Halogenation of pyrazoloquinolines and pyrazoloisoquinolines. Theoretical analysis of the regioreactivity and cross-coupling of 3-halogen derivatives †

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Selective C* ‡ halogenation (I and Br) of pyrazoles **1a**, **3a** and **4a** gave halopyrazoles **5**, **7**–**9**, **11**, **12**. Reactivity differences between **1a**, **3a** and **4a**, and the failure of **2a** to give the expected halopyrazoles **6**, **10** were explained using calculated relative energies of bromination, and inspection of frontier molecular orbitals. Utility of the prepared halides was demonstrated by a series of palladium-catalysed cross-coupling reactions.

Introduction

Haloheteroaromatics are valuable synthetic intermediates in the course of drug discovery, not least because of the ease of functionalisation. Recently, we developed annelation protocols to access the family of tricyclic *N*-hydroxypyrazoles **1b**–**4b** from C-4 and C-5 aryl substituted 1-benzyloxypyrazoles (Fig. 1).[1] Activities as benzodiazepine antagonists,[2] acetylcholinesterase inhibitors,[3] interleukin-1 antagonists,[4] and anti-inflammatory agents[4–7] have been reported for derivatives of the parent ring systems of **1b**–**4b**. Direct functionalisation of C* is previously unexplored. The only reported C* derivatives have been obtained by late assembly of the pyrazole ring, using precursors with the C* substituent already in place.§ A general means of derivatising the C* position would allow structure–activity relationship (SAR) studies of previously inaccessible analogues of **1**–**4**. C* derivatives of **3b** are particularly attractive due to their close resemblance to the potent peptide coupling reagent 1-hydroxy-7-azabenzotriazole (HOAt).[8]

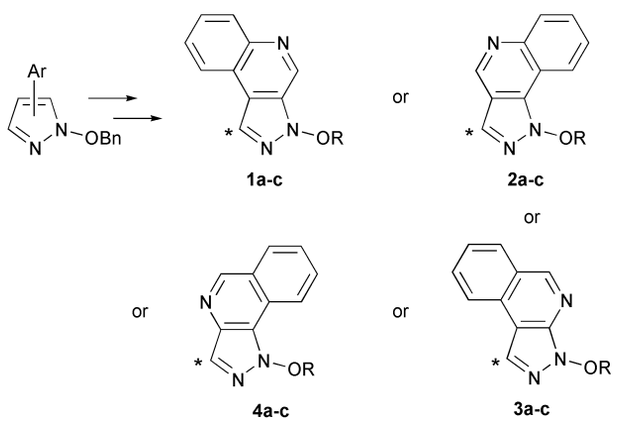

Fig. 1 Hydroxypyrazolo(iso)quinolines **1b**–**4b** prepared from C-4 and C-5 aryl substituted 1-benzyloxypyrazoles *via* the corresponding Bn protected **1a**–**4a**. See ref. 1 for the synthetic details. *N*-Methoxy analogues **1c**–**4c** were used in the theoretical study. See text and supporting information for further details.

Results and discussion

Halogenation of pyrazoloquinolines and pyrazoloisoquinolines 1a–4a

Our goal was to regioselectively halogenate the Bn protected **1a**–**4a** at C*, and examine the utility of the resulting halopyrazoles in a series of test reactions. However, attempted iodination of **1a** with ICl at rt led to no conversion (Table 1, entry 1), similar to the findings regarding the unreactive C-3 of 1-benzyloxypyrazole.[9,10] Trying the recently reported "superactive" reagent "I^+" ($ICl–Ag_2SO_4$ in H_2SO_4)[11] resulted in non-selective overiodination§¶ together with substantial BnO cleavage. The deprotected *N*-hydroxypyrazole **1b** exhibited much greater reactivity towards ICl, as shown by the quantitative iodination of **1b** at C-1 after 3 h, though the OH group was lost. By contrast with **1a**, when **4a** was treated with ICl (Table 1, entry 8) under identical conditions, a new thermodynamically unstable compound arose.‖ This could be due to a single-electron transfer induced by light and Cl_2 in ICl. Therefore, the iodination was re-attempted with the exclusion of light, only to give recovery of starting material after 16 h at rt. However, on raising the temperature to reflux, **4a** was consumed after *ca.* 24 h, and **8** was isolated as the sole product (Table 1, entry 9). These conditions were then used to attempt iodination of **1a**–**3a**. The summary in Table 1 reveals striking trends in the regioreactivity of **1a**–**4a** towards ICl. Compound **1a** required 93 h for conversion to **5** (entry 2) whereas **3a** was converted to **7** in only 6 h (entry 6). Finally, **2a** did not give **6** at all (entry 4). Instead, a complex mixture of iodinated products resulted, including iodination of the Bn ring. This contrasts with the clean mono-iodinations of **1a**, **3a** and **4a**.** Thus the susceptibility of **1a**–**4a** to C* iodination is as follows: **3a** > **4a** ⩾ **1a**, with failure for **2a**.

† Spectral and theoretical data are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b006435l/

‡ C* indicates C-3 for pyrazoles **2** and **4** and C-1 for pyrazoles **1** and **3**.

§ See ref. 1 for typical syntheses of these ring systems.

¶ At least 3 I were incorporated into the substrate according to LC/MS.

‖ Converted back to **4a** upon standing in $CDCl_3$ solution.

** No further iodination of **5**, **7** or **8** occurred even when ICl treatment was prolonged.

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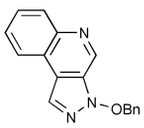
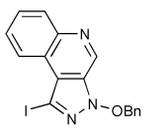
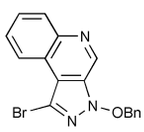
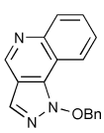
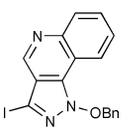
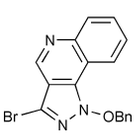
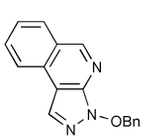
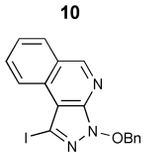
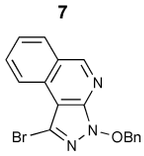
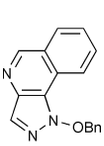
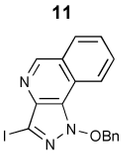
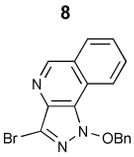
Table 1 Iodination and bromination of pyrazoles **1a**–**4a**

Entry	Substrate	Product	Reaction conditions[a]	Reaction time/h	Yield (%)
1	 **1a**	 **5**	A	168	0[b]
2			C	93	72
3		 **9**	B	6	84
4	 **2a**	 **6**	C	16	0[c]
5		 **10**	B	0.5	0[c]
6	 **3a**	 **7**	C	6	91
7		 **11**	B	1	96
8	 **4a**	 **8**	A	16	0[d]
9			C	24	78
10		 **12**	B	1	85

[a] Iodinations and brominations were conducted using ICI or Br_2 in $CHCl_3$. Reaction conditions (A) room temperature; (B) room temperature, exclusion of light; (C) 62 °C, exclusion of light. [b] No conversion. [c] Complex mixture. [d] See text.

As bromoheteroaromatic compounds are also desirable, **1a**–**4a** were treated with bromine at rt. Compounds **3a** and **4a** were brominated at roughly the same rate (Table 1, entries 7 and 10) whereas **1a** reacted more sluggishly (entry 3) and bromination of **2a** resulted in a complex mixture of products (entry 5), all in keeping with the iodination results. The reactivity towards Br_2 at C* of **1a**–**4a** is then **3a** ≈ **4a** ⩾ **1a**, with failure for **2a**.

Preferred attack at the pyrazole nucleus can first be understood by comparison of the classical valence bond structures of the σ-intermediates. For reasons which will become apparent, we introduce model 1-methoxy analogues of **1a**–**4a**, denoted **1c**–**4c** (Fig. 1). The σ-intermediates are denoted $\mathbf{1c}_n$ to $\mathbf{4c}_n$ where ***n*** indicates the position of Br^+ addition. Some examples are given in Fig. 2. Only the most "stable" classical resonance form, that in which all atoms possess an octet structure, is drawn here in each case. By comparing $\mathbf{1c}_1$, $\mathbf{1c}_4$–$\mathbf{1c}_9$ we can easily see that only $\mathbf{1c}_1$ possesses two aromatic rings, while $\mathbf{1c}_4$–$\mathbf{1c}_9$ are essentially non-aromatic. The same is apparent for $\mathbf{2c}_3$, $\mathbf{3c}_1$ and $\mathbf{4c}_3$, which can likewise be drawn with preserved aromaticity whereas $\mathbf{2c}_4$–$\mathbf{2c}_9$, $\mathbf{3c}_5$–$\mathbf{3c}_9$, and $\mathbf{4c}_5$–$\mathbf{4c}_9$ respectively cannot. Classically then, we would expect electrophilic attack at C*, but this does not explain the observed reactivity differences, and in particular the failure to obtain **6**.

However, such clear reactivity differences should be amenable to investigation by *ab initio* molecular orbital theory, including frontier orbital analysis. Two parallel approaches were pursued: quantitative comparison of the relative energies of regional bromination, and qualitative inspection of the HOMOs of the substrates. Frontier orbital analysis provides an indication of the transition state, which relates to reaction

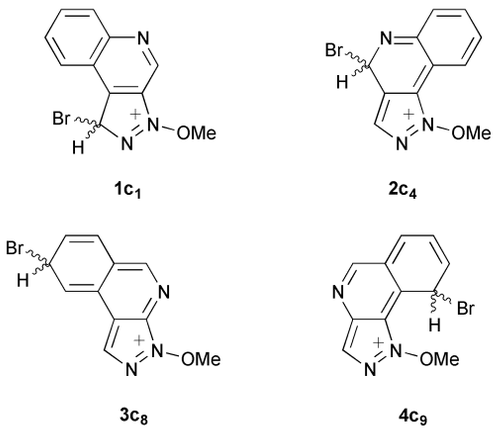


Fig. 2 Some examples of cationic bromine adducts of **1c**–**4c**.

barrier height and kinetics, while the thermodynamic approach measures the relative energy of a short-lived high energy minimum on the reaction path. By the Hammond postulate, the transition state and the high energy intermediate of the rate limiting step most likely resemble each other, and either may be used as an indication of the course of the reaction by a perturbative approach. Comparisons can be made between structures, and also within a single substrate where there are competing reaction sites. The reason for modelling *N*-methoxy substrates (**1c**–**4c**, Fig. 1) was to substantially reduce computational expense, the extra phenyl ring not playing a significant role in the reaction. It being of interest to compare the relative ease of bromination at C* with other competing positions, the cationic complexes formed from all five available aromatic positions on each substrate were considered, $\mathbf{1c}_n$ to $\mathbf{4c}_n$. Geometry optimisation (Gaussian 98[12]) was performed using the HF/6-31G(d) method.††[13] All minima were validated by frequency calculations, and inclusion of thermodynamic terms found to have negligible effect (see supporting information for full energies and geometries). The results are shown in Fig. 3 (Spartan 5.1[14]). The comparisons are presented in Table 2, and for ease of interpretation, the energies (kcal mol^{-1}) are corrected relative to the bromination of **4c** at C-3 to give $\mathbf{4c}_3$ (Scheme 1). In Fig. 3, the HOMO is depicted as a map of the orbital co-efficient onto the van der Waals surface of the substrate—a red to blue spectrum indicating low to high HOMO density. Relative energies of bromination at each site are also indicated. Compare in particular the densities proximal to the C* position (bottom left), and the associated energies. The least electron density over C* is observed for **2c**, which has a bromination energy 9 kcal higher than that of **4c**. The qualitative orbital picture and the relative thermodynamics are concordant, and in excellent agreement with experiment, that the reactivity order is **4c** ≈ **3c** ≫ **1c**, and that side-reactions (*e.g.* $\mathbf{2c}_6$, $\mathbf{2c}_8$) are favoured over C* bromination of **2c**. The observed reactivities are thus rationalised in terms of electronic structure.

Cross-coupling reactions

The synthetic utility of the prepared halopyrazoles was examined in halogen–metal exchange and cross-coupling reactions. Halogen–metal exchange seemed like an attractive route to substituents at C*.‡‡ However, I–Mg exchange with **7** using *i*-PrMgBr at 0 °C resulted in migration of the BnO group to C*.§§ Oxidative zinc insertion[15] also failed. Next investigated were cross-coupling reactions—a powerful tool for functionalisation of heteroaromatics.[16] Pd(0)-catalysed cross-coupling of 4-tolylboronic acid to **9**, **11** and **12** (Table 3, entries 1, 4 and 6) revealed that the Suzuki reaction[17,18] is successful. Extending the cross-coupling to boronic acids having bulky (entry 2), electron-withdrawing (entry 3) and heteroaromatic groups (entry 5) was straightforward, demonstrating the generality of the method. In addition, examples of Negishi[19] (entry 7) and Sonogashira[20] and their co-workers (entry 8) couplings show the versatility of the accessed halopyrazoles.

Table 2 Gas phase (*ab initio*) energies of model species

	E_0 (HF/6-31G(d))/ hartree	$\Delta\Delta E_0$ [a]/kcal mol^{-1}
1c	−659.73638	
$\mathbf{1c}_1$	−3229.36761	2.49
$\mathbf{1c}_4$	−3229.34804	14.78
$\mathbf{1c}_6$	−3229.35654	9.44
$\mathbf{1c}_7$	−3229.36284	5.49
$\mathbf{1c}_8$	−3229.35493	10.45
$\mathbf{1c}_9$	−3229.36285	5.48
2c	−659.74057	
$\mathbf{2c}_3$	−3229.36186	8.73
$\mathbf{2c}_4$	−3229.33478	25.73
$\mathbf{2c}_6$	−3229.36775	5.04
$\mathbf{2c}_7$	−3229.35134	15.33
$\mathbf{2c}_8$	−3229.36715	5.41
$\mathbf{2c}_9$	−3229.35691	11.84
3c	−659.74109	
$\mathbf{3c}_1$	−3229.37580	0.31
$\mathbf{3c}_5$	−3229.34121	22.02
$\mathbf{3c}_6$	−3229.34252	21.19
$\mathbf{3c}_7$	−3229.36913	4.50
$\mathbf{3c}_8$	−3229.33404	26.52
$\mathbf{3c}_9$	−3229.36797	5.23
4c	−659.73625	
$\mathbf{4c}_3$	−3229.37146	0.00
$\mathbf{4c}_5$	−3229.36149	6.25
$\mathbf{4c}_6$	−3229.34500	16.60
$\mathbf{4c}_7$	−3229.35020	13.34
$\mathbf{4c}_8$	−3229.34087	19.20
$\mathbf{4c}_9$	−3229.35252	11.88

[a] $E_0 = E$ + ZPE. $\Delta E_0 = E_0 - E_0$(**1c**–**4c**). $\Delta\Delta E_0 = \Delta E_0 - \Delta E_0(\mathbf{4c}_3)$.

Conclusion

C* iodination and bromination of **1a**, **3a** and **4a** was achieved by the exclusion of light. The observed differences in regioreactivity, including the refractory **2a**, were rationalised using energies from *ab initio* calculations and examination of the HOMOs. Utility of the prepared halopyrazoles was demonstrated by a series of Pd-catalysed cross-coupling reactions.

Experimental

General

The 1- and 3-(benzyloxy)pyrazoloquinolines/isoquinolines **1a**–**4a** were prepared by the known procedures.[1] 1-Benzyloxypyrazole was prepared as previously reported.[9] $Pd(PPh_3)_4$ was prepared as previously described.[21] The boronic acids were purchased from Strem Chemicals, Inc. All other solvents and reagents were commercially available and used without further purification, except THF which was distilled from

†† The popular Hartree–Fock theory with a 6-31G(d) basis set is currently a sensible first choice for this kind of problem, having a favourable trade-off between accuracy and cost, while semi-empirical methods are known to be inadequate, DFT methods are less sound for frontier orbital analysis, and correlated methods significantly more expensive.[13]

‡‡ This technique has been employed previously to prepare a range of C-4 substituted 1-benzyloxypyrazoles. See ref. 10.

§§ When less than 1 eq. of *i*-PrMgBr was used, **7** was isolated together with the migrated product. A C* non-migrated product could not even be intercepted by addition of an electrophile (MeOD).

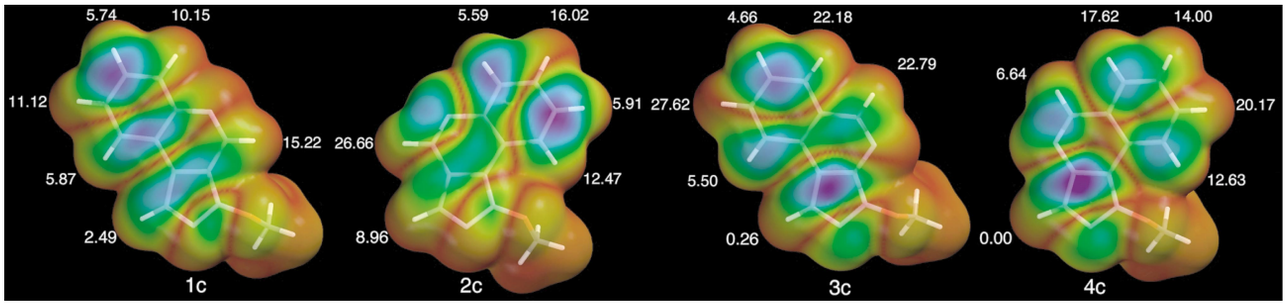
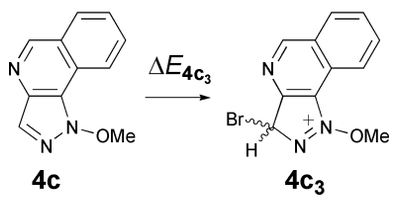


Fig. 3 Structures **1c**–**4c**, optimized at HF/6-31G(d),[12] with the van der Waals surfaces (isodensity 0.002 electron au^{-3}) having the absolute density coefficient of the HOMOs mapped as spectra from red (0.00) to blue (0.02). Printed in white are the relative gas phase energies (kcal mol^{-1}, ZPE uncorrected) pertaining to the adducts formed by the respective bromination of each aromatic methine, *i.e.* **1c**$_n$–**4c**$_n$, relative to C-3 bromination of **4c**.



Scheme 1

Na–benzophenone under nitrogen and DMF which was sequentially dried with and stored over 3 Å molecular sieves. A 1.0 M solution of $ZnCl_2$ was prepared by flame drying anhydrous $ZnCl_2$ *in vacuo* and dissolving it in dry THF. Melting points are uncorrected. Elemental analyses were performed by Microanalytical Laboratory, Department of Physical Chemistry, University of Vienna, Austria. NMR spectra were recorded on 300 MHz Bruker and Varian spectrometers with tetramethylsilane as internal standard.

Iodination

3-Benzyloxy-1-iodo-3*H*-pyrazolo[3,4-*c*]quinoline (5). Compound **1a** (20 mg, 0.07 mmol), ICl (34 mg, 0.21 mmol) and K_2CO_3 (50 mg, 0.35 mmol) in $CHCl_3$ (10 mL) were refluxed with exclusion of light. After 93 h, the reaction was cooled to rt, quenched with 1 M $Na_2S_2O_3$ (30 mL), extracted with CH_2Cl_2 (3 × 25 mL), dried over $MgSO_4$ and evaporated to dryness. Flash chromatography (heptane–EtOAc, 6 : 1) gave 21 mg (72%) of **5** as yellow crystals, mp 156–158 °C (EtOAc–heptane). R_f (EtOAc–heptane, 1 : 2) 0.34. δ_H ($CDCl_3$) 9.05 (dd, J = 8.1, 1.6 Hz, 1H), 8.61 (s, 1H), 8.15 (dd, J = 8.1, 1.4 Hz, 1H), 7.80–7.60 (m, 2H), 7.40–7.25 (m, 5H), 5.49 (s, 2H). δ_C ($CDCl_3$) 160.11, 133.12, 130.36, 130.13, 130.05, 129.80, 129.65, 129.02, 127.91, 127.57, 122.37, 121.06, 120.00, 81.75, 80.11. Found: C, 49.8; H, 3.15; N, 9.85. $C_{17}H_{12}IN_3O$·0.5 H_2O requires C, 49.8; H, 3.2; N, 10.25%.

3-Benzyloxy-1-iodo-3*H*-pyrazolo[3,4-*c*]isoquinoline (7). Similarly, **3a** after 24 h reaction time and flash chromatography using heptane–EtOAc (4 : 1) gave 91% of **7** as yellow crystals, mp 109–111 °C (EtOAc–heptane). R_f (EtOAc–heptane, 1 : 2) 0.42. δ_H ($CDCl_3$) 9.02 (d, J = 8.3 Hz, 1H), 9.00 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.90 (dt, J = 7.7, 1.2 Hz, 1H), 7.61 (dt, J = 7.6, 1.0 Hz, 1H), 7.55–7.30 (m, 5H), 5.53 (s, 2H). δ_C ($CDCl_3$) 154.83, 141.61, 133.40, 131.89, 129.99, 129.86, 129.49, 129.25, 128.53, 126.02, 125.88, 125.51, 119.56, 109.79, 81.55. Found: C, 49.95; H, 3.05; N, 10.0. $C_{17}H_{12}IN_3O$·0.5 H_2O requires C, 49.8; H, 3.2; N, 10.25%.

1-Benzyloxy-3-iodo-1*H*-pyrazolo[4,3-*c*]isoquinoline (8). Similarly, **4a** gave 78% of **8** as off-white crystals, mp 182–183 °C (EtOAc–heptane). R_f (EtOAc–heptane, 1 : 2) 0.32. δ_H ($CDCl_3$) 8.82 (dd, J = 7.2, 2.0 Hz, 1H), 8.59 (s, 1H), 8.13 (dd, J = 7.3, 2.0 Hz, 1H), 7.85–7.68 (m, 2H), 7.50–7.30 (m, 5H), 5.53 (s, 2H). Found: C, 50.8; H, 3.0; N, 10.25. $C_{17}H_{12}IN_3O$ requires C, 50.9; H, 3.0; N, 10.45%.

Bromination

3-Benzyloxy-1-bromo-3*H*-pyrazolo[3,4-*c*]quinoline (9). To a solution of **1a** (130 mg, 0.47 mmol) and K_2CO_3 (240 mg, 1.50 mmol) in CH_2Cl_2 (20 mL) at rt, was added Br_2 (240 mg, 1.50 mmol), with exclusion of light. After 6 h at rt, the reaction was quenched with 1 M $Na_2S_2O_3$ (30 mL) and worked up as described for **5**. Flash chromatography (heptane–EtOAc, 4 : 1) gave 140 mg (84%) of **9** as white crystals, mp 124–125 °C (EtOAc–heptane). R_f (EtOAc–heptane, 1 : 2) 0.44. δ_H ($CDCl_3$) 8.82 (dd, J = 7.2, 2.0 Hz, 1H), 8.59 (s, 1H), 8.13 (dd, J = 7.3, 2.0 Hz, 1H), 7.81–7.65 (m, 2H), 7.40–7.22 (m, 5H), 5.49 (s, 2H). δ_C ($CDCl_3$) 142.89, 135.41, 133.08, 130.31, 130.30, 130.08, 130.02, 128.98, 128.25, 127.49, 121.50, 120.76, 118.10, 113.27, 81.64. Found: C, 57.4; H, 3.35; N, 11.65. $C_{17}H_{12}BrN_3O$ requires C, 57.65; H, 3.4; N, 11.85%.

3-Benzyloxy-1-bromo-3*H*-pyrazolo[3,4-*c*]isoquinoline (11). Using the same procedure, **3a** after 1 h reaction time and flash chromatography (heptane–EtOAc, 4 : 1) gave 96% of **11** as yellow crystals, mp 123–124 °C (EtOAc–heptane). R_f (EtOAc–heptane, 1 : 2) 0.46. δ_H ($CDCl_3$) 9.00 (s, 1H), 8.81 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.88 (dt, J = 7.1, 1.3 Hz, 1H), 7.63 (dt, J = 7.6, 1.1 Hz, 1H), 7.55–7.30 (m, 5H), 5.50 (s, 2H). δ_C ($CDCl_3$) 160.80, 155.31, 142.25, 133.43, 132.37, 129.93, 129.51, 129.35, 128.61, 126.13, 125.60, 121.24, 112.15, 106.55, 81.43. Found: C, 57.45; H, 3.4; N, 11.7. $C_{17}H_{12}BrN_3O$ requires C, 57.65; H, 3.4; N, 11.85%.

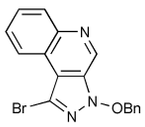
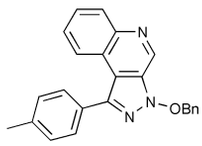
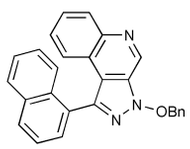
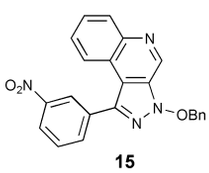
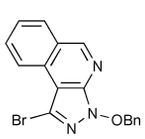
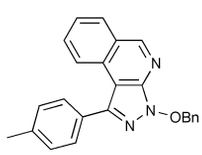
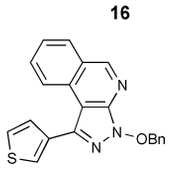
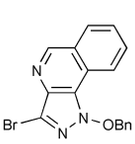
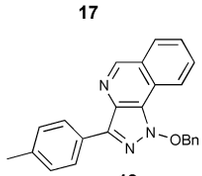
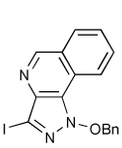
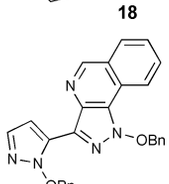
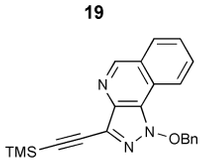
1-Benzyloxy-3-bromo-1*H*-pyrazolo[4,3-*c*]isoquinoline (12). Similarly, **4a** gave 85% of **12** as pale yellow crystals, mp 166–168 °C (EtOAc–heptane). R_f (EtOAc–heptane, 1 : 2) 0.36. δ_H ($CDCl_3$) 9.01 (s, 1H), 8.42 (dd, J = 8.0, 0.8 Hz, 1H), 8.10 (dd, J = 8.0, 1.4 Hz, 1H), 7.85–7.70 (m, 2H), 7.51–7.30 (m, 5H), 5.53 (s, 2H). δ_C ($CDCl_3$) 150.84, 132.81, 131.30, 131.17, 130.04, 129.64, 128.96, 128.81, 128.32, 127.72, 124.83, 121.98, 121.93, 81.17, one carbon signal consists of overlapping peaks. Found: C, 57.45; H, 3.25; N, 11.65. $C_{17}H_{12}BrN_3O$ requires C, 57.65; H, 3.4; N, 11.85%.

General procedure for Suzuki couplings

A solution of halopyrazole **9**, **11**, **12**, (0.1 mmol), boronic acid (0.1 mmol) and K_2CO_3 (2.0 M, 0.2 mL) in toluene (2 mL) and EtOH (0.2 mL) was degassed by bubbling N_2 through the solution for 30 min, before adding $Pd(PPh_3)_4$ (4 mol%). After three cycles of evacuation and re-filling with N_2, the mixture was heated to 80 °C, until full conversion was observed by TLC. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). Drying ($MgSO_4$) and evaporation *in vacuo* gave the crude product, which was purified by preparative TLC (silica gel) or flash chromatography.

3-Benzyloxy-1-(4-methylphenyl)-3*H*-pyrazolo[3,4-*c*]quinoline (13). Following the general procedure using **9**, *p*-tolylboronic acid and a reaction time of 6 h and preparative TLC (heptane–EtOAc 1 : 1) gave 85% of **13** as off-white crystals, mp 109–

Table 3 Pd-catalysed cross-coupling reactions of halopyrazoles **8**, **9**, **11** and **12**

Entry	Substrate	Product	Reaction conditions[a]	Yield[b] (%)
1	 **9**	 **13**	A	85
2		 **14**	A	87
3		 **15**	A	63
4	 **11**	 **16**	A	86
5		 **17**	A	77
6	 **12**	 **18**	A	94
7	 **8**	 **19**	B	63
8		 **20**	C	77

[a] Reaction types: (A) Suzuki–Miyaura; (B) Negishi; (C) Sonogashira. Details in Experimental section. [b] Isolated yields of chromatographically pure products.

111 °C (heptane–EtOAc), R_f (heptane–EtOAc, 2 : 1) 0.30. δ_H($CDCl_3$) 8.71 (s, 1H), 8.22 (dd, J = 8.1, 1.1 Hz, 1H), 8.12 (dd, J = 7.6, 0.8 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.58 (dt, J = 7.0, 1.4 Hz, 1H), 7.47 (dt, J = 7.5, 1.2 Hz, 1H), 7.42–7.25 (m, 5H), 5.53 (s, 2H), 2.50 (s, 3H). δ_C ($CDCl_3$) 143.08, 140.70, 138.83, 135.99, 133.55, 130.38, 130.05, 129.83, 129.80, 129.48, 129.44, 128.89, 127.61, 127.14, 126.80, 122.71, 122.04, 116.70, 81.18, 21.46. Found: C, 78.45; H, 5.6; N, 11.0. $C_{24}H_{19}N_3O$ requires C, 78.9; H, 5.25; N, 11.5%.

3-Benzyloxy-1-naphthalen-1′-yl-3*H*-pyrazolo[3,4-*c*]quinoline (14). Similarly **9** and α-naphthylboronic acid using a reaction time of 6 h and flash chromatography (heptane–EtOAc 6 : 1 ⟶ 3 : 1) gave 87% of **14** as yellow crystals, mp 135–136 °C (heptane–EtOAc), R_f (heptane–EtOAc, 2 : 1) 0.34. δ_H ($CDCl_3$) 8.83 (s, 1H), 8.13–7.15 (m, 16H), 5.59 (s, 2H), 2.50 (s, 3H). δ_C ($CDCl_3$) 143.04, 138.49, 135.97, 133.79, 133.47, 132.28, 130.53, 130.13, 129.88, 129.66, 129.46, 128.90, 128.81, 128.52, 127.72, 126.86, 126.77, 126.29, 125.91, 125.63, 125.48, 123.00, 121.65, 118.47, 81.12. Found: C, 80.2; H, 4.95; N, 10.1. $C_{27}H_{19}N_3O$·0.2 H_2O requires C, 80.05; H, 4.85; N, 10.35%.

3-Benzyloxy-1-(3-nitrophenyl)-3*H*-pyrazolo[3,4-*c*]quinoline (15). Following the general procedure using **9**, 3-nitrophenyl-

boronic acid, 3 h reaction time and preparative TLC (heptane–EtOAc 1 : 1), 63% of **15** was obtained as yellow crystals, mp 153–154 °C (heptane–EtOAc), R_f (heptane–EtOAc, 2 : 1) 0.64. δ_H ($CDCl_3$) 8.73 (s, 1H), 8.71 (t, J = 1.8 Hz, 1H), 8.40 (ddd, J = 8.3, 2.3, 1.1 Hz, 1H), 8.20–8.16 (m, 2H), 8.09–8.05 (m, 1H), 7.77 (t, J = 8.2 Hz, 1H), 7.63 (dt, J = 8.3, 1.5 Hz, 1H), 7.52 (dt, J = 8.3, 1.4 Hz, 1H), 7.42–7.30 (m, 5H), 5.55 (s, 2H). δ_C ($CDCl_3$) 148.60, 143.29, 137.93, 136.04, 135.48, 135.28, 133.25, 130.81, 130.13, 130.08, 130.00, 129.89, 129.05, 128.15, 127.45, 124.55, 123.70, 122.14, 121.35, 116.78, 81.50.¶¶

3-Benzyloxy-1-(4-methylphenyl)-3*H*-pyrazolo[3,4-*c*]isoquinoline (16). Similarly, **11** and *p*-tolylboronic acid after 6 h reaction time and preparative TLC (heptane–EtOAc 1 : 1) afforded 86% of **16** as yellow crystals, mp 147–148 °C (heptane–EtOAc), R_f (heptane–EtOAc, 2 : 1) 0.33. δ_H ($CDCl_3$) 9.04 (s, 1H), 8.24 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.73–7.30 (m, 11H), 5.58 (s, 2H), 2.48 (s, 3H). δ_C ($CDCl_3$) 154.37, 142.20, 139.21, 138.60, 133.94, 131.71, 131.20, 130.96, 129.92, 129.62, 129.47, 129.34, 129.14, 128.53, 125.68, 125.40, 122.43, 104.88, 80.96, 21.31.¶¶

3-Benzyloxy-1-(3-thienyl)-3*H*-pyrazolo[3,4-*c*]isoquinoline (17). In the same way, **11** and 3-thienylboronic acid after 2 h reaction time and preparative TLC (heptane–EtOAc 6 : 1) gave 77% of **17** as off-white crystals, mp 117–119 °C (heptane–EtOAc), R_f (heptane–EtOAc, 2 : 1) 0.28. δ_H ($CDCl_3$) 9.05 (s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.73–7.30 (m, 10H), 5.58 (s, 2H). δ_C ($CDCl_3$) 154.48, 142.06, 134.60, 134.46, 133.86, 131.91, 130.85, 129.91, 129.67, 129.18, 128.60, 128.55, 126.25, 125.72, 125.50, 125.00, 122.39, 105.27, 81.05.¶¶

1-Benzyloxy-3-(4-methylphenyl)-1*H*-pyrazolo[4,3-*c*]isoquinoline (18). Similarly, **12** and *p*-tolylboronic acid (15.4 mg, 0.11 mmol) using a reaction time of 6 h and preparative TLC (heptane–EtOAc 1 : 1) afforded 94% of **18** as off-white crystals, mp 211–212 °C (heptane–EtOAc), R_f (heptane–EtOAc, 2 : 1) 0.43. δ_H ($CDCl_3$) 9.03 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.42 (d, J = 8.2 Hz, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.79 (dt, J = 8.1, 1.4 Hz, 1H), 7.68 (dt, J = 7.5, 1.3 Hz, 1H), 7.52–7.30 (m, 7H), 5.57 (s, 2H), 2.45 (s, 3H). δ_C ($CDCl_3$) 143.08, 140.70, 138.83, 135.99, 133.55, 130.38, 130.05, 129.83, 129.80, 129.48, 129.44, 128.89, 127.61, 127.14, 126.80, 122.71, 122.04, 116.70, 81.18, 21.46. Found: C, 78.85; H, 5.3; N, 11.5. $C_{24}H_{19}N_3O$ requires C, 78.9; H, 5.25; N, 11.5%.

1-Benzyloxy-3-(1-benzyloxypyrazol-5-yl)-1*H*-pyrazolo[4,3-*c*]-isoquinoline (19). To a solution of 1-benzyloxypyrazole (25 mg, 0.14 mmol) in THF (2 mL) at –78 °C under N_2, was added a solution of *n*-BuLi in hexanes (0.085 mL, 2.0 M), and after 5 min at –78 °C a solution of $ZnCl_2$ in THF (0.22 mL, 1.0 M) was added. The solution was allowed to warm to rt, stirred at rt for an additional 30 min, before **8** (88 mg, 0.22 mmol) and $Pd(PPh_3)_4$ (3 mg, 0.0029 mmol) in DMF (4 mL) was added, the reaction was heated to 80 °C for 1 h, cooled to rt and quenched with sat. aq. NH_4Cl (10 mL). Addition of H_2O (10 mL), extraction with Et_2O (3 × 15 mL), drying ($MgSO_4$), evaporation *in vacuo*, and preparative TLC (eluent ethyl acetate–heptane, 2 : 1) afforded 42 mg (63%) of **19** as yellow crystals, mp 174–175 °C (heptane–EtOAc). R_f (heptane–EtOAc, 2 : 1) 0.34. δ_H ($CDCl_3$) 9.04 (s, 1H), 8.51 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.82 (dt, J = 7.5, 1.1 Hz, 1H), 7.72 (dt, J = 7.5, 1.1 Hz, 1H), 7.61–7.55 (m, 2H), 7.46 (d, J = 2.3 Hz, 1H), 7.50–7.40 (m, 2H), 7.36–7.20 (m, 8H), 7.18 (d, J = 2.3 Hz, 1H), 5.55 (s, 2H), 5.54 (s, 2H). δ_C ($CDCl_3$) 150.49, 134.13, 133.36, 133.09, 131.14, 129.91, 129.81, 129.55, 128.85, 128.81, 128.34, 127.91, 127.32, 126.97, 121.96, 121.85, 105.68, 80.86, 80.69, four carbon signals consisted of overlapping peaks.¶¶

1-Benzyloxy-3-(2-trimethylsilylethynyl)-1*H*-pyrazolo[4,3-*c*]-isoquinoline (20). Compound **8** (10.0 mg, 0.025 mmol) and ethynyl(trimethyl)silane (3.5 mg, 0.035 mmol) were dissolved in 3 mL of dry Et_3N under N_2. After three cycles of evacuation and re-filling with N_2, copper iodide (0.4 mg, 0.002 mmol) and $Pd(PPh_3)_2Cl_2$ (0.7 mg, 0.001 mmol) were added. The reaction was stirred at 55 °C for 3 h, before cooling to rt and aqueous work up as described for the Suzuki couplings followed by preparative TLC (heptane–EtOAc 1 : 1) gave 7.2 mg (77%) of **20** as yellow crystals, mp 134–137 °C (heptane–EtOAc). R_f (heptane–EtOAc, 2 : 1) 0.44. δ_H ($CDCl_3$) 9.05 (s, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.85–7.27 (m, 7H), 5.55 (s, 2H), 0.39 (s, 9H).¶¶

¶¶ The compound was unstable and a correct microanalysis could not be obtained. When dissolved in $CDCl_3$ NMR signals from benzaldehyde emerged upon standing. A clean ^{1}H-NMR spectrum of the freshly prepared compounds is included in the supplementary material.

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