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Process Development and Large-Scale Synthesis of a PDE4 Inhibitor

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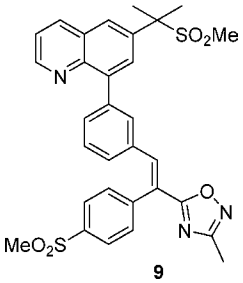
Abstract:

An efficient, scalable synthesis of the PDE4 inhibitor, 6-[1-methyl-1-(methylsulfonyl)ethyl]-8-(3-{(*E*)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]vinyl}phenyl)-quinoline benzenesulfonate (10) is described. The synthesis is highly convergent, generating the penultimate 9 by coupling aldehyde 7 and oxadiazole 8 in a Knoevenagel reaction. The process consists of a total of nine chemical steps, five of which comprise the sequence to prepare aldehyde 7 via Skraup reaction, bromination, sulfone formation, methylation and Suzuki−Miyaura cross-coupling, and a two-step sequence for the synthesis of oxadiazole 8 that includes the methylamidoxime and oxadiazole steps. The final two steps are Knoevenagel coupling and salt formation. The process produced the drug candidate 10 in 46% overall yield from 2-bromo-4-methylaniline (1) on multikilogram scale.

Introduction

Type-4 cyclic adenosine 3′,5′-monophosphate (c-AMP) specific phosphodiesterase (PDE-IV) is an enzyme responsible for the hydrolysis of the second messenger c-AMP to AMP in many cell types.[1] High levels of c-AMP inhibit the production of cytokines and other molecules that modulate the inflammatory response. Inhibition of PDE4 suppresses antigen-induced release of histamine in vitro, and PDE4 inhibitors have emerged as potential targets for intervention in inflammatory diseases.[2] PDE4 inhibitors such as **9** are being developed for the treatment of pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD) that together afflict an estimated 600 million people worldwide.[3]



9

The synthetic route[4] used to prepare **9** by Merck medicinal chemists was suitable for delivery of multigram quantities of the final product. However, the synthesis was not directly amenable to large-scale production. The quinoline ring in **9** was prepared by condensing 2-bromo-4-methylaniline (**1**) with glycerol in a Skraup reaction. To our knowledge, the Skraup reaction had not been used previously on a large scale. The Skraup reaction is usually run in refluxing mineral acid and typically gives low yields. In addition, the Skraup reaction is exothermic, and the potential for accumulation of reagents and a large exotherm during the addition of glycerol was a major concern.[5] In fact, a quote from the *Organic Reactions* review states *that the conditions under which the earlier Skraup syntheses were carried out often resulted in reactions of uncontrollable violence*.[6] Clearly, significant development would be required to render the requisite Skraup reaction amenable to scale-up.

The second step in the reaction sequence involved benzylic bromination of the product of the Skraup reaction, 6-methyl-8-bromoquinoline (**2**). The yield for the radical-induced bromination was moderate (63%) due to the incomplete conversion of starting material and the formation of the undesired α,α-dibromo compound **3a**. Furthermore, the bromination procedure was originally performed in

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(1) Claveau, D.; Chen, S. L.; O'Keefe, S.; Zaller, D. M.; Styhler, A.; Liu, S.; Huang, Z.; Nicholson, D. W.; Mancini, J. A. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 752−760.

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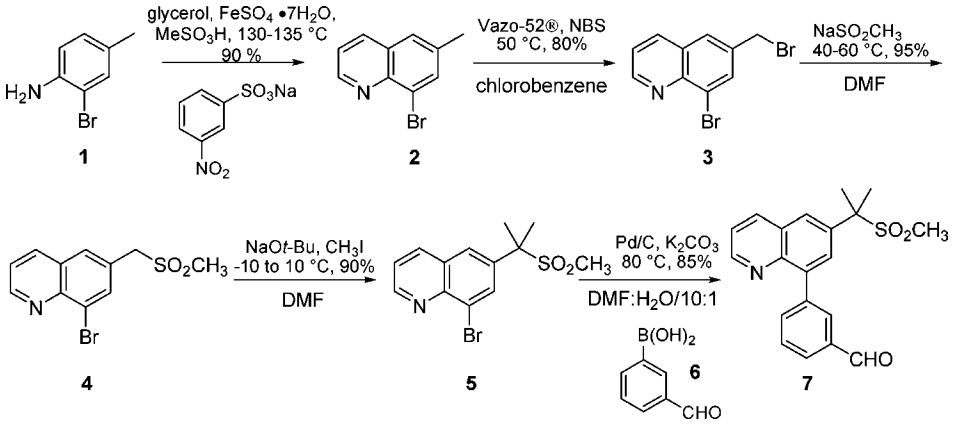
Scheme 1. **Preparation of aldehyde 7 from 2-bromo-4-methylaniline (1)**



carbon tetrachloride, making this procedure unsuitable for further scale-up.

Other process concerns were identified in the methylation step used to introduce two methyl groups which had the potential of forming impurities that were difficult to remove, high levels of residual palladium resulting from the Suzuki−Miyaura cross-coupling reaction to append the 8-aryl substituent using the homogeneous catalyst $Pd(PPh_3)_4$, control of the double bond geometry in the Knoevenagel reaction, and identification of a stable and pharmaceutically acceptable form of the final product.

In this contribution, we describe the process development and multikilogram scale preparation of compound **10**, the benzensulfonic acid salt of **9**, to support programs in preclinical and clinical development. An efficient synthesis of this compound was accomplished by addressing several processing issues in the original synthesis to make it more practical prior to scale-up. Our ultimate goal was to develop a safe and productive synthesis for preparing **10** on multikilogram scale.[7]

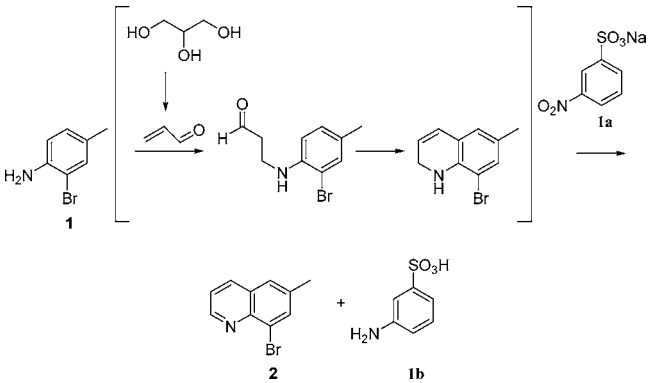
Results and Discussion

We believed that the original route to aldehyde **7** would be viable for large-scale production if we could make the necessary improvements. The optimized procedure for the preparation of aldehyde **7** is shown in Scheme 1.

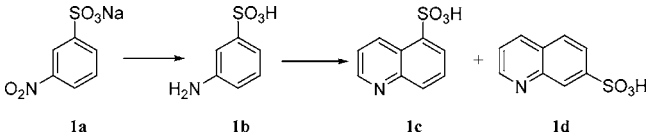
Skraup Reaction. The Skraup reaction is an efficient method for the construction of the quinoline ring system. The Skraup reaction is proposed to occur as four successive steps (Scheme 2): (1) dehydration of glycerol to acrolein, (2) addition of the aromatic amine to acrolein, (3) ring closure and dehydration to form the dihydroquinoline, and (4) oxidation of the dihydroquinoline to quinoline.[8] None of the proposed intermediates are observed by HPLC or GC even as the reaction rate slows down near the end of the reaction.

The exothermic nature of these steps presents a significant challenge on a large scale. Indeed, the Skraup reaction with **1** was shown to have a significant exotherm upon scale-up.

Scheme 2. **Skraup reaction process**



Scheme 3. **Quinoline impurities**



To circumvent a sudden exotherm during the reaction, the addition rate of glycerol was controlled to preclude the accumulation of glycerol. In practice, the optimized procedure is to add sodium *m*-nitrobenzenesulfonate and iron sulfate heptahydrate to methane sulfonic acid, followed by the addition of 2-bromo-4-methylaniline (**1**), resulting in an exotherm that warms the batch to ∼60 °C. The reaction mixture is then slowly heated to 120 °C, and glycerol is added over ca. 10 h.[9] It is important to allow the reaction to proceed to a conversion of >99% since the starting material, 2-bromo-4-methylaniline (**1**), inhibits the following radical-induced bromination and cannot be effectively removed during the workup.

It is interesting to note that an excess of glycerol is required for the Skraup reaction. In addition to the loss due to polymerization, some of this material is consumed to form two quinoline sulfonic acids (**1c** and **1d**) derived from the expected aniline byproduct **1b** (Scheme 3). These byproducts are easily removed during the extraction workup (see below).

Once the reaction is complete, the reaction temperature is lowered to 70−80 °C, and the batch is diluted with water.

(7) Desmond, R.; Conlon, D. A.; Drahus, A.; Ho, G.-J.; Pipik, B.; LeBlond, C.; Vailaya, A. U.S. Patent 6,835,837, 2004.

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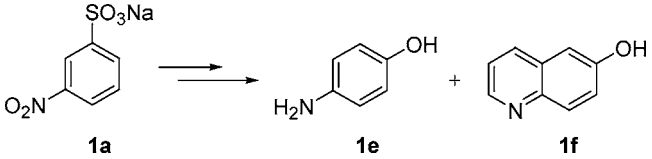
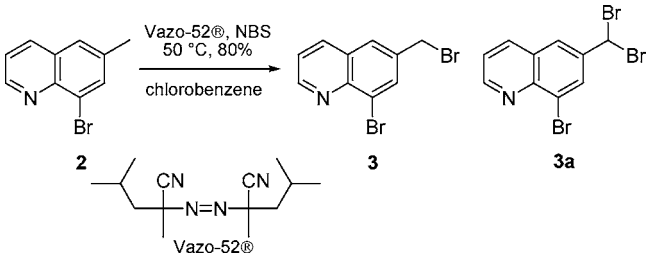
(9) In the pilot plant an emergency water quench was set up prior to the heatup to 120 °C and glycerol addition.

Scheme 4. **Phenolic impurities generated during the Skraup reaction**



1a **1e** **1f**

Scheme 5. **Radical bromination of 2**



2 **3** **3a**

Neutralization of the methanesulfonic acid is accomplished by the addition of 10 M NaOH and 1 M $NaHCO_3$.[10] Methyl *tert*-butyl ether (MTBE) extraction of bromomethylquinoline **2** followed by aqueous washes gives a solution of **2** in 90−92% assay yield. Two phenolic impurities (**1e** and **1f**) (Scheme 4) are formed during the reaction at levels of 0.5−1%, depending upon the reaction temperature and time.[11] It was found that the presence of these impurities inhibits the radical bromination used in the subsequent step and therefore must be controlled in the Skraup step.

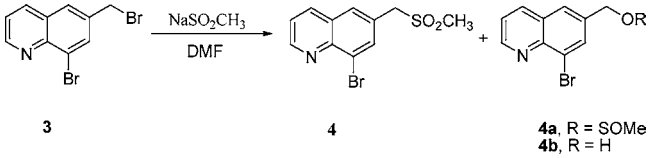
These impurities were completely removed after two dilute H_3PO_4 washes (0.02 M, pH ≈ 2) with ∼2−3% loss of **2**. The product **2** was then extracted into aqueous sulfuric acid (1.2 M). This extraction did not remove 2,6-dibromo-4-methylaniline, an impurity in the starting material which also inhibited the radical bromination. Aqueous hydrochloric acid could not be used for this extraction because the hydrochloride salt of **2** crystallized from the acid solution. Finally, bromomethylquinoline **2** was extracted into chlorobenzene, the solvent used in the radical bromination, after neutralization with aqueous sodium hydroxide.

Bromination. As shown in Scheme 1, the next step in the process is the radical bromination of **2**. In our initial work we utilized *N*-bromosuccinimde (NBS) and 2,2′-azobisisobutyronitrile (AIBN) as the radical initiator for the benzylic bromination of the bromomethylquinoline product from the Skraup reaction to produce **3**. The formation of **3a** increased dramatically toward the end of the reaction as the concentration of **3** increased (Scheme 5). To avoid over-bromination, we crystallized **3** from solution by the addition of an antisolvent (cyclohexane) after ∼70−80% conversion. Additional NBS and AIBN were then added to push the reaction to completion, giving a 12:75:13 ratio of **2**/**3**/**3a** at the end of reaction and **3** in 68−71% isolated yield.

(10) The use of 1 M $NaHCO_3$ simplified the neutralization by removing the need to monitor the pH.

(11) We speculated that **1e** arises from a Bamberger rearrangement of the phenylhydroxylamine intermediate formed during the partial reduction of nitrobenzene in the Skraup reaction. Impurity **1f** is formed from **1e** during the Skraup reaction. We did not determine if nitrobenzene was formed by loss of H_2SO_4 from sodium *m*-nitrobenzenesulfonate under the acidic reaction conditions or was present in this reagent.

Scheme 6. **Sodium methanesulfinate coupling with 3**



3 **4**

AIBN required a reaction temperature of ∼70 °C for radical initiation and produced a highly toxic byproduct, tetramethylsuccinonitrile, by homocoupling of two isobutyronitrile radicals.[12] While the level of tetramethylsuccinonitrile was expected to be low, we decided to change the radical initiator. On the basis of the solubility of the product **3** in chlorobenzene it seemed possible that running the reaction at a lower temperature, where the desired product **3** would crystallize directly from the reaction solution, might be a simpler way to effectively reduce the undesired over-bromination which forms **3a**.[13] Thus, Vazo-52 was selected as the initiator, and the reaction was carried out at ∼50 °C, giving a ratio of 7:88:5 for **2**/**3**/**3a** at the end of reaction. The use of Vazo-52 did present some challenges due to the handling and storage issues associated with this low-temperature initiator.[14] In addition, due to the large exotherm associated with the reaction, NBS and Vazo-52 were charged in two portions to address safety concerns.[15] Compound **3** was isolated as a mixture with succinimide, the byproduct from NBS, by diluting the reaction mixture with cyclohexane. Succinimide was easily removed by washing the crude solid with aqueous methanol. From this mixture, **3** was isolated in 75−86% yield. In addition to the increased yield, the decomposition product from Vazo-52 is much less toxic than that from AIBN.[16]

Sulfone Formation. Displacement of the benzylic bromide in **3** with sodium methanesulfinate generates the sulfone **4**. Initially, the sulfone formation was carried out in DMF (1.5 mL/g substrate **3**), and the reaction was quenched by the addition of water which concomitantly crystallized **4**. The addition of water to the reaction mixture at this concentration resulted in the formation of a thick slurry, making agitation difficult. To simplify the isolation, the reaction was run less concentrated (4 mL/g). The reaction mixture was allowed to react at 15−20 °C until ∼90% conversion was achieved and was then heated to 75−80 °C to ensure complete conversion. Although the amount of the side product sulfinate ester **4a** (see Scheme 6) increases at a higher reaction temperature, the elevated temperature was required for complete conversion. The sulfinate ester **4a** can be converted to **4** under the reaction conditions[13] via an intermolecular reaction with sodium methanesulfinate.[17] Furthermore, we

(12) Tetramethylsuccinotrile is highly toxic; the oral toxicity in rats (lethal dose for 50% of the test animals) is 60 mg/kg. DuPont Product Literature (http://www.dupont.com/vazo/faq.html).

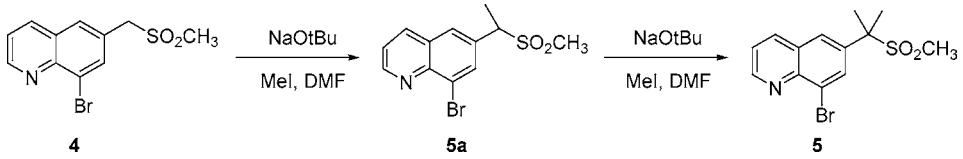
(13) Subsequent work demonstrated that the α,α-dibromomethyl compound could be converted to the desired sulfone in the next step, see Xu, F.; Savary, K.; Williams, J. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2003**, *44*, 1283−1286.

(14) The maximum recommended storage temperature for Vazo-52 is 10 °C.

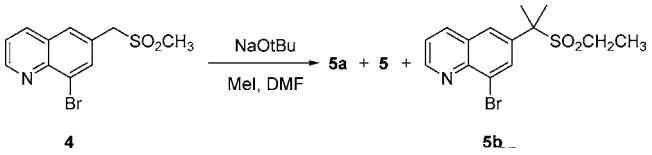
(15) With the split charge the maximum adiabatic temperature rise was reduced to 65 °C.

(16) The oral toxicity in rats (lethal dose for 50% of the test animals) for the decomposition products of Vazo-52 is 5000 mg/kg. DuPont Product Literature (http://www.dupont.com/vazo/faq.html).

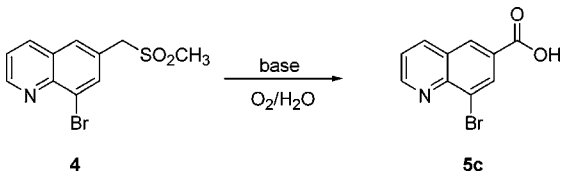
Scheme 7. **Alkylation with methyl iodide**



Scheme 8. **Impurity formation during alkylation**



Scheme 9. **Carboxylic acid impurity formed from anion oxidation**



found that the product crystallized directly from the reaction mixture upon addition of water at 50−60 °C. Due to partial protonation, **4** is more soluble under acidic conditions; therefore, sodium bicarbonate was added to increase the pH and reduce the loss of **4**. Sulfone **4** was isolated in 96% yield.

Methylation. In the next step of the process, it was necessary to introduce two methyl groups on the benzylic carbon between the aromatic ring and the sulfone group in **4** to generate **5** (Scheme 7). A significant issue for this step was the potential to form two impurities which are difficult to remove downstream; thus, it was critical that their production be minimized. An undercharge of base and/or methyl iodide resulted in the incomplete conversion of the intermediate monomethyl derivative **5a**. However, an overcharge resulted in the formation of the dimethylethyl sulfone **5b** (Scheme 8). With these factors in mind, we attempted to carefully control the charges during our initial work with limited success. One equivalent of base (sodium *tert*-butoxide) was added followed by 1 equiv of methyl iodide. The reaction was assayed by HPLC to monitor conversion, and then this process was repeated. For each batch, an HPLC assay was performed after 2 equiv of sodium *tert*-butoxide and methyl iodide were added. The assay was used to determine the amount of residual monomethylated intermediate **5a** that remained (typically 6−12%). Then a third charge of sodium *tert*-butoxide and methyl iodide was made on the basis of the amount of **5a** remaining.

A variety of other bases were screened for the dimethylation reaction with no base showing advantage over sodium *tert*-butoxide. Further improvement on the selectivity of the reaction was realized during screening studies which explored the effect of water concentration on this reaction. This revealed that, at higher water concentration (4000−6000 μg/mL, 0.9−1.3 equiv), the reaction remains a solution or very thin slurry, and better conversion of intermediate **5a** to product **5** was obtained. In addition, at the higher water concentrations, we did not generate the difficult-to-reject dimethylethyl sulfone impurity **5b** even with an excess charge of reagents. At low water concentration (<1000 μg/mL), the reaction mixture becomes a very thick slurry that is difficult to stir, and the reaction does not go to completion. With more water present, the sodium *tert*-butoxide charged to the reaction is rapidly converted to hydroxide which is more selective in deprotonation at the benzylic position. Hydroxide is not strong enough to significantly deprotonate the sulfone methyl in **5** ($pK_a \approx 33$)[18] as needed to form **5b**.

The equilibration to hydroxide as base was tested by adding solid sodium *tert*-butoxide to a solution of the sulfone and methyl iodide in dry DMF. Since there was no water present, equilibration of base to hydroxide did not occur, and a large amount of dimethylethyl sulfone **5b** was formed. Conversely, at the higher water concentration the benzylic anion is generated, and less of the overalkylated ethyl impurity **5b** is formed. Attempts to replace sodium *tert*-butoxide with sodium hydroxide either directly or under phase transfer conditions did not result in an improvement.

If the acting base is sodium hydroxide, which will not deprotonate the sulfone methyl, then an excess of base and methyl iodide should not result in formation of large amounts of **5b**. For the large-scale synthesis, following the addition of 2 equiv of base and methyl iodide, a standard third charge of 15 mol % of sodium *tert*-butoxide and methyl iodide was made. This procedure was successfully implemented to give **5** in 90−92% yield and 99.5 HPLC area % (LCAP).

During reaction optimization, a previously seen low-level impurity was formed at elevated levels in several experiments. This impurity was isolated and identified by LC/MS and NMR as the carboxylic acid impurity **5c** (Scheme 9).

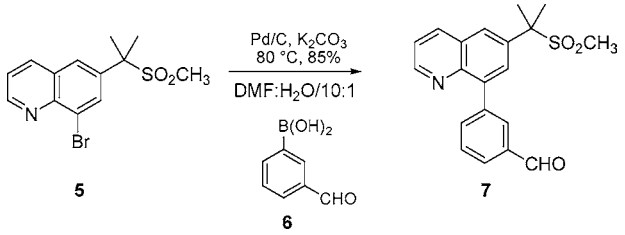
We speculated that this impurity is generated by oxidation of the sulfone anion and determined that degassing is a critical parameter in the dimethylation reaction. To demonstrate that this impurity was being formed via reaction with oxygen, an experiment was performed where the sulfone anion was prepared in DMF at ambient temperature without degassing. The anion was then quenched and the resulting reaction mixture analyzed by HPLC, revealing elevated levels of **5c**. Therefore, the reaction mixture was thoroughly degassed using vacuum and nitrogen back fills for the large-scale preparation, and the level of **5c** at the end of reaction was nearly undetectable, and none was observed in the isolated product.

Suzuki−Miyaura Cross-Coupling. The final step in the synthesis of aldehyde **7** is the Suzuki−Miyaura cross-coupling reaction of the dimethyl sulfone **5** and 3-formylphe-

(17) (a) Kornblum, N.; Ackermann, P.; Swiger, T. J. *J. Org. Chem.* **1980**, *45*, 5294−5298. (b) Creary, X. *J. Org. Chem.* **1985**, *50*, 5080−5084.

(18) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321−325.

Scheme 10. **Suzuki coupling reaction with Pd/C**

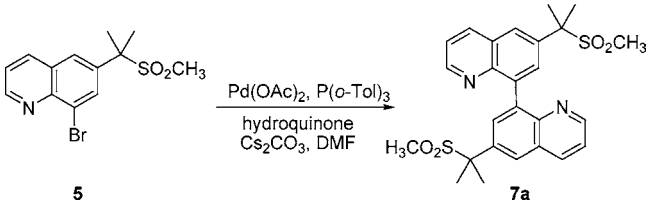


nyl boronic acid **6** (Scheme 10). Our initial screening of several homogeneous palladium catalysts identified Pd(dppf)-Cl_2 as an excellent catalyst for this coupling.[19] Unfortunately, the isolated aldehyde **7** contained high levels of residual palladium (3500 ppm) as well as iron (1160 ppm) from the dppf ligand. Reduction of the residual Pd concentration and removal of the dppf ligand to acceptable levels represented a major challenge for the production of **7** of suitable quality. A major objective during the design of a suitable process was the control of the palladium level in the isolated aldehyde **7**. To avoid the purification required to remove these metals, we investigated the heterogeneous (Pd/C) catalyzed reaction.[20] Palladium catalysts from several different suppliers were evaluated, and we determined that the optimum catalyst for the reaction to form **7** had nonreduced palladium (5% or 10% Pd) distributed on the activated carbon surface (an eggshell dispersion). Both dry catalyst and water-wet catalyst performed equally well in the reaction.[21] The Pd/C catalyzed Suzuki−Miyaura reaction was shown to give **7** in excellent yield with low levels of residual palladium after a simple filtration and precipitation. The low level of residual palladium is an important criterion for pharmaceuticals, and the use of a heterogeneous catalyst is motivated by the ease of separation of the palladium from the product. In the example above, leaching of palladium from the carbon support occurred during the reaction followed by subsequent precipitation of Pd during the course of the reaction, prompting us to refer to this as a *quasi*-heterogeneous reaction.

Screening studies showed that aqueous DMF was the best solvent system for this reaction and that powdered K_2CO_3 was the most effective base. Extra fine grade potassium carbonate[22] was used to minimize mass transfer limitations ensuring complete conversion. Optimization of the Pd level (2.6 mol %) and reaction conditions (DMF/water, 10:1, 3 equiv of K_2CO_3, and 80 °C) resulted in reproducible, isolated yields of aldehyde **7** of 85−92%.

In the typical procedure all the reagents are charged, and the reaction mixture is thoroughly degassed using vacuum and nitrogen back fills. The degassing minimizes the loss of 3-formylphenyl boronic acid due to homocoupling and

Scheme 11. **Homocoupled sulfone impurity**



formation of the known biaryl.[23] In addition, we observed lower residual palladium levels in reactions that were degassed. The reaction mixture is heated to 80 °C and stirred for 1.5 h. The Pd/C and the other inorganic byproducts are removed by filtration, and the waste cake is washed with hot DMF to ensure a good recovery of the aldehyde. The filtration and waste cake washing are performed at temperatures above 40 °C to prevent loss of the aldehyde by crystallization.

The issue with this step was the low mass balance of the reaction that was originally attributed to loss of product on the waste cake during filtration. Our investigations identified the formation of the homocoupled sulfone **7a** (LC−MS/MS) that was completely removed during the isolation. An authentic sample of **7a** was prepared using the procedure described by Rawal et al.[24] (Scheme 11).

The aldehyde intermediate **7** was isolated by the addition of water (equal volume) to the combined filtrate and washes at 50−60 °C. The aldehyde crystallized without seeding and was isolated by filtration. We were pleased to find that the residual palladium levels were very low in the isolated material (18−80 ppm) and were reduced to <10 ppm during further processing.

Methylamidoxime Preparation and Oxadiazole Synthesis. The first step in the preparation of the oxadiazole **8** is the formation of methylamidoxime **8a** from hydroxylamine[25] and acetonitrile.[26,27] This step is complicated by the energetic nature of the starting material, hydroxylamine, and the product **8a**. In the process, acetonitrile is heated to 70−72 °C and a 50 wt % aqueous solution of hydroxylamine is added slowly over at least 4 h to avoid the accumulation of the reagents. The reaction is very exothermic, and to minimize the potential for charging the hydroxylamine too quickly, the charge was done in two discrete portions. Performing the charge in this manner ensured complete consumption of the hydroxylamine and provided an easily controlled reaction with a negligible heat-release rate. Following the hydroxylamine addition, the reaction mixture was cooled to ∼30 °C, seeded, and cooled further to ca. 0 °C, and the resulting slurry was filtered. Due to the thermal instability of the product, **8a**, drying of the isolated solid was done in a vacuum oven at ∼25 °C.

(19) The cross-coupling reaction is inhibited by phosphine; however, chelating phosphines such as dppf can be used. See Wallow, T. I.; Novak, B. M. *J. Org. Chem*. **1994**, *59*, 5034−5037.

(20) Conlon, D. A.; Pipik, P.; Ferdinand, S.; LeBlond, C. R.; Sowa, J. R., Jr.; Izzo, B.; Collins, P.; Ho, G.-J.; Williams, J. M.; Shi, Y.-J.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931−935.

(21) We found that many commercial samples of Pd/C were catalysts for this cross-coupling. We used a dry, 5% Pd/C (C6064) from Engelhard and water wet 5% Pd/C (A405023-5) and 10% Pd/C (A402032-10) catalysts from Johnson Matthey in this study.

(22) Extra fine K_2CO_3 was purchased from the Armand Products Co., Princeton, NJ 08543.

(23) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559−2560.

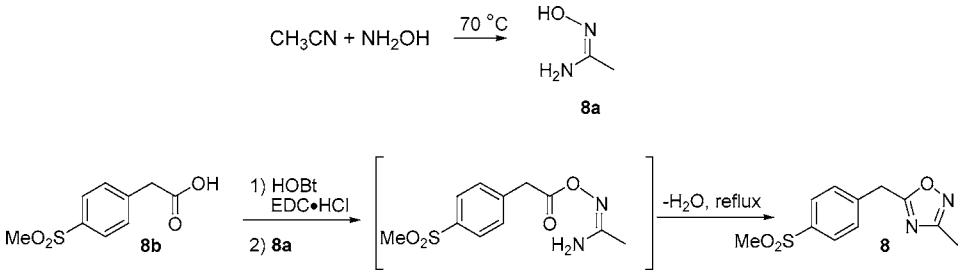
(24) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org Lett*. **1999**, *1*, 1205−1208.

(25) CAUTION: Hydroxylamine is a possible mutagen and is known to cause severe skin, eye, and respiratory tract burns. Heating hydroxylamine solutions may result in an exothermic decomposition, see ref 27.

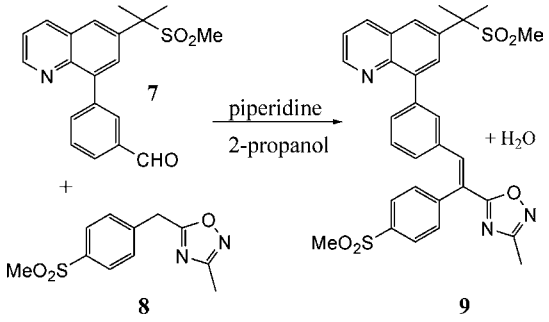
(26) Eloy, F.; Lenaers, R. *Chem. Rev.* **1962**, *62*, 155−183.

(27) Hett, R.; Krähmer, R.; Vaulont, I.; Leschinsky, K.; Snyder, J. S.; Kleine, P. H. *Org. Process Res. Dev*. **2002**, *6*, 896−897.

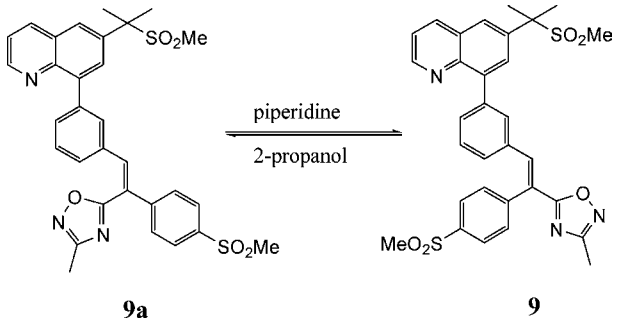
Scheme 12. **Formation of the oxadiazole**



Scheme 13. **Knoevenagel coupling to prepare 9**



Scheme 14. **Double bond isomers of 9**



For the formation of oxadiazole **8**, we initially investigated methods with literature precedent that involved activation of 4-methanesulfonylphenyl acetic acid (**8b**) with *N*,*N*′-carbonyldiimidazole (CDI), *N*,*N*′-dicyclohexylcarbodiimide (DCC), or formation of an acid chloride or anhydride to facilitate coupling with methylamidoxime **8a**. These procedures were not suitable for large-scale processing because **8** was obtained in low-yield or required chromatography to afford product with acceptable purity; therefore, we sought a more efficient route to **8**. The method developed involved activation of **8b** using standard peptide coupling reagents 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt)[28] followed by displacement with methylamidoxime (Scheme 12). It was critical to ensure that the active ester formation was complete prior to the addition of methylamidoxime. Lower conversion due to hydrolysis of the active ester was observed if the water from the HOBt hydrate was not removed. In addition, the conversion was lower when all the reagents were charged at once. Cyclization and dehydration occurred upon heating, and the oxadiazole was produced in 90% yield on a 30-kg scale using this method.[29]

Knoevenagel Coupling. The Knoevenagel reaction[30] was an attractive approach for the formation of the penultimate **9** that contained a trisubstituted double bond (Scheme 13).

The possibility of forming a mixture of double bond isomers was a major concern; however, the isolated product was shown to be exclusively the desired isomer. The reaction is reversible, and the water formed must be removed to drive the reaction to completion. The coupling step was performed in 2-propanol (IPA) at reflux (bp 82 °C) with piperidine as the base. Under these conditions, the reaction remains a slurry throughout because the starting material **7** (aldehyde, 0.15 mg/mL) and product **9** (free base, 0.03 mg/mL) have limited solubility in IPA. Water formed during the condensation was removed by returning the distillates to the reaction vessel after passing through a bed of molecular sieves.

A mixture of **9**/**9a** isomers was initially observed in the supernatant of the reaction by HPLC (Scheme 14); however, as the reaction proceeded, the desired product **9** crystallized out. Toward the end of reaction we isolated the desired product **9** by filtration, and any residual undesired **9a** was rejected in the filtrate. The reaction required 22 h to go to completion, was cooled to 20−25 °C, and then stirred for 4 h prior to isolation of the product by filtration.

Compound **9** is light sensitive, and isomerization of the double bond was observed upon exposure to light in both the solid state and in solution. Care was then taken to protect **9** from exposure to light.

Benzenesulfonate Salt Formation. In an effort to identify a stable and pharmaceutically acceptable form of the final product, screening experiments were performed with the free base **9**, and several different crystalline salts were discovered. One of them was the crystalline benzenesulfonate **10** (Scheme 15).

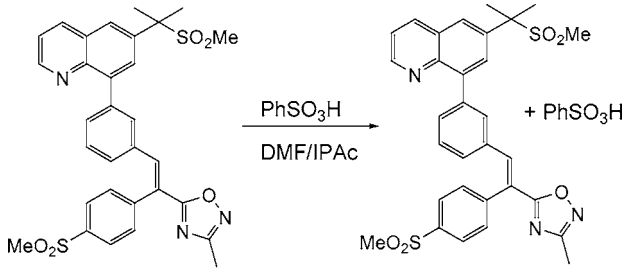
During our investigations, several different crystal forms of **10** were observed. Development of a solvent system to ensure reproducible production of the desired crystal form was needed. In our investigations, it was found that solvates were formed with methanol, ethanol, acetonitrile, and acetone, at or below room temperature. This excluded the use of these and similar solvents in the production of **10**. Two different solvent systems were found to reproducibly give the desired crystal form. These systems are *N*,*N*-dimethylformamide (DMF)/isopropyl acetate (IPAc) and

(28) CAUTION: HOBt will decompose, possibly violently, if heated above its melting point. See Bright, R.; Dale, D. J.; Dunn, P. J.; Hussain, F.; Kang, Y.; Mason, C.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2004**, *8*, 1054−1058.

(29) Pipik, B.; Ho, G.-J.; Williams, J. M.; Conlon, D. A. *Synth. Commun.* **2004**, *34*, 1863−1870.

(30) (a) Jones, G. *Org. React.* **1967**, *15*, 204−599. (b) Tietze, L.; Beifuss, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Elmsford, NY, 1991; Vol. 2, pp 341−394.

Scheme 15. **Final salt formation**



acetic acid/isopropyl alcohol. The DMF/IPAc system was selected for large-scale preparation because it afforded better yields. The free base **9** and benzenesulfonic acid (1.2 equiv) were dissolved in an 80:20 (v/v) mixture of DMF/IPAc at 40 °C. The clear, yellow solution was transferred through a line filter to a second vessel and seeded with **10**. Additional isopropyl acetate was added to the reaction solution as an antisolvent at 40 °C to crystallize **10**. It was found that the level of residual DMF in isolated **10** was lower if the crystallization was performed at a temperature of 40 °C or above.[31] Once the antisolvent addition was complete, the slurry was slowly cooled from 40 to 5 °C over 5 h and then stirred for an additional 5 h. The product was isolated with the desired crystal form in 91% yield and with acceptable residual DMF levels.

Conclusion

An efficient and safe process for the preparation of the drug candidate **10** was developed which provided many significant advantages over the original process used by Merck medicinal chemists. The synthesis is highly convergent, coupling aldehyde **7** and oxadiazole **8** to yield the penultimate **9**. The process for preparing **10** with the preferred crystal form was scaled up successfully and reliably in 46% overall yield from commercially available 2-bromo-4-methylaniline (**1**) on multikilogram scale in a pilot-plant facility.

Experimental Section

General. Starting materials were obtained from commercial suppliers and were used without further purification. HPLC analyses were performed on a Hewlett-Packard Series 1100 liquid chromatograph equipped with a UV detector. The area percent (LCAP) reported has been corrected for detector response. NMR spectra were obtained at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C. All coupling constants are reported in hertz (Hz). Microanalysis was performed by Quantitative Technologies, Inc.

8-Bromo-6-methylquinoline (2). Sodium *m*-nitrobenzenesulfonate (2.67 kg, 11.8 mol) was added to methanesulfonic acid (10 L) at 20 °C followed by iron sulfate heptahydrate (156.8 g, 0.564 mol). This addition is slightly exothermic and raised the temperature to 27 °C. To the resulting mixture was added 2-bromo-4-methylaniline (3.50 kg, 18.8 mol) through an addition funnel with stirring over 30 min, flushed with methanesulfonic acid (0.5 L), and agitated until the solid dissolved (~15 min). The addition is exothermic, and the temperature reached ~60 °C after the addition. The reaction mixture was heated to 118−125 °C, and glycerol (4.33 kg, 47.0 mol) was added through an addition funnel over 4−8 h. After stirring at 125−133 °C for 10−16 h, the mixture was cooled to ~80 °C and diluted with cold DI water (10 L) keeping the temperature <90 °C. After cooling to ~20 °C with an ice bath, the mixture was neutralized with cold aqueous NaOH (10 M, 15.6 L). Solka floc (500 g) was added, and the mixture was further neutralized with 1 M aqueous $NaHCO_3$ (1 M, 16 L). The mixture was cooled to 10−20 °C, and MTBE (30 L) was added. After stirring for 4−6 h, the mixture was filtered through a centrifuge (10-μm bag), and the phases were separated. The (top) MTBE layer was washed with 20 L of brine (95% saturation). The aqueous layers were back extracted with MTBE, and the organic phases were combined (3.97 kg of product as a 7−9 wt % MTBE solution in 95% yield). For characterization purposes, the hydrochloride salt of 8-bromo-6-methylquinoline can be prepared. Mp 195−211 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (s, 3H), 7.91 (s, 1H), 8.03 (dd, J = 5.3, 8.2 Hz, 1H), 8.20 (s, 1H), 8.84 (d, J = 8.2 Hz, 1H), 9.67 (d, J = 4.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.4, 111.5, 121.1, 126.3, 129.0, 132.5, 138.9, 140.6, 143.9, 146.1. Anal. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; Br, 35.98; N, 6.31. Found: C, 53.94; H, 3.35; Br, 36.06; N, 6.15.

8-Bromo-6-(bromomethyl)quinoline (3). The MTBE solution from the Skraup reaction (~47 L, 3.95 kg, 17.8 mol) was washed with 2 × 70 L of 0.02 M aqueous H_3PO_4, and then the MTBE layer was extracted with 42 L of 1.2 M aqueous H_2SO_4, followed by 14 L of 1.2 M aqueous H_2SO_4, while maintaining temperature at 10−20 °C during extraction. The H_2SO_4 extracts were combined, and chlorobenzene (49 L) was added. The mixture was then neutralized to pH > 5 with 10 M aqueous NaOH (13.3 L). The phases were separated, and the chlorobenzene layer was washed with 28 L of brine, concentrated to ~11 L, and filtered (325 g/L, 3.46 kg, 15.6 mol). To the solution at ~20 °C was added NBS (1.52 kg, 8.5 mol) and Vazo-52 (155 g, 0.62 mol). The mixture was degassed by vacuum and purged with N_2 three times. The mixture was heated to 48−52 °C over 1 h and maintained at 48−52 °C for 8 h. The batch was cooled to ~20 °C, and a second charge of NBS (1.52 kg, 8.5 mol) and Vazo-52 (155 g, 0.62 mol) were made. The vessel was purged with nitrogen and heated back to 48−52 °C for 10 h. The batch was allowed to cool to 20−25 °C, and cyclohexane (11 L) was added over 1 h. After stirring at ~20 °C for 2 h, the mixture was cooled to 0−5 °C and held at this temperature for 2 h. The slurry was filtered, and the cake was washed with 5.2 L of cold (0−5 °C) 1:2 chlorobenzene/cyclohexane, followed by 10 L of cyclohexane. After air-drying for 2−4 h the cake was further dried at 30 °C under full vacuum to remove residual solvents (<1 wt % organic solvents). The solid was slurry washed with 3

(31) DMF is a Class 2 solvent, and residual levels must be controlled. See ICH Harmonised Tripartite Guideline; Impurities: Guideline for Residual Solvents Q3C; 17 July 1997.

× 11 L of 10 v/v% MeOH in water. The solid was dried at 30 °C under full vacuum to a constant weight (3.75 kg, 98.7 wt %, 79%). Mp 156−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (s, 2H), 7.48 (dd, J = 4.3, 8.3 Hz, 1H), 7.78 (d, J = 1.4 Hz, 1H), 8.09−8.14 (m, 2H), 9.04 (dd, J = 1.5, 4.2 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.8, 122.4, 125.4, 127.5, 129.0, 133.9, 136.6, 136.7, 144.9, 151.7. Anal. Calcd for $C_{10}H_7Br_2N$: C, 39.91; H, 2.34; Br, 53.10; N, 4.65. Found: C, 39.81; H, 2.12; Br, 53.23; N, 4.54.

8-Bromo-6-[(methylsulfonyl)methyl]quinoline (4). Powdered sodium methanesulfinate (1.7 kg, 16.7 mol) was added to dry DMF (14 L, KF = 226 μg/mL) −3 to 0 °C, followed by the addition of **3** (4.00 kg, 13.3 mol), and the temperature of the slurry was maintained at 0−10 °C. The mixture was stirred at 13−17 °C for 3 h. The mixture was then heated to 75−80 °C for 1 h. The slurry was diluted with water (42 L), while maintaining the batch temperature at 75−80 °C. After the water addition was complete, the batch was heated to 90 °C and then cooled to 20 °C. Sodium bicarbonate (223 g) was added, and the slurry was cooled to 0−5 °C and stirred for 4 h. The mixture was filtered and the cake washed sequentially with 2 × 6.7 L of cold (0−4 °C) 1:4 DMF/water and 6.7 L of chilled water. After air-drying for 2 h, the solid was further dried at 40−50 °C until constant weight. Isolated yield: 3.91 kg, 12.75 mol, 96%. Typical quality: 98 wt % and 97−98 LCAP. Mp 149−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (s, 3H), 4.41 (s, 2H), 7.53 (dd, J = 4.3, 8.3 Hz, 1H), 7.90 (s, 1 H), 8.11 (d, J = 1.3 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 9.03, (dd, J = 0.7, 4.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.8, 60.4, 122.7, 125.9, 127.2, 129.2, 130.1, 134.6, 136.8, 145.3, 152.3. Anal. Calcd for $C_{11}H_{10}BrNO_2S$: C, 44.01; H, 3.36; Br, 26.62; N, 4.67; S, 10.68. Found: C, 43.04; H, 3.34; Br, 26.19; N, 4.46; O, 12.96; S, 10.01.

8-Bromo-6-[1-methyl-1-(methylsulfonyl)ethyl]quinoline (5). Sulfone **4** (1648 g, 5.49 mol) was dissolved in DMF (24 L, KF = 5280 μg/mL), and the solution was degassed using vacuum and nitrogen back fills; the solution was then cooled to −10 to −5 °C under N_2. Solid sodium *tert*-butoxide (528 g, 5.49 mol) was added, while maintaining the temperature at −10 to −5 °C. Neat methyl iodide (779 g, 5.49 mol) was added while maintaining the temperature at −10 to −5 °C. A second charge of solid sodium *tert*-butoxide (528 g, 5.49 mol) was then added in one portion to the reaction mixture at −10 °C. A second charge of the neat methyl iodide (781 g, 5.5 mol) was added to the deep-red reaction mixture, while maintaining the reaction temperature between −10 and −3 °C. A third portion of sodium *tert*-butoxide (79 g, 0.83 mol) was added, followed by methyl iodide (120 g, 0.85 mol). The batch was stirred for 60 min and for 40 min between −10 and −5 °C, and then aqueous acetic acid solution (2 vol % acetic acid, 25 L) was slowly added, and the temperature reached ∼10 °C. The resulting slurry was stirred for 6 h at −5 to 0 °C and filtered. The solid was washed sequentially with 2 × 5 L of cold (10−14 °C) 3:1 water/DMF (v/v) solution and 3 L of water and then dried in a vacuum oven at ∼35 °C (nitrogen sweep) to a constant weight. Isolated yield: 1647 g of 98 wt % **5**, 88% isolated yield.

Monomethyl methyl sulfone 5a: mp 172−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (d, J = 7.2 Hz, 3H), 2.75 (s, 3H), 4.35 (q, J = 7.1 Hz, 1H), 7.54 (dd, J = 4.1, 8.1 Hz, 1H), 7.93 (d, J = 1.9 Hz, 1H), 8.15 (d, J = 1.9 Hz, 1H), 8.21 (dd, J = 1.5, 8.3 Hz, 1H), 9.10 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.2, 38.2, 64.0, 122.7, 125.8, 128.4, 129.1, 133.2, 133.4, 136.8, 145.3, 152.2. Anal. Calcd for $C_{12}H_{12}BrNO_2S$: C, 45.87; H, 3.85; Br, 25.43; N, 4.46; S, 10.21. Found: C, 45.74; H, 3.47; Br, 25.68; N, 4.65; S, 10.57.

Dimethyl sulfone 5: mp 205−207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 6H), 2.62 (s, 3H), 7.54 (dd, J = 4.1, 8.2 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 1.3, 8.1 Hz, 1H), 8.38 (d, J = 2.1 Hz, 1H), 9.10 (dd, J = 1.5, 4.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.8, 35.0, 64.4, 122.6, 125.4, 127.8, 128.8, 132.6, 136.9, 137.3, 144.9, 152.3. Anal. Calcd for $C_{13}H_{14}BrNO_2S$: C, 47.57; H, 4.30; Br, 24.34; N, 4.27; S, 9.77. Found: C, 47.47; H, 3.93; Br, 24.43; N, 4.25; S, 9.81.

Dimethyl ethyl sulfone 5b: mp 210−212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J = 7.5 Hz, 3H), 1.97 (s, 6H), 2.71 (q, J = 7.5 Hz, 1H), 7.53 (dd, J = 4.2, 8.2 Hz, 1H), 8.07 (d, J = 2.2, 1H), 8.22 (dd, J = 1.6, 8.3 Hz, 1H), 8.37 (d, J = 2.2 Hz, 1H), 9.09 (dd, J = 1.7, 4.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 5.2, 22.9, 41.2, 64.3, 122.5, 125.2, 127.7, 128.7, 132.6, 137.1, 137.3, 144.7, 152.2. Anal. Calcd for $C_{14}H_{16}BrNO_2S$: C, 49.13; H, 4.71; Br, 23.35; N, 4.09; S, 9.37. Found: C, 49.07; H, 4.42; Br, 23.51; N, 4.09; S, 9.37.

3-{6-[1-Methyl-1-(methylsulfonyl)ethyl]quinolin-8-yl}-benzaldehyde (7). Potassium carbonate (3410 g, 24.7 mol), Pd/C (5%, 438 g), dimethyl sulfone **5** (2700 g, 96 wt %, 7.90 mol), and 3-formyl boronic acid **6** (1727 g, 11.5 mol) were combined. The solids mixture was degassed using five vacuum/nitrogen back-fill cycles. DMF (26.1 L) was added, followed by water (2.6 L) under slight nitrogen purge. The reaction mixture was degassed again using five vacuum/nitrogen back-fill cycles and then heated at ∼80 °C for 2 h. The waste cake and Pd/C were removed by filtering the hot mixture (∼60 °C) through a bed of solka floc. The Pd/C was rinsed with hot DMF (2 × 2.9 L, 60 °C). The filtrate was heated to 50−60 °C and diluted with water (24 L). The hazy solution was seeded, and the suspension was aged for 1 h to generate a seed bed. Additional water (8.0 L) was slowly added. The slurry was cooled to ∼10 °C and aged for 6−8 h. The mixture was filtered, and the solid was washed with 1:1 DMF/water (v/v) (4 L) and water (4 L). After drying by suction (N_2 sweep) for 2−3 h, the solid was dried in a vacuum oven (N_2 sweep) until constant weight. Isolated yield: 2446 g (85% yield corrected for wt %). Mp 182−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 6H), 2.66 (s, 3H), 7.51 (dd, J = 4.1, 8.2 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.98 (m, 2H), 8.08 (d, J = 2.1 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 8.23 (m, 1H), 8.28 (m, 1H), 9.00 (dd, J = 1.8, 4.2 Hz, 1H), 10.13 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.9, 35.0, 64.7, 122.0, 128.0, 128.3, 128.9, 128.9,

129.9, 132.3, 135.8, 136.4, 136.8, 137.0, 139.7, 140.0, 145.4, 151.6, 192.4. Anal. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96; S, 9.07. Found: C, 67.86; H, 5.11; N, 3.92; S, 8.99.

Methylamidoxime (8a). Acetonitrile (25.2 L) was heated to 70 °C, and hydroxylamine solution (2.5 kg, 37.8 mol, 50 wt % solution) was added slowly over 4 h while the temperature was maintained at 70 °C. (*CAUTION: Heating hydroxylamine solutions may result in an exothermic decomposition.*) The reaction is exothermic, and the temperature is maintained by the rate of addition of hydroxylamine solution. The reaction mixture was stirred for an additional 3 h and then cooled to 0 °C for 2 h and filtered. The isolated solid is dried in a vacuum oven at ambient (∼25 °C) temperature. The isolated yield was 1.51 kg (54%).

3-Methyl-5-[4-(methylsulfonyl)benzyl]-1,2,4-oxadiazole (8). Hydroxybenzotriazole hydrate (2.06 kg, 13.4 mol) was suspended in acetonitrile (25 L), and 2.5 L was distilled off at 1 atm under nitrogen to azeotropically remove water. [*CAUTION: Hydroxybenzotriazole will decompose, possibly violently, if heated above its melting point (155−160 °C).*][32] After cooling to 25−30 °C, 4-methylsulfonylphenylacetic acid (2.5 kg, 11.67 mol) was added, followed by EDC hydrochloride (2.68 kg, 14.0 mol). The resulting mixture was stirred at 20−30 °C for 30 min. Methylamidoxime (1.14 kg, 14.0 mol) was added to the slurry over 10 min. The resulting mixture was then heated at reflux for 12 h. The solution was solvent switched to ethyl acetate under reduced pressure (100−200 mBar, 40−50 °C) by continuous distillation of ∼40 L of ethyl acetate and concentrated to a final volume of ∼27 L. After cooling to ∼20 °C, aqueous $NaHCO_3$ (1 M, 20 L) was added slowly with vigorous stirring. The aqueous layer was removed, and the organic layer was washed with DI water (7.5 L). The aqueous solutions were back extracted with 17.5 L of ethyl acetate. The combined ethyl acetate solution was concentrated to ∼7 L (100−200 mBar, 50−70 °C) and diluted with 2-propanol (17.5 L). The solution was further concentrated to ∼12.5 L. The solution was allowed to cool to 10−20 °C, and the desired product precipitated. After stirring for 2 h the mixture was filtered; the solid was washed with 2 × 2.5 L of 2-propanol and then air-dried for 2 h. The solid was further dried in an oven at 30−35 °C under vacuum (N_2 sweep) to constant weight. Isolated yield: 2.6 kg, 88%. Mp 90−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (m, 2H), 7.52 (m, 2H), 4.27 (s, 2H), 3.02 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 176.3, 167.4, 139.9, 139.6, 129.9, 127.9, 44.4, 32.6, 11.4. Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.34; H, 4.69; N, 11.0.

6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-(3-{(*E*)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]-vinyl}phenyl)quinoline (9). Aldehyde **7** (3.18 kg, 9.0 mol) was suspended in 2-propanol (38 L). To the slurry was added the oxadiazole **8** (2.4 kg, 9.5 mol) followed by piperidine (1.05 L, 10.6 mol) at 20 °C. The mixture was heated at reflux, and the distillates were returned to the flask through a bed of molecular sieves for 22 h. After cooling to 20−25 °C and stirring for 4 h, the slurry was filtered, and the solids were washed with 2 × 5 L of 2-propanol. Isolated yield: 4.7 kg, 89%.

9: mp 201−203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 6H), 2.43 (s, 3H), 2.64 (s, 3H), 3.03 (s, 3H), 7.13 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.48−7.51 (m, 2H), 7.63−7.66 (m, 3H), 7.91 (d, J = 2.3 Hz, 1H), 7.96−7.99 (m, 2H), 8.03 (d, J = 2.3 Hz, 1H), 8.12 (s, 1H), 8.24 (dd, J = 1.6, 8.3 Hz, 1H), 8.96 (dd, J = 1.7, 4.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.7, 22.8, 34.9, 44.5, 64.6, 121.9, 124.2, 127.5, 128.1 (2 C), 128.5, 129.7, 129.9, 131.2, 132.4, 132.9, 133.3, 135.6, 136.9, 139.5, 139.8, 140.2, 140.4, 140.6, 145.1, 151.4, 167.8, 176.2. Anal. Calcd for $C_{31}H_{29}N_3O_5S_2$: C, 63.35; H, 4.97; N, 7.15; S, 10.91. Found: C, 63.41; H, 4.81; N, 7.02; S, 10.72.

9a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (s, 6H), 2.46 (s, 3H), 2.63 (s, 3H), 3.08 (s, 3H), 7.18 (br d, J = 7.8 Hz, 1H), 7.46−7.51 (o m, 2H), 7.57 (br s, 1H), 7.60−7.62 (o m, 3H), 7.73 (br d, J = 7.8 Hz, 1H), 7.97−7.99 (m, 2H), 8.03 (d, J = 2.3 Hz, 1H), 8.09 (d, J = 2.3 Hz, 1H), 8.26 (dd, J = 1.7, 8.3 Hz, 1H), 9.00 (dd, J = 1.8, 4.2 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.8, 22.7 (2C), 34.9, 44.6, 64.6, 121.7, 124.4, 127.6, 127.9 (2 C), 128.0, 128.2 (3C), 128.4, 129.9, 131.6, 132.3, 134.2, 135.7, 136.9, 139.4, 140.0, 140.3, 141.2, 143.5, 145.3, 151.3, 167.8, 174.9.

6-[1-Methyl-1-(methylsulfonyl)ethyl]-8-(3-{(*E*)-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-[4-(methylsulfonyl)phenyl]-vinyl}phenyl)quinoline benzenesulfonate (10). Free base **9** (996.6 g, 98.44 wt %, 1.0 equiv), 80:20 *N*,*N*-dimethylformamide/isopropyl acetate (v/v) (5.08 L) and benzenesulfonic acid (324 g, 98 wt %, 1.2 equiv) were combined. The resulting slurry was warmed to 40 °C for 30 min to afford a clear yellow solution. The solution was transferred through a line filter to a second vessel and seeded with **10** (62.1 g). Isopropyl acetate (2.9 L) was added to the reaction solution at 40 °C, and the slurry was stirred for 2 h to generate a seed bed. Additional isopropyl acetate (16.2 L) was added slowly over 3 h. Once the antisolvent addition was complete, the reaction slurry was slowly cooled from 40 to 5 °C over 5 h and then stirred for an additional 5 h. The product was isolated by vacuum filtration and washed with 95:5 isopropyl acetate/DMF (1 × 5 L slurry wash and 1 × 5 L displacement wash) and isopropyl acetate (2 × 5 L displacements washes), followed by tray drying in a vacuum oven at 35 °C. Isolated product (1136.5 g, 98.2 wt %, 91.3% isolated yield). Mp 210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 6H), 2.43 (s, 3H), 2.72 (s, 3H), 3.01(s, 3H), 6.85 (s, 1H), 7.30−7.43 (m, 6H), 7.65−7.70 (m, 4H), 7.88 (d, J = 8.2 Hz, 2H), 7.98−8.06 (m, 3H), 8.30 (d, J = 1.5 Hz, 1H), 8.90 (d, J = 10.9 Hz, 1H), 9.79 (d, J = 4.3 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 176.86, 168.87, 148.79, 147.99, 147.64, 141.93, 141.27, 140.44, 139.62, 136.74, 136.45, 135.89, 135.69, 134.77, 132.99, 132.33, 132.28, 132.13, 130.67, 130.29, 130.25, 129.97, 128.92, 128.77, 126.71, 126.56, 123.78, 65.36, 44.43, 35.73, 22.91, 11.79. Anal. Calcd for $C_{37}H_{35}N_3O_8S_3$: C, 59.58; H, 4.73; N, 5.63, S 12.90. Found: C, 59.51; H, 4.69; N, 5.63, S, 12.87.

(32) The acetonitrile solution of HOBt was not shock sensitive by drop weight testing.

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