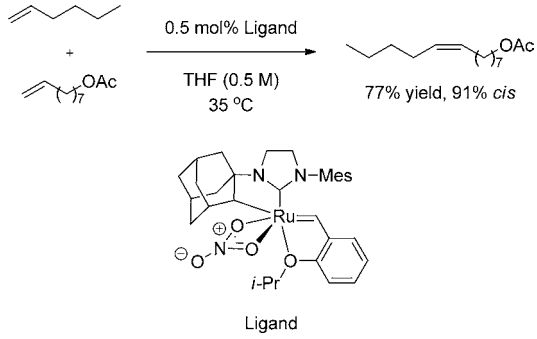
Cu-CATALYZED TRIFLUOROMETHYLATION OF HETEROARENES



Chu and Qing describe a Cu-catalyzed oxidative trifluoromethylation of heteroarenes with CF_3SiMe_3 via direct C−H activation (*J. Am. Chem. Soc.* **2012**, *134*, 1298). The choice of a successful mixture of catalyst and oxidant for the trifluoromethylation is substrate dependent. Thus, $Cu(OAc)_2$, ligand 1,10-phenanthroline, and cobases *t*-BuONa and NaOAc mediate the oxidative trifluoromethylation of 1,3,4-oxadiazoles using either air or di-*tert*-butyl peroxide as an oxidant. In contrast, $Cu(OH)_2$ and Ag_2CO_3 are the best catalyst and oxidant, respectively, for the trifluoromethylation of indoles. The combination of a strong base and a weak base enhances the efficiency of the reaction by limiting the formation of homocoupled products observed when *t*-BuONa is used as a single base. Preliminary mechanistic investigations suggest that the reaction takes place via a $CF_3Cu(I)L_n$ intermediate and that the trifluoromethylation of indoles might involve a trifluoromethyl radical.

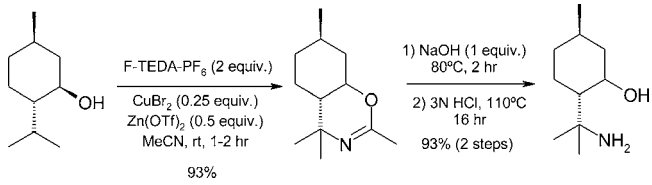
Ru CATALYSTS FOR *cis*-SELECTIVE OLEFIN METATHESIS

The synthesis of *cis*-olefins via olefin metathesis continues to test the imagination of catalyst designers trying to overcome the formation of the thermodynamically favored *trans*-olefins. Chemists in the group of Grubbs describe the development of a Ru metathesis catalyst that affords high levels of cis selectivity for a variety of cross-metathesis



reactions in *J. Am. Chem. Soc.* **2012**, *134*, 693. Thus, systematic structure−reactivity relationship studies demonstrate that bidentate catalysts containing a Ru−C bond with an adamantyl group and a nitrato ligand are the best in terms of turnover numbers (~1000) and selectivity. While bidentate ligands appear to be unique in their capacity to promote catalyst initiation, catalysts with nitrato ligands are more stable to oxygen than the carboxylate counterparts and easier to purify. The new catalysts do not require a rigorous exclusion of protic solvents or high temperatures to operate efficiently.

INTERMOLECULAR RITTER-TYPE C−H AMINATION OF UNACTIVATED sp^3 CARBONS



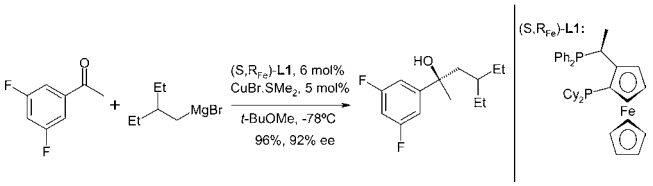
The direct conversion of C−H bonds to C−N bonds is an area of intense research interest, and numerous studies have been reported, which utilize metallonitrene intermediates. Baran and co-workers have developed an operationally simple, scalable, copper-catalyzed amination for both hydrocarbons and functionalized compounds (*J. Am. Chem. Soc.* **2012**, *134*, 2547). In addition, both the catalyst and nitrogen source are readily available, and the substrate can be used as the limiting reagent. Anion exchange of the commercially available Selectfluor reagent is carried out to facilitate solubility of the reagent in acetonitrile. After extensive screening, both a copper salt and a Lewis acid were also found to be necessary for optimum conversions. Initially, alcohol substrates were evaluated with the belief that the reaction proceeded through a dihydrooxazine intermediate. However, ketones and unfunctionalized hydrocarbons also performed well under the reaction conditions. The reaction is believed to proceed through a Ritter-type reaction, which occurs via two SETs. A significant isotope effect is observed indicating that C−H bond cleavage takes place in the rate-determining step. Finally, the ease of hydrolysis of the acetamide group is highlighted.

ASYMMETRIC COPPER-CATALYZED ADDITION OF GRIGNARD REAGENTS TO ARYL ALKYL KETONES

The catalytic addition of readily available Grignard reagents to ketones to generate chiral tertiary alcohols has proved problematic. Alternative strategies to achieve this trans-

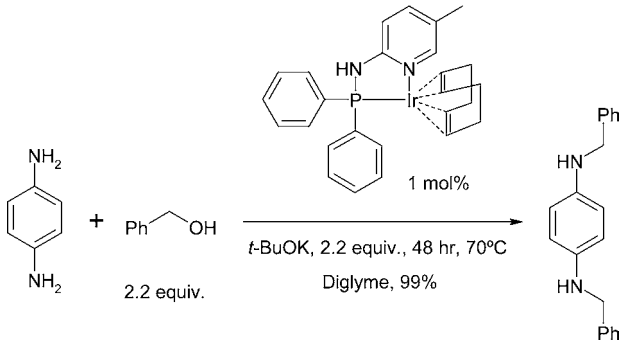
dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

formation have focused on organozinc and organotitanium reagents. Workers from Groningen have reported on the use



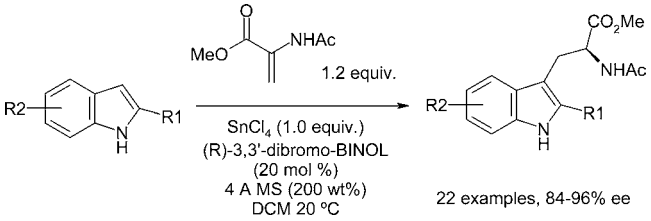
of copper to catalyze this reaction for acetophenones in the presence of a Josiphos-type ligand (*Angew. Chem., Int. Ed.* **2012**, *51*, 3164). Initial results provided a high ee and excellent yield at −78 °C indicating that the catalysts has a particularly high turnover frequency, and as such can outcompete the uncatalyzed reaction as well as reduction and enolization. No clear trends could be determined with respect to steric or electronic effects for the substrate with even an *o*-bromo substituent being well tolerated. In contrast, although the yields were invariably excellent for all the Grignard reagents, only those with significant steric bulk (such as branched alkyl chains) displayed high enantioselectivities. The group hypothesize that the reaction proceeds through initial transmetalation of the Grignard to a chiral copper species, in which the alkyl group is more reactive than in the original Grignard. The carbonyl function is doubly activated in a chairlike transition state through coordination to both the magnesium and the copper to facilitate the alkyl group transfer.

THE IRIDIUM-CATALYZED SYNTHESIS OF SYMMETRICALLY AND UNSYMMETRICALLY ALKYLATED DIAMINES UNDER MILD REACTION CONDITIONS



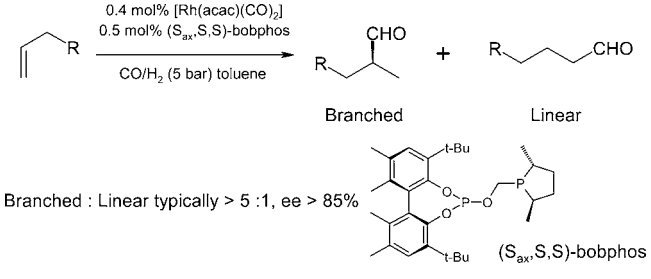
Kempe has developed an iridium catalyst (which is stabilized by an anionic P,N-ligand) and has utilized this in the symmetrical and unsymmetrical monoalkylation of both benzenediamines, and the pharmacologically important diamine, Dapson (*Adv. Synth. Catal.* **2012**, *354*, 847). The catalyst is simple to prepare, and is significantly more active in the alkylation of amine derivatives, thus enabling the reaction to be carried out under mild reaction conditions (70 °C), increasing both the selectivity and the functional group tolerance. Control of the stoichiometry of the alcohol enables either complete dialkylation or sequential monoalkylation to be achieved in generally high yield. Secondary alcohols, though, are unreactive with this catalyst even at elevated temperatures. The selectivity of the catalyst system enables amino alcohols to be utilized as the alkylating agents without the need to protect the aliphatic primary amine. The unsymmetrical dialkylation of Dapson had previously only been carried out in a multistep fashion but is now easily achieved in a single high-yielding step to enable a number of new analogues to be synthesized.

ENANTIOSELECTIVE SYNTHESIS OF TRYPTOPHAN DERIVATIVES BY A TANDEM FRIEDEL−CRAFTS CONJUGATE ADDITION/ASYMMETRIC PROTONATION REACTION



Tryptophan derivatives are important building blocks in the development of new drugs as well as the total synthesis of natural products. Reisman has reported on a novel efficient methodology to access chiral tryptophan derivatives via a tandem Friedel−Crafts conjugate addition/asymmetric protonation reaction (*J. Am. Chem. Soc.* **2012**, *134*, 5131). The reaction requires no preactivation of the indole substrates, and the resulting stereogenic center is set solely by catalyst-controlled enantioselective protonation. Commercially available methyl-2-acetamidoacrylate is utilized as the conjugate acceptor, and the reaction is significantly accelerated in the presence of the chiral ligand. The addition of molecular sieves is to scavenge adventitious water or HCl, which might promote a racemic background protonation. Twenty mole percent of the optimized catalyst was consistently used to provide the higher observed enantioselectivity across the widest range of functionalized substrates. Dropping the catalyst loading to 5 mol % led to a diminished ee most likely from competition from the achiral $SnCl_4$-promoted background reaction. Stoichiometric tin is required due to binding of the acetamido ester product to tin, resulting in product inhibition. The substrate scope is fairly broad with respect to substitution at the 2-position of the indole, and a number of further transformations of the functionalized products are described.

AN ASYMMETRIC HYDROFORMYLATION CATALYST THAT DELIVERS BRANCHED ALDEHYDES FROM ALKYL ALKENES

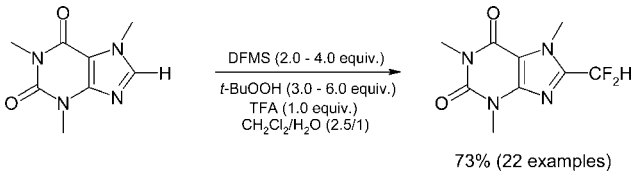


The ability to control formation of the branched aldehyde from a simple terminal alkyl olefin in an asymmetric catalytic hydroformylation process is a high-value transformation for which no general solution currently exists. However, Clarke has recently reported significant progress towards this goal (*Angew. Chem., Int. Ed.* **2012**, *51*, 2477) with the use of the hybrid ligand

dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

"bobphos". This novel ligand is a combination of the well-established hydroformylation ligands, Kelliphite and Ph-bpe. With vinyl acetate, "bobphos" provides exclusively the branched aldehyde in 83% ee under rhodium-mediated hydroformylation conditions. For this substrate, the ligand demonstrates a classic matched/mismatched scenario with the other diastereomer only providing 32% ee. With linear alkenes, the vast majority of ligands tested to date have exhibited high selectivity for the linear aldehyde. However, under the "bobphos" mediated conditions, both good selectivity and high enantioselectivity were observed for the branched aldehyde. It is interesting to note that, typically when a hybrid ligand is generated from two very successful ligands, it tends to perform worse than the parents. In this study, the hybrid significantly outperforms the original ligands for the substrates evaluated. These reactions tend to be run at fairly mild temperatures for optimal ee. Furthermore, in none of the reactions studied was alkene isomerization observed.

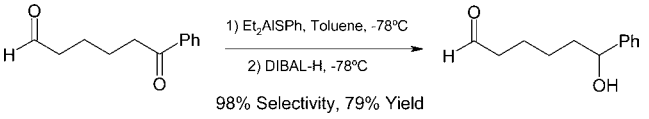
A NEW REAGENT FOR DIRECT DIFLUOROMETHYLATION



Baran and co-workers have reported on the invention of a new reagent for the direct difluoromethylation of a series of heteroarene substrates (*J. Am. Chem. Soc.* **2012**, *134*, 1494). The study utilized difluoromethylsulfonyl chloride as a convenient commercial starting material and through systematic variation of the metal counterion identified $Zn(SO_2CF_2H)$ (DFMS) as the optimum precursor for the CF_2H radical. This material is an air-stable solid, which is now commercially available. The reaction is simple to perform at ambient temperature in aqueous media under air. TFA is added in a number of cases for improved rate and conversion though is not essential. The reaction is also tolerant of several functional groups including halides, nitriles and esters. Both electron-rich and electron deficient heterocycles perform well, and high regioselectivities are observed. In general, C−H functionalization takes place at the most electron-deficient position. This nucleophilic radical difluorination is in contrast to the previously reported electrophilic trifluoromethylation using $NaSO_2CF_3$, and this is very powerfully illustrated by the variations in regioselectivity for the reactions of the two systems with dihydroquinine and vareniclene. DFMS is also reactive towards other substrates such as aromatic thiols, and enones. Furthermore, variations in the regioselectivity for pyridines can be tuned by appropriate selection of the solvent system in which the reaction is performed.

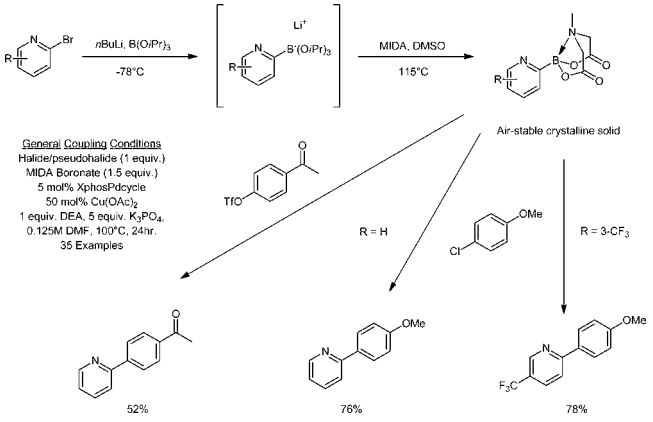
HIGHLY CHEMOSELECTIVE REDUCTION OF CARBONYL GROUPS IN THE PRESENCE OF ALDEHYDES

The ability of carry out the chemoselective reduction of aldehydes in the presence of less reactive carbonyl functions can be easily achieved. However, the opposite transformation is more challenging, and requires protection of the aldehyde prior to carrying out the desired reaction. Markó, et al. (*Org. Lett.* **2012**, *14*, 1306) has devised an elegant solution to this problem, which enables the highly chemoselective reduction of



both ketones and esters in the presence of aldehydes. The reaction takes advantage of an *in situ* protection of an aldehyde as the O,S-aluminum acetal using diethyl aluminium benzenethiolate. These species were found to be surprising robust, and were unaffected by the DIBAL-H reduction of ketones and esters. The reaction was optimized based on the temperature, solvent, and the stoichiometry of the aluminum species. In all the cases evaluated, both high yields and excellent selectivities were obtained in both competition experiments and on intramolecular variants of the reaction. The reaction is efficient for both aliphatic and aromatic substrates, and tolerates steric hindrance around both carbonyl groups.

A GENERAL SOLUTION FOR THE 2-PYRIDYL PROBLEM

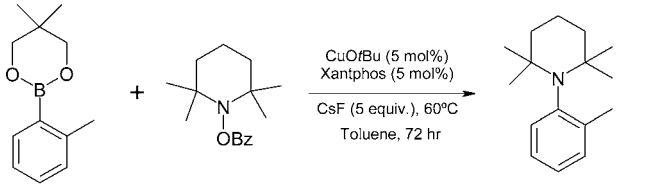


The 2-pyridyl subunit is highly prevalent unit in bioactive molecules and natural products, and considerable effort has been expended to develop 2-pyridyl organometallic reagents that can be efficiently employed in cross-coupling reactions. The major challenge to developing such reagents, and their employment in robust cross-coupling reactions is the sensitivity of the 2-pyridyl−boron bond. Several potential solutions have been proposed, but they all suffer from limitations, such as lack of stability of the boron substrates, or inefficient reactions with more challenging coupling partners. Burke has demonstrated the coupling of the corresponding MIDA−boronates, and has developed general coupling conditions that are effective for a wide range of halide/pseudohalide coupling partners (*Angew. Chem., Int. Ed.* **2012**, *51*, 2667). The synthesis of the MIDA−boronates, which exist as easy to isolate, air-stable crystalline solids, is reported. Extensive screening of palladium/ligand combinations, copper salts, bases, solvents, and temperatures led to the key finding that an alcohol additive in the presence of copper salts promoted the coupling of activated aryl chlorides. A working hypothesis based on the alcohol promoting an initial trans-ligation of the MIDA−boronate revealed that a 2:1 ratio of copper(II) acetate and diethanolamine (DEA) was critical to

dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

reaction success. In addition, extensive mechanistic studies are reported.

SYNTHESIS OF HINDERED ANILINES: COPPER-CATALYZED ELECTROPHILIC AMINATION OF ARYL BORONIC ESTERS

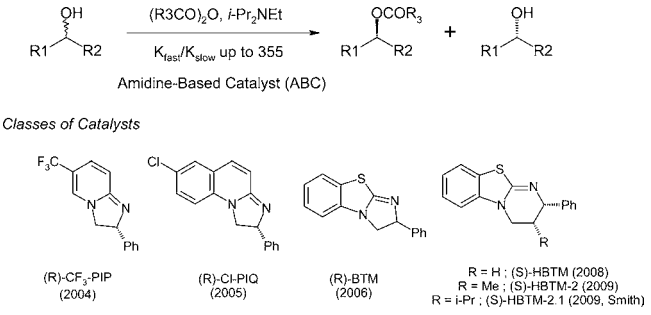


1.2 equiv. 1 equiv. 89% (30 examples)

The synthesis of hindered anilines remains a significant challenge in synthetic chemistry. Current methods to achieve this involve the formation of highly reactive intermediates, such as benzynes or organometallic reagents. For both approaches, an excess of one of the coupling components is required. Lalic and co-workers have reported on a viable solution to this problem utilizing readily available neopentyl boronate esters as the coupling partner with *O*-benzoylhydroxylamine as the electrophile (*Angew. Chem., Int. Ed.* **2012**, DOI: 10.1002/anie.201200840). The neopentyl ester was chosen due to its ability to undergo faster transmetalation than the corresponding pinacol esters. Lithium *tert*-butoxide was found to be the optimum base, and the catalyst was prepared from copper *tert*-butoxide and Xantphos. The reaction was generally run at 60 °C in concentrated isooctane solution. This combination of lithium *tert*-butoxide and a noncoordinating solvent prevented the decomposition of the electrophile that had hindered initial attempts to optimize the reaction. With these conditions, excellent yields were obtained across a range of substrates, and good functional group compatibility was observed. To further extend the substrate scope and allow the reaction to be performed in the presence of acidic functional groups, conditions were developed to utilize CsF as the base with toluene as the solvent. This proved particularly beneficial for the coupling of ortho-substituted boronate esters with unhindered electrophiles. A putative mechanism is provided suggests initial transmetalation from boron to copper followed by electrophilic amination of the aryl copper species. Finally, the reactive copper alkoxide is generated with the lithium alkoxide.

KINETIC RESOLUTION OF SECONDARY ALCOHOLS USING AMIDINE-BASED CATALYSTS

The kinetic resolution (KR) of secondary alcohols still remains a widely used method for the preparation of secondary chiral alcohols. Enyzmatic methods have often been adopted to achieve this goal—and have proved to be very successful. However, there are several limitations with employing enzymes as catalysts, and given this, a large amount of work has been devoted to developing low-molecular weight enantioselective acylation catalysts for this transformation. Birman and co-workers have published a comprehensive account of the use of their amidine-based catalysts (ABC) and provided guidance for the initial selection of a catalyst based on the structural nature of the substrate of the secondary alcohol under investigation (*J. Org. Chem.* **2012**, *77*, 1722). One of the key elements for a successful resolution using these catalysts is the presence of a π-system adjacent to the hydroxyl group. Cl-PIQ is the catalyst of choice for allylic alcohols, while BTM is widely used for the KR of benyzlic and propargylic alcohols. Caution must



be exercized utilizing the BTM catalyst as this is prone to deactivation by water. The HBTM series of catalysts are typically more active, and as such, reactions can be performed at depressed temperature to optimize selectivity. Examples using the HBTM catalysts in the KR of cycloalkanols employing this strategy are reported. Initial studies indicating that in some cases the undesired enantiomer in the KR reaction may serve to inhibit the reaction catalyst are also provided. The ease of preparation, and availability in both enantiomeric forms suggest that these catalysts can provide a practical alternative to enzymes.

VERIFICATION OF DESIGN SPACES DEVELOPED AT SUBSCALE

For any QbD-developed process, a key element is its design space, and this is first developed at small scale using mechanistic and multivariate models as well as prior knowledge. At small scale critical quality attributes and potential critical process parameters are identified. The preliminary design space must then be scaled-up in order to be defined for commercial equipment; key and critical process parameters are determined (confirmed) for commercial-scale operation. A final process model is thus defined, requiring verification. In a relatively short paper, a large Pfizer group (10 authors) share with us some of their experience about presenting design space verification data to the regulators (Garcia, T., et al. *J. Pharm. Innov.* **2012**, DOI: 10.1007/s12247-012-9123-0). Among other things, the team states that: "...in some instances regulators may be reluctant to accept theoretical science-based approaches, preferring to see confirmatory data generated from batches manufactured at commercial scale". High-level strategies for defining and verifying design space at scale are briefly presented, with a corresponding general decision tree diagram. The authors reiterate the importance of systematic investigation of the impact that scale-independent, scale-dependent, and combinations thereof have on critical attributes. The decision tree diagram has elements that appear "simple" when in fact they can be quite complex to implement. For example, one decision point requires an answer to the question: "Can the equipment be readily scaled using platform technology or simple scaling factors?" Even if one has already developed an extensive scale-up database, some of this information must be carefully presented to support the answer to such a question. Given the cost of large-scale experimentation and the need to use the material produced at scale, the factor ranges available for experimentation are inevitably limited. The authors confirm that their approach is also to use a highly fractionated factorial design (e.g., four experiments) in order to verify the commercial-scale design space. The strategies discussed apply for both drug product and drug substance.

dx.doi.org/10.1021/op300090w | *Org. Process Res. Dev.* 2012, 16, 716−726

THE SOLUBILITY−PERMEABILITY INTERPLAY WHEN USING COSOLVENTS FOR SOLUBILIZATION: REVISING THE WAY WE USE SOLUBILITY-ENABLING FORMULATIONS

With approximately 40% of new lipophilic drug candidates, their effective oral absorption continues to be a challenge in drug development. A specific complication arises from the fact that when drug solubility is enhanced (for example when formulations include cosolvents) the membrane permeability of the drug can decrease. A meaningful, QbD compatible formulation development requires good product and process understanding, that allows for formulation optimization, maximizing both solubility as well as membrane permeability. A team from Abbott and the Ben Gurion University report their findings and recommendations on this topic, in particular as they relate to BCS class II drugs, of low solubility and high permeability (Miller, J. M., et al. *Mol. Pharm.* **2012**, DOI: 10.1021/mp2004460u). The drug model selected was progesterone, and the cosolvents used were propylene glycol and polyethylene glycol-400 (PEG-400). A mass transfer quantitative model was developed to describe the interplay between drug solubility and its membrane permeability. This article has 51 references.

CHARACTERIZING THE IMPACT OF HYDROXYPROPYLMETHYL CELLULOSE ON THE GROWTH AND NUCLEATION KINETICS OF FELODIPINE FROM SUPERSATURATED SOLUTIONS

Generation of drug substance as an amorphous material in order to enhance oral bioavailability is an intense area of research. In a supersaturated system, controlled inhibition of crystallization of both nucleation and growth is challenging, especially when the goal is to use very small amounts of pharmaceutically acceptable inhibitors. A team from Abbott and Purdue University report their findings on this topic (Alonzo, D. E., et al. *Crys. Growth Des.* **2012**, *12*, 1538). The model drug used was felodipine, and the inhibitor employed at ppm levels was HPMC (hydroxypropylmethyl cellulose). Experiments were conducted in the presence and the absence of seed crystals, and at various levels of supersaturation. Theoretical and empirical models were used to explain the experimental findings. The relative impact of predissolved HPMC was stronger on nucleation than on growth.

POPULATION BALANCE MODELING WITH SIZE-DEPENDENT SOLUBILITY: OSTWALD RIPENING

Ostwald ripening is often used in crystallization process design in order to minimize the population of fine particles and thus obtain suitable particle size distributions. Even though the phenomenon was reported at the end of the 19th century, its fundamental understanding continues to emerge. The Mazzotti ETH group recently published a population balance model describing Ostwald ripening (Iggland, M., et al. *Cryst. Growth Des.* **2012**, *12*, 1489). The numerical solution of the model is compared with the predictions of classical Lifshitz−Slyozov−Wagner (LSW) theory. The model developed is capable of avoiding certain assumptions necessary when other available models are used. The model can also handle populations with bimodal particle size distributions, an advantage over the classical LSW theory. In addition to certain experimental challenges, the computational effort required to obtain the full numerical solution of the model may challenge its broad industrial application.

Mark McLaughlin

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

Magnus Widegren

Almac Sciences, 22, Seagoe Industrial Estate, Portadown, Craigavon, County Armagh, Northern Ireland BT63 5QD, U.K. E-mail: magnus.widegren@almacgroup.com

Soumendu Paul

Consultant, Lucknow, India. E-mail: spaaul@yahoo.com

Antonio Ramirez

Bristol-Myers Squibb, One Squibb Drive, New Brunswick, New Jersey 08903, United States. E-mail: antonio.ramirez1@bms.com

Paul Richardson

Pfizer, 10578 Science Center Drive, San Diego, California 09121, United States. E-mail: paul.f.richardson@pfizer.com

Andrei Zlota

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

Trevor Laird*

Editor

AUTHOR INFORMATION

Corresponding Author

*trevor@scientificupdate.co.uk