Highlights from the Literature

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

As we head into a new millennium process R&D chemists must continue to produce syntheses that are simple, safe, reliable, efficient, and environmentally sound. This is a tough challenge as the structure of target molecules is becoming increasingly more complex. To achieve simplicity, reliability, and efficiency in new processes, the fundamentals of chemical reactivity and selectivity must be well understood. Designing new reactions for old, eliminating side reactions, and making synthetic methodology more general and accessible on scale are all themes and challenges for the 21st century. Not only must we invent solutions to new chemical problems, but we must also learn from our past experience and try not to "re-invent the wheel". For example, many "older reactions" (such as the aldol condensation and Diels Alder reaction) have had a "modern day" twist added to broaden the scope of their synthetic utility.

A publication by Abbott Laboratories (*Tetrahedron Lett.* **1999**, 7175) concerning the synthesis of endothelin antagonist ABT-627 (Figure 1) exemplifies the necessity to "invent" new chemistry. They report a novel cyclisation strategy (Scheme 1) of an *E*-oxime ether using TMSOTf in the presence of tributylamine at ambient temperature to give diastereomeric 1,2-oxazine products in a 9:1 ratio. The stereochemistry at the newly formed sp^3 stereocentres are directed by the one sp^3 piperonyl (Pip) stereocentre in the starting material as a consequence of a chairlike transition state (Figure 1). The N−O bond of the product is subsequently cleaved and the product amino alcohol elaborated to the chiral pyrrolidine.

To highlight the fact that new drug entities are becoming more complex in structure, a group at Searle have recently disclosed an enantioselective synthesis of a dual 5-HT_4/5-HT_3 serotonergic azanoradamantane SC-52491 (*Tetrahedron* **1999**, 11787). Their approach utilises a number of classical organic transformations, some of which are outlined in Scheme 2. An asymmetric Diels−Alder reaction between cyclopentadiene and fumaric acid diethyl-(*S*)-lactate ester in triethylamine as solvent furnished the cycloadduct **1** in excellent yield and 91−95% diastereomeric excess. Saponification, iodolactonisation followed by functional group interconversion gave the amide **2** which was converted to the amine **3** by Hofmann-type rearrangement using hydroxytosyloxy iodobenzene. Amine **3** was converted to the alkene **4** prior to ozonolysis with reductive work up and acidification to give the lactone **5**. Ring-opening of **5** with ammonia gave amide **6**. Reduction with borane followed by functional group manipulation gave the azanoradamantane amine **7**. Carbonyldiimidazole (CDI) coupling with 4-amino-5-chloro-2-methoxybenzoic acid in DMF followed by conversion to the crystalline hydrochloride salt gave SC-52491 in >99% ee in a 15-step sequence in 12% overall yield.

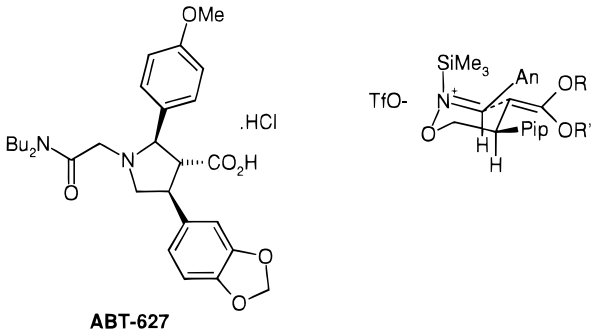

Figure 1.

Ma et al. at Abbott Laboratories have demonstrated that asymmetric dipolar cycloaddition reactions of azomethine ylids and chiral α,β-unsaturated *N*-acyloxazolidinones provide a fast and synthetically efficient route into chiral 3,4-disubstituted pyrrolidines (*Tetrahedron Asymmetry* **1997**, 883). These chiral pyrrolidines are common building blocks for a variety of natural and unnatural compounds possessing biological acivity. One example of the cycloaddition reaction is shown in Scheme 3. Although the diastereoselectivity is modest, the yields are excellent and the group have demonstrated the method on multigram scale.

A group at the R.W. Johnson Pharmaceutical Research Institute have recently published (*Tetrahedron Lett.* **1999**, 7721) an enantioselective hydrogenation of a chiral enamine to produce a key building block required in the preparation of the orally active antagonist of the platelet fibrinogen receptor (GPIIb/IIIa antagonist) RWJ-53308 (Scheme 4). The enantiomerically pure enamine is prepared by heating methyl nicotinoylacetate and (*S*)-1-(4-methoxyphenyl)ethylamine in toluene with AcOH under reduced pressure. Following hydrogenation (>99% de, 60% yield over two steps after recrystallisation) the removal of the 4-methoxy-α-methylbenzyl group was achieved using a combination of formic acid and triethylsilane. Use of the more classical α-methyl benzylamine in this sequence proved more problematic in the protecting-group removal stage.

Merck have reported their synthesis of the potent potassium channel blocker L-768,673, a compound selected for the treatment of ventricular arrhythmia and the prevention of sudden cardiac death (SCD) (*Tetrahedron* **1999**, 909). One of the features in that synthesis is the one-pot resolution of an amine involving an in situ racemisation. As shown in Scheme 5, the achiral amine is resolved in the presence of 3,5-dichlorosalicylaldehyde (2 mol %), water (1.5−2.0 mol)

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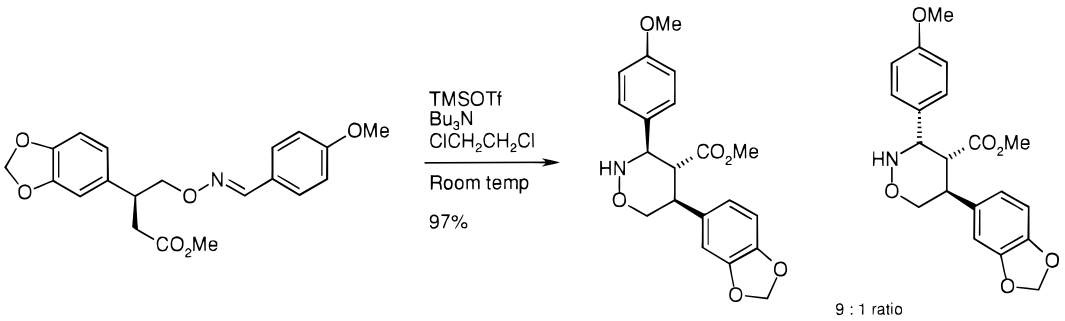
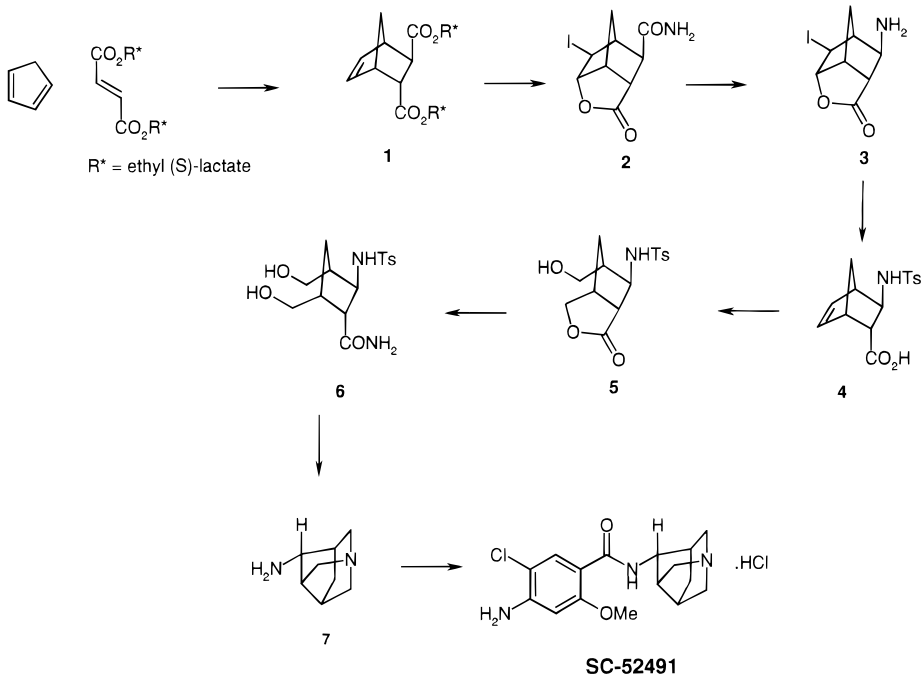
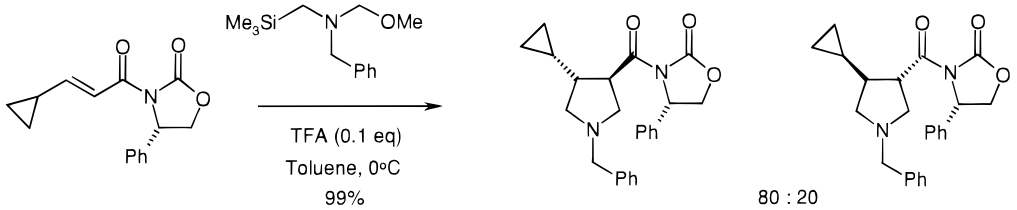
Scheme 1



Scheme 2



Scheme 3



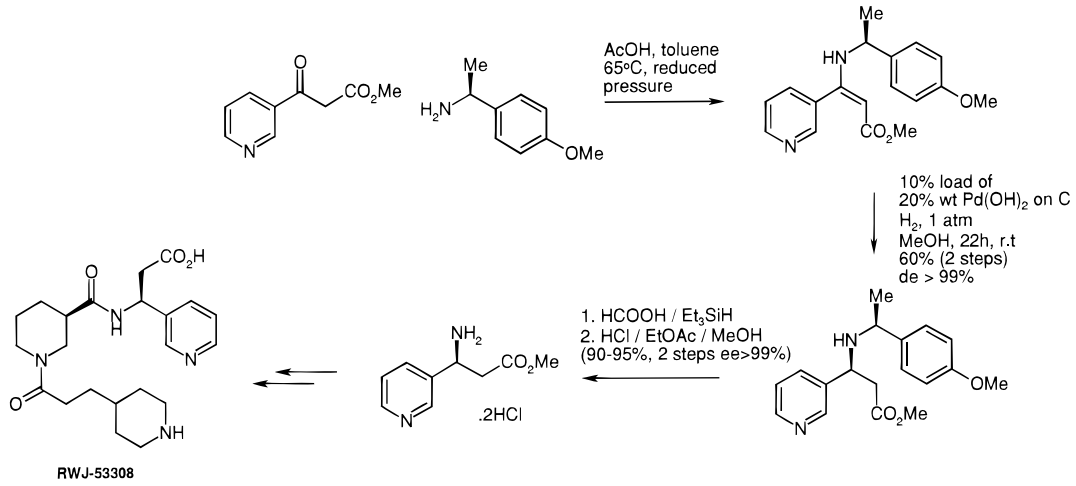
and (*R*)-mandelic acid to produce the resolved amine as its mandelate hydrate salt in 92% yield and 99.4% ee.

A group at Novartis (*Tetrahedron Lett.* **1998**, 6991) have used sodium 2-ethylhexanoate as a mild acid scavenger in the acylation reaction of amines with acid chlorides. This inexpensive reagent is readily soluble in common organic solvents such as ethers and toluene and sodium chloride precipitates during the course of reaction.

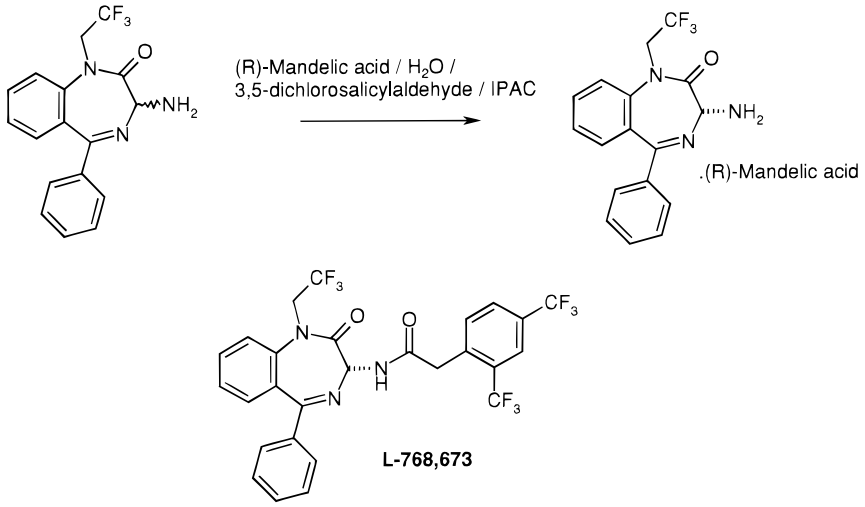
One-pot reactions that involve multiple steps are of significant importance in organic synthesis. A group at Schering-Plough have recently disclosed (*Synth. Commun.* **1999**, 3011) a "one-pot − four step" procedure for the preparation of (*S*)-benzyl 4-hydroxy-2-pentynoate from (*S*)-3-butyn-2-ol. Protection of the secondary alcohol (Scheme 6) with 0.55 equiv HMDS (Hexamethyldisilazane) at pH 6−6.5 gave the TMS ether which was deprotonated using lithium hexamethyldisilazide generated in situ using catalytic amounts (0.1 equiv) of HMDS and BuLi (1.1 equiv). The lithio anion was quenched using benzyl chloroformate and the TMS group removed with 6 N H_2SO_4 to give the product in 72% overall yield. Attempted deprotonation in the absence of HMDS caused decomposition. This protocol provides convenient operation on scale.

Continuing the theme of protection and deprotection, Kumar et al. (*Chem. Lett.* **1999**, 857) have reported the iodine catalysed mild and efficient tetrahydropyranylation/depyranylation of alcohols and phenols. Reaction of either an alcohol or phenol with stoichiometric amounts of dihydropyran in DCM with catalytic quantities of resublimed iodine gave the protected compounds in excellent yields and

Scheme 4



Scheme 5



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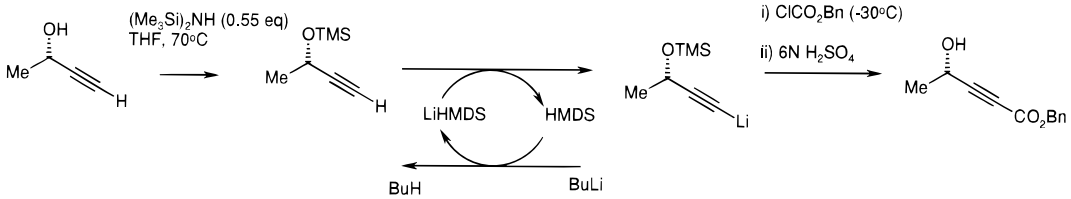

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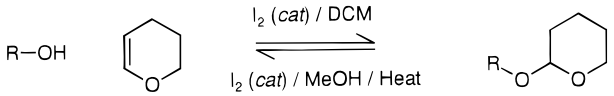
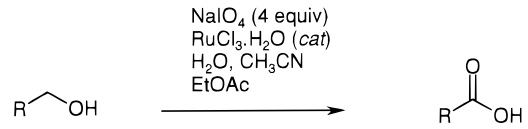


Scheme 8

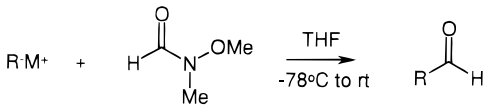


generally in a couple of hours. Deprotection of the THP ethers could be achieved using the same catalyst but changing the solvent to methanol at reflux (Scheme 7).

Novartis have reported (*Synth. Commun.* **1999**, 2937) an improved and practical procedure for the oxidation of primary alcohols to carboxylic acids (Scheme 8) under the Sharpless conditions ($NaIO_4/RuCl_3 \cdot H_2O$/water/acetonitrile) using ethyl acetate as solvent in place of toxic and environmentally undesirable carbon tetrachloride. They demonstrate the protocol on a wide variety of alcohols, and the yields range from 69 to 95%.

Formylation of a carbanion is a fundamental C−C bond-forming reaction in organic synthesis. Lipshutz has demonstrated (*Tetrahedron Lett.* **1999**, 7889) that the treatment of organolithiums, Grignard reagents, or enolates with *N*-methoxy-*N*-methylformamide leads to formylated products in good yields (Scheme 9). This protocol (akin to the Weinreb acylation technique) offers an attractive higher yielding alternative to the DMF-mediated formylation reaction.

Scheme 9



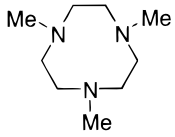
Perrier and Labelle at the Merck Frosst Centre for Therapeutic Research have reported a technique enabling *liquid-phase synthesis* with a *solid-phase work up* (*J. Org. Chem.* **1999**, *64*, 2110). They use a quinoline group as a handle to precipitate intermediates in a synthetic sequence as isolable insoluble bisulphate salts. In the "neutral state" the intermediates are organic soluble, and reactions may be performed in solution. Scheme 10 illustrates the technique, and the group have shown the technique to be compatible with a variety of synthetic transformations including a palladium coupling, Fe reduction, and amidation. This technique could find an important application in scalable chemistry as well as in combinatorial chemisty.

Whilst transition metal catalysis provides selective transformations of use to the process chemist, the expense of the metal and ligand, the recycling of the homogeneous catalysts, product contamination, and reactor cleansing are major issues. The development of catalysts which combine low leaching levels with easy recycling is a significant goal. Supported liquid-phase catalysis utilises the hydrophilic surface of a glass bead to adhere a polar solvent, and a transition metal catalyst can reside in this layer. This noncovalent method of support offers process advantages, namely easy separation and recycling. Catalysts derived from guanidinium phosphines and palladium acetate have now been shown by the group of Williams at Bath, UK (*Syn. Lett.* **1999**, 1645) to catalyse Heck, Sonogashira, and alkylation reactions with low leaching of the catalyst, and easy separation and recycling of the palladium.

The use of supported reagents in chemistry offers potential environmental advantages, although whether the potential can be realised in practice is open to question. A recent review (Chesney, A. *Green Chem.* **1999**, *1*, 209) highlights the latest examples of reagents supported on ion exchangers rather than on polymers. The author, who works in the ion-exchange industry indicates that the simplicity of use, stability, and the ease of reuse should encourage more industrial chemists to try these methodologies.

Asymmetric epoxidation of $\alpha-\beta$ unsaturated ketones continues to attract a lot of attention and modified versions of the Julia reaction (H_2O_2-polypeptides) and new asymmetric phase-transfer catalysed processes have been recently reported. Enders has also used oxygen in conjunction with a complex generated from a chiral aminoalcohol and diethylzine, and other groups (Jackson, UK, and Shibasaki, Japan) have used hydroperoxides with various catalysts. The group of Pu at the University of Virginia (Yu, H-B. et al. *J. Org. Chem.* **1999**, *64*, 8149) have now prepared polymeric binaphthyls, and combined with zinc, these catalysts assist the epoxidation process of $\alpha-\beta$-unsaturated ketones with β-alkyl groups, using *tert*-butylhydroperoxide as the oxidising agent.

An unusual combination of manganese acetate, the ligand trimethyl triazacyclononane (**8**), and ascorbic acid efficiently



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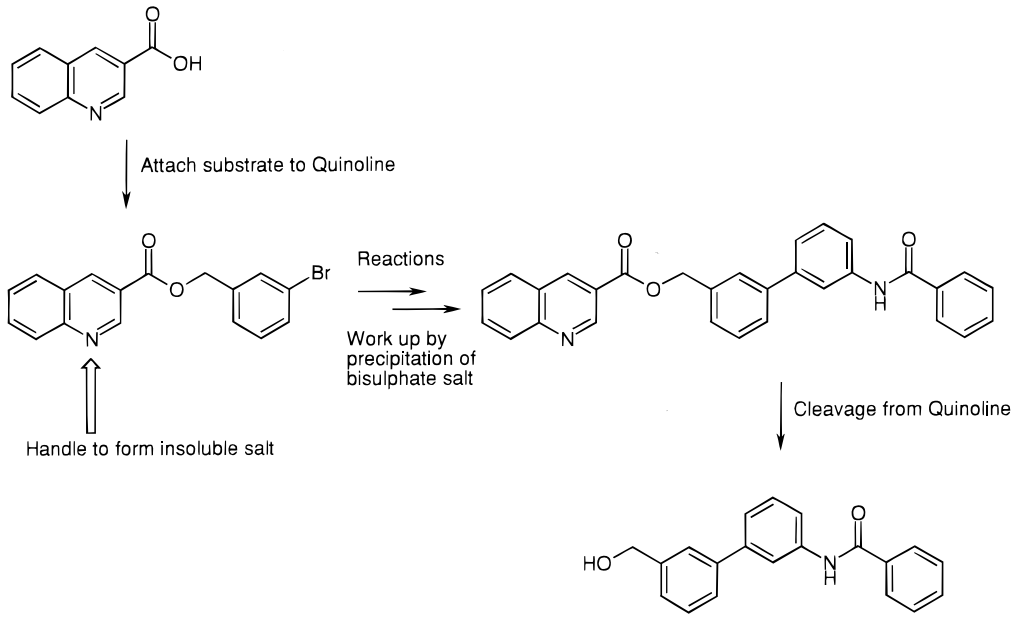
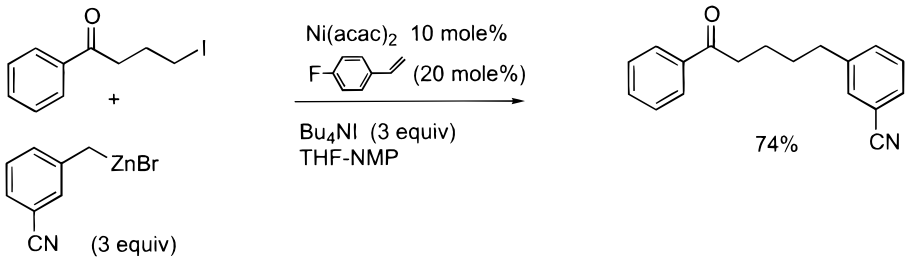
catalyses the epoxidation of olefins and the oxidation of secondary alcohols (to ketones) and of primary alcohols (to acids) using hydrogen peroxide as the oxidising agent. High yields and good catalyst turnover are observed (Bakessel, A. et al. *Tetrahedron Lett.* **1999**, *40*, 7965).

The Suzuki and related reactions continue to attract attention, and a group at the University of Tennessee at Knoxville (Kabalka, G. W. et al. *Org. Lett.* **1999**, *1*, 1423)

Scheme 10



Scheme 11



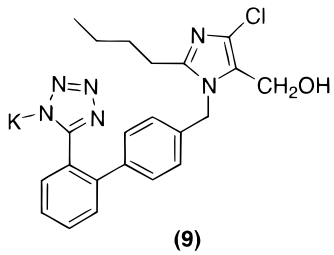
claim that the reaction of an iodide with boronic acid can be carried out without solvent, provided a commercially available $KF-Al_2O_3$ is used with palladium black. The solid-state methodology allows for recycling of the catalyst.

In the same issues, the group of Knochel at Munich (Pibar, M. et al. *Org. Lett.* **1999**, *1*, 323) describe the use of Bu_4NI, not only to accelerated palladium-catalysed cross couplings, but to allow a nickel(0)-catalysed reaction between functionalised benzylic zinc reactions and alkyl iodides under mild conditions (Scheme 11).

A summary of progress on the use of chloroarenes rather than bromides or iodides in C−C, C−N and C−O bond-forming reactions has appeared (Sturmer, R. *Angew. Chem., Int. Ed* **1999**, *22*, 3397). The author, from BASF, indicates that these processes will be used industrially in the future, particularly if the new efficient catalysts are commercially available.

Conjugate addition reactions to acrolein often result in extensive polymerisation as well as the desired product, so this is not normally an attractive methodology in industry. A recent communication (Uehira, S. et al. *Org. Lett.* **1999**, *1*, 1383) describes the use of a $TiCl_4-Bu_4NI$ reagent to add aldehydes to acrolein, often with high syn selectivity (Scheme 12). Vinyl ketones can also be used.

Merck's losartan potassium (Cozaar, **9**) was the first angiotensin II antagonist to gain approval for hypertension. The key step in the published synthesis is a regioselective N-alkylation of **10** using a benzylic bromide, either **11** or **12**. There has been interest amongst fine chemical suppliers,



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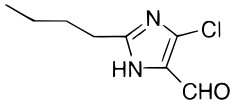

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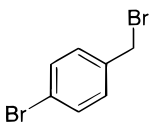

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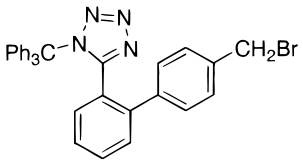
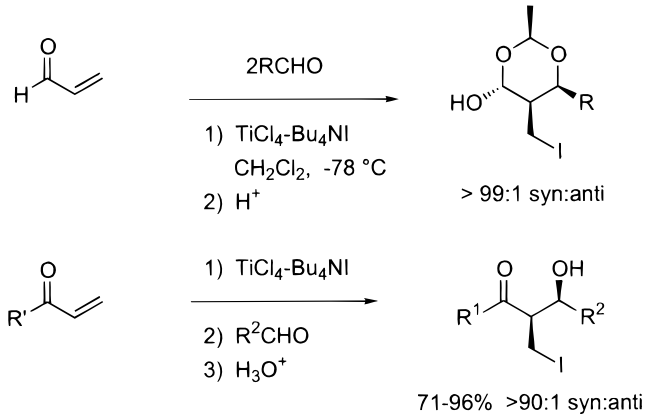


(12)

therefore, in the synthesis of the aldehyde **10** by an

Scheme 12

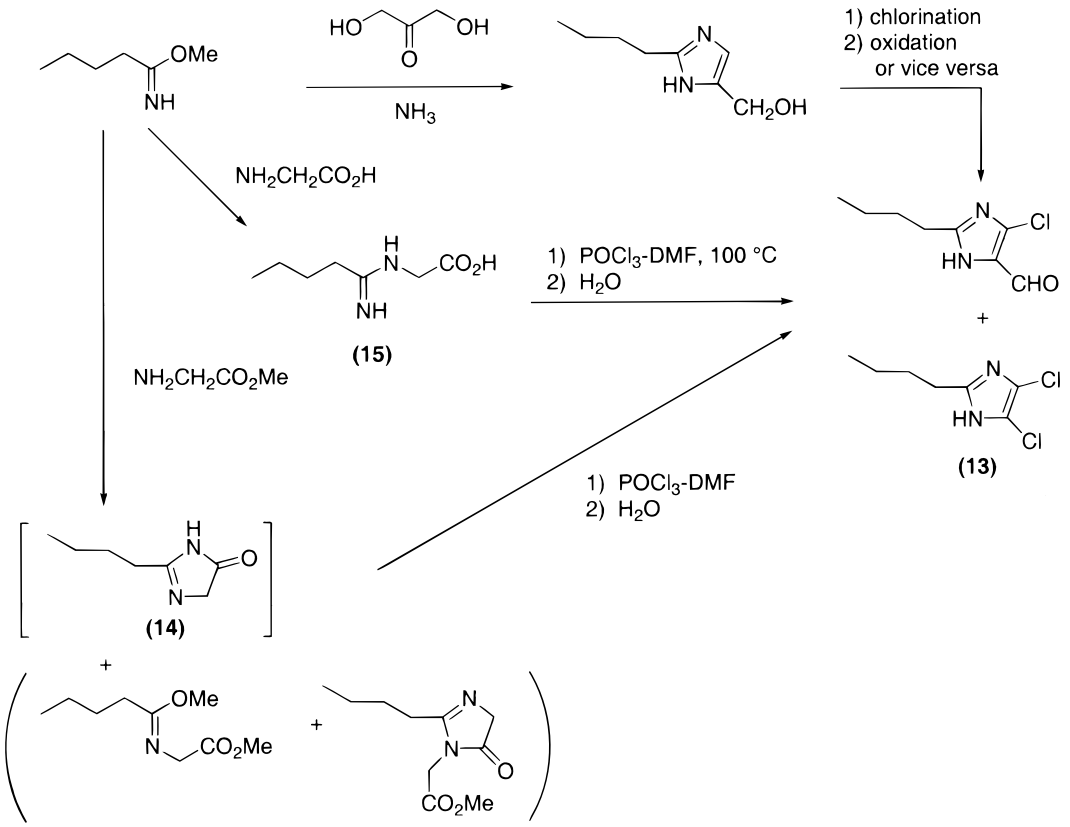


economical and scalable methodology. A number of processes have been patented, including the attractive method coupling an imidate hydrochloride with dihydroxyacetone (Scheme 13) followed by oxidation−chlorination or chlorination−oxidation. The major byproduct in both of these protocols is the dichloroimidazole **13**. Workers at Lonza in Switzerland (Griffiths, G. J. et al. *J. Org. Chem.* **1999**, *64*, 8084) now report on alternative methods shown in Scheme 13, via the unstable imidazolinone **14**, followed by treatment with $POCl_3$DMF or via the amidine. The study examines the effect of minor changes in the reaction conditions on yield and byproduct formation and is an excellent study of targeted process research, although no scale up information is given.

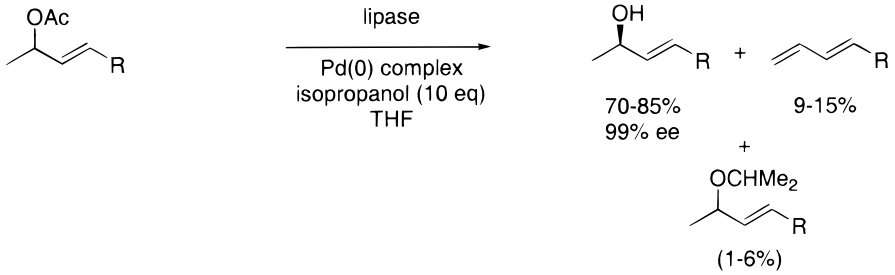
The conversion of a racemic allylic acetate into single enantiomer allylic alcohol using a lipase coupled to a palladium complex, which causes "in situ" racemisation of the unreactive isomer in the hydrolysis step, has been reported by Williams in the UK, and similar processes have been described by the groups of Bäckvall and Reetz. A recent report from Korea (Choy, Y. K. et al. *J. Org. Chem.* **1999**, *64*, 8423) reports on the use of organic solvents to speed up the reaction, (which is now a transesterification), since early reports indicated a 19-day reaction time. Thus, treatment of allylic acetates with lipases such as those from *Pseudomonas cepacia* or *Candida antartica*, which are available in immobilised forms, using excess isopropanol as transesterification agent and THF as solvent gave high yields of allylic alcohols in 98−99% ee. The only problem was that some elimination and substitution byproducts occurred. (Scheme 14). The reactions, however, are still slow (1−2 days) under conditions currently used.

Enzymatic processes have often poor space-time-yields so that it was surprising to see a report of a process being

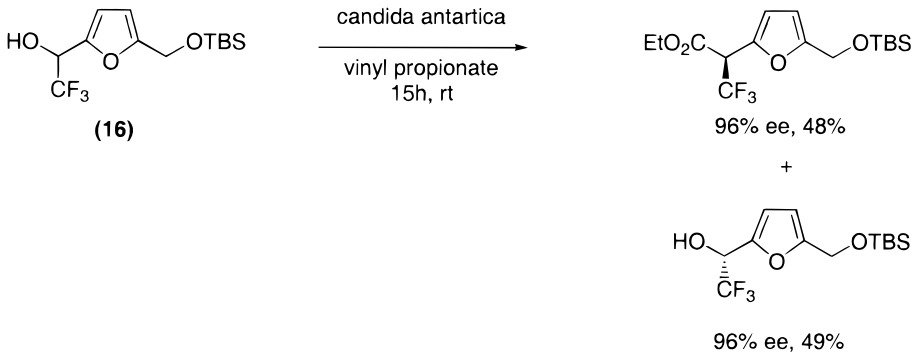
Scheme 13



Scheme 14



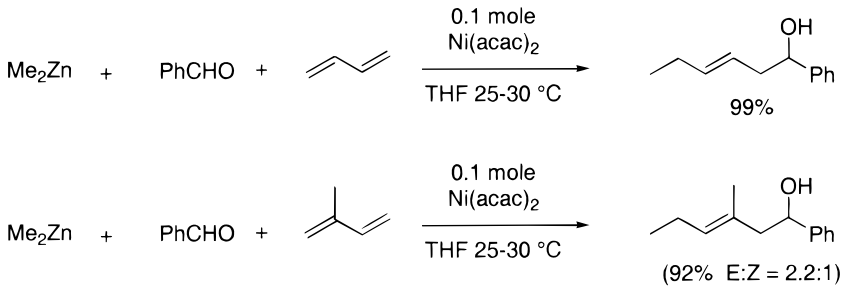
Scheme 15



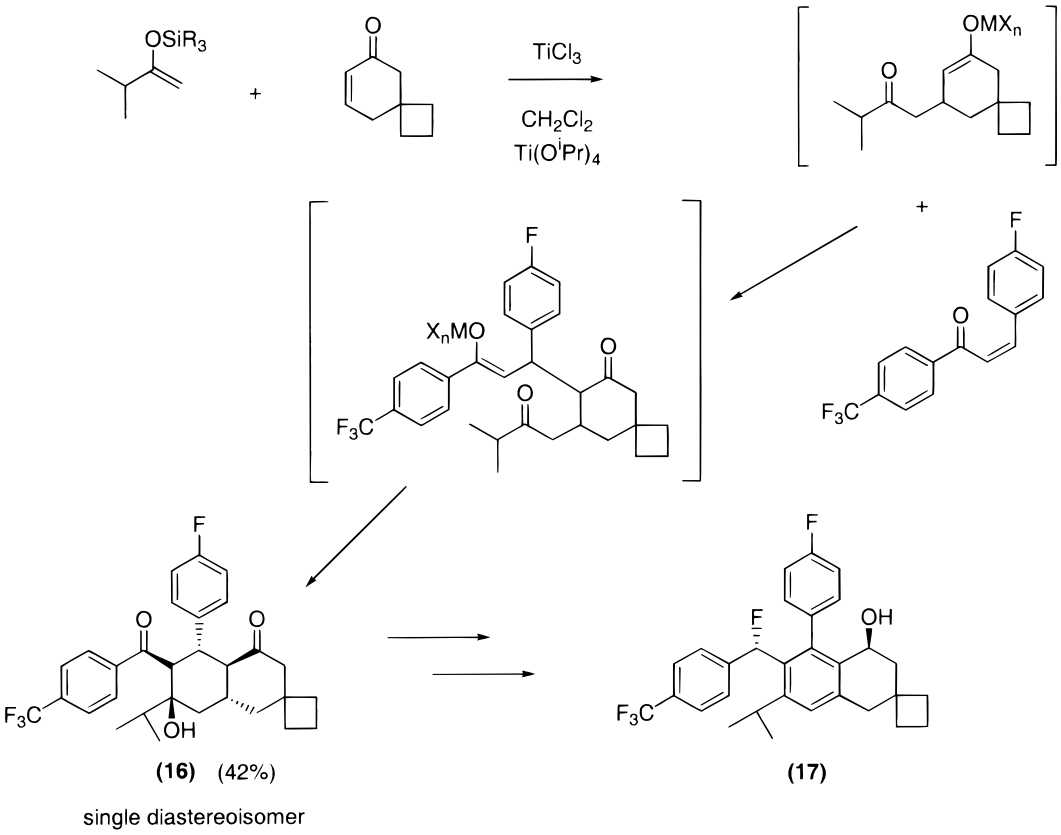
carried out without solvent. The enzymatic resolution of the furanol derivative **16**, useful in the manufacture of ferroelectric or antiferroelectric liquid crystals, takes place neat, allowing the enzyme to be filtered off and recycled and the products to be isolated by distillation. (Kilazume, T. et al. *Green Chem.* **1999**, *1*, 221) see Scheme 15.

It is always pleasant to report on new and simple reactions which have potential for large-scale use. The reaction of stoichiometric dimethyl zinc with a mixture of benzaldehyde and butadiene gave high yields of a three-component connection product (Scheme 16) in the presence of nickel acetylacetonate (Tamaru, Y. et al. *Angew. Chem., Int. Ed.*

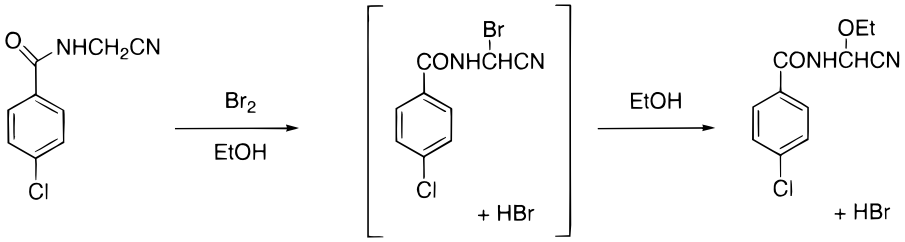
Scheme 16



Scheme 17



Scheme 18



1999, *38*, 3386). With aliphatic aldehydes and ketones, yields are lower, and adducts with 2 mol of diene are additionally formed.

Compounds such as **16** are cholesteryl ester transfer protein (CETP) inhibitors, potentially useful in the treatment of arteriosclerosis, but the structures are synthetically demanding for industry. Workers at Bayer in Wuppertal (Paulsen, H. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 3373) have devised a synthesis in which stereoselective Mukaiyama−Michael/Michael/Aldol domino cyclisation is the key step in the production of the penta-substituted aromatic ring. The 14-step synthesis of the CETP inhibitor **16** has been carried out on a kilogram scale (Scheme 17).

Polyoxometalates have been widely used as catalysts in oxidations and in acid-catalysed processes, but there have been no reports of their use (alone) as reduction catalysts—reductions in the presence of noble metals have, however, been occasionally observed. It has now been shown by an Israeli group (Kogan, V. et al. *Angew. Chem., Int. Ed.* **1999**, *38*, 3331) that Keggin-type polyoxometalates supported on

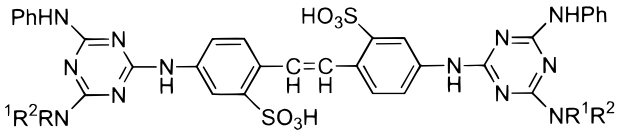
alumina catalyse the reduction by hydrogen of ketones to hydrocarbons, a reaction classically carried out under Wolff−Kishner or Clemmenson conditions. In many cases quantitative yields are obtained, but conditions are severe (300 °C, 23−54 atm). Reactions can be run without solvent.

A short review on chemical aspects of scale up has recently appeared (Atherton, J. H. *Spec. Chem.* **1999**, *19*, 238). It exemplifies the important principle that chemical rate constants are scale-independent, whereas physical parameters are not, and this dichotomy is a common reason for a fall in performance on scale up. Thus, processing time, heat transfer, phase separations, gas desorption, power input, mixing time, and mass transfer rates (two-phase systems) can all change with scale. A good example mentioned in the article is shown in Scheme 18 where bromination of the amide-nitrile is fast and exothermic and the intermediate is unstable in the presence of HBr. In the lab the first reaction was complete in a few minutes, and the mixture was immediately quenched into ethanol. The reaction was complete in about 10 min. In the plant, because of the exotherm, the addition of bromine would take several hours, and by that time most of the intermediate would have decomposed prior to the addition of the batch to ethanol. Use of a continuous stirred tank reactor (CSTR), where bromine and a solution of the amide-nitrile in ethyl acetate were simultaneously dosed and the reaction mixture was directly and continuously added to ethanol, produced a 96% yield of product, provided the residence time in the CSTR was around 40 s.

The article also discusses two -and three-phase reactions including an example of a nitrile reduction (to a primary amine) which had scaled up to 1000 L reactor (with a turbine agitator) without problems. Further scale up to a 5000 L reactor equipped with a small (0.3 m diameter) high-speed impeller, however, caused problems. The agitator is highly efficient in dispersing the hydrogen gas in the vicinity of the agitator but is poor at promoting bulk mixing, resulting in addition of the product (RCH_2NH_2) to the first formed intermediate (RCH═NH) to give large quantities of secondary amine $(RCH_2)_2NH$. This process could be repeated in the lab with poor agitation or hydrogen starvation. This common problem is usually solved by carrying out the reaction in the presence of ammonia, which traps the intermediate imine, and hydrogenolysis then occurs to give the product. In the above case the product also reacted with ammonia; thus, the solution was to use a solvent which protonated the product, preventing nucleophilic addition.

In the November issue of *CHEMTECH* which has a section on touring the Internet, "Chemical Safety & Health Information" is highlighted (p 54). Carol DeAngelo lists the web sites where MSDS information, toxicity data, EPA and FDA legislation, and chemical hygiene information can be obtained. *CHEMTECH* is being renamed *Chemical Innovation* in the year 2000.

In an article in *Green Chemistry*, Stuart Cook of Hickson & Welch (UK) describes how a change in the process to produce a stilbene-based optical brightener **18** has reduced



(18)

waste and emissions using an evolutionary approach (Cook, S. *Green Chem.* **1999**, *1*, G138). The seven-step process starting with toluene has been improved and waste—much of this being acid—is often recycled. Cleaner technologies were also introduced in the oxidation step (to produce the stilbene double bond) and in the reduction of nitro groups to amines. Cook suggests that an open mind to innovative R&D work is the secret along with the avoidance of long-term company researchers constraining new workers with an "it cannot be done, we tried it years ago" attitude. Second-generation process development is both cost-effective and environmentally beneficial.

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