Organic Process Research & Development **1998**, *2,* 282−286

Highlights from the Literature

Some Items of Interest to Process R&D Chemists and Engineers, Selected by the Editor

I mentioned automation in process development in a previous editorial. I predict that this hot topic will start a revolution in the way we carry out process R&D in the future. A recent article (Studt, J. *R&D Mag.* **1997**, *39* (12, Nov), p38) is entitled "Combinatorial chemistry successes create new process demands", and it essentially seeks the views of senior process chemists in companies such as Pfizer and Zeneca about this new area, coupled with an overview of equipment and techniques (most of which were presented at a UK meeting on this topic in 1997—a further meeting on automation in process development will take place in November 1998 in Chester, UK). This is a good overview of this fascinating area.

There have been a number of excellent reviews from Organon chemists on combinatorial chemistry (Hermkens, P. H. H.; et al. *Tetrahedron* **1997**, *53*, 5643; **1996**, *52*, 4527), and their latest review of solid-phase synthesis (Brown, A. R.; et al. *SynLett* **1998**, No. 8, 817) is up to the same standard. For those chemists and engineers interested in automation, the earlier *Tetrahedron* reports provided a table of commercially available equipment for solid-phase organic chemistry in the high price category (>$125,000), whereas the latest paper in *SynLett* tabulates low-budget (<$30,000) equipment. Many of the companies mentioned in the report can also provide equipment on a much larger scale, more suitable for process chemists.

The generation of α,*β*-acetylenic aldehydes directly from acetylides is not normally a high yielding process, since overaddition to a secondary alcohol takes place. Michel Journet et al. at Merck Process R&D in Rahway, NJ (*Tetrahedron Lett.* **1998**, *39* (36), 6427) have overcome this by simply reacting the lithium acetylide with DMF and then quenching the intermediate (**1**) into aqueous potassium phosphate (Scheme 1). The quench is the key to the high yield, since byproducts (**2**−**4**) can arise from release of dimethylamine, which adds to the α,*β*-acetylenic aldehyde product (**5**). By addition of the intermediate to a phosphate buffer (10% aqueous KH_2PO_4, 4 equiv), 94−98% yields could be obtained. The mild conditions of the quench (pH 4.1−6.7) are compatible with acid-sensitive protection groups (Scheme 2).

The cost-effective production of biaryl-containing compounds is becoming increasingly important, since these structural units occur in pharmaceuticals, liquid crystals, etc., and in previous highlights I have mentioned the coupling of aryl chlorides in the Heck and Suzuki methods. Joseph Miller and Robert Farrell from Catalytica Pharmaceuticals (*Tetrahedron Lett.* **1998**, *39* (36), 6441) report that the Negishi method—the cross coupling of aryl zincs with aryl chlorides—works well with a Ni(acac) and bis(diphenylphosphino)ferrocene (dppf) catalyst to give unsymmetrical biaryls in 63−89% yield, mostly above 80%. The conditions are suitable for a wide variety of functionalities (nitrile, ketone, ester, etc.) which would normally react under Grignard-type conditions, and the process works with unactivated chlorides. $Cl_2Pd(dppf)CH_2Cl_2$ is also an effective catalyst, but Ph_3P and racemic BINAP are not. An example of two alternative approaches to a simple biphenyl is shown in Scheme 3. The organozinc compounds can be made from aryl bromides using activated zinc or by transmetalation of Li or Mg compounds.

Barry Trost et al. (*Tetrahedron Lett.* **1998**, *39* (36), 6445) have discovered that terminal alkynes add to acceptor alkynes under palladium catalysis to yield *E*-enynes which can be converted to *Z*-enynes using phenyl selenyl radicals. Enynes with ester groups could then be converted to *Z*-enediynes (Scheme 4).

I have often isolated byproducts from reactions in dichloromethane, where the solvent has participated in alternative processes. It comes as no surprise, then, to find that reaction of m-CPBA in dichloromethane can lead to chlorination of dichlorovinyl ethers. Normally reaction of m-CPBA with olefins is faster than reaction with dichloromethane to give chlorine, so chlorinated products are observed only when slow reacting vinyl ethers are used (Lakhrissi, M.; et al. *Tetrahedron Lett.* **1998**, *39* (36), 6453). In the same issue (p 6515), Chinese workers mention that the standard peptide-coupling reagents hydroxybenzotriazole (HOBt), 3-hydroxy-4-oxo-3,4-dihydro-1,2,3 benzotriazole (HOOBt), and *N*-hydroxy-succinimide (HOSu) also react with dichloromethane and dichloroethane in the presence of triethylamine. At room temperature the reactions were slow, but at elevated temperature good yields of mono and bis adducts could be obtained. HOSu in dichlormethane did not react at room temperature, so it may be the best reagent (and least expensive?) for larger scale work if chlorinated solvents must be used.

Aldehyde-oximes (aldoximes) are reported to be easily oxidised to nitriles using potassium peroxymonosulphate, and these reactions work well in the absence of solvent under microwave activation. (Bose, D. B.; et al. *Tetrahedron Lett.* **1998**, *39* (36), 6533). Aldehydes can now be easily protected as their acylals, $[RCH(OAc)_2]$, by reaction with acetic anhydride in the presence of scandium triflate (2 mol %).

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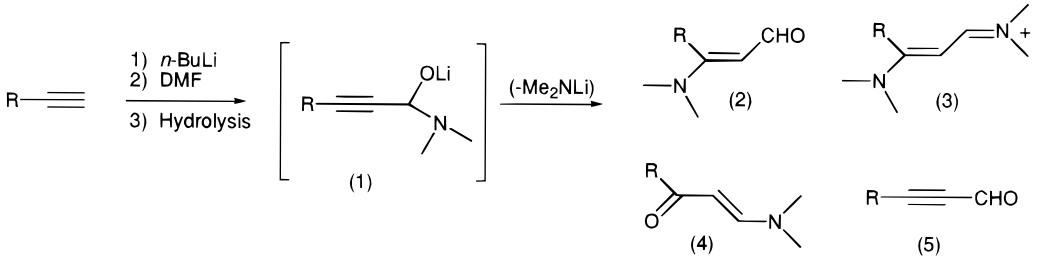
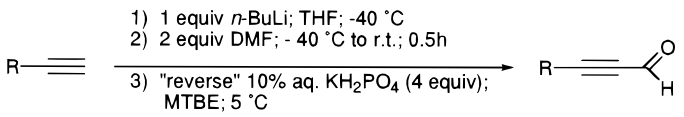
Scheme 1

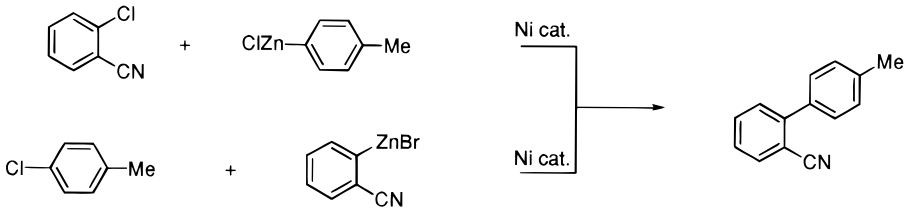


Scheme 2

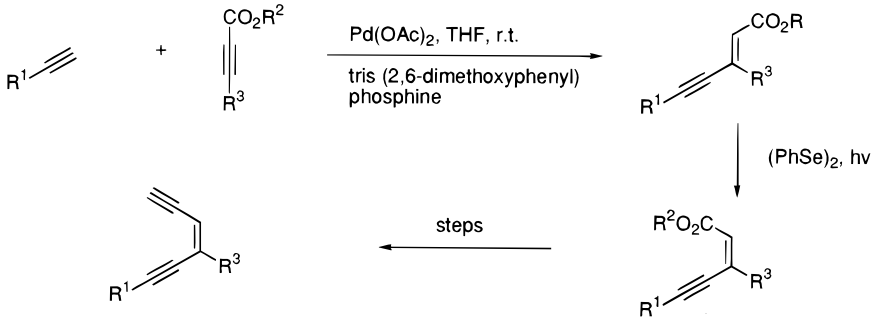


R	Yield (%)
Ph	97
$TBSO(CH_2)_3$	98
$THPO(CH_2)_2$	97
$THPOCH_2$	94
n-C_4H_9	95

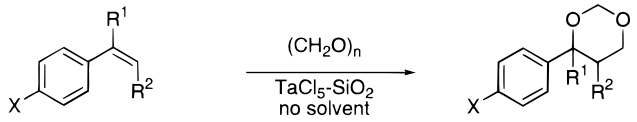
Scheme 3



Scheme 4



Scheme 5



(Aggarwal, V.; et al. *SynLett* **1998**, No. 8, 849). Deprotection is by using the same catalyst in the presence of water.

Microwave activation of the Prins reaction between styrene derivatives and paraformaldehyde in the presence of $TaCl_5-SiO_2$ catalyst (Scheme 5) reduces the reaction time from 10−12 h (refluxing dioxan, 110 °C) to 3−5 min (no solvent, solid phase on silica). (Chandrasekhar, S.; et al. *SynLett* **1998**, No. 8, 851). With the availability of larger scale microwave reactors, these methods may soon be common in the fine chemical industries.

M. P. Dutta (*SynLett* **1998**, No. 8, 857) reports that reductive coupling of aldimines to vicinal diamines takes place using zinc powder and 10% aqueous sodium hydroxide in the absence of organic solvents. Alternatively, magnesium in methanol gives a similar reaction in lower yield, but the reaction is much faster. In a paper in the same issue (p 873), French workers recommend Zn/TMSCl in MeCN as the preferred reagent, giving 97% yields of a 50:50 mixture of diamines. They suggest that this method works well on larger scale, though the work up involves a very exothermic NH_4Cl/NH_4OH quench which may be difficult to control on a kilogram scale. The following paper describes how the mixture of diamines can be converted to the C_2 symmetrical isomer by isomerisation of the meso with lithium and isoprene (Scheme 6).

Zinc is also suggested as the catalyst for reaction of acid chlorides with thiols to give thiolesters (ibid., p 877).

The HIV protease inhibitors (Chart 1) have come onto the market over the last 3 years for the treatment of AIDS, and some of these drugs are made on the 200−300 tonnes/annum scale. They are high-dose drugs, some requiring a patient to take 1 kg per year, so there is a need to bring the cost per kilogram down to low levels, if third world countries, where AIDS is on the increase, are to be able to afford them.

Scheme 6

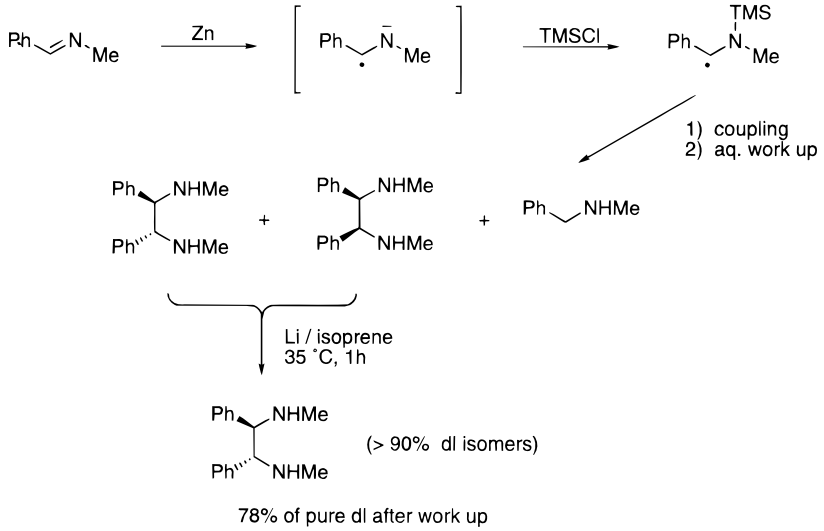
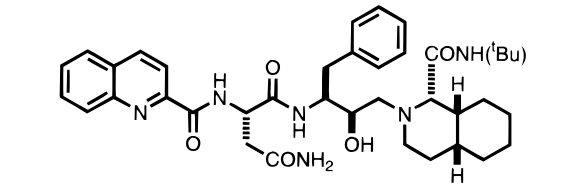
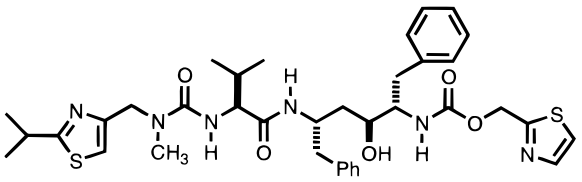


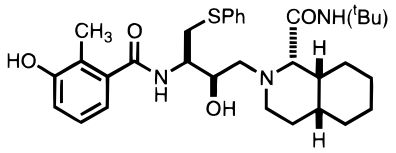
Chart 1. **The leading HIV protease inhibitors**



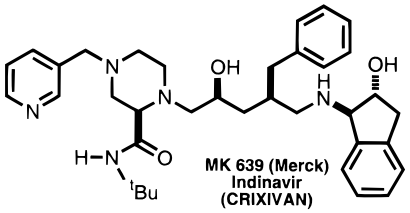
Ro 31-8959 (Roche)
Saquinavir
(INVIRASE)



ABT 538 (Abbott)
Ritonavir
NORVIR



AG 1343 (Agouron)
Nelfinavir
VIRACEPT



MK 639 (Merck)
Indinavir
(CRIXIVAN)

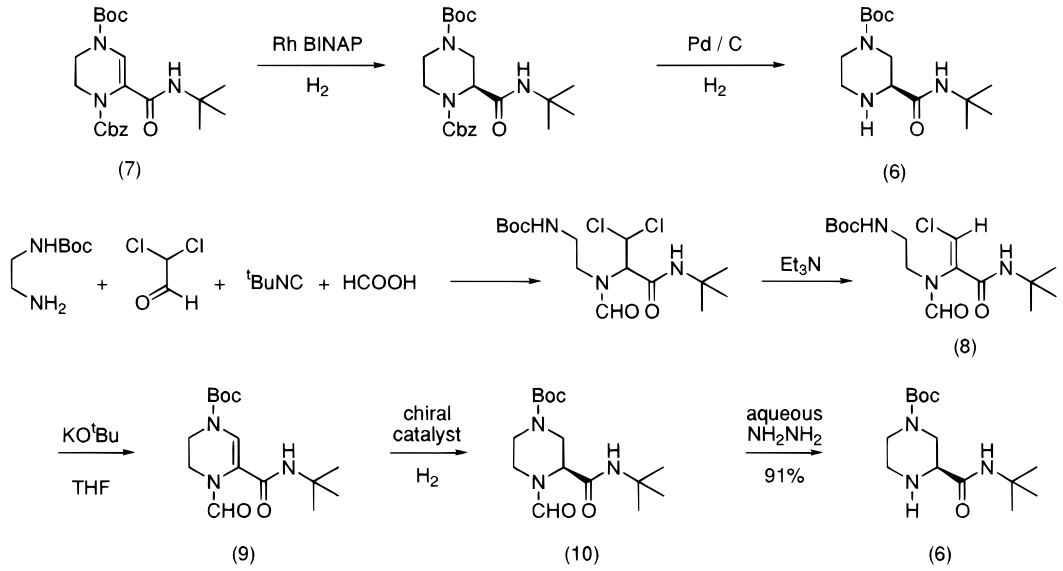
In Merck's production scale synthesis of Indinavir (Crixivan), the piperazine (**6**) is the key intermediate, being made from cyanopyrazine by a sequence involving a Ritter reaction, hydrogenation of the ring, a relatively efficient resolution, and Boc protection. Enantioselective hydrogenation of a tetrahydropyrazine (**7**) is an attractive alternative to this, though it does require double protection on each nitrogen, one group of which is hydrogenolysed. The difficulty with this approach has been an efficient synthesis of the precursor (**7**) (Scheme 7).

It has been reported (Rossen, K.; et al. *Tetrahedron Lett.* **1998**, *38*, 6823) that reaction of Boc-protected ethylenediamine with dichloroacetaldehyde, *tert*-butylisocyanide, and formic acid in an Ugi reaction yields an adduct, which on elimination of HCl gives a single isomer of the vinyl chloride (**8**). This can be cyclised to the desired doubly protected tetrahydropyrazine (**9**) and reduced asymmetrically to the intermediate (**10**). For the cyclisation step, the choice of base was crucial, with amine bases, LDA or BuLi proving useless and alkoxides best ($KOBu^t$ better than Na and Li salts), and the amount of base, concentration (0.05 M!), and solvent (THF) critical parameters. In the deprotection step, most reagents (e.g., NaOH) which removed the aldehyde caused racemisation, but aqueous hydrazine gave the required product (**6**) in 91% yield and 98% ee (Scheme 7). Whether this new process is competitive with the original cyanopyrazine process remains to be seen—the new process is novel but is rather atom inefficient, not as robust, and at present, has a low space−time yield.

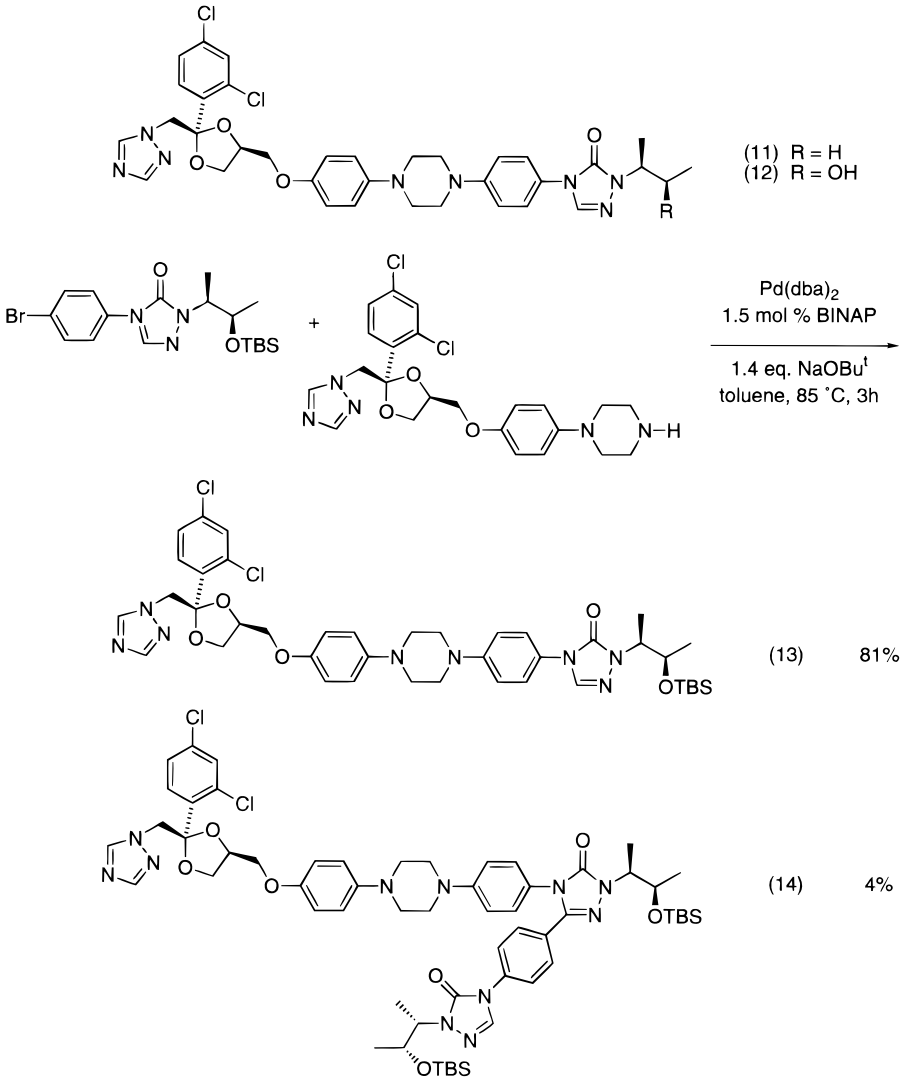
In the same issue (*Tetrahedron Lett.* **1998**, *39*, 6845), workers at Sepracor (USA) have used palladium-catalysed amination, mentioned in last month's highlights, as the key step in the synthesis of itraconazole (Sporanex, **11**) and its active metabolite hydroxyitraconazole (**12**), well-known antifungal agents. The amination reaction (Scheme 8) to give the required compound (**13**, 81%) is accompanied by a Heck reaction leading to the byproduct (**14**, 4%). Deprotection with tetrabutylammonium fluoride gives hydroxy-itraconazole (**12**) in 91% yield (99.8% ee).

The selective reduction of α,β-unsaturated aldehydes is an important industrial process particularly in fragrance, flavour, and vitamin manufacture. The most successful two-phase processes use ruthenium catalysts with sulphonated phosphane ligands as (pre)catalysts. A recent paper (Joo, F.; et al. *Angew. Chem., Int. Ed.* **1998**, *37* (7), 968) from the Hungarian Academy of Sciences discusses the influence of pH on the selectivity of hydrogenation. At pH above 6, cinnamaldehyde is reduced to the alcohol, whereas below

Scheme 7



Scheme 8



pH 5, carbonyl reduction is suppressed and slow double bond hydrogenation occurs. The results are explained by invoking a pH-dependent equilibrium between different Ru catalysts. Providing constant pH conditions in these hydrogenations is vital for selectivity and affects the rates of reactions markedly.

The study of heterogeneous catalytic processes is sometimes hindered by the inability to monitor the mechanistic details under typical reaction conditions. A new NMR technique, involving monitoring reactions by solid-state ^{13}C magic angle spinning NMR spectra, has been reported (Haw, J. F.; et al. *Angew. Chem., Int. Ed.* **1998**, *37* (7), 948), which relies on a novel pulse quench catalytic reactor to cool samples quickly for NMR evaluation. The catalyst is cooled by 150 K in the first 170 ms of a quench; for a reaction carried out at 623 K on a zeolite-catalysed process, it takes only 1 s to bring the temperature to ambient, and spectra are recorded soon after at 77 K. The technique allows mechanistic studies on fast reactions to be followed.

This part of the journal is always a useful section in which to highlight safety issues which have come to my attention during my reading (please feel free to inform me of articles I have missed!). I enjoyed reading an excellent review on the Morita−Baylis−Hillman reaction (Ciganek, E.; *Org. React.* **1997**, *51*, 201) and was interested to note a warning from the author that some reaction products (e.g., from reaction of formaldehyde with methyl acylate and of aldehydes with aryl acrylates) have given rise to SEVERE CONTACT DERMITITIS. Nevertheless, this reaction (now correctly attributed to the discoverer Morita as well as Baylis and Hillman) is of industrial importance and can be carried out neat or in a wide range of solvents (including water); it is also accelerated under microwave conditions.

Trevor Laird
Editor

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