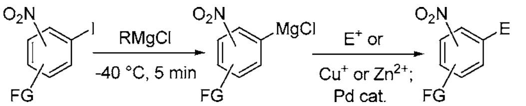
Organic Process Research & Development **2005**, *9*, 376–385

Highlights from the Literature

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

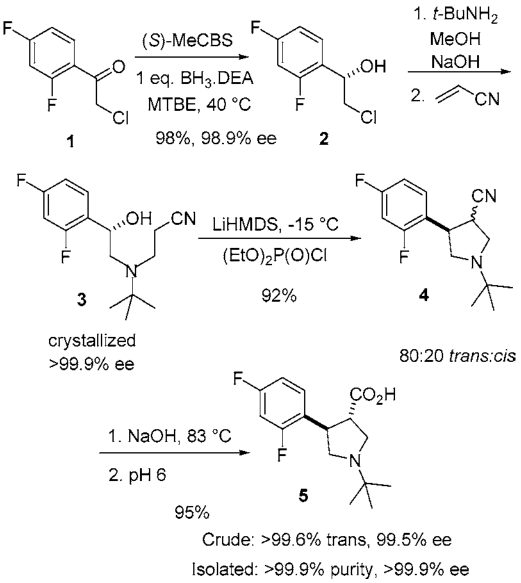
Functionalized Nitroarylmagnesium Halides via Iodine−Magnesium Exchange



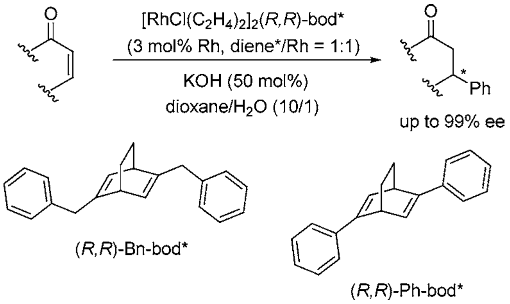
Following up on several communications on this topic, Knochel and co-workers now give a full account of the preparation and use of nitroarylmagnesium halide reagents (*J. Org. Chem.* **2005**, *70*, 2445−2454). The paper amply demonstrates the power of the iodine−magnesium exchange reaction for the synthesis of highly functionalized aromatic and heteroaromatic Grignard reagents bearing a nitro group in the ortho, meta, or para positions. A key general aspect of this iodine−magnesium exchange chemistry is the ability to form functionalized reactive organometallic species at temperatures more readily achievable on large scale than those commonly associated with the alternative lithium−halogen exchange reaction. More specific to the case of nitrated haloaromatics is the fact that the preparation of Grignard reagents from these substrates by insertion of magnesium metal is not feasible due to competing reduction of the nitro functionality. A multitude of subsequent reactions are described, including quenching with various standard electrophilic species and transmetalation (to copper or zinc) followed by electrophilic quenching or cross-coupling reactions. Given the versatility of the nitro group towards further transformations, this method represents a useful addition to the already well-developed halo−magnesium exchange chemistry.

Multikilogram-Scale Enantioselective Synthesis of a 3,4-Disubstituted Pyrrolidine

In support of a recent drug program, Chung and co-workers at Merck developed an efficient approach to 3,4-disubstituted pyrrolidines based around an enantioselective intramolecular nitrile-stabilized anion cyclization (*J. Org. Chem.* **2005**, *70*, 3592−3601). The paper briefly outlines alternative routes initially explored before providing a detailed description of the elegant route that was eventually used to prepare multikilogram quantities of the target compound. The chemistry began with an efficient CBS reduction of a cheaply available α-chloroacetophenone derivative **1** that was optimized to require 0.1 mol % of the catalyst and give the alcohol **2** in 98% isolated yield with 98.9% ee. Introduction of the *tert*-butylamine fragment (via the epoxide) followed by conjugate addition to acrylonitrile were optimized to proceed in high yield through careful study of the effects of solvents and several additives. Activation of alcohol **3** as the diethyl phosphate proved optimal, avoiding ionization/scrambling of the benzylic center but reactive enough to undergo the desired intramolecular S_N2 displacement with essentially complete inversion. The final transformation involved a kinetically controlled epimerization/saponification sequence, funneling everything into the desired trans compound **5** in high yield. Overall, the synthesis comprised five steps with no chromatography and delivered the target in 71% overall yield and >99.9% chemical and optical purity.



Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Enones

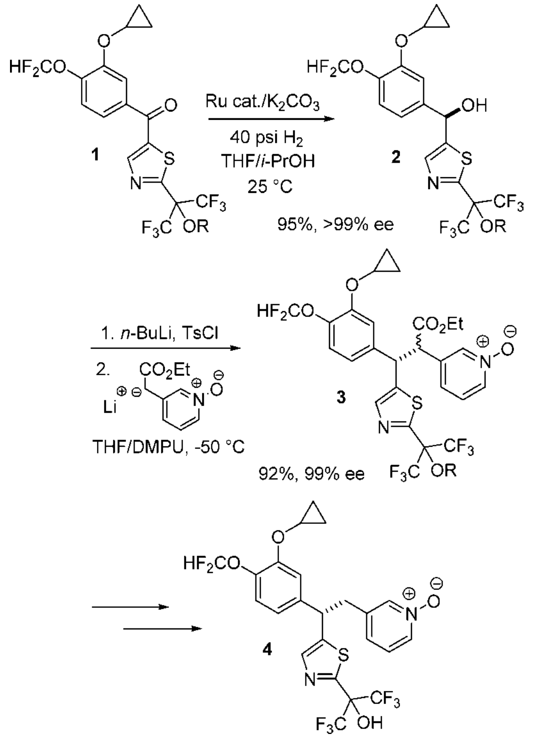


The rhodium-mediated 1,4-addition of arylboronic acids to enones represents a powerful method for the catalytic asymmetric construction of carbon−carbon bonds. In this paper (*J. Org. Chem.* **2005**, *70*, 2503−2508), Hayashi and co-workers describe the enantioselective preparation of novel C_2-symmetric bicyclo[2.2.2]octa-2,5-diene ligands and their application in the aforementioned reaction. In addition to

10.1021/op050095v CCC: $30.25

providing high yields and enantiomeric excesses for a variety of enone and arylboronic acid substrates, the authors note that these catalytic systems exhibit greater activity (complete reaction after 1 h at 30 °C) than alternative phosphine-based systems.

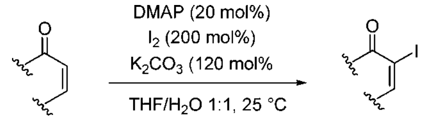
Stereoselective Enolate Alkylation with a Chiral Secondary Tosylate



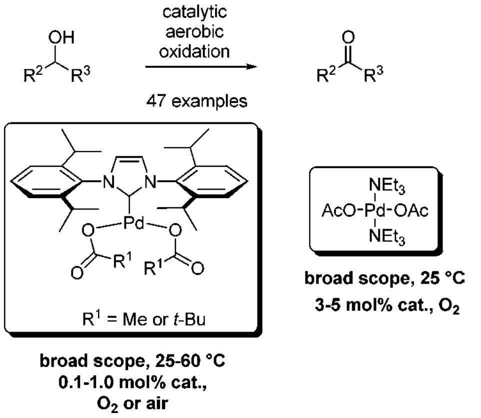
O'Shea, Chen, and co-workers at Merck report on their development of a practical synthetic approach to a phosphodiesterase-4 inhibitor, compound **4** (*J. Org. Chem.* **2005**, *70*, 3021−3030). The synthetic strategy revolved around the formation of the molecule's trisubstituted benzylic stereocenter. The first key step was the introduction of chirality via an asymmetric reduction of aryl−heteroaryl ketone **1**. Although BINAL-H was shown to be effective in terms of enantiomeric excess, the stoichiometric nature of this reduction would be prohibitively expensive in the long term. Consequently, an alternative catalytic process was developed using Noyori's RuCl$_2$(*R*-xylBINAP)(*R*,*R*-DAIPEN) complex, giving the benzylic alcohol in excellent yield and ee. Activation of alcohol **2** as the tosylate and in situ displacement with the lithium enolate of ethyl 3-pyridyl acetate *N*-oxide were shown to proceed with high stereoselectivity under carefully controlled conditions. Enolate alkylation at −40 °C or lower resulted in virtually zero erosion of optical purity, while higher temperatures returned material with significantly reduced ee. Multikilogram-scale experimental details are provided.

α-Iodination of Enones Using Iodine in an Aqueous Medium

α-Iodinated enones are potentially useful intermediates in organic synthesis, especially with respect to transition-metal-mediated coupling reactions. The Krafft group has developed a practically convenient procedure that can be used to prepare the α-iodo products from a variety of cyclic and acyclic enone precursors using molecular iodine (*Synlett* **2005**, 1263−1268). Assuming a Morita−Baylis−Hillman (MBH) mechanism to be operating, the group studied the effect of a variety of standard nucleophilic catalysts and found 0.2 equiv of DMAP to be optimal in most cases. Additionally, the use of a mixed aqueous−organic solvent system was found to be critical. This effect was attributed to the stabilization of charged MBH-type intermediates. The authors note that the new procedure has greater substrate scope than previous methods; however, an attempted extension to the iodination of α,*β*-unsaturated esters and nitriles led to only moderate yields.



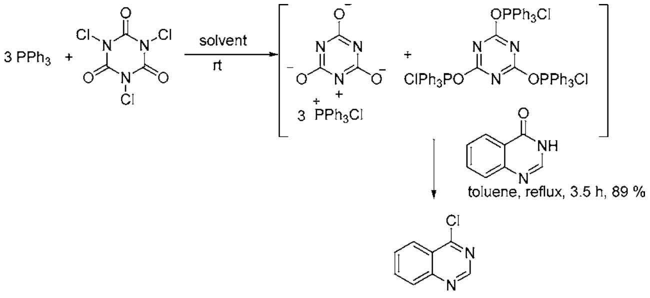
Pd-Catalyzed Aerobic Oxidation of Alcohols



Although changes of oxidation state are usually avoided whenever possible, these reactions are often inevitable features of synthetic routes to complex organic substances. A recent article by Sigman and co-workers (*J. Org. Chem.* **2005**, *70*, 3343−3352) describes a catalytic method for the oxidation of alcohols to ketones that offers advantages over more traditional procedures. Major issues with many standard oxidation methods include the use of stoichiometric toxic reagents, cryogenic conditions, and/or the production of copious amounts of waste. Alternative approaches, employing catalysts in conjunction with stoichiometric terminal co-oxidants (e.g., *N*-methylmorpholine *N*-oxide) suffer similarly. A more attractive co-oxidant is molecular oxygen; however, previous attempts to use oxygen involved forcing conditions and exhibited poor substrate scope. In this paper, the Sigman group has addressed many of these issues and developed two efficient catalytic systems employing low levels of Pd(OAc)$_2$ along with either triethylamine or an imidazolium carbene ligand and molecular oxygen as the co-oxidant. The methods are very mild and have broad substrate scope, although a disadvantage is the use of molecular sieves. The authors comment that the simplest Pd(OAc)$_2$/Et$_3$N system is very general; however, to achieve the mildest conditions and lowest catalyst loadings the use of the carbene ligand is key. The imidazolium carbene ligand inhibits catalyst decomposition, allowing for greater turnovers, but is sufficiently resistant to oxidation (cf. phosphine ligands).

Improved Method for Chlorination of Nitrogen-Containing π-Deficient Heteroaromatics

Chloroheteroaromatics are versatile synthetic precursors to interesting and biologically active compounds. The chlorination of the hydroxyheteroaromatics is usually done using $POCl_3$, $POCl_3/PCl_5$, $POCl_3/R_3N$, or NCS/PPh_3. One main drawback of using $POCl_3$ is the aqueous workup where the chloro compound can go back to the starting hydroxyheteroaromatic compound because of the heat generated in the quenching of $POCl_3$. The black byproduct derived from decomposition of NCS/PPh_3 interferes with the purification of the chloro compounds. Sugimoto and Tanji of University of Shizuoka, Japan, have reported (*Heterocycles* **2005**, *65*, 1810) that these problems can be circumvented by using a combination of PPh_3 and trichloroisocyanuric acid to afford the corresponding chloro compound in moderate to good yields. Workup, however, involves evaporation of solvent and chromatography (Scheme 1) presumably to remove Ph_3PO. The authors have also done some experiments by varying the reaction time, temperature, and solvent (toluene and xylene) and observed that toluene tends to give a better yield.

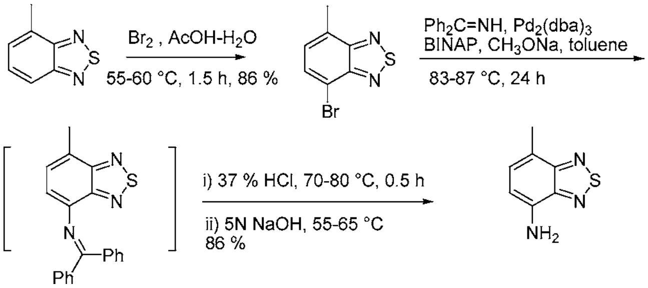


Synthesis of Heterocyclic Compounds under Microwave Conditions

Su and Guo of the University of Science and Technology of China have reviewed (*Heterocycles* **2004**, *63*, 903) synthesis of a wide array of heterocyclic compounds under microwave conditions. The compounds reviewed include five-membered heterocycles (pyrroles, oxazolines, oxazoles, isoxazolines, imidazoles, pyrazoles, thiazoles, triazoles, etc.), six-membered heterocycles (pyridines, pyrimidinones, piperazines, etc.), and a number of fused heterocycles (benzofurans, indoles, isatins, quinolines, coumarins, quinazolines, etc.)

Palladium-Catalyzed Amination with Benzophenone Imine as an Alternative to Aromatic Nitration–Reduction Sequence

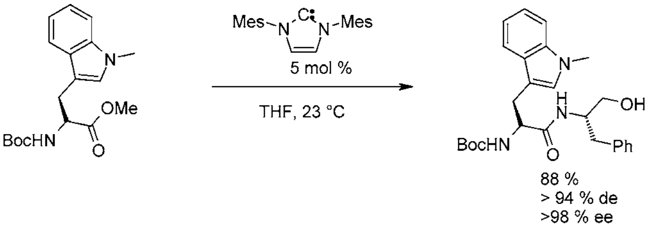
Liu, Prashad, and others at Process R&D of Novartis Pharmaceutical Corporation, New Jersey, U.S.A. were trying to accomplish the synthesis of 7-amino-4-methyl-2,1,3-benzothiadiazole and 7-amino-4,6-dimethyl-2,1,3-benzothiadiazole which are intermediates in the synthesis of interesting biologically active compounds (*J. Heterocycl. Chem.* **2003**, *40*, 713). The original synthetic route involved the nitration of the corresponding benzothiadiazole and the reduction of the resultant nitro compound. However, unlike the 4-ethyl-2,1,3-benzothiadiazole derivative (which afforded exclusively 7-nitro regioisomer in 83% yield) or 4-chloromethyl-2,1,3-benzothiadiazole (which afforded exclusively 7-nitro regioisomer in 81% yield), the 4-methyl-2,1,3-benzothiadiazole afforded a mixture of 7-nitro (53%) and 5-nitro (12%). The low yield as well as the poor regioselectivity made this route unattractive for large-scale reactions. Another limitation is the safety concerns associated with the nitration reaction on a large scale. The group has devised an alternate method involving the Buchwald methodology of using benzophenoneimine as ammonia equivalent and circumvented this problem.



They were able to produce 14 kg of 7-amino-4-methyl-2,1,3-benzothiadiazole in the pilot plant in high yields.

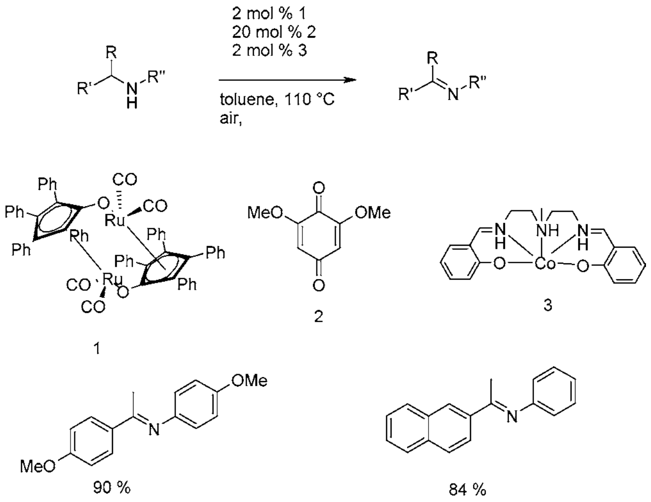
N-Heterocyclic Carbene-Catalyzed Amidation of Unactivated Esters with Amino Alcohols

Movassaghi, M. et al. (*Org. Lett.* **2005**, *7*, 2453) have developed a catalytic method for the amidation of unactivated esters with amino alcohols under mild conditions with wide functional group tolerence. The conversion is catalyzed by the N-heterocyclic carbene IMes (**1**) prepared in situ from *N,N*-bismesitylimidazolium chloride and potassium *tert*-butoxide. Both aromatic and aliphatic esters may be employed in the reaction giving products in high yield.



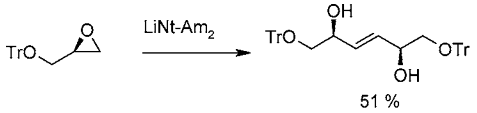
Ruthenium-Catalyzed Aerobic Oxidation of Amines

Bäckvall, J. E. and co-workers (*Chem. Eur. J.* **2005**, 2327) have developed an efficient substrate-selective aerobic oxidation of amines. The reaction can be used for the preparation of ketimines and aldimines in good to high yields. The principal for this aerobic oxidation is that the electron transfer from the amine to the oxygen occurs stepwise via a ruthenium catalyst (**1**), a quinone (**2**), and a cobalt salen complex (**3**). The influence of the substrate structure on the reaction kinetics was also studied; electron-withdrawing groups on the aromatic ring inhibit the reaction if microwave radiation is not used.



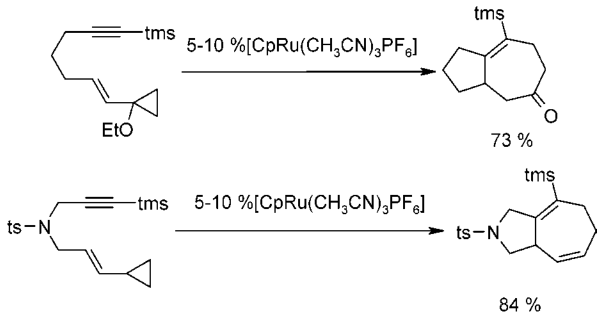
Dimerization of Terminal Epoxides Using Hindered Lithium Amides

Hodgson, D. M. et al. (*Org. Lett.* **2005**, *7*, 2305) have found that the reaction of hindered lithium amides with readily available enantiopure terminal epoxides gives 2-ene-1,4-diols via carbenoid dimerization of the corresponding α-lithiated epoxides. The methodology was used for a three-step synthesis of D-mannitol and D-iditol from (*S*)-trityl-glycidyl ether.



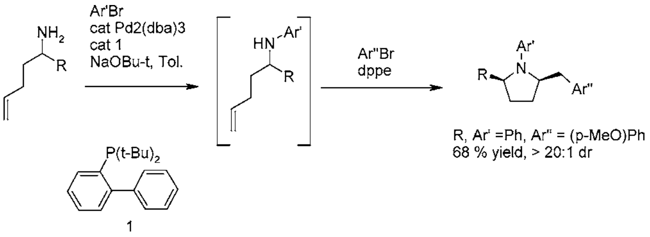
Syntheses of Seven-Membered Rings: Ruthenium-Catalyzed Intramolecular [5 + 2] Cycloadditions

Trost, B. M. et al. (*Chem. Eur. J.* **2005**, *11*, 2577) have investigated the scope and limitations of the Ru-catalyzed cycloaddition and compared it with the Rh-catalyzed reaction. They have also shown the power of this methodology towards natural product total synthesis by the formation of various polycyclic systems from readily available cyclopropylenyne substrates. The Ru-catalyzed cycloadditions proceed under very mild conditions, and usually the reactions are complete within a few hours at room temperature.



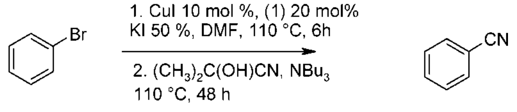
Palladium-Catalyzed Tandem N-Arylation/Carboamination Reactions for the Stereoselective Synthesis of *N*-Aryl-2-benzyl Pyrrolidines

Wolfe, J. P. and co-workers (*Org. Lett.*, published online May 26, 2005, http://dx.doi.org/10.1021/ol050647u) have developed a tandem N-arylation/carboamination of γ-amino alkenes with two different aryl bromides which provides a rapid entry to differentially arylated *N*-aryl-2-benzyl pyrrolidine derivatives in good yields and diastereoselectivity. The selective diarylation is achieved in a telescoped process by an in situ modification of the palladium catalyst via phosphine ligand exchange.



Mild and Efficient Copper-Catalyzed Cyanation of Aryl Iodides and Bromides

Cristau, H.-J. et al. (*Chem. Eur. J.* **2005**, *11*, 2483) have developed an efficient copper-catalyzed cyanation of aryl bromides and iodides using a catalytic amount of a ligand and a catalytic amount of potassium iodide. The cyanide source is acetone cyanohydrin. The best ligand was found to be 1,10-phenantroline (**1**). The reaction is performed at 100 °C in benzonitrile. The use of acetone cyanohydrin prevents poisining of the catalyst from cyanide as only small amounts of free cyanide are available at any given time.



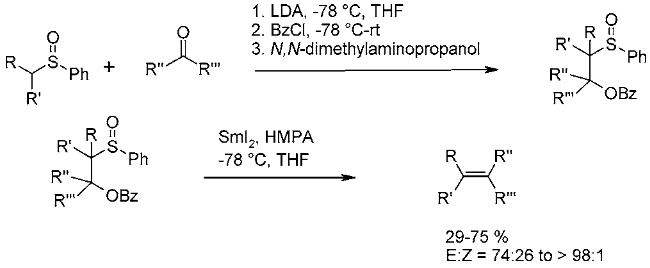
80 %

The Potential of Palladacycles: More than Just Precatalysts

Dupont, J. et al. (*Chem. Rev.* **2005**, *105*, 2527–2572) have reviewed the work that has been done on the most popular class of organopalladium derivatives, the palladacycles. The review concentrates on the synthesis and structural aspects of palladacycles as well as their applications as chiral auxiliaries and as mesogenic and photoluminescent agents and their biological applications. There is also an interesting section on total synthesis with palladacycles as intermediates.

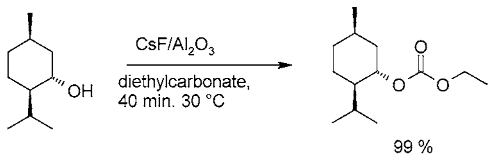
Sulfoxides in Julia–Lythgoe Olefination: Efficient and Stereoselective Preparation of Di-, Tri-, and Tetrasubstituted Olefins.

Marko, I. and co-workers (*Org. Lett.* **2005**, *7*, 2373) have investigated a novel modification of the classical Julia–Lythgoe olefination, using sulfoxides instead of sulfones. The reaction affords after in situ benzoylation and samarium iodide/HMPA or DMPU-mediated reductive elimination, 1,2-di-, tri-, and tetrasubstituted olefins in moderate to good yields and *E*/*Z* selectivity. The reaction conditions are mild, and the scope of the reaction is broad.



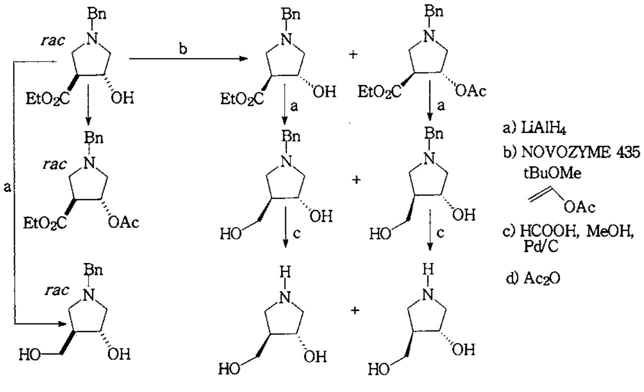
New Highly Active and Selective Catalytic Synthesis of Unsymmetrical Organic Carbonates.

Figueras, F. et al. (*Eur. J. Org. Chem.* **2005**, 1972) have developed an efficient and selective synthesis of organic carbonates by direct condensation of an alcohol and diethyl carbonate in the presence of a recyclable heterogeneous solid-base CsF/α-Al_2O_3 catalyst. The catalyst is activated at 393 K for 4 h and produced quantitative yields within less than 1 h.

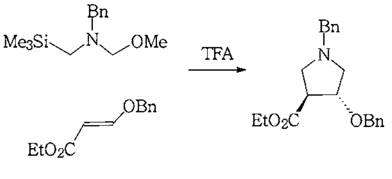


Lipase Resolution

Tyler and Clinch from Industrial Research Limited (New Zealand) claimed a method for preparing chiral 3-hydroxy-4-hydroxymethyl-pyrrolidines (WO 2005/033076A1), key intermediates to purine phosphorylase inhibitors (WO 2004/018496). Enzymatic methods for the production of either (3*R*,4*R*)- and (3*S*,4*S*)-3-hydroxy-4-hydroxymethylpyrrolidine using (*Candida antartica*) lipase (NOVOZYME 435) resolution of *N*-substituted *rac*-*trans*-3-hydroxy-4-carboxyethyl-pyrrolidines, are disclosed in the patent.



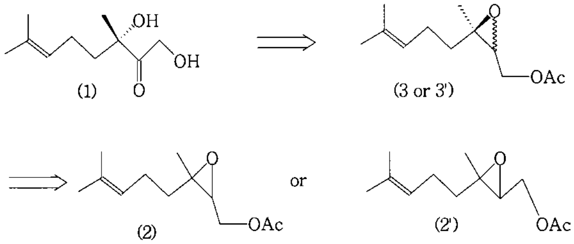
rac-Pyrrolidine substrates were synthesised from ethyl *trans*-3-benzyloxyacrylate and *N*-(methoxymethyl)-*N*-trimethylsilylbenzylamine, in TFA.



Either *N*-benzyl or *N*-BOC precursors can be used as enzyme substrates. Claimed ee's are higher than 90%.

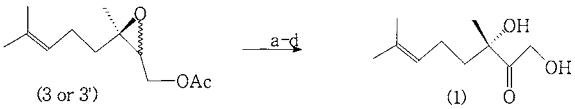
Chiral Chemoenzymatic Pheromone Synthesis

Tashiro and Mori (*Tetrahedron: Asymmetry* **2005**, *16*, 1801) reported the production of (*S*)-1,3-dihydroxy-3,7-dimethyl-6-octen-6-one (**1**), the aggregation pheromone of the Colorado potato beetle (*Leptinotarsa decemlineata*). Pheromones are compounds with a great potential for use in agricultural chemistry and are completely compatible with good environmental concerns. In this paper a good method to produce this aggregation pheromone is described. Both (±)-2,3-epoxynerol (**2**) and (±)-2,3-epoxygeraniol (**2′**) can be used as starting materials since stereochemistry in C-2 is lost (see below).



(±)-2,3-Epoxynerol (**2**) yielded (2*S*,3*R*)-2,3-epoxyneryl acetate (**3**), while (±)-2,3-epoxygeraniol (**3**) afforded (2*R*,3*R*)-2,3-epoxygeranyl acetate. To obtain (2*S*,3*R*)-2,3-epoxyneryl acetate at 98.8% ee, (±)-2,3-epoxynerol was subjected to enzymatic kinetic resolution, three times, with lipase PS (AMANO) and vinyl acetate.

Final synthesis was carried out by using **2** or **2′** as substrate via inversion of (3*R*)-configuration ($HClO_4$/DMF) methanolysis, primary hydroxyl protection (TBDPSCl), oxidation (SO_3•py/DMSO), and deprotection.



a) $HClO_4$/MeOH, c) TBPSCl/Et_3N/DMAP, d) SO_3.py, d) TBAF/THF

Although the process as a whole must be further optimized, the importance of this compound justifies further studies.

Statins

Michael Muller reports (*Angew. Chem., Int. Ed.* **2005**, *44*, 362) a highlight on the chemoenzymatic synthesis of building blocks to statins' side chains. Statins are known inhibitors of HMG-CoA reductase and have been used in therapy to reduce LDL cholesterol. The synthesis of these pharmaceuticals requires as APIs, 6-substituted-3,5-dihydroxy-carboxylic acid derivatives. Several microbial and enzymatic procedures to carry out the synthesis of these APIs are described in this account.

Enzyme Promiscuity

Kazlauskas reports (*Curr. Opin. Chem. Biol.* **2005**, *9*, 195) the promiscuity of biocatalysts, thus showing the ability of a single active site to catalyze more than one chemical transformation. This so-called catalytic promiscuity was earlier reviewed by Bornscheuer and Kaslaukas (*Angew. Chem., Int. Ed.* **2004**, *43*, 6032).

Morley and Kazlauskas (*Trends Biotechnol.* **2005**, *23*, 231) reported that the effect of closer mutations is generally related to improving enantio- and substrate selectivity. In these reviews, they emphasized that a single mutation can greatly increase (675-fold) catalytic activity as observed for β-lactamase (Vakulenko et al. *J. Biol. Chem.* **1999**, *274*, 23052).

Also described are the exchange and overlapping of enzymatic activity. For example, phosphatases and (V-dependent) haloperoxidades overlap their activities (Littlechild et al., *J. Mol. Recognit.* **2002**, *15*, 291).

Four-amino-acid-substitution in a fatty acid denaturase yielded a hydroxylase (Broun et al. *Science* **1998**, *282*, 1315; Broadwater, Whittle, and Shanklin *J. Biol. Chem.* **2002**, *277*, 15613).

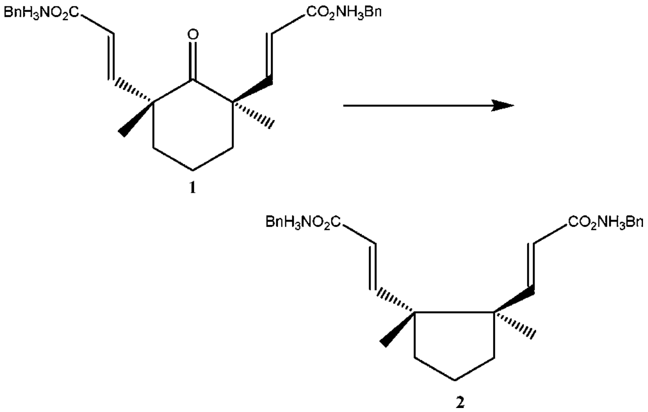
Enzyme promiscuity is expected to have a tremendous impact in organic synthesis in the next years.

Rapid "Green" Predictable Microwave Synthesis

In a special report from the Center for Green Chemistry of Monash University and CSIRO Molecular Science, Australia, Roberts, B. A., Strauss, C. R., Eds. Towards Rapid "Green" Predictable Microwave Assisted Synthesis (*Acc. Chem. Res.* **2005**, published online May 19, 2005, http://dx.doi.org/10.1021/ar040278m) report the construction of continuous as well as batch microwave reactors for large-scale synthesis. The capabilities of these reactors—rapid heating, cooling including interactive software for calculating optimal conditions—are highlighted through some selected chemical reactions such as Fischer indole synthesis, Hofmann eliminations, Pd-catalyzed reactions such as Heck, Suzuki, and Stille coupling, etc.

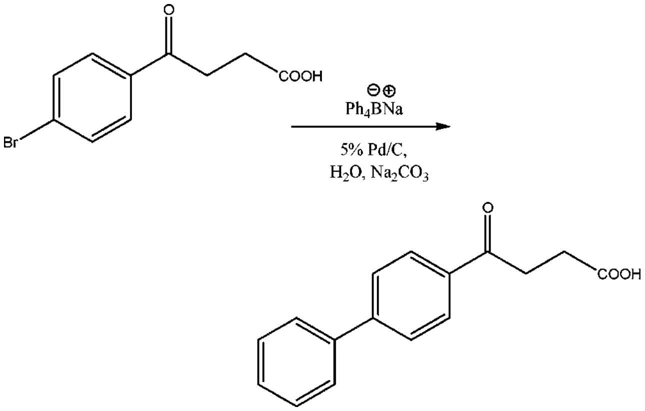
Photochemistry with Sunlight

Perhaps, in recent years one finds the phrase "green chemistry" in the chemical literature more often than it has ever been. Conversion of multigram quantities of crystalline reactants to value-added crystalline products by sunlight without the need for external reagents or purification is truly a green chemistry (crystal-to-crystal conversion). To reach this stage, "one must identify suitable reactions, develop mechanistic models to establish generality and ascertain the experimental feasibility of the method" says C. J. Mortko and M. A. Garcia-Garibay (*J. Am. Chem. Soc.* **2005**, *127*, 7294−7295). Irradiation of ionic micro crystals of **1** with a medium-pressure Hg lamp ($\lambda = 290$) or sunlight produces **2** in quantitative yield.



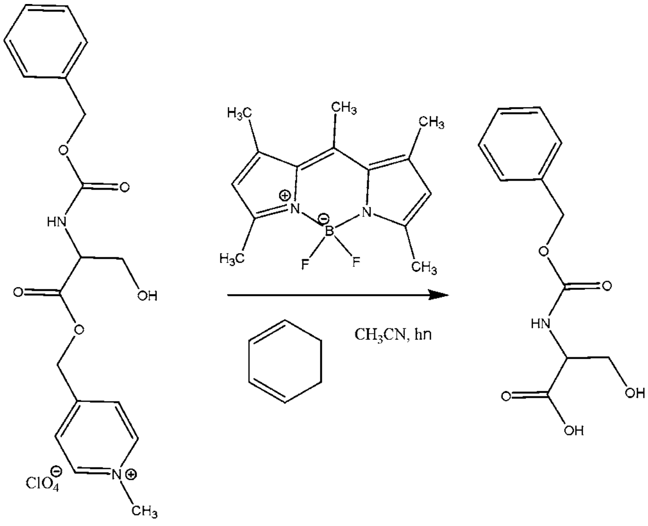
Suzuki Reactions in Water

The Suzuki reaction is widely used for the preparation of biaryl compounds; usually it requires palladium salts, organic ligands, and organic solvents. G. Lu, R. Franzen, Q. Zang, and Y. Xu (*Tetrahedron Lett.* **2005**, *46*, 4255−4259) found that Suzuki reaction (Ph_4BNa and aryl bromides) can be carried out in water in the presence of small amount of Pd on carbon and an inorganic base without any phosphorus ligand. Sodium carbonate or sodium phosphate but not the corresponding potassium salts give good yields. Yields are equally good for electron withdrawing or donating bromoaryl carboxylic acids and phenols. Hindered aryl halides give lower yields. All four aryl groups on boron are transferred. Therefore, the reaction needs only 0.25 equiv of boron reagent.



Visible Light for Deprotection

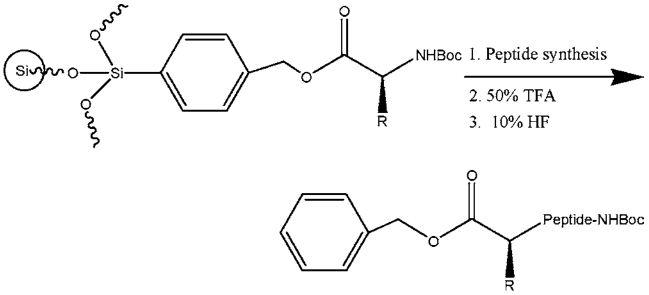
Commonly used photoremovable protecting groups generally require UV light for activation. These reagents have



limitations such as requirement of expensive equipment, undesirable UV absorption by the protected molecule itself, etc. C. Sundararajan and D. E. Falvey (*J. Am. Chem. Soc.* **2005**, *127*, 8000−8001) disclosed methodology which utilizes visible light to deprotect *N*-methyl 4-picolinium esters of carboxylic acids, amino acids, and phosphoric acids. The deprotection happens in the presence of light-absorbing photosensitizers and a radical scavenger. The reaction is complete in 5 min and gives quantitative yields of the deprotected acids.

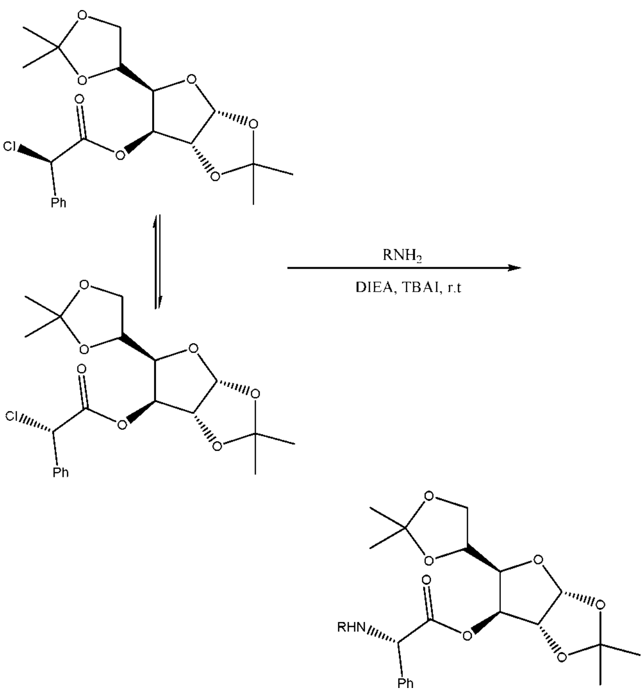
Removal of Substrates from Solid Supports

Solid-phase synthesis and combinatorial chemistry are indispensable and complementary tools for many medicinal chemists. Currently utilized solid phase organic synthetic methods involve the cleavage of substrate form the solid support and then separation of desired molecules from byproducts. The workup typically includes extraction and filtration or centrifugation, causing loss in yields. R. A. Houghten and Y. Yu (*J. Am. Chem. Soc.* **2005**, *127*, 8582−8583.) find a reasonable solution by choosing a volatizable solid support and linkers that can be completely removed by complete decomposition followed by volatilization during the final cleavage step of the synthetic process. In this case the solid support is standard silica gel, which is coupled to a linker and then to the ^{t}Boc-protected amino acid via cesium salt. After a standard peptide-coupling reaction sequence the silica support is volatilized with hydrofluoric acid. The majority of commonly used protecting groups in peptide synthesis (except ^{t}Boc) are stable to these conditions.



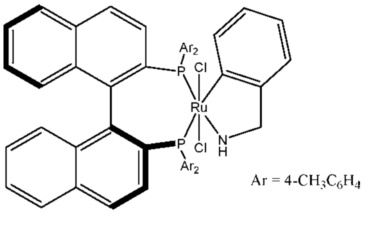
Asymmetric Synthesis of Amino Acid Derivatives

Chiral auxiliary mediated dynamic resolution of α-halo acid derivatives is well recognized in chemical literature. Diastereoselection is often achieved reasonably well with a variety of commonly available resolving agents. Nucleophilic substitution of halo esters appears to be convenient for asymmetric synthesis of α-amino acid derivatives via carbohydrate-mediated dynamic resolution (H. J. Kim, E.-K. Shin, J.-Y. Chang, Y. Kim, and Y. S. Park, *Tetrahedron Lett.* **2005**, *46*, 4115−4117). The reaction can be run in solvents such as $CHCl_3$, THF, ether, or hexane at room temperature, and diethylisopropylamine is the ideal base. Tetrabutylammonium iodide is essential for high yields as well as for enhanced optical enrichment.



Asymmetric Reduction of *tert*-Butyl Ketones

Asymmetric reduction of tertiary alkyl or aryl ketones with high enantiomeric purity is generally difficult. T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei (*J. Am. Chem. Soc.* **2005**, *127*, 8288−8289) report that chiral Ru complex **1** effects asymmetric hydrogenation of various *tert*-butyl ketones with high substrate/catalyst ratio (up to 100000:1) under mild conditions. Reduction is accomplished in ethanol, containing *tert*-butyl alcohol, and hydrogen at 20 atm to give quantitative yield with 98% ee. Under optimal conditions aliphatic, olefinic and aromatic *tert*-alkyl ketones are hydrogenated with equally high enantioselectivity.



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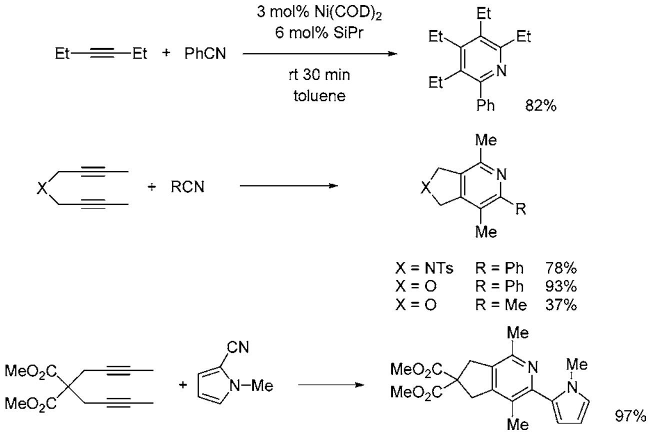
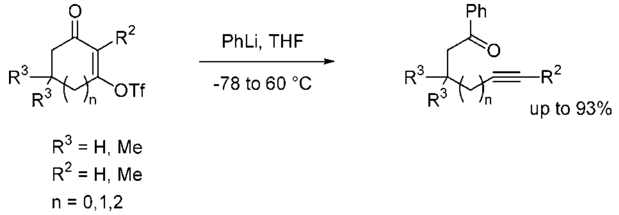
Synthesis of Multisubstituted Pyridines

Although the synthesis of pyridines via transition-metal-catalysed cycloaddition between alkynes and nitriles has been described many times, conditions used are rather harsh or substrate versatility is limited. A new nickel-catalysed process, however, occurs at ambient temperature (McCormick, M. M. et al. *J. Am. Chem. Soc.* **2005,** *127,* 5030). The catalyst is $Ni(COD)_2$ with ligands from the N-heterocyclic carbene family; SiPr, 1,3-bis-(2,6-diisopropylphenyl)4,5-dihydroimidazol-2-ylidene, is the best.



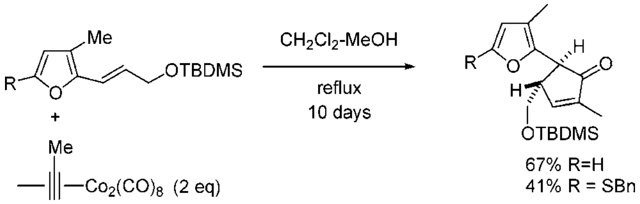
Preparation of Acetylenic Ketones by Ring Cleavage of Cyclohexenones

Addition of Grignard reagents to enol-triflates derived from cyclohexanedeones leads to ring opening and high to moderate yields of acetylenicketones (Kamijo, S. et al. *J. Am. Chem. Soc.* **2005**, *127*, 5028). Alkyllithiums also give good results and higher yields in many cases.

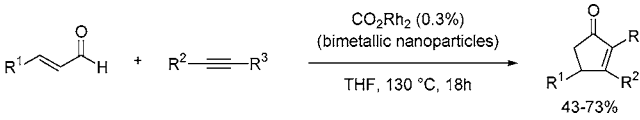


Intermolecular Pausen−Khand Reaction

An excellent review on this reaction has recently appeared (Gibson, S. E. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022). The review discusses how the reactivity of the alkene partners is influenced by (a) the presence of other coordination sites on the alkene and (b) the energy of the LUMO of the alkene, and how this knowledge has led to a broadening of the scope of the reaction.



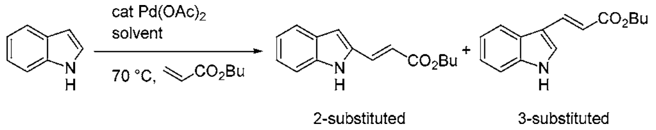
The recent report of Chung (*Org. Lett.* **2004**, *6*, 1183) is highlighted; in this example an unsaturated aldehyde acts as both alkene partner and source of carbon monoxide and makes the Pauson−Khand reaction more synthetically attractive.



Palladium-Catalysed Intermolecular Alkenylation of Indoles

One of the disadvantages of many of the currently popular C−C bond-forming strategies (e.g., Heck, Suzuki, Sonagashira reactions) is the requirement for the aryl or vinyl component to be substituted by halogen or an equivalent group. In the 1960s Fujiwara and Moritani developed an oxidative Heck reaction which gets around this problem to some extent.

Now the group of Gaunt at Cambridge, UK, has reported that indoles can be reacted with unsaturated esters in the presence of palladium catalysts and an oxidizing agent and that the position of substitution is controlled by choice of solvent (Grimster, N. P. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125). The reaction has been extended to a wide variety

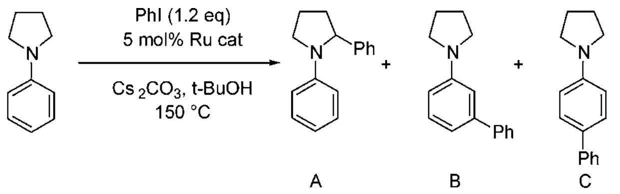


oxidant	solvent	ratio 3:2 subst.	yield
Cu $(OAc)_2$	DMF	>95.5	54
Cu $(OAc)_2$	DMSO	>95.5	66
$Cu(OAc)_2$	(3.1) DMF/AcOH	1:1	54
tBuOOBz	(3:1) dioxane/AcOH	1:7	58
tBuOOBz	(3:1) MeCN/AcOH	>95.5	65
$Cu(OAc)_2$	(10:1) DMF/DMSO	>95.5	79

of alkenylations using vinyl ketones, styrenes, and even cyclohexane. It is suggested that palladation to give the 3-isomer initially takes place, but under the influence of acid, migration to the 2-position takes place, followed by reaction with the olefinic component.

Selective Arylation of *N*-Phenylpyrrolidine by C−H Functionalization

Despite much progress in C−H bond functionalisation, it is still rare to find an sp^3 C−H bond that is converted to a C−C bond by an intermolecular catalytic reaction. A recent report describes arylation of a pyrrolidine ring using a ruthenium-catalysed reaction (Sezen, B. et al. *J. Am. Chem. Soc.* **2005**, *127*, 5284). Whilst this method is not yet a practical synthetic method, it sets a precedent for future exciting work in this area.



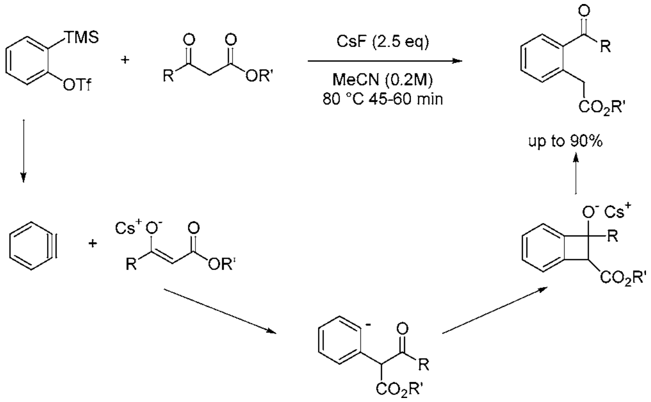
catalyst	A	B	C
$Ru(H_2)$ (CO) $(PCy_3)_3$	32	6	4
Ru(Ph) (I) (CO) $(PCy_3)_3$	34	5	4
Ru (H_2) (H_2) $(PCy_3)_3$	40	7	4
Ru (H_2) (H_2) $(PCy_3)_3$ [a]	59	9	4

[a] 10 mol %

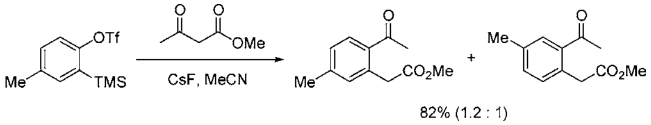
Direct Acyl-Alkylation of Arynes

Arynes can be generated under mild conditions by the method of Kobayashi, which involves fluoride-initiated elimination of an orthosilylaryl triflate. Reaction with a

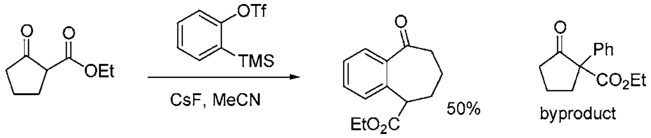
β-diketone would be expected to give the C-phenylated product, but a recent report shows that the major product is the acyl-alkyl product, where the intermediate has undergone acyl transfer. Optimised conditions for the production of the acyl-alkylated product have recently been described (Tambar, U. K. et al. *J. Am. Chem. Soc.*, **2005**, *127*, 5340).



When there is a substituent on the benzyne, a mixture of products is obtained.

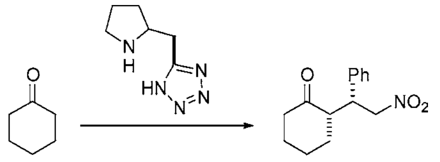


With cyclic β-ketoesters, large rings can be formed.



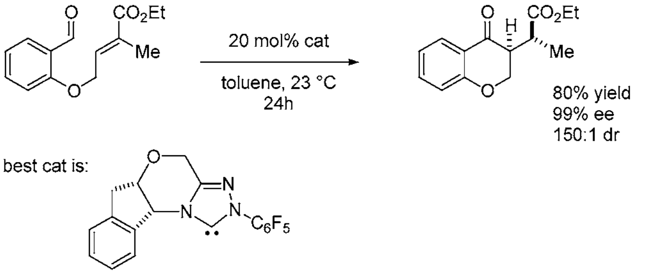
An Improved Organocatalyst Based on Homoproline

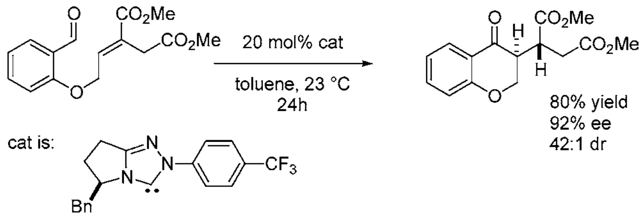
In recent years, organocatalytic reactions using proline as catalyst have been widely studied. However, the reactions usually require polar solvents such as DMSO, since proline is insoluble in many organic solvents. Tetrazole analogues often outperform proline, and it is now reported that the tetrazole analogue of homoproline, when used in a mixture of ethanol and 2-propanol (1:1) gives high yields in catalysis of Michael reactions (Mitchell, C. E. T. et al. *SynLett* **2005**, 611).



Highly Enantio- and Diastereoselective Catalytic Intramolecular Stetter Reaction

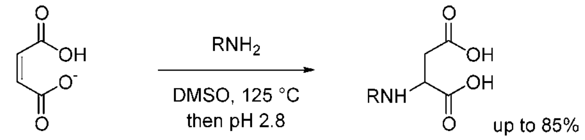
The full paper from the group of Rovis at Colorado State University on this important atom-efficient reaction has now appeared (Read de Alaniz, J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 6284). The Rovis catalysts are 1,2,4-triazolium salts which in the presence of base generate carbenes which seem to be the more selective catalysts.





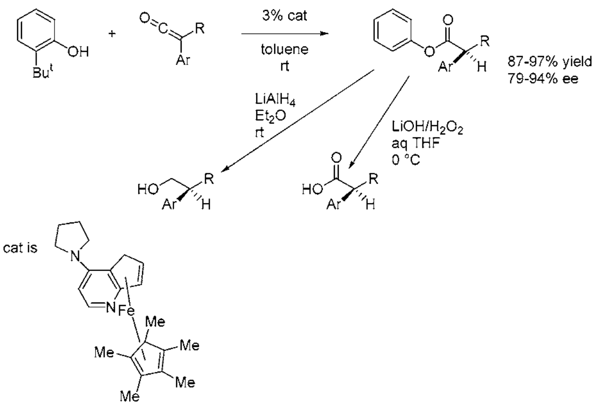
Practical Synthesis of Functionalised Aspartic Acids

Reaction of primary amines with monoalkyl maleates in DMSO at 125 °C gives good yields of functionalised aspartic acids. It is important to use either the monolithium or sodium salt of maleic acid—use of potassium gives side reactions. Uncharged maleic acid does not react, but isomerises to fumaric acid (Piispanen, P. S. et al. *Tetrahedron Lett.* **2005**, *46*, 2751).



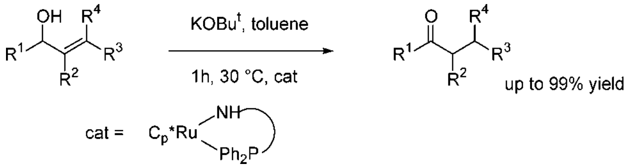
Catalytic Asymmetric Synthesis of Esters

Ketenes can be converted enantioselectively to esters in the presence of a phenol and a ferrocene-type catalyst (Wiskur, S. L. et al. *J. Am. Chem. Soc.* **2005**, *127*, 6176). Highest enantioselectivity occurs with 2-*tert*-butylphenol, and these esters can be converted to carboxylic acids or alcohols in high yield without loss of selectivity.

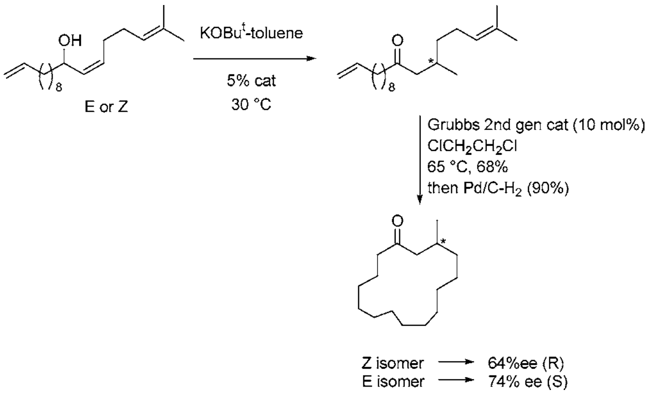


Isomerization of Allyl Alcohols to Saturated Ketones

This highly atom-efficient process is potentially very useful in industry. The group of Ikariya in Tokyo have now reported an improved catalyst for this transformation and have applied it to an asymmetric synthesis of the important product muscone (Ito, M. et al. *J. Am. Chem. Soc.* **2005**, *127*, 6172). The catalyst is a half-sandwich ruthenium complex with phosphorus-amino ligands.



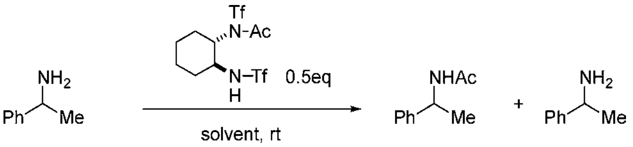
Using a chiral PN-ligand asymmetric dynamic kinetic resolution converts racemic secondary alkylic alcohols to optically active ketones, although ee's are as yet moderate (~66% ee). The asymmetric synthesis of muscone uses the above isomerisation followed by ring-closing metathesis using Grubbs second-generation catalyst, followed by catalytic hydrogenation.



Enantioselective N-Acylation of Racemic Amines: A Spectacular Salt Effect

Kinetic resolution via acylation of amines is normally carried out using enzymes as catalysts, and there are relatively few nonenzymatic methods. It has recently been shown by the group of Miaskowski in France that the monoacetyl-ditriflate of cyclohexane-diamine serves as a highly enantioselective acylating agent for primary amines (Arseniyadis, S. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314) and that the process shows an unusual solvent-mediated reversal of selectivity.

It has now been reported that addition of salts, especially quaternary ammonium salts, not only causes a reversal of selectivity but also increases reaction rate and selectivity. In the presence of trioctylmethylammonium chloride, all solvents examined (THF, dioxane, toluene, methylene chloride) gave the (*S*)-product, although ee was highest in THF. The concentration of the salt has a dramatic effect on ee, as shown in the table.



toluene	56% ee (*R*)
DMF	72% ee (*S*)
DMPU	32% ee (*S*)
THF	42% ee (*R*)
THF + LiBr	42% ee (*S*)
THF + $(Oct)_3NMeCl$	90% ee (*S*)

salt concentration (M)	salt/substrate	ee
1	25:1	90 (*S*)
0.1	2.5:1	80 (*S*)
0.01	1:4	30 (*S*)
0.001	1:40	0
0.0001	1:400	26 (*R*)
0	0	42 (*R*)

Crystalline Polymorph Selection and Discovery with Polymer Heteronuclei

A method of using polymers as heteronuclei for the selection and discovery of organic polymorphs was recently reported (Lang, M. D. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14834; *J. Pharm. Sci.* **2002**, *91*, 1186; **2003**, *92*, 2260). The method allowed the production of a new polymorph (IV) of carbamazepine, a molecule whose polymorphism has been studied for over 30 years. Essentially the methodology comprises preparation of libraries of insoluble polymers with a defined set of functionality. The polymers are all cross-linked terpolymers where one component is the cross linker. These are then used as heteronuclei in standard crystallisation.

The latest report from the University of Michigan team is concerned with the compound 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile usually named ROY because of its red, orange, and yellow polymorphs. Previous studies have shown that there are six known polymorphs. Using a diverse set of polymer libraries and only ethanol as solvent, all six polymorphs were produced, and excellent single crystals of each were produced after a few days experimentation.

In contrast, when the antibiotic sulphamethaxazole (for which two forms are known) was studied, two new polymorphs, in addition to the existing two, were produced by evaporative crystallization in the presence of polymer heteronuclei.

These results show the power of the new method, which is compatible with high-throughput screening methods (Price, C. P. et al. *J. Am. Chem. Soc.* **2005**, *127*, 5512).

Trevor Laird*
Editor

Ulf Tilstam
Lilly Development Centre S.A., B-1348
Mont-Saint-Guibert, Belgium
E-mail: tilstam_ulf@lilly.com

Mark McLaughlin
Merck & Co. Inc., Rahway, NJ 07065, U.S.A.
E-mail: mark_mclaughlin@merck.com

Joseph Swaroop Mathen
Pharmacore, Inc., High Point, NC 27409, U.S.A.
E-mail: jsmathen@vsnl.com

Octavio Augusto Ceva Antunes
Instituto de Quimica, UFRJ,
Rio de Janeiro RJ21949-900, Brasil
E-mail: octavio@iq.ufrj.br

Ramaiah Muthyala
University of Minnesota, Minneapolis, MN 55455, U.S.A.
E-mail: muthy003@umn.edu

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