REVIEW

Rapid analogue syntheses of heteroaromatic compounds

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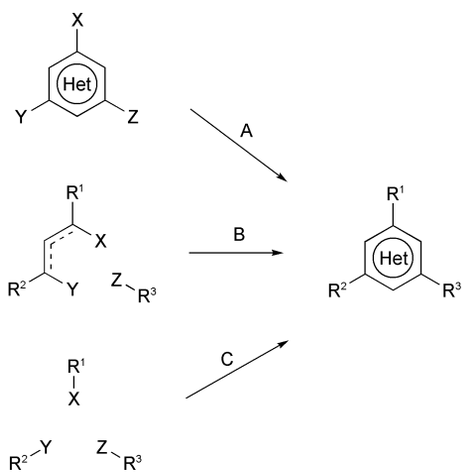
1 Introduction

Aromatic heterocycles are widespread and valuable synthetic templates for the preparation of new compounds with specific biological or material properties. The pursuit of these properties requires efficient synthetic routes that allow rapid assembly and variation of multiple pendant substituents on the heteroaromatic core, or the construction of diverse aromatic heterocycles with defined substitution patterns. As in the previous review,[1] this article considers recent chemistry illustrating such rapid analogue syntheses (RAS), concentrating on the introduction of substituent variety to 5- and 6-membered heteroaromatic compounds and their fused derivatives through the formation of bonds to the ring atoms. The more general topics of heteroaromatic syntheses and ring-forming reactions have been comprehensively reviewed in this journal.[2] An excellent text, covering the literature to 1999, on the preparation of substituted heteroaromatic compounds using palladium chemistry has been published.[3] The chemistry reviewed here concerns the production of single compounds by solution-phase methods, often through parallel synthesis taking advantage of automated techniques. Combinatorial chemistry with the substrate on the solid-phase is not examined, and the production of libraries of mixtures is also excluded. A full compilation of the uses of solid-supported reagents in synthesis and purification has been published[4] and a review of the hybrid 'resin-capture–release' strategy has also appeared.[5]

Three strategies for RAS have been used to guide the selection of examples for this review, defined by the degree of intactness of the heteroaromatic core at the point of substituent introduction (Scheme 1). The simplest analysis involves addition of substituents to activated heteroaromatic rings (Route A) and encompasses the bulk of the material included here. This is very well researched for single points of substitution, and dramatic advances have been made in controlling the selective reaction of polyfunctional aromatic heterocycles. The use of transition metal-catalysed coupling reactions dominates this approach.

The assembly of a substituted linear precursor and cyclisation to an aromatic heterocycle has enhanced potential for RAS when a tandem ring-forming–substitution sequence is used (Route B). In this context palladium-mediated coupling–cyclisation reactions of alkynes and allenes have been particularly prominent. Cycloadditions also provide a highly efficient means to introduce substituent diversity in the ring-forming step.



Scheme 1

Many routes to simple heteroaromatic compounds involving short synthetic sequences can be adapted for RAS. Examples in this article will be restricted to one-pot syntheses starting from simple components which minimise the number of separate synthetic operations. Extending this principle, multicomponent reactions (Route C) offer the opportunity to rapidly construct more densely functionalised compounds, and the possibility of varying the heteroaromatic core within an array of defined substituents derived from a common reagent set.

2 Substitution of polyfunctional heteroaromatics

2.1 Halogenation–transition metal catalysed coupling

Progress continues to be made in the preparation of selectively halogenated or metalated heteroaromatics and their subsequent substitution. The transformations of 4-chlorobenzo[*c*][2,7]-naphthyridine[6] illustrate the versatility of heteroaryl halides as substrates for RAS (Scheme 2).

Several new procedures for the preparation of heteroarylhalides have been reported. The successful use of aqueous $KICl_2$ to iodinate imidazoles and pyrazoles (4 examples, 79–95% yield)† was critically dependent on the order of addition of the reagents.[7] 4-Iodopyrazoles with both electron-donating and electron-withdrawing substituents were prepared by oxidative iodination[8] (CAN-I_2, 6 examples, 79–98% yield) and

† 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 yield, have been omitted.

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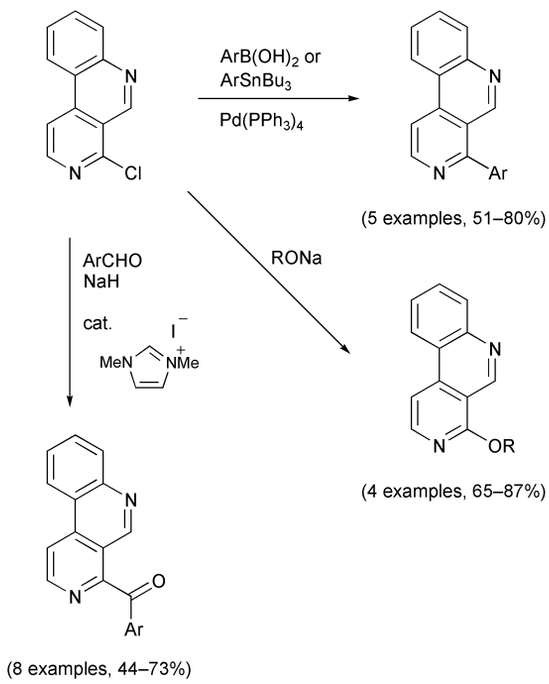
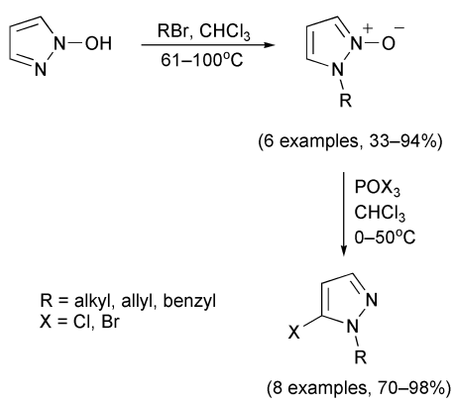


Scheme 2

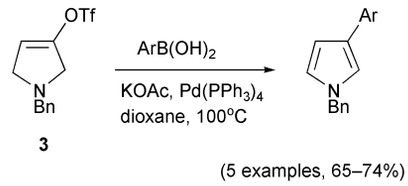


Scheme 3

1-hydroxypyrazoles were converted to the uncommon 1-alkyl-5-halopyrazoles in two steps *via* pyrazole 1-oxides[9] (Scheme 3). Controlled regioselective mono- or dibromination of activated pyridines was achieved with NBS in MeCN, CCl_4 or MeOH where the reaction was most efficient for 2- or 4-amino- and 2-hydroxy- or 2-alkoxypyridines[10] (8 examples, 65–95% yield). Various hydroxyheteroarenes were converted to the corresponding bromides using P_2O_5–Bu_4NBr as an alternative to phosphorus oxybromide[11] (11 examples, 58–95%), and a combination of HMPT, CBr_4 and LiBr was successful in transforming an inosine base to the 6-bromopurine riboside where related methods had failed.[12] 2-Bromopyrones were prepared by bromo-decarboxylation of the carboxylic acids with NBS–LiOAc.[13]

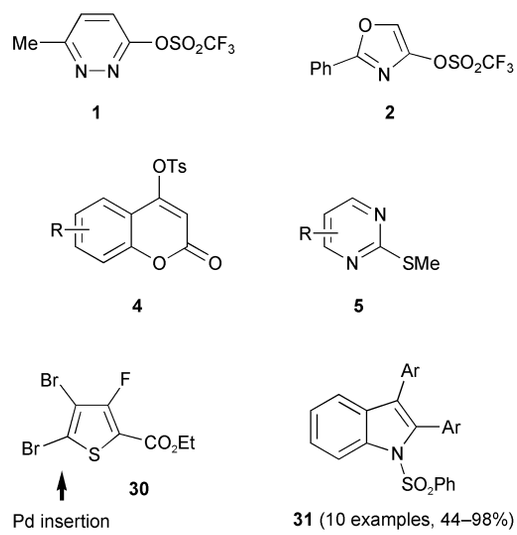
Heteroaryl trifluoromethanesulfonate esters are good alternative substrates to halides for transition metal catalysed coupling reactions, as demonstrated by the first Stille and Suzuki couplings to a 3-trifluoromethylsulfonyloxypyridazine **1**[14] (6 examples, 22–84% yields). Highly substituted vinylstannanes and vinylaluminates were coupled to the 4-trifluoromethylsulfonyloxyoxazole **2** (8 examples, 60–84% yields) in the context of studies towards phorboxazole A.[15] 3-Arylpyrroles were prepared by tandem Suzuki–dehydrogenation reactions of the triflate‡ **3**[16] (Scheme 4). 4-Tosyloxycoumarins **4** were shown to be excellent partners for the coupling of arylstannanes[17]

‡ The IUPAC name for triflate is trifluoromethanesulfonate.



Scheme 4

(7 examples, 14–74% yields), alkynes[18] (13 examples, 68–98% yields) and organozinc reagents[18] (8 examples, 42–85% yields). Unexpectedly, methylthio-substituted azaheteroaromatics, particularly pyrimidines **5**, were found to cross-couple efficiently with benzylzinc bromide under palladium catalysis, provided that the -SMe group occupied an activated position relative to a ring nitrogen atom[19] (8 examples, 51–89%). Phenylation[20] [Ph_4BNa, $Pd(OAc)_2$] and cyanation[21] of simple heteroaryl halides were enhanced by microwave irradiation.



Recent examples[22–52] of RAS at single points of substitution by transition metal catalysed coupling to heteroaryl halides and equivalents are detailed in Table 1 and Fig. 1.

Synthetically useful selective reactions were demonstrated for several polyhaloheteroaromatics and some of these preliminary studies have led to multiple substitution sequences (see Section 3). Dichloro- and dibromopyridines were monocarbonylated[53,54] and monoaminated[55,56] with the expected preference for reaction of 2-halo substituents where present. Sequential Suzuki coupling of phenylboronic acid to 2,4,6-trichloropyrimidine occurred cleanly at positions 4, 6 then 2[57] and 2,4-dichloropyrimidines also coupled with boronic acids at C-4 first.[58] Coupling to dibromo-, diiodo and triiodopyrimidines was much less selective.[57] While Suzuki coupling to 2,6-dichloro-9-benzylpurine was selective for the 6-position, this selectivity was reversed for the 2-iodo-6-chloro analogue.[45] Mixed halogenated bisthiophenes[59] and the dibromothiophene **30**[60] reacted selectively under palladium catalysis. 2,3-Di- and 2,3,5-tribromobenzofurans underwent Negishi and Sonogashira couplings at the 2-position[61] (Scheme 5). In contrast, dibromo- and diiodoindoles gave a library of 2,3-diarylindoles **31**[62] but did not show useful differentiation between the halides to allow unsymmetrical substitution. A directing group strategy based on selective chelation of palladium was used to differentiate phenanthroline bishalides[63] (Scheme 6).

2.2 Metalation–transition metal catalysed coupling

Metalation of heteroaromatics can be achieved by deprotonation, halogen–metal exchange or activation of C–H bonds with transition metals. The metalated species may be used in

Table 1 Transition metal catalysed cross-couplings to heteroaryl halides

Heteroaryl halides	Coupling partners/ catalysts/ reagents	Notes	Ref.
2- and 3-Halothiophenes	$RNH_2/Pd_2(dba)_3$, BINAP/Cs_2CO_3	40–98%, 10 Examples; moderate electron-withdrawing substituents were required on the thiophenes (–CN, $–CO_2Me$); less effective with 2° acyclic amines	22
2- and 3-Bromothiophenes	$Ar_2NH/Pd(OAc)_2$, $PBu^t{}_3/Bu^tONa$	36–81%, 7 Examples; electron-rich thiophenes	23
4-Trifluoromethylsulfonyloxyfuran-2(5*H*)-one	$RB(OH)_2/Pd(MeCN)_2Cl_2$, Ph_3As/Ag_2O R = alkenyl and substituted cyclopropyl	63–85%, 9 Examples; optically active cyclopropyl boronates coupled with retention of configuration	24
1-Aryl-5-bromopyrazoles **6**	$ArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$ Vinyltributyltin/$Pd(PPh_3)_4$ $RC{\equiv}CH/Pd(PPh_3)_4$, $CuBr{\cdot}SMe_2/Et_3N$	94–97%, 4 Examples 90–95%, 4 Examples 91–96%, 4 Examples	25
4-Halo-3-ethoxy-5-methylisoxazoles	$ArB(OH)_2$, $ArSnBu_3/Pd(PPh_3)_2Cl_2/(NaHCO_3)$ $RCH{=}CH_2$, $RC{\equiv}CH/Pd(PPh_3)_2Cl_2/K_2CO_3$, Bu_4NBr	49–96%, 9 Examples 58–98%, 4 Examples	26
2-, 3-, 4-Halopyridines	9-Alkyl-9-BBN/$Pd(PPh_3)_4/K_2CO_3$	60–93%, 12 Examples	27
2-Halopyridines	$R_1R_2N–NHR_3$/various Pd°, bisphosphines/base	42–95%, 11 Examples; synthesis of BOC- and benzophenone protected 2-pyridylhydrazines	28
2-, 3-, 4-Chloropyridines	$ArB(OH)_2/PdCl_2$, PS–CH_2PPh_2/K_3PO_4	72–92%, 6 Examples; 3-phase system (PS, H_2O, toluene); recovered polymer-bound catalyst retained activity for 6 further cycles	29
2-, 3-, 4-Chloropyridines	RNH_2, $R_2NH/Pd(OAc)_2$, (*o*-biphenyl)$PR_2/NaOBu^t$	70–98%, 10 Examples; excess RNH_2 was required to minimise bisarylation	30
2-, 3-, 4-Halopyridines	RNH_2, $R_2NH/Pd_2(dba)_3$, ligand **7a**/$KOBu^t$	70–99%, 12 Examples	31
2-Bromopyridines	2-Pyridylstannanes/$Pd(PPh_3)_4$	50–87%, 9 Examples; reagents prepared on large scale from 2-aminopyridines	32
3-Halo-2-pyridones **8**	Alkyl-, allyl-, vinylstannanes/various Pd^{II}	23–81%, 7 Examples; analogues of the nAChR ligand[a] (−)-cytisine	33
3-Amino-6-chloro- and 3-amino-6-iodopyridazines	$ArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$ $HetArSnBu_3/PdCl_2(PPh_3)_2$	63–91%, 14 Examples; chloride and iodide showed similar reactivities 87–99%, 4 Examples	34
3-Amino-6-chloropyridazine	$ArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$	35–60%, 11 Examples	35
5-Bromo-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-one **9**	$ArB(OH)_2/Pd(PPh_3)_4/K_2CO_3$	70–98%, 6 Examples; *N*-protection was essential for successful coupling; the MOM group was removed with HCl or Lewis acids	36,37
4-Chloro-, 5-chloro, 4,5-dichloropyridazin-3(2*H*)-ones **10**,**11**	$ArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$	**10** 85–100%, 24 Examples	38
	$ArNH_2$, $HetArNH_2$/various Pd, BINAP/various base	**11** 81–100%, 11 Examples	39
6-Chloro-2,4-diaminopyrimidine **12** and triazine **13**	$ArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$	**12** 73–86%, 6 Examples **13** 70–77%, 4 Examples	40
1,3-Dibenzyl-5-iodouracil **14**	$ArNH_2$, RNH_2, $R_2NH/(CuOTf)_2$, phen, dba/Cs_2CO_3	42–77%, 9 Examples; a $Ni(COD)_2$–dppf catalyst extended the range of amines	41
2-Iodo-4-azaindoles **15** and 2-iodo-7-azaindole **16**	$ArB(OH)_2$, aryl-, vinyl-, allylstannanes, $RCH{=}CH_2/Pd(OAc)_2$/LiCl, KOAc	Suzuki 49–86%, 12 Examples; Stille 49–84%, 8 Examples; Heck 52–92%, 6 Examples; Suzuki reactions of **16** were faster and higher yielding than analogous reactions of **15**	42
4-Chloro-7-azaindole **17** and 6-chloro-7-azaindole **18**	$ArB(OH)_2$, $HetArB(OH)_2/Pd_2(dba)_3$, $PBu^t{}_3$/KF	**17**, **18** 40–94%, 8 Examples; the chlorides were inert under Sonogashira and Heck conditions therefore the 4-iodo and 6-bromo analogues were used instead	43
7-Iodopyrazolo[1,5-*a*]pyridine **19**	Aryl-, vinylstannanes, $ArB(OH)_2$, $TMSC{\equiv}CH/Pd(PPh_3)_4/NaHCO_3$ (Suzuki)	Stille 60–82%, 4 Examples; Suzuki 80–85%, 2 Examples; Sonogashira 66–77%, 2 Examples; couplings of CN^- and amines were also demonstrated	44
6-, 8-Halopurines **20**, **21**, **22**	$ArB(OH)_2$, $RCH{=}CHB(OH)_2/Pd(PPh_3)_4/K_2CO_3$	61–98%, 19 Examples; aqueous conditions generally gave higher yields	45
2-Bromo-6-benzyloxy-2′-deoxyinosine	$RNH_2/Pd(OAc)_2$, BINAP/Cs_2CO_3	40–94%, 5 Examples	46
2-Chloro-6-(4-methoxyphenylamino)-9-isopropylpurine **23**	$ArB(OH)_2$, $ArNH_2$, $ArOH/Pd_2(dba)_3$, ligand **7b**/Cs_2CO_3 (Suzuki), $KOBu^t$ (anilines and phenols)	90–97%, 12 Examples	47
3-Iodoimidazo[1,2-*a*]pyridines **24**	$ArB(OH)_2$, $HetArB(OH)_2/Pd(PPh_3)_4$/various bases	47–91%, 9 Examples; the coupling efficiency was dependent on the 2-substituent and required optimisation of both the base and solvent	48
6-Chloro-2-(4-fluorophenyl)imidazo[1,2-*b*]pyridazine **25**	$ArB(OH)_2$, $HetArB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$, NaOH	43–90%, 9 Examples; Na_2CO_3 was the most generally useful base, but NaOH offered improvements in some cases	49
4-, 6-Bromobenzimidazoles **26**	R_1R_2NH/various Pd, bisphosphines/$NaOBu^t$	54–97%, 6 Examples; the 5-bromo analogue gave only reduction products	50
Tricyclic halogenated *N*-benzyloxypyrazoles **27**, **28**	$ArB(OH)_2$, ArZnCl, TMSCCH/various Pd	63–94%, 8 Examples; direct halogenation of the parent heterocycles was examined in detail	51
Tetracyclic quinoline triflates **29**	$RSnBu_3$ or $ArB(OH)_2/Pd(PPh_3)_4$/LiCl or $NaHCO_3$	72–96%, 7 Examples	52

[a] nAChR = nicotinic acetylcholine receptor.

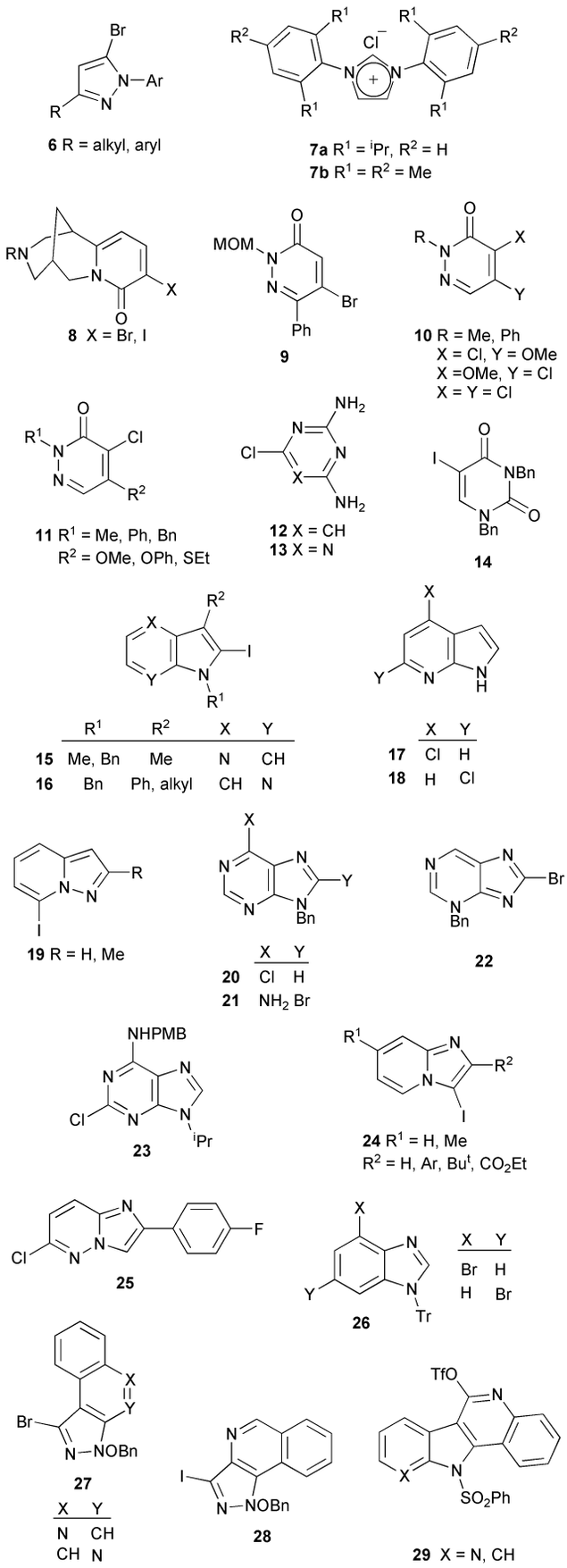
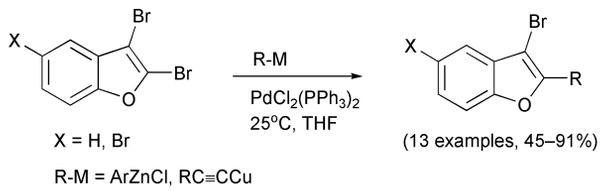
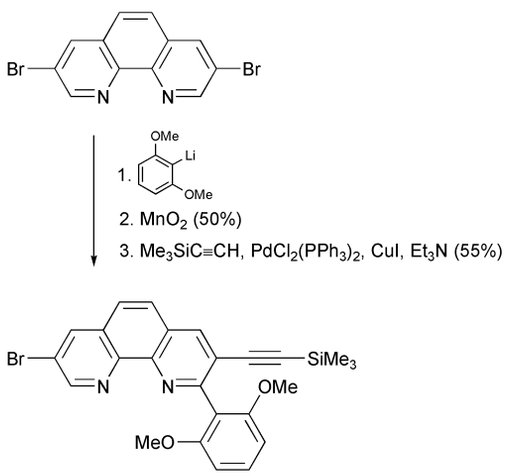


Fig. 1 The heteroaryl halides which are collated in Table 1.

coupling reactions directly or after transmetalation, or quenched with halogen sources to generate new heteroaryl halides, sometimes exploiting 'halogen dance' sequences to generate new substituent patterns. The literature on directed



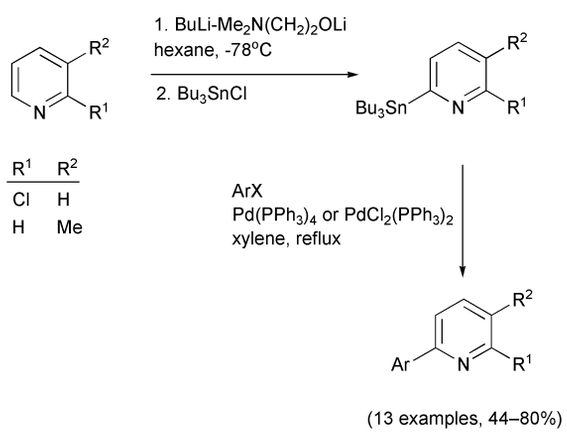
Scheme 5



Scheme 6

metalation of diazines (1991–1999) has been comprehensively reviewed.[64,65]

Fort and co-workers explored further the reaction of pyridines in apolar solvents with excess (3–4 eq.) butyllithium–lithium dimethylamino ethoxide, showing that 3- and 4-chloropyridine were deprotonated at the 2-position[66] while 2-(diphenylphosphino)-,[67] 2-chloro-[68] and 3-methylpyridine[69,70] were selectively lithiated at the 6-position. In the last two cases, transmetalation to the stannane and substitution by Stille couplings were demonstrated (Scheme 7). Regioselective

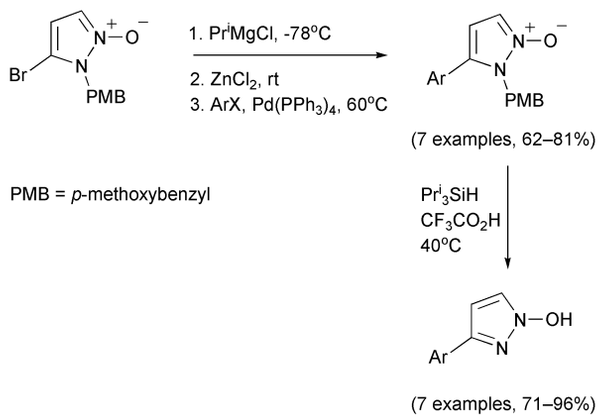


Scheme 7

deprotonations of 2- and 3-bromopyridines by aminozincates were tunable depending on the amine ligand, giving a high yielding route (66–86%) to 2,3-, 2,6- and 3,4-dihalopyridines after quenching with iodine.[71]

The groups led by Quéguiner and Knochel continued to develop the generation of polyfunctional heteroarylmagnesium reagents through selective halogen–metal exchange with alkyl Grignard reagents as the metal source.[72] Although most general for iodinated compounds, the methodology was also effective for brominated heterocycles, and was demonstrated for several substrates including imidazoles,[73,74] pyridines,[74,75] uracils,[74] pyrazolones,[74] thiophenes,[74] pyrroles[74] and diazines.[76] Excellent selectivities were seen in the single exchange reactions of

dibromopyridines,[75] which were also achieved using lithium tributylmagnesate[77] and could be controlled by a form-amidine *ortho*-directing group.[78] Thiophenes and thiazoles were deprotonated directly at the 2-position with Pr^iMgCl at room temperature.[79] Vedsø and co-workers used halogen–magnesium exchange in conjunction with new brominated pyrazole 1-oxides (*cf*. Scheme 3) to give RAS of 3-aryl-1-hydroxypyrazoles by cross-coupling[80] (Scheme 8). 3-Ethoxy-4-

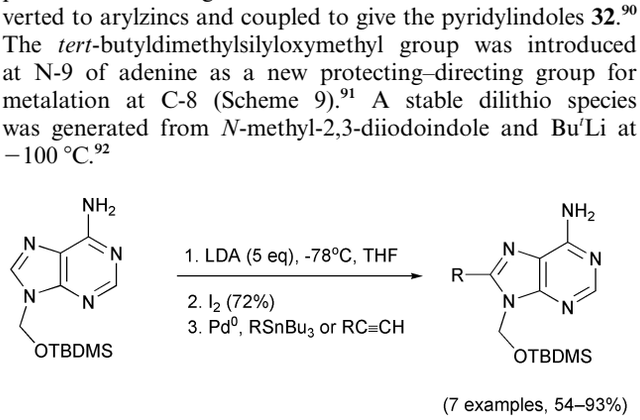


Scheme 8

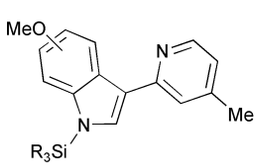
iodo-5-methylisoxazole was treated similarly.[26] Lithium stannylcuprates gave halogen–tin exchange in pyrazoles and isoxazoles,[81] while halopyridines were converted to the corresponding (trimethylstannyl)pyridines by photostimulated radical nucleophilic substitution using trimethylstannyl ions, and subsequently coupled to aryl halides.[82,83]

A systematic study of lithiation–halogen dance sequences on dichloropyridines was carried out by Schlosser and co-workers to delineate regioselective routes to trihalopyridines.[84,85] Polyfunctional-1-benzyloxyimidazoles were built up and manipulated using combinations of directed lithiation–halogen quench and halogen–lithium exchange reactions.[86] Conditions for the selective single bromine–lithium exchange of 2,5-dibromopyridine at either position on a large scale were presented.[87]

Whereas *N*-(2,2-diethylbutanoyl) protected indole gave controllable 2-, 3- or 7-metalation depending on the base,[88] the bulky *N*-(triisopropyl) group led to deprotonation solely at the 3-position by Bu′Li–TMEDA.[89] *N*-Trialkylsilyl protection also prevented metal migration in 3-lithioindoles which were converted to arylzincs and coupled to give the pyridylindoles **32**.[90] The *tert*-butyldimethylsilyloxymethyl group was introduced at N-9 of adenine as a new protecting–directing group for metalation at C-8 (Scheme 9).[91] A stable dilithio species was generated from *N*-methyl-2,3-diiodoindole and Bu′Li at −100 °C.[92]

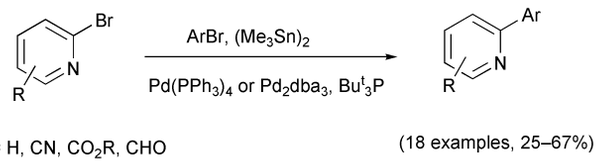


Scheme 9



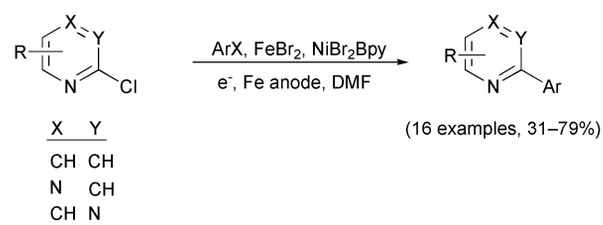
32 (3 examples, 58–75%)

Avoiding the explicit preparation of organotin compounds, a one-pot cross-coupling of electron-deficient 2-bromopyridines and aryl bromides was accomplished using hexamethylditin and palladium catalysis[93] (Scheme 10). Gosmini and co-workers



Scheme 10

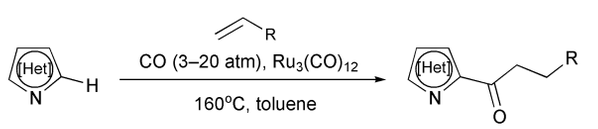
described electrochemical methods for the direct coupling of aryl halides and 2-haloazines using a nickel catalyst in the presence of an iron anode[94,95] (Scheme 11). Cobalt catalysed



Scheme 11

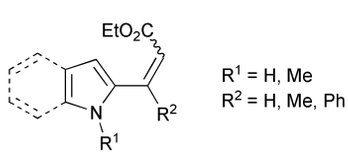
coupling of aryl halides to 4-chloroquinolines also involved a sacrificial iron anode[96] (8 examples, 50–81%).

Direct activation and carbonylation of C–H bonds adjacent to an sp^2 nitrogen in a variety of 5-membered heteroarenes was possible using $Ru_3(CO)_{12}$ as a catalyst with alkenes and CO under high pressure[97] (Scheme 12). With alkyl-substituted



Scheme 12

terminal alkenes the major product (>90 : 10) was the result of linear coupling, whilst styrenes often gave substantial amounts of the branched isomers. Some highly functionalised alkenes were well tolerated in the reaction. The addition of pyrroles and indoles (and one furan) to alkynoates to give the alkenes **33**, most often with *cis* geometry, was catalysed by $Pd(OAc)_2$.[98] Insertion of cationic Pd^{II} into the heteroaryl C–H bond was proposed as the first step in the catalytic cycle after investigation of the mechanism by deuterium labelling experiments. The Heck reaction was adapted for the synthesis of 3-arylfurans *via* butenolides, starting from 2,5-dihydro-2,5-dimethoxyfuran[99] (Scheme 13).



33 (8 examples, 52–83%)

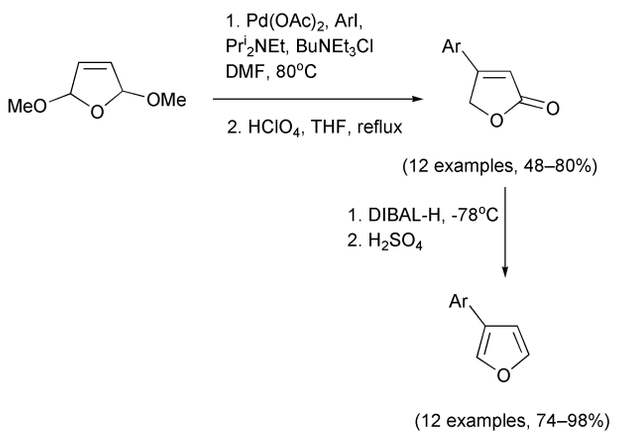
Recent examples of RAS at single points of substitution by coupling to heteroaryl metal compounds are detailed in Table 2 and Fig. 2.

2.3 *N*-Arylation of heteroaromatics

The *N*-arylation of heteroarenes with boronic acids using stoichiometric copper(II) compounds under oxidising conditions

Table 2 Transition metal catalysed cross-couplings to metalated heteroaromatics

Metalated heterocycles	Coupling partners/ catalysts/ reagents	Notes	Ref.
2-Thiazolylzinc bromide	ArX, HetArX/$Pd(PPh_3)_4$	27–78%, 11 Examples; one-pot procedure; the 2-(1-naphthyl)-thiazole product was selectively metalated at C-5 (Bu^nLi, $ZnCl_2$) and coupled to a further ArX (38–79%, 2 examples)	100
2-Trimethylsilyl-1,3-thiazol-5-ylzinc chloride **34**	ArX, HetArX/$Pd(PPh_3)_4$	26–88%, 9 Examples; one-pot procedure; 5-(1-naphthyl)thiazole product was halodesilylated (48–62%), metalated at C-2 (Zn) and coupled to ArX (22%)	100
2-Benzyloxymethyl-5-(tributylstannyl)-tetrazole **35**	ArX, HetArX/$Pd(PPh)_3$, CuI	35–91%, 8 Examples; stannane prepared *via* lithiation of protected tetrazole (67%); BOM deprotection with acid or H_2–$Pd(OAc)_2$ (43–91%, 9 examples)	101
Pyran-2-onyl 5-boronate **36**	Steroidal vinyl triflates/ $PdCl_2(dppf)/K_3PO_4$	52–91%, 6 Examples; bufadienolide steroids; the boronate was prepared by coupling of 5-bromo-2-pyrone and pinacolborane[103] ($PdCl_2(PPh_3)_2$–Et_3N, 70%)	102
5-(2-Oxopyranyl)zinc iodides **37**	ArX, HetArX, vinyl halides/ $Pd_2(dba)_3$, PPh_3	64–79%, 6 Examples; 5-iodo-2-pyrone starting materials prepared by iodolactonisation of pent-2-en-4-ynoic acids	104



Scheme 13

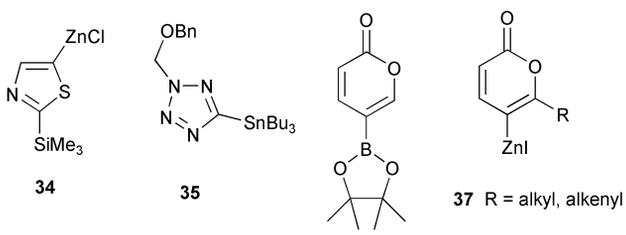
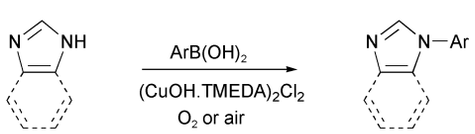


Fig. 2 The metalated heterocycles which are collated in Table 2.

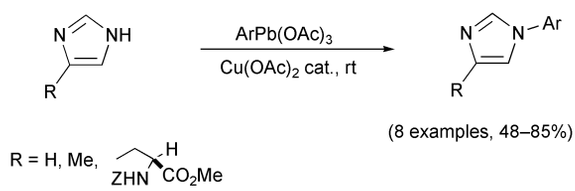
was developed to give general *catalytic* methods for *N*-arylation of imidazoles,[105–108] indazoles,[108] pyridones[108] and other heterocycles.[108] The reaction of imidazoles and arylboronic acids catalysed by $[CuOH{\cdot}TMEDA]_2Cl_2$ proceeded in either aqueous or anhydrous (CH_2Cl_2) media exposed to air or oxygen[105,106] (Scheme 14). Catalyst optimisation for more diverse substrates was required, with $Cu(OAc)_2$–TEMPO being one of the most generally applicable systems.[108] For the selective arylation of N-9 of 2,4-dichloropurine, stoichiometric $Cu(OAc)_2$ in air was effective[47] (4 examples, 43–47%). The stoichiometric procedure



solvent		ref
CH_2Cl_2	(8 examples, 52–98%)	105
H_2O	(8 examples, 26–53%)	106

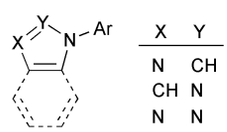
Scheme 14

was shown to promote *N*-phenylation of indazole using phenyltrimethylstannane[109] while the catalytic version was applied to the *N*-arylation of imidazoles by aryllead(IV) reagents[110] where exclusive reaction at the less crowded nitrogen of unsymmetrical imidazoles was observed (Scheme 15). Various *N*-aryl



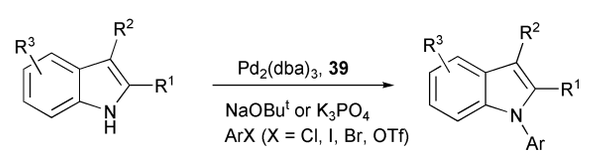
Scheme 15

mono- and bicyclic azoles **38** were efficiently prepared with diaryliodonium salts under copper catalysis.[111]

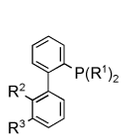


38 (6 examples, 80–94%)

Buchwald and co-workers found that a very general and efficient *N*-arylation of unsubstituted and substituted indoles by aryl halides and triflates was possible using palladium(0) catalysis with biaryl phosphine ligands **39**[112] (Scheme 16). Side reactions of the indoles, such as C-3 arylation by Heck coupling, were minimised with the appropriate choice of ligand: while ligand **39b** was effective for aryl chlorides and bromides, the ligands **39a** or **39c** were needed to couple triflates and iodides. Carbene ligands such as **7** (Fig. 1) were useful in the



R^1	R^2	R^3
H	H	H
Ar, Me	H	H
H	H	7-OEt, 5-OMe, 5-F
Me	Me	H
H	CH_2CO_2Et	H



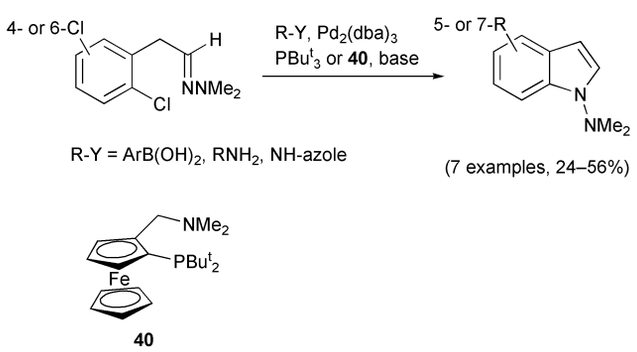
	R^1	R^2	R^3
39a	c-C_6H_{11}	NMe_2	H
39b	Bu^t	Pr^i_2	H
39c	Bu^t	–fused benzo–	

Scheme 16

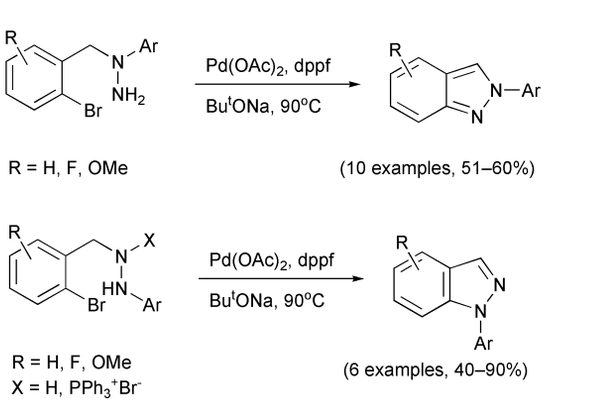
Table 3 Nucleophilic substitution of heteroaryl halides and equivalents

Heteroaromatic	Nucleophile/conditions	Notes	Ref.
4-Chloropyridine (HCl salt)	RNH_2, R_2NH/ 0.8 GPa pressure, 70–100 °C, NaOH	58–93%, 11 Examples; hindered amines (Bu^tNH_2, Pr^i_2-NH) did not react	119
2,3- 2,6- 2,5-Dibromopyridines	$LiCH_2CN$/ −78 °C–rt, THF, 0.04 M in substrate	11–97%, 11 Examples; selective displacement of 2-Br was seen in most cases	120
3-Amino-6-chloropyridazine	RONa, RSNa/ alcohol or dioxane, reflux, 14–60 h	81–98%, 7 Examples; contrary to precedents, high pressure was not needed	121
2-Chloro-4,6-dimethoxy-pyrimidine	RONa, ArONa/ catalytic $MeSO_2Na$ (5–10%), K_2CO_3, DMF, 120 °C	66–83%, 4 Examples; significant rate enhancement was achieved with sodium methanesulfinate *via* formation of the 2-pyrimidylsulfone	122
2,4,6-Trichloropyrimidine	*para* substituted $ArNH_2$/ EtOH, rt–reflux	62–99%; 10 Examples; regioselective (>10 : 1) mono-substitution of the 4-Cl group was seen in EtOH but not in less polar solvents; electron-deficient $ArNH_2$ (4-CN, 4-NO_2) did not react	123
2,4,6-Trichloropyrimidine	Carbamates $R^1O(CO)NHR^2$/ NaH, DMF, rt R^1 = Bn, Bu^t; R^2 = H, alkyl, aryl or R^1–R^2 = $(CH_2)_2$	74–100%, 7 Examples; good selectivity (*ca.* 9 : 1) was achieved for 4- *vs.* 2-substitution, with BOC-carbamates giving the best yields and regioselectivities	124
5-(Benzotriazol-1-yl)-1,2,3-thiadiazoles **42**	ArOH, ArSH, BnSH/NaH, DMF, rt	11–76%, 9 Examples; displacement of benzotriazole, presumed to proceed through the ring-opened tautomer **43**	125
6-Mesitylenesulfonyl-2′-deoxyguanosine **44**	ROH, ArOH/DABCO, DBU, rt RNH_2, R_2NH; 50 °C, 1,2-dimethoxyethane	Alcohols 55–90%, 11 Examples; activation of the sulfonate by initial displacement with DABCO; amines 77–94%, 4 examples; direct S_NAr	126

palladium-catalysed coupling of aryl bromides and indoles[31] (9 examples, 61–100%) and *N*-arylation of pyrroles, indoles and carbazoles by aryl bromides was catalysed by $Pd(OAc)_2$–PBu^t_3 in the presence of potassium or rubidium carbonates (7 examples, 65–96%).[113] By application of this latter reaction in an intramolecular sense, *o*-chloroarylacetaldehyde dimethylhydrazones were cyclised to the corresponding *N*-dimethylaminoindoles[114] (6 examples, 18–74%) and when certain dichlorinated arene starting materials were used, simultaneous cyclisation and coupling with boronic acids, amines or azoles was possible (Scheme 17). Another palladium-catalysed intramolecular *N*-arylation, coupled with spontaneous *in situ* oxidation, was developed to give diverse 1- and 2-arylindazoles[115,116] (Scheme 18). For 1-arylindazoles, the hydrazine starting materials could be stored and reacted as their more stable triphenylphosphonium adducts.

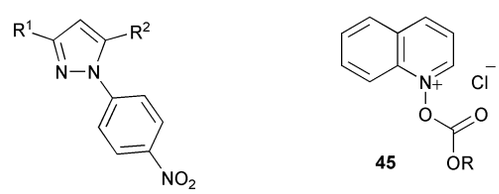


Scheme 17



Scheme 18

The direct nucleophilic displacement of 4-fluoronitrobenzene by pyrazoles usually gives mixtures of N-1 and N-2 arylated products, but was found to give good to excellent N-1 selectivity for the formation of 3-alkoxymethyl-5-alkyl- or 3-aryl-5-alkylpyrazoles **41**.[117,118] For the 3-alkoxymethyl substrates, the solvent dependence of the outcome suggested that cation chelation lay behind the regioselectivity.



2.4 Nucleophilic substitution of heteroaromatics

Nucleophilic displacement of halides from heteroaromatic cores, usually by the S_NAr mechanism, remains a particularly useful route into *N*-, *O*- and *S*-substituted compounds. Recent examples of RAS by nucleophilic substitution at single sites are detailed in Table 3 and Fig. 3.

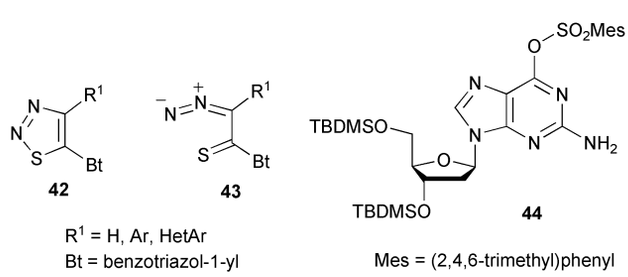
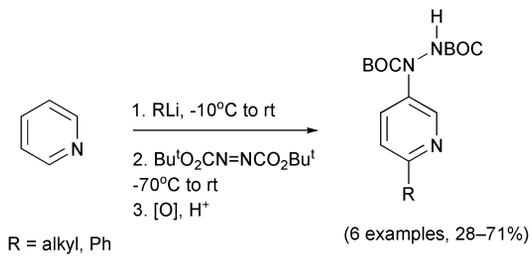


Fig. 3 Structures for Table 3.

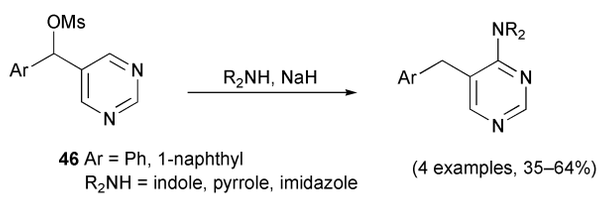
An unusual tandem S_NAr displacement–S_N2 dealkylation was developed for the substitution of 2-chlorobenzothiazole and 2-chlorobenzoxazole by tertiary amines[127] (8 examples, 41–89%). *N*-Methyl, ethyl and benzyl groups were cleaved from the amine component by the chloride released in the first nucleophilic substitution. Complications were seen with

N-ethylpyrrolidine due to competitive opening of the pyrrolidine ring in the second step. 2-Quinolines were prepared by regioselective addition of Grignard reagents to *N*-oxycarbonylalkoxyquinolinium chlorides[128] **45** followed by *in situ* carbonate elimination to regenerate the heteroaromatic ring (8 examples, 32–82%). The product anions from the addition of organolithiums to pyridine were trapped with di-*tert*-butyl azodicarboxylate to yield 2-substituted-5-hydrazinopyridines after oxidation on work-up (Scheme 19).[129] 4,5-Disubstituted



Scheme 19

pyrimidines were formed by remote displacement of the benzylic mesylate **46** with azoles[130] (Scheme 20) where

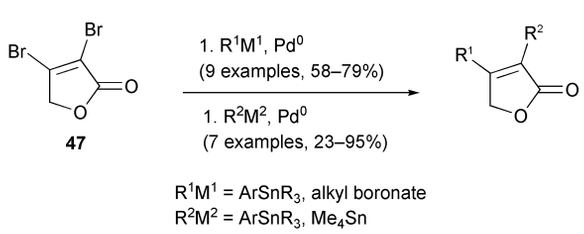


Scheme 20

the mechanism was envisaged as nucleophilic addition to C-4, with loss of the mesylate, followed by a [1,3] hydride shift. In each case, small amounts of the corresponding 2,5-disubstituted pyrimidines were also observed.

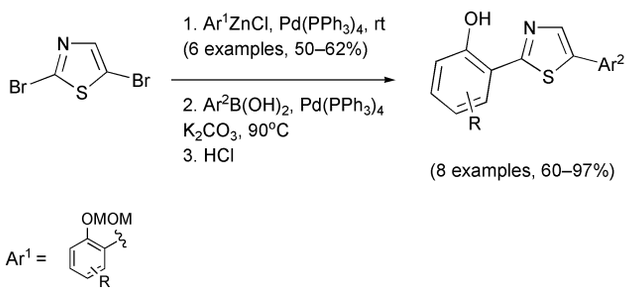
2.5 Multiple sequential substitution

More diverse compounds can be made when the foregoing methodologies for substitution at single centres are applied sequentially to polyfunctional cores. Selective reactions of dihaloheteroaromatics (see Sections 2.1 and 2.2) are the basis of many such strategies. Thus Rossi, Bellina and co-workers prepared the dibromofuran-2-one **47** which was, with appropriate catalyst optimisation, coupled with arylstannanes[131,132] or alkyl boronates[133] with good regioselectivity, followed by reaction with a second organotin (Scheme 21). 3,4-Dialkynylpyridazin-



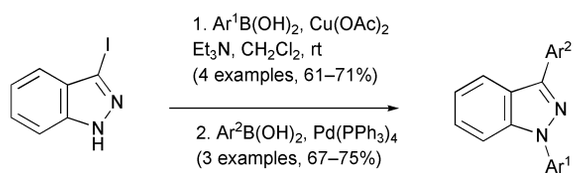
Scheme 21

2-ones **48** were reached by sequential Sonogashira couplings on either of the isomeric 3(4)-chloro-4(3)-trifluoromethylsulfonyloxy precursors, with the trifluoromethylsulfonyloxy group reacting first in both cases.[134] Suzuki couplings to the intermediate 3(4)-chloropyridazinones were also possible (4 examples, 78–98%). Large conjugated arrays of 2,2′-bipyridines were efficiently constructed from 2-chloro-5-iodopyridine by chemoselective alkyne coupling to the 5-iodide followed by Stille couplings of 2-pyridylstannanes to the 2-chloride.[135] Stille and Sonogashira reactions of 2-amino-3,5-dibromopyrazine were selective for the 5-bromo substituent and were followed by a second Stille or a Suzuki coupling as the first step in the syntheses of analogues of the chemiluminescent *Cypridina* luciferin[136] and coelentrazine[137] natural products. The core rings of the hapalindole alkaloids were built up from the 3-bromo-4-iodoindole **49** by Stille coupling to the iodide (76%) and Heck reaction of the bromide (81%).[138] Fort and co-workers extended the selective nickel-catalysed amination of 2,6- and 3,5-dichloropyridines (see Section 2.1) to produce unsymmetrical diaminopyridines.[56,139] In the syntheses of fusaric§ and fusarinolic acid§, monocarbonylation of 2-iodo-5-bromopyridine at the more reactive 2-position was followed by Negishi or Sonogashira coupling to the 5-bromide.[140] The 2-position was also the site of the first coupling in the synthesis of 2,5-diarylthiazoles[141] and cystothiazole[142] from 2,5-dibromothiazole by Bach and Heuser (Scheme 22). By combining the



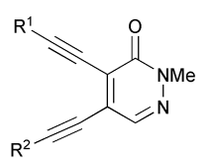
Scheme 22

different behaviour of arylboronic acids under palladium- and copper-mediated processes, 1,3-diarylindazoles were prepared from 3-iodoindazole[143] (Scheme 23). This was carried out

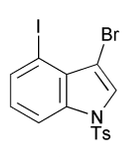


Scheme 23

successfully in a one-pot procedure in the presence of the two metal species by separate addition of the boronic acids (2 examples, 68–71%) where *N*-arylation occurred first.



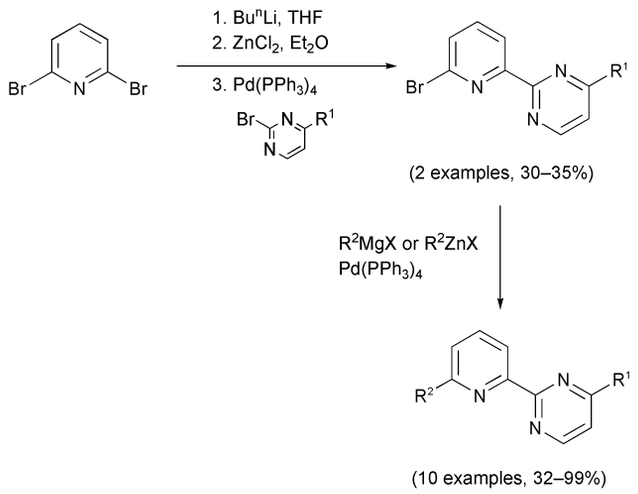
48



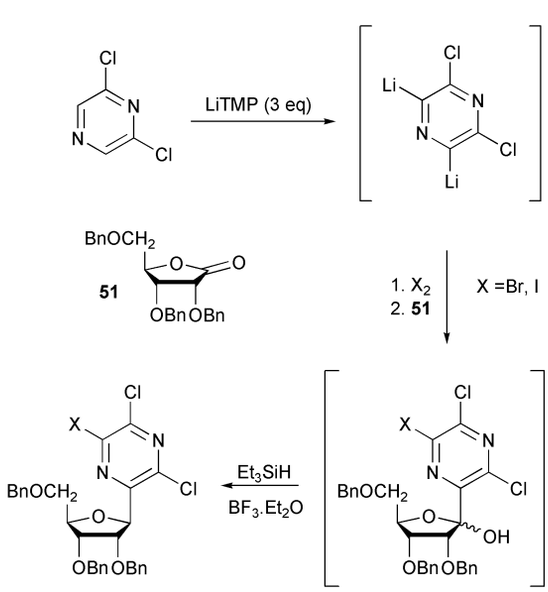
49

Polyfunctional metalated heteroaromatics featured in many recent examples of RAS, such as the preparation of pyrimidylpyridine fungicides by sequential Negishi couplings starting with 6-bromopyridylzinc chloride[144] (Scheme 24), from which reagent heteroarotinoids **50** were prepared by double Negishi or Negishi–Sonogashira couplings.[145] Vedsø and co-workers combined their routes to 2- and 5-arylthiazoles (see Table 2) to give 2,5-diaryl substitution by metalation[100]–Negishi coupling of 2-bromo- or 2-trimethylsilylthiazole. Controlled sequential reaction of 3,5-dilithio-2,6-dichloropyrazine with electrophiles was used to prepare halogenated pyrazine

§ The IUPAC name for fusaric acid is 5-butyl pyridine-2-carboxylic acid. The IUPAC name for fusarinolic acid is 5-(3-hydroxybutyl) pyridine-2-carboxylic acid.

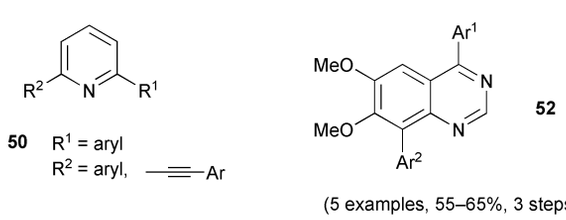


Scheme 24

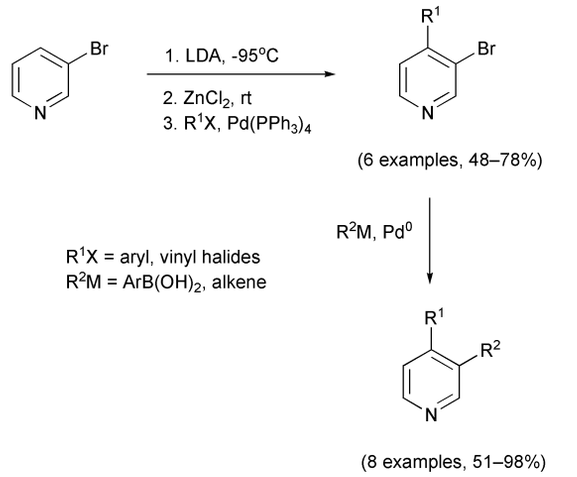


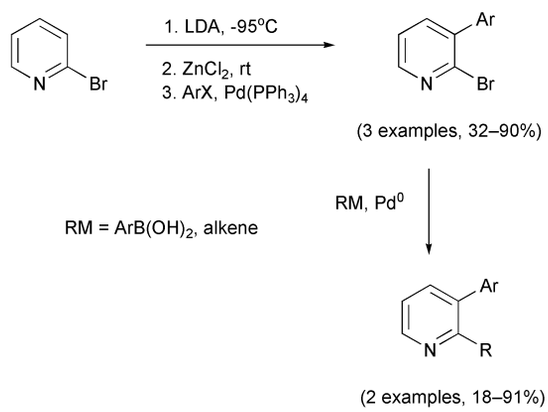
Scheme 25

C-nucleosides[146] (Scheme 25) while two discrete lithiations on 2-chloropyrazine at C-3 then C-6 produced analogues of the plant growth inhibitor septorin.[147] To prepare 5,6-bis(alkynyl)-nucleosides with good overall yields, Sonogashira coupling to 5-iodouracils was followed by selective lithiation at C-6 and generation of the C-6 iodide, to which further alkynes were coupled.[148]



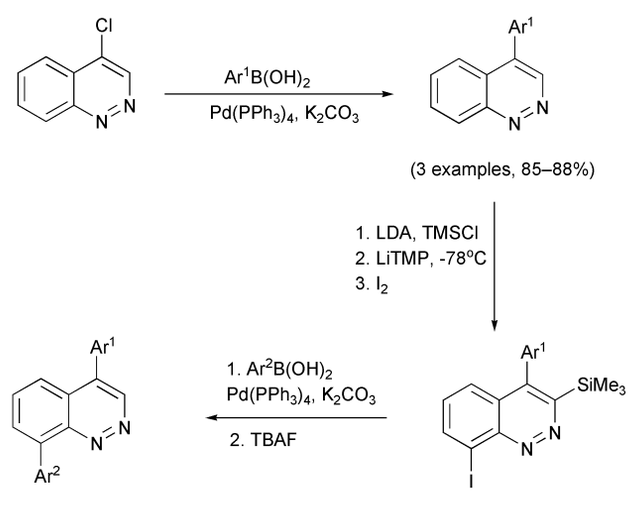
In a versatile procedure, Gallagher and co-workers built up 2,3- and 3,4-disubstituted pyridines from 2- and 3-bromopyridines respectively, exploiting the directing effect of the bromo substituent to achieve regioselective *ortho* metalation in each case, and using the resulting (bromopyridyl)zinc species in the first of two coupling reactions[149] (Scheme 26, *cf*. Scheme 24). By changing the base to LiTMP at −78 °C, partial migration of the metal from C-3 to C-4 was observed with 2-bromopyridine, leading to a direct, albeit lower yielding, entry to 2,4-diarylpyridines.





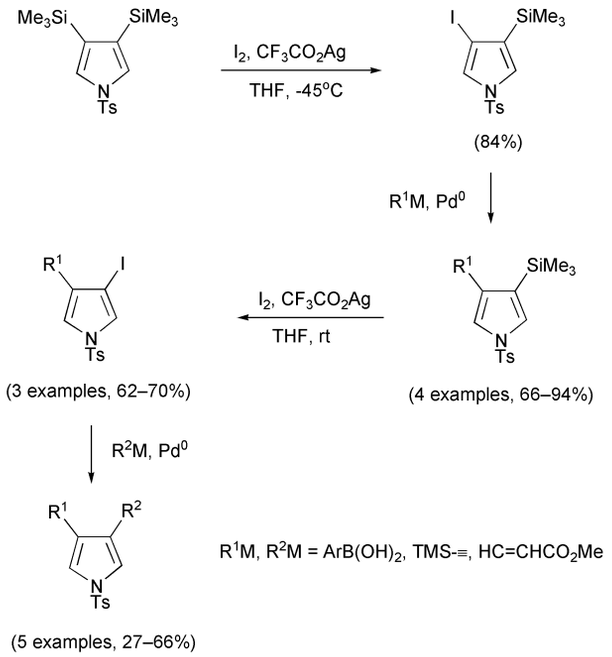
Scheme 26

A double lithiation strategy, in which one metalation served to introduce a temporary *C*-trimethylsilyl blocking group, combined with two Suzuki couplings gave a series of 4,8-diarylcinnolines[150] (Scheme 27). With an appropriate *ortho*



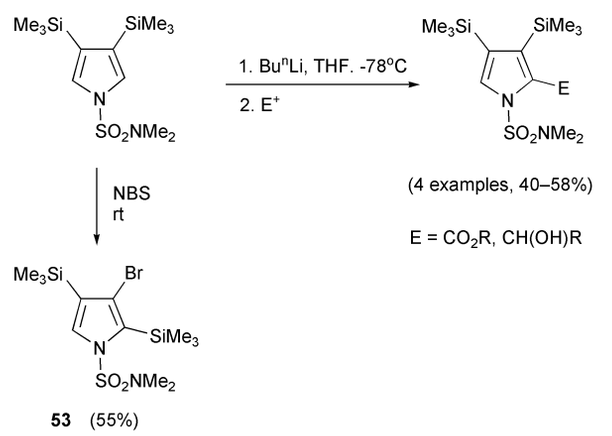
Scheme 27

directing group present in the substrate the silylation step was not necessary, leading to the 4,8-diaryl-6,7-dimethoxyquinazolines **52**. In both routes, nitroarene substituents were not tolerated in the deprotonation step. The use of the trimethylsilyl group as a masked halide on an electron-rich heteroaromatic through *ipso* halodesilylation was extensively explored by Wong and co-workers in the synthesis of di- and trisubstituted



Scheme 28

pyrroles by palladium-mediated couplings.[151,152] Various *N*-protecting groups were investigated, with toluene-*p*-sulfonyl showing the greatest utility in the simpler sequences[151] (Scheme 28). Halogen–metal exchange of *N*-triisopropylsilyl protected 3-trimethylsilyl-4-halopyrroles was demonstrated, and the resulting lithiopyrroles were alkylated or added to aldehydes. To give 2,3,4-trisubstituted products, a strong *ortho* directing group was required on the nitrogen, allowing lithiation at C-2 early in the synthesis[152] (Scheme 29). Bromodesilylation with

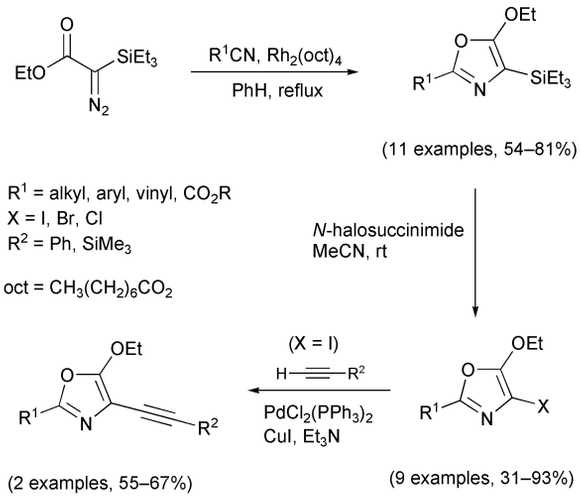


Scheme 29

NBS at room temperature gave substantial quantities of the substitution–rearrangement product **53** which could also be elaborated to trisubstituted products. 4-Triethylsilyloxazoles, generated by rhodium(II) catalysed condensation of nitriles and (triethylsilyl)diazoacetates, underwent *ipso* halodesilylation and subsequent Sonogashira coupling to give trisubstituted oxazoles[153] (Scheme 30).

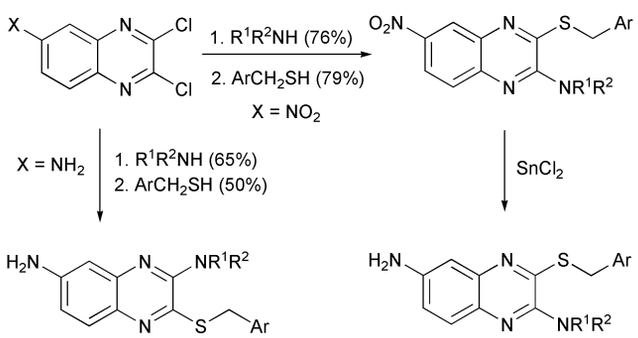
Sequential nucleophilic substitution of cyanuric chloride¶ with differentially protected piperazines gave an efficient route to *s*-triazine-containing macrocycles.[154] An interesting control of the regiochemistry of the stepwise nucleophilic displacement of 2,3-dichloro-6-substituted quinoxalines was achieved by changing the electronic properties of the 6-substituent (NH_2 *vs.*

¶ The IUPAC name for cyanuric chloride is 2,4,6-trichloro-*s*-triazine.



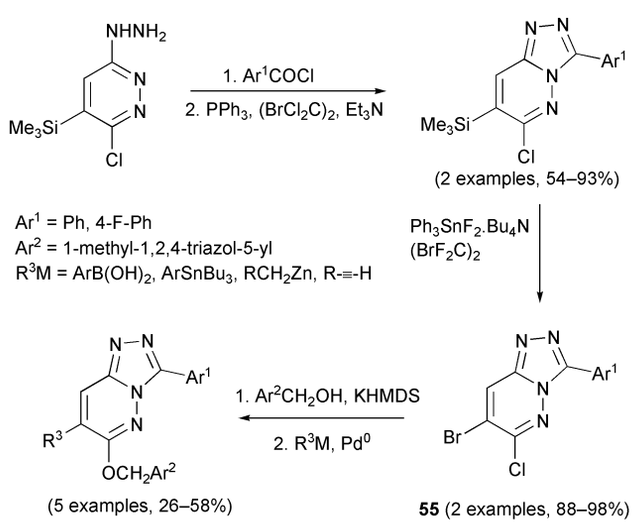
Scheme 30

NO_2), which allowed the preparation of the regioisomeric compounds while retaining the optimum order of addition of the nucleophiles; amine followed by thiol (Scheme 31).[155]



Scheme 31

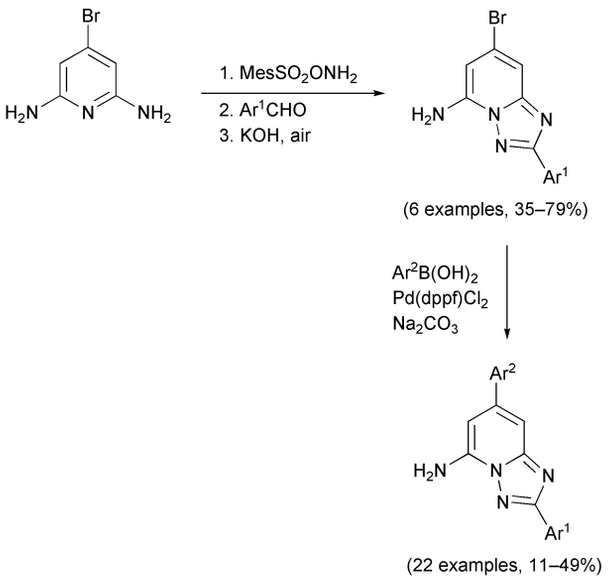
1,4-Dichlorophthalazine underwent monosubstitution with *N*-methylpiperazine (70%) and subsequent Suzuki couplings to provide the phthalazines **54**.[156] Nucleophilic substitution and palladium catalysis were also combined in the RAS of trisubstituted 1,2,4-triazolo[4,3-*b*]pyridazines *via* the dihalide **55**[157] (Scheme 32). A trimethylsilyl group served as a masked



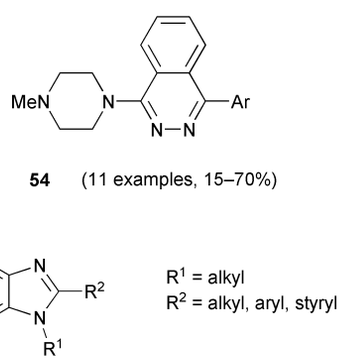
Scheme 32

halide in the synthesis of **55** and unusual nucleophilic conditions were required for the silicon to bromine conversion on the electron-deficient ring. Selective displacement of the chloroimidate group with alkoxide was followed by a full range of

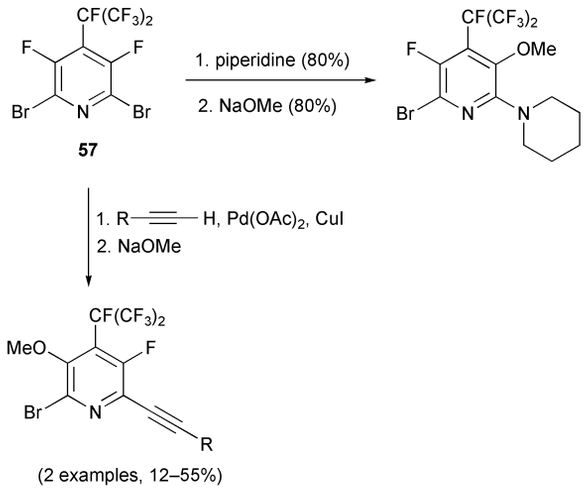
palladium-catalysed couplings to the bromide. 7-Amino-1,2,4-triazolo[1,5-*a*]pyridines with two variable substituents were prepared from 2,6-diamino-4-bromopyridine by chemoselective amination of the pyridine nitrogen and a one-pot condensation–cyclisation–oxidation with varied aldehydes to form the triazole ring, after which Suzuki coupling with a large number of aryl- and heteroarylboronic acids was demonstrated[158] (Scheme 33). Starting from 5-amino-4,6-dichloropyrimidine, displacement of one chloride by an amine was followed by an oxidative cylisation with aldehydes in the presence of $FeCl_3$ absorbed on silica gel to generate the 6,8,9-trisubstituted purines **56**.[159]



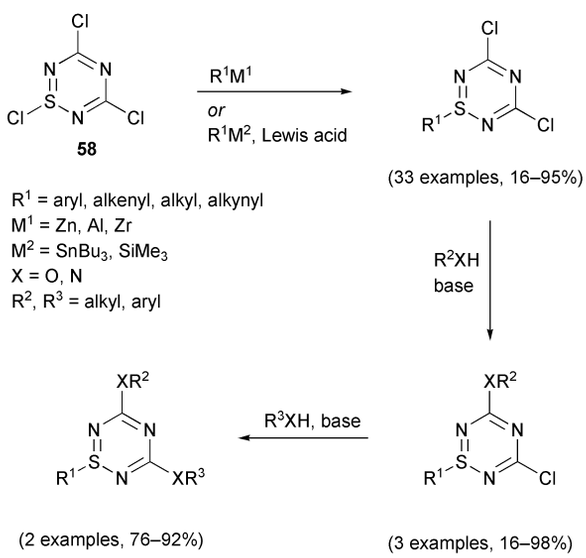
Scheme 33



A fascinating variation of the multiple nucleophilic addition strategy was realised by Chambers, Sandford and co-workers using very reactive pentafluoropyridine as the starting scaffold, and exploiting the preference of hard and soft nucleophiles to attack at C–F and C–Br centres respectively.[160] For example, after perfluoroalkylation at C-4 and dibromination at C-2 and C-6, piperidine reacted selectively with the substrate **57** at the C-2 bromide, and subsequent sodium methoxide treatment displaced the adjacent fluoride (Scheme 34). Interestingly, reversing the order of these steps removed the regioselectivity of the second displacement. Sonogashira couplings to **57** were also incorporated into the approach. Sequential nucleophilic substitution of the trichlorothiatriazine **58** widened the scope of RAS to include a sulfur centre in the heteroaromatic core.[161] Selective nucleophilic attack at the sulfur was best achieved with zinc, aluminium or zirconium species and an equivalent substitution was also possible with arylsilanes, arylstannanes and enol ethers through Lewis acid catalysed mechanisms (Scheme 35).

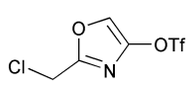


Scheme 34



Scheme 35

Subsequent nucleophilic displacement of the second and third chlorides with amines and alcohols was possible, though the selectivities for mono- over disubstitution in the first of these steps were not always high. Strategies for RAS through sequential substitutions can apply to centres removed from the heteroaryl core in systems such as the orthogonally functionalised oxazole **59**.[162]



59

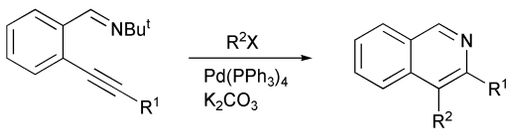
3 Tandem ring formation and substitution

The synthesis of heteroaromatic cores by the cyclisation of linear precursors can be incorporated into RAS approaches, particularly where a tandem ring-formation –substitution sequence is available. Palladium-mediated coupling–cyclisation reactions of alkynes and allenes have found widespread use for this purpose.

3.1 Annulation of alkynes and equivalents

Intramolecular iodocyclisation of alkynes gave 3-iodobenzo[*b*]-thiophenes[163] from which tubulin binding agents were prepared *via* halogen–metal exchange. Similar iodocyclisations led to various 4-iodoisoquinolines,[164] 4-iodonaphthyridines[164] and

3-iodofurans.[165] Such intramolecular annulation of alkynes becomes particularly relevant for RAS when diverse substituents can be added in tandem with the ring formation, and palladium catalysis can enable this by using the organopalladium complex formed upon oxidative addition to halides as the activating species for heterocyclisation to the alkyne, followed by reductive elimination to effect the coupling. For example, Larock and Dai prepared 3,4-disubstituted isoquinolines[166] from *N*-*tert*-butyl-*o*-(alk-1-ynyl)benzaldimines and activated halides (Scheme 36). Some competition from the



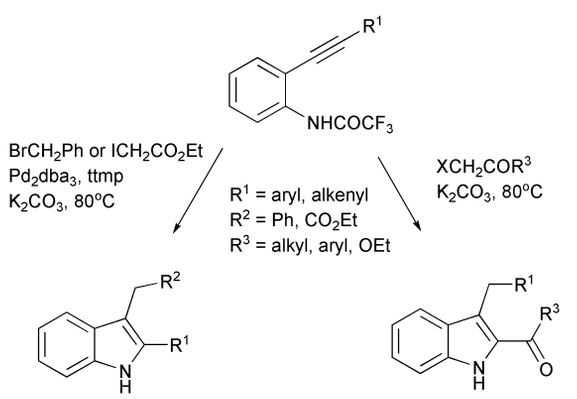
R^1 = aryl, alkenyl, alkyl
R^2 = aryl, allyl, benzyl

(16 examples, 30–80%)

Scheme 36

thermal cyclisation to give 3-substituted isoquinoline side-products was observed with hindered or electron-rich coupling partners. A related reaction starting with 2-alkynylbenzonitriles led to either isoquinolines or isoindoles depending on the steric properties of the alkynyl substituent.[167] Likewise, 2-alkynylbenzoic acids predominantly underwent cyclisation to isobenzofuranones on reaction with aryl halides and palladium catalysis.[168]

Cacchi and colleagues devised two divergent cyclisations of 2-alkynyltrifluoroacetanilides to give complementary 2,3-disubstituted indoles[169,170] (Scheme 37). Palladium-mediated



(12 examples, 41–78%)

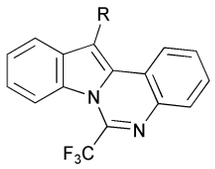
(10 examples, 52–80%)

ttmp = tri(2,4,6-trimethoxyphenyl)phosphine

Scheme 37

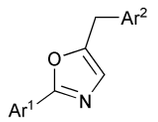
cyclisation with ethyl iodoacetate or benzyl bromide occurred as anticipated with the halide coupling to the internal carbon of the alkyne.[169] Alternatively, *N*-alkylation of the anilide with an α-halocarbonyl compound could be followed by nucleophilic 5-*exo*-*dig* cyclisation without the need for the catalyst.[170] The palladium-catalysed methodology was applied to the synthesis of indolo[1,2-*c*]quinazolines **60** from a symmetrical bis-(anilido)alkyne.[171] 2,3-Disubstituted indoles were also prepared from the *in situ* condensation and palladium-catalysed cyclisation of 2-alkynylanilines and aliphatic aldehydes.[172] 2,5-Disubstituted oxazoles **61** resulted from the tandem coupling–cyclisation of aryl halides and *N*-propargylamides‖, where the mechanism involved coupling of the alkyne and aryl halide followed by base-mediated cyclisation.[173]

1,2-Allenyl ketones were cyclised *via* γ-allylpalladium species, using Pd(PPh$_3$)$_4$ and Ag$_2$CO$_3$ in the presence of aryl and alkenyl



60

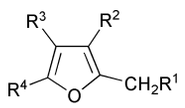
R = aryl, alkenyl
(16 examples, 22–97%)



61

(22 examples, 11–83%)

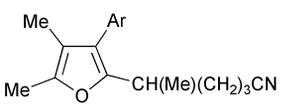
halides, to yield di-, tri- or tetra-substituted furans **62** in good to excellent yields.[174] Tetrasubstituted furans **63** were prepared by the reduction of 4,5-epoxyalk-2-ynyl esters with SmI$_2$ followed by an *in situ* palladium-catalysed cyclisation–coupling of the intermediate 2,3,4-trien-1-ols with aryl halides.[175]



62

(17 examples, 51–94%)

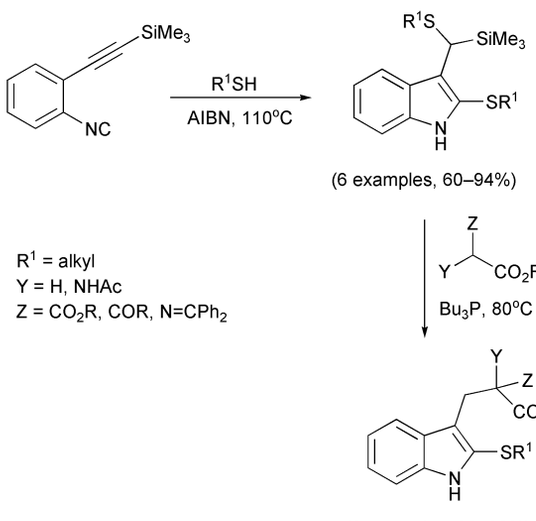
R^1, R^2 = H, alkyl
R^3, R^4 = H, alkyl, Ph



63

(7 examples, 40–73%)

2,3-Disubstituted indoles were made from 2-alkynylphenylisonitriles by a radical cascade mediated by thiols.[176] Following the cyclisation, elaboration at the benzylic position with carbon nucleophiles was possible (Scheme 38). The tin hydride-



(6 examples, 60–94%)

R^1 = alkyl
Y = H, NHAc
Z = CO$_2$R, COR, N=CPh$_2$

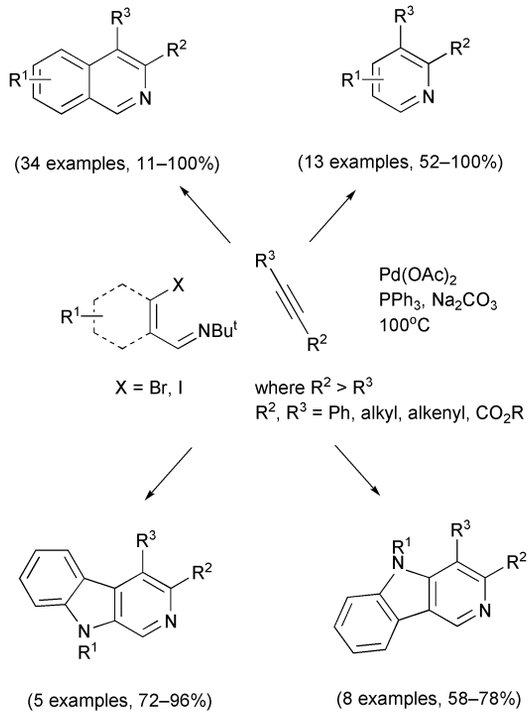
(8 examples, 33–98%)

Scheme 38

mediated radical cyclisation of 2-alkenylphenylisonitriles developed by Fukuyama and co-workers was used to generate 2-stannylindoles which, after conversion to the corresponding iodides, also allowed the preparation of 2,3-disubstituted indoles.[177]

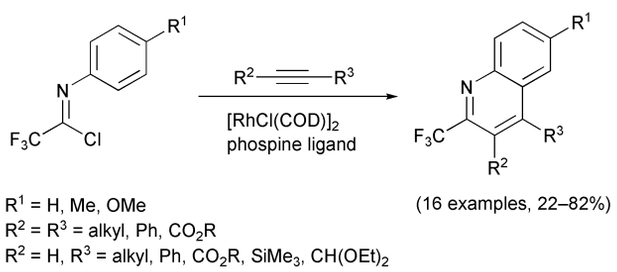
Intermolecular alkyne annulations provide versatile syntheses of substituted heteroaromatics, particularly when good regioselectivity is achieved with unsymmetrical internal alkynes. Continuing to explore the palladium-catalysed coupling–cyclisation of alkynes to substrates containing a β-halovinylimine fragment, Larock and co-workers prepared pyridines,[178] iosoquinolines[179] and β- and γ-carbolines[179] (Scheme 39). In most cases good to excellent regioselectivity was obtained with unsymmetrical alkynes, where the larger substituent occupied the position adjacent to the nitrogen atom in the product as a result of carbon–carbon bond formation to the less hindered end of the triple bond in the coupling. A similar

‖ The IUPAC name for propargyl is prop-2-yne.



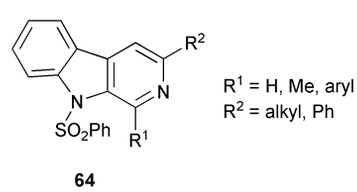
Scheme 39

process starting with iodouracil bearing an amidine led to pyrido[2,3-*d*]pyridines (9 examples, 48–96%).[180] The β-carbolines **64** with varied 1- and 3-substituents were prepared from 2-acyl-3-iodoindoles by sequential Sonogashira coupling of terminal alkynes and 6-*endo*-*dig* cyclisation with ammonia.[181] By using a rhodium(I) catalyst, *N*-aryl trifluoroacetimidoyl chlorides were coupled and cyclised with alkynes to give 2-trifluoromethylated quinolines without the need for an *ortho* halide in the substrate[182] (Scheme 40). Although the method



Scheme 40

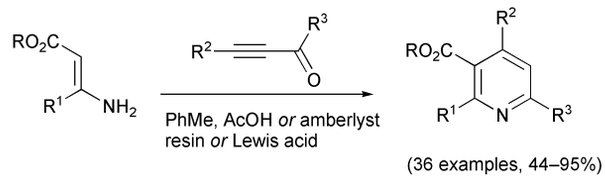
was low yielding with electron-poor arenes (R^1 = Cl), generally excellent (>95 : 5) regioselectivities resulted with unsymmetrical alkynes, where the smaller substituents or electron withdrawing groups occupied the 3-position of the quinoline ring. Similarly avoiding the need for *o*-halo functionality, 2,3-disubstituted indoles were prepared directly by ruthenium-catalysed hydroamination of propargyl alcohols with anilines.[183]



64

(11 examples, 16–70%, 2 steps)

Alkynyl ketones have featured in several RAS studies, including the preparation of a diverse set of β-heteroaryl α-amino acids by Baldwin and co-workers through condensation–cyclisation reactions from a common precursor.[184,185] This approach also yielded alkynyl substituted pyrazoles and pyrimidines from dialkynyl ketones,[186] and a similar strategy gave β-pyridazinyl and β-triazinyl α-amino acids from vicinal tricarbonyl substrates.[187] Mild acid-mediated conditions were found by Bagley and co-workers to give an improved, high yielding Bohlmann–Rahtz synthesis of tetrasubstituted pyridines in a one-pot procedure[188] (Scheme 41). Some sensitive

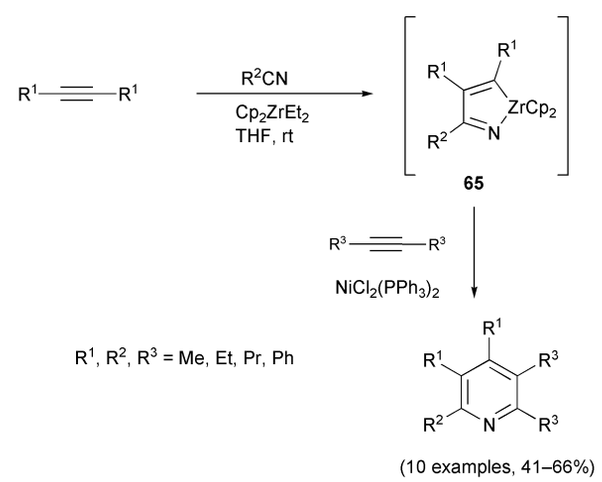


R^1 = Me, Ar; R^2 = H, Ph, $SiMe_3$; R^3 = Me, CO_2Et

Scheme 41

alkynyl ketones or aminocrotonates failed to give products with acetic acid due to decomposition, but this was circumvented by using Amberlyst resin. Lewis acids also catalysed the reaction,[189] which was applied to 2,6-diaminopyrimidin-4-one to generate disubstituted pyrido[2,3-*a*]pyrimidine folate inhibitors[190] (6 examples, 62–96%). A two step synthesis of 2-alkyl-4-aminopyridines (8 examples, 25–83%) involved the acylation of 4-lithio-*cis*-1-methoxybuten-1-yne followed by aminolysis of the intermediate alkynyl ketones under high pressure.[191] 2,5-Disubstituted furans (7 examples, 57–80%) were synthesised by chromium(II)-mediated addition of unsubstituted alkynyl ketones to aldehydes in the presence of TMSCl and water.[192]

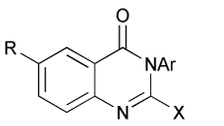
The co-cycloaddition of two different symmetrical internal alkynes and a nitrile to give single regioisomers of simple pentasubstituted pyridines was achieved using stoichiometric zirconium and nickel.[193] Transmetalation of the intermediate zirconacycle **65** promoted the second alkyne addition in a one-pot protocol (Scheme 42). Single products were also obtained



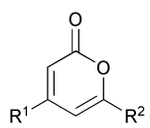
Scheme 42

when unsymmetrical internal alkynes were used in the second step. A palladium-catalysed three-component coupling of *o*-iodophenols, carbon monoxide and internal alkynes gave 3,4-disubstituted coumarins (11 examples, 43–78%) where, unusually, the insertion of the alkyne into the aryl–Pd bond occurred in preference to the insertion of carbon monoxide.[194] Unsymmetrical alkynes reacted with reasonable to very good regioselectivity. The palladium-catalysed cyclocarbonylation of *o*-iodoanilines with carbon monoxide and heterocumulenes (isocyanates, carbodiimides or ketenimines) under high pressure (300 psi CO) gave the products **66** where

carbon monoxide insertion took place at the expected position.[195] Simple allenylstannanes and β-iodo vinylic acids gave 4,6-disubstituted 2-pyrones **67** where the regioselectivity of the palladium-catalysed heteroannulation suggested a reaction sequence involving Stille coupling to the halide followed by cyclisation *via* a π-allylpalladium species.[196] Further examples of multicomponent reactions mediated by palladium catalysis are detailed in Section 4.



X	**66**
OH	(10 examples, 68–90%)
NHAr	(9 examples, 55–90%)
CHR^1COR^2	(11 examples, 45–99%)

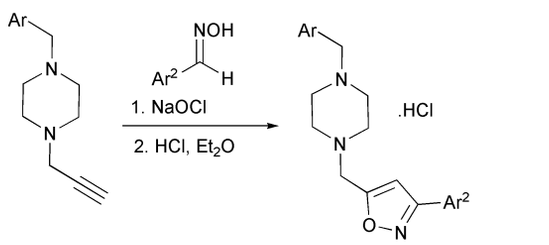


67

(9 examples, 79–87%)

3.2 Cycloadditions

The inherent atom economy and convergence of cycloaddition chemistry has been exploited in RAS of heteroaromatics. For example, a small library of G-protein coupled receptor ligands was prepared by the [3 + 2] dipolar cycloaddition of arylnitrile oxides and propargylamines, where simple precipitation of the amine hydrochlorides served to isolate the products in acceptable purity[197] (Scheme 43). The [3 + 2] cycloaddition was

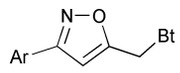


(20 examples, 40–94% yield, 65–100% purity)

Scheme 43

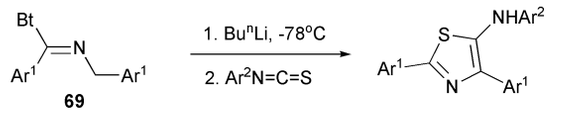
applied in an iterative sense to construct oligoisoxazole metal chelators.[198] Substituted alkynylstannanes underwent the cycloaddition with high regioselectivity to yield 5-stannylisoxazoles (9 examples, 35–80%).[199] In contrast, alkynylboronates delivered either the 4- or 5-boronate isoxazole isomers with the regiocontrol dependent on the alkyne substitution: terminal alkynes gave predominantly the 5-boronates, while internal triple bonds led to the 4-boronate isomers exclusively (5 examples, 27–90%).[200] 3-Aryl-4-methoxycarbonyl isoxazoles (11 examples, 43–96%) were prepared with complete regioselectivity by cycloaddition–elimination of arylnitrile oxides with methyl 3-(*p*-nitrobenzoyloxy)acrylate, which represented a useful reversal of the regioselectivity observed in the usual reaction with methyl propiolate.[201]

Katritzky and co-workers have exploited the cycloaddition chemistry of benzotriazole-bearing substrates to generate polysubstituted heteroaromatics[202,203] The cycloaddition of nitrile oxides and propargylbenzotriazole gave 3-arylisoxazoles **68**.[202] Generation of the nitrile oxide from an oxime by chlorination (NCS) and elimination ($KHCO_3$), and the subsequent cycloaddition, were successfully telescoped into a single step for a few cases (3 examples, 94–100%). The azomethine ylides generated by lithiation of the imines **69** reacted with isothiocyanates to give trisubstituted thiazoles in good yield (Scheme 44).[203] A new route to aminopyrazoles was developed based on the [4 + 1] cycloaddition of isocyanides and azoalkenes, formed *in situ* by elimination of *N*-BOC α-halohydrazones[204] (Scheme 45).



68 Bt = benzotriazol-1-yl

(6 examples, 52–100%)

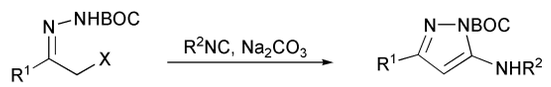


69

Bt = benzotriazol-1-yl

(13 examples, 35–81%)

Scheme 44



X = Cl, Br

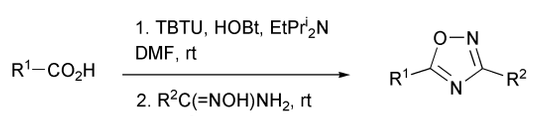
R^1 = Ph, CO_2Et; R^2 = alkyl, aryl

(7 examples, 50–96%)

Scheme 45

3.3 One-pot bimolecular coupling–cyclisation

Although there is an abundance of short synthetic sequences for the preparation of 5- and 6-membered aromatic heterocycles,[2] not all are sufficiently tolerant of diverse substitution to be readily applicable to RAS, and the development of mild conditions compatible with polyfunctional substrates remains a useful goal. For example, the use of the uronium salt TBTU as an activating agent allowed a rapid parallel synthesis of 1,2,4-oxadiazoles[205] (Scheme 46). The cyclodehydration step in this



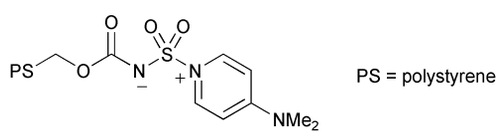
(26 examples, 54–96% yield)
(90–99% purity)

R^1 = aryl, alkyl, alkylamino

R^2 = aryl, heteroaryl

Scheme 46

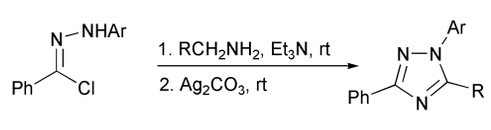
case was achieved thermally, but this reaction was also promoted by tetrabutylammonium fluoride at room temperature[206] (21 examples, 50–98%). Procedures for the cyclodehydration of 1,2-diacylhydrazines to 1,3,4-oxadiazoles were developed by Brain and Brunton using either the solid-supported, modified Burgess reagent **70** and a guanidine base (13 examples, 33–



70

PS = polystyrene

100% yields, HPLC purities 80–100%) or toluene-*p*-sulfonyl chloride and the solid-supported phosphazene base P-BEMP (15 examples, 38–100%, HPLC purities 85–100%).[207] The reactions were heated conventionally (yields quoted) or by microwave irradiation (see below), and required no further purification after filtration and evaporation. A mild oxidative cyclisation of 1,2,4-triazenes to 1-aryl-1,2,4-triazoles was achieved using silver carbonate[208] (Scheme 47), and combin-



(11 examples, 37–69%)

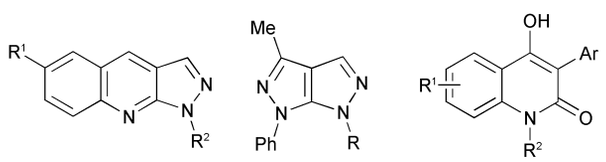
Scheme 47

Table 4 Microwave-assisted one-pot bimolecular reactions giving heteroaromatics

Heteroaromatic products	Substrates/reagents/conditions	Notes	Ref.
2-Phenyl-4-aryloxazoles	$ArC(=O)CH_2R$, PhCN (5 eq.)/$Hg(TsO)_2$ (1 eq.)/2–4 min, domestic microwave	50–86%, 8 Examples; mechanism involved oxidation by Hg(II); also effective for 2-oxoalkanoate starting materials (2 examples; 47–60%)	212
Benzo[*b*]furan-2-carboxylates	Salicylaldehydes, $ClCH_2CO_2R/K_2CO_3$ (2 eq.), Bu_4NBr (0.5 eq.)/8–10 min, 160–300 W	65–96%, 12 Examples	213
2,5-Diarylpyrroles	1,4-Diarylbut-2-ene-1,4-diones,$RNH_3^+HCO_2^-$(R=H,*n*-Bu,Ph,Bn)/Pd–C/PEG 200, 0.5–2 min, 200 W	56–92%, 9 Examples; tandem alkene reduction–Paar–Knorr synthesis	214
Pyrazolo[3,4-*b*]quinolines **71** and pyrazolo[3,4-*c*]-pyrazoles **72**	2-Chloro-3-formylquinolines or 5-chloro-4-formyl-pyrazoles, R^1NHNH_2/TsOH/1.5–2.5 min, 300 W	78–97%, 8 Examples; tandem hydrazone formation and intramolecular S_NAr on the chloroimidate	215
4-Substituted quinolines	Substituted anilines, various alkyl vinyl ketones/$InCl_3$–SiO_2/5–12 min, 600 W	55–87%, 15 Examples; solvent-free conditions; tandem Michael addition–cyclisation–aromatisation; thermal conditions polymerised the ketones	216
2-Aryl or 2-heteroaryl 4-aminoquinazolines	Anthranilonitrile, ArCN or (HetAr)CN/^{t}BuOK (0.1 eq.)/0.3–3 min, 700 W	73–93%, 10 Examples; solvent-free conditions	217
4-Hydroxyquinolones **73**	Substituted anilines, 2-aryl malonates (2 eq.)/15 min, 500 W, open vessel with N_2 stream	8–94%, 16 Examples; solvent-free conditions; electron-withdrawing substituents on the aniline reduced yields, as did bulky *N*-substitution	218

ations of DAST or Deoxo-Fluor with bromotrichloromethane were suitable for the cyclisation–oxidation of β-hydroxy amides to oxazoles[209] (11 examples, 54–88%).

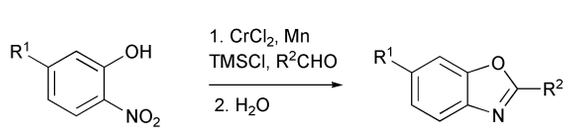
Microwave-assisted reactions have assumed increasing prominence in RAS, enabling faster throughput, solvent-free conditions and, in many cases, extending the range of substituents tolerated compared to the sometimes extreme and inefficient thermal conditions. The enhanced efficiency of cyclodehydration steps under microwave irradiation is of particular note, as in the 1,3,4-oxadiazole synthesis discussed above[207] (26 examples, 49–100%), the clay-catalysed cyclodehydration of α-aryloxy acetophenones to 3-aryl benzofurans[210] (14 examples, 76–92%) and the preparation of 2,4-disubstituted imidazoles[211] related to the nortopsentins from indolyl ketoamides and ammonium acetate (9 examples, 50–75%). Examples of bimolecular one-pot syntheses of heteroaromatics using microwave irradiation are collected in Table 4 and Fig. 4.[212–218]



71 **72** **73**

Fig. 4 Structures for Table 4.

A one-pot NBS oxidation of ethyl β-ethoxyacrylate and thermal condensation with thioureas led to 2-aminothiazole-5-carboxylates[219] (5 examples, 60–98%) while *in situ* oxidative α-tosyloxylation of ketones with PhI(OH)OTs was combined with a cyclocondensation with amidines to generate di- and trisubstituted 1*H*-imidazoles[220] (12 examples, 42–67%). A chromium–manganese redox-couple was used for an elegant synthesis of benzoxazoles from *o*-nitrophenols and aldehydes by a domino reduction–condensation–oxidation sequence[221] (Scheme 48). Electron-withdrawing groups *para* (or *ortho*) to the nitro group were essential for good yields in this reaction.

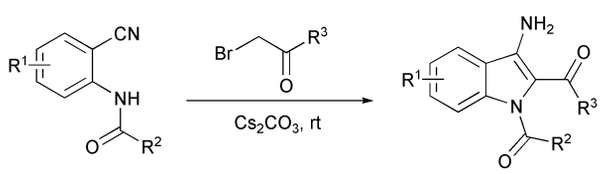


(10 examples, 31–81%)

R^1 = F, CO_2R
R^2 = alkyl, aryl

Scheme 48

The synthesis of a large library of 3-amino-1,2-diacylindoles was achieved by tandem *N*-alkylation–cyclisation of 2-amidobenzonitriles and α-bromoketones mediated by caesium carbonate[222] (Scheme 49). Significantly, the only other base



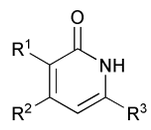
R^1 = H, alkyl, halo
R^2 = Ar, HetAr, cycloalkyl
R^3 = Ar, HetAr, alkyl, cycloalkyl

(205 examples, 4–92%)

Scheme 49

found to effect this reaction was sodium hydride, which was not practical for the parallel synthesis protocol. Of the 280 reactions essayed, 205 gave isolable products after filtration and automated reverse-phase HPLC purification, with amides bearing electron-withdrawing R^2 substituents proving the least efficient substrates. A similar alkylation–intramolecular aldol sequence gave 2-substituted benzo[*b*]thiophenes from α-halocarbonyl compounds and 2-mercaptobenzaldehydes, themselves prepared by *o*-lithiation of the benzaldehydes and quenching with elemental sulfur[223] (9 examples, 26–50%).

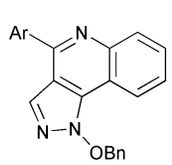
A direct route to trisubstituted 2-pyridones **74** and 3-substituted isoquinolin-1-ones was developed by condensation of γ-lithiated α,β-unsaturated acids and nitriles.[224] Although quite complex product mixtures were produced, the desired pyridones could be isolated by precipitation with water and crystallisation. Begtrup and co-workers prepared 4-substituted pyrazolo[4,3-*c*]quinolines **75** by tandem condensation–intramolecular S_NAr of 4-lithio-5-(2-fluorophenyl)pyrazoles and arylnitriles.[225] The strategy was adapted to give 9-substituted pyrazolo[4,3-*c*]quinolines (4 examples, 53–71%) by intramolecular cyclisation of 5-lithiopyrazoles onto Schiff bases.



74

(13 examples, 13–85%)

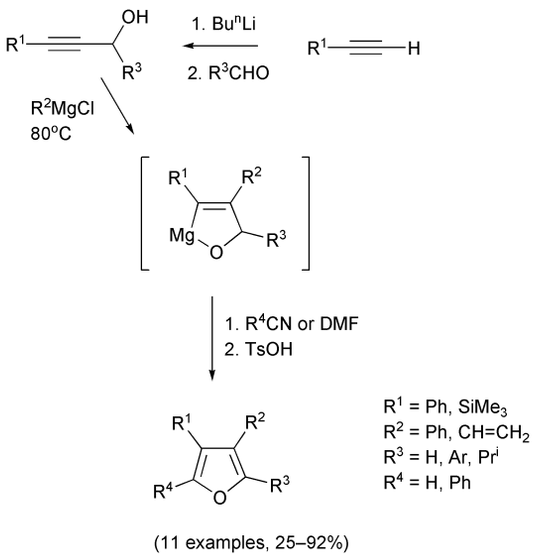
R^1, R^2 = H, alkyl, fused benzo
R^3 = alkyl, aryl



75

(9 examples, 27–69%)

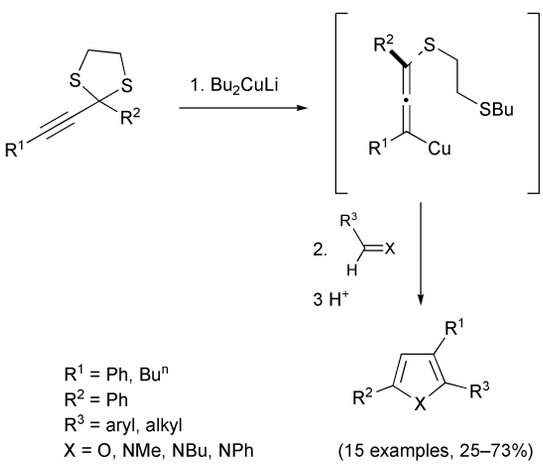
Di- and trisubstituted furans resulted from the carbomagnesiation of propargyl alcohols and cyclocondensation with DMF or nitriles[226] (Scheme 50). Control over the substitu-



(11 examples, 25–92%)

Scheme 50

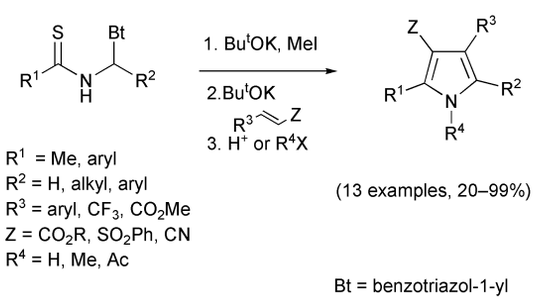
ent pattern was enhanced by generating substituted propargyl alkoxides *in situ* from lithioalkynes and aldehydes, leading to tri- and tetrasubstituted products. Cupration of propargylic dithioacetals and reaction with aldehydes or imines led, *via* the putative thioallenylcopper species, to trisubstituted furans and pyrroles[227] (Scheme 51).



(15 examples, 25–73%)

Scheme 51

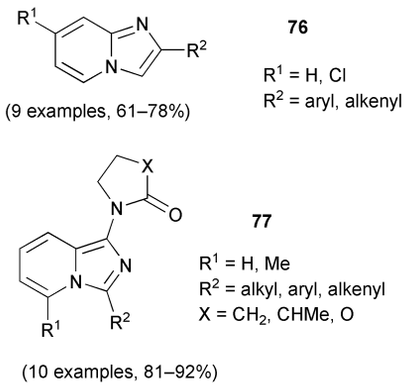
The utility of Katritzky's α-(benzotriazol-1-yl) stabilised anions in heterocyclisation chemistry is well established (*cf.* Section 3.2), and was demonstrated in the generally very high yielding one-pot synthesis of polysubstituted pyrroles from *N*-(benzotriazolyl)thioamides[228] (Scheme 52). Alkylation of



(13 examples, 20–99%)

Scheme 52

2-aminopyridines with 1-chloromethylbenzotriazole gave the pyridinium salts, which condensed with aldehydes under basic conditions *via* ylide formation to yield imidazo[1,2-*a*]pyridines **76**.[229] The Mannich reaction products of pyridine-2-carboxaldehydes, benzotriazole and pyrrolidin-2-ones or oxazolidinones were isolated by filtration and used without purification in a subsequent Lewis acid mediated cyclocondensation with nitriles, leading to imidazo[1,5-*a*]pyridines **77**.[230]



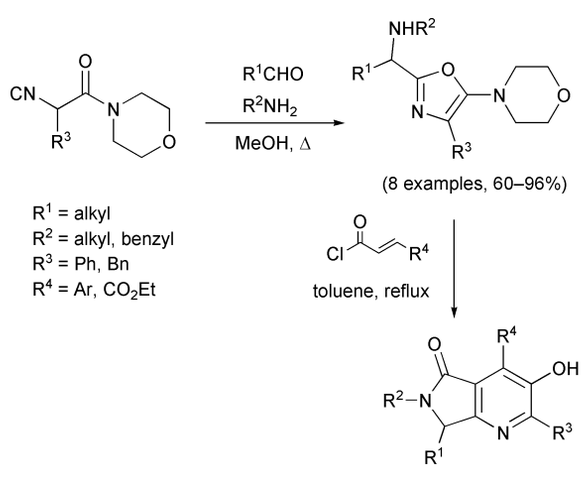
(9 examples, 61–78%)

(10 examples, 81–92%)

4 Multi-component reactions

Multi-component reactions can provide powerful means for rapidly constructing polysubstituted heteroaromatics without further elaboration, provided that the substitution needed to enable and guide the assembly of the heterocycle is congruent with that desired in the target molecules. A wide-ranging review of the multi-component reactions applied in combinatorial approaches to drug discovery, including relevant purification and automation techniques, has been published.[231] The majority of multi-component processes exploit the α-addition reactivity of isocyanides, and an historical perspective on the importance of the Ugi four-component reaction and related isocyanide reactions has appeared.[232]

A novel three-component Ugi-type reaction led to 2,4,5-trisubstituted oxazoles in good yield[233] (Scheme 53). Moreover,



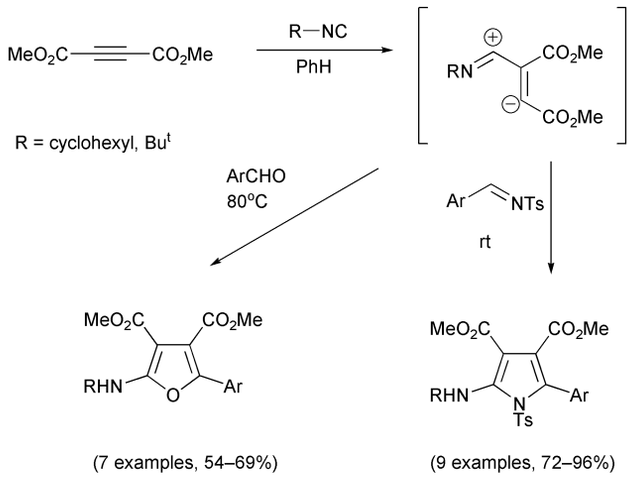
(8 examples, 60–96%)

(8 examples, 55–68%)

Scheme 53

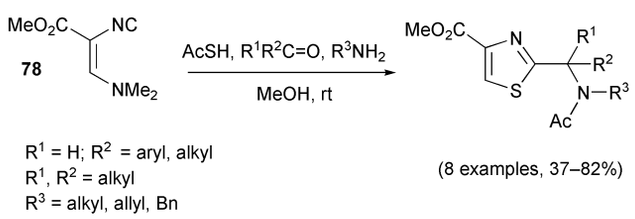
treatment of the 5-aminooxazole products with α,β-unsaturated acid chlorides gave an additional library of pyrrolopyridines by tandem *N*-acylation–intramolecular Diels–Alder cycloaddition–retro-Michael cycloreversion.

A different combination of isocyanide and cycloaddition chemistry was pursued by Nair and co-workers, leading to multi-component syntheses of 2-aminofurans[234] and 2-aminopyrroles[235] (Scheme 54). Here, the zwitterion formed from isocyanide addition to dimethyl acetylenedicarboxylate under-



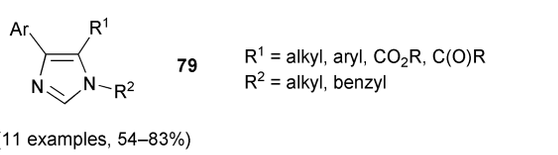
Scheme 54

went intermolecular 1,3-dipolar cycloaddition to aldehydes or *N*-tosylimines. Heck and Dömling prepared 2,4-disubstituted thiazoles[236] by using the isocyanoacrylate **78** and a thiocarboxylic acid in the Ugi four-component reaction, where the intermediate linear thioamide cyclises onto the β-aminoacrylate (Scheme 55). A range of 1,4,5-trisubstituted imidazoles **79** were

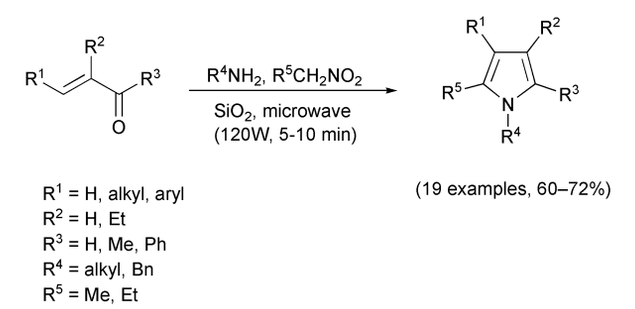


Scheme 55

prepared from the reaction of aryl tosylisonitriles, related to van Leusen's TosMIC reagent, with the imines formed *in situ* from aldehydes and primary amines.[237] By using glyoxylic acid as the carbonyl component, 1,4-disubstituted imidazoles were produced (7 examples, 53–87%), while replacing the amine component with ammonium acetate led to 4,5-disubstituted imidazoles (7 examples, 23–81%) and omitting the amine altogether gave 4,5-disubstituted oxazoles (5 examples, 62–79%).

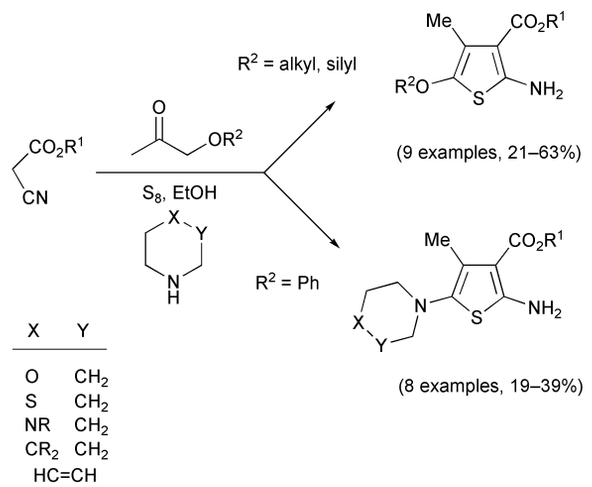


A three-component coupling of α,β-unsaturated aldehydes, primary amines and nitroalkanes to give polysubstituted pyrroles was achieved using microwave irradiation when the reagents were absorbed onto silica gel[238,239] (Scheme 56). The reaction of aldehydes or cyclic ketones with primary amines



Scheme 56

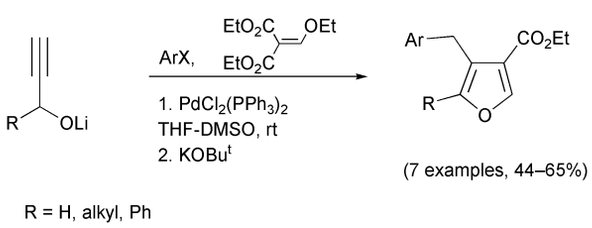
and Δ^1-nitroalkenes absorbed on alumina similarly led to tetra- and pentasubstituted pyrroles[239] (27 examples, 71–86%). Polysubstituted imidazoles[240] were prepared by another solvent-free, microwave-enhanced reaction between aldehydes, 1,2-diketones and amines absorbed on acidic alumina impregnated with ammonium acetate (8 examples, 67–82% yields, 75–85% HPLC purities). During studies to extend the Gewald three-component thiophene synthesis to 5-alkoxythiophenes, a novel four-component condensation was uncovered when attempts were made to incorporate a 5-phenoxy substituent[241] (Scheme 57). With 6-membered cyclic secondary amine bases



Scheme 57

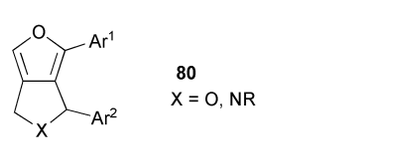
only, the 5-aminothiophenes were isolated instead of the expected 5-phenoxy substituted products.

A number of recent reports have shown how palladium-catalysed processes can be employed in multi-component reactions to give aromatic heterocycles (*cf.* Section 3.1). For example, simple 5-aryl-1,2,4-oxadiazoles were prepared by coupling of amide oximes and aryliodonium salts in a carbon monoxide atmosphere[242] (8 examples, 52–79%). Balme and co-workers developed a three component reaction of lithium propargyl alkoxides, aryl halides and diethyl ethoxymethylene malonate with palladium catalysis to give intermediate 2-ethoxy-4-benzylidenetetrahydrofurans through Michael addition of the alkoxide to the ethoxymethylene malonate and subsequent palladium-catalysed coupling–cyclisation of the enolate, alkyne and aryl halide.[243] The intermediates underwent decarboxylation on treatment with potassium *tert*-butoxide *in situ* to yield trisubstituted furans (Scheme 58). Furo[3,4-*c*]-

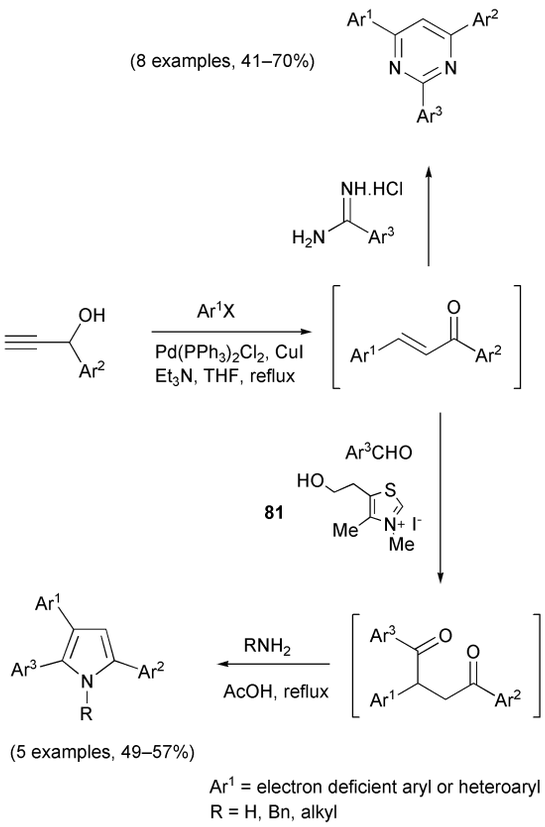


Scheme 58

heterocycles **80** were produced by a related union of propargyl alkoxides or amines with arylidene β-ketosulfones through Michael addition, followed by palladium-catalysed double intramolecular cyclisation.[244]



Müller and co-workers used the palladium-catalysed Sonogashira coupling–isomerisation of propargyl alcohols and electron-deficient aryl halides to prepare chalcones that could be condensed with amidine salts in a three component, one-pot sequence to provide 2,4,6-triarylpyrimidines[245] (Scheme 59).



Scheme 59

The isomerisation step required an electron-deficient arene bonded to the alkyne, but no limitations were observed on the nature of the other two aryl substituents. The intermediate chalcones could be employed in a four component, one-pot process, through Stetter reaction with aryl aldehydes mediated by the thiazolium salt **81**, followed by Paal–Knorr condensation with amines to generate polysubstituted pyrroles.[246]

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