JOURNAL OF combinatorial CHEMISTRY

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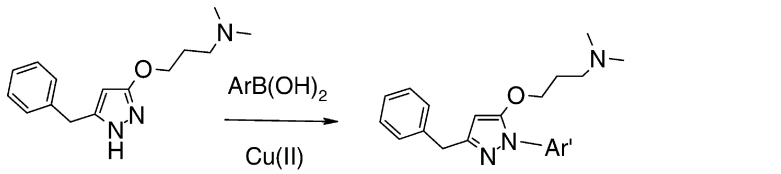
J. Comb. Chem., **2004**, 6 (3), 385-390• DOI: 10.1021/cc034065k • Publication Date (Web): 05 February 2004



Regioselective, mild conditions.

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Copper (II)-Mediated Arylation with Aryl Boronic Acids for the N-Derivatization of Pyrazole Libraries

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Received November 17, 2003

A N-derivatized 3-dimethylaminopropyloxypyrazole library was prepared using solution-phase parallel synthesis. The library was designed using physicochemical constraints designed to remove non-membrane-permeable molecules. Cupric acetate-mediated N-arylation with aryl boronic acids proceeded regioselectively to form the N-2-substituted derivatives. The presence of the 3-dimethylaminopropyloxy group was found to completely control the regioselectivity of the arylation. Presence of a dimethylaminoethyloxy or dimethylaminobutyloxy group gave a lesser degree of regioselectivity. The scope of the method as applied to library synthesis is discussed.

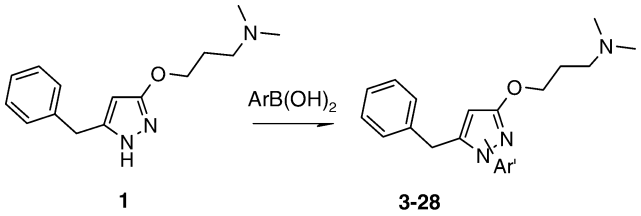
Introduction

The ability to prepare small focused libraries is central to the final optimization process for drug discovery. Ideally, reactions should be carried out in a parallel fashion with simple workups utilizing filtration rather than liquid−liquid extractions.[1] In connection with our studies directed toward the discovery of activators of the soluble guanylate cyclase (sGC) enzyme,[2,3] we needed to explore *N*-aryl substitution of a series of pyrazole derivatives.

To derivatize the pyrazole species at the nitrogen heteroatom with aryl groups a cupric acetate/arylboronic acid arylation was envisaged; this has been used successfully in arylations of other nitrogen-containing heterocycles, including imidazoles, triazoles, indazoles, and pyrazoles (Scheme 1).[4−6] In our previous study, 3-(3-dimethylaminopropyloxy)-5-benzyl-1*H*-pyrazole **1**, (Chart 1) was identified as a more active variant of our original lead benzydamine, **2**, and this was used as the intermediate for derivatization.

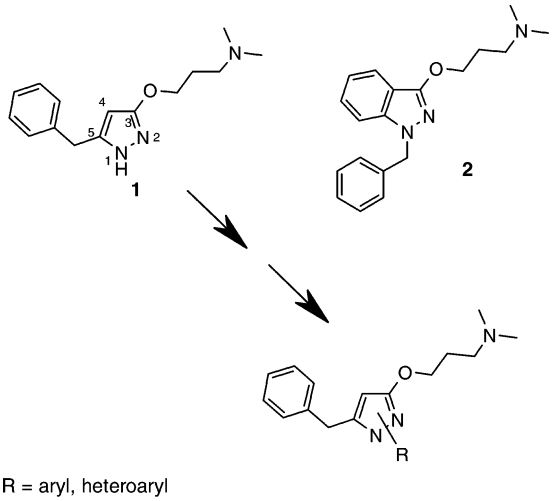
Library Design. Our previous investigations into the evaluation of indazole and pyrazole compounds as sGC activators indicated a general lipophilicity requirement for inhibition of platelet aggregation.[2,3] To select the compounds for synthesis, a virtual product library was generated; log *P* values were calculated[7] for the virtual library, eliminating potential products with clog *P* > 3.0 and > 5.0. Products with molecular weight >500 were eliminated, in line with Lipinski's rules for drug-like substances.[8] Reactive functional groups[9] were also eliminated. A Craig diagram of σ (electronic effect of substituent) versus π (hydrophobicity) was used. A total of 26 boronic acids were selected.

Scheme 1. Generation of *N*-Arylpyrazole Library[a]



[a] Reagents: $Cu(OAc)_2$, py, CH_2Cl_2, 4-Å molecular sieves; air; 2 days.

Chart 1. N-Derivatization of Target Pyrazole[a]



[a] Numbering convention used in the text is indicated.

Results

***N*-Arylation.** *N*-Arylation of **1** was effected by adopting an aryl/heteroaryl C−N bond cross coupling reaction via an

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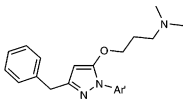
10.1021/cc034065k CCC: $27.50
Published on Web 02/05/2004

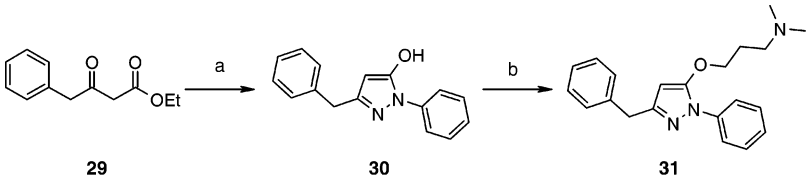
Table 1. Synthetic Scope of the $Cu(OAc)_2$ Arylation[a]



Compound	Ar'	Yield	Compound	Ar'	Yield	Compound	Ar'	Yield
3		27	**12**		3	**20**		0
4		15	**13**		3	**21**		0
5		47[b]	**14**		15	**22**		0
6		12	**15**		39	**23**		0
7		15	**16**		45	**24**		0
8		8	**17**		9	**25**		0
9		8	**18**		33	**26**		0
10		5	**19**		52	**27**		0
11		11				**28**		0

[a] A 1:5 mixture of N1/N2 products.

Scheme 2. Regioselective Synthesis of **31** (Equivalent to **3**)[a]

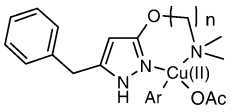


29 **30** **31**

[a] Reagents: (a) $PhNHNH_2$, EtOH; (b) 3-(dimethylamino)-1-propanol, ADDP, Bu_3P, toluene.

arylboronic acid/cupric acetate system (Scheme 1).[4,5] The starting material **1** was reacted with the corresponding aryl/heteroaryl boronic acid and cupric acetate in dichloromethane in the presence of pyridine and 4-Å molecular sieves. The reaction mixture was then stirred with a scavenger resin and filtered through a pad of Celite, and the product was isolated by flash chromatography to yield the products **3**−**28** (Table 1). NMR experiments (nOe, NOESY) were unsuccessful in establishing the regioisomeric identity of the products so a single analogue was synthesized by an alternative route (Scheme 2). Reaction of intermediate **29**[10] with phenylhydrazine in MeOH selectively affords the N-2 phenylated pyrazole **30** in 46% yield. Alkylation of the hydroxy group was effected using Mitsunobu conditions to afford the N-2 phenylated analogue **31** in 53% yield. Comparison of ^1H and ^{13}C NMR spectra of the species synthesized via the phenyl hydrazine route **31** and via phenylboronic acid cross-coupling **3** showed the two compounds to be identical. The chemical shifts for the C4−H of the products where only one isomer was obtained (**3**, **4**, **6**−**19**) are consistently around δ 5.3 ppm, whereas in the case of the reaction yielding two isomers (**5**), the C4−H shift for what is assumed to be the *N*-1 arylated isomer is around δ 5.5 ppm. Therefore, it is reasonable to propose that the N-2 aryl isomer is formed in each case, although it is not definitively established, with the only exception being the *p*-methoxy compound **5**, which yielded a 1:5 mixture of N-1 and N-2 substituted compounds. The yields of the library are shown in Table 2. Compounds **20**−**28** failed to give any isolable products. The full range of designed substrates is deliberately shown here to illustrate the scope of the current method, as applied in parallel synthesis conditions. The arylation under these conditions is not applicable to hindered or electron-deficient hetero-

Table 2. Modeling Studies of the Energies of the Putative Intermediate Complex

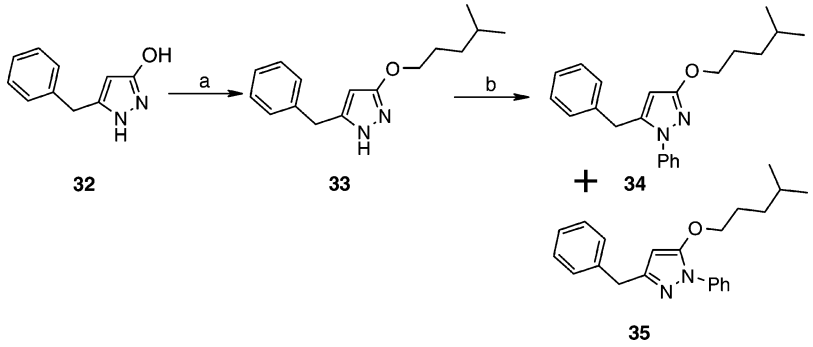


n = 2,3,4

pyrazole side chain length, n =	energy of N-2-coordinated species kcal mol^{-1} [a]	energy of N-1-coordinated species kcal mol^{-1} [a]	observed product ratio N-2/N-1
2	7.01	50.33	4:1
3	12.89	40.19	99:1
4	15.12	35.91	2:1

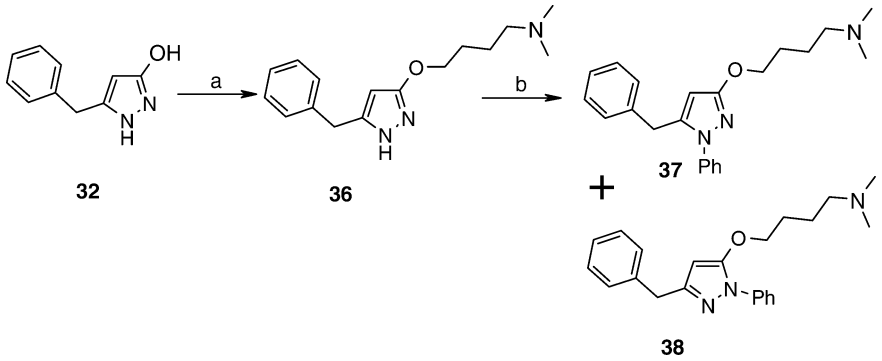
[a] For coordination of the resonance form shown.

Scheme 3. Effect of Side Chain on Regioselectivity[a]



[a] Reagents: (a) 4-methyl-1-pentanol, ADDP, Bu_3P, toluene, (b) $Cu(OAc)_2$, $PhB(OH)_2$, py, CH_2Cl_2, 4-Å molecular sieves, air, 2 days.

Scheme 4[a]



[a] Reagents: (a) 4-(dimethylamino)-1-butanol, ADDP, Bu_3P, toluene, (b) $Cu(OAc)_2$, $PhB(OH)_2$, py, CH_2Cl_2, 4-Å molecular sieves; air; 3 days.

cycles. Although sufficient product for biological screening was isolated in 60% of cases, reasonable synthetic yields were only obtained for relatively electron-rich boronic acids. Thus, using these conditions, it would be sensible to exclude electron-deficient examples from large libraries in order to avoid unnecessary reagent loss and labor. The eventual library produced is of a composition markedly different from the planned version.

We hypothesized that the dimethylamino group on the side chain at the 3′-position might bind to copper and be involved in the direction of the arylation to occur selectively at the N-2 heteroatom. To explore this further, synthesis of the C-analogue of **1** was carried out using the same Mitsunobu chemistry as previously described[2,3] (see Scheme 3) using 4-methylpentan-1-ol as the nucleophile to afford **33** in 47% yield. Arylation of the N-heteroatom of **33** was effected in a similar fashion to afford a mixture of the N-1 and N-2 phenylated isomers **34** and **35**, respectively, in a 38:62 ratio. The lack of any regioselectivity in the arylation demonstrates that the dimethylamino nitrogen atom in **1** has an important role in the stereoselectivity, possibly coordinating to the Cu-(II) species so that the substituted pyrazole acts as a bidentate ligand. Collman and co-workers have shown that arylation using a binuclear copper (II) catalyst with a chelating amine ligand can induce regioselectivity in the N-arylation of imidazoles.[11] The effect of the dimethylaminoalkoxy side chain in our system was further investigated by synthesis and N-arylation of the 2′-dimethylaminoethyloxy and 4′-dimethylaminobutyloxy analogues. The 3-position side chain of 5-benzyl-3-(4′-dimethylaminobutyloxy)pyrazole **36** was introduced via the same Mitsunobu protocol used for **33** (Scheme 4). 5-Benzyl-3-(2′-dimethylaminoethyloxy)pyrazole **41** was synthesized by *N*-Boc protection of the parent pyrazole and then hydride-mediated alkylation with dimethylaminoethyl chloride, followed by deprotection (Scheme 5).

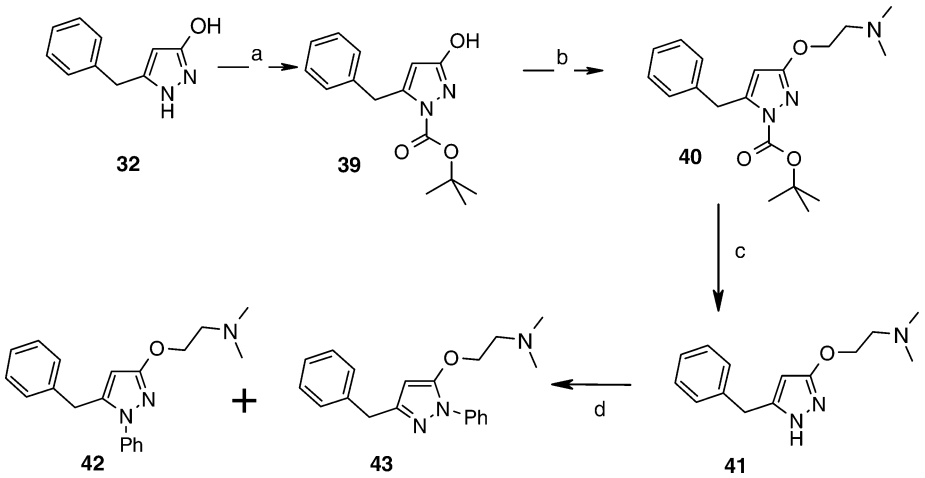
N-Arylation of these two analogues gave mixtures of the N-1 and N-2 arylpyrazoles in an ∼1:4 ratio for compounds **37** and **38** and a 1:2.5 ratio for compounds **42** and **43**. It seems, therefore, that the 3-dimethylaminopropyloxy side chain has the optimum characteristics for the direction of the arylation of the pyrazole.

We further speculated on whether the control of regioselectivity seen for the 3′-dimethylaminopropyloxy group was occurring by an inter- or intramolecular mechanism. The pyrazole bound to copper could intermolecularly direct the arylation of another substrate molecule (in a fashion similar to the binuclear copper complexes described by Collman).[11] Alternatively, regioselectivity could be controlled intramolecularly by directing the binding of copper and the subsequent transfer of the aryl group from copper to the pyrazole nitrogen or by kinetic factors.

Use of the binuclear Cu(II)−TMEDA complex previously described for the arylation of the 3-C analogue **33** gave a 7:1 ratio of the N-2 and N-1 isomers, consistent with the observed 6:1 ratio of products seen for imidazole arylation.[11] We reasoned that if the 3-dimethylaminopropyloxypyrazole was directing the reaction intermolecularly, then a preformed Cu(II)−pyrazole species may be able to direct the arylation of another substrate.

Copper (II) acetate and **1** were stirred together in dichloromethane for 18 h in an attempt to form a bidentate copper−pyrazole complex. Then the 3-C analogue **33** was added, followed by phenylboronic acid, to see if the preformed Cu−

Scheme 5[a]



[a] Reagents: (a) Boc_2O, triethylamine, CH_2Cl_2, 25 °C; (b) NaH, dimethylaminoethyl chloride, DMF, 100 °C; (c) TFA, CH_2Cl_2, 25 °C; (d) $Cu(OAc)_2$, $PhB(OH)_2$, py, CH_2Cl_2, 4-Å molecular sieves; air; 3 days.

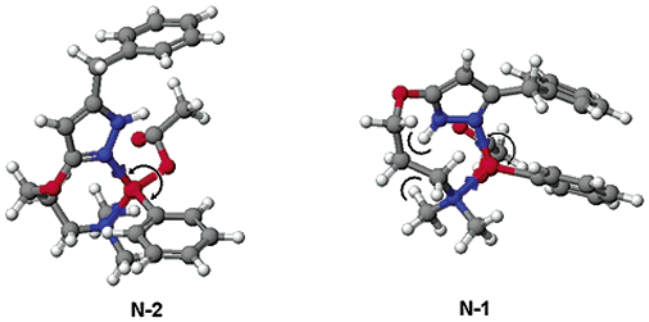


Figure 1. Modeled intermediate Cu−pyrazole complexes.

pyrazole complex could induce stereoselectivity in the arylation of the 3-C substrate. ^{1}H NMR analysis of the complex crude product mixture showed that the 3-C analogue was present in a roughly 1:1 mixture of the N-2 and N-1 isomers. This would appear to indicate that the 3′-dimethylamino analogue does not exert intermolecular regioselectivity. We therefore propose that the observed regioselectivity is more likely to be due to intramolecular direction or the relative stability of the intermediates that give the N-1 and N-2 products.

Modeling studies were carried out on the putative bidentate pyrazole−copper intermediate complex (Figure 1) for each of the side chain lengths studied. Pyrazoles are known to usually coordinate copper via the "pyridine-like" nitrogen,[12] and so we calculated the relative energies of the N-1- and N-2-coordinated species for both resonance forms, that is, for coordination of a pyridine-like and a pyrrole-like nitrogen at either position. Results were broadly similar: in each case, the N-2-coordinated species was of much lower energy than the N-1-coordinated complex, by >20 kcal mol^{-1} (Table 2). However, this stability of the complexes does not fully explain the observed product ratios, in which only the $n = 3$ case shows complete regioselectivity. In light of the difference in energies, we would expect the $n = 2$ case to be the most regioselective. We therefore reason that there are several factors at work, for example, rates of formation of monodentate and bidentate copper-pyrazole complexes and the rate of subsequent aryl transfer. The high energy of the N-1 bidentate complex is due to the strain imposed upon the molecule by the steric interactions shown, which also appear to give an unfavorable geometry for transfer of the aryl group (Figure 1). It is likely that the N-1 bidentate complex is not formed under these reaction conditions, and the N-1 substituted product is formed by a reaction pathway involving the monodentate complex.

Conclusion

The copper mediated N-arylation reported here has not to our knowledge been previously employed for parallel solution- phase synthesis. The mild conditions and ease of product isolation should make it amenable for general use in the synthesis of medicinal chemistry libraries and for automated platforms, such as the Trident.[13] Currently, the chemistry is not practicable with hindered or electron-deficient substrates. The effect of the remote dimethylamino group on regioselectivity indicates that coordinating species may influence the course of the reaction where there is more than one potential product.

Experimental Section

Computational Methods. The geometrical structures of the complexes analyzed were drawn in BioMedCAChe version 5.0, and structure optimization was performed using the augmented MM2 parameters. A conjugated gradient with a convergence value of 0.001 kcal/mol was used in all calculations. Distances calculated with this method were in accordance with X-ray structures of similar complexes.

General. All starting materials were either commercially available or reported previously in the literature unless noted. Solvents and reagents were used without further purification. Reactions were monitored by TLC on precoated silica gel plates (Kieselgel 60 F_{254}, Merck). Purification was performed by flash chromatography using silica gel (particle size 40−63 μM, Merck). ^{1}H, ^{13}C, and NOESY NMR spectra were recorded on a Bruker AMX-300 or Bruker AMX-400 spectrometer. Chemical shifts are reported as parts per million (δ) relative to TMS as an internal standard. Mass spectra were recorded on either a VG ZAB SE spectrometer (electron impact and FAB) or a Micromass Quattro electrospray LC/mass spectrometer. Analytical HPLC was recorded using a

Gilson system. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Microanalaysis was carried out by the Analytical Services Section, University College London. All yields reported in the Experimental Section are isolated yields.

General Procedure for N-Arylation of 3-(3′-(Dimethylamino)-1′-propoxy)-5-benzyl-1*H*-pyrazole (1). 3-(3′-(dimethylamino)-1′-propoxy)-5-benzyl-1*H*-pyrazole (150 mg, 0.58 mmol), cupric acetate (157 mg, 0.87 mmol), pyridine (92 mg, 94 μL, 1.16 mmol), and the corresponding arylboronic acid (0.64 mmol, 1.1 equiv) were dissolved in anhydrous dichloromethane (10 mL) and stirred in a loosely capped test tube in the presence of 4-Å molecular sieves (1 g) for 3 days at room temperature. MP-Carbonate resin (3.5 mmol/g, 540 mg) was added directly to the reaction vessel and stirred for an additional day. The reaction mixture was then filtered through Celite and washed with MeOH, and the organic filtrate was concentrated under reduced pressure. The product was then isolated by flash chromatography using MeOH/$CHCl_3$ (8:92) as eluent to afford the resulting product.

3-[(3-Benzyl-1-phenyl-1*H*-pyrazol-5-yl)oxy]-*N*,*N*-dimethylpropan-1-amine (31). Prepared using the same conditions as for **2** from 3-benzyl-1-phenyl-1*H*-pyrazol-5-ol **30** (278 mg, 1.11 mmol) and 3-dimethylaminopropan-1-ol (170 mg, 195 μL, 1.65 mmol). Purification by flash chromatography using EtOH/ethyl acetate/NH_3, (19:80:1) as eluent afforded the product as a red oil. Yield: 197 mg, 53%; ^{1}H NMR ($CDCl_3$, 300 MHz) identical to compound (**3**).

3-(4′-Methylpentyloxy)-5-benzyl-1*H*-pyrazole (33). 3-Hydroxy-5-benzyl-1*H*-pyrazole[10] (750 mg, 4.31 mmol), 4-methyl-1-pentanol (658 mg, 801.6 μL, 6.38 mmol), and tributylphosphine (1.631 g, 1.99 mL, 6.47 mmol) were dissolved in toluene (10 mL) in a round-bottomed flask under a N_2 atmosphere. While stirring, 1,1′-(azodicarbonyl)-dipiperidine (1.31 g, 6.47 mmol) was added, forming a clear gel. The reaction mixture was then heated to 78 °C overnight and allowed to cool, and the reduced Mitsunobu reagent was filtered off as a white solid and washed with toluene. The organic extracts were washed with 1 M HCl (2 × 30 mL) and then dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography using *n*-hexane/EtOAc (9−8:1) as eluent afforded the product as a white solid, which was crystallized from *n*-hexane to furnish the pure product as a white fluffy solid. Yield: 526 mg, 47%; mp 74−75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.10 (m, 5H), 5.66 (s, 1H), 4.21 (t, 2H), 4.06 (s, 2H), 1.93 (2H), 1.73 (m, 1H), 1.45 (m, 2H), 1.03 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 27 °C) δ = 137.30, 128.8, 128.7, 126.9, 69.3, 35.0, 32.8, 27.8, 27.2, 22.5; MS (EI) *m*/*z* 258. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.39; H, 8.53; N, 10.84.

3-Benzyl-5-[(4-methylpentyl)oxy]-1-phenyl-1*H*-pyrazole (34) and (35). Method A: Cupric Acetate Catalysis. Prepared according to the general procedure for N-arylation from 3-(4′-methylpentyloxy)-5-benzyl-1*H*-pyrazole (113 mg, 0.44 mmol), phenylboronic acid (54 mg, 0.44 mmol), pyridine (69 mg, 70 μL, 0.88 mmol), and cupric acetate (119 mg, 0.658 mmol). The products were obtained as an inseparable mixture of the regioisomers (by SiO_2 normal phase and C18 reversed-phase chromatography). ^{1}H NMR indicates a 4:1 mixture of regioisomers, as evidenced by the integration of the C4 H at δ 5.40 (N-2 isomer) and 5.30 (N-1 isomer). LC/MS shows one peak at 23 min. C18 3−97% MeCN in H_2O. 335 $[MH]^+$.

Method B: Catalysis Using Binuclear Copper−TMEDA Complex. The binuclear copper−TMEDA complex was prepared according to the method of Collman.[11] 3-(4′-Methylpentyloxy)-5-benzyl-1*H*-pyrazole (30 mg, 0.12 mmol), phenylboronic acid (29 mg, 0.24 mmol), and the copper complex (6 mg, 10 mol %) were stirred in dichloromethane (1 mL) for 3 days. The products were identified as a 6:1 mixture of the two regioisomers by ^{1}H NMR.

Method C: Attempted Direction of Regioselectivity by Preformed Copper−Pyrazole Species. 3-[(3-Benzyl-1-phenyl-1*H*-pyrazol-5-yl)oxy]-*N*,*N*-dimethylpropan-1-amine **1** (15 mg, 58 μmol) was stirred with 1 equiv of cupric acetate in dichloromethane (1 mL) for 18 h, and then 3-(4′-methylpentyloxy)-5-benzyl-1*H*-pyrazole **33** (15 mg, 58 μmol), phenylboronic acid (7 mg, 58 μmol) and pyridine (10 mg, 10 μL, 0.12 mmol) were added, and the mixture was stirred for 3 days. The products were obtained as an inseparable mixture of the regioisomers. ^{1}H NMR indicates a 3:2 mixture of regioisomers as evidenced by the integration of the C4 H peaks. LC/MS shows one peak at 25 min C18 3−97% MeCN in H_2O. 335 $[MH]^+$.

5-Benzyl-3-hydroxy-1-(*tert*-butoxycarbonyl)pyrazole (39). A solution of di-*tert*-butyl dicarbonate (632 mg, 2.9 mmol) and triethylamine (417 μL, 3.0 mmol) in dichloromethane-(10 mL) was added to a suspension of 5-benzyl-3-hydroxy-1*H*-pyrazole 31 (500 mg, 2.9 mmol) in dichloromethane (30 mL) with stirring. The mixture was stirred at room temperature for 4 h, and then the solvent was removed in vacuo. The residue was subjected to column chromatography (5% methanol/dichloromethane) to give 475 mg, 60% of the title compound as a waxy white solid. mp 168−170 °C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.18 (m, 5H), 5.42 (s, 1H), 4.28, (s, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 27 °C) δ 163.5, 148.8, 148.1, 137.4, 128.9, 128.5, 126.7, 100.2, 85.2, 34.5, 27.9; MS (FAB+) *m*/*z* 275 $[MH]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.87; H, 6.60; N, 10.65.

3-(2′-(Dimethylamino)-1′-ethoxy)-5-benzyl-1-*tert*-butoxycarbonylpyrazole (40). Sodium hydride (52 mg of a 60% suspension in mineral oil, 1.3 mmol) was added to **39** (300 mg, 1.1 mmol) in dry DMF (10 mL) with stirring. After 30 min, a prestirred mixture of sodium hydride (1.3 mmol) and dimethylaminoethyl chloride hydrochloride (190 mg, 1.3 mmol) in DMF (5 mL) was added, and the reaction mixture was heated at 100 °C under a nitrogen atmosphere for 3 h. After cooling, water (50 mL) was added, and the mixture was extracted with diethyl ether (3 × 50 mL), the combined organic extracts were dried over sodium sulfate, and the solvent was removed in vacuo to give a yellow oil. Flash column chromatography (95:4:1 EtOAc/EtOH/NH_3) furnished the title compound as a yellow oil. Yield, 125 mg, 33%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.20 (m, 3H), 7.16 (d, 2H), 5.45 (s, 1H), 4.32 (t, 2H), 4.18 (s, 2H), 3.65 (t, 2H), 2.80 (s, 6H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$,

27 °C) δ 163.6, 148.6, 148.0, 137.7, 128.7, 128.5, 126.6, 99.9, 84.5, 66.2, 58.2, 45.6, 34.7, 27.9; MS (FAB+) *m*/*z* 346 $[MH]^+$.

3-(2′-(Dimethylamino)-1′-ethoxy)-5-benzyl-1*H*-pyrazole (41). Compound **40** (250 mg, 0.73 mmol) was stirred in 50:50 trifluoroacetic acid/dichloromethane (6 mL) for 3 h. The solvent was then removed in vacuo to give an oil. Trituration with diethyl ether gave a white fluffy solid. Yield, 101 mg, 39% (based on TFA salt); mp 125−127 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.18 (m, 5H), 5.54 (s, 1H), 4.20 (t, 2H), 3.91 (s, 2H), 2.67 (t, 2H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 27 °C) δ 144.5, 137.4, 128.7, 128.5, 126.8, 89.5, 63.1, 56.4, 43.2, 32.5; MS (FAB+) *m*/*z* 246 $[MH]^+$. Anal. Calcd for $C_{14}H_{19}N_3O$. $C_2HF_3O_2$: C, 53.48; H, 5.61; N, 11.69. Found: C, 53.20; H, 5.57; N, 11.45.

3-(4′-(Dimethylamino)-1′-butoxy)-5-benzyl-1*H*-pyrazole (36). Prepared by the same method as for **2** from 5-benzyl-3-hydroxypyrazole **31** (500 mg, 2.9 mmol) and 4-(dimethylamino)-1-butanol (558 μL, 4.2 mmol). Purification by flash chromatography using ethyl acetate/ethanol/NH_3 (80:19:1) as eluent afforded the product as a yellow oil. Yield, 60 mg, 8%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.15 (m, 5H), 5.74 (s, 1H), 4.02 (t, 2H), 3.87 (s, 2H), 2.33 (t, 2H), 2.21 (s, 6H), 1.73−1.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 27 °C) δ 139.9, 129.6, 129.5, 127.6, 89.6, 70.2, 60.3, 45.3, 28.3, 24.8; MS (FAB+) *m*/*z* 274 $[MH]^+$.

3-Benzyl-5-(2′-*N*,*N*-dimethyl-1′-ethyloxy)-1-phenyl-1*H*-pyrazole (42) and (43). Prepared under the same conditions as for **3**, from 3-(2′-(dimethylamino)-1′-ethoxy)-5-benzyl-1*H*-pyrazole (101 mg, 0.41 mmol), phenylboronic acid (55 mg, 0.45 mmol), copper (II) acetate (112 mg, 0.62 mmol), pyridine (66 μL, 0.82 mmol), and 4-Å molecular sieves (0.5 g) in dichloromethane (2 mL). The products were identified as a 4:1 mixture of the two regioisomers by ^{1}H NMR.

3-Benzyl-5-(4′-*N*,*N*-dimethyl-1′-butyloxy)-1-phenyl-1*H*-pyrazole (37) and (38). Prepared under the same conditions as for **3** from 3-(4′-(dimethylamino)-1′-butoxy)-5-benzyl-1*H*-pyrazole 60 mg, 0.22 mmol), phenylboronic acid (31 mg, 0.25 mmol), copper (II) acetate (60 mg, 0.33 mmol), pyridine (636 μL, 0.45 mmol), and 4-Å molecular sieves (0.5 g) in dichloromethane (1.5 mL). The products were identified by ^{1}H NMR as a 2:1 mixture of the two regioisomers, which were inseparable by column chromatography.

Acknowledgment. This work was supported by a generous grant from the BBSRC under the U.K. Government Technology Foresight initiative involving Tripos Inc. (St. Louis, MO) and Automation Partnership (Melbourn, Herts, U.K.). Chi-Kit Woo was funded in part by Argonaut Technologies.

Supporting Information Available. NMR and mass spectral data for compounds **3**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC034065K