REVIEW

Rapid analogue syntheses of heteroaromatic compounds

Ian Collins

Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, UK CM20 2QR. E-mail: ian_collins@merck.com

Received (in Cambridge, UK) 10th May 2000
Published on the Web 3rd August 2000

Covering 1998 and 1999.

1 Introduction

Heteroaromatic templates are widely used in medicinal and agrochemical chemistry as scaffolds for the design of non-natural, biologically active agents, and in materials science as the building blocks for novel polymers. An increasing amount of published literature describes new synthetic routes for the preparation of these compounds that allow variation of substituents in efficient and flexible ways. Such 'rapid analogue' syntheses (RAS) tend to concern the production of single compounds by solution-phase chemistry, often through parallel synthesis, and aim to produce diverse structures quickly as a starting point to address more complex problems in biological or materials science. The importance of this field and the challenges and opportunities it raises have been succinctly and eloquently summarised by Snieckus.[1]

Contemporary developments in regiospecific halogenation, metalation and transition metal catalysed couplings to heteroaromatic compounds have found extensive use in this context and form the bulk of the material discussed in this article, which concentrates on bond formation to ring atoms as opposed to the modification of side-chains. Additionally, new routes for the assembly of appropriately functionalised heterocyclic cores have emerged, including the development of multi-component reactions and the use of solid-supported reagents to enhance the practicality of the approach.[2] Frequently the key bond formations are commonplace reactions: the challenge of the field lies in their combination in short, flexible and general synthetic schemes.

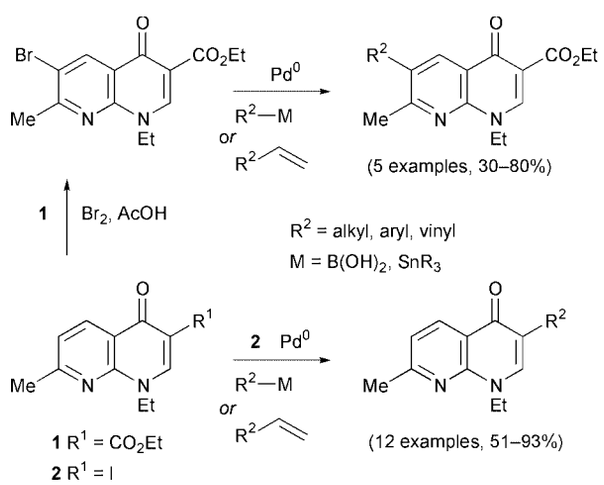
This review will draw together and compare recent work on the solution-phase synthesis of 5- and 6-membered heteroaromatic compounds and their fused derivatives where the synthetic strategy is specifically for, or is readily applicable to, RAS as defined above. Combinatorial chemistry on the solid-phase, other than the use of polymer-supported reagents, is not examined. Regular reviews in this series have covered the wider topics of heteroaromatic synthesis[3] and transition metal catalysed reactions.[4]

2 Basic strategies

2.1 Transition metal catalysed coupling to heteroaromatics

2.1.1 Halogenation–coupling

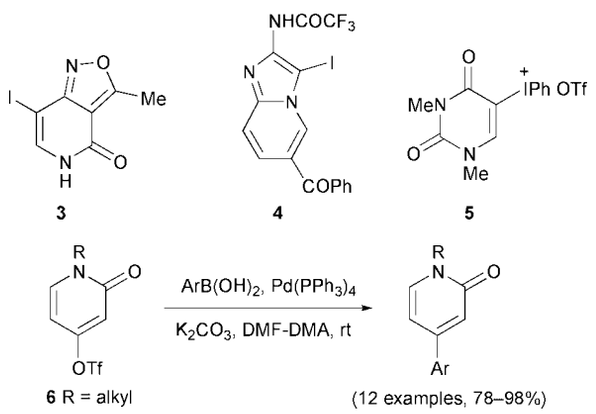
One of the simplest RAS routes to heteroaromatics involves direct halogenation of the heterocycle according to its inherent preference for electrophilic substitution, followed by transition metal catalysed couplings to the halide. For example, the nalidixic acid core **1** (Scheme 1)† was brominated at the 7-position and subject to palladium catalysed C–C bond formations.[5] By decarboxylation to give the unsubstituted core the reactivity of the 4-pyridone ring was revealed, enabling selective iodination to give the 3-iodo-1,8-naphthyridine **2** which was again a substrate for palladium catalysed couplings. Similarly,



Scheme 1

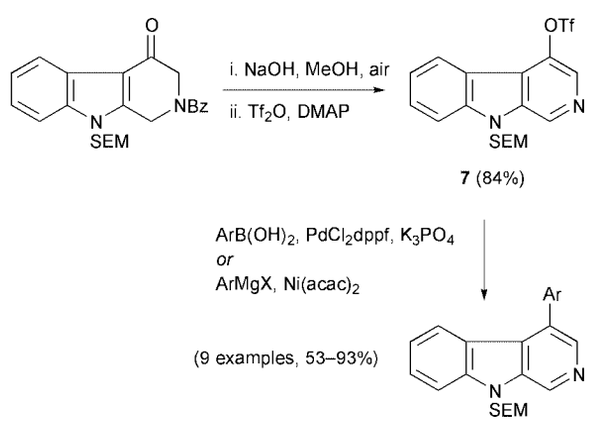
† Throughout this article the number of examples refers to those that fall within the yield range quoted. In some cases additional examples, generally of lower yields, have been omitted.

direct iodination of a 2-pyridone ring with ICl gave the isoxazolopyridone **3**[6] whilst Barluenga's reagent (Ipy_2BF_4) was used to ensure selective formation of the iodide **4**.[7] Halogenation of hydroxyheteroaromatics with triphenylphosphine and *N*-halosuccinimides was proposed as a convenient alternative to the standard reaction with phosphorus oxyhalides.[8] As an alternative to simple halides, the phenyliodonium triflate **5** was prepared by reaction of 1,3-dimethyluracil with $PhI(OAc)_2 \cdot 2TfOH$.[9] The salt **5** was significantly more reactive than either the 5-iodo or 5-stannyluracil in palladium catalysed Stille or Suzuki reactions (*e.g.* **5** coupled with vinylstannanes in 0.1–1 h at room temperature, 76–95%). Heteroaryl triflates are often readily prepared from the hydroxylated precursors and offer an alternative substrate for transition metal catalysed couplings, as for the 4-triflyloxy-2-pyridone **6** (Scheme 2) where selective *N*-alkylation was combined with Suzuki and Sonogashira couplings to give diverse tyrosine phosphatase ligands.[10] The non-aqueous, room temperature couplings of the arylboronic acids were particulary suited for automation. Negishi coupling of 2-pyridylzinc bromide to simple 2-triflyloxypyridines gave a high yielding synthesis of 2,2′-bipyridine ligands.[11]

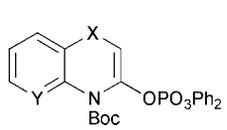


Scheme 2

The 4-triflyloxy-β-carboline **7** was prepared in multi-gram quantities by oxidation and triflation of a saturated precursor (Scheme 3).[12] Although the reactions of **7** were highly solvent and catalyst dependent, optimum conditions for Suzuki and Kumada couplings were found that provided a range of 4-aryl-β-carbolines from this single intermediate. The enol triflate formed from benzoxazin-3-one was too unstable for further use, but related diphenyl phosphates readily coupled under Stille (**8a**, 6 examples, 82–96%) and Suzuki (**8a**, **8b** and **8c**, 70–98%) conditions.[13,14]



Scheme 3

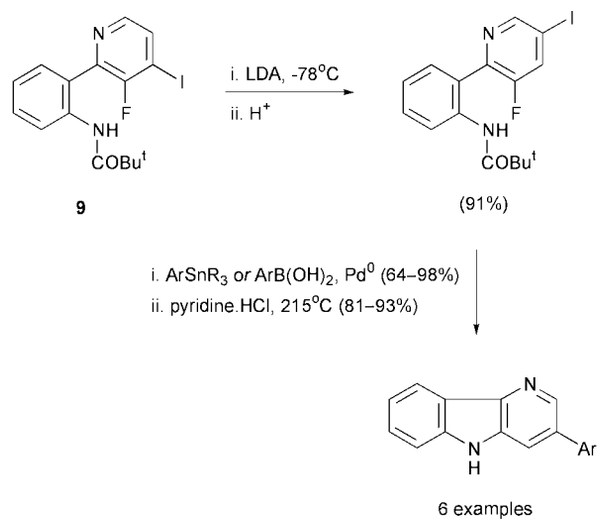


	X	Y
8a	O	CH
8b	O	N
8c	S	CH

Further examples of this synthetic approach are collated in Tables 1 and 2 (Section 2.1.5).

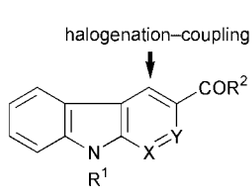
2.1.2 Metalation–halogenation–coupling

Halogen-dance reactions initiated by ring deprotonation have been exploited extensively by Quéguiner and co-workers to provide new iodinated quinolines[15,16] and pyridines[17] suitable for transition metal catalysed couplings. In the latter case, rearrangement of the 4-iodopyridine **9** was followed by Suzuki or Stille couplings and subsequent intramolecular S_NAr cyclisation led to a series of β-substituted-δ-carbolines (Scheme 4). By quenching the rearrangement with other electrophiles (*e.g.* MeI, C_2Cl_6) limited variation of the adjacent α-substituent was also achieved.



Scheme 4

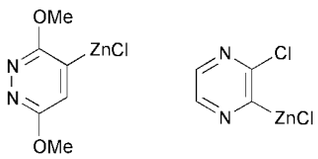
There are several recent examples of directed *ortho* metalation of heteroaromatics and quenching with halogens to produce coupling substrates: an *N*-benzyloxy substituent served as a directing group to prepare 2-iodo-1-(benzyloxy)imidazole[18] (87%), while *N*-protection with the 2,2-diethylbutanoyl (DEB) moiety directed metalation to the 7-position of 3-methylindole to give 3-methyl-7-bromoindole[19] (57%). An important advance was the introduction of lithium di-*tert*-butyltetramethylpiperidinozincate (TMP-zincate) as the base.[20] This chemoselective reagent was very effective for the α-zincation of both electron-rich and electron-deficient heteroaromatics, leading in high yields to 2-iodothiophenes (62–86%), 2-iodopyridine (76%) and 1-iodoisoquinoline (93%). The conventional deprotonation with LiTMP was used to prepare the 4-iodo-α-carboline **10a** which was a good substrate for Suzuki couplings.[21] Methyllithium was adequate to metalate the β-carbolines **10b** and **10c** providing the 4-iodo and 4-bromo derivatives respectively.[22,23] For successful Heck, Stille and Sonogashira couplings of the iodide the tertiary amide was essential (70–98%), whereas the 4-bromo compound underwent Buchwald amination ($BnNH_2$, 52%) in the presence of the secondary amide N–H. Selective *ortho* lithiation followed by halogenation and coupling was also performed on pyridine *N*-oxides[24] and 4-chloropicolinanilide.[25]



	X	Y	R^1	R^2
10a	N	CH	Me	NPr^i_2
10b	CH	N	Me	N(Me)Ph
10c	CH	N	SO_2Me	N(H)Ph

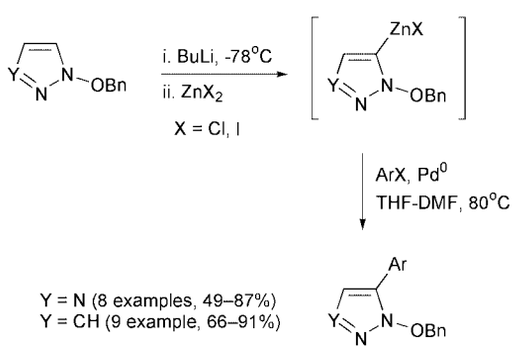
2.1.3 Metalation–transmetalation–coupling

Another basic component of RAS strategies is the production of heteroarylmetal species, most commonly of boron, tin or zinc, from regioselectively lithiated heterocycles and their subsequent use in transition metal catalysed couplings. For example, lithiation of 2-methoxypyridine in the 6-position with BuLi–$Me_2N(CH_2)_2OLi$ gave the 6-(bromozinc) derivative after transmetalation. Palladium catalysed Negishi couplings (7 examples, 64–74%) were efficiently carried out in a one-pot process to yield bis-heteroaromatic compounds.[26] The analogous process with 6-(tributylstannyl)-2-methoxypyridine was markedly less efficient (31–46%). The zincated pyridazine **11** and pyrazine **12** were also found to be useful coupling partners, and notably more stable than their lithiated precursors.[27]

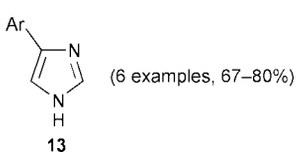


11 **12**

Vedsø, Begtrup and co-workers were able to exploit the stabilising effect of *N*-benzyloxy substitution to prepare metalated 1,2,3-triazoles[28] and pyrazoles[29] for subsequent high yielding coupling reactions (Scheme 5). Again, the zinc reagents were more versatile than the tin analogues. 4-Aryl-1-(benzyloxy)pyrazoles were prepared from 4-iodo-1-(benzyloxy)-pyrazole by magnesiation, transmetalation to zinc and Negishi cross-coupling (10 examples, 57–89%).[30] Likewise, 4-aryl-imidazoles **13** were accessible from *N*-trityl-4-iodoimidazole by Grignard formation and transmetalation to the zinc or tin species.[31] In this case the heteroarylmetals showed comparable efficiency in the coupling steps. The groups of Quéguiner and Knochel have reported related methodology for the magnesiation of functionalised halopyridines[32,33] and 5-iodouracil[34] which should find similar use. Double Grignard formation from 2,6-bis(5-bromo-2-thienyl)pyridine and Kumada coupling was the basis of a route to alternating thiophene–pyridine oligomers.[35] 3-Aryl- and 3-heteroaryl-7-azaindoles were easily made from *N*-TBDMS protected 3-stannyl-7-azaindole (Scheme 6), in turn derived from the 3-bromoheterocycle by lithiation.[36] Similarly prepared *N*-TBDMS protected indole-3-boronic acid also performed well in Suzuki couplings[37] whilst *N*-Boc protection was used in the palladium catalysed coupling of indolyl-2-boronates.[38]

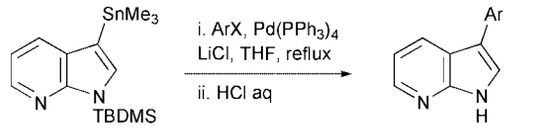


Scheme 5



13

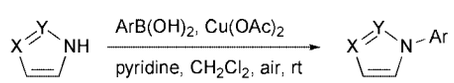
Further heteroarylmetal compounds used in cross-coupling reactions are described in Tables 1 and 2 (Section 2.1.5).



Scheme 6

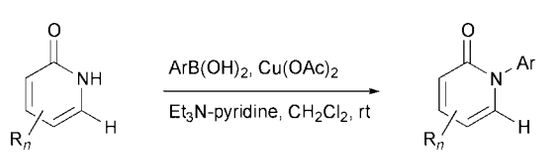
2.1.4 *N*-Arylation of heteroaromatics

A significant area of progress has been the *N*-arylation of heteroaromatics mediated by palladium or copper. The DuPont groups led by Chan and Lam were able to apply their recently discovered stoichiometric cupric acetate–arylboronic acid arylation reaction to azoles (Scheme 7).[39] The cross-coupling was effective with nucleophilic heteroarenes such as pyrazole, imidazole and their benzo-fused analogues, but yields were disappointing with electron deficient triazoles and tetrazoles. Surprisingly then, simple indoles and pyrroles also gave unsatisfactory results. This was overcome by the Merck KGaA. group with the perhaps antiintuitive expedient of *ortho* carboxy substitution, giving *N*-aryl 2-carboxyindoles and pyrroles in moderate yields (21–50%).[40] Using a mixture of triethylamine and pyridine as the base, the same group extended the reaction to substituted 2-pyridones (Scheme 8) and 3-pyridazinones. Here, 6-substitution in the 2-pyridones was generally detrimental (yields <10%), presumably on steric grounds, although binuclear heteroaromatics such as **14** and **15** were successfully *N*-arylated. Hartwig and co-workers prepared *N*-aryl indoles and pyrroles by cross-coupling with aryl halides using catalytic palladium(0) and the recently introduced tri(*tert*-butyl)-phosphine ligand (5 examples, 64–88%).[41] A palladium(II) and copper(II) catalyst mixture featured in the highly efficient *N*-arylation of 1,2,3-benzotriazole[42] (15 examples, 87–98%) while Buchwald and co-workers used catalytic copper(II) triflate–benzene to prepare *N*-aryl imidazoles from aryl halides[43] (10 examples, 62–99%). The longer established *N*-phenylation with triphenylbismuth diacetate and catalytic copper(II) acetate was applied to various azoles (Scheme 9) and was found to be equally applicable to electron rich and electron deficient heterocycles provided *N*,*N*,*N*′,*N*′-tetramethylguanidine was added in the latter case.[44]

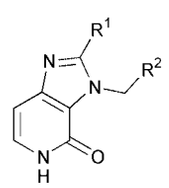


X	Y	Yield (%)
CH	N	45–76
N	CH	62–72
N	N	11, Ar = o-tolyl

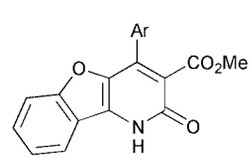
Scheme 7



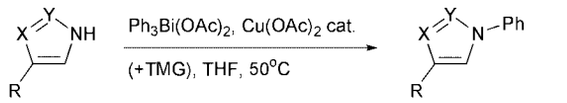
Scheme 8



14



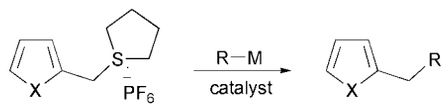
15



R	X	Y	Yield (%)
H	CH	CH	44
H	N	CH	60*
Ph	N	N	87*

* denotes addition of TMG
TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine

Scheme 9



25

X	M	catalyst	Yield (%)
O, S, NBoc	$SnBu_3$	Pd^0, CuI, $(PhO)_3P$	60–97
O, S	$B(OH)_2$	$Pd(PhCN)_2Cl_2$, $(PhO)_3P$	55–84
O, S	ZnCl	$Pd(PhCN)_2Cl_2$, $(PhO)_3P$	53-67

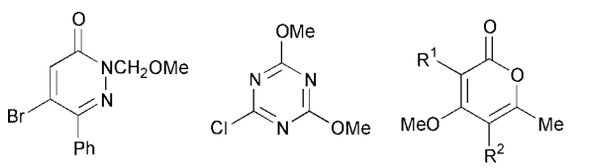
Scheme 10

2.1.5 Examples of RAS by transition metal catalysed coupling to heteroaromatics

The electronic activation of C–Cl bonds in azaheteroaromatics, *e.g.* 2-chloropyridines, has been an advantage as many of these systems will undergo transition metal catalysed coupling reactions with standard catalyst combinations. Advances in general methodology for the coupling of unactivated chloroarenes, as recently reviewed,[45] should widen the scope of this strategy further.

Some recent examples of transition metal catalysed cross-couplings with heteroaryl halides or heteroaryl metal species which may be useful for RAS are compiled in Table 1 (monocyclic) and Table 2 (bi- and polycyclic). In many cases the heteroaromatic coupling partners were made by the methods discussed above.

These strategies involve coupling to core atoms of the heteroaromatic. In contrast, Liebeskind and co-workers have described a route that permits RAS through Stille, Suzuki and Negishi couplings to the stable heterobenzylic sulfonium salts **25**[72] (Scheme 10). Extensive optimisation was necessary to find effective catalyst systems based on the weak donor ligand triphenyl phosphite to avoid reactions of the ligand with the activated salts. Although the *N*-Boc-pyrrole derivative was effectively coupled under Stille conditions, its reactions with boronic acids and organozincs were not synthetically useful. Cross-couplings with heteroarylmetals are not always straight-



16 **17** **18a** R^1 = I, R^2 = H; **18b** R^1 = H, R^2 = Br

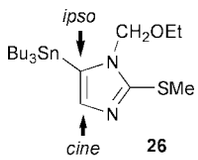
Fig. 1

Table 1 Further examples of transition metal catalysed cross-couplings to monocyclic heteroaromatics

Heterocycles[a]	Coupling partners/catalysts/reagents	Notes	Ref.
2-Chloropyridines	$ArB(OH)_2/Pd(PPh_3)_4/K_2CO_3$	46–83%, 7 examples	46
2-Chloro- and 2-bromopyridines	$ArB(OH)_2/Pd(PPh_3)_4/KOBu^t$	77–86%, 3 examples of coupling to hindered arylboronic acids	47
2-Iodo- and 2-bromopyridines	$HetArM/Pd(PPh_3)_4/Na_2CO_3$ HetAr = thiazole, imidazole, furan, thiophene, pyrrole; M = B, Sn, Zn	20–40%, 7 examples; inhibitors of endothelin converting enzyme-1	48
2-Chloropyridines	$ArX/NiX_2bpy/Mg$ or Zn anode	40–80%; electrochemical *in situ* generation of ArZnX for cross-couplings	49
2-Chloro- and 2-triflyloxy-3-nitropyridines	Vinyltributyltin/$Pd(PPh_3)_4$	69–86%, 2 examples; ribonucleotide reductase inhibitors	50
	Methyl acrylate/$Pd(OAc)_2/PPh_3$	51%, 1 example	
3-Iodo-5-chloropyridine	Bicyclo[2.2.1]alkenes/$Pd(OAc)_2/Ph_3As$	75–96%, 4 examples incl. epibatidine; Ph_3As gave higher yields than PPh_3	51
4-Chloropyridines	$ArB(OH)_2$/various Pd^0	50–82%, 7 examples; catalyst optimisation was required for carboxy and carboxamide substituted 4-chloropyridines	46
4-Bromo-1-alkyl-2-pyridones	Indole-2-Met/$Pd(PPh_3)_4$ Met = ZnCl or $SnBu_3$	51–71%, 4 examples; *N*-SEM protection of the indole was superior to *N*-(4-methoxybenzene)sulfonyl protection	52
2-Bromopyrimidine	$HetArSH/Pd(PPh_3)_4/KOBu^t$ HetAr = substituted pyrimidine-2-thiols	58–88%, 5 examples; Pd catalysis was essential for substitution with these thiols; unprotected –OH were tolerated in the nucleophilic component	53
2-Methoxymethyl-5-bromo-6-phenylpyridazin-3-one (**16**)	$RC{\equiv}CH/(Ph_3P)_2PdCl_2$, CuI/Et_3N	70–85%, 4 examples; *N*-protection with the MOM group was essential	54
	$RSnBu_3/(Ph_3P)_2PdCl_2$	80–90%, 2 examples; Heck coupling with styrene was also successful (40%)	
2-Chloro-4,6-dimethoxy-1,3,5-triazine (**17**)	RC=CH/$Pd(PPh_3)_4$, CuI/Pr^i_2EtN	46–90%, 4 examples; Sonogashira couplings with Pd(10%)/C as the Pd source were also successful (25–100%, 3 examples)	55
N-Boc-Pyrrole-2-boronic acid	ArX and $HetArX/Pd(PPh_3)_4/Na_2CO_3$	15–98%, 11 examples; yields were best for electron deficient Ar, although an *o*-methoxy substituent was also associated with higher yields	56
N-Tosyl-2-formyl-3-iodopyrrole	$ArB(OH)_2$ and $HetArB(OH)_2/PdCl_2$-dppf/$Ba(OH)_2$	61–98%, 7 examples incl. several hindered $ArB(OH)_2$; coupling was not achieved with Pd^0 catalysts lacking the bidentate dppf ligand	57
5-Bromo-2-formylfuran	$ArB(OH)_2/Pd(OAc)_2/K_2CO_3$, Bu_4NBr	46–76%, 7 examples; water was the solvent; these 'ligandless' Pd conditions were effective for Suzuki couplings to 4- and 5-bromo-2-formylthiophenes	58
4-Bromofuran-2(5*H*)-ones	$ArB(OH)_2$ and $HetArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$	61–85%, 9 examples	59
3- and 5-Halo-2-pyranones (**18ab**)	$ArB(OH)_2$/ $Pd(PPh_3)_4$ or $Pd(dba)_2/K_2CO_3$	38–87%, 11 examples; $Pd(dba)_2$ was optimum for **18a**, $Pd(PPh_3)_4$ for **18b**	60

[a] For structures **16**–**18** see Fig. 1.

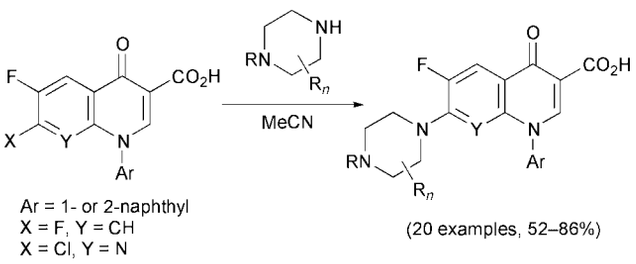
forward: the 5-stannylimidazole **26** was found to give a mixture of not only the expected *ipso* substitution product with a 3-iodoindole, but also the *cine* substitution pattern (46% and 36% yields respectively).[73] The latter compound was thought to arise from competitive Heck reaction of the 5-stannylimidazole.



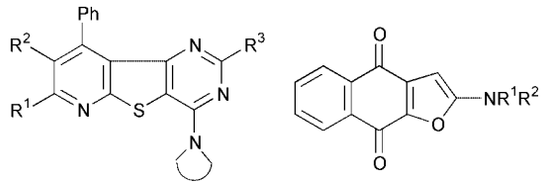
26

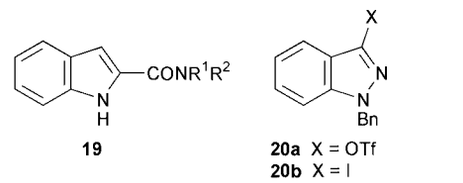
2.2 Nucleophilic aromatic substitution

Simple aromatic nucleophilic substitution of activated carbon–halogen bonds in heteroaromatics is an invaluable component of RAS, particularly for the installation of oxygen- or nitrogen-linked substituents. For example, a series of antiviral quinolone and naphthyridine derivatives were made by selective nucleophilic displacement of activated halides with piperazines[74] (Scheme 11). Similarly, the antiallergic pyridothienopyrimidines **27**[75] and the naphthofuranoquinones **28**[76] resulted from S_NAr on the chloro precursors.



Scheme 11





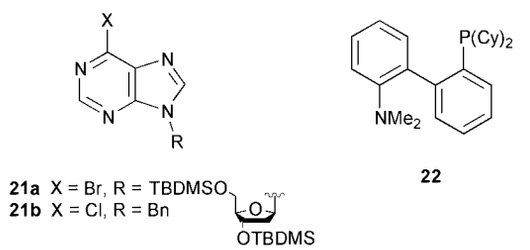


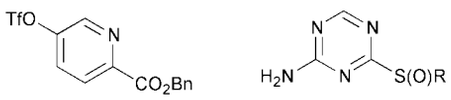
Fig. 2

Table 2 Further examples of transition metal catalysed cross-couplings to bi- and polycyclic heteroaromatics

Heterocycles[a]	Coupling partners/catalysts/reagents	Notes	Ref.
N-Boc-Indole-2-boronic acid	ArX and HetArX/$Pd(PPh_3)_4/Na_2CO_3$	26–66%, 3 examples; electron rich ArX failed to couple and significant dimerisation of the indole was seen in all cases	56
2-Iodoindole	R^1R^2NH, CO/$(PPh_3)_4PdCl_2/Bu_3N$	33–97%, 8 examples; aminocarbonylation giving 2-carboxamidoindoles (**19**); tolerant of acidic functionality and successful with *N*-alkoxyamines	61
6-Bromo- and 6-iodoindoles	CH_2=$CHCH_2SnBu_3$ and $HetSnBu_3$/$Pd(PPh_3)_4$, CuI	43–93%, 15 examples; lower yields were associated with unstable tin reagents	62
3-Triflyloxy-1-benzylindazole (**20a**)	2-Trimethylstannyl-5-(methoxy-carbonyl)furan/$Pd(PPh_3)_4$	52%; the coupling was also successful with *in situ* generation of the furanyltin (37%); preparation of the guanylate cyclase activator YC-1	63
3-Iodo-1-benzylindazole (**20b**)	$ArB(OH)_2$ and $HetArB(OH)_2/Pd(PPh_3)_4/NaHCO_3$	68–79%, 6 examples; coupling of unprotected 3-iodoindazole was also possible with (2-furyl)$B(OH)_2$ (65%); preparation of YC-1	64
4- and 6-bromo-1-tritylbenzimidazoles	RNH_2, piperazines, morpholine/$Pd_2(dba)_3$, BINAP or dppf/NaO^tBu or Cs_2CO_3	54–97%, 5 examples; *N*-protection was essential; Cs_2CO_3 was needed to couple the 6-Br analogue; 5-Br-benzimidazole did not couple; 5-HT_{1A} ligands	65
6-Bromopurines (**21a**)	$ArNH_2/Pd_2(dba)_3$, **22**/K_3PO_4	52–72%, 6 examples; Buchwald's electron rich ligand **22** and a mild base were compatible with the labile sugar substituent	66
6-Iodopurine	RC≡CH/$(PPh_3)_2PdCl_2$, CuI/R_3N	63–82%, 4 examples; coupling was successful with and without *N*-protection;	67
6-Chloropurine	CH_2=$CHSnBu_3/(PPh_3)_2PdCl_2$ then ArX/ $Pd(OAc)_2$	71–97%, 7 examples; tandem Stille–Heck was developed to give cytokinine analogues; Stille vinylation required *N*-protection	67
6-Chloro-9-benzylpurine (**21b**)	$ArB(OH)_2/Pd(PPh_3)_4/K_2CO_3$	62–95%, 6 examples; aqueous conditions were better for electron poor and heterocyclic boronic acids	68
7-Iodoisoxazolopyridone (**23**)	$ArSnBu_3$ or CH_2=$CHSnBu_3/Pd_2(dba)_3$, $AsPh_3$	74–78%, 2 examples; Ph_3As was the optimum ligand for these Stille couplings	69
Tricyclic imidoyl chloride (**24**)	$RNH_2/Pd_2(dba)_3$, BINAP/$NaOBu^t$	65–93%, 9 examples; superior to the uncatalysed S_NAr displacement with 1° amines, which was low yielding and required excess amine	70
N-Alkyl-3,6-dibromocarbazoles	RMgX or $ArMgX/NiCl_2$(dppp) or $NiCl_2$(dmpe)	56–90%, 12 examples; double Kumada coupling	71

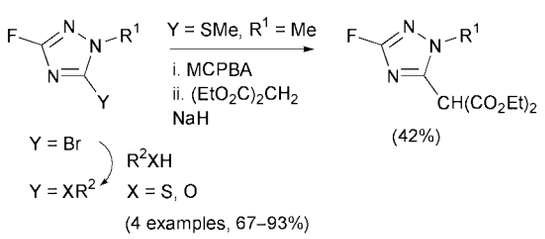
[a] For structures **19**–**24** see Fig. 2.

Two reports were made of the synthesis of antihistamine 2-aminobenzimidazoles from 2-chlorobenzimidazoles. While the first[77] described thermal conditions for the substitution (9 examples, 21–57%), the second[78] showed that reaction under high pressures (13 kbar) was efficient (7 examples, 66–91%) and could be superior for displacements with moderately hindered amines (*e.g.* isopropylamine). Nucleophilic substitution with amines was also demonstrated for 5-bromothiophene-2-carbaldehyde[79] and the 3-triflyloxypyridine **29**.[80] Ion-exchange resins were used as scavengers for excess amine in the purification of 2-aminopyrimidines made by parallel solution-phase S_NAr reactions.[81] Instead of a halide or sulfonate, the alkylsulfinyl triazines **30** were used at Hoffmann-La Roche as the precursors to a small library of bis-aminotriazines (6 examples, 79–95%).[82] Selective *N*-arylation of 4-pyridone was achieved with a variety of electron deficient haloaromatics, including 2-chloropyridines, 2-chloropyrimidine and 2-chlorobenzthiazole (75–80%).[83]

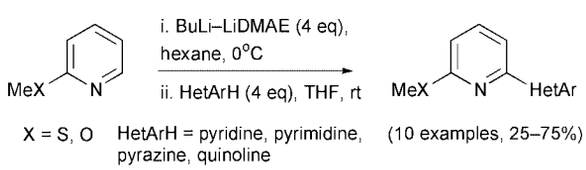


29 (4 examples, 60–75%) **30**

Substitution of haloheteroaromatics by carbon nucleophiles can be problematic, but at Novartis this was overcome for 3-bromo-5-fluoro-1,2,4-triazoles by selective conversion of the bromide to a sulfonate[84] (Scheme 12). An important direct access to carbon-linked bis-azacycles was found by Fort and Gros *via* vicarious nucleophilic substitution of hydrogen with lithiated pyridines[85] (Scheme 13). Four equivalents of the metalating base and the electrophilic component were necessary for good yields of the bis-heterocycles. There was no need for a separate oxidation step as the addition products rearomatised spontaneously on exposure to air. The monosubstitution of 3,6-dichloropyridazine with pyrrolylmagnesium bromide was also successful and allowed the synthesis of analogues of the bis-heterocycle by further substitution of the remaining halide.[86] Analogues of the oestrogen receptor modulator raloxifene were made by Michael addition–elimination of aryl Grignards to 2-dialkylamino-3-aroylbenzo[*b*]thiophenes.[87]



Scheme 12

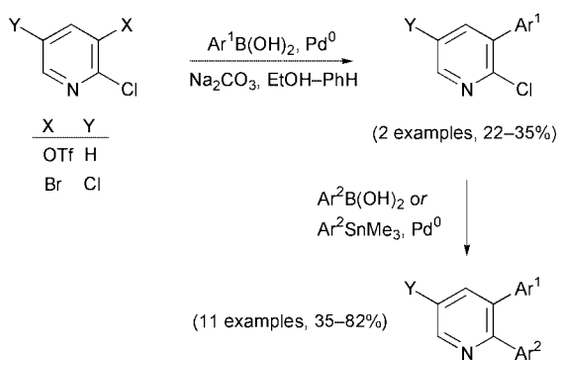


Scheme 13

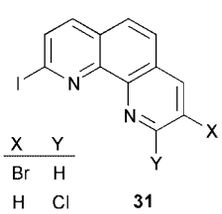
3 Rapid multiple substitution

3.1 Sequential transition metal catalysed coupling

The simple reactions discussed above become more powerful for rapid analogue generation if they can be applied sequentially to a polyfunctionalised heteroaromatic core without the need for additional manipulations between the attachment of the pendant substituents. The inherent polarisation of heteroaromatic ring atoms can assist in the selective reaction of such polyfunctional cores, although this may equally present problems of undesired reactivity to be overcome. For example, the Merck group described sequential Suzuki and Stille couplings on polyhalopyridines[88] (Scheme 14). Low yields in the first couplings were due to competition between coupling to the C(3)–X and activated C(2)–Cl bonds, although an unactivated C(5)–Cl bond remained untouched. This interference from the C(2)–Cl bond was avoided by starting with the 2-aminopyridine and converting this substituent to a halide in an additional intervening step. Conditions for the selective palladium catalysed carbonylations of 2,3-dichloro-, 2,5-dichloro- and 2,3,6-trichloropyridines at the activated C(2)–Cl bond were described by the process group at Lonza.[89,90] The dihalo-1,10-phenanthrolines **31** underwent sequential Suzuki and Sonogashira couplings, where the double activation of the C(2)–I bond ensured this centre reacted first.[91]

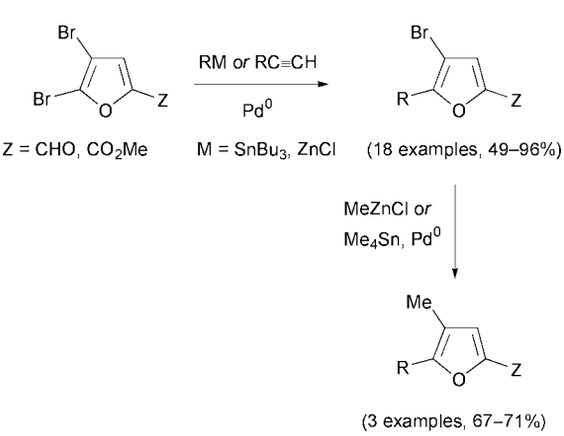


Scheme 14



31

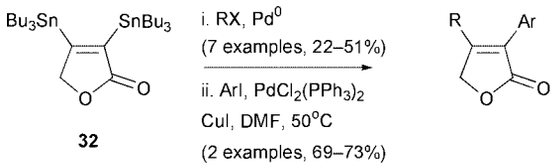
Bach and Krüger have worked extensively on serial couplings to 2,3-dibromofurans[92–94] (Scheme 15). The C(2)–Br bond reacted readily in high yield, but more effort was required to find conditions to couple to the less reactive C(3) centre. The electron withdrawing 5-substituent was not essential for the couplings, but gave an additional point of substituent attachment by Wittig and related processes, leading to 2,3,5-trisubstituted furans.



Scheme 15

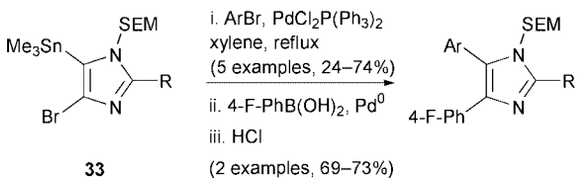
Bis-metalated heteroaromatics can also be used for sequential couplings, as was shown by Sweeney and co-workers for the

3,4-distannylfuran-5(2*H*)-one **32**[95] (Scheme 16). The greater reactivity of the 4-stannyl group was predicted from the relative reactivity of the corresponding monostannylated compounds. Tandem Stille couplings were also successful on symmetrical 2,6-bis(tributylstannyl)pyridine[96] and a general preparation of 1,2-distannyl heteroaromatics following treatment of the 1,2-dibromides with trimethyltin sodium in tetraglyme was reported.[97]



Scheme 16

Sequential coupling to heteroaromatics bearing both halo and metal functionality is also possible: the vicinal bromostannane **33** (Scheme 17) was subject to Stille conditions without substantial homocoupling, followed by Suzuki couplings to the bromide.[98] The starting materials themselves were accessible from *N*-SEM-2,4,5-tribromoimidazole by selective metalation or Suzuki coupling to the 2-bromo substituent. Knochel and co-workers have described the selective monomagnesiation and reaction of dibromoheteroaromatics, including imidazoles similar to those discussed above, although the mixed metal–halo species were not used in coupling reactions.[99] Stille cross-coupling of 2-tributylstannyl-6-bromo-3,5-lutidine was also reported, where the steric hindrance of the flanking methyl groups retarded homocoupling side-reactions.[100]



Scheme 17

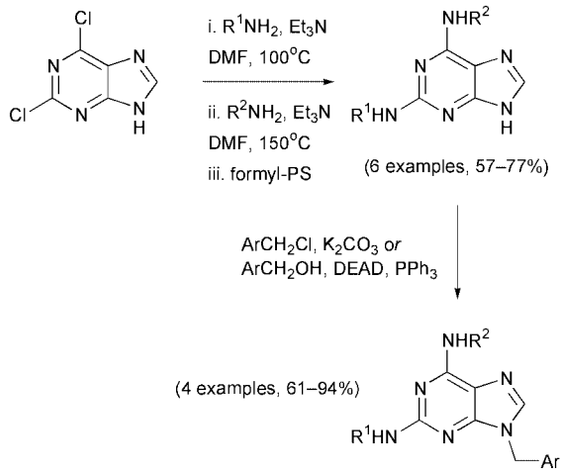
3.2 Sequential nucleophilic aromatic substitution

Polyhaloheteroaromatics can be excellent substrates for sequential nucleophilic displacements and recent work has described the RAS of diaminopurines by this approach. A library of 2,3,9-trisubstituted purines was prepared by Abell and Fiorini using solution-phase parallel synthesis where formyl-resin capture served to remove excess amine reagents[101] (Scheme 18). After two nucleophilic displacements, selective alkylation of N-9 was presumably controlled by the steric hindrance at N-7 due to the adjacent C-6 substituent. A similar sequence was exemplified starting from 2-amino-6-chloropurine. Other groups have reported RAS from 9-alkyl-2-iodo-6-chloropurines **34**.[102,103] Selective displacement of the 6-chloro substituent by amines was possible at moderate temperature (45 °C) while more forcing conditions (120–140 °C) were needed for the second substitution.[102]

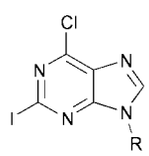
Trisubstituted triazines were formed from cyanuric chloride by three sequential S_NAr displacements with amine or alcohol nucleophiles[104] (Scheme 19). This parallel synthesis was carried out in automated fashion using a solid-supported liquid–liquid extraction as the main purification technique. The same approach was applied to libraries of disubstituted pyrimidines, quinoxalines and quinazolines; again using either amine or alcohol nucleophiles.

3.3 Mixed sequential coupling–nucleophilic substitution

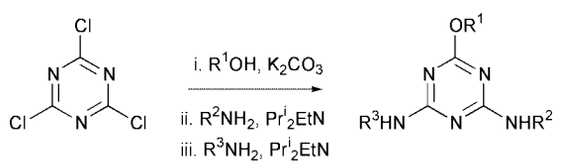
The combination of monosubstitution of 3,6-dichloropyridazine with amines followed by Suzuki coupling provided



Scheme 18

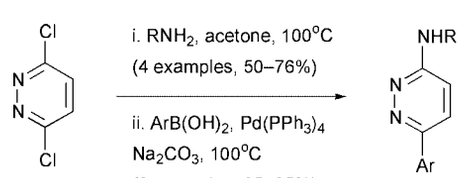


34 R = alkyl



Scheme 19

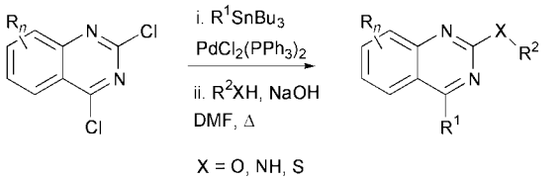
a simple preparation of acetylcholinesterase inhibitors[105] (Scheme 20). The inverted sequence of Suzuki coupling followed by nucleophilic amine substitution was applied to 2,4-dichloro-6-methylpyrimidine, where exclusive reaction of the 4-chloro group was seen in the first step.[106] 3,6-Dichloropyridazine and other dichloroazaaromatics were desymmetrised by reaction with HI–NaI to give monoiodoheterocycles which underwent coupling reactions selectively at the C–I bond.[107]



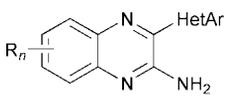
Scheme 20

Three commercial groups have reported RAS of binuclear heteroaromatics by sequential S_NAr–coupling reactions. At Novartis, phosphodiesterase inhibitors were made from 2,4-dichloroquinazolines by first substituting at the more reactive 4-position in a Stille coupling[108] (Scheme 21). The 2-chloro substituent was then displaced by amines, alcohols or thiols in good yields (50–90%), or could be subject to further palladium catalysed coupling with alkylzincs. A series of 2-amino-3-heterocyclylquinoxalines **35** were prepared at Parke–Davis from 2,3-dibromoquinoxalines by reaction with ammonia followed by Suzuki or Stille couplings (16 examples, 52–98%).[109]

The group at Shionogi found the reactivities of 2,4-dichloroquinoline and 5,7-dichloropyrazolo[1,5-*a*]pyrimidine towards carbon nucleophiles were controlled by the addition of LiCl[110] (Scheme 22). In the presence of the additive, uncatalysed

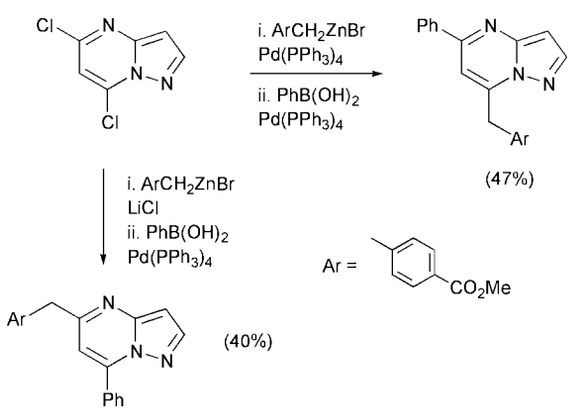


Scheme 21



35

addition of benzylzincs occurred at the C–Cl bond α to nitrogen, whereas various coupling reactions mediated by palladium took place at the γ-position first without the need for the additive.



Scheme 22

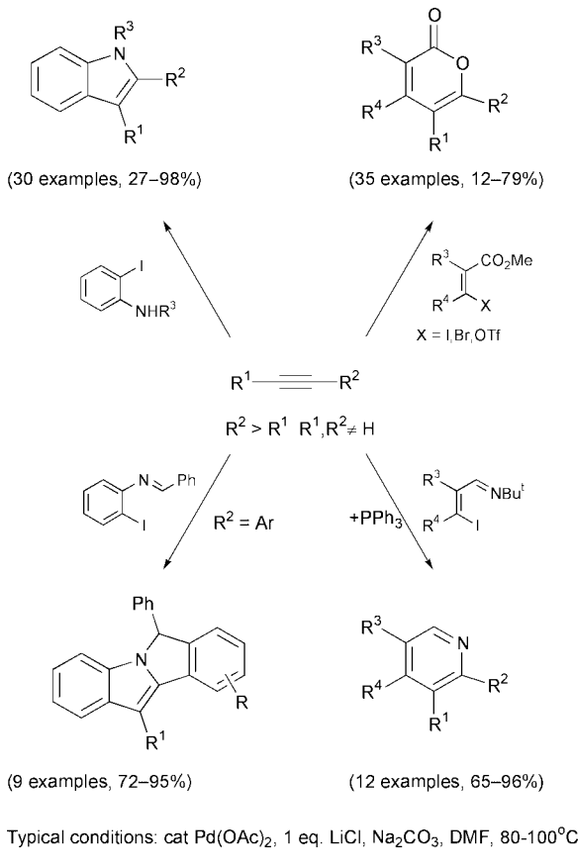
4 New strategies for ring construction suitable for rapid analogue synthesis

The previous sections have dealt with ways of appending substituents to intact heteroaromatic cores. Much recent methodology concerns new ways of constructing the cores where diversity of substitution can be introduced during the cyclisation step, as well as providing functionalised heterocycles suitable for further RAS.

4.1 Annulation of alkynes and equivalents

Larock and co-workers have pioneered RAS using the palladium catalysed intermolecular heteroannulation of internal alkynes (Scheme 23). A general and practical set of conditions, in which the inclusion of stoichiometric lithium chloride was essential, gave indoles,[111] α-pyrones,[112,113] isocoumarins,[113] pyridines,[114] isoquinolines[114] and isoindolo[2,1-*a*]indoles[115] depending on the coupling partner. Although the reaction was limited to internal alkynes, the use of trimethylsilylacetylenes followed by desilylation afforded compounds equivalent to the reaction of monosubstituted alkynes. Regioselectivity was generally good to excellent, with the larger alkyne substituent usually occupying the position adjacent to the heteroatom. This was rationalised as a result of minimising steric interactions between the alkyne and the aryl coupling partner during the insertion of the alkyne into the aryl–Pd bond.[111] The methodology was used to prepare optically active tryptophans.[116]

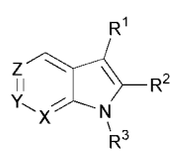
Similar chemistry was developed for the preparation of 5-, 6- and 7-azaindoles **36**[117,118] and pyrrolo[3,2-*c*]quinolines **37**.[119] A group at Abbott reported a two-step palladium(0) and copper(I) catalysed process for the synthesis of 5-azaindoles which was applicable to terminal alkynes and in some cases was successful



Typical conditions: cat $Pd(OAc)_2$, 1 eq. LiCl, Na_2CO_3, DMF, 80-100°C

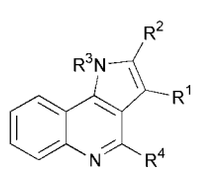
Scheme 23

as a single-step process.[120] Monosubstituted allenes were used in place of internal alkynes in the palladium catalysed iminoannulation to yield pyridines and isoquinolines[121] (14 examples, 10–85%).



36 $R^2 > R^1$ $R^1,R^2 \neq H$

R^3	X	Y	Z	Yields (%)		ref
H,Me,Bn	N	CH	CH	27–88	(16 examples)	117
H	N	CH	CH	47–77	(4 examples)	118
H	CH	N	CH	19–73	(4 examples)	118
H	CH	CH	N	22–65	(3 examples)	118

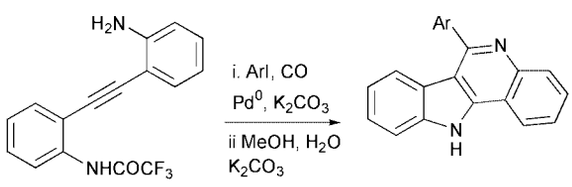


$R^2 > R^1$ R^1, $R^2 \neq H$

37 (17 examples, 58–85%)

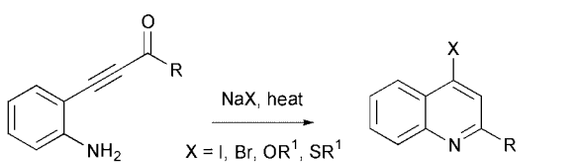
Several articles have described the cyclisation of α-alkynylanilines prepared as discrete intermediates by Sonogashira or Castro–Stephens couplings and triggered by nucleophilic addition or palladium catalysed coupling to the triple bond. For example Cacchi, Marinelli and co-workers prepared indolo[3,2-*c*]quinolines by carbonylative cyclisation of the bis(anilino)alkyne **38** (Scheme 24) in a one-pot process.[122] The same group made simple 2-substituted quinolines from β-(*o*-aminophenyl)-α,β-ynones using palladium catalysed transfer hydrogenation to effect the cyclisation[123] (10 examples, 55–85%). Arcadi and co-workers used the same precursors but triggered the cyclisation by conjugate nucleophilic addition to give 2,4-disubstituted quinolines[124] (Scheme 25). The produc-

tion of 4-haloquinolines by this route allowed further RAS by palladium catalysed couplings. Alternatively the 4-alkoxy- and 4-thioalkylquinolines were good substrates for 1,3-dipolar cycloadditions with azides and nitrile oxides, generating more complex heteroaromatic cores. 2-Styrylindoles were constructed by a tandem Sonogoshira–Suzuki–cyclisation sequence, in which the three palladium catalysed reactions could be carried out in one pot.[125] Grigg and co-workers prepared substituted benzofurans and isoquinolin-1-ones from the intramolecular cyclisation of aryl iodides onto neighbouring allenes, followed by anion capture with azide and 1,3-dipolar cycloadditions in a cascade process.[126]



38 (10 examples, 35–86%)

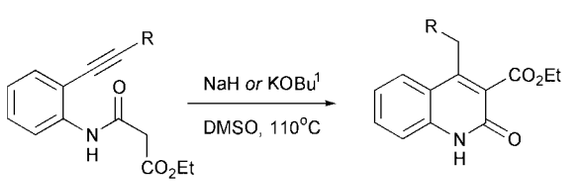
Scheme 24



R = aryl, vinyl (10 examples, 32–98%)

Scheme 25

Conjugate addition of amines to (*o*-silyloxyphenyl) alkynyl ketones led to chromen-4-ones[127] (7 examples, 54–96%) and 2,3-disubstituted quinolines were prepared by the cyclisation of *o*-alkynylisocyanobenzenes induced by O-, N- and C-nucleophiles[128] (12 examples, 65–94%). The intramolecular cyclisation of ethyl *N*-(*o*-alkynyl)malonoanilides under strongly basic conditions gave 3,4-disubstituted-2(1*H*)-quinolones, which were elaborated to trisubstituted analogues by conversion to the 2-triflyloxy derivatives and subsequent palladium catalysed C–C bond formations[129] (Scheme 26). An acid promoted cyclisation of (*o*-alkynyl)benzoates and analogues gave intermediate isobenzopyrylium salts, which were aminated with ammonia to give 3-arylisoquinolines[130] (7 examples, 21–74%).

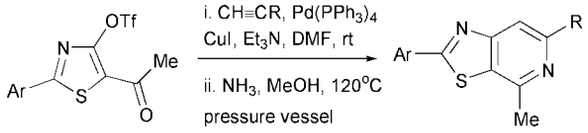


R = aryl, heteroaryl, vinyl (12 examples, 33–75%)

Scheme 26

Arcadi and co-workers described a synthesis of thiazolo-[5,4-*c*]pyridines starting from the 5-acetyl-4-thiazolyltriflates **39**[131,132] (Scheme 27). Sonogashira coupling was followed by cyclisation with ammonia to form the six membered ring. The thiazole triflates were also substrates for Suzuki, Stille and alkoxycarbonylation reactions (6 examples, 64–95%) or direct displacement of the 4-triflyloxy group with amines, alcohols and thiols (4 examples, 44–94%).[132]

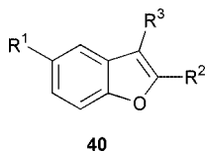
Arcadi, Cacchi and co-workers also reported a synthesis of 2,3-disubstituted benzo[*b*]furans **40** *via* iodocyclisation of *o*-alkynylphenols to form the heterocycle, followed by palladium mediated couplings to the iodinated products.[133] The intermediate 3-iodobenzofuran (**40** R^1 = Me, R^2 = Ph, R^3 = I) could



39 (10 examples, 41–77%)

Scheme 27

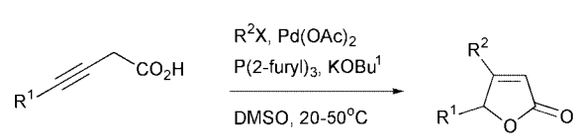
be converted to the 3-trimethylstannyl species (Sn_2Me_6, $Pd(OAc)_2(PPh_3)_2$; 68%) which was a competent partner in the Stille coupling.



40

1,2,4-Trisubstituted furans were made in a one-pot reaction from the conjugate addition of alkynylboronates to enones followed by cyclisation under acidic conditions[134] (10 examples, 31–97%). Various polysubstituted furans were prepared from (*Z*)-2-en-4-yn-1-ols by two methods: cycloisomerisation with palladium(II) iodide gave simple alkyl and aryl substituted products[135] (15 examples, 23–90%), whilst furan-2-acetic esters were obtained when the cycloisomerisation was carried out under oxidative carbonylation conditions[136] (15 examples, 44–75%).

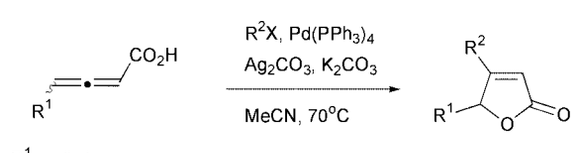
The intermediate palladium(II) species from oxidative addition of palladium(0) to aryl halides was found to promote cyclisation of 3-ynoic acids with concomitant coupling of the palladium-bound organic group, leading to 4,5-disubstituted-furan-2(5*H*)-ones[137] (Scheme 28). Unfortunately the method did not extend to unsubstituted 3-ynoic acids. Ma and co-workers have prepared similar butenolides from 1,2-allenic acids using a palladium(0)–silver(I) co-catalysed process[138] (Scheme 29). As this direct method failed with alkynes as the coupling partners, a two step alternative was developed in which halolactonisation of the 1,2-allenic acids (4 examples, 81–91%) was followed by Sonogashira or Negishi–Knochel couplings (15 examples, 65–99%) to the intermediate 4-halobutenolides.[139,140] Palladium catalysed couplings to 3-bromo-5-(*Z*)-ylidenefuran-2(5*H*)-ones, constructed by a palladium mediated cyclisation, were also described[141] (4 examples, 36–92%). 3-Substituted isocoumarins **41** were made by palladium(0) catalysed tandem coupling–cyclisation of 2-(2′,2′-dibromovinyl)benzoates and organostannanes.[142]



R^1 = alkyl, aryl
R^2 = aryl, alkenyl, alkynyl

(7 examples, 15–76%)

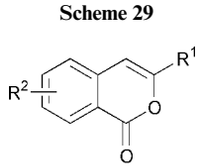
Scheme 28



R^1 = alkyl
R^2 = aryl, alkenyl

(8 examples, 59–79%)

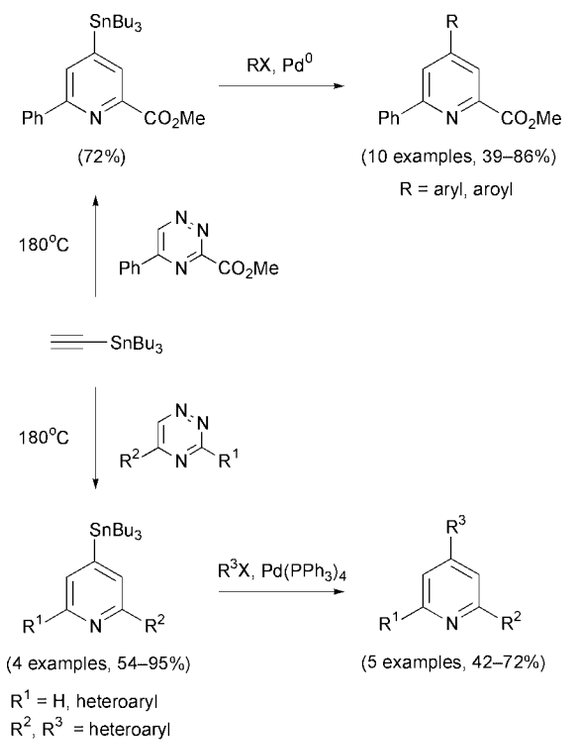
Scheme 29



41

4.2 Cycloadditions

The atom economy and increase in structural complexity inherent in Diels–Alder and other concerted cycloadditions make these attractive reactions for incorporation into rapid analogue syntheses. Sauer and co-workers have worked extensively on the inverse electron demand Diels–Alder cycloadditions of ethynyltributyltin as a means of constructing functionalised monomeric and oligomeric heteroaromatics.[143–148] The regioselective thermal cyclisation of 1,2,4-triazines with ethynyltributyltin gave good yields of 4-stannylpyridines which were elaborated to di- and trisubstituted pyridines by palladium catalysed couplings[143,144] (Scheme 30). As well as using the pyridylstannanes directly, *ipso* substitution with elemental halogens was also successful. This strategy was applied to the synthesis of linear and branched oligopyridines.[145,146]

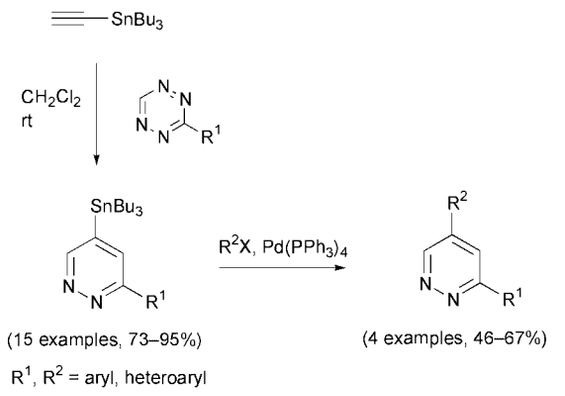


Scheme 30

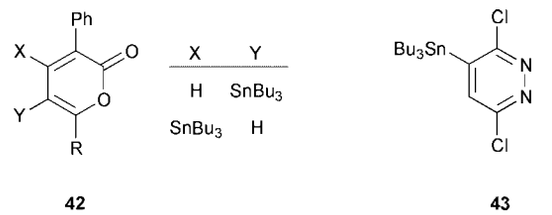
The cycloadditions of 1,3,4-oxadiazin-6-ones were less regioselective but still afforded reasonable yields of the separable α-pyrones **42**.[147] In contrast to the 1,2,4-triazines, which required forcing conditions (180 °C), 3-aryl-1,2,4,5-tetrazines reacted with ethynyltributyltin at room temperature to give selectively the corresponding 5-stannylpyridazines.[148] Again, further transformation of the stannyl substitutent was easily achieved (Scheme 31). A similar outcome was reported for the very reactive 3,6-dichloro-1,2,4,5-tetrazine, which gave the stannylpyridazine **43**.[149]

Ghosez and co-workers revisited the hetero-Diels–Alder cycloadditions of 2-azadienes with electron-poor alkynes and have refined this to a 'one-pot', tandem reaction by devising a convenient *in situ* preparation of the 2-azadienes from *N*-silylimino ethers and acyl chlorides.[150] Substituted 2-pyridones and pyrimidin-2-ones were prepared in generally good yields by this process (13 examples, 43–94%).

Another significant body of work in this area has been that of Padwa and co-workers who have recently published full details of the preparation of highly substituted 2-pyridones by the [3 + 2] cycloadditions of isomünchnones to activated olefins[151,152] (Scheme 32). The initial 3-hydroxy-2-pyridones were readily transformed to the triflates, amongst the first examples of these compounds to be reported, which were used

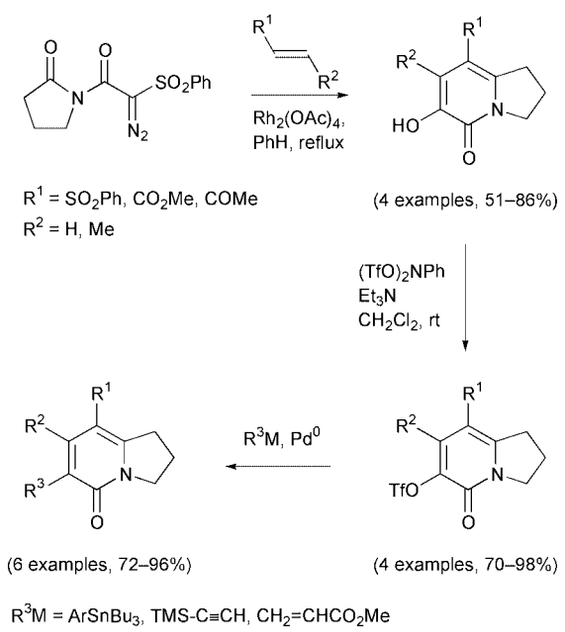


Scheme 31



42 **43**

to introduce further 3-substituents by Stille, Sonogashira and Heck couplings. By decarboxylation of the cycloaddition product with methyl acrylate and electrophilic bromination at the 5-position of the resulting 3-hydroxy-2-pyridone, the 5-bromo-3-triflyloxy-2-pyridone **44** was produced. Selective sequential C–C bond formations to **44** were possible, with the triflate showing the expected higher reactivity towards palladium mediated couplings (4 examples, 53–71%).

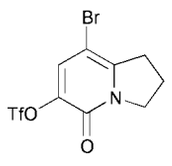


Scheme 32

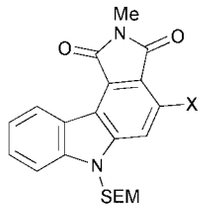
Analogues of the protein kinase C inhibitor staurosporin were made at Synthélabo starting with the Diels–Alder cycloaddition of *N*-methylmaleimide and 2-vinylindoles, leading to the triflate or bromide **45** after aromatisation.[153] Suzuki and Stille cross-couplings to the substrates **45** were successful (5 examples, 67–95%). Substituted 3-bromopyrazoles were assembled starting with the 1,3-dipolar cycloaddition of a bromonitrilimine with alkynes or alkenes.[154]

4.3 Cyclodehydrations

Many heteroaromatics are conveniently prepared by cyclodehydrations and several recent reports describe the application

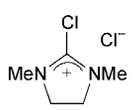


44

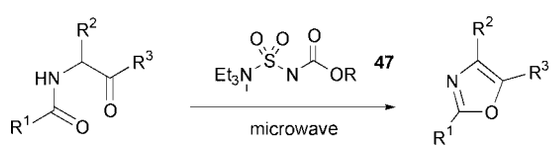


45 X = OTf, Br

of this route to RAS: 2-chloro-1,3-dimethylimidazolinium chloride **46** was proposed as an equivalent to DCC to prepare simple butenolides, oxazolidin-5-ones, 1,3,4-oxadiazoles and thiadiazoles under neutral conditions.[155] 1,1′-Carbonyldiimidazole was used both to couple and then cyclodehydrate carboxylic acids and benzamidoximes, giving 1,2,4-oxadiazoles in a one-pot, automated parallel synthesis (20 examples, 45–69%).[156] The Burgess reagent **47** (R = Me) was particularly effective for the cyclisation of 2-acylamino ketones to oxazoles when used under microwave irradiation (Scheme 33).[157] Simple *N*-aryl and *N*-alkyl pyrroles were also prepared by microwave irradiation of hexane-2,5-dione and amines (8 examples, 75–90%).[158]



46



(8 examples, 80–100%)

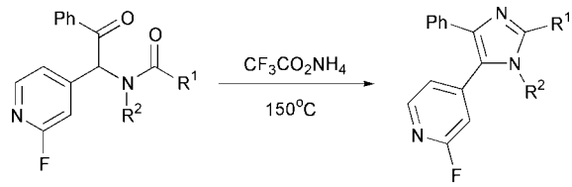
R^1 = alkyl, aryl R^2 = H, Me, CO_2Me R^3 = H, Me, Ph

Scheme 33

Tetrasubstituted imidazoles were formed under neutral conditions on treatment of *N*-(2-oxoalkyl)amides with ammonium trifluoroacetate at high temperature[159] (Scheme 34). The precursors were unstable to the standard acidic conditions for this cyclisation. A one-pot protocol involving sequential condensation of amidines with α,β-unsaturated trifluoromethyl ketones followed by dehydration and oxidation gave the 4-trifluoromethylpyrimidines **48**[160] (13 examples, 40–86%). Similar reaction sequences were developed for the automated parallel synthesis of mono- and polynuclear pyridines from chalcones and 1,3-dinucleophiles (*e.g.* 3-aminocrotononitrile and 2-aminobenzimidazole), where air oxidation was sufficient to achieve aromatisation.[161] Another one-pot method involving cyclodehydration was applied to the synthesis of 1*H*-indazoles in which the cyclisation precursor was formed by an initial S_NAr displacement[162] (Scheme 35). Although general with regard to the ketone and aryl substituents, aryl hydrazines were less reliable and hydrazine itself failed to react. Simple 2-arylquinazolines were formed in a similar manner from the condensation and S_NAr cyclisation of benzamidines with *o*-fluorobenzaldehydes[163] (10 examples, 55–73%).

4.4 Anionic cyclisations

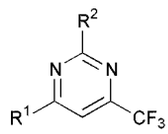
Tosylmethyl isocyanide (TosMIC) is a useful equivalent of the C–N=C synthon for heterocyclic synthesis through the condensation of its α-anion with electrophiles, and was used to prepare simple 5-aryloxazoles by solution-phase parallel synthesis[164] (13 examples, 54–84%). Van Leusen and co-workers have prepared the C-stannylated-α-lithio derivative of TosMIC, which



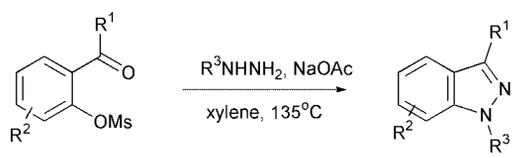
(9 examples, 59–87%)

R^1 = aminoalkyl, cyclo(aminoalkyl) R^2 = H, alkyl

Scheme 34



48
R^1 = aryl, alkyl
R^2 = aryl



(9 examples, 41–91%)

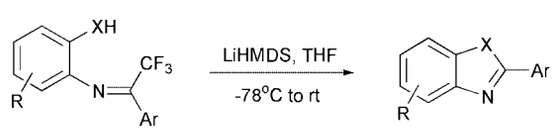
Scheme 35

was condensed *in situ* with Michael acceptors to generate polysubstituted pyrroles[165] (Scheme 36). After methylation or acylation of the free NH, the 2-(trimethylstannyl)pyrroles were good substrates for Stille cross-couplings to aryl halides (4 examples, 21–71%).

R = Ph, CO_2Me
Z = CO_2R, COR, CN, NO_2 (6 examples, 40–90%)

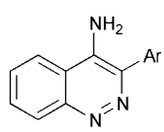
Scheme 36

Kiselyov and colleagues at Amgen have shown the versatility of an anionically activated trifluoromethyl group in the synthesis of cinnolines **49** from *o*-trifluoromethylphenyl hydrazones through the generation of intermediate difluoro quinomethanes.[166] 4-Aminoquinolines were made in a similar fashion,[167] but in the cyclisation of related imines the trifluoromethyl group underwent displacement to give 2-arylbenzimidazoles and benzoxazoles[168] (Scheme 37).



X = O, NH (9 examples, 66–79%)

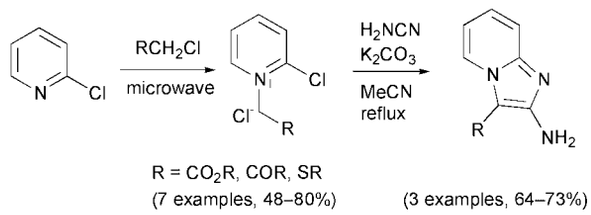
Scheme 37



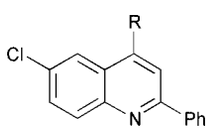
49 (8 examples, 63–76%)

Microwave irradiation was essential for reliable, high yielding *N*-alkylation of 2-chloropyridine at the outset of a synthesis

of 2-aminoimidazo[1,2-*a*]pyridines[169] (Scheme 38). Subsequent aromatic nucleophilic substitution of the 2-chloropyridinium salts (or ylides) with cyanamide was followed by base-promoted cyclisation. A variety of heterocyclic cores were made starting with vicarious nucleophilic substitution of hydrogen in nitroarenes by the α-anion of cinnamyl phenyl sulfone, leading to bi- and tricyclic systems.[170] In the case of the quinolines **50** (R = SO_2Ph) subsequent displacement of the 4-arylsulfonyl group with a wide range of nucleophiles was possible (7 examples, 42–92%).

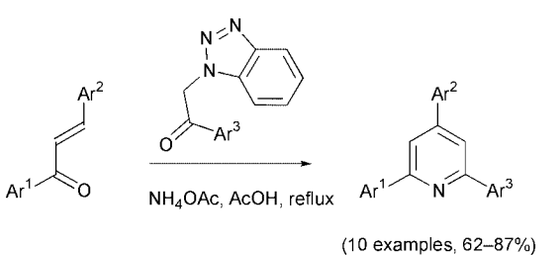


Scheme 38



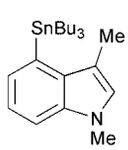
50

α-Benzotriazolyl ketones, as championed by Katritzky and co-workers, have proved very valuable in heteroaromatic synthesis and were used recently to make 2,4,6-triarylpyridines in an efficient condensation with Michael acceptors under conditions that generated the ammonia required for pyridine formation[171] (Scheme 39). The stabilised anions of the α-benzotriazolyl ketones could also be added to the chalcones as a separate step and tricyclic structures were obtained from cyclic ketones.



Scheme 39

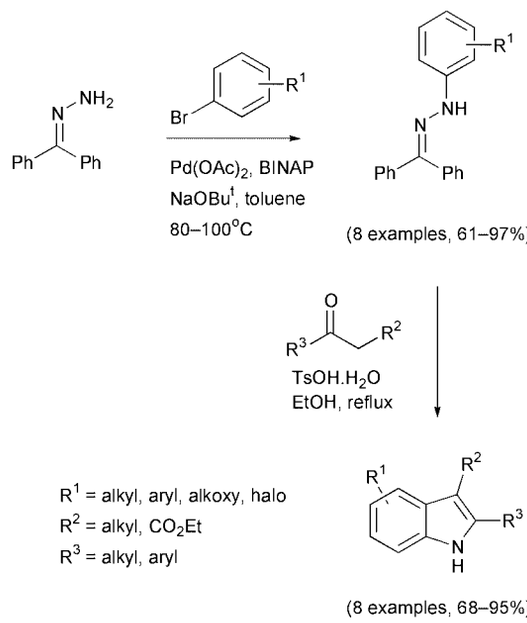
Diverse trisubstituted pyrazoles were formed from the condensation of β-tosylhydrazino phosphonates with aldehydes[172] (17 examples, 17–88%). The Bartoli reaction of Grignard reagents and nitrobenzenes to give substituted indoles was shown to extend to a greater variety of substitution patterns than previously explored,[173] whilst the potential RAS substrate **51** (65%) was made from *N*-(2-bromoallyl)-*N*-methyl-2-fluoroaniline using a 'lithium dance' cyclisation.[174]



51

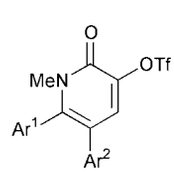
4.5 Miscellaneous ring forming reactions

Buchwald and co-workers proposed an updating of the Fischer indole synthesis using palladium catalysed C–N bond formation that permitted rapid and diverse substitution on the indole ring[175] (Scheme 40). In the simplest manifestation, benzophenone hydrazone was coupled to aryl bromides to generate the aryl hydrazone precursors which underwent deprotection and Fischer cyclisation on acid treatment. A 'one-pot' variant of the route was also effective (6 examples, 54–92%). *N*-Alkyl and *N*-aryl substitution of the indoles was efficiently incorporated by anionic alkylation or a second palladium mediated coupling to the intermediate aryl hydrazones. Palladium catalysis also featured in the preparation of 5-aryloxadiazoles, where acylation of amidoximes was achieved with the acyl palladium species formed from carbonylation of aryl iodides (6 examples, 40–70%).[176]



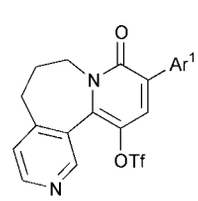
Scheme 40

Highly substituted 2-pyridones were made by Vilsmeier formylation–cyclisation of an *N*-acyl enamine (48%), leading to the 3-triflyloxy-2-pyridone **52**.[177] Palladium catalysed couplings to **52** gave a diverse set of 3-substituents (16 examples, 21–70%). Katritzky and co-workers have described the use of a benzotriazole iminium salt as a Vilsmeier type reagent for the production of alkyl and aryl substituted 3-cyanopyridines from dienamines.[178] The tricyclic 5-triflyloxy-2-pyridone **53** was reached *via* an uncommon 7-*exo*-*trig* radical cyclisation (50%).[179] Palladium catalysed cross-couplings to this compound were also successful (6 examples, 67–93%) (*cf.* Scheme 32).



52

Ar^1 = 4-pyridyl
Ar^2 = 4-methoxyphenyl



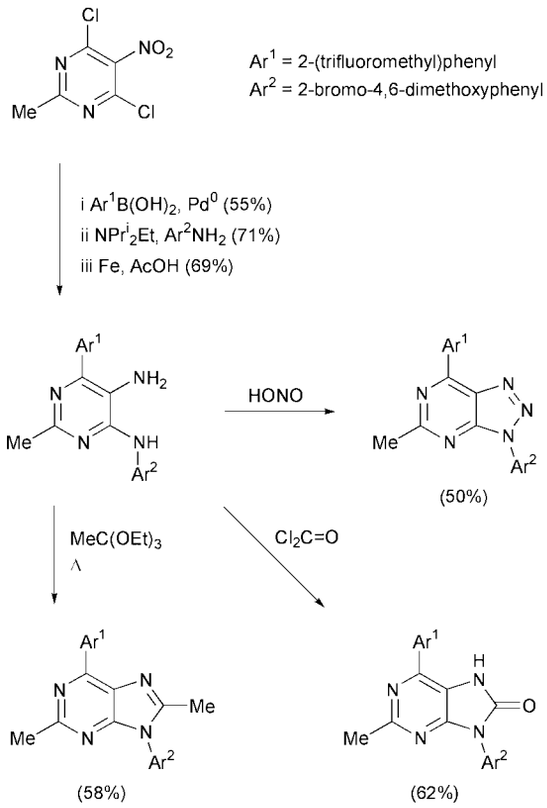
53

Ar^1 = 4-methylthiazol-2-yl

The use of cyclisation reactions as a point at which to introduce diversity was illustrated in the synthesis of antagonists of corticotrophin-releasing hormone[180] (Scheme 41). The diamine cyclisation precursor was assembled by sequential palladium catalysed coupling and nucleophilic aromatic substitution, and was easily converted to a number of different binuclear heterocycles.

5 Multi-component reactions

Multi-component cyclisation reactions, rather than tandem processes of which many examples are described above, can



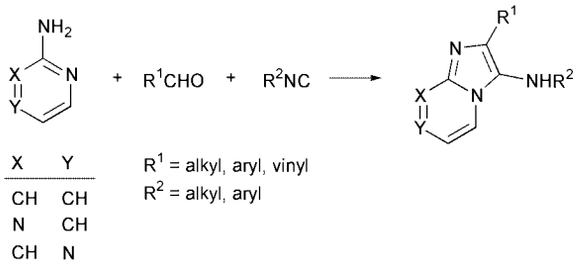
Scheme 41

offer a truly 'one-pot' synthesis of substituted heterocycles. Limitations to diversity may arise, however, when only a restricted range of one or more of the components is available. A recent review discussed the conceptual background to this area and the tools available to assist the discovery of new multicomponent reactions.[181]

Several academic and industrial groups have independently described a three-component preparation of annulated 3-aminoimidazoles which derives from the Ugi condensation (Scheme 42). In the simplest version 2-aminopyridines were condensed with isonitriles and aldehydes to give 3-aminoimidazo[1,2-*a*]pyridines under acid[182,183] or Lewis acid[184] catalysis. Microwave irradiation of the neat reagents absorbed on montmorillonite K10 clay were also effective conditions.[185] The reaction was easily extended to incorporate 2-aminopyrimidines[182,183,185] and 2-aminopyrazines[182–185] as starting materials. Bienaymé and Bouzid further demonstrated the condensation with more diverse heterocyclic replacements for the amidine component (6 examples, 33–90%), leading to a range of [5,5] binuclear heterocycles such as **54**.[182] By replacing the amidine and isonitrile components with β-(*N,N*-dimethylamino)-α-cyanoacrylates and trimethylsilyl azide (as a hydrazoic acid source), these researchers also developed a multicomponent synthesis of tetrazoles[186] (Scheme 43).

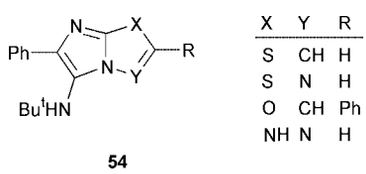
A three-component condensation of aliphatic aldehydes, nitroalkanes and alkylamines gave 1,2,3,4-tetraalkyl pyrroles[187] (Scheme 44). The reaction proceeded by α,β-unsaturated imine formation through a Lewis acid catalysed aldol-type condensation followed by conjugate addition of the nitroalkane. With α,β-unsaturated aldehydes the addition of the nitroalkane and cyclisation took place without the need for catalysis (4 examples, 19–60%). 1,2,3,5-Tetraalkyl- and 1,2,3,4,5-pentaalkylpyrroles were formed from α,β-unsaturated ketone starting materials (5 examples, 34–80%).

The three-component Gewald synthesis of thiophenes involving the condensation of β-ketoesters, cyanoacetate and elemental sulfur was optimised as the starting point for an automated synthesis of tetrasubstituted thiophenes[188]

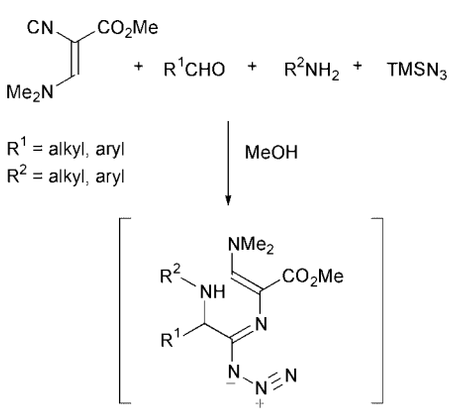


Yields (%)		conditions	ref
40–98	(25 examples)	5% $HClO_4$, MeOH	182
38–91	(7 examples)	AcOH, MeOH	183
35–95		$Sc(OTf)_3$, CH_2Cl_2-MeOH	184
56–88	(14 examples)	K10 clay, microwaves, neat	185

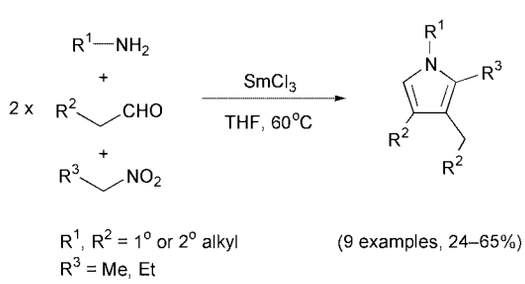
Scheme 42



54



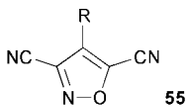
Scheme 43



Scheme 44

(4 examples, 52–71%). The isoxazoles **55** were prepared by the reaction of aldehydes and acetyl chloride on cyano-*aci*-nitroacetate.[189] Although the acetyl chloride was not incor-

porated in the product, it was essential for activation of the intermediate dinitronates to intramolecular cyclisation.



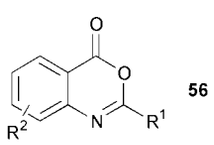
55

R = alkyl, aryl, heteroaryl
(6 examples, 10–93%)

6 Rapid analogue synthesis with solid-supported reagents

The strong current interest in reactions on the solid phase, particularly combinatorial chemistry using solid-supported substrates, has revitalised the related area of solid-supported reagents. Although there are often important issues of reaction kinetics to be addressed when using such reagents, the relative ease of separating the spent reagents from the products can render this an attractive option for RAS. This topic was covered thoroughly in a recent review[190] and only contemporary applications to heteroaromatic syntheses will be summarised here. The use of solid-supported reagents to achieve rapid purification of solution phase synthesis products has also been reviewed.[191]

Several reports deal with solid-supported dehydrating agents as alternatives to the reagents discussed in Section 4.3. For example, disubstituted oxadiazoles were prepared from 1,2-diacylhydrazines using polymer-supported Burgess reagent **47** (R = $(CH_2)_2$PEG) (*cf.* Scheme 33) under microwave irradiation[192] (16 examples, 70–98%). Products of excellent purity (typically 95% by HPLC) were obtained by filtration of the mixture through silica gel to remove the polymer. Polymer-bound 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was used by two groups for automated syntheses of libraries of benzoxazinones **56** by cyclodehydration of urea,[193,194] amide[194] or carbamate[194] derivatives of anthranilic acid.



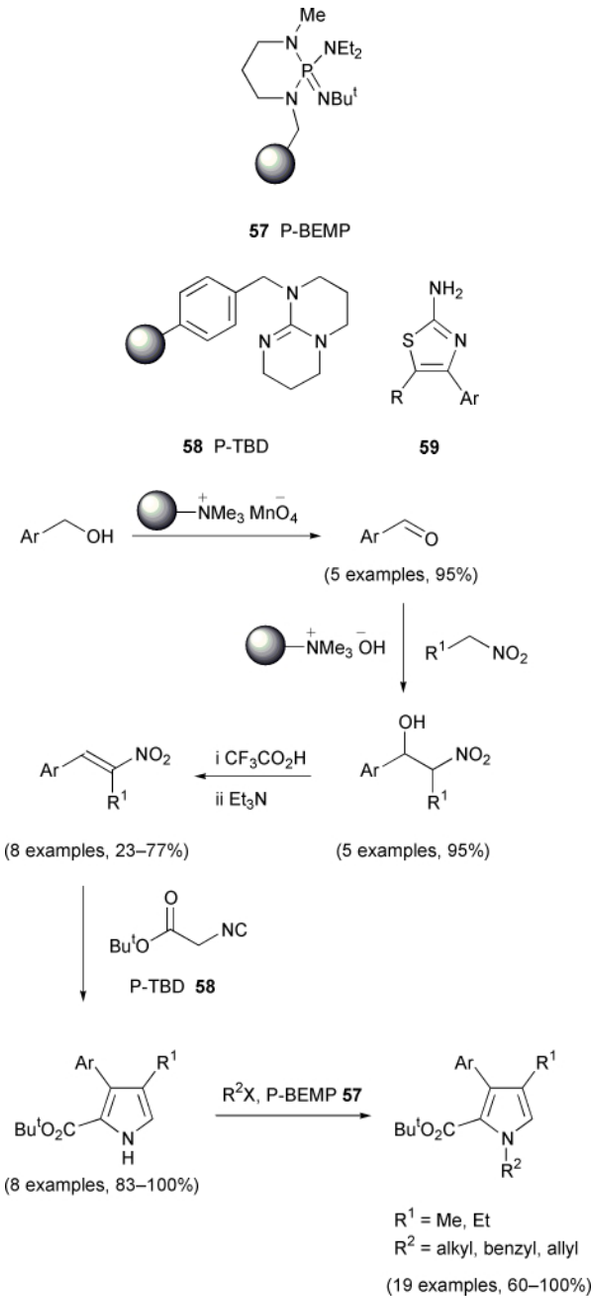
56

R^1 = aryl, alkyl, NHR, OR
R^2 = H, alkyl, halo, NHR, OR

Palladium(0) phosphine complexes supported on reversed phase silica gel were good catalysts for Heck couplings to halogenated heteroaromatics.[195] Tribromide anions immobilised on Amberlyst basic resin provided a superior brominating agent to homogeneous conditions in the aromatisation of 1,4-dihydropyridazines to tetrasubstituted pyridazines[196] (22 examples, 83–96%). Polystyrene-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (P-BEMP) **57** was a useful strong base for the *N*-alkylation of weakly acidic heterocycles such as indole and pyrazole.[197]

Ley and co-workers have provided some compelling examples of heteroaromatic RAS using solid-supported reagents such as those described above: An array of 1,2,3,4-tetrasubstituted pyrroles was produced using solid-supported reagents in all the key steps[198] (Scheme 45). In addition to performing oxidations, Henry condensations, condensations with *tert*-butyl isocyanoacetate and *N*-alkylations with solid-supported reagents, several steps used polymeric reagents to purify the intermediates. Excellent purities (typically >95% by HPLC) were attained for the final products and most intermediates.

A three step rapid analogue synthesis of 3-arylbenzofurans was also presented which used polymer-supported pyridinium



57 P-BEMP

58 P-TBD

59

(5 examples, 95%)

(8 examples, 23–77%)

(5 examples, 95%)

P-TBD **58**

(8 examples, 83–100%)

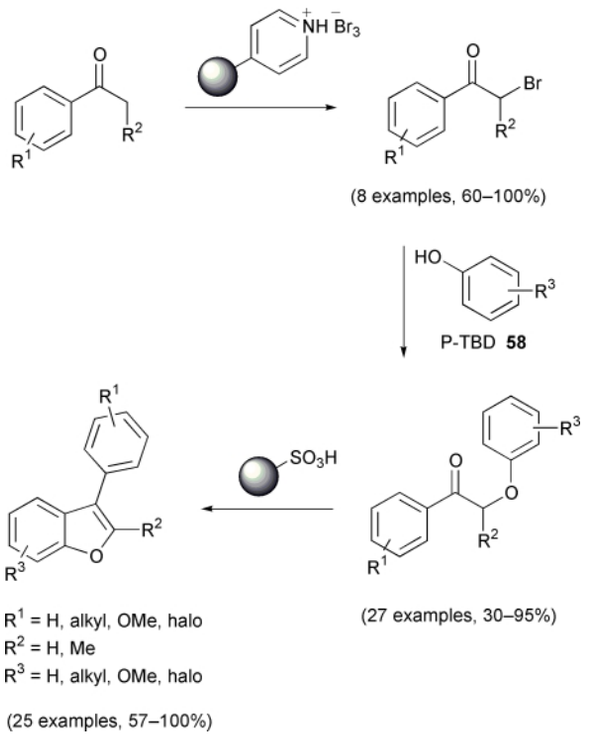
R^1 = Me, Et
R^2 = alkyl, benzyl, allyl
(19 examples, 60–100%)

Scheme 45

tribromide as the brominating agent to prepare α-bromoacetophenones as the first step[199] (Scheme 46). Again, the purities of the intermediates and final compounds were high. The sequence tolerated a range of aromatic substitution, except electron-withdrawing nitro and trifluoromethyl groups which inhibited the cyclisation to the benzofurans. The α-bromoacetophenones produced in this synthesis also reacted with thiourea in the presence of P-TBD **58** to give 2-aminothiazoles **59** (9 examples, 47–95%).[200]

7 Conclusion

From the foregoing selection of recent articles it can be seen that the rapid analogue synthesis of heteroaromatics is a field of significant contemporary interest. As indicated in the introduction, such syntheses are principally a practical means to generate diverse chemical structures to address wider scientific questions. This is amply demonstrated by the high proportion of reports made in the context of medicinal or materials research, by both academic and commercial research groups.



Scheme 46

8 References

1 V. Snieckus, *Med. Res. Rev.*, 1999, **19**, 342.
2 D. M. Coe and R. Storer, *Mol. Diversity*, 1999, **4**, 31.
3 T. L. Gilchrist, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 2849.
4 L. Haughton and J. M. J. Williams, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 2645.
5 C. Plisson and J. Chenault, *Heterocycles*, 1999, **51**, 2627.
6 R. C. F. Jones, C. E. Dawson, M. J. O'Mahony and P. Patel, *Tetrahedron Lett.*, 1999, **40**, 4085.
7 C. Hamdouchi, J. de Blas and J. Ezquerra, *Tetrahedron*, 1999, **55**, 541.
8 O. Sugimoto, M. Mori and K. Tanji, *Tetrahedron Lett.*, 1999, **40**, 7477.
9 K. R. Roh, J. Y. Kim and Y. H. Kim, *Tetrahedron Lett.*, 1999, **40**, 1903.
10 J. Fu, Y. Chen and A. L. Castelhano, *Synlett*, 1998, 1408.
11 S. A. Savage, A. P. Smith and C. L. Fraser, *J. Org. Chem.*, 1998, **63**, 10048.
12 C. A. Busacca, M. C. Eriksson, Y. Dong, A. S. Prokopowicz, A. M. Salvagno and M. A. Tschantz, *J. Org. Chem.*, 1999, **64**, 4564.
13 C. Buon, P. Bouyssou and G. Coudert, *Tetrahedron Lett.*, 1999, **40**, 701.
14 F. Lepifre, C. Buon, R. Rabot, P Buoyssou and G. Coudert, *Tetrahedron Lett.*, 1999, **40**, 6373.
15 E. Arzel, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron Lett.*, 1998, **39**, 6465.
16 E. Arzel, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron*, 1999, **55**, 12149.
17 E. Arzel, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Heterocycles*, 1999, **50**, 215.
18 B. L. Eriksen, P. Vedsø, S. Morel and M. Begtrup, *J. Org. Chem.*, 1998, **63**, 12.
19 T. Fukuda, R. Maeda and M. Iwao, *Tetrahedron*, 1999, **55**, 9151.
20 Y. Kondo, M. Shilai, M. Uchiyama and T. Sakamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3539.
21 C. Papamicaël, G. Dupas, G. Quéguiner and J. Bourguignon, *Heterocycles*, 1998, **47**, 991.
22 A. Batch and R. H. Dodd, *Heterocycles*, 1999, **50**, 875.
23 A. Batch and R. H. Dodd, *J. Org. Chem.*, 1998, **63**, 872.
24 F. Trécourt, B. Gervais, O. Mongin, C. Le Gal, F. Mongin and G. Quéguiner, *J. Org. Chem.*, 1998, **63**, 2892.
25 M. V. Nora de Souza and R. H. Dodd, *Heterocycles*, 1998, **47**, 811.
26 P. Gros and Y. Fort, *Synthesis*, 1999, 754.
27 A. Turck, N. Plé, A. Leprêtre-Gaquère and G. Quéguiner, *Heterocycles*, 1998, **49**, 205.
28 J. Felding, P. Uhlmann, J. Kristensen, P. Vedsø and M. Begtrup, *Synthesis*, 1998, 1181.
29 J. Kristensen, M. Begtrup and P. Vedsø, *Synthesis*, 1998, 1604.
30 J. Felding, J. Kristensen, T. Bjerregaard, L. Sander, P. Vedsø and M. Begtrup, *J. Org. Chem.*, 1999, **64**, 4196.
31 M. C. Jetter and A. B. Reitz, *Synthesis*, 1998, 829.
32 F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais and G. Quéguiner, *Tetrahedron Lett.*, 1999, **40**, 4339.
33 L. Bérillon, A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, G. Cahiez and P. Knochel, *Synlett*, 1998, 1359.
34 M. Abarbi and P. Knochel, *Synlett*, 1999, 1577.
35 O. Meth-Cohn and H. Jiang, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 3737.
36 M. Alvarez, D. Fernández and J. A. Joule, *Synthesis*, 1999, 615.
37 I. Kawasaki, H. Katsuma, Y. Nakayama, M. Yamashita and S. Ohta, *Heterocycles*, 1998, **48**, 1887.
38 M. Ishikura, I. Agata and N. Katagiri, *J. Heterocycl. Chem.*, 1999, **36**, 873.
39 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941.
40 W. W. K. R. Medersk, M. Lefort, M. Germann and D. Kux, *Tetrahedron*, 1999, **55**, 12757.
41 J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaugnessy and L. M. Alcazar-Roman, *J. Org. Chem.*, 1999, **64**, 5575.
42 I. P. Beletskaya, D. V. Davydov and M. Moreno-Mañas, *Tetrahedron Lett.*, 1998, **39**, 5617.
43 A. Kiyomori, J.-F. Marcoux and S. L. Buchwald, *Tetrahedron Lett.*, 1999, **40**, 2657.
44 A. Y. Federov and J.-P. Finet, *Tetrahedron Lett.*, 1999, **40**, 2747.
45 R. Stürmer, *Angew. Chem.*, *Int. Ed.*, 1999, **38**, 3307.
46 O. Lohse, P. Thevenin and E. Waldvogel, *Synlett*, 1999, 45.
47 H. Zhang, F. Y. Kwong, Y. Tian and K. S. Chan, *J. Org. Chem.*, 1998, **63**, 6886.
48 M. A. Massa, W. C. Patt, K. Ahn, A. M. Sisneros, S. B. Herman and A. Doherty, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2117.
49 C. Gosmini, S. Lasry, J.-Y. Nedelec and J. Perichon, *Tetrahedron*, 1998, **54**, 1289.
50 J. Li, S.-H. Chen, X. Li, C. Niu and T. Doyle, *Tetrahedron*, 1998, **54**, 393.
51 J. C. Namyslo and D. E. Kaufmann, *Synlett*, 1999, 114.
52 B. Danieli, G. Lesma, M. Martinelli, D. Passarella, I. Peretto and A. Silvani, *Tetrahedron*, 1998, **54**, 14081.
53 M. S. Harr, A. L. Presley and A. Thorarensen, *Synlett*, 1999, 1579.
54 I. Estevez, A. Coelho and E. Raviña, *Synthesis*, 1999, 1666.
55 R. Menicagli, S. Samaritani and S. Gori, *Tetrahedron Lett.*, 1999, **40**, 8419.
56 C. N. Johnson, G. Stemp, N. Anand, S. C. Stephen and T. Gallagher, *Synlett*, 1998, 1025.
57 C. Franc, F. Denonne, C. Cuisinier and L. Ghosez, *Tetrahedron Lett.*, 1999, **40**, 4555.
58 J. C. Bussolari and D. C. Rehborn, *Org. Lett.*, 1999, **1**, 965.
59 J. Boukouvalas, N. Lachance, M. Ouellet and M. Trudeau, *Tetrahedron Lett.*, 1998, **39**, 7665.
60 S. Cerezo, M. Moreno-Mañas and R. Pleixats, *Tetrahedron*, 1998, **54**, 7813.
61 J. M. Herbert and A. H. McNeill, *Tetrahedron Lett.*, 1998, **39**, 2421.
62 R. Benhida, F. Lecubin, J.-L. Fourrey, L. R. Castellanos and L. Quintero, *Tetrahedron Lett.*, 1999, **40**, 5701.
63 D. W. Gordon, *Synlett*, 1998, 1065.
64 V. Collot, P. Dallemagne, P. R. Bovy and S. Rault, *Tetrahedron*, 1999, **55**, 6917.
65 M. L. López-Rodriguez, A. Viso, B. Benhamú, J. L. Rominguera and M. Murcia, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2339.
66 M. K. Lakshman, J. C. Keeler, J. H. Hilmer and J. Q. Martin, *J. Am. Chem. Soc.*, 1999, **121**, 6090.
67 A. Bråthe, L.-L. Gundersen, F. Rise, A. B. Eriksen, A. V. Vollsnes and L. Wang, *Tetrahedron*, 1999, **55**, 211.
68 M. Havelková, M. Hocek, M. Česnek and D. Dvořák, *Synlett*, 1999, 1145.
69 R. C. F. Jones, G. Bhalay, P. A. Carter, K. A. M. Duller and S. H. Dunn, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 765.
70 J. Rouden, A. Bernard and M.-C. Lasne, *Tetrahedron Lett.*, 1999, **40**, 8109.
71 M. Park, J. R. Buck and C. J. Rizzo, *Tetrahedron*, 1998, **54**, 12707.
72 S. Zhang, D. Marshall and L. S. Liebeskind, *J. Org. Chem.*, 1999, **64**, 2796.
73 T. Choshi, S. Yamada, J. Nobuhiro, Y. Mihara, E. Sugino and S. Hibino, *Heterocycles*, 1998, **48**, 11.
74 Y.-S. Oh and S.-H. Cho, *J. Heterocycl. Chem.*, 1998, **35**, 17.
75 J. M. Quintela, C. Peinador, C. Veiga, L. González, L. M. Botana, A. Alfonso and R. Riguera, *Bioorg. Med. Chem.*, 1998, **6**, 1911.
76 J. Koyanagi, M. Ogawa, K. Yamamoto, K. Nakayama and A. Tanaka, *J. Heterocycl. Chem.*, 1998, **35**, 301.

77 H. Göker, G. Ayhan-Kilcigil, M. Tunçbilek, C. Kus, R. Ertan, E. Kendi, S. Özbey, M. Fort, C. Garcia and A. J. Farré, *Heterocycles*, 1999, **51**, 2561.
78 I. C. Barrett and M. A. Kerr, *Tetrahedron Lett.*, 1999, **40**, 2439.
79 D. Prim, G. Kirsch and J.-F. Nicoud, *Synlett*, 1998, 383.
80 L. Schio, G. Lemoine and M. Klich, *Synlett*, 1999, 1559.
81 M. J. Suto, L. M. Gayo-Fung, M. S. S. Palanki and R. Sullivan, *Tetrahedron*, 1998, **54**, 4141.
82 T. Masquelin, Y. Delgado and V. Baumlé, *Tetrahedron Lett.*, 1998, **39**, 5725.
83 F. You and R. J. Twieg, *Tetrahedron Lett.*, 1999, **40**, 8759.
84 A. Zumbrunn, *Synthesis*, 1998, 1357.
85 P. Gros and Y. Fort, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 3515.
86 R. A. Jones and A. P. Whitmore, *Tetrahedron*, 1998, **54**, 9519.
87 D. A. Bradley, A. G. Godfrey and C. R. Schmid, *Tetrahedron Lett.*, 1999, **40**, 5155.
88 R. W. Friesen, C. Brideau, C. C. Chan, S. Charleson, D. Deschênes, D. Dubé, D. Ethier, R. Fortin, J. Y. Gauthier, Y. Girard, R. Gordon, G. M. Greig, D. Riendeau, C. Savoie, Z. Wang, E. Wong, D. Visco, L. J. Xu and R. N. Young, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2777.
89 Y. Bessard and J. P. Roduit, *Tetrahedron*, 1999, **55**, 393.
90 Y. Bessard and R. Crettaz, *Heterocycles*, 1999, **51**, 2589.
91 S. Toyota, C. R. Woods, M. Benaglia and J. S. Siegel, *Tetrahedron Lett.*, 1998, **39**, 2697.
92 T. Bach and L. Krüger, *Tetrahedron Lett.*, 1998, **39**, 1729.
93 T. Bach and L. Krüger, *Synlett*, 1998, 1185.
94 T. Bach and L. Krüger, *Eur. J. Org. Chem.*, 1999, 2045.
95 R. Mabon, A. M. E. Richecœur and J. B. Sweeney, *J. Org. Chem.*, 1999, **64**, 328.
96 U. S. Schubert and C. Eschbaumer, *Org. Lett.*, 1999, **1**, 1027.
97 T. N. Mitchell, K. Böttcher, P. Bleckmann, B. Costisella, C. Schwittek and C. Nettelbeck, *Eur. J. Org. Chem.*, 1999, 2413.
98 L. Revesz, F. Bonne and P. Makavou, *Tetrahedron Lett.*, 1998, **39**, 5171.
99 M. Abarbri, F. Dehmel and P. Knochel, *Tetrahedron Lett*, 1999, **40**, 7449.
100 Y.-H. Fan and J. Haseltine, *J. Heterocycl. Chem.*, 1999, **36**, 869.
101 M. T. Fiorini and C. Abell, *Tetrahedron Lett.*, 1998, **39**, 1827.
102 M. Legraverend, O. Ludwig, E. Bisagni, S. Leclerc, L. Meijer, N. Giocanti, R. Sadri and V. Favaudon, *Bioorg. Med. Chem.*, 1999, **7**, 1281.
103 E. Camaioni, S. Costanzi, S. Vittorio, R. Volpini, K.-N. Klotz and G. Cristalli, *Bioorg. Med. Chem.*, 1998, **6**, 523.
104 C. R. Johnson, B. Zhang, P. Fantauzzi, M. Hocker and K. M. Yager, *Tetrahedron*, 1998, **54**, 4097.
105 I. Parrot, Y. Rival and C. G. Wermuth, *Synthesis*, 1999, 1163.
106 A. J. Cocuzza, F. W. Hobbs, C. R. Arnold, D. R. Chidester, J. A. Yarem, S. Culp, L. Fitzgerald and P. J. Gilligan, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1057.
107 A. J. Goodman, S. P. Stanforth and B. Tarbit, *Tetrahedron*, 1999, **55**, 15067.
108 B. Charpiot, J. Brun, I. Donze, R. Naef, M. Stefani and T. Mueller, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2891.
109 J. J. Li and W. S. Yue, *Tetrahedron Lett.*, 1999, **40**, 4507.
110 T. Shiota and T. Yamamori, *J. Org. Chem.*, 1999, **64**, 453.
111 R. C. Larock, E. K. Yum and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652.
112 R. C. Larock, X. Han and M. J. Doty, *Tetrahedron Lett.*, 1998, **39**, 5713.
113 R. C. Larock, M. J. Doty and X. Han, *J. Org. Chem.*, 1999, **64**, 8770.
114 K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 1998, **63**, 5306.
115 K. R. Roesch and R. C. Larock, *Org. Lett.*, 1999, **1**, 1551.
116 C. Ma, X. Liu, S. Yu, S. Zhao and J. M. Cook, *Tetrahedron Lett.*, 1999, **40**, 657.
117 S. S. Park, J.-K. Choi, E. K. Yum and D.-C. Ha, *Tetrahedron Lett.*, 1998, **39**, 627.
118 F. Ujjainwalla and D. Warner, *Tetrahedron Lett.*, 1998, **39**, 5355.
119 S. K. Kang, S. S. Park, S. S. Kim, J.-K. Choi and E. K. Yum, *Tetrahedron Lett.*, 1999, **40**, 4379.
120 L. Xu, I. R. Lewis, S. K. Davidsen and J. B. Summers, *Tetrahedron Lett.*, 1998, **39**, 5159.
121 J. J. H. Diederen, R. W. Sinkeldam, H.-W. Frühauf, H. Hiemstra and K. Vrieze, *Tetrahedron Lett.*, 1999, **40**, 4255.
122 S. Cacchi, G. Fabrizi, P. Pace and F. Marinelli, *Synlett*, 1999, 620.
123 S. Cacchi, G. Fabrizi and F. Marinelli, *Synlett*, 1999, 401.
124 A. Arcadi, F. Marinelli and E. Rossi, *Tetrahedron*, 1999, **55**, 13233.
125 M. S. Yu, L. Lopez de Leon, M. A. McGuire and G. Botha, *Tetrahedron Lett.*, 1998, **39**, 9347.
126 M. Gardiner, R. Grigg, V. Sridharan and N. Vicker, *Tetrahedron Lett.*, 1998, **39**, 435.
127 A. S. Bhat, J. L. Whetstone and R. W. Brueggemeier, *Tetrahedron Lett.*, 1999, **40**, 2469.
128 M. Suginome, T. Fukuda and Y. Ito, *Org. Lett.*, 1999, **1**, 1977.
129 A. Arcadi, S. Cacchi, G. Fabrizi, F. Manna and P. Pace, *Synlett*, 1998, 446.
130 J. D. Tovar and T. M. Swager, *J. Org. Chem.*, 1999, **64**, 6499.
131 A. Arcadi, O. A. Attanasi, B. Guidi, E. Rossi and S. Santeusanio, *Chem. Lett.*, 1999, 59.
132 A. Arcadi, O. A. Attanasi, B. Guidi, E. Rossi and S. Santeusanio, *Eur. J. Org. Chem.*, 1999, 3117.
133 A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and L. Moro, *Synlett*, 1999, 1432.
134 C. D. Brown, J. M. Chong and L. Shen, *Tetrahedron*, 1999, **55**, 14233.
135 B. Gabriele, G. Salerno and E. Lauria, *J. Org. Chem.*, 1999, **64**, 7687.
136 B. Gabriele, G. Salerno, F. De Pascali, M. Costa and G. P. Chiusoli, *J. Org. Chem.*, 1999, **64**, 7693.
137 R. Rossi, F. Bellina, M. Biagetti and L. Mannina, *Tetrahedron Lett.*, 1998, **39**, 7599.
138 S. Ma and Z. Shi, *J. Org. Chem.*, 1998, **63**, 6387.
139 S. Ma, S. Shi and Z. Yu, *Tetrahedron Lett.*, 1999, **40**, 2393.
140 S. Ma, Z. Shi and Z. Yu, *Tetrahedron*, 1999, **55**, 12137.
141 R. Rossi, F. Bellina and L. Mannina, *Tetrahedron Lett.*, 1998, **39**, 3017.
142 L. Wang and W. Shen, *Tetrahedron Lett.*, 1998, **39**, 7625.
143 J. Sauer and D. K. Heldmann, *Tetrahedron Lett.*, 1998, **39**, 2549.
144 J. Sauer, D. K. Heldmann and G. R. Pabst, *Eur. J. Org. Chem.*, 1999, 313.
145 G. R. Pabst, O. C. Pfüller and J. Sauer, *Tetrahedron*, 1999, **55**, 5047.
146 G. R. Pabst and J. Sauer, *Tetrahedron*, 1999, **55**, 5067.
147 J. Sauer, D. K. Heldmann, K.-J. Range and M. Zabel, *Tetrahedron*, 1998, **54**, 12807.
148 J. Sauer and D. K. Heldmann, *Tetrahedron*, 1998, **54**, 4297.
149 T. J. Sparey and T. Harrison, *Tetrahedron Lett.*, 1998, **39**, 5873.
150 L. Ghosez, E. Jnoff, P. Bayard, F. Sainte and R. Beaudegnies, *Tetrahedron*, 1999, **55**, 3387.
151 A. Padwa, S. M. Sheehan and C. S. Straub, *J. Org. Chem.*, 1999, **64**, 8648.
152 C. S. Straub and A. Padwa, *Org. Lett.*, 1999, **1**, 83.
153 G. McCort, O. Duclos, C. Cadilhac and E. Guilpain, *Tetrahedron Lett.*, 1999, **40**, 6211.
154 F. Foti, G. Grassi and F. Risitano, *Tetrahedron Lett.*, 1999, **40**, 2605.
155 T. Isiobe and T. Ishikawa, *J. Org. Chem.*, 1999, **64**, 6989.
156 T. L. Deegan, T. J. Nitz, D. Cebzanov, D. E. Pufko and J. A. Porco, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 209.
157 C. T. Brain and J. M. Paul, *Synlett*, 1999, 1642.
158 T. N. Danks, *Tetrahedron Lett.*, 1999, **40**, 3957.
159 C. F. Claiborne, N. J. Liverton and K. T. Nguyen, *Tetrahedron Lett.*, 1998, **39**, 8939.
160 K. Funabiki, H. Nakamura, M. Matsui and K. Shibata, *Synlett*, 1999, 756.
161 D. G. Powers, D. S. Casebier, D. Fokas, W. J. Ryan, J. R. Troth and D. L. Coffen, *Tetrahedron*, 1998, **54**, 4085.
162 S. Caron and E. Vazquez, *Synthesis*, 1999, 588.
163 H. Kotsuki, H. Sakai, H. Morimoto and H. Suenaga, *Synlett*, 1999, 1993.
164 B. A. Kulkarni and A. Ganesan, *Tetrahedron Lett.*, 1999, **40**, 5637.
165 H. P. Dijkstra, R. ten Have and A. M. van Leusen, *J. Org. Chem.*, 1998, **63**, 5332.
166 A. S. Kiselyov and C. Dominguez, *Tetrahedron Lett.*, 1999, **40**, 5111.
167 L. Smith and A. S. Kiselyov, *Tetrahedron Lett.*, 1999, **40**, 5643.
168 A. S. Kiselyov, *Tetrahedron Lett.*, 1999, **40**, 4119.
169 J. A. Vega, J. J. Vaquero, J. Alverez-Builla, J. Ezquerra and C. Hamdouchi, *Tetrahedron*, 1999, **55**, 2317.
170 Z. Wróbel, *Tetrahedron*, 1998, **54**, 2607.
171 A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko and S. A. Essawy, *Synthesis*, 1999, 2114.
172 N. Almirante, A. Benicchio, A. Cerri, G. Fedrizzi, G. Marazzi and M. Santagostino, *Synlett*, 1999, 299.
173 A. P. Dobbs, M. Voyle and N. Whittall, *Synlett*, 1999, 1594.
174 J. Barluenga, F. Fañanás, R. Sanz and Y. Fernández, *Tetrahedron Lett.*, 1999, **40**, 1049.
175 S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 10251.
176 J. R. Young and R. J. DeVita, *Tetrahedron Lett.*, 1998, **39**, 3931.
177 I. Collins and J. L. Castro, *Tetrahedron Lett.*, 1999, **40**, 4069.
178 A. R. Katritzky, A. Denisenko and M. Arend, *J. Org. Chem.*, 1999, **64**, 6076.

179 A. Nadin and T. Harrison, *Tetrahedron Lett.* 1999, **40**, 4073.
180 A. J. Cocuzza, D. R. Chidester, S. Culp, L. Fitzgerald and P. Gilligan, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1063.
181 L. Weber, K. Illgen and M. Almstetter, *Synlett*, 1999, 366.
182 H. Bienaymé and K. Bouzid, *Angew. Chem.*, *Int. Ed.*, 1998, **37**, 2234.
183 K. Groebke, L. Weber and F. Mehlin, *Synlett*, 1998, 661.
184 C. Blackburn, B. Guan, P. Fleming, K. Shiosaki and S. Tsai, *Tetrahedon Lett.*, 1998, **39**, 3635.
185 R. S. Varma and D. Kumar, *Tetrahedron Lett.*, 1999, **40**, 7665.
186 H. Bienaymé and K. Bouzid, *Tetrahedron Lett.*, 1998, **39**, 2735.
187 H. Shiraishi, T. Nishitani, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 1998, **63**, 6234.
188 B. P. McKibben, C. H. Cartwright and A. L. Castelhano, *Tetrahedron Lett.*, 1999, **40**, 5471.
189 N. Nishiwaki, T. Nogami, T. Kawamura, N. Asaka, Y. Tohda and M. Ariga, *J. Org. Chem.*, 1999, **64**, 6476.
190 D. H. Drewry, D. M. Coe and S. Poon, *Med. Res. Rev.*, 1999, **19**, 97.
191 R. J. Booth and J. C. Hodges, *Acc. Chem. Res.*, 1999, **32**, 18.
192 C. T. Brain, J. M. Paul, Y. Loong and P. J. Oakley, *Tetrahedron Lett.*, 1999, **40**, 3275.
193 B. O. Buckman, M. M. Morrissey and R. Mohan, *Tetrahedron Lett.*, 1998, **39**, 1487.
194 J. P. Parlow and D. L. Flynn, *Tetrahedron*, 1998, **54**, 4013.
195 M. S. Anson, A. R. Mirza, L. Tonks and J. M. J. Williams, *Tetrahedron Lett.*, 1999, **40**, 7147.
196 O. A. Attanasi, P. Filippone, C. Fiorucci, E. Foresti and F. Mantellini, *J. Org. Chem.*, 1998, **63**, 9880.
197 W. Xu, R. Mohan and M. M. Morrisey, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1089.
198 M. Caldarelli, J. Habermann and S. V. Ley, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 107.
199 J. Habermann, S. V. Ley and R. Smits, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 2421.
200 J. Habermann, S. V. Ley, J. J. Scicinski, J. S. Scott, R. Smits and A. W. Thomas, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 2425.