JOC Article

Practical Synthesis of a p38 MAP Kinase Inhibitor

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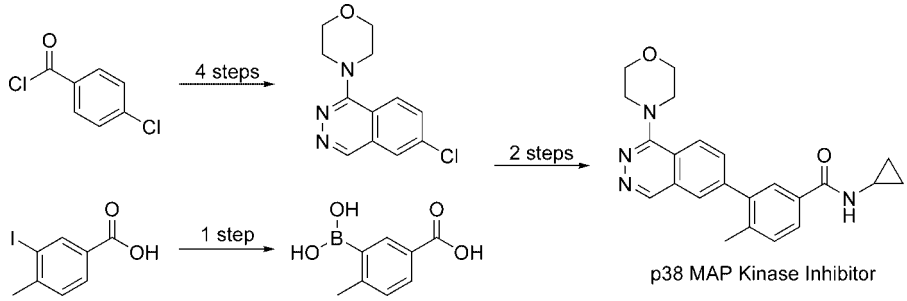

p38 MAP kinase inhibitors have attracted considerable interest as potential agents for the treatment of inflammatory diseases. Herein, we describe a concise and efficient synthesis of inhibitor **1** that is based on a phthalazine scaffold. Highlights of our approach include a practical synthesis of a 1,6-disubstituted phthalazine building block **24** as well as the one-pot formation of boronic acid **27**. Significant synthetic work to understand the reactivity principles of the intermediates helped in selection of the final synthetic route. Subsequent optimization of the individual steps of the final sequence led to a practical synthesis of **1**.

Introduction

p38 mitogen-activated protein (MAP) kinases are intracellular serine/threonine kinases that positively regulate the production and action of several pro-inflammatory mediators, specifically the release of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in response to stress.[1] These cytokines are involved in autoimmune disease states like rheumatoid arthritis (RA), Crohn's disease (inflammatory bowel disease), and psoriasis. Biological agents that sequester TNF-α show impressive clinical efficacy in the treatment of these diseases.[2] Small molecule inhibitors of p38 MAP kinase have been shown to be efficacious in clinical studies as alternatives for these biological agents.[3] Our medicinal chemistry team's work toward the discovery of p38 MAP kinase inhibitors has resulted in suitable phthalazine-based candidates that were selected for further development.[4] Herein, we describe process research and development toward the phthalazine derivative **1** which has culminated in an efficient and scalable synthesis of this drug candidate.

The original synthetic route to prepare **1** (Scheme 1)[4] was reasonably short and efficient. However, it required 4-bromo-2-methylbenzonitrile (**2**), which was difficult to source, and other expensive stoichiometric reagents such as $AgNO_3$ and bis(pinacolato)diboron. Moreover, the hydrative cyclization of 2-(dibromomethyl)benzonitrile **3** to hydroxyisoindolinone **4** proved precarious, and the removal of the insoluble silver byproducts (light-sensitive silver bromide, silver oxide, metallic silver) during the reaction workup was problematic and deemed not scalable. In order to address these issues, a number of silver-free hydrative cyclization conditions to form **3** were briefly

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(1) (a) Chen, Z.; Gibson, T. B.; Robinson, F.; Silvestro, L.; Pearson, G.; Xu, B.; Wright, A.; Vanderbilt, C.; Cobb, M. H. *Chem. Rev.* **2001**, *101*, 2449. (b) Raingeaud, J.; Gupta, S.; Rogers, J. S.; Dickens, M.; Han, J.; Ulevitch, R. J.; Davis, R. J. *J. Biol. Chem.* **1995**, *270*, 7420.

(2) Etanercept, infliximab, and adalimumab are TNF-α blockers currently approved in the US and elsewhere for the treatment of various inflammatory diseases.

(3) (a) Gaestal, M.; Mengel, A.; Bothe, U.; Asadullah, K. *Curr. Med. Chem.* **2007**, *14*, 2214. (b) Peifer, C.; Wagner, G.; Laufer, S. A. *Curr. Top. Med. Chem.* **2006**, *6*, 113. (c) Margutti, S.; Laufer, S. A. *ChemMedChem* **2007**, *2*, 1116.

(4) Herberich, B.; Cao, G.-Q.; Chakrabarti, P. P.; Falsey, J. R.; Pettus, L.; Rzasa, R. M.; Reed, A. B.; Reichelt, A.; Sham, K.; Thaman, M.; Wurz, R. P.; Xu, S.; Zhang, D.; Hsieh, F.; Lee, M. R.; Syed, R.; Li, V.; Grosfeld, D.; Plant, M. H.; Henkle, B.; Sherman, L.; Middleton, S.; Wong, L. M.; Tasker, A. S. *J. Med. Chem.* **2008**, *51*, 6271.

(5) A one-pot hydrolysis/cyclization attempt under the conditions (1-BuOH, aq NaOH, 120 °C) developed for cyclizations of *o*-cyanobenzaldehydes (Sato, R.; Ohmori, M.; Kaitani, F.; Kurosawa, A.; Senzaki, T.; Goto, T.; Saito, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2481) led to a complex mixture of products.

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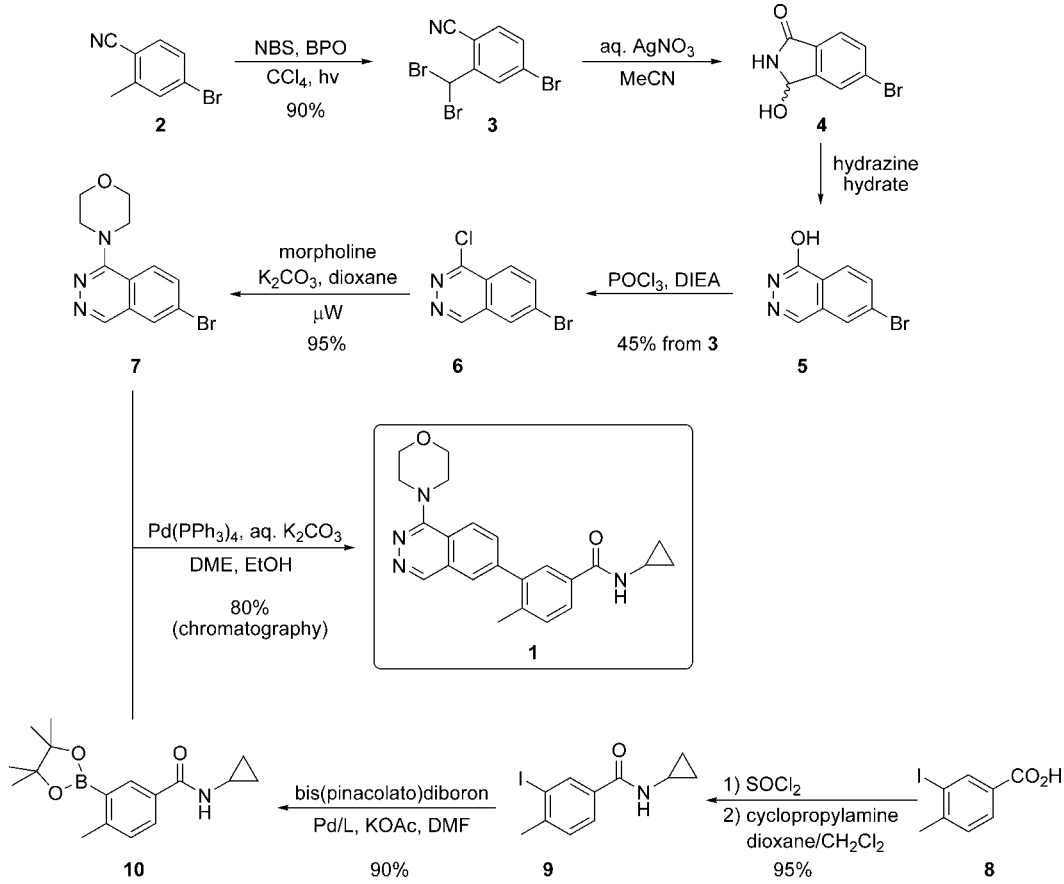
SCHEME 1. Original Discovery Synthesis of a Lead Drug Candidate 1



investigated, largely without success.[5] These findings combined with the relatively high cost of 4-bromo-2-methylbenzonitrile (**2**)[6] led us to focus on the development of a more practical synthesis of 1,6-difunctionalized phthalazines. Other issues that needed to be addressed included the development of a practical synthesis of the boronic acid building block as well as a more controlled isolation and purification of **1**. Strategically, it was also desirable to avoid the use of palladium in the last step of the synthetic sequence to reduce potential issues with removal of trace metal contaminants. Toward this end, two synthetic approaches for the synthesis of **1** were proposed (Scheme 2), both of which relied on the synthesis of key building blocks **24** and **27**. As will be discussed below, we found that the order of bond construction was important for the successful synthesis of **1**. Initially, we investigated installation of the morpholine substituent late in the synthesis (first-generation approach, Scheme 2). This route presented difficulties detailed below that prompted us to pursue a strategy similar to that demonstrated in the discovery approach (cf. Scheme 1). Thus, we successfully developed a sequence in which early morpholine installation afforded **37**, which was coupled with **27** followed by amidation to yield **1** (second-generation approach, Scheme 2).

Results and Discussion

Development of a Phthalazine Building Block. Precursors of a 6-substituted phthalazin-1-ol system such as hydroxyisoindolinones **I** can be obtained by directed *ortho*-metalation (D*o*M) of a suitable *para*-substituted benzamide **III**[7] using alkyllithium or amide bases followed by reaction with a formyl donor (Scheme 3).[8,9] The main advantage of this approach is the inherent regiospecificity—only a single *lithio*-regioisomer **II** is expected to form due to the symmetry of the amide **III**. Furthermore, the amide functionality is one of the strongest *ortho*-directing groups,[10] and methodology for *ortho*-functionalization of benzamides by directed *ortho*-lithiation is well established.[11] Compared to tertiary amides (e.g., diisopropylbenzamides), secondary amides such as **III** require an additional 1 equiv of the lithium base for the initial *N*-deprotonation, but this initial deprotonation also protects them against attack of the alkyllithium species.[12]

(6) $153/25 g or $1200/mol (Aldrich catalog price).

(7) A number of inexpensive *para*-substituted benzoic acids or *para*-substituted benzoyl chlorides are readily available.

(8) (a) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, 1183. (b) Metallinos, C. Development of New Directed Metalation Groups for the (-)-Sparteine-Mediated Synthesis of Ferrocenes with Planar Chirality. Ph.D Thesis, Queen's University, Kingston, Ontario, Canada, 2001.

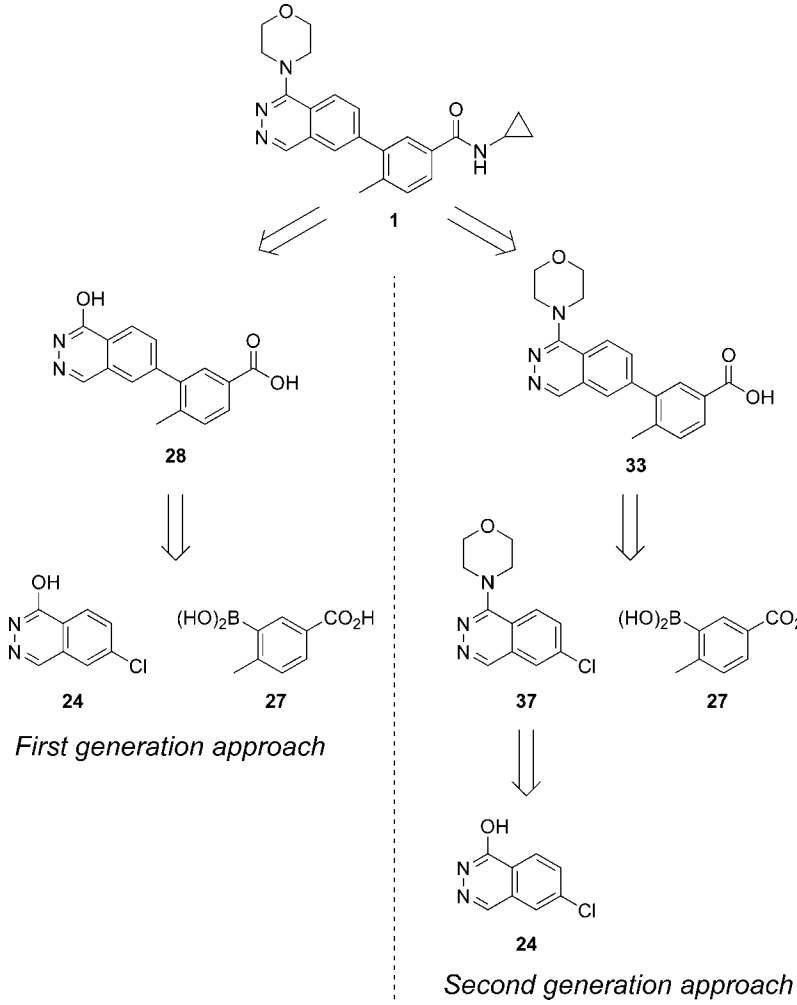
(9) Epsztajn, J.; Brzezinski, J. Z.; Czech, K. *Monatsh. Chem.* **1993**, *124*, 549.

(10) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

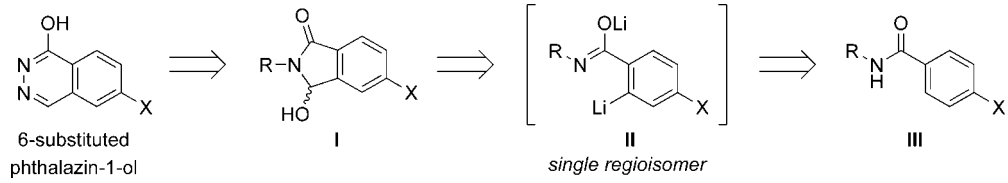
(11) Recent examples of *ortho*-functionalization of benzamides via a directed *ortho*-lithiation approach: (a) Olivier, A.; Sperry, J.; Larsen, U. S.; Brimble, M. A. *Tetrahedron* **2008**, *64*, 3912. (b) Khanolkar, A. D.; Lu, D.; Ibrahim, M., Jr.; Thakur, G. A., Jr.; Porreca, F.; Veerappan, V.; Tian, X.; George, C.; Parrish, D. A.; Papahatjis, D. P.; Makriyannis, A. *J. Med. Chem.* **2007**, *50*, 6493. (c) Clayden, J.; Hebditch, K. R.; Read, B.; Helliwell, M. *Tetrahedron Lett.* **2007**, *48*, 8550. (d) Uchiyama, M.; Naka, H.; Matsumoto, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 10526. (e) Cornella, I.; Kelly, T. R. *J. Org. Chem.* **2004**, *69*, 2191. (f) Martin, C.; Macintosh, N.; Lamb, N.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 1021.

(12) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790.

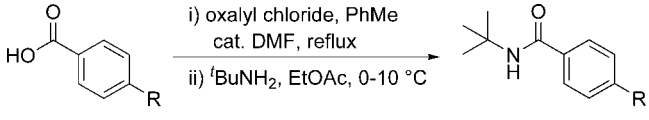
SCHEME 2. Key Disconnections in the Retrosynthesis of 1



SCHEME 3. Directed *ortho*-Lithiation Approach to Precursors of 6-Substituted Phthalazin-1-ol



SCHEME 4. Preparation of *N-tert*-Butylbenzamides 12a−c



11a R = Br
11b R = NO_2
11c R = Cl

12a R = Br (67%)
12b R = NO_2 (86%)
12c R = Cl (84%)

A series of *N-tert*-butylbenzamides (**12a**−**c**) were prepared from commercially available benzoic acids (**11a**−**c**) in good yields and excellent purity (>99% by HPLC) (Scheme 4).

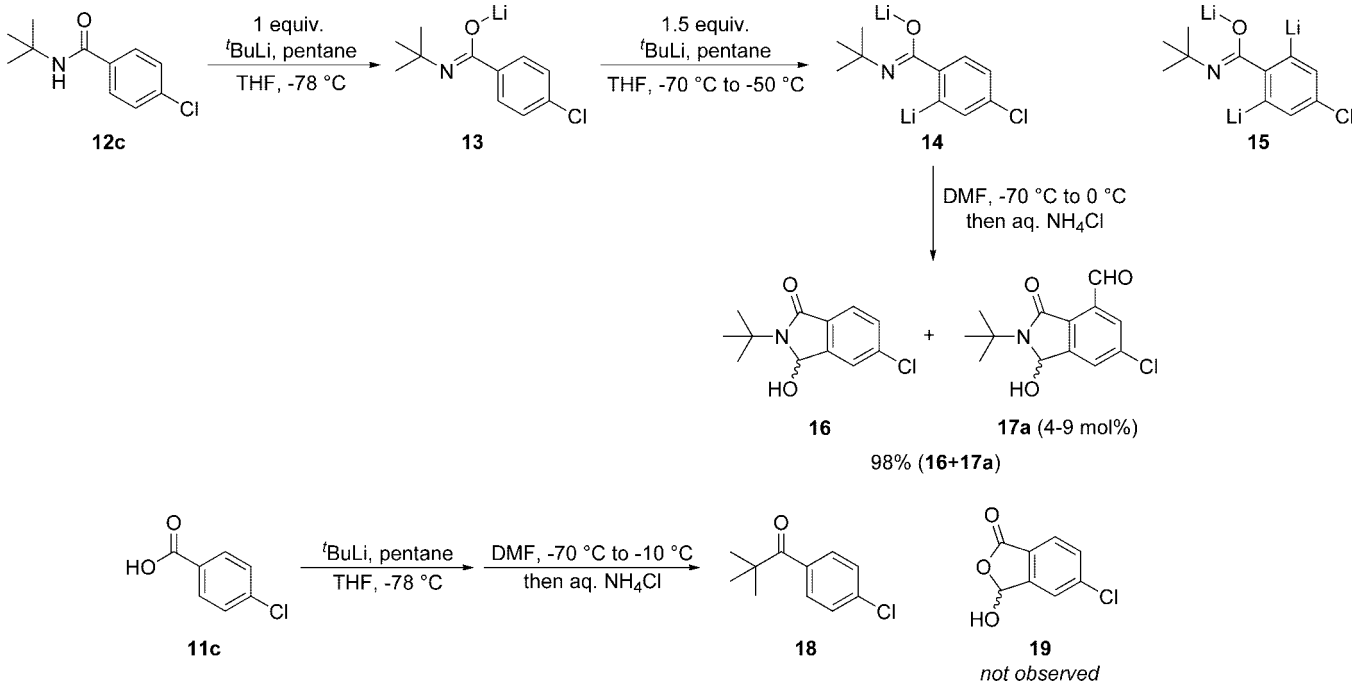
Initial attempts to effect deprotonation of **12a** using lithium diisopropylamide (3 equiv of LDA, THF/heptane/PhEt, −50 °C to rt) were unsuccessful. After quenching with iodine or *N,N*-dimethylformamide to trap the lithiated species **II**, no iodinated or formylated products were detected, and nearly 100% of starting material was recovered. The more acidic analogue **12b** was similarly unreactive (2.5 equiv of LDA, THF/heptane/PhEt, −75 °C, 1 h).[13,14] Due to the inability of a lithium amide base to generate the lithiated species **II**, more basic organolithium reagents were investigated. Since *p*-bromobenzamide **12a** was expected to undergo a competitive halogen−lithium exchange[15] and *p*-nitrobenzamide **12b** was found to give multiple products under D*o*M conditions (2.5 equiv of ^{t}BuLi, THF/pentane, −78 °C, 15 min), D*o*M studies on *p*-chlorobenzamide **12c** were carried out. Benzamide **12c** was successfully *ortho*-lithiated using excess *tert*-butyllithium (2.5 equiv of ^{t}BuLi, THF/pentane, −78 °C, 1 h) followed by trapping with a formyl donor (DMF,

(13) These results confirm that kinetic basicity of LDA (as well as other lithium dialkylamides, e.g., LTMP) is insufficient for the directed *ortho*-metalation (DoM) reaction of aromatic carbocycles.[14]

(14) (a) Equilibrium pK_a values in DMSO: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456, and references cited therein. (b) Equilibrium pK_a values in water: Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; pp 329−331, and references cited therein.

(15) Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R.; Bonde, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 4431.

SCHEME 5. *ortho*-Formylation Using ^{t}BuLi Followed by DMF Quench



−70 to 0 °C, then aq NH_4Cl) to afford hydroxyisoindolinone **16** in excellent yield (89−94%). Formation of **16** was accompanied by a small amount (4−9 mol % by ^{1}H NMR) of a structurally related impurity, which was identified as the bis-formylated product **17a** (Scheme 5).

In an attempt to simplify the synthesis of the phthalazine precursor, 4-chlorobenzoic acid (**11c**) was submitted to the lithiation/formylation conditions (2.5 equiv of ^{t}BuLi, THF/pentane, −78 °C, 15 min, then DMF −70 to −10 °C, then aq NH_4Cl) with the expectation that lithium carboxylate would act as an *ortho*-directing group.[16] The desired 5-chloro-3-hydroxyisobenzofuran-1(3*H*)-one (**19**) was not formed, and the reaction provided (4-chlorophenyl)-*tert*-butylketone (**18**) via nucleophilic attack of *tert*-butyllithium on lithium 4-chlorobenzoate.

In a typical experiment, the alkyllithium solution was added to a precooled solution of **12c**, giving the lithium amidate **13** as a homogeneous solution. During the addition of the remainder of the alkyllithium solution, the reaction mixture gradually became heterogeneous, presumably a result of decreasing polarity of the reaction medium[17] and concomitant formation of lithiated species **14**. Due to the large amount of precipitates in the reaction, mechanical agitation was found to be necessary in these experiments. A number of issues were identified in the development of more scalable reaction conditions for the synthesis of **16**: the use of an undesirable lithiation reagent (^{t}BuLi), cryogenic temperatures (<−70 °C), and selectivity (**16** versus **17a**). A comparison of different lithium reagents (^{t}BuLi in pentane, ^{n}BuLi in hexanes, MeLi in diethoxymethane) (2.0−2.5 equiv) was thus initiated.[18,19] Use of *n*-butyllithium allowed for an increase in the deprotonation temperature to −22 °C. An impurity **17a** that was observed in minor amounts on a small scale (1.4 mol %) became more prominent (>5 mol %) upon scaleup (see below for further discussion).[20] Use of less basic methyllithium[21] in place of *n*-butyllithium mitigated this problem, led to clean formation of **14** (as judged by DMF-quenched aliquots), and gave the most favorable **16/17a** ratio (≤2.5 mol % of **17a**) after sequential addition of DMF (2.0 equiv) and aq NH_4Cl. Conversion of **12c** to **16** could be successfully performed at 0 °C without any significant side reactions, thereby obviating cryogenic conditions. Importantly, no significant increase in the impurity formation was observed upon increase in reaction scale. Based on its improved selectivity toward the formation of **16**,[22] thermal stability, and favorable mechanical properties of the reaction mixtures,[23] methyllithium was selected for further development of this *ortho*-lithiation/formylation process.

Considerable experimental effort was devoted to understanding the origin of the undesired bis-formylated product **17a** in order to suppress its formation. Two scenarios that could account for the impurity **17a** are possible: (i) via lithium *o*,*o*-dilithiobenzamidate **15**[24] (Scheme 5); (ii) via iterative lithiation/formylation during DMF quench. Apart from a correlation of alkyllithium strength and magnitude of **17a** detected after DMF quench, no

(16) (a) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419. (b) Nguyem, T.-H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765. (c) Yang, K.; Blackman, B.; Diederich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg, G. I. *J. Org. Chem.* **2003**, *68*, 10030. (d) Palmer, B. D.; Boyd, M.; Denny, W. A. *J. Org. Chem.* **1990**, *55*, 438.

(17) At the end of alkyllithium addition, the reaction medium consists of at 2/3 v/v THF and 1/3 v/v alkyllithium solvent (pentane, hexanes, or diethoxymethane).

(18) The molarity of the alkyllithium reagents was determined immediately prior each experiment using the 1,10-phenanthroline/menthol method: Ho-Shen, L.; Paquette, L. *Synth. Commun.* **1994**, *24*, 2503.

(19) For a more detailed summary of the experiments, see Table 1 in the Supporting Information.

(20) The extended time required to add DMF on a larger scale was a major factor contributing to increased amounts of **17a**, while use of unnecessarily strong base (^{t}BuLi or ^{n}BuLi versus MeLi) exacerbated the issue.

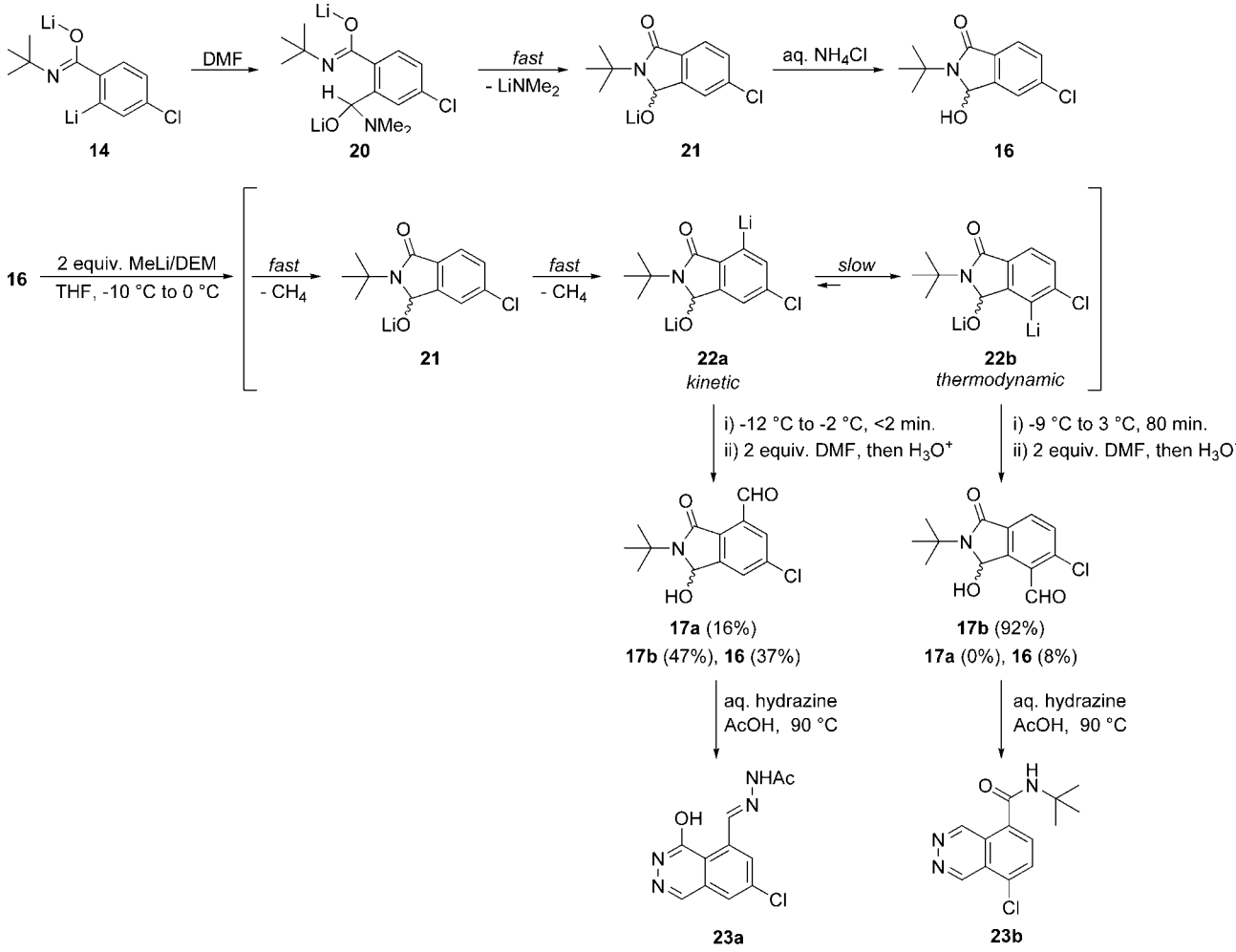
(21) Approximate pK_a of conjugate acids in water ^{t}BuLi (53), ^{n}BuLi (50), MeLi (48).[14b]

(22) Minimization of **17a** was desirable as it could not be readily cleared from **16**.

(23) The ability to agitate reaction mixtures by the end of the lithiation period. Reactions using *n*-butyllithium in hexanes or *n*-hexyllithium in hexanes tend to give thick gelatinous mixtures.

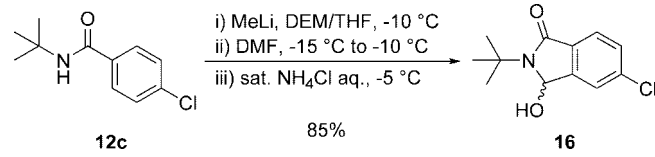
(24) A similar *o*,*o*-dilithioamide was postulated by: Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948.

SCHEME 6. Mechanism of the Formation of 17a



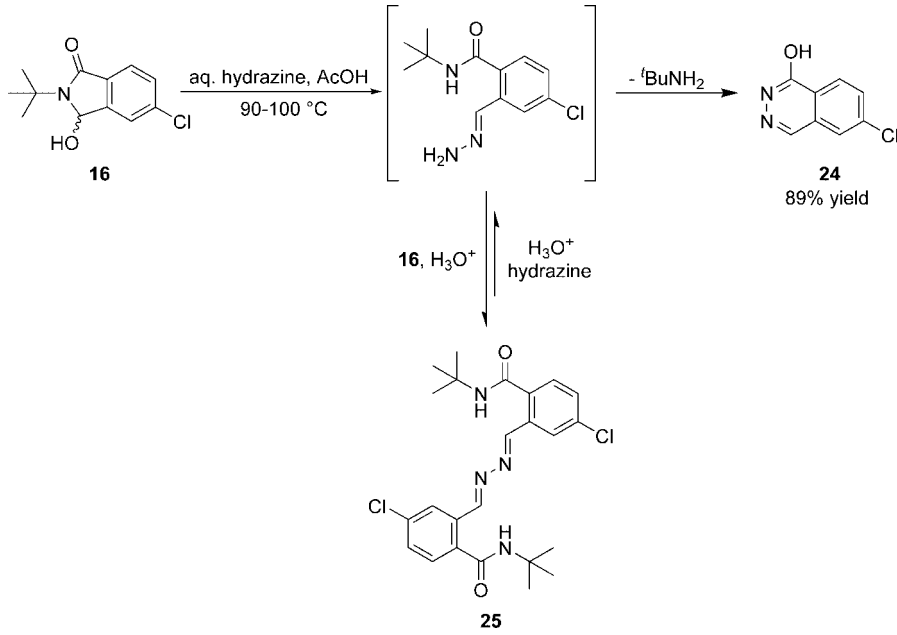
other evidence for the formation of **15** was found under all the conditions examined. In order to discount a mechanism involving intermediacy of **15**, addition of a large excess of base (2.5−3.0 equiv) along with deaggregating agents (TMEDA or HMPT) under varying reaction temperatures (−78 to 0 °C) was used. These conditions did not decrease the resulting **16/17a** ratio, but instead we found that the amount of **17a** was highly dependent on the mode of the DMF quench. Normal quench with 2−3 equiv of DMF always led to varying amounts of **17a** (≤20%); however, no **17a** was detected during inverse quench of a reaction mixture aliquot into excess DMF in THF. On the basis of this observation, a subsequent deprotonation during the DMF quench to **16** seems likely (iterative lithiation/formylation mechanism). Lithium dimethylamide (a byproduct of the reaction of **14** with DMF) or residual methyllithium could be responsible for the deprotonation of a fraction of one of the short-lived intermediates (**20** or **21**), leading consequently to **17a**. Considering that lithium amides are not sufficiently basic to deprotonate arenes—LDA failed to react with **12a** or **12b** (vide supra)—it seems more plausible that residual methyllithium is the culprit. In a set of control experiments, **16** was allowed to react with MeLi (2 equiv), and this was followed by a DMF quench. The product distribution was highly dependent on the extent of the lithiation period. Two regioisomeric aldehydes **17a/17b** (1:3 by LC) were produced as a result of DMF quench immediately after MeLi addition (<2 min with MeLi). On the other hand, prolonged incubation (DMF quench 1.5 h after MeLi addition) afforded aldehyde **17b** cleanly. Both aldehydes readily ring-expanded in the presence of hydrazine hydrate to give phthalazines **23a** and **23b**, respectively. The lithiation experiments clearly indicate that fast kinetic deprotonation leading to **22a**[25] was followed by a relatively slow equilibration to thermodynamically favored **22b** (Scheme 6). On the basis of these results, formation of the undesired side product **17a** using the previously described *ortho*-lithiation/formylation protocol can be explained as follows: In the presence of sufficient excess of alkyllithium (≥2 equiv), amide **12** undergoes conversion to **14** with some of the unreacted alkyllithium remaining. During DMF quench, aryllithium **14** reacts with DMF to produce transient species **20**, that rapidly collapses to form **21**. The relative amount of **21** and DMF present in the reaction mixture during the normal quench makes **21** statistically more accessible to secondary reaction with any residual alkyllithium leading to **22a**. The kinetic nature of this process is consistent

SCHEME 7. Optimized *ortho*-Formylation of 12c

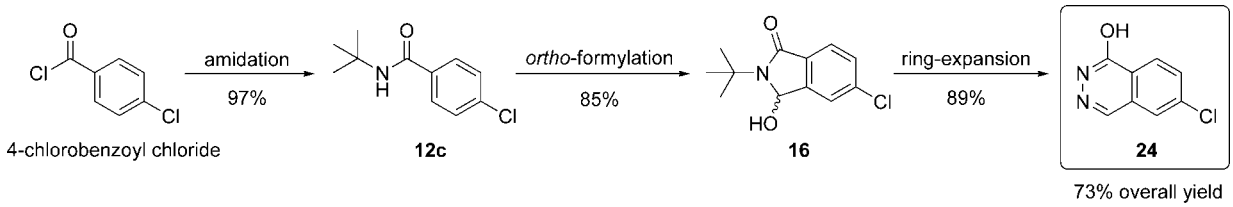


(25) An aromatic ring in a related unsubstituted isoindolone was lithiated at the position adjacent to the amide carbonyl (cf. ref 8b, pp 29 and 30).

SCHEME 8. 6-Chlorophthalazin-1-ol (24) via Ring Expansion of Hydroxyisoinolinone 16 Using Hydrazine



SCHEME 9. An Efficient Three-Step Process to 6-Chlorophthalazin-1-ol (24)



with absence of aldehyde **17b**, as only **17a** is found in crude or isolated samples of **16**.

Following the optimized *ortho*-formylation protocol, amide **12c** in THF (8 vol) was deprotonated using ~3 M MeLi in diethoxymethane (2.05 equiv) at ≤−10 °C over ≥3 h, followed by a normal quench with DMF (2.0 equiv) at −15 to −10 °C and then a final neutralization using satd aq NH_4Cl at ≤−5 °C to afford hydroxyisoindolinone **16** (98.5% LC purity) in 85% yield (Scheme 7). Under these conditions, formation of the undesired product **17a** was minimized (typically 0.7−0.9% **17a** by LC in crude reaction mixtures). Since the byproduct is efficiently rejected in the next reaction step, there was no need to implement the more complicated inverse quench procedure for the scale-up of this reaction.

Hydroxyisoindolinone **16** readily reacted with a stoichiometric amount of hydrazine hydrate (65 wt %, 1.05 equiv) in acetic acid at elevated temperatures (>50 °C) to produce 6-chlorophthalazin-1-ol (**24**). In order to minimize an accumulation of hydrazine in the reaction mixture,[26] hydrazine hydrate was added dropwise to a slurry of **16** in acetic acid at 100 °C. No starting material **16** was detected, and no intermediates were observed upon completion of the addition of hydrazine hydrate over 10 min, indicating that the reaction is at least as fast as the addition. When the reaction was performed at lower temperatures (≪90 °C), the bis-hydrazone intermediate **25** was observed at significant concentrations by LC/MS (Scheme 8). Under optimized conditions, the reaction was conducted at 90−93 °C using 1.05 equiv of hydrazine hydrate. The ring-expanded product **24** was isolated via direct filtration from the reaction mixture in high yield (89%) due to its low solubility in acetic acid and most organic solvents (<5 mg/mL). The starting material impurity **17a** was converted into *N*-acetylhydrazone **23a** (Scheme 6) under the reaction conditions and was efficiently rejected in the mother liquors.[27]

In summary, this work resulted in the development of an efficient process for the preparation of the 6-chlorophthalazin-1-ol (**24**) building block from commercially available 4-chlorobenzoyl chloride in a three-step sequence in an overall yield of 73%, which could be carried out on multikilogram scale (Scheme 9).

Development of 3-Borono-4-methylbenzoic Acid Building Block. The first-generation route to the *N*-cyclopropyl-4-methylbenzamide tail piece **10** of drug candidate **1** was deemed not economically viable due to the high cost of bis(pinacolato)diboron used in the palladium-catalyzed carbon−boron bond formation step (Scheme 1). Substitution of the diboron reagent with the less expensive pinocolborane following the literature protocol (dioxane, Et_3N, cat. $Pd(dppf)Cl_2$)[28] led to a sluggish reaction with only 66% conversion to **10** along with formation of the reduction product (5% of des-iodo-**9**).

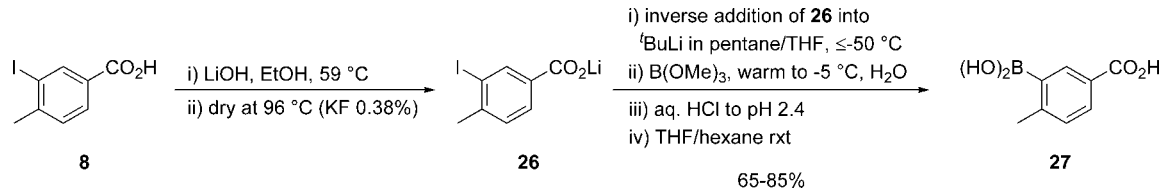
We decided to pursue the preparation of the corresponding arylboronic acid **27** (Scheme 2), which seemed more attractive than pinacol ester **10** for a number of reasons: (i) the amide

(26) Accumulation of hydrazine is a safety hazard on scale.

(27) 2.5% of **17a** by LC in the starting hydroxyindolinone **16** led to an acceptable <0.5% of **23a** by LC in isolated 6-chlorophthalazin-1-ol (**24**).

(28) Cameron, K. S.; Pincock, A. L.; Pincock, J. A.; Thompson, A. *J. Org. Chem.* **2004**, *69*, 4954.

SCHEME 10. Lithium-Based Synthesis of Boronic Acid 27

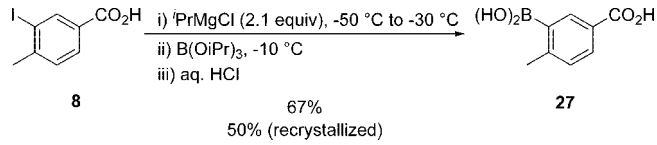


bond can be constructed late in the sequence, i.e., after the palladium-catalyzed cross-coupling, affording additional control point and facilitating palladium removal,[29] and (ii) arylboronic acid **27** should be readily available from 3-iodo-4-methylbenzoic acid (**8**) in a short sequence involving halogen−metal exchange followed by quench with alkylborate[30] and hydrolysis.

In order to circumvent a net reduction of the aryl iodide **8** during the iodine−lithium exchange, masking of the acidic carboxylic function was necessary.[31] This could be achieved by formation of the anhydrous lithium carboxylate **26**[32] that could be conveniently converted into crystalline boronic acid **27** in 50−70% yield using a one-pot protocol (1.1−1.2 equiv of ^{n}BuLi in hexanes, THF, −78 °C; then $B(OMe)_3$, −78 to 0 °C; then aq HCl 0 °C to rt). Performing the reaction at less cryogenic conditions (−50 °C) led to incomplete conversion of **26** and extensive formation of multiple *n*-butylated side products arising from both nucleophilic attack of ^{n}BuLi on carboxylate carbonyl and Wurtz-type reactions between intermediate aryllithium and *n*-butyl iodide.

Using *tert*-butyllithium (2.1 equiv) instead of *n*-butyllithium (1.1 equiv) allowed for a clean iodine−lithium exchange at −50 to −55 °C with no butylated side products observed.[33] However, the amount of *p*-toluic acid formed under these conditions was increased. We speculated that the generated aryllithium intermediate competes with *tert*-butyllithium for *tert*-butyl iodide and, indeed, found that this side reaction could be effectively minimized by inverse addition of a precooled solution of lithium 3-iodo-4-methylbenzoate (**26**) in THF into a solution of *tert*-butyllithium in pentane/THF[34] keeping the internal temperature at or below −50 °C. Thus generated, the aryllithium was quenched with trimethyl borate (−50 to −5 °C) followed by hydrolysis via addition of water (−5 °C to rt). Under these basic aqueous conditions, the intermediate boronic ester was rapidly hydrolyzed into the water-soluble lithium salt of **27**. Aqueous workup, followed by pH adjustment using aq HCl, led to crude **27**, and then recrystallization from THF/hexanes afforded boronic acid **27** in 65−85% overall yield (96.2−99.3% LC purity) starting from aryl iodide **8** (Scheme 10). Significantly, we found that the hydrocarbon content in the reaction mixture must be kept relatively low (initially at most 0.9:1.0 v/v) for a successful halogen−lithium exchange to occur and that if the pentane fraction deviated slightly upward from this ratio (e.g., due to lower than expected titer of commercial 1.7 M ^{t}BuLi in pentane), the halogen−lithium exchange reaction was significantly hindered. This gave rise to some reproducibility issues,[35] such that an alternative alkylmagnesium-based sequence for the synthesis of boronic acid **27** was sought.

SCHEME 11. Magnesium-Based Synthesis of Boronic Acid 27



In our previous work, we found that the direct reaction of **8** with organolithiums had led to deiodination, due to the comparable rates of deprotonation and iodine−lithium exchange.[36] In stark contrast, treatment of **8** with 1 equiv of isopropylmagnesium chloride at −50 °C lead to a relatively clean deprotonation of the carboxylic acid that is accompanied by less than 10% reduction to *p*-toluic acid (**29**). The addition of a second equivalent of isopropylmagnesium chloride to this mixture resulted in iodine−magnesium exchange.[37] The arylmagnesium species thus formed was then quenched with triisopropylborate, and then the resulting borate complexes were hydrolyzed with aq hydrochloric acid. The resulting boronic acid was isolated by crystallization from THF/heptane (67%). The reduction to *p*-toluic acid (10%) and the formation of bisarylboronic acid (up to 15%) are two side reactions that explain the relatively low yield of this sequence. Recrystallization from THF/heptane was used to further upgrade the purity of this compound. Overall, this one-pot protocol offers a clear advantage over the two-step protocol involving intermediate isolation of the lithium salt.[38]

Development of the First-Generation Suzuki Coupling. The Suzuki reaction coupled a boronate ester and an aryl bromide for construction of the key aryl−aryl bond. The synthesis of the phthalazinol building block described above allowed access to the corresponding aryl chloride, thereby making this palladium-catalyzed coupling more challenging. Initial conditions used to carry out the Suzuki coupling between **24** and **27** (1 mol % of $Pd_2(dba)_3$, 5 mol % of ligand, 5 equiv

(29) Use of transition-metal catalysts in the final step of the synthetic sequence can be complicated by issues related to removal of metal residues. For a reference, see: Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.

(30) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997.

(31) Halogen−lithium exchange occurs at competitive rates to deprotonation; see: Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R.; Bonde, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 4431.

(32) Two protocols could be used: (1) **8**, LiOH (1.0 equiv), EtOH, followed by solvent removal and oven drying, affording anhydrous solid lithium carboxylate **26**; (2) **8**, LiOH (1.0 equiv), 3 Å molecular sieves, THF, followed by filtration, affording anhydrous THF solution of lithium carboxylate **26**.

(33) *tert*-Butyl iodide rapidly reacts with excess *tert*-butyllithium to form isobutylene, isobutane, and lithium iodide.

(34) A freshly titrated commercial 1.7 M ^{t}BuLi in pentane (2.1 equiv, 4.6 vol relative to **26**) was diluted by addition into anhydrous THF (5.0−7.8 vol per **26**) resulting in ca. 0.64−0.81 M ^{t}BuLi in pentane/THF (0.9:1.0 to 0.6:1.0 v/v).

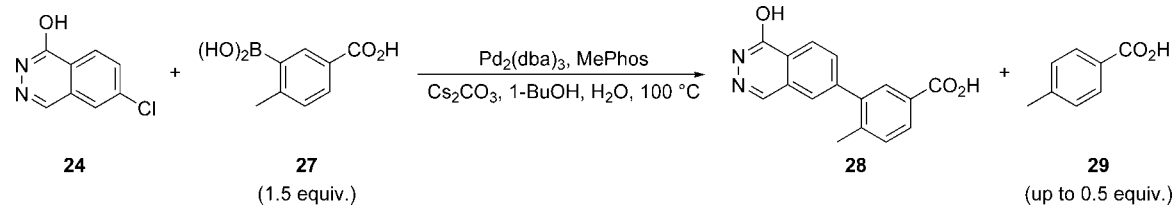
(35) Likely due to impeded deaggregation of ^{t}BuLi and decreased solubility of **26** in pentane-rich pentane/THF mixtures.

(36) (a) Only limited examples of in situ deprotonation of a carboxylic acid followed by halogen−metal exchange with another reagent have been reported. Deprotonation with dibutylmagnesium: Kato, S.; Nonoyama, N.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2002**, *43*, 7315. (b) Deprotonation with methylmagnesium bromide: Kopp, F.; Wunderlich, S.; Knochel, P. *Chem. Commun.* **2007**, 2075. (c) One isolated example of using ^{n}BuLi for both deprotonation and halogen−metal exchange has been reported for a sterically hindered benzoic acid. Wang, Q.; Qu, D.; Ren, J.; Chen, K.; Tian, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2661.

(37) For a comprehensive review about the preparation of organomagnesium reagents, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

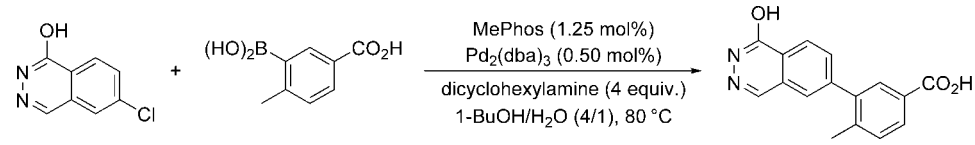
(38) Exploration of the scope of this method for the synthesis of other boronic acid with free carboxylic acid groups is currently ongoing and will be reported in due course.

SCHEME 12. Initial Suzuki Coupling Conditions Leading to 28



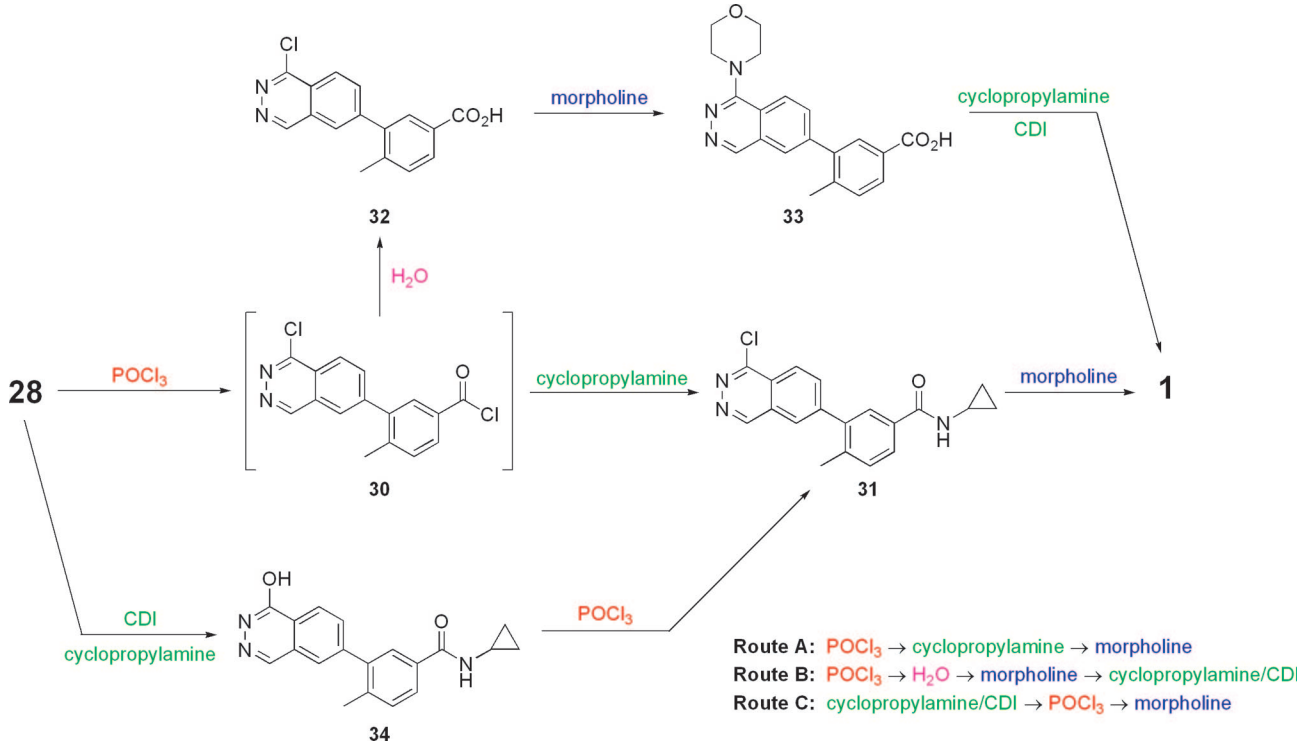
24 **27** (1.5 equiv.) **28** **29** (up to 0.5 equiv.)

SCHEME 13. Optimized Suzuki Coupling of 24 and 27



24 **27** (1.1 equiv.) 86-91% (0.5-10 mol% **29**) **28**

SCHEME 14. Proposed Routes from 28 to Drug Candidate 1



of Cs_2CO_3, 1-BuOH, water, 100 °C) were found by screening several ligands (*N*-heterocyclic carbene ligands, biphenyldialkylphosphines). Buchwald's biphenyl ligands containing a dicyclohexylphosphino- (Cy_2P-) moiety were found to be particularly effective, and structurally the simplest competent monodentate ligand, 2′-methyl(dicyclohexylphosphino)biphenyl (MePhos), was selected for the initial development.[39,40] Protodeboronation of **27** leading to **29** was found to be a major side reaction necessitating use of a significant excess (1.5 equiv) of the boronic acid in order to reach complete conversion of the aryl chloride **24**. As a result, approximately 50 mol % of *p*-toluic acid (**29**) (Scheme 12) was contained in the crude reaction mixture.

The inability to clear the *p*-toluic acid side product (up to 10 mol % in the isolated product) combined with the large excess of valuable boronic acid **27** required identification of Suzuki coupling conditions which would eliminate or at least minimize protodeboronation. The protodeboronation of **27** proceeds even in the absence of palladium catalyst. The rate of this process correlates with base strength in the following approximate order: $K_2CO_3 > K_3PO_4 > KOAc \gg$ alkylamines. Thus, using dicyclohexylamine in the Suzuki coupling of **24** and **27** (1.1 equiv) led to clean formation of **28** with significantly less *p*-toluic acid (up to 10 mol %).[41] Inferior results were obtained with structurally related diisopropylamine (poor conversion/impurity profile) or some other mild organic (TEA, poor conversion/impurity profile) or inorganic bases (KOAc, 50% conversion).

(39) Respective $^tBu_2P$-analogues of these ligands were not effective.

(40) 2-Dicyclohexylphosphinobiphenyl ligands in Suzuki coupling reactions: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(41) A related recent application of dicyclohexylamine to minimize protodeboronation in a Suzuki reaction: (a) Payack, J. F.; Vazquez, E.; Matty, L.; Kress, M. H.; McNamara, J. *J. Org. Chem.* **2005**, *70*, 175.

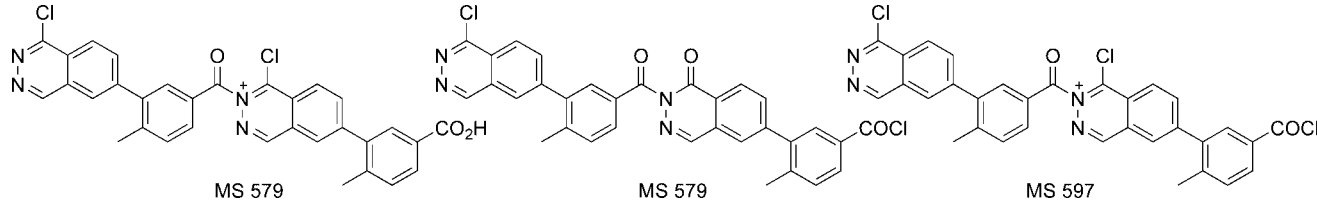
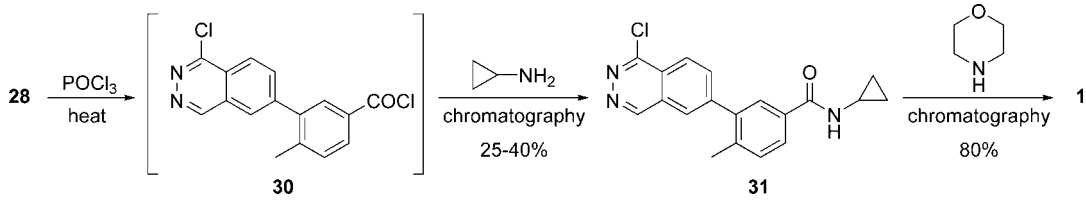
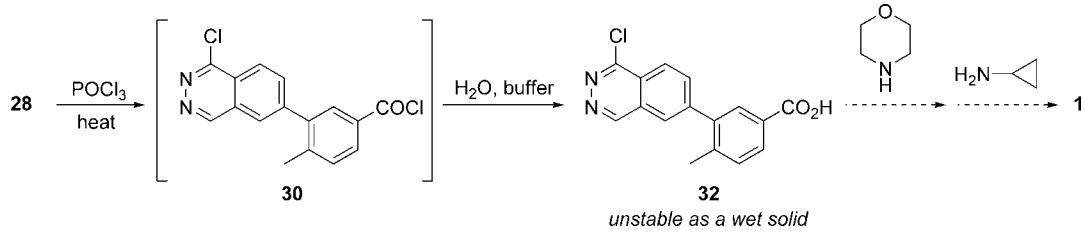


FIGURE 1. Proposed structures of chlorination impurities MS 579 and MS 597 (Route A).

SCHEME 15. Preparation of 1 (Route A)



SCHEME 16. Unsuccessful Isolation of Hydrolytically Labile Chloro Acid 32 (Route B)



Use of an excess of dicyclohexylamine (4 equiv)[42] was critical for a smooth and fast coupling reaction. The reaction conditions were subsequently optimized: **24**, **27** (1.1 equiv), $Pd_2(dba)_3$ (0.50 mol %), MePhos (1.25 mol %), Cy_2NH (4 equiv), 1-butanol/water (4/1 v/v, 7.0 vol) at 80 °C. Complete conversion of **24** (<1% by LC) was typically observed after 17−20 h with most or all of the residual **27** (initially 10 mol % excess) converted into **29** (0.5−10 mol %). The crude product was extracted into aqueous 5 N NaOH (6 equiv), washed with MTBE (2.5 vol), and precipitated using aq HCl to afford **28** (86−91% isolated yield) (Scheme 13). Modest rejection of *p*-toluic acid was observed during workup and isolation, and it remained the major impurity (up to 10 mol %). In addition, the product that was isolated using this procedure was significantly colored and contained relatively high levels of residual Pd (approximately 500 ppm).

Development of the First-Generation End-Game. Three routes toward **1** starting from intermediate **28** can be envisaged (Scheme 14):

Route A was conceptually and practically the earliest approach which was successfully used to prepare multiple lots of **1**. It consists of two steps: (i) exhaustive chlorodehydroxylation and acid chloride formation followed by a cyclopropylamine quench to establish both cyclopropylamide and 1-chlorophthalazine functionality and (ii) aromatic nucleophilic substitution in the phthalazine ring using morpholine to afford **1**. Reaction of **28** with $POCl_3$ leads to the formation of the desired acid chloride/1-chlorophthalazine intermediate **30**, but it is accompanied by dimeric species (Figure 1) and other largely unidentified oligomeric side products. The presence of multiple electrophilic and nucleophilic moieties in the intermediate makes control over competitive reaction rates challenging.

Quenching of the reaction mixture with cyclopropylamine followed by aqueous workup and chromatographic isolation from a complex mixture afforded **31** in 25−40% yield, and then reaction of **31** with morpholine afforded **1** in 80% yield after chromatography (Scheme 15). Several attempts to improve assay yields of **31** beyond the initially observed range by modifying reaction parameters such as amount of $POCl_3$, reaction solvent, temperature, or inverse or normal quench failed. The overall yield of this sequence was not satisfactory (20−32%), and combined with the need for chromatographic purification of both **31** and the final product **1**, it was deemed a nonpractical route.

Route B takes advantage of a selective hydrolysis of the more reactive acid chloride in intermediate **30**, thereby theoretically allowing for an additional isolation and control point at the stage of intermediate **32**. However, in practice, isolation of the chloro acid **32** was difficult. The material was sensitive to aqueous acid[43] or aqueous base,[44] and the neutralized wet solid of **32** was found to rapidly degrade at room temperature (Scheme 16). The same persistent impurities MS 579 and MS 597 were obtained in the formation of **32** as were identified in route A (Figure 1). For these reasons, a demonstration of the downstream chemistry was not pursued.

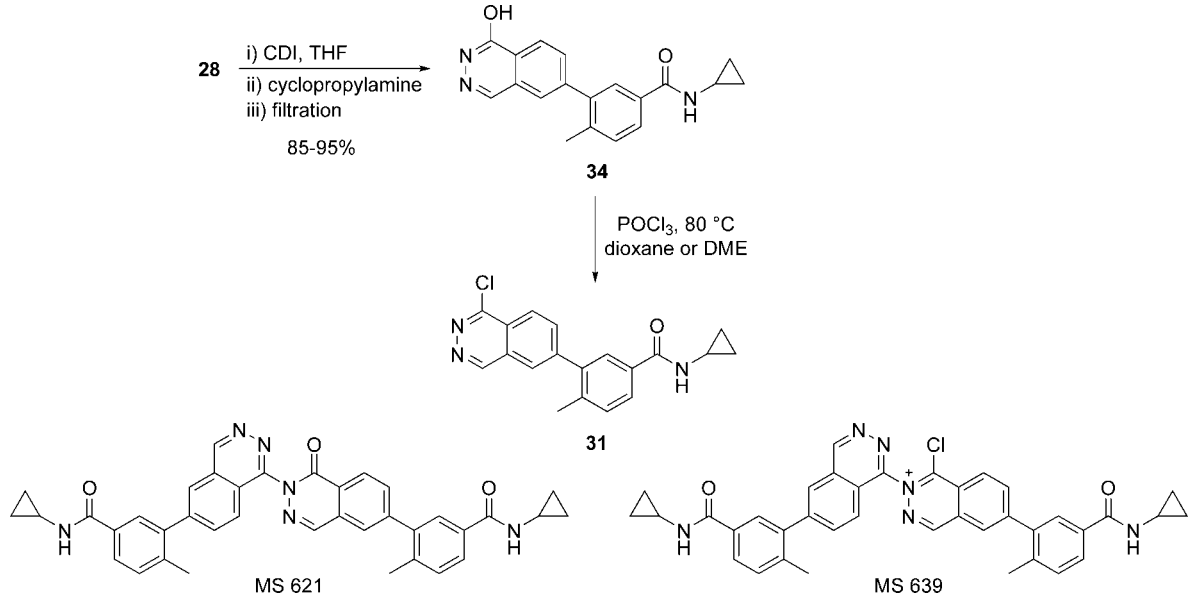
Route C (Scheme 14), in which the order of steps is reversed as compared to route A and B, was the final attempt to utilize the hydroxy acid **28** for synthesis of **1**. Thus, carbonyldiimidazole promoted the formation of the cyclopropylamide **34** in 85−95% yield. The subsequent chlorodehydroxylation in dioxane or 1,2-dimethoxyethane produced the desired chloroamide **31** as a major product; however, dimeric side products MS 639 and MS 621 were also formed in substantial quantities (Scheme 17). Moreover, mixtures of **31** and these impurities were found to be prone to further oligomerization. Transformation of the

(42) 3 equiv of Cy_2NH was sufficient for a complete conversion at the expense of extended reaction time.

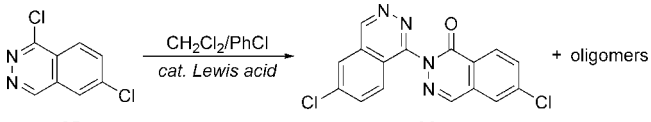
(43) Rapid hydrolysis back to **28** and oligomerization to MS 579, MS 597, and higher molecular weight products.

(44) Typically, 1-chlorophthalazines are fairly inert to aqueous base due to their limited solubility. Chlorophthalazine acid **32** carboxylate salt is water soluble, which can explain its unusual hydrolytic lability.

SCHEME 17. Proposed Structure of Dimeric Side Products MS 621 and MS 639 (Route C)



SCHEME 18. Dimerization of 1,6-Dichlorophthalazine (35)



hydroxyl function of **34** into a suitable leaving group using sulfonyl chlorides (TsCl, MsCl) was also unsuccessful.

While Route A was able to deliver material for initial biological testing, it was insufficient for further scale-up. The limited success with the first-generation approach helped us recognize that the functionalization of advanced intermediate **28** would be impractical and led us to focus on earlier functionalization of building block **24**, leading to a revision of the synthetic plan (Scheme 2).

Development of the Second-Generation Process Synthesis. The original transformation of 6-bromophthalazin-1-ol (**5**) to 1-chloro-6-bromopthhalazine (**6**) was performed in neat phosphorus oxychloride (>10 equiv) with diisopropylethylamine (1 equiv)[45] at reflux. Removal of excess $POCl_3$ followed by aqueous workup and chromatography afforded **6** in a good yield (Scheme 1). The above protocol was successfully applied to 1-chlorophthalazin-1-ol (**24**); however, the large excess of reactive $POCl_3$ as well as the need for a chromatographic purification were identified as potential development areas. A brief screen of reaction conditions demonstrated that the transformation of **24** to **35** may be carried out at a reasonable rate with only 2.0 equiv of $POCl_3$ and in the absence of a tertiary amine additive using any number of cosolvents (MeCN, DME, DCE, 1,4-dioxane, 84−93% conversion after 2.5 h).[46] After 3−5 h at 80 °C, the heterogeneous reaction mixtures were quenched with ice−water, and in the case of water-miscible solvents (MeCN, DME, and dioxane), the resulting solids were isolated by filtration (42−71% yield). Unfortunately, the wet solids isolated from the water-miscible solvents generally hydrolyzed back to **24** to some extent upon drying at room temperature. Alternatively, application of water-immiscible 1,2-dichloroethane (DCE) as cosolvent provided 1,6-dichlorophthalazine (**35**) in 85% yield after phase-cut and solvent evaporation, and we found that a solution of **35** in DCE was relatively stable[47] to dilute aqueous HCl even at 70 °C. Thus, a workup that would include extraction of the product into an organic solvent was preferable for further development of this chlorodehydroxylation reaction. Several potential solvents[48] were considered on the basis of their water immiscibility, boiling point, compatibility with $POCl_3$, product solubility, and ICH solvent limit. Eventually, the selection was narrowed down to toluene or chlorobenzene, both of which facilitated complete conversion of the reaction within 3−5 h at 90 °C. Formation of a viscous material was observed in toluene, whereas the reaction mixture in chlorobenzene remained a stirable suspension making it the solvent of choice for further development. The reaction in chlorobenzene (5.0 vol) proceeded to completion with as little as 1.5 equiv of $POCl_3$, but since the reaction rate was found to be sensitive to particle size of **24**,[49] 2.0 equiv of $POCl_3$ was used to ensure consistent conversion (≤1.0% **24** by LC). Controlled addition of 2.5 N NaOH aq (20 vol) was used to quench excess $POCl_3$ (≤5 °C). Dilution of the mixture with dichloromethane (10 vol.) during NaOH quench was found to be important to keep **35** in the organic layer.[50] Isolation of crude **35** (>96.6% by LC) was performed by either removal of the organic solvent,[51] or crystallization was induced *via* addition of heptane to the CH_2Cl_2/chlorobenzene solution (>99% by LC, approximately 80% overall yield). Occasionally, solutions of

(45) Addition of a tertiary amine provides a source of "soluble chlorides" increasing the overall reaction rate, see: (a) VanSickle, A. P.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 895.

(46) No conversion observed in 2-methyltetrahydrofuran or chloroform. MeCN = acetonitrile, DME = 1,2-dimethoxyethane, DCE = 1,2-dichloroethane.

(47) At least for a brief period of time (e.g., 10 min).

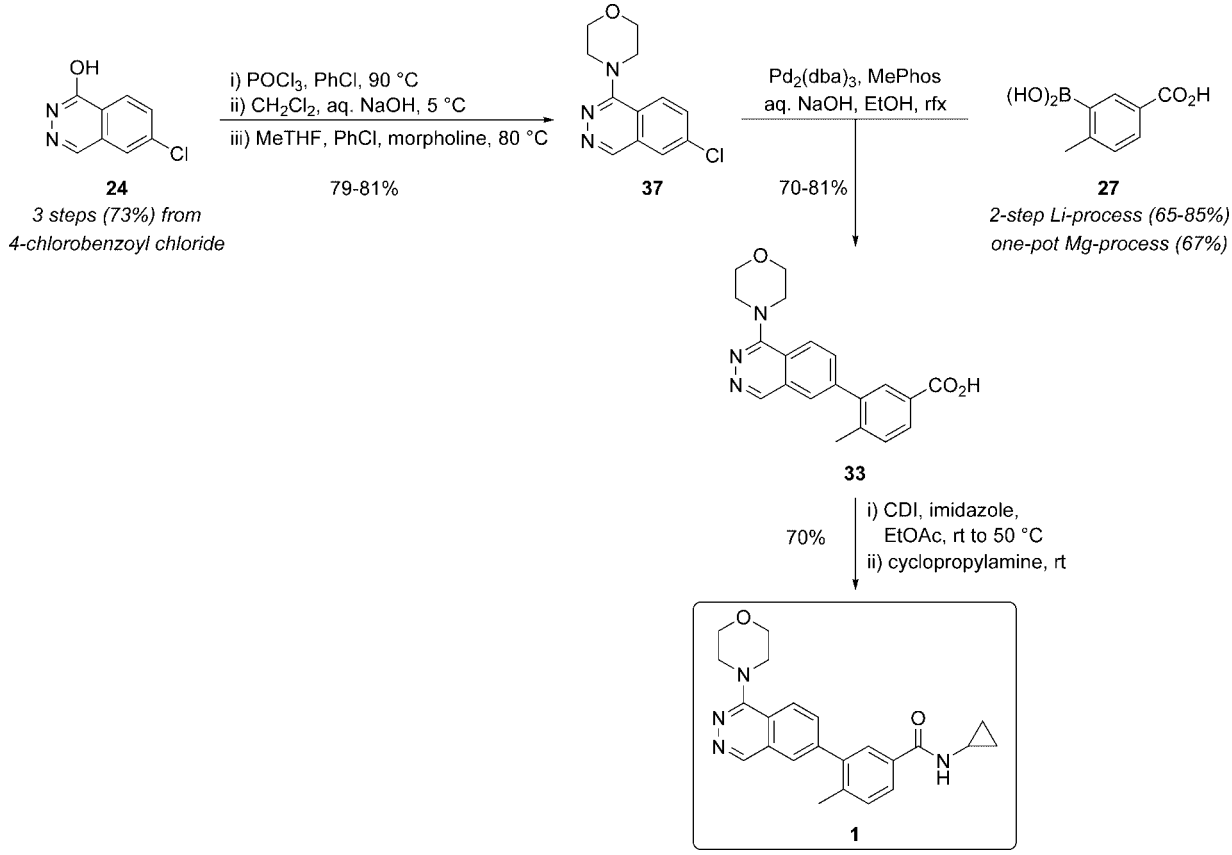
(48) 1,2-Dichlorethane (DCE), toluene, chlorobenzene, anisole. (a) Reaction temperature of approx. 80 °C was required for conversion. (b) anisole was found to undergo significant demethylation under $POCl_3$ reaction conditions. (c) good solubility was required for a phase-split after an aqueous quench. (d) DCE was eliminated due to a low ICH guideline limit (5 ppm).

(49) **24** is sparingly soluble in most organic solvents (<5 mg/mL).

(50) **35** is not sufficiently soluble in pure chlorobenzene at room temperature (0.05 g/mL).

(51) Remaining chlorobenzene (approximately 10 wt %) was readily tolerated in the subsequent step.

SCHEME 19. Second-Generation Process Synthesis of Drug Candidate 1



crude **35** in CH_2Cl_2/chlorobenzene developed a highly colored (orange-red) insoluble precipitate which consisted of a complex mixture of oligo- and polymeric products, the dimer **36** with MS 343 was identified as a major component of the complex mixture (Scheme 18).[52]

The stability of **35** was therefore investigated under a broad range of conditions. Addition of an aqueous acid or an aqueous base to a solution of **35** in CH_2Cl_2/PhCl had no effect.[53] Similarly, presence of air or visible light would not trigger the decomposition. Aliquots of a solution of **35** could be aged under most any given conditions (acid, base, light, air, etc.) for *multiple days* without any apparent change, however, the product would typically rapidly decompose soon after the first sampling.[54] Eventually, this key observation led to a hypothesis of a Lewis acid[55] triggered decomposition. Indeed, rapid decomposition of **35** with concomitant formation of an orange-red precipitate was observed in the presence of Lewis acids such $SbCl_5$ (solution in CH_2Cl_2) or $MgCl_2$ (solid).

These stability issues encountered with compound **35** led us to develop the chlorodehydroxylation and S_NAr amination step into a through-process. Thus, 1,6-dichlorophthalazine (**35**) solution in CH_2Cl_2/PhCl was prepared and partially concentrated to remove volatile CH_2Cl_2. After dilution of the resulting chlorobenzene solution with 2-methyl-THF, the 1,6-dichlorophthalazine (**35**) was treated with morpholine (4 equiv) at 80 °C to produce **37**, which was isolated in 79−81% overall yield (100% by LC) by filtration[56] (Scheme 19).

The Suzuki reaction of **37** and **27** using conditions similar to the ones developed earlier (0.50 mol % of $Pd_2(dba)_3$, 2.0 mol % of MePhos, 2 equiv of K_2CO_3, 1-butanol, water, 100 °C) provided a clean coupling reaction to afford **33**. Compared to the previous substrate combination, far less protodeboronation of boronic acid **27** was observed, even in the presence of an inorganic base, and complete conversion of **37** could be obtained with only 1.1 equiv of boronic acid.[57] Although **33** could be cleanly produced in 1-butanol/water mixture, product isolation from this solvent system was problematic. Addition of acid to the postreaction mixture led to extensive foaming due to CO_2 evolution from the carbonate base and did not lead to precipitation of the product. Extractive workups of the acidified mixtures afforded crude **33** with poor recovery and purity. 1-Butanol was identified as a major factor complicating product isolation, causing biphasic mixtures with water in which the zwitterion **33** would partition in a pH-dependent manner. In order to solve these isolation issues, a screen for alternative Suzuki conditions was initiated. Water-miscible alcoholic solvents (ethanol, 1-propanol) with a number of bases (Na_2CO_3, K_2CO_3, NaOH, dicyclohexylamine) were compared. Clean conversion[58] was observed in most cases at 80 °C, however, the EtOH/NaOH combination was particularly attractive, as the reaction mixture could be concentrated by vacuum distillation and then pH

(52) Similar dimerization of 1-chlorophthalazine in the presence of Brønsted acid has been described: Badger, G. M.; McCarthy, I. J.; Rodda, H. J. *Chem. Ind.* **1954**, 964.

(53) This was presumably due to immiscibility and the resulting poor phase transfer.

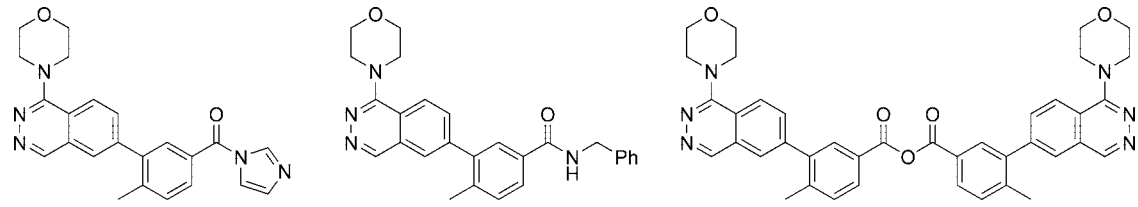
(54) Samples were pulled using Hamilton microsyringes equipped with a steel needle.

(55) A steel needle used during sampling was a source of Lewis acid.

(56) Water was added to solubilize the morpholine hydrochloride byproduct.

(57) The potency of the boronic acid was determined by quantitative ^1H NMR using maleic acid as internal standard.

(58) Crude LC purity: 84−89% **33** (NaOH), 93% **33** (Na_2CO_3 or K_2CO_3).



38 39 40

FIGURE 2. Acylimidazolide, Benzylamide, and Anhydride.

adjusted using aq HCl to give crystalline **33**. Additional advantages of using NaOH were shorter reaction time and no foaming during acidification. Eventually, the Pd/L ratio was increased to 1.00:1.25[59] to improve catalyst reactivity, which allowed lowering of the palladium loading to 0.50 mol %. The EtOH to caustic ratio was conserved at 4:1 (v/v) as reducing the amount of caustic gave sluggish reactions, while more dilute base led to increase in the relative rate of protodeboronation. At least 3 equiv of NaOH was required for a smooth reaction (with 2.0 equiv, reaction stalled at 80% conversion). The reaction proceeded at temperatures as low as 65 °C, but at the expense of reaction rate. Prolonged heating of the reaction mixture led primarily to an increased hydrolytic cleavage of the morpholine moiety from both **33** and **37**, which contributed to an increased level of **28**. Most of this side product was cleared to the mother liquors during isolation, along with other process impurities such as **29** and des-chloro-**37**. During early development of this reaction it was noted that addition of THF before final pH adjustment had a beneficial effect on the crystallinity of **33**. Moreover, a large fraction of the residual palladium and other colored impurities were cleared by this cosolvent. After optimization, isolation of the product was performed by adjusting the crude aqueous THF solution to pH 3.4, at which point **33** was determined to be the least soluble.

In summary, the optimized Suzuki coupling protocol developed thus far was as follows, aryl chloride **37** was reacted with boronic acid **27** (1.15 equiv) in the presence of $Pd_2(dba)_3$ (0.25 mol %) and MePhos (0.63 mol %) in a mixture of 10 N NaOH aq (2 vol) and EtOH (8 vol) at reflux (78−80 °C, 2.5 h). Extraction of the crude product into the aqueous layer was followed by dilution with THF, pH adjustment using aq HCl (pH 3.4) and filtration to afford advanced intermediate **33** in 70−81% yield (97.7−98.9% by LC). This proved to be a scaleable process that could be carried out efficiently on >2 kg scale (Scheme 19).

The introduction of the cyclopropylamide moiety was the last remaining challenge for the completion of the synthesis of **1**. Initial attempts at activation of **33** as the acid chloride using oxalyl chloride or thionyl chloride in a variety of solvents (THF, toluene, dichloromethane), followed by reaction with cyclopropylamine were unsuccessful. The acidic reaction conditions led to the formation of insoluble salts and complete conversion to **1** could not be achieved. In contrast, activation of **33** using 1,1-carbonyldiimidazole was successful. The neutral reaction conditions led to the clean formation of acylimidazolide **38**, which was hydrolytically unstable under the HPLC conditions (0.1% TFA in MeCN/water) and could not be monitored directly. The activation reaction could, however, be monitored by quenching an aliquot of the reaction mixture with an excess of benzylamine to the give benzylamide **39**, which was readily monitored by HPLC. Reaction of the activated intermediate **38** with cyclopropylamine was facile, and complete conversion was usually observed within 2 h at rt. The CDI-coupling reaction could be successfully carried out in a variety of solvents including THF, dichloromethane, DMF, ethyl acetate, isopropyl acetate, MTBE, or toluene. All investigated reaction conditions led to 2−4% of starting material **33** remaining (as judged by HPLC), and the addition of excess CDI or heating of the reaction mixture to elevated temperatures (50 °C) did not increase the conversion. A subtle effect of imidazole as an additive was noted in the reaction, as the presence of imidazole (1 equiv) led to slightly less formation of the acid (2−3 vs ∼4%). Investigation of the CDI reaction by ^{1}H and ^{13}C NMR (THF-d_8 as solvent) showed the presence of two distinct sets of signals. The major one could clearly be attributed to acylimidazolide **38**, and the minor set of signals was assigned as the anhydride **40**.[60] The formation of the anhydride is consistent with the HPLC data. Quench of the reaction mixture with an amine leads to formation of 1 equiv each of **33**, and the starting acid molecule per anhydride. The observation that imidazole as an additive reduces anhydride formation is consistent with the mechanism of the CDI activation, in which the initially formed acyl 1*H*-imidazole-1-carboxylate is either attacked by imidazole to form **38**, or by a second equivalent of acid to form anhydride **40**. Since **33** has low solubility in the reaction solvent, making the reaction dissolution controlled, the imidazole has the additional beneficial effect increasing the solubility of **33** and hence the rate as well.[61]

In an optimized procedure, the reaction was carried out in ethyl acetate using 1.5 equiv of CDI and 1 equiv of imidazole. Activation proceeded smoothly at rt, followed by a short heating to 50 °C to achieve maximum conversion. Cyclopropylamine was added at room temperature to give the amide **1**, which could be isolated in high yield (85%). Since the isolated material contained high levels of ethyl acetate (2−3%) that could not be removed by drying of the material, a reslurry of the crude product in a mixture of isopropanol and water was implemented to reduce the solvent levels to <5000 ppm (82% recovery). The CDI-coupling procedure efficiently reduces residual palladium in the final product from 100−150 ppm Pd to <10 ppm. Presumably imidazole acts as a good ligand for palladium thereby keeping the metal residues in solution during the crystallization of **1**.

Summary

A concise synthesis of p38 MAP kinase inhibitor **1** was developed. *ortho*-Metalation of a simple raw material was

(59) Initially, 1.00:2.00 Pd/L was used.

(60) The chemical shifts of the second set are distinct both from **33** and the imidazolium salt of **33**. Integration compared to **38** and comparison of this data point with the amount of starting material by HPLC suggest a dimeric structure.

(61) Solubility of **33** at rt with and without imidazole as determined by HPLC: 0.9 vs 0.2 mg/mL in ethyl acetate; 3.5 vs 2.3 mg/mL in THF.

leveraged for the efficient construction of the phthalazine core **24**, and the boronic acid building block **27** could be accessed by direct iodine−magnesium exchange of a substituted benzoic acid **8**. Judicial choice of the order of bond disconnections facilitated assembly of the two key fragments to the final molecule. Detailed optimization of the final four reaction steps (chlorodehydroxylation, S_NAr with morpholine, Suzuki coupling, and final amide coupling) provided an efficient, scaleable, and inexpensive synthesis of key target **1** in good overall yield (31% in six steps from 4-chlorobenzoyl chloride).

Experimental Section

***N-tert*-Butyl-4-chlorobenzamide (12c).** A 1 L jacketed reactor equipped with mechanical stirrer, reflux condenser, nitrogen blanket, dropping funnel, and temperature probe was charged with 4-chlorobenzoyl chloride (95%, 110 g, 0.60 mol) and dichloromethane (0.44 L). The resulting solution was cooled to 0 °C under nitrogen with stirring. *tert*-Butylamine (142 mL, 1.32 mol) was slowly added from a dropping funnel at ≤10 °C, followed by dichloromethane (10 mL) rinse. The reactor contents were warmed to 23 °C over approximately 30 min. NaOH aq (5 N) was slowly added from a dropping funnel at ≤25 °C. The reaction mixture was stirred until all the solids dissolved. The layers were separated, and the upper aqueous layer was discarded. The lower organic layer was concentrated by vacuum distillation (300−400 Torr, 33 °C) until approximately 0.35 L of the distillate was collected. Heptane (0.20 L) was charged, and the distillation was continued until approximately 0.12 L of the additional distillate was collected. The precipitated product was collected by filtration, rinsed with heptane (0.20 L), and oven-dried at 40 °C to afford *N-tert*-butyl-4-chlorobenzamide (**12c**) as colorless needles (129 g, 99.3% LC purity, 96.6% yield): mp 136−137 °C; HRMS (*m/z*) [M + H^+] calcd for $[C_{11}H_{15}ClNO]^+$ 212.08367, found 212.08363; IR 3357, 2981, 2963, 2929, 1635, 1592, 1569, 1538, 1485, 1452, 1399, 1386, 1362, 1313, 1277, 1220, 1137, 1113, 1092, 1012, 873, 846, 758, 722 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.85 (bs, 1 H), 7.83 (d, J = 8.5 Hz, 2 H), 7.49 (d, J = 8.5 Hz, 2 H), 1.38 (s, 9 H) ppm; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 165.1, 135.4, 134.4, 129.2, 127.9, 50.8, 28.5 ppm. Anal. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.53; H, 6.88; N, 6.64.

2-*tert*-Butyl-5-chloro-3-hydroxyisoindolin-1-one (16). A 50 L jacketed reactor equipped with mechanical stirrer, reflux condenser, nitrogen blanket, dropping funnel, and temperature probe was inerted with nitrogen and charged with *N-tert*-butyl-4-chlorobenzamide (**12c**) (2.33 kg, 11.0 mol) and anhydrous THF (18.6 L). The resulting solution was cooled to ≤−20 °C under nitrogen. Methyllithium solution in diethoxymethane (8.40 wt %, 5.90 kg, 22.5 mol) was slowly added at ≤−17 °C (methane off-gas, exotherm) resulting in a gradual color change from light orange to deep red. The resulting solution was allowed to warm and held at −10 °C with efficient agitation for at least 3 h during which a deep red solution gradually turned into a thick pinkish suspension. The reaction mixture was cooled back to ≤−20 °C, and DMF (1.7 L, 22 mol) was added slowly at ≤−15 °C and then allowed to react as it warmed to −10 °C. Saturated aq NH_4Cl (8.0 L) was slowly added at ≤−5 °C (ammonia off-gas, exotherm) with efficient agitation. The internal temperature was then adjusted to 20 °C over approximately 30 min. After settling, the phases were separated, and the lower aqueous layer was discarded. The organic layer was evaporated to dryness yielding crude product as a yellow paste. The pasty solid was slurried in toluene (10 L) and stirred at 100 °C for 1 h followed by cooling to 20 °C over approximately 5 h. The product was isolated by filtration, the wet cake was rinsed with toluene (2 − 1 L), and dried in a vacuum oven at 50 °C to constant weight to afford 2-*tert*-butyl-5-chloro-3-hydroxyisoindolin-1-one (**16**) as an off-white powder (2.15 kg, 98.5% LC purity, 85.4% yield): mp 185−186 °C; HRMS (*m/z*) [M + H^+] calcd for $[C_{12}H_{15}ClNO_2]^+$ 240.07858, found 240.07800; IR 3227, 2968, 1665, 1614, 1458, 1419, 1389, 1368, 1360, 1302, 1259, 1210, 1199, 1151, 1120, 1073, 1048, 1021, 935, 911, 886, 863, 845, 811, 772, 685 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.60−7.53 (m, 3 H), 6.43 (d, J = 10.0 Hz, 1 H), 6.02 (d, J = 10.0 Hz, 1 H), 1.52 (s, 9 H) ppm; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 165.8, 146.8, 136.4, 131.3, 129.3, 123.7, 123.3, 80.9, 53.9, 28.0 ppm. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.65; H, 6.13; N, 5.87.

6-Chlorophthalazin-1-ol (24). A 30 L jacketed reactor equipped with mechanical stirrer, reflux condenser, nitrogen blanket, dropping funnel, and temperature probe was made inert with nitrogen and charged with 2-*tert*-butyl-5-chloro-3-hydroxyisoindolin-1-one (**16**) (2.06 kg, 8.59 mol) and glacial acetic acid (6.4 L). The resulting thick slurry was heated to 90 °C with agitation. At approximately 80 °C, a homogeneous solution was obtained. Hydrazine hydrate (54 wt%) (0.53 kg, 9.0 mol) was added dropwise (exotherm) keeping the internal temperature between 90 and 93 °C over approximately 3 h. The resulting suspension was continued to stir at 90 °C as the conversion of starting material was monitored by LC (<1% within 1.5 h). Deionized water (12.8 L) preheated to 80 °C was transferred into 30 L jacketed reactor maintaining the reaction mixture at 80−90 °C followed by ramping down to 20 °C over approximately 4 h time. At this point, the resulting uniform suspension was transferred onto a filter. The filter cake was rinsed with deionized water (2−3.0 L). The wet cake was air-dried overnight to afford crude product as a large yellow crystals (1.67−1.92 kg, 108−124% theory). Two batches of crude 6-chlorophthalazin-1-ol (3.59 kg) from two identical runs were combined in a 30 L reactor and slurried in dichloromethane (18.0 L) at 20 °C for 1 h with efficient agitation. Product was collected by filtration, rinsed with dichloromethane (4.0 L), and oven-dried at 50 °C to constant weight to afford 6-chlorophthalazin-1-ol (**24**) as pale yellow crystals (2.76 kg, >99% LC purity, 89.0% yield): mp 271−273 °C (lit.[62] mp 272.2−273.5 °C); HRMS (*m/z*) [M + H^+] calcd for $[C_8H_6ClN_2O]^+$ 181.01632, found 181.01591; IR 3160, 3063, 3043, 2913, 1649, 1610, 1595, 1556, 1489, 1411, 1362, 1329, 1248, 1217, 1161, 1084, 1064, 920, 898, 872, 845, 780, 675 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.79 (bs, 1 H), 8.34 (s, 1 H), 8.22 (d, J = 8.5 Hz, 1 H), 8.08 (s, 1 H), 7.88 (d, J = 8.5 Hz, 1 H) ppm; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 159.0, 138.3, 137.2, 131.9, 131.3, 127.9, 126.2, 126.1 ppm. Anal. Calcd for $C_8H_5ClN_2O$: C, 53.21; H, 2.79; N, 15.51. Found: C, 53.08; H, 2,92; N, 15.62.

3-Borono-4-methylbenzoic Acid (27) (Organomagnesium Process). A 0.5 L jacketed reactor equipped with mechanical stirrer, reflux condenser, nitrogen blanket, and temperature probe was charged with 3-iodo-4-methylbenzoic acid (**8**) (30.0 g, 114 mmol) and anhydrous THF (150 mL). The batch temperature was adjusted to <−50 °C, and isopropylmagnesium chloride solution (1.93 M in THF, 125 mL, 240 mmol) was added at a controlled rate keeping the batch temperature between −60 and −50 °C. The mixture was aged at −50 °C for 1 h, at which point HPLC analysis (aliquot quenched into THF/water) showed <2% starting material remaining. The mixture was warmed to −40 °C, and then triisopropyl borate (40 mL, 171 mmol) was added between −40 and −30 °C. The reaction mixture was warmed to −10 °C and aged for 3 h, at which point HPLC analysis (aliquot quenched into THF/water) showed <15% *p*-toluic acid. Water (150 mL) was added while keeping the batch temperature <20 °C, followed by adjustment to pH 1−2 by addition of hydrochloric acid and stirring for 12 h. The layers were separated, and the bottom aqueous layer was extracted with THF (60 mL). The combined organic layers were washed with half-saturated brine (60 mL), and the solvent was partially removed by vacuum distillation keeping the batch temperature <45 °C. The final volume was adjusted to ∼150 mL. Heptane (450 mL) was slowly charged to the stirred THF solution, and the resulting suspension was aged for >60 min with stirring before the product

(62) Vaughan, W. R.; Baird, S. L., Jr. *J. Am. Chem. Soc.* **1946**, *68*, 1314.

was collected by vacuum filtration. The wetcake was rinsed with heptane/THF (3/1 v/v, 120 mL) and dried on the filter under a stream of nitrogen for >60 min affording the crude product. The crude product was charged into a clean reactor. THF (120 mL) was added, and the resulting mixture was subjected to a polishing filtration (Teflon, 0.45 μm) and transferred into a second clean reactor. The first reactor was rinsed with THF (15 mL), and the rinse was transferred through the filter into the second reactor. Heptane (450 mL) was slowly charged to the stirred THF solution. The resulting suspension was aged for >60 min with stirring before the product was collected by vacuum filtration (Teflon 0.45 μm). The wet cake was rinsed with heptane/THF (3/1 v/v, 60 mL) and dried on the filter under a stream of nitrogen for >60 min affording 3-borono-4-methylbenzoic acid (**27**) (12.9 g, 86 wt %, 99.95% LC purity, 54% corrected yield): mp 157−167 °C; HRMS (*m*/*z*) [M − H$^+$] calcd for [$C_8H_8O_4B$]$^-$ 179.05211, found 179.05191; IR 3280, 2833, 2558, 1683, 1605, 1571, 1493, 1408, 1347, 1304, 1266, 1205, 1176, 1135, 1095, 1030, 936, 921, 852, 819, 769, 760, 730, 699, 656 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.24 (br s, 2H), 8.00 (d, J = 1.9 Hz, 1 H), 7.78 (dd, J = 8.0 Hz, J = 1.9 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 168.3, 147.4, 136.7, 134.7, 130.3, 130.0, 127.3, 22.7 ppm.

6-Chloro-1-morpholinophthalazine (37). A 1 L jacketed reactor equipped with mechanical stirrer, reflux condenser, nitrogen blanket, and temperature probe was charged with 6-chlorophthalazin-1-ol (**24**) (22.3 g, 123 mmol), chlorobenzene (112 mL), and phosphoryl chloride (23.0 mL, 247 mmol). The resulting suspension was heated to 90 °C[63] with efficient agitation. After approximately 2 h at 90 °C, the reaction mixture was checked periodically for conversion (stirred aliquots were diluted with aq phosphate pH 7 buffer/acetonitrile mixtures and analyzed by HPLC). Complete conversion (≤1% 6-chlorophthalazin-1-ol) was typically obtained within 6 h. At this point, the resulting thick slurry was cooled to room temperature. Dichloromethane (223 mL) was added, and the suspension was cooled to ≤−10 °C. Aqueous sodium hydroxide (2.5 N, 445 mL, 1.11 mol) was added dropwise with efficient agitation maintaining internal temperature at approximately −4 °C (≤0 °C) (approximately 2.5 mL/min using a peristaltic pump over 3 h time). The reaction mixture was then allowed to warm to room temperature with stirring. After settling, the lower organic layer was retained. The upper aqueous layer (pH 10) was extracted with dichloromethane (112 mL). The combined organic layers contained approximately 21.3 g of 1,6-dichlorophthalazine (**35**) (87% assay yield) by HPLC. The crude 1,6-dichlorophthalazine solution (ca. 0.25 M, 433 mL) was transferred into a clean and dry 1 L jacketed reactor fitted with distillation head. Dichloromethane was removed by vacuum distillation (130−290 Torr/45 °C jacket, batch ≤39 °C). To the resulting thick orange slurry was added 2-methyltetrahydrofuran (89 mL) followed by morpholine (43 mL, 0.49 mol). The resulting fluid suspension was heated to 80 °C with stirring to afford briefly a dark solution at approximately 40 °C, and then heavy crystalline material started to appear. After 15 h at 80−85 °C, complete conversion of 1,6-dichlorophthalazine (**36**) was determined by HPLC. The resulting suspension was cooled to 20 °C over 40 min. Deionized water (156 mL) was added, and the resulting triphasic mixture was cooled and aged at 4 °C until a constant product concentration in mother liquors was obtained. The light orange suspension was passed through a filter. The filter cake was rinsed sequentially with deionized water (45 mL) and 2-methyltetrahydrofuran (2 − 22 mL). The wet cake was air-dried and then vacuum-dried at 60 °C to afford 6-chloro-1-morpholinophthalazine (**37**) as a dense crystalline material (24.6 g, >99.5% LC purity, 80.0% yield): mp 166−168 °C; HRMS (*m*/*z*) [M + H$^+$] calcd for [$C_{12}H_{13}ClN_3O$]$^+$ 250.07417, found 250.07351; IR 3076, 2968, 2894, 2863, 2846, 1608, 1578, 1537, 1480, 1462, 1449, 1410, 1394, 1355, 1302, 1267, 1258, 1219, 1167, 1151, 1130, 1110, 1073, 1033, 1002, 974, 942, 923, 871, 851, 834, 784, 722, 675, 655 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.29 (s, 1 H), 8.24 (d, J = 2.0 Hz, 1 H), 8.14 (d, J = 8.5 Hz, 1 H), 7.94 (dd, J = 2.0 Hz, 8.5 Hz, 1 H), 3.91−3.84 (m, 4 H), 3.44−3.38 (m, 4 H) ppm; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 158.9, 147.0, 136.3, 132.4, 129.2, 126.7, 126.0, 118.8, 66.0, 51.3 ppm. Anal. Calcd for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.67; H, 4.89; N, 16.83.

4-Methyl-3-(1-morpholinophthalazin-6-yl)benzoic Acid (33). A 250 mL three-necked round-bottom flask equipped with mechanical stirrer, nitrogen blanket, reflux condenser, and temperature probe was charged with 6-chloro-1-morpholinophthalazine (**37**) (10.0 g, 40.0 mmol), 3-borono-4-methylbenzoic acid (**27**) (84.4 wt %, 9.22 g, 43.4 mmol), $Pd_2(dba)_3$ (91.7 mg, 100 μmol), and 2′-methyl(dicyclohexylphosphino)biphenyl (91.2 mg, 250 μmol), and made inert with nitrogen. Ethanol (64 mL) was added, and the mixture was stirred until a uniform suspension was obtained. Aqueous sodium hydroxide (10 N, 16.0 mL, 0.16 mol) was added in one portion (adiabatic temperature change from 20 to 32 °C). The resulting biphasic mixture was heated and held at reflux with stirring (78−80 °C). Conversion of 6-chloro-1-morpholinophthalazine in the upper organic layer was monitored by LC (<0.5% within 2.5 h).[64] After complete conversion was determined, the reaction mixture was allowed to cool. Activated carbon (Darco KB-B, −100 mesh, 2.0 g) was added at ≤30 °C, followed by deionized water (40 mL). The resulting mixture was stirred overnight at 20 °C. The contents of the flask were passed through a pad of Celite. The filter-medium was rinsed sequentially with water (40 mL) and ethanol (2 × 20 mL). Combined filtrates were concentrated by distillation (155 mL of distillate was collected). The remaining cloudy orange solution (65 mL) was diluted with deionized water (35 mL) and extracted with isopropyl acetate (2 × 50 mL). The crude aqueous solution of the sodium salt of the product was transferred into a clean 250 mL three-necked round-bottom flask (equipped with a mechanical stirrer, pH probe, and dropping funnel) and diluted with tetrahydrofuran (50 mL). The solution was adjusted to pH 3.4 using conc. HCl aq. The resulting fine suspension was aged at 20 °C and filtered through a fine fritted funnel. The filter cake was rinsed sequentially with deionized water (15 mL) and tetrahydrofuran (2 × 15 mL). The wet cake was air-dried and vacuum-dried at 55 °C to a constant weight to afford 4-methyl-3-(1-morpholinophthalazin-6-yl)benzoic acid (**33**) as a light tan crystalline solid (10.8 g, 77.0% yield): mp 190−192 °C; HRMS (*m*/*z*) [M + H$^+$] calcd for [$C_{20}H_{20}N_3O_3$]$^+$ 350.14992, found 350.14897; IR 3421, 2994, 2887, 2886, 2399, 1704, 1621, 1568, 1555, 1485, 1426, 1398, 1363, 1301, 1271, 1262, 1229, 1129, 1110, 1070, 1032, 1019, 949, 933, 919, 864, 839, 792, 767, 716, 700, 681, 658 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.03 (bs, 1 H), 9.38 (s, 1 H), 8.20 (d, J = 8.5 Hz, 1 H), 8.15 (bs, 1 H), 7.99 (dd, J = 2 Hz, 8.5 Hz, 1 H), 7.94 (dd, J = 2 Hz, 8.0 Hz, 1 H), 7.89 (s, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 3.95−3.86 (m, 4 H), 3.51−3.43 (m, 4 H), 2.35 (s, 3 H) ppm; ^{13}C NMR (DMSO-d_6, 101 MHz) δ 166.9, 159.0, 148.0, 143.7, 140.4, 139.8, 133.0, 131.0, 130.4, 128.9, 128.8, 128.2, 126.8, 124.0, 119.2, 66.1, 51.2, 20.2 ppm. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 66.56; H, 5.48; N, 11.43.

***N*-Cyclopropyl-4-methyl-3-(1-morpholin-4-yl-phthalazin-6-yl)-benzamide (1).** A three-necked flask equipped with mechanical stirrer, nitrogen blanket, reflux condenser, and temperature probe was charged with 4-methyl-3-(1-morpholinophthalazin-6-yl)benzoic acid (**33**) (47.0 g, 135 mmol), imidazole (9.16 g, 135 mmol), and ethyl acetate (235 mL). Stirring was established, and 1,1-carbonyldiimidazole (32.7 g, 202 mmol) was added in one portion. The reaction mixture was stirred for 1 h at 20 °C and then heated for 2 h at 50 °C. Quenching an aliquot of the reaction mixture into neat benzylamine followed by HPLC analysis indicated high conversion (>97%) to the acylimidazolide **38**. The reaction mixture

(63) Internal temperature should not exceed approximately 95 °C as it leads to formation of sticky and highly colored byproducts that can compromise the batch.

(64) Prolonged heating adversely affects the impurity profile.

was cooled to rt and filtered through a medium glass frit into a clean three-necked flask to remove trace inorganic impurities. Cyclopropylamine (37.3 mL, 538 mmol) was added over 10 min, keeping internal temperature at <30 °C. The product started crystallizing out within 30 min. After the mixture was stirred for 16 h at rt, the solids were collected by vacuum filtration, rinsed with ethyl acetate (25.0 mL), and dried on the filter under a stream of nitrogen to afford crude **1** (42.6 g). A three-necked flask equipped with mechanical stirrer, nitrogen blanket, reflux condenser, and temperature probe was charged with 2-propanol (308 mL), water (103 mL), and the crude product **1** (41.2 g). Stirring was initiated, and the mixture was heated to 70−75 °C for 4 h. The suspension was cooled to rt and aged at rt for 1.5 h. The solids were collected by vacuum filtration, rinsed with a mixture of 2-propanol/water (1/1 v/v, 50 mL), and dried in the vacuum oven at 60 °C for 15 h to afford *N*-cyclopropyl-4-methyl-3-(1-morpholin-4-yl-phthalazin-6-yl)benzamide (**1**) as a colorless solid (35.5 g, 70%): mp 235−237 °C; HRMS (*m*/*z*) [M + H^+] calcd for $[C_{23}H_{25}N_4O_2]^+$ 389.1972, found 389.1972; IR 3238, 1650, 1537, 1455, 1392, 1364, 1307, 1263, 1113, 1025, 941, 923, 865, 840, 818, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.13 (s, 1 H), 8.07 (d, J = 8.3 Hz, 1 H), 7.80−7.72 (m, 4H), 7.38 (d, J = 8.3 Hz, 1 H), 6.65 (br s, 1H), 4.02−3.97 (m, 4H), 3.59−3.53 (m, 4H), 2.98−2.88 (m, 1H), 2.31 (s, 3H), 0.90−0.83 (m, 2H), 0.67−0.62 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.2, 159.7, 148.1, 144.7, 140.1, 138.9, 132.9, 132.5, 130.9, 128.6, 128.5, 126.7, 126.6, 124.0, 120.2, 66.9, 51.6, 23.2, 20.4, 6.7 ppm.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **1**, **12c**, **16**, **17a**, **17b**, **23a**, **24**, **27**, **28**, **33**, **34**, **35**, (^1H NMR), **37** and **39**. Experimental procedures and characterization data for **17a**,**b**, **23a**,**b**, **26**−**28**, **34**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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