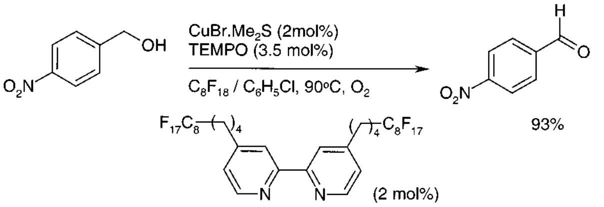
Organic Process Research & Development **2000**, *4*, 306–311

Highlights from the Literature

Some Items of Interest to Process R&D Chemists and Engineers as Selected by Trevor Laird and Stephen A. Hermitage

Although the oxidation of primary and secondary alcohols is of importance, there are surprisingly few oxidants that are catalytic and use hydrogen peroxide or oxygen as co-oxidants. Knochel et al. (*Tetrahedron Lett.* **2000**, *41*, 4343) have reported that a catalytic amount of perfluoroalkyl substituted bipyridine (2 mol%) (Scheme 1), CuBr·Me_2S (2 mol%) and TEMPO (3.5 mol%) facilitate the oxidation of various alcohols to aldehydes and ketones in a fluorous biphasic system of chlorobenzene and perfluorooctane directly with oxygen. The catalyst can be used for several runs without loss of reactivity. Wang and co-workers at Boehringer Ingelheim Pharmaceuticals have reported a practical synthesis (*Tetrahedron Lett.* **2000**, *41*, 5321) of 1,3-diaryl-5-alkylpyrazoles by a regioselective N-arylation reaction of 3,5-disubstituted pyrazoles with 4-fluoronitrobenzene. They build the pyrazole as shown in Scheme 2 by firstly condensing 3-acetylpyridine with methyl propionate in the presence of KO^{t}Bu to give the diketone as its enol tautomer. In a one-pot elaboration the reaction mixture is neutralised with HCl and conversion to the pyrazole effected with hydrazine. N-arylation was achieved by heating at 70 °C with KO^{t}Bu, DMSO and 4-fluoronitrobenzene. The group have performed the chemistry on a >500g scale. Bergmeier and Arason at The Ohio State University have reported (*Tetrahedron Lett.* **2000**, *41*, 5799) the one-pot conversion of trityl ethers into esters using the corresponding acyl chloride as the only reagent. The procedure worked well for aliphatic acid chlorides, even with secondary or benzylic trityl ethers, but was not compatible with acid sensitive functionalities (Scheme 3).

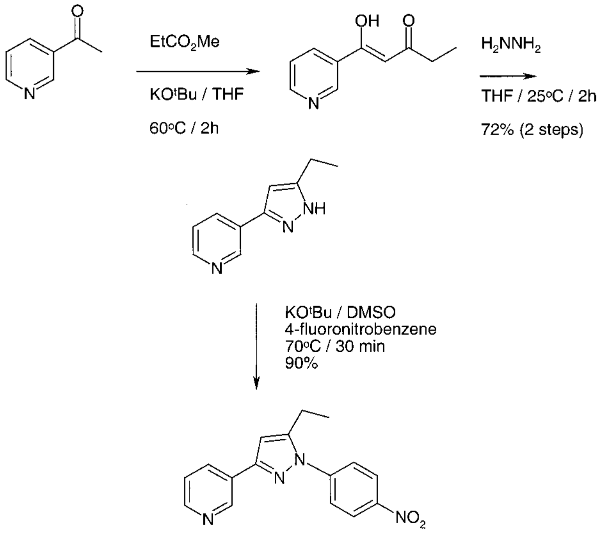
Scheme 1



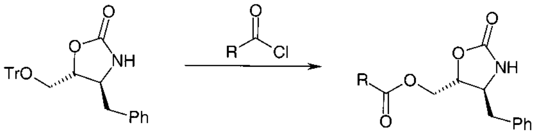
It is interesting to note the synthetic versatility of metal silanolates. Laganis and Chenard in 1984 (*Tetrahedron Lett.* **1984**, *25*, 5831) reported metal trimethylsilanolates as organic soluble equivalents for O_2^-. In their method both aryl and alkyl esters and acyl chlorides were treated with KOTMS to generate carboxylic acid potassium salts under mild *non-aqueous* conditions (Scheme 4).

Chiral diamines and their derivatives form an important class of ligand in asymmetric catalysis. These ligands have been used in epoxidations, Diels Alder cycloadditions, alkene dihydroxylations, cyclopropanations, and aziridinations. Busacca at the Boehringer Ingelheim Pharmaceutical group have reported their practical four-step method for the preparation of (1*S*)-tert-butyl-1,2-ethylenediamine (*Tetrahedron Asymmetry* **2000**, *11*, 1907) in which the intermediates are crystalline (Scheme 5). Although this approach would have a number of “issues” associated with larger-scale manufacture, the route is high-yielding and provides the chiral diamine in 99.3% ee. Marshall and Yanik report (*Tetrahedron Lett.* **2000**, *41*, 4717) the stereoselective synthesis of substituted ketopyranose subunits of polyketide natural products by intramolecular alkoxycarbonylation of δ-alkynyl alcohols. In their key reaction Pd catalysis is used to effect the reaction described in Scheme 6 with *p*-benzoquinone being used as the Pd(0) reoxidant. This reaction builds complicated functionality from simple starting materials in good yield. Conde and co-workers at

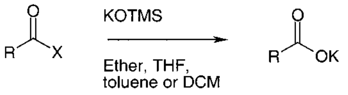
Scheme 2



Scheme 3



Scheme 4



R = alkyl or acyl
X = OR' or Cl

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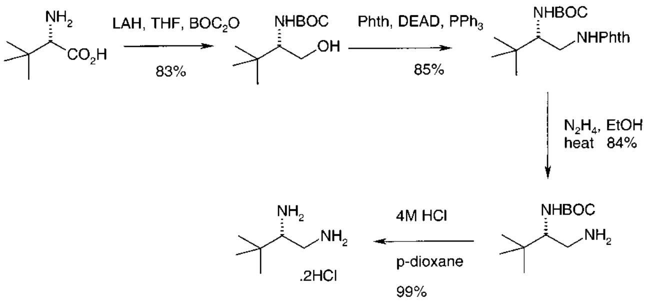
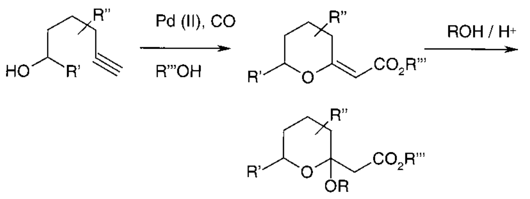
Scheme 5

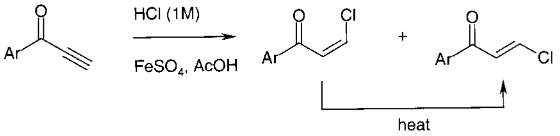


Scheme 6



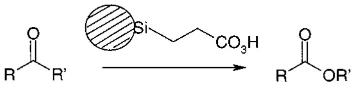
SmithKline Beecham have reported (*Tetrahedron Lett.* **2000**, *41*, 4709) the reaction of aromatic acetylenic ketones with aqueous HCl promoted by catalytic $FeSO_4$ to give a *E*:*Z* mixture of β-chlorovinylketones which isomerised almost exclusively to the *E*-β-isomer upon heating (Scheme 7).

Scheme 7



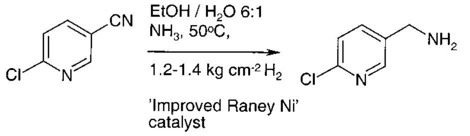
Peroxycarboxylic acids are active reagents for the Baeyer–Villiger oxidation of ketones to lactones or esters. Their use, however is often disputed on environmental and safety grounds because of the requirement of at least stoichiometric amounts in the reaction. Most peracids are also reported to have insufficient stability in solution for large-scale application. Clark and coworkers at the University of York have recently described how hexagonal mesoporous silica (HMS)-supported peroxycarboxylic acids are efficient reagents in the Baeyer–Villiger (BV) oxidation of cyclic and linear ketones to lactones and esters, respectively, at room temperature in hexane. In their report (*Synlett* **2000**, 1052) they describe how tetraethoxysilane may be co-polymerised with cyanoethyl triethoxysilane, hydrolysed with H_2SO_4, and oxidised with acidic H_2O_2 to generate the polymer-supported peracid which may be recovered after use in the BV oxidation (Scheme 8).

Scheme 8

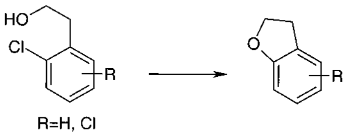


Tanaka and colleagues at the Yokohama research centre, Mitsubishi Chemical Corporation have described (*Bull. Chem. Soc. Jpn.* **2000**, *73*, 1227) the highly selective hydrogenation of 6-chloro-3-pyridinecarbonitrile (Scheme 9) using an improved Raney nickel catalyst. Their catalyst was prepared from an alloy of low nickel content (Ni 38%, Al 62%) and subjected to heat treatment in water (98 °C, 2 h). In particular the hydrogenation was performed on multi-hundred-kilogram scale to give the product amine in 86% yield and ~2% of the dechlorinated byproduct. Zhu and coworkers at Bristol-Myers Squibb have reported (*Tetrahedron Lett.* **2000**, *41*, 4011) the copper(I)-catalysed intramolecular cyclisation reaction of 2-(2'-chlorophenyl)-ethanol to give 2,3-dihydrobenzofuran (Scheme 10). Having screened a variety of solvents and bases for their reaction the optimum conditions involved treatment of the substrate with 1.25 equiv NaH followed by 5 mol % CuCl in either pyridine at 115 °C for 2 h or in toluene/EtOAc at 110 °C for 24 h with ~91% conversion. Also at Bristol-Myers Squibb Polniaszek and co-workers have reported the Claisen condensation of chloroacetic acid dianion with N-BOC α-amino acid methyl esters to give the corresponding α-chloroketones in high yield and enantiomeric excesses (*Synlett* **2000**, 902) (Scheme 11). Interestingly a modest excess (3.5 equiv) of the dianion was required to effect high conversions in the condensation. One equivalent is required to deprotonate the carbamate NH of the substrate (self-protecting the substrate to racemisation), one equivalent is required to effect the condensation, and a final equivalent is required to deprotonate the intermediate resultant β-ketoester. An interesting side reaction is also observed; the $ClCH_2CO_2Li$ produced as a consequence of NH deprotonation may react with the dianion to generate, after work up, α-chlorosuccinic acid. Marcoux, Corley and co-workers at Merck have reported (*Org. Lett.* **2000**, 2339) α-aryl ketones to react with vinamidinium hexafluorophosphate salts to give access to the corresponding 3-arylpyridines. The annulation reactions proceed in good to excellent yields with vinamidinium salts containing electron-withdrawing groups at the β-position (R″). The reaction was applied to the preparation of the COX-2 inhibitor 5-chloro-3-(4-methylsulphonyl)phenyl-2-

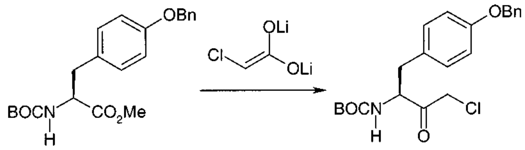
Scheme 9



Scheme 10

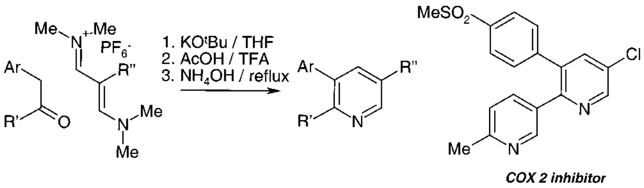


Scheme 11

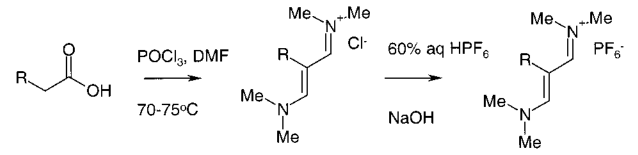


(2-methyl-5-pyridinyl)pyridine (Scheme 12) as well as that of a series of analogues.In a separate publication the group describe (*J. Org. Chem.* **2000**, *65*, 4571) the preparation of the vinamidinium species as depicted in Scheme 13. The hexafluorophosphate salts are easily handled and provide an alternative to the more commonly used perchlorate and chloride salts of organic cations. Endo and Douglas from Bristol Myers Squibb have reported a practical preparation of 3-chloro-4-methoxybenzylamine hydrochloride (*Synth. Commun.* **2000**, *30*, 2609), an important synthetic building block in pharmaceutically active molecules especially in the cardiovascular area. In their procedure sulfuryl chloride selectively chlorinates 4-methoxybenzylamine with very little polychlorinated byproducts being observed. The product is isolated as its HCl salt (Scheme 14).

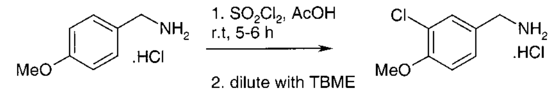
Scheme 12



Scheme 13



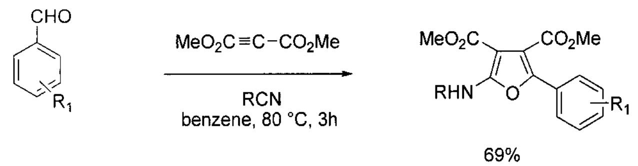
Scheme 14



Ripin and co-workers at Pfizer have reported a safe scalable method for the oxidation of carbon−boron bonds using Oxone® [$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$] (*Tetrahedron Lett.* **2000**, *41*, 5817). They have used this protocol in the oxidative work up of hydroboration reactions circumventing the more traditional hydrogen peroxide approach. The oxidation could be performed at lower temperatures and is dose-rate controlled. In addition to these safety features Oxone® is a solid which allows for accurate weighing and charging.

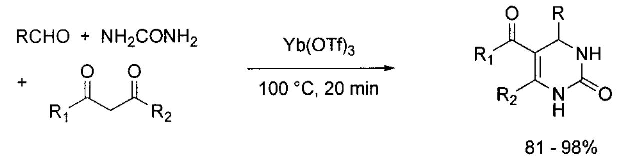
Multicomponent reactions seem all the rage these days, and thus the search for new processes continues. A group at the Regional research laboratory at Trivandrum, India, report that isocyanides react with acetylene dicarboxylic esters and aldehydes to give aminofurans (Nair, V. et al. *Chem. Commun.* **2000**, 1019), see Scheme 15. It will be interesting to see if this can be extended to other functional groups in the future.

Scheme 15



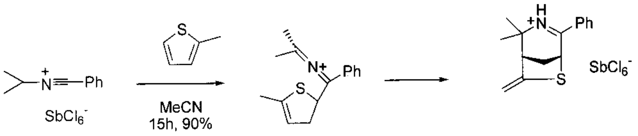
On a similar theme, the Biginelli reaction is found to work best with Ytterbium triflate catalysis under solventless conditions (Ma, Y. et al. *J. Org. Chem.* **2000**, *65*, 3864), see Scheme 16.

Scheme 16



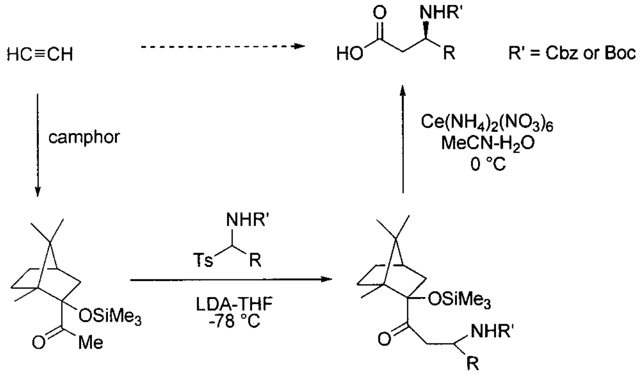
An unusual reaction leading to a novel heterobicyclic system occurs via an ene reaction of a nitrilium salt to give an azoniaallene followed by fast cyclisation to the product (Henninger, J. et al. *J. Org. Chem.* **2000**, *65*, 3569), Scheme 17.

Scheme 17



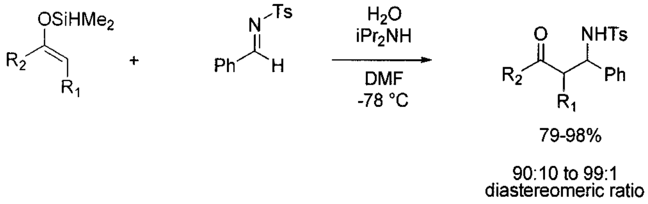
The Mannich and similar reactions (aza-aldol reactions) are much less used in synthesis than the aldol reaction for two reasons: first, the poorer electrophilicity of the azomethine function relative to the carbonyl, and second, the preference of enolisable azomethines to undergo α-deprotonation rather than addition. One strategy to overcome these problems has been to use trialkylsilylenol ethers or ketene acetals as nucleophiles, and this has been exploited in enantioselective Mannich reactions by the group of Kobayashi (*Chem. Rev.* **1999**, *99*, 1069). A newer approach, involving the use of arylsulphonylalkyl carbonates has been reported from the group of Palomo at San Sebastian, Spain (Palomo, C. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063). The chiral auxiliary method uses acetylene and camphor as the key building blocks in a *β*-amino acid synthesis (Scheme 18).

Scheme 18



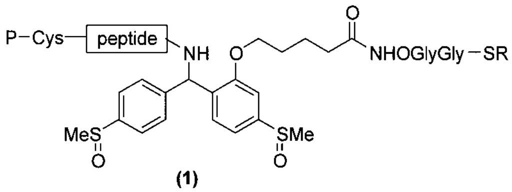
The Mannich reaction can also give good diastereoselectivity under certain conditions. The group of Hosomi at Tsukuba in Japan have found that dimethylsilylenolates react with *n*-sulphonylimines under basic conditions to give β-amino ketones in up to 99:1 *anti*:*syn* ratios (Miura, K. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1958), see Scheme 19.

Scheme 19



The presence of water is crucial for high yields. Since water is generated in the reaction of aldehydes with $TsNH_2$ to prepare the imine, it is feasible to simply mix the silylenol ether, aldehyde, and $TsNH_2$ together—surprisingly no aldol adduct is formed. It is suggested that water causes a small amount of Me_2HSiOR to be formed and this acts as a catalyst in the process.

Although solid-phase synthesis of peptides is used on a small scale for up to approximately 50 amino acids, side products accumulate during chain assembly and deprotection. As a result, and for cost reasons, protein synthesis is dominated by approaches that are more convergent, such as the assembly of smaller peptide fragments. A technique known as native chemical ligation uses a highly selective coupling of two unprotected peptides, one of which bears an N-terminal cysteine group, while the other contains a C-terminal thioester group. Usually, these reactions are carried out in solution and as many as four peptide fragments have been linked sequentially, but often yields after HPLC purification are low. In principle, performing ligation reactions on a solid phase would eliminate the need for chromatography, but the method has been constrained by the complexity of selecting a compatible set of chemistries, resin linker, and protecting groups. With the new linker (**1**) (Figure 1), a peptide containing all 20 natural amino acids and two disulplude bonds has been synthesised on solid support and purified in 20% overall yield (Brik, A. et al. *J. Org. Chem.* **2000**, *65*, 3829). The strategy should facilitate the synthesis of large polypeptides.

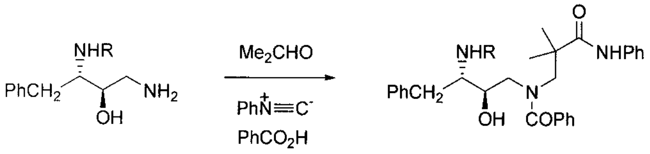


(1)

Figure 1.

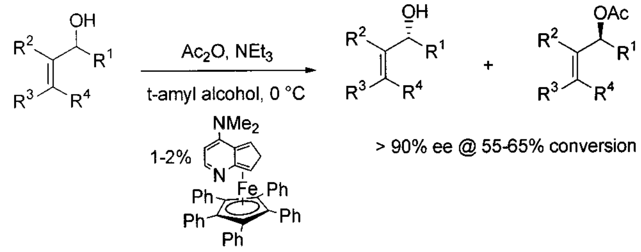
Steve Stinson's articles in *Chemical and Engineering News* are always interesting because much of the discussion is of industrial chemistry, most of which has not yet been published but only presented in lecture format. In a recent issue (*Chem. Eng. News* **2000**, 59), he describes industrial and academic work presented at conferences including work carried out on the Ugi reaction at Pharm-Eco laboratories on the synthesis of HIV protease inhibitor-type compounds (Scheme 20).

Scheme 20



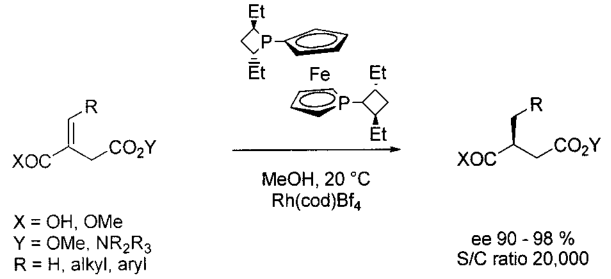
In the mid to late 1990s several groups reported on non-enzymatic catalysts for acylation and thus kinetic resolution of alcohols. The general order of reactivity was arylalkylcarbinols > cycloalkanols > propargylic > allylic alcohols. The group of Fu at MIT have now found (Bellemin-Laponnaz, S. et al. *Chem. Commun.* **2000**, 1009) that most families of allylic alcohols can be kinetically resolved with good selectivity using a planar-chiral DMAP derivative as catalyst, with selectivity factors in the range 5−80 (Scheme 21).

Scheme 21



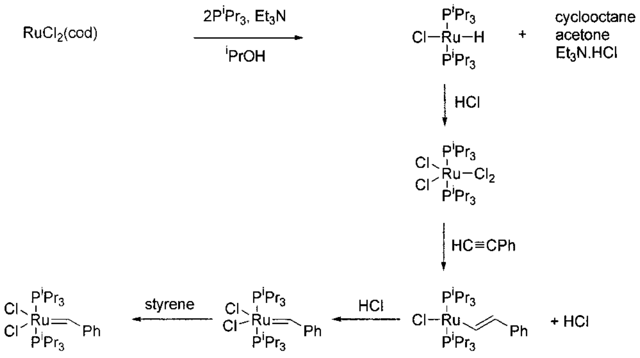
The attainment of both high catalytic efficiency and high enantioselectivity remains a formidable challenge in industrial organic chemistry. New hydrogenation catalysts from the group of Burk at Chirotech Technology (Berens, U. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1981) combine both assets and demonstrate superiority over previous systems in the rhodium-catalysed hydrogenation of itaconate and succinate derivatives (Scheme 22). The phosphetane catalysts (named Ferro TANE ligands) are conveniently prepared from chiral 1,3-diols via the cyclic sulphates.

Scheme 22



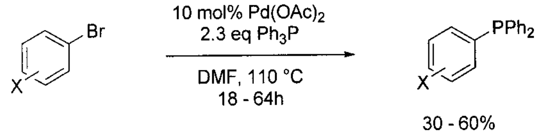
A simple one-pot procedure for the synthesis of ruthenium benzylidenes (Grubb's catalyst) has been developed by workers at Ciba Speciality Chemicals in Basel (van der Schaaf, P.A. et al. *Chem. Commun.* **2000**, 1045). The method involves reacting a novel 14-electron ruthenium hydride, prepared from $RuCl_2$(cod) and two bulky phosphines in boiling isopropanol (no hydrogen!), with hydrogen chloride, an alkyne, and styrene. The mechanism is as shown in Scheme 23. The catalysts are, of course, used in olefin metathesis.

Scheme 23



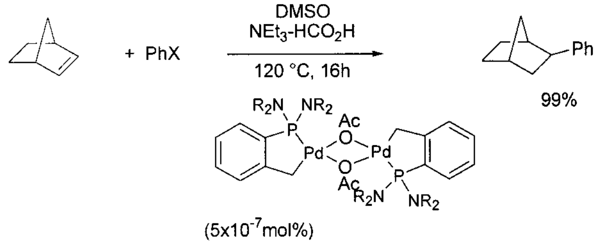
A general method of synthesising aryl phosphines by palladium-catalysed phosphination of substituted aryl bromides using triarylphosphines as the phosphinating agent has been developed. The method tolerates ketone, aldehyde, ester, nitrile, ether, and chloride functional groups (Kwong, F. Y. et al. *Chem. Commun.* **2000**, 1069). The catalyst is either $Pd(Ph_3P)_4$ or $PdOAc_2$ (Scheme 24). Although yields are only moderate, this one-step method is more attractive than previous multistep options.

Scheme 24



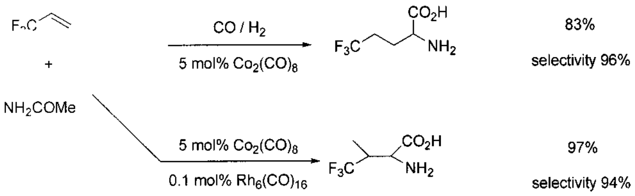
Attempts to achieve industrial scale palladium-catalysed C—C bond formation rely on good catalyst turnover and on the ability to use arylchlorides rather than iodides (e.g., in the Heck reaction). Phospha palladacycles often give turnover numbers (TON) in the 100,000 range and by fine-tuning the phosphorus ligand figures greater than 200,000 could be achieved. A recent report from the group of Buono at Marseilles (Brunel, J. M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1946) indicates that new catalysts, which are stable to air, moisture, and heat, give turnover numbers of 196,000,000 and turnover frequency of 12,000,000 in the Heck reaction, provided DMSO is used as a solvent (Scheme 25). Iodides work best, but bromides and triflates can also be used. Other aryl iodides give similar TON under similar conditions.

Scheme 25



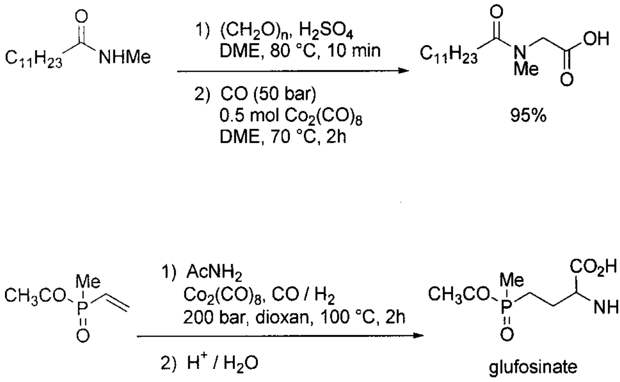
Atom efficient, multicomponent reactions that lead to high-value products from inexpensive starting materials are desirable in industrial methods of synthesis and for environmental reasons. Amido carbonylation is a process which has attracted attention recently, and a new review from the group of Beller at Rostock (*Angew. Chem., Int. Ed.* **2000**, *39*, 1011) shows the potential of the methodology in the synthesis of α-amino acids. Some useful examples are shown in Scheme 26.

Scheme 26



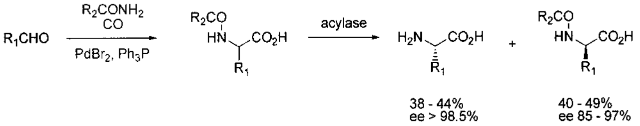
Hoechst has used the methodology in the pilot plant manufacture of *N*-acylsarcosines in a two-step process (Scheme 27) and in the synthesis of the herbicide glufosinate.

Scheme 27



The newer palladium catalysts are more active and can be combined with enzyme resolution to produce a range of enantiomerically pure amino acids (Scheme 28).

Scheme 28



For the future, asymmetric amidocarbonylations are the objective—at present Beller's group report a 10% ee with chiral phosphine ligands and that groups at Gottingen and Hoechst Marion Roussel (now Aventis) have also achieved some success but still with low ee's.

Soluble polymeric catalysts prepared from poly (*N*-isopropylacrylamide) have a lower critical solution temperature (LCST) which allows them to quantitatively phase separate from water on heating, and this property has been used to design water soluble catalysts which can easily be recycled (Bergbreiter, D. E. et al. *J. Amer. Chem. Soc.* **1996**, *118*, 6092). Adaptation of these materials by incorporation of complexing groups such as hydroxamic acids can lead to polymers that can quantitatively recover metals from water—as yet this has only been tried successfully with iron and copper.

(Bergbreiter, D. E. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1040). The method can be extended to recovering metals from organic solvents by using a fluorous phase soluble hydroxamic acid polymer, and extracting the metal into the fluorous phase. Thus iron can be quantitatively extracted from methanol using a perfluorinated ether (FC-77) as extraction solvent, and the polymer could be reused after removal of the iron by EDTA treatment. These polymers may have value in the removal of precious metals from organic substances in final step drug manufacture or in effluent treatment.

More than 1% of the total global energy consumption is currently used for ammonia production and, consequently, a continuous effort has been made to improve both the Haber−Bosch process and the promoted iron-based catalyst discovered by Mittasch and co-workers. The results have a significant impact on the consumption of fossil fuels. Despite much recent work, the preferred industrial catalyst is still an iron catalyst similar to that developed almost 100 years ago. It has now been found that ternary nitrides (Fe_3Mo_3N, Co_3Mo_3N and Ni_2 Mo_3N) exhibit high catalytic activities in ammonia synthesis and that promotion of Co_3Mo_3N with caesium results in higher activity than the commercial multi-promoted iron catalyst (Jacobsen, C. J. H. *Chem. Commun.* **2000**, 1057)

A new generation of three-dimensional plant design software is helping chemists and chemical engineers to design new production facilities in shorter time by automating the creation of complex engineering drawings. This helps to speed construction of new plant by minimising design problems. For more details see “Building a Better Chemical Plant” (Witecki, W.S. et al. *Chemical Innovation* **2000**, 31).

Finally, if you are a reader who likes to write papers, it is recommended that a review article by F. M. Menger on Gemini Surfactants is consulted on how to make a potentially humdrum topic seem very glamorous (Menger, F. M. et al. *Angew. Chem., Int. Ed.* **2000**, *39*, 1907). The review is presented for the general reader with no knowledge of colloid chemistry and is full of “quotable” comments. In his concluding remarks he compares writing a review to something like preparing a buffet dinner:

“Multiple dishes are set forth, and the hungry can select or not select; consume as presented or enhance with spices and sauces; come back for more or resist the temptation. With both buffets and reviews, the hope is that the participant ends up reasonably content. There is, however, a philosophic difference between buffets and reviews. In a buffet, the diner will quickly become sated and ready to leave. With a well-written review, at least a few readers might want to continue on, perhaps for many years.”

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