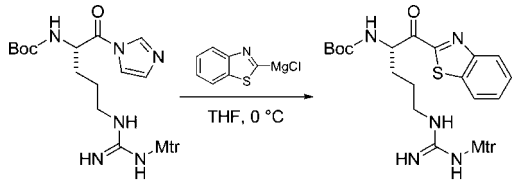
Organic Process Research & Development **2008,** *12,* 138–145

Highlights from the Literature

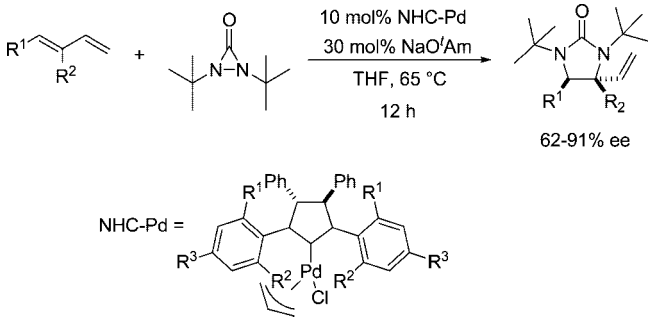
Some Items of Interest to Process R&D Chemists and Engineers

Large-Scale Preparation of Benzothiazol-2-ylmagnesium Chloride



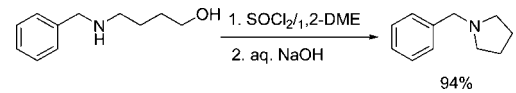
An efficient process to produce kilogram quantities of RWJ-56423 (argininyl-tryptase inhibitor) via a key argininylbenzo[*d*]thiazole intermediate is described by Kenney and co-workers at both Johnson & Johnson and Cilag AG (*J. Org. Chem.* **2007**, *72*, 9798−9801). Initial attempts to generate the benzothiazolyl ketone functionality of RWJ-56423 by reacting 2-lithiobenzothiazole with a dipeptidyl Weinreb amide were not successful. A variety of activated arginine esters and benzo[*d*]thiazole nucleophiles were evaluated as coupling partners. This led to the selection and optimization of an argininyl imidazolide ester, as the electrophile, and benzothiazol-2-yl MgCl nucleophile. A detailed stability study of the benzothiazolyl Grignard species and degradation pathways was crucial in determining the appropriate reaction parameters.

Asymmetric Diamination of Conjugated Dienes and Trienes



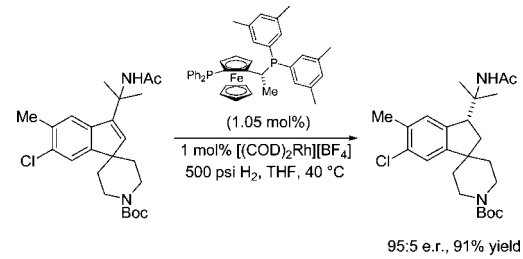
Chiral NHC−Pd complexes are demonstrated to be catalysts for the asymmetric diamination of conjugated dienes and trienes in a report from the Shi group (*J. Org. Chem.* **2008**, *73*, 749−751). Using di*tert*-butyldiaziridinone as nitrogen source, diamination products are obtained in moderate yield and enantioselectivity. The carbene structure has a large impact on both the reactivity and enantioselectivity. Bulky catalysts are more active, giving high conversions using 5 mol % catalyst. Conversely, certain less bulky catalysts seem to provide better enantioselectivity (90–91% ee), whereas the conversion is low. The authors suggest that compared to the chiral phosphine-based catalysts, the NHC−Pd systems offer greater potential for tuning and are likely to be more stable and active. Further studies along these lines are ongoing.

Chlorination/Cyclodehydration of Amino Alcohols with $SOCl_2$



A simple, one-pot preparation of cyclic amines via chlorination of amino alcohols using $SOCl_2$ is reported by Xu and co-workers at Merck (*J. Org. Chem.* **2008**, *73*, 312−315). This approach obviates the need for protecting group strategies commonly employed for this type of reaction sequence. The reaction was studied using in situ NMR, and investigation of alternative addition modes led to the establishment of the optimum procedure in which the substrate is added to a solution of $SOCl_2$. The process was applied to 10 aminoalcohols with yields ranging from 79 to 99%.

Synthesis of a Tertiary Carbinamide via Asymmetric Hydrogenation

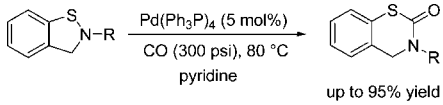


A practical, enantioselective approach to a pharmaceutically useful spiropiperidineindane bearing a tertiary carbinamide is reported by Limanto and co-workers at Merck (*J. Org. Chem.* **2008**, *73*, 1639−1642). The developed route comprises seven steps in the longest linear sequence, four isolations, and affords 30% overall yield. The key transformation is an asymmetric hydrogenation of a sterically hindered tertiary allylic carbinamide, which is catalyzed by a Rh-Josiphos system. Optimal conditions involve the use of 1 mol % of Rh-Josiphos(BF_4) in THF at 40 °C under 500 psi of H_2, which affords the desired product in 91% yield, 95:5 enantiomeric ratio after crystallization from MeCN. The hydrogenation susbtrate is accessible from commercially available *N*-Boc-4-piperidone.

Highly Regioselective Pd-Catalyzed Carbonylation of Benzisothiazoles

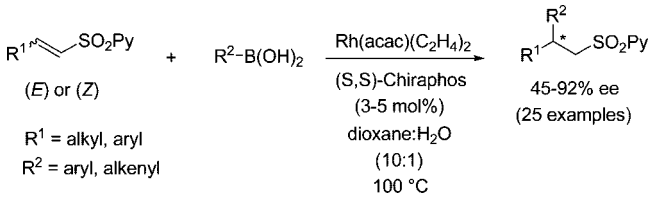
A novel approach toward the synthesis of 3-substituted-3,4-dihydro-2*H*-1,3-benzothiazin- 2-ones is described by the Alper group (*J. Org. Chem.* **2008**, *73*, 1612−1615). Pd-

Published on Web 02/29/2008
10.1021/op800032x CCC: $40.75



catalyzed carbonylation of 2-substituted-2,3-dihydro-1,2-benzisothiazoles proceeds with total regioselectivity at the N−S bond of the benzisothiazole precursor, and the reaction tolerates a number of substituents, including primary and secondary alkyl groups and benzylic and naphthylmethyl functionalities. The paper provides seven examples with yields ranging from 56 to 92%.

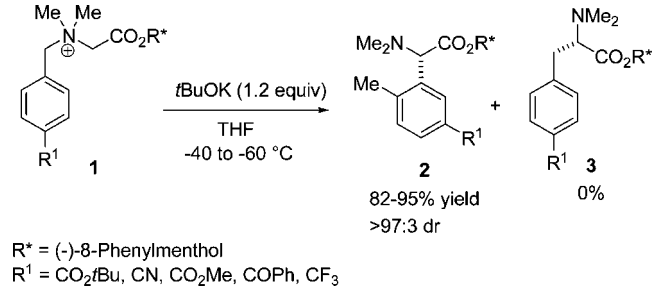
Rh-Catalyzed Asymmetric Addition of Boronic Acids to Unsaturated Sulfones



A method for the Rh-catalyzed enantioselective catalytic conjugate addition of organoboronic acids to α,β-unsaturated sulfones is described by the Carretero group (*J. Org. Chem.* **2007**, *72*, 9924−9935). The scope of the reported method is limited to the use of unsaturated sulfones bearing a 2-pyridyl group, which serves to coordinate the Rh; other sulfones such as vinyl phenyl sulfones are inert under the reaction conditions. Among a variety of chiral ligands tested, Chiraphos provided the best asymmetric induction. This [Rh(acac)(C_2H_4)$_2$]/Chiraphos catalyst system is applicable to the addition of both aryl and alkenyl boronic acids to *cis* and *trans* unsaturated 2-pyridyl sulfones; arylboronic acids tend to give the best enantioselectivity. The enantioenriched sulfone products are potentially useful building blocks for asymmetric synthesis. For instance, the straightforward elimination of the 2-pyridylsulfonyl group by either Julia−Kociensky olefination or alkylation/desulfonylation sequences provides a variety of functionalized chiral compounds, such as allylic substituted alkenes or α-substituted ketones and esters.

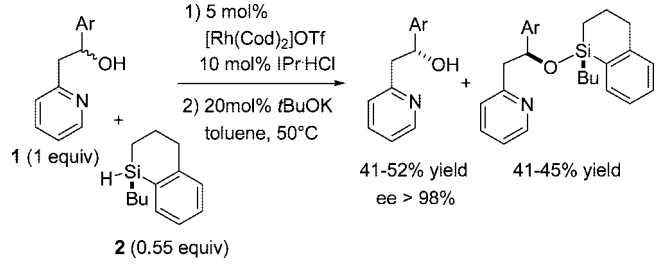
Sommelet−Hauser Rearrangement

The Sommelet−Hauser and the Stevens rearrangement of stabilized ammonium ylides are base-catalyzed sigmatropic processes that convert a readily available N−C bond into a new C−C bond. The Stevens [1,2]-rearrangement has enjoyed synthetic utility to yield α-benzyl amino acids. Takama and Kimura at Nigata University reported the asymmetric rearrangement of an ammonium ylide derived from proline to yield the corresponding α-aryl proline via a Sommelet−Hauser [2,3]-rearrangement when reacted in the presence of *t*-BuOK under cryogenic conditions (*Angew. Chem., Int. Ed.* **2007**, *46*, 8869−8871). The methodology was expanded to various *p*-benzyl substituted ammonium salts derived from *N*-Bn-*N*,*N*-dimethylglycine (−)-8-phenylmenthol ester (**1**). The reaction provided the desired esters **2** with high yields (82–95%) and diastereoselectivities (dr > 97:3). Interestingly, no product arising from the Stevens rearrangement (**3**) was detected.



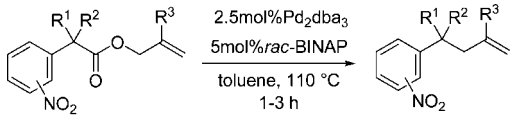
Kinetic Resolution of Alcohols Using Chiral Silanes

The selectivity factor *s* is a useful parameter for determining the efficiency of a resolution. It is defined as the ratio of the rate constants for the reaction of the chiral catalyst/reagent with the fast- and slow-reacting enantiomers. While the desired values are $s > 200$, just a handful of reagents meet such requirements. Klare and Ostrich reported a rhodium-catalyzed Si−O coupling in which a silicon stereogenic silane selects one of the two enantiomeric transition-metal substrate complexes with $s \approx 900$ (*Angew. Chem., Int. Ed.* **2007**, *46*, 9335−9338). Kinetic resolution of different nitrogen-donor containing alcohols resulted in 50% conversion with 90–99% ee's. The process might enable racemization of the slow-reacting alcohol prior to Si−O coupling and therefore extending the methodology to perform dynamic kinetic resolution.



Decarboxylative Coupling of Nitrobenzene Acetic Esters

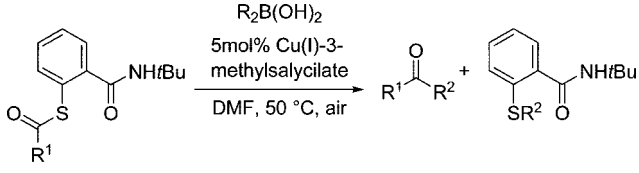
In *J. Am. Chem. Soc.* **2007**, *129*, 14860−14861 Waetzig and Tunge (University of Kansas) report the catalytic decarboxylative sp^3−sp^3 coupling of nitrobenzene acetic esters. Under optimized conditions, treatment of a variety of *o*- and *p*-nitro phenyl acetic esters with 5 mol % Pd_2dba_3 and 5 mol % rac-BINAP in toluene at 110 °C affords the desired products in 77–96% yields. Whereas the reaction is successful for a variety of α,α-disubstituted *p*-nitro phenyl acetic esters, the scope with respect to *o*-nitro phenyl acetic esters is limited to the α-monosubstituted analogues. Terminally substituted allyl electrophiles do not undergo the desired transformation, yielding mostly the 1,3-pentadiene elimination product. Since *p*-nitro phenyl acetic esters crowded in the α-position underwent facile decarboxylation, it is plausible that decarboxylation occurs before the formation of the C−C bond. Furthermore, the rate of reaction increases with the stability of the postulated benzylic anion, suggesting that the decarboxylation is the rate-limiting step. The resulting nitro arenes can be subjected to reductive cyclizations to afford highly coveted dihydroquinolones or quinolines.



o-NO_2 or *p*-NO_2

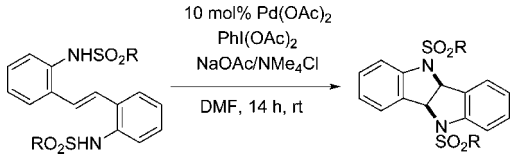
Cu(I)-Catalyzed coupling of Thiol Esters and Boronic Acids

Villalobos, Srogl and Liebeskind (Emory University) describe an unprecedented method for the construction of C−C bonds: the Cu(I)-catalyzed coupling of thioesters and boronic acids to give ketones (*J. Am. Chem. Soc.* **2007**, *129*, 15734−15735). Earlier work suggested that the formation of stable Cu-SR complexes accounts for the need of stoichiometric Cu(I) carboxylate. The system was rendered catalytic by regenerating the Cu carboxylate catalyst from the intermediate Cu-SR species using a second, sacrificial equivalent of boronic acid. The latter reacts with the Cu-SR species forming a thioether and releasing a Cu oxygenate of undefined oxidation state. The reaction works best with *o*-substituted NH*t*-Bu thiosalicylamides, which react with (aromatic, heteroaromatic, or alkenyl) boronic acids and 5 mol % Cu((I)−3-methylsalicylate in DMF at 50 °C in open to air to yield the desired ketones along with equimolar amounts of the thioether byproducts. While this is a powerful methodology for selective functionalization of complex molecules, the drawbacks of the process—byproduct formation and use of excess boronic acid—should be carefully considered.



R_1 = Ph, *p*-Tol, Me, *n*-Pro, ω-decynyl, (*E*)-propenyl
R_2 = 4-$MeOC_6H_4$, 2-BrC_6H_4, furan-3-carbaldehyde-5-yl, 2-naphtyl, 2-furyl, 2-thienyl

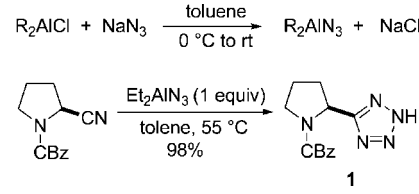
Pd(II)-Catalyzed C−N Bond Formation: Construction of Bis-indolines



Kilian Muñiz at the Université Louis Pasteur (Strasbourg Cedex, France) reported the $Pd(OAc)_2$-catalyzed formation of bis-indolines from stilbene derivatives via the diamination of internal alkenes (*J. Am. Chem. Soc.* **2007**, *129*, 14542−14543). The reaction is highly stereospecific and furnishes chiral C_2-symmetric products from *E*-alkenes. Optimized conditions employ 1.4 equiv of $PhI(OAc)_2$ as the oxidant, as well as a combination of NaOAc and NMe_4Cl as the base (1.1 equiv) in DMF at room temperature. Pd-tosylamide precoordination poses the path for the selective *anti*-aminopalladation by the second amino group. The Pd catalyst exercises a remarkable flexibility throughout the course of the reaction: (1) catalyzes the initial regioselective Csp^2 amination of the alkene, and 2) installs the second N−C sp^3 bond stereospecifically. The sequential, regioselective transfer of two sulfonamides to an internal alkene provides convenient access to heterocyclic structures such as bis-indolines, annelated indolines, and bi-pyrrolidines

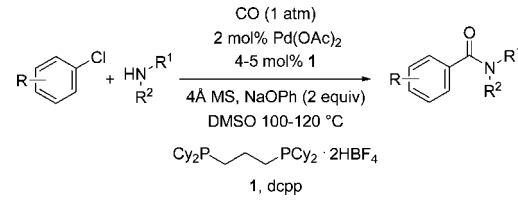
Synthesis of 5-Substituted Tetrazoles

The widespread incorporation of the tetrazole functionality into angiotensin II antagonists—sartans—has elicited the development of numerous methods for the synthesis of tetrazoles in industrial scale. Aureggi and Sedelmeier (Novartis Pharma AG) recently described the use of organic aluminum azides for the direct conversion of nitriles into tetrazoles (*Angew. Chem., Int. Ed.* **2007**, *46*, 8440−8444). The reagents were readily prepared by the addition of an equimolar amount of dialkyl aluminum chloride to sodium azide in an aprotic solvent (toluene, xylene). The temperature of the cycloaddition step (−40 to 120 °C) was adjusted depending on the reactivity of the substrates, and an impressive array of tetrazoles were isolated (45–97% yield) with high purity after a simple aqueous workup and crystallization. Both enantiomers of **1** were synthesized for the first time under very mild conditions, and the preparation of (*R*)-**1** was scaled up to 1.5 kg with good reproducibility (WO2007/009716 2007).



Palladium-Catalyzed Aminocarbonylation of Aryl Chlorides at Room Temperature

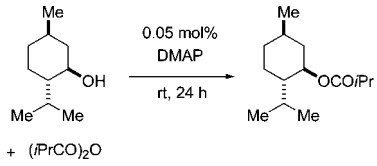
The group of Stephen Buchwald at MIT reported a general methodology for the carbonylation of aryl chlorides (*Angew. Chem, Int. Ed.* **2007**, *46*, 8460−8463). The transformation proceeds at atmospheric CO pressure and moderate temperatures (100–120 °C). Electron-rich, bulky biphosphine 1,3-bis(dicyclohexylphosphino)propane (dcpp, **1**) was the most efficient of the ligands screened and could be used as the air-stable tetrafluoroboric acid adduct. Primary, secondary, aromatic, and benzyl amines are all readily converted into amides. Electron-rich, -neutral, and -poor allyl chlorides are compatible with the carbonylation conditions. NaOMe mediates the acyl transfer and facilitates the otherwise challenging transformation.



Solvent-Free DMAP-Catalyzed Esterification

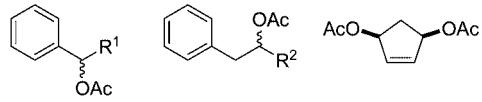
Ishihara and co-workers have found that low amounts of 4-*N*,*N*-dimethylaminopyridine (DMAP) promote the acylation of alcohols with acid anhydrides without the aid of an auxiliary base or a solvent (*J. Am. Chem. Soc.* **2007**, *129*, 14775−14779). The reaction of *l*-menthol with $(i\text{PrCO})_2O$ proceeded faster

when carried out neat in the presence of 0.05–2 mol% DMAP. Interestingly, esters amenable to purification by distillation were synthesized without the use of solvent throughout the process. The paper is peppered with numerous examples, such as the quantitative acylation of polyols (glycerol, methyl glucopyranoside, L-ascorbic acid), the high-yielding preparation of the plasticizer tributyl citrate by acetylation, and the acetylation of α,α-dimethylbenzyl alcohol—nonconducive under solvent-free conditions—by using heptane.



Pig Liver Esterases: Different Isoenzymes, Different Selectivities

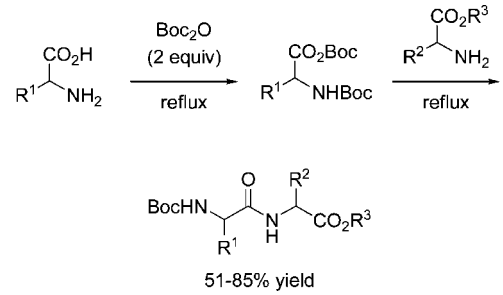
Commercially available pig-liver esterases (PLE) consist of mixtures of several isoenzymes that differ in isoelectric point, molecular weight, sensitivity toward, and most importantly, substrate specificity. Bornscheuer and colleagues at Greifswald University and Evonik Degussa used reverse transcriptase-polymerase chain reaction (RT-PCR), cloning, and functional expression in *Escherichia coli* to identify, characterize, and produce five novel PLE isoenzymes named PLE1 -formerly γ-PLE- to PLE5 (*Angew. Chem, Int. Ed.* **2007**, *46*, 8492−8494). The enantioselectivity of the PLE isoenzymes differed substantially in the kinetic resolution of secondary alcohols esters **1** and **2** as well as the desymmetrization of the *meso*-diacetate **3**. In the case of **1**, the *R*-alcohol was obtained with *E*-values increasing from 17 (PLE1) to 94 (PLE5). For acetates **2**, a switch in enantiopreference took place: PLE1 and PLE2 gave the *S*-alcohol, while PLE3–5 preferred the (*R*)-enantiomers. In the case of **3**, the commercial PLE from Fluka and PLE1–3 showed pro-(*R*)-selectivity (60% ee and 80% ee, respectively) but PLE4–5 favored the *pro*-(*S*)-acetate (ee 17–42%). The different compositions of commercial PLEs have a strong impact on enantiopreferences and enantioselectivities. The availability of individual PLE isoenzymes allows tailoring the biocatalyst to the specific synthetic problem.



1, R^1 = Me, Et **2**, R^2 = Et, Pr **3**

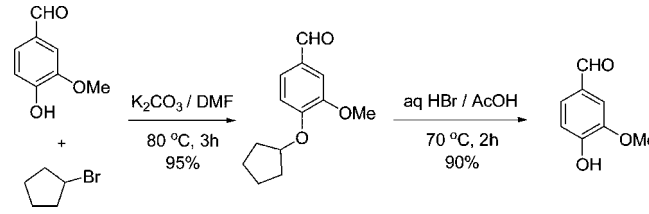
Boc$_2$O as an Activating Reagent in Peptide Synthesis

Di-*tert*-butyl-dicarbonate can be used simultaneously both as a protecting and activating group in peptide chemistry. This has been recently shown by Laulloo and co-workers at University of Mauritius and Boehringer Ingelheim Chemicals (*Synth. Commun.* **2007**, 4191−4197). In an expedient one pot-procedure, the treatment of glycine with 2 equiv of Boc$_2$O in the presence of K$_2$CO$_3$ followed by addition of L-phenylalanine ethyl ester afforded the desired dipeptides in 74% yield. The method, which involves only one purification step, appears to be general and can be implemented in different solvents, depending on the solubility of the amino acids.



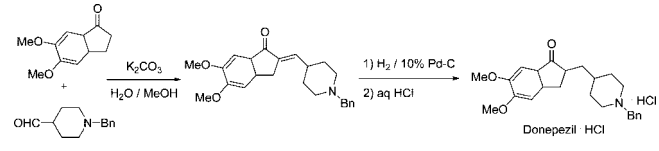
Cyclopentyl Ethers to Protect Phenols

Gajera and co-workers at Glenmark Research Centre (Mumbai, India) report the use of cyclopentyl ethers for the protection of phenols (*Synth. Commun.* **2007**, 2877−2880). For example, the cyclopentyl ether of vanillin was prepared in excellent yields by reaction with cyclopentyl bromide in the presence of K$_2$CO$_3$ using DMF as solvent. Selective decyclopentylation of the protected vanillin could be achieved using 48% aqueous HBr in AcOH. Interestingly, decyclopentylation is preferred over demethylation under these conditions. The cyclopentyl ether is stable under several bromination and oxidation conditions, appears to be more resistant than analogous isopropyl ethers and easier to cleave than the corresponding methyl ethers.



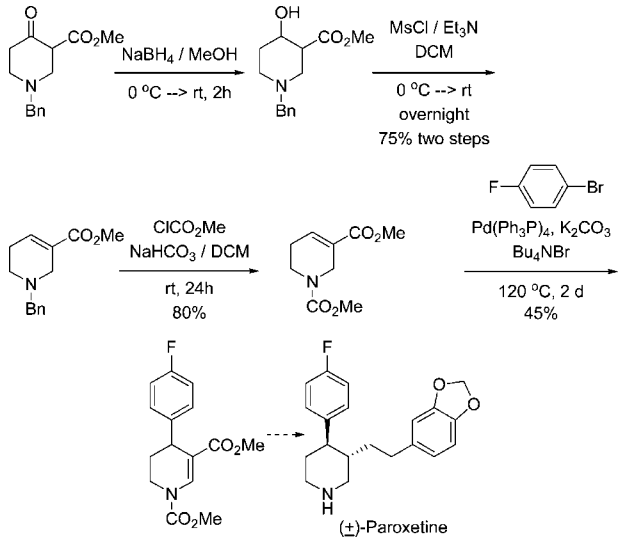
Alternative Syntheses of Donepezil, (±)-Paroxetine, and Venlafaxine

Chemists at Natco Pharma Ltd. and Andhra University (India) developed an efficient and industrially viable synthesis of Donepezil, a memory-enhancing drug used in the treatment of Alzheimer's disease (*Synth. Commun.* **2007**, 2847−2853). Following an exhaustive review of the current syntheses of donepezil, the authors describe a simple preparation that involves the condensation of commercially available 5,6-dimethoxy-1-indanone with 1-benzyl-4-piperidenecarboxaldehyde in the presence of K$_2$CO$_3$ in aqueous MeOH at reflux. The resulting alkylidene is isolated by crystallization with good yields (75–80%, 96% purity). In the second step, hydrogenation of this intermediate using 10% Pd−C in MeOH (25 °C, 2 h) followed by treatment with aqueous HCl affords donepezil HCl with 65% yield and 99.8% purity.

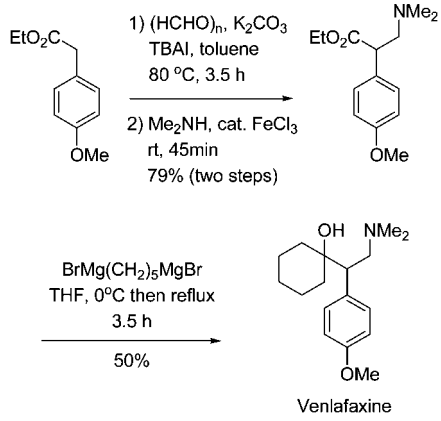


(−)-Paroxetine hydrochloride is an antidepressant marketed under trade names such as Paxil and Seroxat. Chavan and co-workers at the National Chemical Laboratory in Pune (India) developed an alternate synthesis based on a Heck reaction (*Synth. Commun.* **2007**, 3143−3149). Thus, the double Michael

addition of benzylamine to methyl acrylate followed by Dieckmann condensation affords an intermediate ketoester that can be reduced with $NaBH_4$ in MeOH. Subsequent mesylation and elimination of MsOH provides the *N*-benzyl piperideine required to explore the Heck arylation. Whereas several attempts to introduce the aryl group failed, substitution of the *N*-benzyl group by an *N*-methoxycarbonyl moiety enabled the desired coupling to give a key intermediate toward the synthesis of (±)-paroxetine.

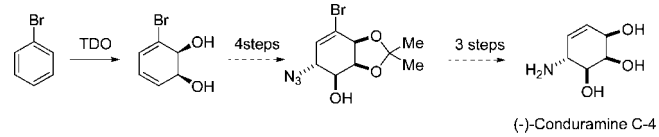


Chavan and co-workers also disclose a practical synthesis of the novel antidepressant (±)-venlafaxine in *Synth. Commun.* **2007**, 3901−3906. The key final step involves the installation of the tertiary alcohol using a Grignard reaction of an intermediate amino ester with 1,5-dibromopentane. This methodology circumvents former literature procedures that require the use of strong organolithium bases, anhydrous organic solvents, and hydrides that are not suitable for a large-scale synthesis.

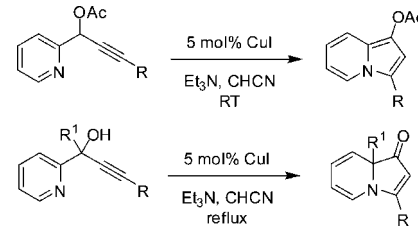


Chemoenzymatic Synthesis of (−)-Conduramine C-4

Researchers at Universidad de la Republica (Uruguay) describe the chemoenzymatic synthesis of the new cyclitol (2)-conduramine C-4 in *Synth. Commun.* **2007**, 3509−3518. Bellomo and co-workers achieved a 23% overall yield executing a series of elegant substrate-controlled reactions from an enantiopure bromocyclohexenedienediol. The latter was obtained by fermentation of bromobenzene with *Pseudomonas putida* 39/D in a biocatalytic process mediated by toluene dioxygenase dihydroxylase (TDO). The authors report the inhibitory activities of (2)-conduramine C-4 and the corresponding synthetic intermediates against glycosidases, and provide valuable hypotheses to ascertain structure–activity relationships.

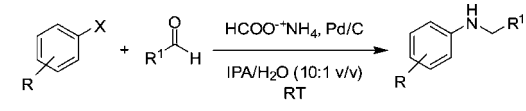


Efficient Synthesis of Indolizines and Indolizinones



Recent approaches to indolizines have focused on Au, Pd/Cu, Pt, or $InCl_3$-catalyzed reactions. Drawbacks of these approaches include expensive catalysts, ligands, elevated temperatures, long reaction times, or need for individual tuning based on the nature of substrate. To circumvent these issues, a more general, practical, and economical approach for the formation C-1 oxygenated indolizines and indolizinones has been reported by Liu and co-workers at the Shanghai Institute for Organic Chemistry (*J. Org. Chem.* **2007**, *72*, 7783). A variety of 2-pyridyl-substituted propargylic acetates underwent the cycloisomerization in under 3 h at room temperature in the presence of 5 mol % CuI and 1.0 equiv of Et_3N in acetonitrile. The authors propose two plausible mechanistic pathways for product formation, either nucleophilic attack of the pyridyl nitrogen to the Cu-coordinated allenyl double bond or the direct cyclization of the pyridyl nitrogen on the alkyne due to enhanced electrophilicity from Cu-coordination. The catalyst system is also viable for cyclization/1,2-shift of tertiary propargylic alcohols for the formation of indolizinones, although the authors note it is necessary to elevate the temperature to reflux.

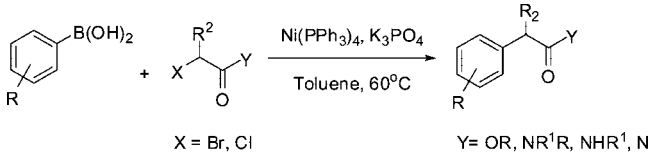
One-Pot Reductive Mono-*N*-alkylation of Aniline and Nitroarene Derivatives Using Aldehydes



An alternative method to perform mono-N-alkylations of anilines and nitroarenes under transfer hydrogenation conditions has been reported by Rhee and co-workers at Hanyang University (*J. Org. Chem.* **2007**, *72*, 9815). The reaction is a fine example of a robust, inexpensive, and environmentally benign procedure, proceeding at ambient temperature under neutral conditions in aqueous 2-propanol. Yields are generally high (>90%, 35 examples) with the

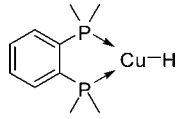
exception of anilines or nitroarenes bearing strongly electron-withdrawing groups. Notably, carboxylic acid and esters on the aryl ring are not reduced under the reaction conditions and the Pd/C catalyst can be reused up to 10× without loss of catalytic activity or chemical yield.

Ni-Catalyzed Mild Arylation of α-Halocarbonyl Compounds with Arylboronic Acids



A nickel-based approach to arylation of α-halocarbonyl compounds has been described by Lei and co-workers at Wuhan University (*Org. Lett.* **2007**, *9*, 5601). Although the analgous Pd-catalyzed reaction is known, the electrophile has been limited to unsubstituted acetic acid derivatives and α-bromosulfoxides due to competitive *β*-hydride elimination. The Ni-catalyzed reaction proceeds in moderate to excellent yields (55%–95%) and has greatly expanded the scope of electrophile to include a variety of α-bromoesters, α-bromoamides, and α-bromoketones while also tolerating electrophiles containing *β*-hydrogens. Although the authors did not postulate a mechanism, they note the importance of the need for anhydrous base for the transformation. In the absence of base or the presence of $K_3PO_4 \cdot 3H_2O$, the reaction was unsuccessful.

(BDP)CuH: A "Hot" Stryker's Reagent for Achiral Conjugate Reductions

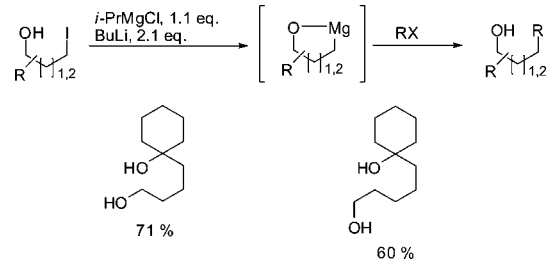


(BPD)CuH

Lipshutz and co-workers at the University of California, Santa Barbara have disclosed a new Stryker-type reagent for achiral conjugate reductions of alkenes and alkynes activated by an ester, ketone, aldehyde, or nitrile (*Org. Lett.* **2008**, *10*, 289). The catalyst, exhibiting S/L ratios of up to 10,000:1, is generated in situ from $Cu(OAc)_2 \cdot H_2O$, 1,2-bis(diphenylphosphino)benzene and PHMS in toluene and *t*-BuOH,. The catalyst performs favorably in direct comparisons to Stryker's catalyst and shows stability at room temperature without loss of catalytic activity for one month. Surprisingly, attempts to use hydrogen to replace PMHS were unsuccessful. The authors postulate the hindrance of hydrogen insertion by the bidentate ligand as opposed to the monodentate triphenylphosphine species used by the traditional Stryker reagent.

Alkoxide-Directed Iodine−Magnesium Exchange at sp^3 Centers

Sequential addition of *i*-PrMgCl and BuLi to sp^3 hybridized iodoalcohols triggers a facile iodine−metal exchange. Intercepting the resulting cyclic Grignard reagents with a slight excess of an electrophile leads to a diverse range of substituted alcohols (Knochel, P. et al.; *Org. Lett.* **2007**, *9*, 4507). The iodine−magnesium exchange strategy is effective with 3-carbon iodoalcohols bearing substituents on the carbinol or adjacent carbons and with the chain-extended homologue 4-iodobutan-1-ol. The exchange proceeds rapidly at −78 °C, affording, after reaction with a range of electrophiles, the corresponding products in low to good yields.



Continuous Flow Reactors: A Tool for the Modern Synthetic Chemist

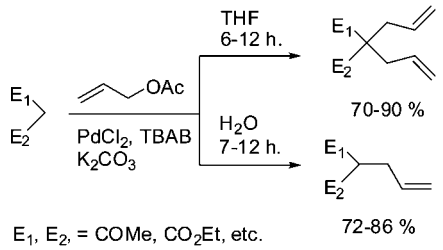
The competitive nature of the chemical industry means that researchers involved in product development and lead compound generation are under continued pressure to identify, and develop, promising programmes of research in order to secure vital intellectual property. The potential of a compound, however, depends not only on structural complexity but also on the ability to prepare the compound via a scaleable synthetic pathway. Consequently, microreaction and continuous flow technologies have captured the attention of the modern synthetic chemist as they enable reactions to be performed with, in many cases, a good level of control. With these features in mind, the review from Watts, P. and Wiles, C. (*Eur. J. Org. Chem.* **2008**, Early View) focuses on recent developments made in the field of microreaction technology, highlighting the advantages associated with its use through the synthesis of a diverse array of molecules.

Solvent-Controlled Highly Selective Bis- and Monoallylation of Active Methylene Compounds by Allyl Acetate with Pd(0) Nanoparticles

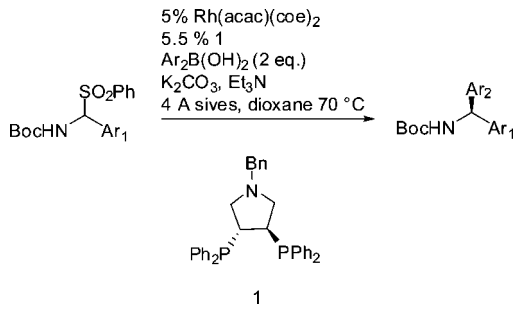
Pd(0) nanoparticles formed in situ have been used as an efficient catalyst for the allylation of active methylene compounds Ranu, B. C. et al. (*Org. Lett.* **2007**, *9*, 4595). Very efficient bisallylation is achieved for a variety of methylene compounds by allyl acetate in THF as solvent. When the reaction is performed in water, the monoallyl derivative is the main product. The recovered nanoparticles can be recycled. The method provides the bisallylated products in good to high yields. In the aqueous procedure the selectivity, mono to bisadduct, is good to excellent, and the yields are good to high.

Catalytic Enantioselective Addition of Arylboronic Acids to N-Boc Imines Generated in Situ

Ellman, J. A. et al. (*Org. Lett.* **2007**, *9*, 5155) have reported for the first time a rhodium-catalyzed enantioselective addition of arylboronic acids to N-Boc imines. The N-Boc imines are generated in situ from stable and easily prepared α-carbamoyl sulfones. The method has been evaluated for a

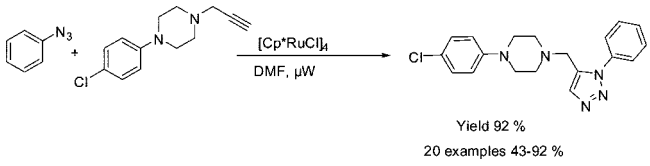


range of functionalized arylboronic acids and N-Boc imines, including electron-poor and -rich as well as ortho-substituted derivatives. The method generates the corresponding bisaryl products with high enantioselectivities in moderate yields.



Ruthenium-Catalyzed Cycloaddition of Aryl Azides and Alkynes

Fokin, V. V. et al. (*Org. Lett.* **2007**, *9*, 5337) have developed a highly active catalytic system for ruthenium-catalyzed cycloaddition of azides and alkynes in DMF utilizing pentamethylcyclopentadienyl ruthenium(II) chloride tetramer, $[Cp^*RuCl]_4$. Aryl azides, a troublesome class of substrates that failed to react cleanly in the original bis(triphenylphosphine) pentamethylcyclopentadienyl ruthenium(II) chloride, $Cp^*RuCl(PPh_3)_2$ can, with the new catalytic system, be readily and regioselectively converted to the corresponding triazoles in DMF at 90–100 °C under microwave heating.



Organocatalytic Asymmetric Mannich Reactions: New Methodology, Catalyst Design, and Synthetic Applications

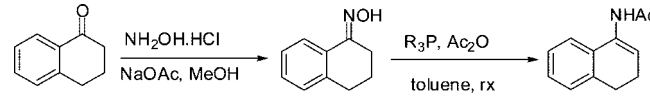
The direct, asymmetric Mannich reaction catalyzed by small organic molecules offers a facile route to optically active α- or *β*-amino acid derivatives and 1,2- and *γ*-amino alcohols. One-pot reactions of unmodified carbonyl donors with preformed or in situ generated imines can be stereochemically controlled with organic catalysts such as proline, chiral pyrrolidines, chiral Brønsted acids, and *Cinchona* alkaloids. The generated Mannich adducts can be further functionalized towards a variety of bioactive molecules. In a review (Schaus, S. E. and Ting, A., *Eur. J. Org. Chem.* **2007**, *35*, 5797) recent contributions are discussed to present the methodology and synthetic advantages achieved so far in the asymmetric Mannich reaction.

Fast DKR of Amines Using Isopropyl 2-Methoxyacetate as Acyl Donor

The dynamic kinetic resolution (DKR) of various primary amine substrates has been performed (Palmans, A. R. A. et al., *Eur. J. Org. Chem.* **2007**, *35*, 5416) using a modified version of the Bäckvall system. A single equivalent of isopropyl 2-methoxyacetate was used as acyl donor in combination with *p*-MeO Shvo complex as the racemization catalyst and Novozym 435 as the acylation catalyst. A reaction temperature of 100 °C was employed to ensure a high racemization rate. Adding 2,4-dimethyl-3-pentanol (DMP) as hydrogen donor at a concentration of 0.5 M successfully suppressed side product formation. Under these modified DKR conditions, complete conversion was observed for most substrates within 26 h showing both high ee values (95–99%) and good chemoselectivity, whereas the original system required a reaction time of 72 h.

An Efficient Synthesis of Enamides from Ketones

A new synthesis of enamides from ketones has been reported by Zhao,H. et al. (*Org. Lett.* **2008**, *10*, 505) that involves a phosphine-mediated reductive acylation of oximes. The resulting enamides were obtained in good yields and purity, permitting a subsequent hydrogenation to access enantiopure acetamides as ligands. The methodology adds a valuable alternative to the current limited number of methods for accessing enamides efficiently. Yields from 54 to 90% were obtained based on 12 examples.



Biodiesel Production

Biodiesel production from vegetable oils and alcohols is still a challenge, especially when the total free acid content is high. To overcome this problem Berchmans and Hirata (*Bioresour. Technol.* **2008**, *99*, 1716) developed a smart process in which *Jatropha curcas* L. seed oil (up to 15% in free fatty acids) is esterified with methanol in two steps. In the first, acid-catalyzed esterification takes place using 0.60 w/w methanol/oil ratio in the presence of 1% w/w H_2SO_4. After water/methanol removal, the remaining oil is treated with 0.24 w/w methanol to oil and 1.4% w/w NaOH and the transesterification is carried out. Yields are about 90% in 2 h.

In the same arena, Demirbas (*Bioresour. Technol.* **2008**, *99*, 1125) reported the production of biodiesel from cottonseed oil in noncatalytic supercritical conditions. The transesterification of linseed oil in supercritical methanol and ethanol was proved to be the most promising process. The most important parameters in this process were the reaction temperature and the molar ratio alcohol to oil. Glycerol was easily separated from biodiesel. Although critical conditions for both methanol and ethanol are not so friendly (512.2 K and 8.1 MPa for methanol and 516.2 and 6.4 MPa for ethanol) this system can be adapted to run under continuous flow conditions.

In a more conventional way, Rashid and Anwar (*Fuel* **2008**, *87*, 265) reported the biodiesel production from rapeseed oil under alkaline catalysis. Best quality was obtained (95–96%

yield) using 600 rpm, 65 °C temperature, 1.0% KOH and 6:1 methanol/oil ratio. A full report on the biodiesel characteristics is presented.

An even more interesting approach to biodiesel production in terms of carbon credits was published by Ramos and co-workers (*Bioresour. Technol.* **2008**, *99*, 1837) where (renewable) ethanol is used. An experimental design was used and the surface response obtained was capable of explaining 98% of the total variance of the system. So, under the predicted conditions, 38 °C, 0.6 wt % NaOH and 11.7:1 molar ratio ethanol/oil, a quantitative ester yield was obtained. Having in mind the difficulties associated with the use of ethanol for biodiesel production, this represents a significant contribution.

An Experimental Investigation of Effusivity as an Indicator of Powder Blend Uniformity

Continuous monitoring and control of complex mixing operations remains to be a challenge in several chemical and pharmaceutical processes, including solids mixing. Direct analytical measurements for online characterization of mixing processes is not always possible, and indirect measurements must be used. A group from the Polytechnic in Montreal and from ratiopharm operations (Leonard, G. et al. *Powder Technology* **2008**, *181*, 149−159) reports the use of effusivity for the assessment of solids mixing uniformity. Effusivity is defined as $\sqrt{k\rho C_p}$where k = thermal conductivity, ρ is the density, and C_p is the heat capacity. Effusivity off-line measurements were executed using a commercially available sensor (based on temperature measurements), employing mixtures of acetaminophen and lactose. Mixing time estimates based on effusivity results compared well with those obtained with both UV as well as density measurements. The authors found that effusivity can be a very useful analytical tool for the mixing of solids of significantly different densities, at concentrations above 10% (API). Models were developed for the dependence of effusivity on the API concentration present in the blends analyzed. For online measurements it is expected that the location of the sensor must be designed carefully. The paper includes an overview of PAT technologies for monitoring blending processes.

Enzyme Activation for Organic Solvents Made Easy

A team from the Rensselaer Polytechnic Institute (Serdakowski, A. L., et al., *Trends Biotechnol.* **2008**, *26*(1), 48−54) reviews the efforts towards enzyme activation based on the use of simple salts. Remarkable results were obtained, such as the use of KCl. When lyophilized in the presence of KCl, the transesterification activity of subtilisin in hexane increased by a factor of 3700. Attempts to understand the salt activation mechanism are described, including empirical models used to characterize the activating salts. One such QSAR model is based on the Jones−Dole B (JDB) coefficient, measuring the salt's impact on water viscosity (in this approach salts are classified into kosmotropes and chaotropes). Other enzymes that were activated for reactions in organic solvents, using the same approach, were α-chymotrypsin, thermolysin, penicillin amidase, soybean peroxidase, horse liver alcohol dehydrogenase, galactose oxidase, and xanthine oxidase. Other enzyme activation technologies are also presented.

Crystal Growth Measurement Using 2D and 3D Imaging and Perspectives for Shape Control

Two groups from the University of Leeds report on the recent developments in online particle shape measurement and control Wang, X. Z., et al. (*Chem. Eng. Science* **2008**, *63*, 1173−1184). The authors review the use of traditional crystal descriptors, such as aspect ratio and latent descriptors based on principal component analysis. An approach for 3D particle shape measurement and control based on the simultaneous 2D measurements obtained from two or more different angles is discussed. One experimental constraint required in this approach is the absence of secondary nucleation or breakage. The authors conclude that the planned direct 3D measurement will be of better accuracy. Estimating crystal growth rates for different crystal faces remains to be a challenging objective, with the exception of the simpler case of rod-like crystals that are practically two-dimensional. Recent developments in morphology modeling and control are reviewed. Improved models can account for nonideal mixing conditions in industrial reactors, as well as for other operational parameters such as supersaturation, cooling rates, solvents, impurities, and additives. Several online high-speed imaging instruments are discussed.

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OP800032X