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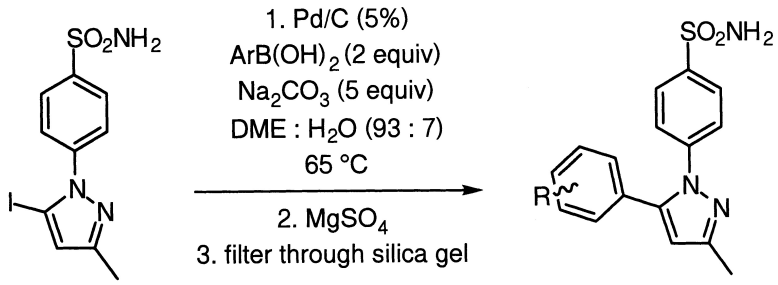

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Synthesis of 4-(5-Iodo-3-Methylpyrazolyl) Phenylsulfonamide and Its Elaboration To a COX II Inhibitor Library by Solution-Phase Suzuki Coupling Using Pd/C as a Solid-Supported Catalyst

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An effective synthesis of 4-(5-iodo-3-methylpyrazolyl) phenylsulfonamide has been developed. This aromatic iodide template served as an efficient oxidative addition partner for the preparation of a solution-phase library of Celecoxib analogues via Suzuki coupling using Pd/C, a readily filterable catalyst.

Introduction

The development of increasingly rapid biological screening techniques continues to press synthetic chemists to prepare compounds with greater efficacy. We have embarked on a program to develop a method for the high-throughput screening of mixtures of compounds using frontal affinity chromatography/mass spectroscopy.[1] To support this effort, we require a steady flow of combinatorial libraries both to validate the system against well-established protein targets and to develop new therapeutic leads against new and less well understood ones. The two enzyme systems that we are investigating first are COX II and factor Xa, both of which have a great deal of literature data with which to validate the new screening methodology. This paper is concerned with the synthesis of a library of COX II inhibitors that are based on the structure of Celecoxib (**1**), which is a potent and selective COX II inhibitor. Both solid- and solution-phase organic synthesis have their own advantages when it comes to preparing libraries of compounds using high-throughput techniques. The main advantage of solid-phase organic chemistry (SPOC) is the ability to drive reactions to completion by using (large) excesses of reagents coupled with an ease of purification by simple filtration.[2] The main disadvantage is the increased rehearsal times associated with adapting solution-phase reactions to the solid where not all reactions transfer seamlessly. This places considerable restrictions on the flexibility of synthetic route design. The principal advantage of solution-phase high-throughput synthesis is that one can use essentially any known reaction without the need for adaptation to the solid phase, and this leads to significantly shortened library rehearsal times. The major drawback with traditional solution-phase synthesis is reaction workup and purification to remove excess or unreacted starting materials. Much has been done recently with the development of solid-supported reagents[3] and scavengers to facilitate high-throughput synthesis using solution-phase methods.[4,5] We[6] and others[3,4] have opted to use solution-phase synthesis where possible; thus, for our pyrazole-based library, we first considered a possible solution-phase approach. The decision for solution-vs-solid phase was decided concurrently with the retrosynthetic analysis.

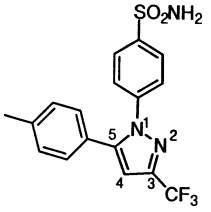

Figure 1. The structure of Celecoxib (Celebrex, Searle−Monsanto), a potent COX II inhibitor.

Perhaps the most commonly used strategy to put the pyrazole substructure together is to condense a hydrazine with 1−3 diketones or their equivalents.[7] However, this route often suffers from poor regioselectivity during ring annulation, and the isomers are difficult to separate. For our purposes, we opted to keep the sulfur moiety as a primary sulfonamide because it has been demonstrated that activity against COX II drops off significantly when the nitrogen is substituted.[8] This meant that there were two potential diversification sites, C3 and C5. Literature data also reveal that a trifluoromethyl group at C3 yields a significant increase in binding to COX II, whereas a simple methyl group vastly reduces it.[8] For our screening validation purposes, we required a vast range of binding capabilities, so we opted to use both of these groups at C3 and to provide the remainder of the diversity through the C5 substituent. In light of the fact that these groups must be aryl to have suitable binding ability to COX II,[8] we reasoned that a metal-mediated coupling procedure would be ideal to install this substituent.[9] However, such a procedure also must to be amenable to high-throughput synthesis. Although there have been published routes to pyrazoles using SPOC methods,[10] we envisioned that a solution-phase route using a solid-supported catalyst would be more suitable, given the structure of our particular pyrazole core and the focus of diversity at C5.

With the library diversification step decided upon, it was also incumbent to devise an effective synthesis of the pyrazole structure that was suitably functionalized for the coupling step. Many of the published routes to arylsulfonamide-substituted pyrazoles have regiochemistry problems and

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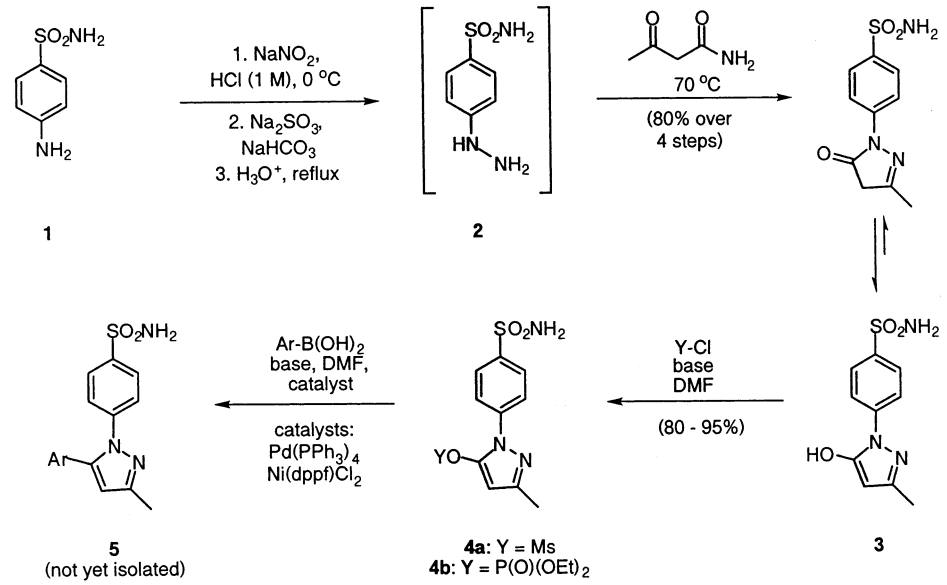
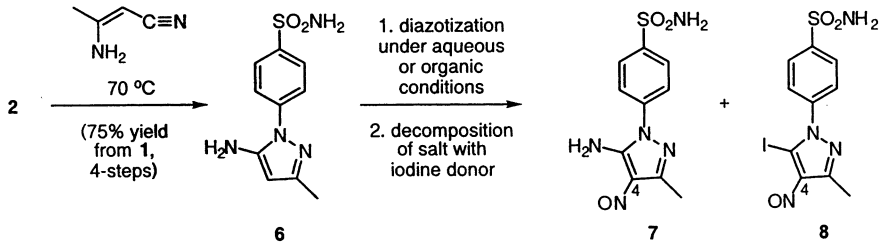
Scheme 1



Scheme 2



often suffer from low yields, which is likely due to their low solubility in most organic solvents. In this report, we detail an effective construction of the pyrazole cross-coupling template and its subsequent elaboration into a small, focused library of C-3 methyl Celecoxib analogues.

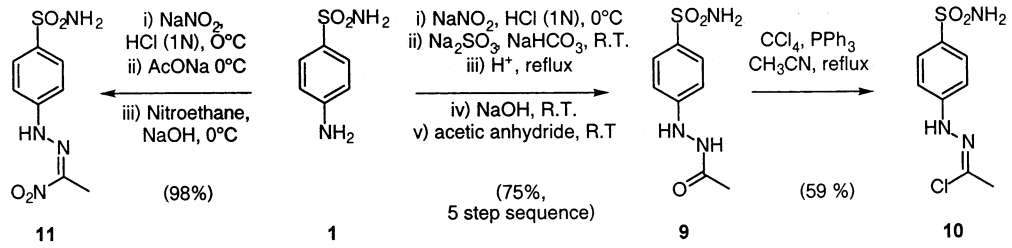
Results and Discussion

Preparation of the Pyrazole Cross-Coupling Template. With some development of appropriate reaction conditions, the pyrazole structure **3** was produced in a streamlined, one-pot procedure from 3-oxobutanamide and 4-aminobenzenesulfonamide **1** (via 4-sulfamoylphenyl hydrazine 2, Scheme 1).[11] Simple capture of the enol tautomer with a variety of electrophiles[12,13] provided the cross-coupling partner(s) **4** directly. However, using a variety of catalysts and reaction conditions, no desired cross-coupling products (**5**) were obtained. At this stage, we were uncertain if it was the nature of the oxidative addition groups on **4**, the stability of the intermediate **4** (e.g., moisture sensitivity), or perhaps it was the sulfonamide moiety that was causing the problem with the coupling.

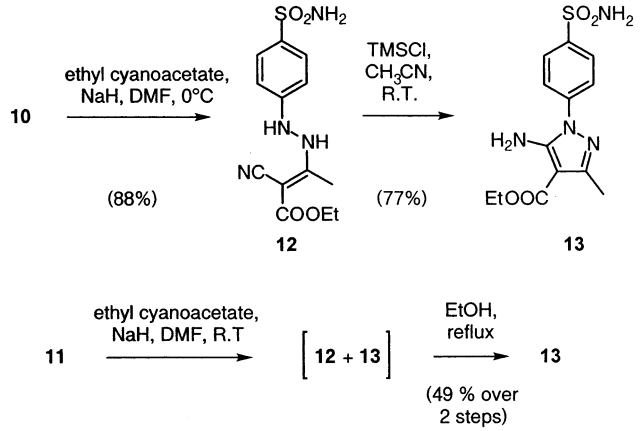
To this end, we tried numerous reaction conditions (e.g., $POCl_3$, $SOCl_2$, PBr_3, Ph_3P/NBS) to generate the corresponding Cl or the Br analogue of **4** from **3** to no avail. Interestingly, it is reported that the 4-nitrophenyl analogue of **3** (instead of sulfonamido) undergoes this transformation readily,[9] which is suggestive that the aryl sulfonamide moiety can cause difficulties for a variety of reactions, possibly including the coupling. However, the sulfonamide is ultimately required in the structure for protein binding, so we left it in the structure and pressed on to try to make the corresponding iodide, which should prove to be the best possible coupling partner in any case. Preparation of the iodide was attempted via the corresponding diazonium salt of **6** that was effectively prepared once again using a one-pot procedure. Unfortunately, **6** proved to be too electron rich for the diazotization step, either with $NaNO_2$ (aqueous) or isoamylnitrite ($CHCl_3$ solvent) oxidizer, leading instead to the nitroso compounds **7** and **8**.[14] To circumvent this problem, we opted to place an ester moiety at C4 which serves two purposes: esterification blocks the position while providing a handle for further potential diversification. The approach to the heterocycle required the formation of an intermediate hydrazone equipped with a suitable leaving group.[15] We first prepared hydrazonyl chloride **10** from sulfanilamide (**1**) via the intermediate **9** (Scheme 3). This was subsequently converted to the pyrazole (**13**) using a two-step substitution/cyclization procedure outlined in Scheme 4.

While the preparation of **10** proceeded suitably well when performed on small amounts of **9**, poor results were obtained upon scale-up. Thus, the corresponding nitrohydrazone **11** was prepared (Scheme 3) in excellent yield in large scale, and it proved to be much more stable to handle[16] than **10**. Substitution proceeded well with **11** to provide **12**, which was conveniently accompanied by some cyclization (**13**), although it did not go to completion, leading to a mixture of

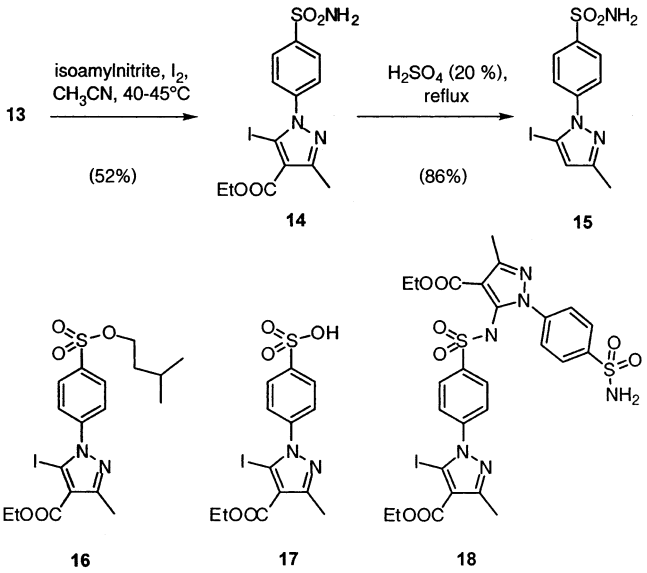
Scheme 3



Scheme 4



Scheme 5

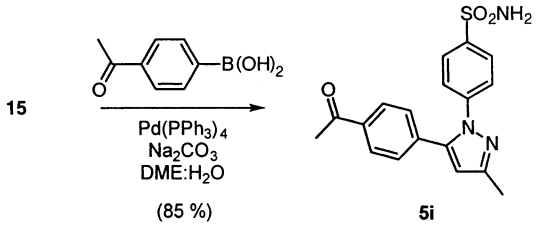


12 and **13** (Scheme 4). This was remedied by isolating the mixture and simply heating it, which provided **13** cleanly.

The next step was the diazotization of the amine and its subsequent capture with iodine (Scheme 5). In halogenated solvents, the reaction proceeded poorly,[17] presumably because of the poor solubility of **13**. Aqueous oxidation/iodination did provide **14**, but as a complex mixture of inseparable products. Changing the solvent of the reaction to acetonitrile yielded the best result, providing **14** in reasonable recovery, along with a reduced number of separable side-products that were identified to be **16**, **17**, and **18**. Saponification/decarboxylation proceeded smoothly in sulfuric acid solution, providing **15** in excellent yield.

Library Preparation. With a suitable quantity of template **15** in hand, we set out to prepare a parallel library of

Scheme 6



Celecoxib analogues. To ensure that the template was suitably reactive, the coupling was first tried with $(PPh_3)_4$-Pd using more-or-less standard conditions[18] with 4-acetylphenylboronic acid, an electron-deficient partner that is known to be a sluggish. The reaction proceeded very well with the only side product being the reduction product (I was replaced by H).

To prepare the actual library, we could not use a soluble catalyst, but rather, we required a supported one that would be removed readily at the end of the synthesis by simple filtration. There has been a considerable volume of work published using solid-supported Pd catalysts for organic synthesis.[4f] One interesting system that has been used for Suzuki couplings is Pd on charcoal,[19] which has even provided good results at a process chemistry scale.[20] By filtering the catalyst during the reaction (which was shown to halt catalyst turnover), it has been demonstrated that the reaction actually takes place on the surface of the support and that the Pd is not solubilized into solution by the substrate. Thus, very low levels of Pd leaching would be expected, which is important for biological screening purposes where metals can impact significantly on results. We are not aware that this catalyst system has been utilized to prepare libraries of compounds via coupling reactions,; thus, we considered this an intriguing and operationally simple choice with which to begin.

Nine parallel reactions were set up on a 100-mg scale with respect to **15** on a Quest model 210 synthesizer (Scheme 7). The reactions were performed in DME with a small amount of water. After they were heated at 65 °C for 2 days, anhydrous $MgSO_4$ was added, and the solutions were filtered through the Teflon frits affixed to the bottom of the reaction tubes. Following DME evaporation, the crude material from these reactions was loaded on top of a silica gel column and passed through to remove the excess boronic acid. We considered using a boronic acid scavenger; however; the convenience of parallel chromatography work stations makes this less of an issue. The compounds prepared are shown in Table 1 along with their yield and purity information.

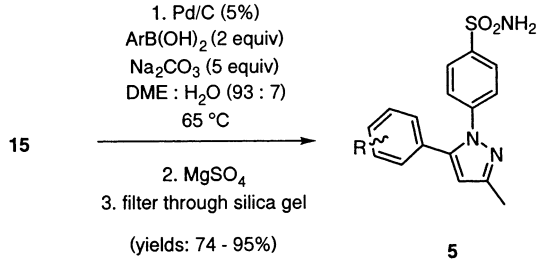
In summary, we have developed a highly effective route for the synthesis of iodopyrazole **15**. This template served

Table 1. Results of Library Preparation from Cross-Coupling of **15** Using Pd/C Catalyst

compd	R	purity[a]	yield[b]
5a	4-OMe	98	95
5b	2-Me	75	74
5c	3-Me	80	85
5d	4-Me	85	84
5e	H	85	87
5f	2-F	85	91
5g	3-F	80	88
5h	4-F	80	93
5i	4-Ac	99	89

[a] Purities are reported on material immediately following library synthesis after filtration through a silica column. Purities were determined by proton NMR spectroscopy. Impurities are excess boronic acid and reduced compound. [b] Yields are reported on material that was carefully purified by a second flash chromatography (average purity by LCMS >98%).

Scheme 7



as the oxidative addition partner for the preparation of a library of Celecoxib analogues via Suzuki coupling using Pd/C as the catalyst. This metal was removed readily along with the water and carbonate in the reaction by a simple filtration through silica gel at the end.

Experimental Section

General Methods. All reactions were carried out under a positive atmosphere of dry nitrogen unless otherwise indicated. All reagents were purchased from Aldrich Chemical Co. and were used without further purification. Melting points are uncorrected. Acetonitrile was distilled from calcium hydride prior to use. Anhydrous DMSO and CCl_4 were stored over 4-Å molecular sieves. Tetrakis(triphenylphosphine)palladium(0) was prepared by reduction of $PdCl_2(PPh_3)_2$ with hydrazine.[21] All ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer, and carbon spectra (100 MHz) were acquired using the APT (attached proton test) pulse sequence which displays positive signals (+) for quaternary carbons and carbons that are attached to an even number of protons. Signals for carbons that are attached to an odd number of protons are negative (−). Proton chemical shifts are listed relative to residual DMSO (δ 2.49). Carbon NMR spectra were recorded relative to the *C*−D heptet resonance in DMSO (δ 39.5 middle peak). Mass spectra were obtained using a PE SCIEX API 2000 triple quadrupole MS with turboionspray ionization. All mass spectra were full-scan experiments (mass range 100−650 amu). The HPLC system was Shimadzu with an LC-8A pump and an SPD-10A VP UV−vis system (λ = 254 nm) with Zorbax SB C18 column (75 × 4.6 mm) with a mobile phase consisting of acetonitrile/H_2O with 0.1% TFA.

4-(2-Acetylhydrazino)sulfonamide (9). A cooled (0 °C) solution of sodium nitrite (474 mg, 6.68 mmol, 1.1 equiv) in water (2.5 mL) was added dropwise over 5 min to a cooled (0 °C) solution of sulfanilamide (**1**) (1.049 g, 5.97 mmol) in hydrochloric acid (1 N, 30 mL, 30 mmol, 5.0 equiv). After stirring for 50 min at 0°C, the mixture was filtered, and the filtrate was added quickly to a mixture of aqueous 40% Na_2SO_3 (6 mL) and aqueous saturated $NaHCO_3$ (24 mL). The mixture was allowed to warm at room temperature where it was stirred for 16 h, after which it was warmed to 70 °C for 1 h. Concentrated HCl was added until the pH reached 1, and the mixture was refluxed for 4 h. After cooling to 0 °C, NaOH (10 N) was added until the pH increased to 10 and then acetic anhydride (1.5 mL, 15.58 mmol, 2.6 equiv) was added dropwise over 4 min. At this time, a precipitate began to form, and after stirring for an additional 30 min at 0 °C, the suspension was filtered. The solid was collected, washed with water, and dried under vacuum, providing 1.03 g of 9 as pale yellow crystals (75%). mp = 218−222 °C (from H_2O). R_f = 0.15 (CH_2Cl_2/MeOH, 90/10). ^1H NMR (DMSO) mixture of rotamers (90/10) in DMSO at 30 °C, major rotamer δ 9.73 (bs, 1H, D_2O exchange), 8.29 (bs, 1H, D_2O exchange), 7.58 (d, J = 8.2 Hz, 2H), 7.01 (bs, 2H, D_2O exchange), 6.74 (d, J = 8.2 Hz, 2H), 1.92 (s, 3H); minor rotamer δ 9.09 (bs, 1H, D_2O exchange), 8.56 (bs, 1H, D_2O exchange), 7.64 (d, J = 8.2 Hz, 2H), 7.05 (bs, 2H, D_2O exchange), 6.74 (d, J = 8.2 Hz, 2H), 1.84 (s, 3H). ^{13}C NMR (DMSO), major rotamer: δ 169.1 (+), 152.0 (+), 133.0 (+), 127.1 (−), 110.9 (−), 20.6 (−). HRMS (EI) calcd for $C_8H_{11}N_3O_3S$ $[M]^+$, 229.0521; found, 229.0511.

4-[2-(1-Chloroethylidene)hydrazino]sulfonamide (10). Carbon tetrachloride (150 μL, 1.55 mmol, 3.5 equiv) in acetonitrile (0.5 mL) was added slowly to a refluxing suspension of **9** (102 mg, 0.44 mmol) and triphenylphosphine (198 mg, 0.75 mmol, 1.7 equiv) in acetonitrile (3.5 mL). A precipitate was formed during the 30-min reflux. The suspension was filtered, and the pale yellow solid was washed with acetonitrile. The filtrate was concentrated, and purification by flash chromatography (Hex/EtOAc, 25/75) provided 65 mg of **10** as white solid (59%). mp = 153−155 °C (from EtOAc/Hex). R_f = 0.40 (Hex/EtOAc, 50/50). ^1H NMR (DMSO) δ 9.67 (bs, 1H, D_2O exchange), 7.66 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 7.06 (bs, 2H, D_2O exchange), 2.39 (s, 3H). ^{13}C NMR (DMSO) δ 147.1 (+), 134.5 (+), 127.1 (−), 124.3 (+), 112.2 (−), 25.4 (−).

4-[2-(1-Nitroethylidene)hydrazino]sulfonamide (11). A cooled solution (0 °C) of sodium nitrite (3.00 g, 42.3 mmol, 1.06 equiv) in water (32 mL) was added dropwise over 15 min to a 0 °C solution of sulfanilamide (7.00 g, 38.9 mmol) in 1 N HCl (120 mL, 120 mmol, 3.0 equiv). After stirring for 30 min, a cooled (0 °C) solution of sodium acetate (10.34 g, 126 mmol, 3.2 equiv) in water (600 mL) was added. Ten min later, nitroethane (3.2 mL, 42.8 mmol, 1.07 equiv) dissolved in a cooled (0 °C) 3 N NaOH solution (15 mL) was added dropwise over 7 min. At this time, a yellow precipitate began to form, and the mixture was stirred for 1 h. The suspension was filtered, and the solid was collected, washed with water, and dried under vacuum with P_2O_5. This procedure provided 10.09 g (98%) of **11** as yellow solid.

mp = 150 °C decomposition (from H_2O). R_f = 0.33 (CH_2Cl_2/MeOH, 92/8). ^{1}H NMR (DMSO) δ 10.67 (bs, 1H, D_2O exchange), 7.78 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.23 (bs, 2H, D_2O exchange), 2.48 (s, 3H). ^{13}C NMR (DMSO) δ 146.1 (+), 145.5 (+), 137.2 (+), 127.5 (−), 114.0 (−), 11.8 (−).

Ethyl 5-Amino-1-[4-(aminosulfony)phenyl]-3-methyl-1H-pyrazole-4-carboxylate (12). *From Hydrazonoyl Chloride* **10**. Ethyl cyanoacetate (300 μL, 2.76 mmol, 1.6 equiv) was added dropwise over 2 min to a suspension of sodium hydride (149 mg, 3.72 mmol, 2.2 equiv, 60% in mineral oil) in DMF (6.0 mL) at 0 °C. After stirring for 10 min, **10** (419 mg, 1.69 mmol), also in DMF (4.0 mL) at 0 °C, was added over 2 min. After stirring for 90 min at 0 °C, aqueous saturated NH_4Cl (75 mL) was added, at which time a solid precipitated out of solution. The suspension was filtered, the solid was washed with water followed by cold methanol, and then it was dried under reduced pressure. The uncyclized compound **12** was obtained as a white solid (481 mg, 88%). This material was used directly in the next step without further purification. mp = 199−201 °C (from MeOH). R_f = 0.33 (CH_2Cl_2/MeOH, 92/08). ^{1}H NMR (DMSO) δ 10.78 (bs, 1H, D_2O exchange), 8.82 (bs, 1H, D_2O exchange), 7.67 (d, J = 8.2 Hz, 2H), 7.08 (bs, 2H, D_2O exchange), 6.80 (d, J = 8.2 Hz, 2H), 4.18 (q, J = 6.9 Hz, 2H), 2.24 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H). ^{13}C NMR (DMSO) δ 172.5 (+), 166.8 (+), 150.2 (+), 135.0 (+), 127.4 (−), 118.2 (+), 111.5 (−), 70.6 (+), 60.1 (+), 16.9 (−), 14.2 (−). HRMS (EI) calcd for $C_{13}H_{16}N_4O_4S$ $[M]^+$, 324.0892; found, 324.0902. Anal. Calcd for $C_{13}H_{16}N_4O_4S$: C, 48.14; H, 4.97; N, 17.27. Found: C, 47.83; H, 5.15; N, 17.03.

Trimethylsilyl chloride (10 mL, 77 mmol, 1.4 equiv) was added over 3 min to a suspension of **12** (17.7 g, 54 mmol) in acetonitrile (400 mL). After stirring for 5 days, the reaction mixture was concentrated, and 6 N HCl (1 L) acid was added. The solution was washed twice with ethyl acetate. The aqueous layer was neutralized with 1 N NaOH and extracted twice with ethyl acetate, and the organic layers were combined. The combined extracts were washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The aminopyrazole (13), obtained as a solid (13.6 g, 77%) was used in the next step without further purification. mp = 198−199 °C (from EtOAc); R_f = 0.40 (Hex/EtOAc, 30/70); ^{1}H NMR (DMSO) δ 7.92 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.45 (bs, 2H, D_2O exchange), 6.50 (bs, 2H, D_2O exchange), 4.21 (q, J = 7.1 Hz, 2H), 2.27 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (DMSO) δ 164.1 (+), 151.0 (+), 149.8 (+), 142.1 (+), 140.4 (+), 126.9 (−), 123.0 (−), 93.6 (+), 58.9 (+), 14.4 (−), 14.3 (−). HRMS (EI) calcd for $C_{13}H_{16}N_4O_4S$ $[M]^+$, 324.0892; found, 324.0889. Anal. Calcd for $C_{13}H_{16}N_4O_4S$: C, 48.14; H, 4.97; N, 17.27. Found: C, 47.59; H, 5.02; N, 16.88.

From α*-Nitrohydrazone **11***. Ethyl cyanoacetate (1.4 mL, 12.88 mmol, 2.4 equiv) was added dropwise over 7 min to a suspension of sodium hydride (496 mg, 12.40 mmol, 2.3 equiv, 60% in mineral oil) in DMF (15 mL) at 0 °C. After stirring for 15 min, **11** (1.4 g, 5.42 mmol) in DMF (10 mL) was added dropwise over 8 min, and the reaction was stirred for 20 min, after which it was warmed to room temperature. After it was stirred for 3 days, aqueous saturated NH_4Cl (100 mL) was added, followed by 50 mL of water, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo.

The residue was resuspended in ethanol (30 mL) and then refluxed for 13 h, at which time the reaction mixture turned homogeneous. After cooling at room temperature, the solvent was removed in vacuo, and 6 N HCl (100 mL) was added. The aqueous layer was washed twice with EtOAc, neutralized with 1 N NaOH, and then extracted twice with EtOAc. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo. Compound **13** was obtained in 49% overall yield (864 mg) and was used without further purification.

*Large-Scale Reaction of **11** to Prepare **12***. Ethyl cyanoacetate (25 mL, 230 mmol, 2.0 equiv) in DMF (100 mL) was added dropwise over 40 min to a suspension of sodium hydride (9.83 g, 245 mmol, 2.1 equiv, 60% in mineral oil) in DMF (150 mL) at 0 °C. After stirring for 5 min, the mixture was allowed to warm to room temperature over 30 min, at which time **11** (29.88 g, 115 mmol) in DMF (250 mL) was added over 40 min. After stirring for 17 h, aqueous saturated NH_4Cl (2 L) was added, and a precipitate formed. The suspension was filtered, and the solid was washed successively with water, cold methanol, ether, ether/hexane, and hexane, after which it was dried under reduced pressure. The uncyclized compound (**12**) was obtained as a pale brown solid (17.7 g, 57%).

Ethyl 1-[4-(Aminosulfony)phenyl]-5-iodo-3-methyl-1H-pyrazole-4-carboxylate (14). Iso-amylnitrite (430 μL, 3.10 mmol, 1.2 equiv) was added dropwise over 10 min to a suspension of **13** (849 mg, 2.6 mmol) and iodine (2.868 g, 11.30 mmol, 4.3 equiv) in acetonitrile (30 mL) at 45 °C. After stirring for 20 min, the mixture was cooled to room temperature, and saturated aqueous $Na_2S_2O_3$ (200 mL) was added. The mixture was extracted twice with ethyl acetate, and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Following solvent removal in vacuo, the solid orange residue was recrystallized from glacial acetic acid (2.5 mL) to provide 589 mg (52%) of **14** as white solid. mp = 174−176 °C (from AcOH). R_f = 0.66 (Hex/EtOAc, 30/70). ^{1}H NMR (DMSO) δ 7.98 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.53 (bs, 2H, D_2O exchange), 4.27 (q, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO) δ 162.0 (+), 152.6 (+), 144.4 (+), 142.1 (+), 127.5 (−), 126.6 (−), 117.4 (+), 94.3 (+), 60.0 (+), 14.2 (−), 14.1 (−). HRMS (EI) calcd for $C_{13}H_{14}IN_3O_4S$ $[M]^+$, 434.9750; found, 434.9750. Anal. Calcd for $C_{13}H_{14}IN_3O_4S$: C, 35.88; H, 3.24; N, 9.65. Found: C, 35.40; H, 3.10; N, 9.44.

4-(5-Iodo-3-methyl-1H-pyrazol-1-yl)sulfonamide (15). Concentrated sulfuric acid (200 mL) was added carefully to a suspension of **14** (4.45 g, 10.2 mmol) in water (800 mL). The suspension was warmed to reflux for 4 days, cooled to room temperature, and extracted with EtOAc. The combined organic extracts were washed successively with water,

aqueous saturated $NaHCO_3$, and water. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. Iodopyrazole **15** was obtained as a white solid (3.22 g, 86%) and was used in the next step without further purification. mp = 248−250°C (from EtOAc). R_f = 0.30 (CH_2Cl_2/MeOH, 95/05); ^{1}H NMR (DMSO) δ 7.95 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.47 (bs, 2H, D_2O exchange), 6.58 (s, 1H), 2.23 (s, 3H). ^{13}C NMR (DMSO) δ 151.9 (+), 143.2 (+), 142.2 (+), 126.5 (−), 125.9 (−), 118.0 (+), 84.4 (−), 13.1 (−). HRMS (EI) calcd for $C_{10}H_{10}IN_3O_2S$ [M]$^+$, 362.9538; found, 362.9561. Anal. Calcd for $C_{10}H_{10}IN_3O_2S$: C, 33.07; H, 2.78; N, 11.57. Found: C, 32.88; H, 2.74; N, 11.32.

General Procedure for the Suzuki Cross-Coupling of 15. The library synthesis was conducted on an argonaut Quest model 210 synthesizer. To each 10 mL Teflon vessel on the Quest was added **15** (102 mg, 0.28 mmol), arylboronic acid (0.56 mmol, 2.0 equiv), sodium carbonate (150 mg, 1.42 mmol, 5.0 equiv), 10% Pd/C (15 mg, 5 mol % Pd atom), and a mixture of DME/H_2O (3 mL, 93:7). The reactions were run with agitation under an atmosphere of dry argon for 2 days at 65 °C. After cooling at room temperature, the mixtures were diluted by EtOAc (3 mL), and anhydrous $MgSO_4$ (400 mg) was added. The suspensions were warmed at 50 °C for 30 min with agitation and cooled to room temperature, and then the solid was filtered off through the Teflon frits at the bottom of each reaction vessel. The solids left behind were resuspended in dry EtOAc (3 mL), warmed at 50 °C for 15 min, cooled to room temperature, and filtered. This wash sequence was repeated twice. The combined filtrates were concentrated and passed through silica gel columns to obtain compounds **5**. Purities are determined on the compounds directly from the library preparation with no further purification. For analytical purposes, compounds **5b** through **5h** were recolumned to provide pure material (all purities were >96% by LCMS). All yields are reported on recolumned material.

4-[5-(4-Methoxyphenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5a). Yield, 95%. Purity (^{1}H NMR), 98%; mp = 200−204 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.79 (d, J = 8.6 Hz, 2H), 7.40 (bs, 2H, D_2O exchange), 7.38 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 6.40 (s, 1H), 3.76 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (DMSO) δ 159.3 (+), 149.4 (+), 143.3 (+), 142.3 (+), 142.1 (+), 129.9 (−), 126.6 (−), 124.5 (−), 122.3 (+), 114.2 (−), 108.5 (−), 55.2 (−), 13.3 (−). ESMS m/z [M + H]$^+$, 344.

4-[5-(2-Methylphenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5b). Yield, 74%. Purity (^{1}H NMR), 75%. mp = 194−196 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.71 (d, J = 8.5 Hz, 2H), 7.35 (bs, 2H, D_2O exchange), 7.30 (d, J = 8.5 Hz, 2H), 7.35−7.18 (m, 4H), 6.38 (s, 1H), 2.31 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (DMSO) δ 149.3 (+), 142.5 (+), 142.1 (+), 141.7 (+), 136.3 (+), 130.4 (−), 130.3 (+), 130.2 (−), 129.2 (−), 126.5 (−), 126.1 (−), 122.8 (−), 109.6 (−), 19.5 (−), 13.3 (−). ESMS m/z [M + H]$^+$, 328.

4-[5-(3-Methylphenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5c). Yield, 85%. Purity (^{1}H NMR), 80%. mp 204−208 °C (from EtOAc); ^{1}H NMR (DMSO) δ 7.78 (d, J = 8.7 Hz, 2H), 7.40 (bs, 2H, D_2O exchange), 7.38 (d, J = 8.7 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.15 (s, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.46 (s, 1H), 2.28 (s, 6H). ^{13}C NMR (DMSO) δ 149.4 (+), 145.5 (+), 142.2 (+), 142.1 (+), 138.0 (+), 130.0 (+), 129.2 (−), 129.0 (−), 128.5 (−), 126.5 (−), 125.6 (−), 124.5 (−), 108.8 (−), 20.9 (−), 13.2 (−). ESMS m/z [M + H]$^+$, 328.

4-[5-(4-Methylphenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5d). Yield, 84%. Purity (^{1}H NMR), 85%. mp 193−195 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.78 (d, J = 8.6 Hz, 2H), 7.40 (bs, 2H, D_2O exchange), 7.39 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.43 (s, 1H), 2.30 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (DMSO) δ 149.4 (+), 143.5 (+), 142.2 (+), 142.1 (+), 138.1 (+), 129.3 (−), 128.3 (−), 127.1 (+), 126.5 (−), 124.6 (−), 108.6 (−), 20.7 (−), 13.2 (−). ESMS m/z [M + H]$^+$, 328.

4-(5-Phenyl)-3-methyl-1H-pyrazol-1-yl)sulfonamide (5e). Yield, 87%. Purity (^{1}H NMR), 85%. mp 195−197 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.78 (d, J = 8.7 Hz, 2H), 7.40−7.37 (m, 7H, D_2O exchange for 2 H), 7.25−7.22 (m, 2H), 6.48 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (DMSO) δ 149.5 (+), 143.4 (+), 142.2 (+), 142.1 (+), 130.0 (+), 128.7 (−), 128.6 (−), 128.5 (−), 126.5 (−), 124.6 (−), 108.9 (−), 13.2 (−); ESMS m/z [M + H]$^+$, 314.

4-[5-(2-Fluorophenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5f). Yield, 91%. Purity (^{1}H NMR), 85%. mp 186−190 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.71 (d, J = 8.3 Hz, 2H), 7.40 (bs, 2H, D_2O exchange), 7.37 (d, J = 8.3 Hz, 2H), 7.51−7.46 (m, 1H), 7.42−7.35 (m, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.25−7.20 (m, 1H), 6.51 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (DMSO) δ 158.5 (+, d, J = 247.3 Hz), 149.6 (+), 142.2 (+), 137.2 (+), 131.3 (−), 131.5 (−, d, J = 8.5 Hz), 126.6 (−), 125.0 (−, d, J = 4.0 Hz), 123.2 (−), 118.2 (+, d, J = 15.2 Hz), 116.1 (−, d, J = 21.7 Hz), 110.3 (−),13.2 (−). ESMS m/z [M + H]$^+$, 332.

4-[5-(3-Fluorophenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5g). Yield, 88%. Purity (^{1}H NMR), 80%. mp 205−209 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.81 (d, J = 8.5 Hz, 2H), 7.41 (bs, 2H, D_2O exchange), 7.40 (d, J = 8.5 Hz, 2H), 7.44−7.39 (m, 1H), 7.23−7.19 (m, 1H), 7.12 (d, J = 9.8 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 6.56 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (DMSO) δ 161.9 (+, d, J = 244.6 Hz), 149.6 (+), 142.5 (+), 142.1 (+), 141.8 (+), 132.2 (+, d, J = 9 Hz), 130.8 (−, d, J = 9.1 Hz), 126.6 (−), 124.7 (−), 124.7 (−), 115.4 (−, d, J = 23.0 Hz), 115.3 (−, d, J = 21.5 Hz), 109.3 (−), 13.2 (−). ESMS m/z [M + H]$^+$, 332.

4-[5-(4-Fluorophenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5h). Yield, 93%. Purity (^{1}H NMR), 80%. mp 232−235 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.79 (d, J = 8.6 Hz, 2H), 7.41 (bs, 2H, D_2O exchange), 7.37 (d, J = 8.6 Hz, 2H), 7.31−7.21 (m, 4H), 6.48 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (DMSO) δ 162.0 (+, d, J = 246.4 Hz), 149.5 (+), 142.4 (+), 142.3 (+), 141.9 (+), 130.7 (−, d, J = 9 Hz), 126.6 (−), 126.5 (+), 124.6 (−), 115.8 (−, d, J = 22.0 Hz), 109.0 (−), 13.2 (−). ESMS m/z [M + H]$^+$, 332.

4-[5-(4-Acetylphenyl)-3-methyl-1H-pyrazol-1-yl]sulfonamide (5i). Yield, 89%. Purity (^{1}H NMR), 99%. mp 172−174 °C (from EtOAc). ^{1}H NMR (DMSO) δ 7.94 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.43 (bs, 2H, D_2O exchange), 7.41 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz,

2H), 6.61 (s, 1H), 2.57 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (DMSO) δ 197.3 (+), 149.7 (+), 142.5 (+), 142.4 (+), 141.9 (+), 136.3 (+), 134.2 (+), 128.6 (−), 128.5 (−), 126.7 (−), 124.8 (−), 109.6 (−), 26.7 (−), 13.2 (−). ESMS *m/z* [M + H]$^+$, 356.

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Supporting Information Available. ^{1}H NMR, ^{13}C NMR, and LCMS spectra for compounds 5a−5i. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Schriemer, D. C.; Bundle, D. R.; Li, L.; Hindsgaul, O. *Angew. Chem., Intl. Ed. Engl.* **1998**, *37*, 3383−3387.
(2) For seminal work in small molecule SPOC, see: Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723−5724.
(3) For seminal work in the development and use of solid-supported reagents in solution-phase synthesis, see: Fridkin, M.; Patchornik, A.; Katchalski, E. *J. Am. Chem. Soc.* **1966**, *88*, 3164−3165.
(4) For recent reviews dealing with solid-supported reagents and applications to combinatorial synthesis, see: (a) Lindner, E.; Schneller, T.; Auer, F.; Mayer, H. A. *Angew. Chem., Intl., Ed. Engl.* **1999**, *38*, 2154−2174. (b) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035−1074. (c) Bhalay, G.; Dunstan, A.; Glen, A. *Synlett* **2000**, 1846−1859. (d) de Miguel, Y. R. *J. Chem. Soc, Perkin Trans 1* **2000**, 4213−4221. (e) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195. (f) Organ, M. G.; Mallik, D. *Optimizing Solid-Phase Chemistry*; Marcel-Dekker: New York, 2001, pp 315−381. (g) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int., Ed. Engl.* **2001**, *40*, 650−679.
(5) For recent reviews dealing with scavenging techniques in combinatorial synthesis, see: (a) Flynn, D. L.; Devraj, R. V.; Naing, W.; Parlow, J. J.; Weidner, J. J.; Yang, S. *Med. Chem. Res.* **1998**, 219−243. (b) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336. (c) Hodges, J. C. *Synlett* **1999**, 152−158. (d) Also see refs 4b and 4e.
(6) (a) Organ, M. G.; Dixon, C. E.; Mayhew, D.; Parks, D. J.; Arvanitis, E. A. *Comb. Chem. High Throughput Screening* **2002**, *5*, 209−216. (b) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Lavorato, D. J.; Siegel, M. G.; Dressman, B. A. *J. Comb. Chem.* **2001**, *3*, 473−476. (c) Organ, M. G.; Mayhew, D.; Cooper, J. T.; Dixon, C. E.; Lavorato, D. J.; Kaldor, S. W.; Siegel, M. G. *J. Comb. Chem.* **2001**, *3*, 64−67. (d) Organ, M. G.; Kaldor, S. W.; Dixon, C.; Parks, D. J.; Singh, U.; Lavorato, D. J.; Isbester, P. K.; Siegel, M. G. *Tetrahedron Lett.* **2000**, *41*, 8407−8411. (e) Organ, M. G.; Dixon, C. E. *Biotechnol. Bioeng. (Comb. Chem.)* **2000**, 71−78.
(7) Elguero, J. *J. Compr. Heterocycl. Chem.* **1984**, *4*, 167−303.
(8) Penning, T. D.; Talley, J. T.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, F. E.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347−1365.
(9) For a related coupling using $(PPh_3)_4Pd$ on substrates without a sulfonamide moiety, see: Wang, X.-j.; Tan, J.; Grozinger, K. *Tetrahedron Lett.* **2000**, *41*, 4713−4716.
(10) Donohue, B. A.; Michelotti, E. L.; Reader, J. C.; Reader, V.; Stirling, M.; Tice, C. M. *J. Comb. Chem.* **2002**, *4*, 23−32. (b) Spivey, A. C.; Diaper, C. M.; Adams, H.; *J. Org. Chem.* **2000**, 65, 5253−5263. (c) Wilson, R. D.; Watson, S. P.; Richards, S. A. *Tetrahedron Lett.* **1998**, *39*, 2827−2830.
(11) Lisitsyn, V. N.; Sazonchik, O. B. *Russ. J. Org. Chem.* **1994**, *30*, 780−784.
(12) For cross-coupling with a mesylate, see: (a) Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyaura, N. *Tetrahedron* **1998**, *54*, 13079−13086. (b) Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531−8534. (c) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060−1065. For cross-coupling with a tosylate, see: (d) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479−1482. (e) Danilo, Z.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049−3051.
(13) For cross-coupling with phosphates, see: (a) Lepifre, F.; Buon, C.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 6373−6376. (b) Yang, Z.; Nan, Y. *Tetrahedron Lett.* **1999**, *40*, 3321−3324. (c) Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757−1758.
(14) Ganesan, A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 6155−6157. (b) Grandberg, I. I.; Klyuchko, G. V. *Zh. Ob. Khim.* **1962**, *32*, 1898−1905.
(15) For construction of the 5-aminopyrazole ring with ester at C4, see: (a) Tanaka, K.; Suzuki, T.; Maeno, S.; Mitsuhashi, K. *J. Heterocycl.. Chem.* **1986**, *23*, 1535−1538. (b) Shawali, A. S.; Hassaneen, H. M.; Sami, M.; Fahham, H. M. *J. Heterocyclic. Chem.* **1976**, *13*, 1137−1140.
(16) Shawali, A. S. *Chem. Rev.* **1993**, *93*, 2731−2777. (b) Abdelhamid, A. O.; Abbas, I. M.; Abdallah, M. A.; Fahmi, A. A.; Shawali, A. S. *J. Heterocycl. Chem.* **1985**, *22*, 813−816. (c) Shawali, A. S.; Hassaneen, H. M.; Sherif, S. M. *J. Heterocycl. Chem.* **1980**, *17*, 1745−1749.
(17) Beck, J. R.; Gajewski, R. P.; Lynch, M. P.; Wright, F. L. *J. Heterocycl. Chem.* **1987**, *24*, 267−270.
(18) Suzuki, A. J. *Organomet. Chem.* **1999**, *576*, 147−168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(19) For cross-coupling using Pd/C as a catalyst, see: (a) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, 67, 2721−2722. (b) Mark, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280.
(20) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248−252.
(21) Coulson, D. R. *Inorg. Synth.* **1990**, *28*, 107−109. (b) Tellier, F.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1985**, *292*, 19−28.

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