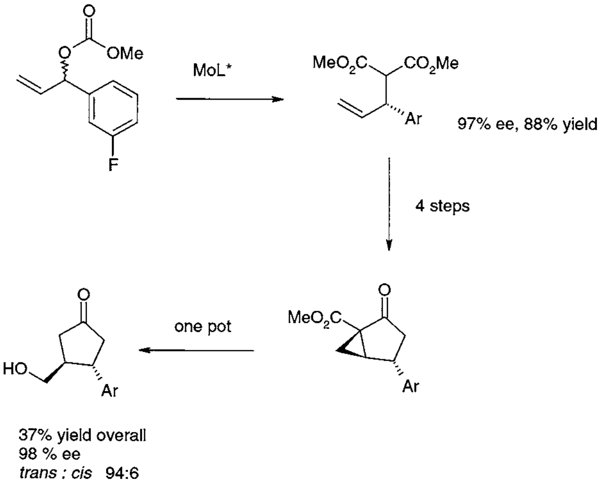
Organic Process Research & Development **2002**, *6*, 742−748

Highlights from the Literature

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

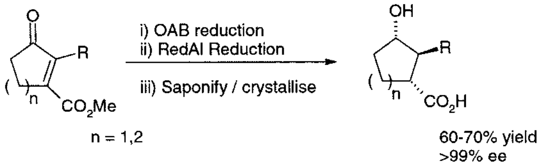
New Route to 3,4-Disubstituted Cyclopentanones

An efficient and practical asymmetric synthesis of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)-cyclopentanone has been described by Palucki and co-workers (*J. Org. Chem.* **2002**, *67*, 5508). An asymmetric molybdenum-catalysed alkylation reaction was used to establish the first stereocentre (see scheme below) and a copper-catalysed intramolecular diastereoselective cyclopropanation reaction used to set the second stereocentre. The last step involved a one-pot ring-opening/deprotection/hydrolysis/decarboxylation sequence that furnished the desired product in good yield. The group reported successful reactions on kilogram scale.

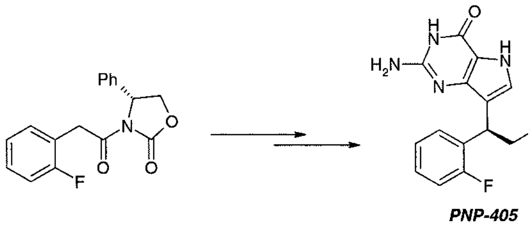


Asymmetric Synthesis of Cyclopentanes and Cyclohexanes

On a theme of the cyclopentane ring structure, Kuethe and co-workers, also at Merck, describe their synthetic efforts (*J. Org. Chem.* **2002**, *67*, 5993) towards an asymmetric synthesis of 1,2,3-trisubstituted cyclopentanes and cyclohexanes as key components of substance P antagonists. Three methods have been developed by the group for the preparation of the 2,3-disubstituted cyclopentenone and cyclohexenone which are key achiral starting building blocks. These intermediates are reduced catalytically with (*R*)-2-methyloxazaborolidine in high yield (82−98%) and excellent ee (89−96%). Directed reduction of the chiral allylic alcohols using RedAl gave exclusively the 1,2-anti stereochemistry (>99:1). Epimerisation of the ester centre followed by saponification/crystallisation afforded the desired hydroxyacids in good yield (65−70%) and in high enantiomeric excess (>99%).



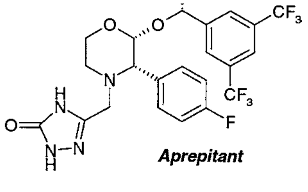
Enantioselective Synthesis of PNP405



An efficient and multigramme synthesis of PNP-405, a purine nucleoside phosphorylase inhibitor, has been described by Prashad and co-workers from Novartis (*J. Org. Chem.* **2002**, *67*, 6612). Their synthesis involved eight steps starting from *o*-fluorophenylacetic acid with 21.6% overall yield and >99.5% enantiopurity. The key stereogenic centre with (*R*)-configuration was created using using Evans asymmetric alkylation methodology.

Practical Asymmetric Synthesis of Aprepitant

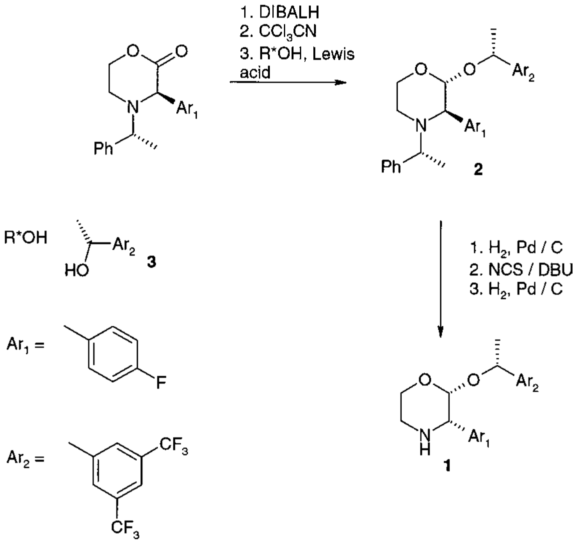
Zhao and co-workers from Merck describe a high-yielding synthesis of aprepitant, a potent substance P receptor antagonist (*J. Org. Chem.* **2002**, *67*, 6743).



In their synthesis the group have developed a streamlined and high-yielding synthesis of the intermediate **1**. The key step of the synthesis featured a highly stereoselective Lewis acid-catalyzed trans acetalization process of the chiral alcohol **3** with the trichloroacetimidate (formed after DIBAL reduction of starting material and reaction with CCl_3CN) followed by inversion of chiral centre in **2**. The six-step synthesis for

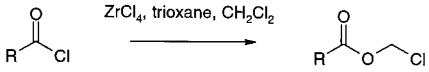
10.1021/op0255985 CCC: $22.00

the preparation of **1** was accomplished in extremely high overall yield (81%) and with only two isolations.



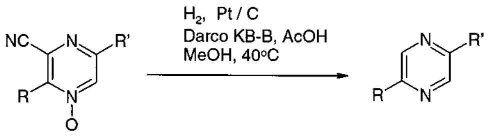
Chloromethyl Esters

A practical synthesis of chloromethyl esters from acid chlorides and trioxane or paraformaldehyde using zirconium tetrachloride as the Lewis acid has been reported by Mudryk from Bristol Myers Squibb (*Tetrahedron Lett.* **2002**, *43*, 6317). The new method is highly chemoselective and has been applied to a variety of acid chlorides.



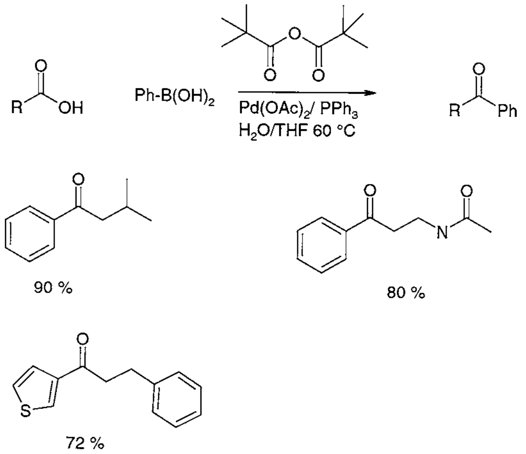
Reductive Decyanation of Pyrazinecarbonitriles

Albaneze-Walker and colleagues from Merck have reported (*Tetrahedron Lett.* **2002**, *43*, 6747) how pyrazinecarbonitriles can be decyanated by hydrogenation with platinum on carbon in the presence of activated carbon under acidic conditions. Pyrazine carbonitrile-*N*-oxides undergo a stepwise reduction to the deoxypyrazinecarbonitriles followed by decyanation to give the pyrazines in good yields.



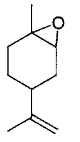
Palladium-Catalyzed Synthesis of Aryl Ketones from Boronic Acids and in Situ Activated Carboxylic Acids

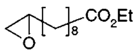
A new palladium-catalyzed cross-coupling reaction between arylboronic acids and mixed anhydrides, generated in situ from carboxylic acids and pivalic anhydride has been reported by L. J. Goossen et al. (*Eur. J. Org. Chem.* **2002**, 3254). Optimization of the new method led to a convenient one-pot ketone synthesis directly from carboxylic and boronic acids in the presence of different (phosphane) palladium complexes in wet THF at 60 °C. The use of 2−3 mol equiv of water strongly facilitated the reaction turnover. Too much water resulted in lower yield. An electron-rich phosphane was found to increase the reactivity of the palladium atom for the activation of the anhydride. Three molar % of the palladium catalyst formed in situ from palladium acetate and a phosphine was found to be necessary for a reasonable turnover. Pivalic anhydride was found to be the best anhydride for the in situ generation of mixed anhydrides as pivalic anhydride itself does not react with the boronic acid under the reaction conditions due to steric hindrance. Under the optimized reaction conditions a variety of different aryl ketones was obtained in good-to-excellent yields. The reaction is generally applicable to a wide range of substrates, and most functional groups are tolerated, although the reaction requires 16 h at 60 °C to go to completion.



Urea−Hydrogen Peroxide/Hexafluoro-2-propanol: An Efficient System for Catalytic Epoxidations

Hexafluoro-2-propanol (HFIP) exhibits a unique ability to release and activate hydrogen peroxide from the urea−hydrogen peroxide adduct (UHP). UHP has been reported to be a safe source of anhydrous hydrogen peroxide. It is a white crystalline solid formed by strong hydrogen bonding between urea and hydrogen peroxide in a 1:1 proportion. UHP is easily handled, without the need for special precautions. UHP is also commercially available and can be stored at +4 °C for months without any change in oxygen content. Due to this high stability, and rather low reactivity, it has been reluctantly used in chemical synthesis. Now D. Bonnet-Delpon et al. (*Eur. J. Org. Chem.* **2002**, 3290) have reported the activation of UHP with hexafluoro-2-propanol for the epoxidation of alkenes. Activated alkenes are epoxidized with UHP in hexafluoro-2-propanol without any catalyst. The epoxidation of cyclooctene is complete in 10 h at 25 °C. With 30% hydrogen peroxide the reaction was still incomplete after 24 h. For unactivated alkenes an efficient catalytic method was developed utilizing perfluorodecan-2-one in 3−5 mol % with 1.2 mol equiv of UHP with regard to the alkene in HFIP. With this new method complete conversion of diand trisubstituted alkenes was observed at temperatures between 25 and 40 °C.


79 %



91 %

Selective Transformations of *β*-Keto Esters Promoted by Basic Ion-Exchange Resins

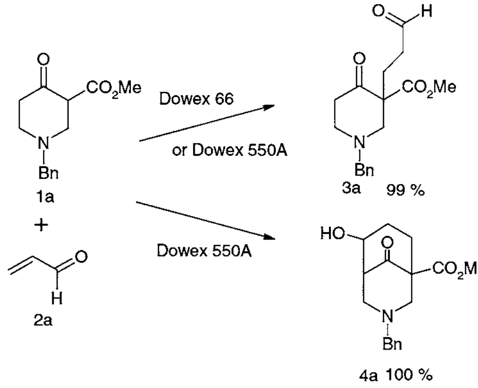
In recent years the development of environmentally friendly heterogeneous reagents and catalysts has received much attention. In this context, a large number of new inorganic, organic, or hybrid heterogeneous catalysts have been found to be efficient in many important organic transformation including the Michael addition. Quite surprisingly, the commercially available, cheap, and environmentally benign basic ion-exchange resins have not been the center of much interest as Michael addition promoters.

Depending on the nature of the Dowex basic ion-exchange resin, the group of J. Rodriguez (*Eur. J. Org. Chem.* **2002**, 3359) found that cyclic *β*-keto esters react with α,*β*-unsaturated aldehydes to give either the corresponding Michael adducts **3** or the highly functionalized bicyclo[3.3.1] nonanes **4** in a one-pot Michael addition−intramolecular aldolisation sequence.

When the weakly basic Dowex 66 resin was used in 100 wt % the piperidone **1a** as its hydrochloride salt was transferred quantatively to the corresponding Michael adduct **3a** with acrolein in methanol at room temperature. No further aldolization reaction took place even at prolonged (48 h) reaction time or when higher amounts of resin were used.

When the more strongly basic resin Dowex 550A was used, **3a** was found to be the sole product when 200 wt % or less of the resin was used. When 300 wt % or more was used, the azabicyclic derivative **4a** was the sole product as a 1.3:1 mixture of axial and equatorial epimers.

Interestingly, the closely related Amberlite resins IRA 410 and the more strongly basic IRA 400 were found to be totally inactive for this transformation even after activation with NaOH solution.



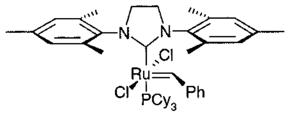
Ru-Catalysed Olefin Cross Metathesis of Styrenes as an Alternative to Cross-Coupling Reactions

Functionalized styrenes are important building blocks. Therefore, their preparation needs to be flexible concerning variations in the olefinic and in the aromatic part. Since the olefinic part often is subjected to further manipulation, it is important that the alkene geometry is controlled during the coupling reaction. The Heck reaction and cross-coupling reactions such as the Suzuki reaction have often been employed because of the availability of aryl halides and boronic acids as well as for the excellent control of olefin geometry. However the latter method is often limited by the access of coupling partners (vinyl halides and triflates). The Heck reaction employs simple olefins; however, the reactions works best with olefins with electron-withdrawing groups.

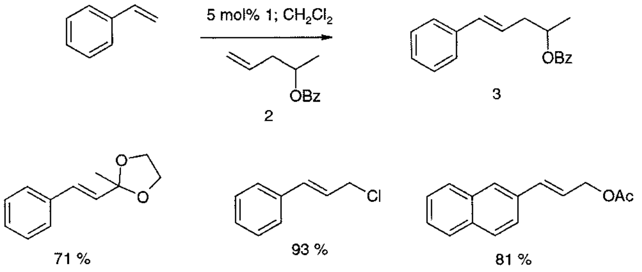
Styrenes have been one of few classes of compounds which have been showing high selectivity in the olefin cross metathesis (CM). Therefore, increasing the efficiency and substrate scope of styrene CM reaction could be an alternative to Heck and other cross-coupling reactions for the synthesis of highly funtionalized styrenes.

The group of R. Grubbs (*Adv. Synth. Catal.* **2002**, *344*, 634) has investigated the olefin CM reaction of styrenes with the imidazolylidene-based catalyst systems such as **1** which has lately been found efficient in other metathesis reactions.

The reaction of styrene with 2 equiv of homoallylic benzoate **2**, catalyzed by 5 mol % of **1** afforded the substituted styrene **3** in 81%. The compatibility of the benzoate functionality, which may eliminate under basic Wittig conditions, is very interesting. It was also found that the reaction also tolerates allylic chlorides and acetates; fully substituted allylic carbons were also tolerated by the reaction. In addition, aryl bromides and vinyl pyridines were found to be suitable substrates for the reaction.



1



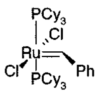
High Turnover Numbers with Ruthenium-Based Metathesis Catalysts

The past few years have seen a significant resurgence of interest in olefin metathesis chemistry. Although some very powerful catalysts have been developed, the relatively high costs of ruthenium, coupled with the high catalyst loading generally employed (typically 0.1−5 mol %), render these systems disadvantageous for use in industrial applications. J. C. Mol et al. (*Adv. Synth. Catal.* **2002**, *344*, 671) have investigated different metathesis catalysts for maximizing the turnover number (TON), a figure that is rarely reported for metathesis catalysts.

Like all metathesis reactions the metathesis of 1-octene is fully reversible. However, when the product ethane is allowed to escape, the reaction is rendered essentially irreversible. Metathesis catalysts also bring about nonproductive metathesis of the product. Because all of these events take place simultaneously, the total turnover number for a given catalyst cannot be calculated with any degree of certainty. Moreover, the active species is the phosphine-dissociated species whose concentration is unknown at any given time. Thus, the only meaningful figure is the effective TON being the total number of 1-octene molecules being transformed per molecule of catalyst.

The effective TONs for the first-generation Grubbs' catalyst **1** and the second-generation catalysts **2a** and **2b** were determined covering a wide temperature range (22−122 °C) for the metathesis of 1-octene. The second-generation catalysts display much higher TONs (up to 640 000) than the first-generation catalyst. Similar high turnover numbers were also reported for other substrates such as methyl oleate or diethyl diallylmalonate. These results strongly imply that the amounts of catalyst used normally for the metathesis reaction are far higher than actually necessary.

For the catalyst **2a** a performance jump at approximately 50 °C was observed that was not seen with **1** or **2b**. Given that metathesis reactions using ruthenium catalysts are normally performed in boiling dichloromethane, better results might be anticipated with a higher-boiling solvent.



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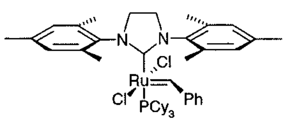
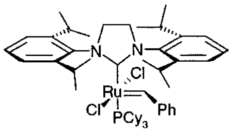


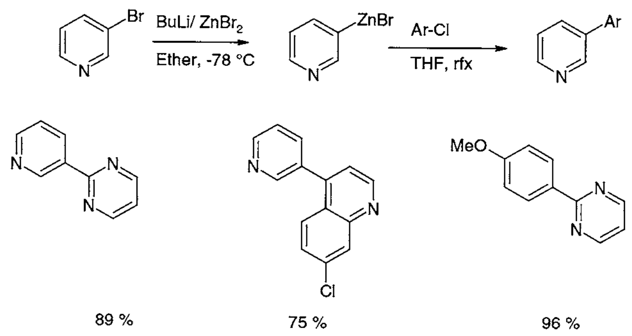
2a



2b

Regioselective Cross-Coupling Reactions of Halopyridines and Pyrimidines

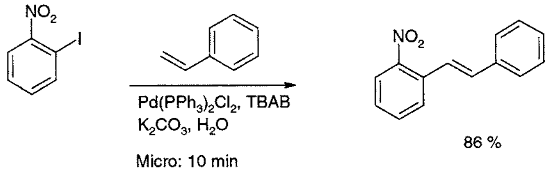
Bipyridines are frequently synthesized by transition-metal-catalyzed cross-coupling reactions., while in contrast pyridylpyrimidines are often prepared via the classical route. N. M. Simkovsky et al. (*Perkin Trans. I* **2002**, 1847) have now reported a high-yielding cross-coupling protocol for the preparation of bipyridines, pyridylpyrimidines, and pyridylquinolines with excellent regiocontrol employing Negishi conditions. The method could also be extended to bromoanisole giving arylated heterocycles in good-to-excellent yields. The major drawback with the method is that the lithiation of pyridine with *n*-BuLi has to be performed in diethyl ether while a solvent switch to the higher-boiling THF has to be performed for the cross-coupling reaction.



Microwave-Accelerated Homogeneous Catalysis in Organic Chemistry

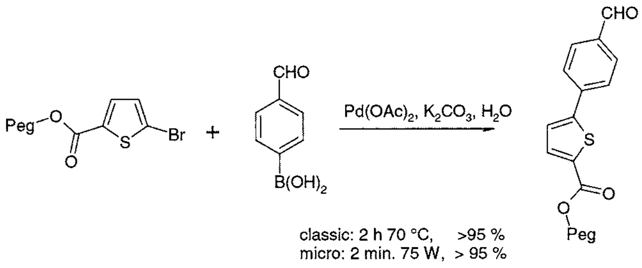
M. Larhed et al. (*Acc. Chem. Res.* **2002**, 35, 717) have summarized the latest results utilizing microwave heating in homogeneous transition-metal-catalyzed reactions. The application of microwaves as an efficient heating for organic reactions was recognized in the mid-1980s. In some cases very high yields and clean reactions have been obtained using small amounts of energy in comparison to traditional ways of heating. The majorities of the microwave-promoted reactions that rely on homogeneous catalysis are catalyzed by palladium and are of four different types: Heck reactions, Sonogashira reactions, cross-coupling reactions, and allylic substitutions.

Heck reactions are very versatile but normally need high temperatures and long reaction times. It has been shown that with microwave heating it is possible to reduce the reaction times from hours to minutes. Also microwave-heated Heck reactions in pure water or aqueous systems have been reported, which is a safe, economical, and environmental friendly alternative.



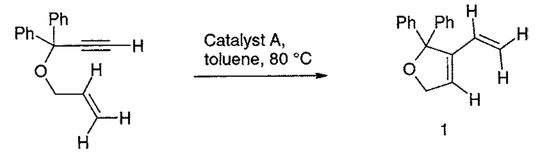
Similarly, the Sonogashira reactions were accomplished in reduced reaction times with microwave heating.

The Suzuki coupling, as one of the most versatile cross-coupling reactions, has received much interest. Here, for instance, a solid-supported reaction been developed in water using PEG as a soluble support. The reaction time was down to 2 min from 2 h under conventional heating. These very short reaction times suggest the possibility to use microwaves as the heating source in continuous tube reactors.

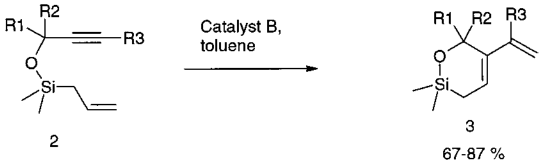


Imidazolium and Imidazolinium Salts as Carbene Precursors for Ruthenium-Catalyzed Diene- and Enyne Metathesis

P. H. Dixneuf et al. (*Adv. Synth. Catal.* **2002**, *344*, 585) have summoned up their latest results in diene and enyne metathesis reaction with in situ prepared catalytic systems. The first system prepared in situ from air-stable components was the system **A** from [RuCl$_2$(*p*-cymene)] $_2$, 1,3-bis(mesityl)imidazolium chloride (ImMesCl), and cesium carbonate in the mol ratio 1:2:4. This catalytic system **A** was able to perform enyne metathesis in toluene at 80 °C to give five- and six-membered ring derivatives with a 1,3-diene unit. With 0.5 mol % it was possible to obtain **1** in 93% isolated yield.



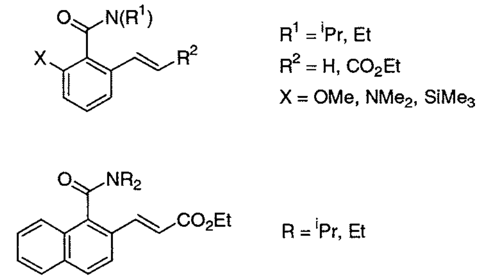
It was observed that the imidazolinylidene ligand leads to a more active catalytic system than that of the 1,3-bis(mesityl)imidazolylidene system. From [RuCl$_2$(*p*-cymene)] $_2$, 1,3-bis(mesityl)imidazolinium chloride (ImH$_2$MesCl), and cesium carbonate in the mol ratio 1:2:4 the catalyst system **B** was prepared. For the cyclization of siloxane the catalyst system **B** appeared to be more active than the catalyst **A**. After 24 h in refluxing toluene catalyst **B** gave complete conversion of the siloxanes **2**, whereas the system **A** only gave 60% conversion.



One advantage of the dienes with the general structure **3** consists of their inertness toward further metathesis and polymerisation. They can be used for further reactions such as the Diels–Alder reaction or oxidative desilylation to the corresponding diols.

Kinetic Resolution of Atropisomers

Atropisomers (e.g., BINAP, BINOL) are commonly used as asymmetric ligands for catalysis, but are difficult to make, other than via resolution methods. A new method of kinetic resolution using Sharpless asymmetric dihydroxylation has achieved excellent separation of aromatic amides with two ortho substituents, where one substituent is an olefin (Rios, R. et al. *J Am. Chem. Soc.* **2002**, *124*, 10272). The amides separated are shown below:

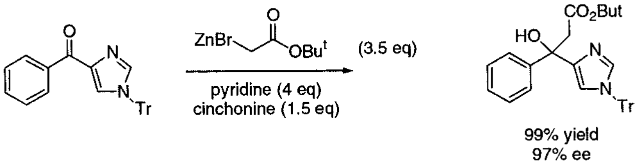


Surprisingly, with some substrates the oxygens in the diol product appear to have been derived by delivery to the olefin face closest to the bulky diisopropylamido group, and the selectivity is dictated by initial olefin geometry.

Asymmetric Reformatsky Reaction

Although there have been several reports of asymmetric Reformatsky reactions, they have either not been general (i.e., only work with aromatic aldehydes), or enantioselectivity has not been high. A recent report (Ojida, A. et al. *Org. Lett.* **2002**, *4*, 3051) describes the asymmetric Reformatsky reaction of aldehydes and ketones in high selectivity.

The best catalysts are the cinchona alkaloids, but enantioselectivity is enhanced by the addition of pyridine. Surprisingly other amines do not work as well. Perhaps catalyst is not the correct term, since ee could also be enhanced by having more then one mole of alkaloid present.

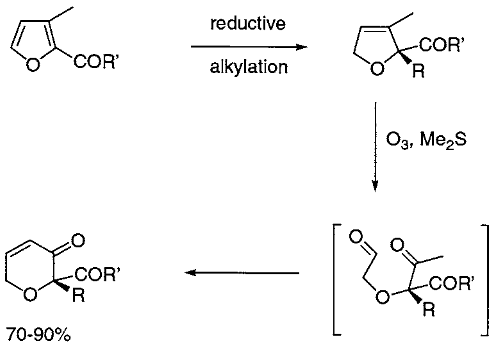


Synthesis of Enantiopure Dihydropyranones

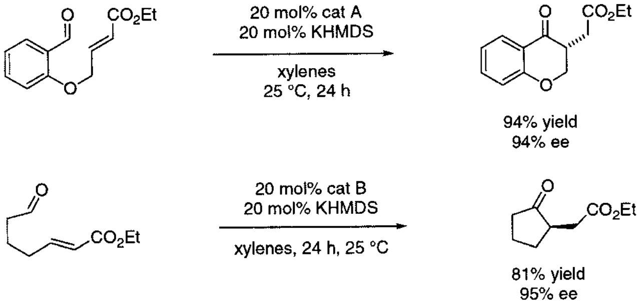
Stereoselective Birch reduction has been widely studied by the group of Donohoe at Manchester and subsequently Oxford, UK. This process has now been adapted to ring-expand furans to dihydropyranones, via ozonolysis and aldol condensation of the resultant intermediates. (Donohoe, T. J. et al. *Org. Lett.* **2002**, *4*, 3059).

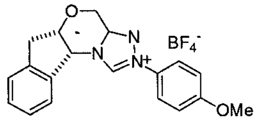
Intramolecular Asymmetric Stetter Reaction

The Stetter reaction—the addition of an aldehyde to an unsaturated nitrile or carbonyl compound—is a useful method of synthesis of 1,4-dicarbonyl compounds. Only one asymmetric variant, however, has been reported (Enders, D. *Helv.*



Chim. Acta **1996**, *79*, 1899). A recent report, however, describes the synthesis of a range of chiral triazolium salts which catalyse the asymmetric Stetter reaction (Kerr, M. S. et al. *J Am. Chem. Soc.* **2002**, *124*, 10298).





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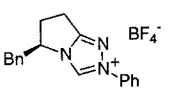
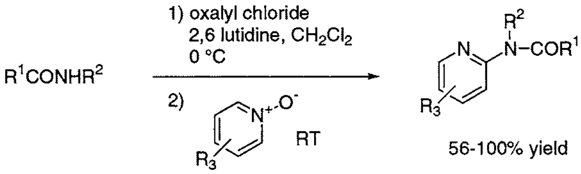


B

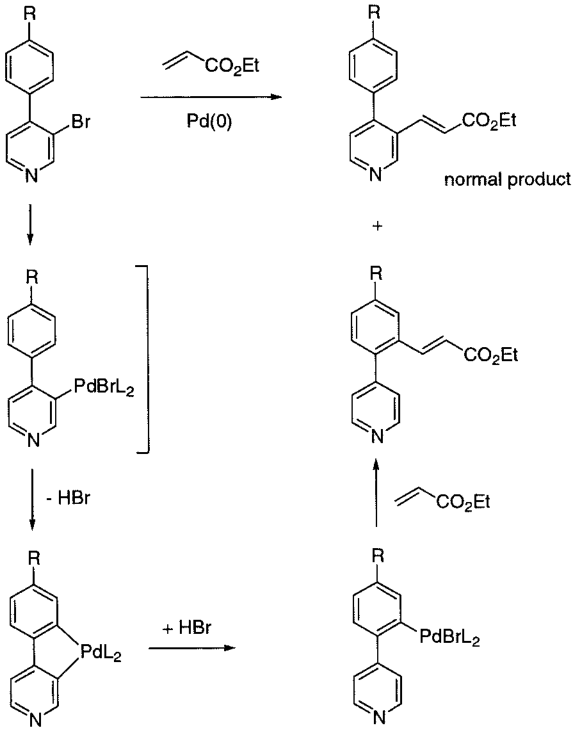
Mild Method for in Situ Reaction of Imidoyl Chlorides

Medicinal chemists at Merck (U.S.A.) have discovered that imidoyl chlorides can be generated by treating secondary amides with oxalyl chloride in dichloromethane at 0 °C in the presence of lutidine (Manley, P. J. et al. *Org. Lett.* **2002**, *4*, 3127). They can then be reacted with pyridine *N*-oxides to give 2-amino pyridine derivatives.



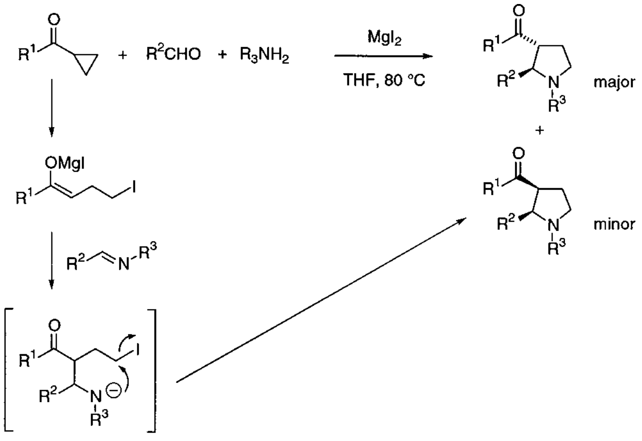
Unusual Byproducts in the Heck Reaction

The group of Gallagher at Bristol has found that, along with the normal Heck coupling product, certain biaryl bromides give abnormal products where the palladium has crossed over to the adjacent ring. This seems to be favoured by electron-withdrawing substituents (Karig, G. et al. *Org. Lett.* **2002**, *4*, 3115). When R = NO$_2$, the products are in a 3:1 ratio, with R = H$_2$, 7:1, and **12** = OMe a 10:1 ratio. Crossover can also occur from the phenyl ring to the pyridine in suitable systems.



Novel Three-Component Synthesis of Substituted Pyrolidines

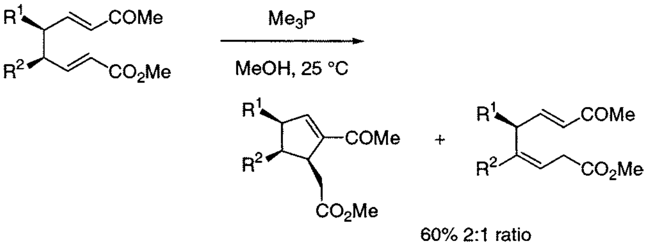
A group at Acadia Pharmaceuticals in Denmark have discovered a new one-pot procedure for the conversion of a cyclopropyl ketone, an aldehyde, and an amine to a pyrrolidine derivative (Bertozzi, F. et al. *Org. Lett.* **2002**, *4*, 3147). The reaction, catalysed by metal iodides, is thought to proceed via critical ring opening of the cyclopropane followed by reaction with an imine formed from the other two reactants. Generally the anti products are preferred or, with some substituents, are the sole product.



Vinylogous Baylis–Hillman Reaction

There have recently been reported two papers on the intramolecular vinylogous Baylis–Hillman reaction (more accurately called the Morita–Baylis–Hillman reaction since Morita was the first to demonstrate the unique C–C bond formation process with phosphine "catalysts"). The two papers (Wang, L. C. et al. *J. Am. Chem. Soc.* **2002**, *124*, 2402 and Frank, S. A. et al. *J. Am. Chem. Soc*. **2002**, *124*, 2404) used tributylphosphine as the catalyst.

In a recent application of the methodology in total synthesis from the group of Roush (Mergott, D. J. et al. *Org. Lett*. **2002**, *4*, 3157), these conditions were found to be unsuccessful. Use of Me_3P, however, lead to successful cyclisation with control of all stereocentres. A major byproduct, however, was the product of olefin migration.



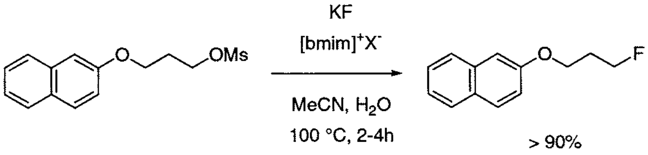
The Nitro Hunsdiecker Reaction

A group of Indian chemists has discovered that treating an α−*β* unsaturated carboxylic acid or an aromatic acid with nitric acid and catalytic AlBN in acetonitrile leads to nitrodecarboxylation (Das, J. P. et al. *Org. Lett*. **2002**, *4*, 3055). A major byproduct from the reaction of 4-methoxycinnamic acid is the aldehyde formed by oxidative clearage. The reaction is envisaged to proceed via radical intermediates.

$$ArCH{=}CH{-}CO_2H \xrightarrow[AIBN]{HNO_3} \underset{30\text{-}80\%}{ArCH{=}CHNO_2} + ArCHO$$

Introduction of Fluorine using KF in an Ionic Liquid

Halogen-exchange reactions for introducing fluorine are well-known and are practiced on large scale, but require vigorous reaction conditions. A group of Korean scientists have now reported that KF in the presence of an ionic liquid *and* an organic solvent allows replacement of ailphatic Cl, Br, OMs, and so forth under less vigorous conditions (Kim, D. W. et al. *J. Am. Chem. Soc*. **2002**, *124*, 10278). Traces of the elimination product are also formed.



CO_2 as a Separation Switch for Ionic Liquid/Organic Mixtures

Ionic liquids (ILs) have been mentioned many times in these Highlights and are the subject of intense focus, owing to their lack of volatility and usefulness as solvents in organic reactions. A challenge for large-scale work is the efficient separation of ILs from nonvolatile products or byproducts, where conventional organic solvents are to be avoided. Supercritical CO_2 can be used to extract organics from ILs without any of the IL going into the CO_2 phase (Blanchard, L. A. *Ind. Eng. Chem. Res*. **2001**, *40*, 287). It has now been shown that solutions of methanol and ILs, which are normally completely miscible, can be induced to form three phases on the addition of CO_2 (Scurto, A. M. et al. *J. Am. Chem. Soc*. **2002**, *124*, 10276). The lower liquid phase is rich in IL, the upper liquid phase is rich in methanol, and CO_2 is in the gas phase. The phase separation is pressure sensitive so that at high pressure the upper phase merges with the gas phase, but this phase *is completely free of IL.*

CO_2 reduces the dielectric constant of methanol from 37.5 (pure methanol) to 4.9 (mol fraction of CO_2 at 0.733), so that it may be impossible to dissolve IL at high CO_2 levels.

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