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Process Development and Pilot-Plant Synthesis of (2-Chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanone

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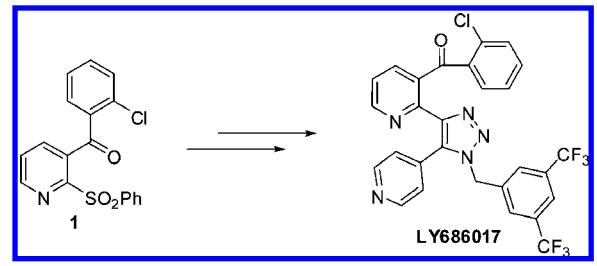
Abstract:

Routes to (2-chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanone, 1, an intermediate in the manufacture of NK1-II inhibitor LY686017 are described which produce 1 in >75% yield and 95% purity. A highly selective telescoped ortho lithation/condensation/oxidation process was developed and successfully scaled to the clinical pilot plant to produce 25 kg of 1. For the pilot-plant campaign, the lithiation step was developed to operate at −50 °C using commercial lithium diisopropylamide (LDA), and the oxidation step employed catalytic TEMPO as the primary and NaOCl as the terminal oxidant. After completion of the pilot-plant campaign second-generation approaches to 1 were developed to improve process greenness where the lithiation and condensation step were operated as warm as −10 °C, the highly efficient AZADO catalyst was used as a substitute for TEMPO in the Anelli−Montanari oxidation, and process mass intensity was reduced 25%.

Introduction

Mammalian tachykinins are peptide neurotransmitters that interact with central nervous system neurokinin receptors, and these interactions are implicated in the manifestations of physiological and behavioral symptoms of anxiety and depression. Inhibition of the NK-1 receptors might cause attenuation of the aforementioned symptoms, a hypothesis bolstered by reports from Merck and Pfizer on their respective NK1 inhibitors.[1] (2-Chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]-methanone, **1**, is an important intermediate in the preparation of **LY686017**, a potent NK1-II inhibitor which has been studied clinically for treatment of depression, anxiety, and alcohol dependency at Eli Lilly and Company (Scheme 1). The synthetic route for the preparation of **1** has been disclosed and includes a highly selective ortho lithiation of 2-benzenesulfonyl pyridine, **2**, at cryogenic temperatures and then condensation with 2-chlorobenzaldehyde, **4**, to produce intermediate alcohol **5**.[2] The crude alcohol is then efficiently oxidized using the Anelli−Montanari protocol with catalytic TEMPO as the primary and NaOCl as the terminal oxidant (Scheme 2). This process was run in the Lilly clinical pilot plant to produce 25 kg of **1** in five lots with 85% average yield and greater than 95% average purity. Some further optimization was performed after the pilot-plant campaign was completed to afford an improved crystallization process which delivered **1** in greater than 98% purity. Significantly, the process mass intensity[3] for the new process was reduced by 25% relative to the pilot-plant process. Among the available oxidation methodologies, the Anelli−Montanari reaction has wide utility and has been used commercially for oxidation of alcohols to carbonyl compounds.[4] The rapid conversions under mild operating conditions are particularly attractive as an important, emerging green oxidation methodology. Despite these successes, TEMPO is an expensive chemical, and for many processes up to 10 mol % is needed to

Scheme 1. **NK1-II inhibitor LY686017**



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(1) (a) Kramer, M. S.; Cutler, N.; Feighner, J.; Shrivastava, R.; Carman, J.; Sramek, J. J.; Reines, S. A.; Liu, G.; Snavely, D.; Wyatt-Knowles, E.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Swain, C. J.; Harrison, T.; Hill, R. G.; Hefti, F.; Scolnick, E. M.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Williams, A. R.; Hewson, L.; Smith, D.; Carlson, E. J.; Hargreaves, R. J.; Rupniak, N. M. J. *Science*. **1998**, *281*, 1640. (b) Kramer, M. S.; Winokur, A.; Kelsey, J.; Preskorn, S. H.; Rothschild, A. J.; Snavely, D.; Ghosh, K.; Ball, W. A.; Reines, S. A.; Munjack, D.; Apter, J. T.; Cunningham, L.; Kling, M.; Bari, M.; Getson, A.; Lee, Y. *Neuropsychopharmacology* **2004**, *29*, 385.

(2) Timpe, C.; Borghese, A.; Coffey, S. D.; Footman, P. K.; Pedersen, S. W.; Reutzel-Edens, S. M.; Tameze, S. L.; Weber, C. WO/2005/042515, 2005. CAN 142:469259.

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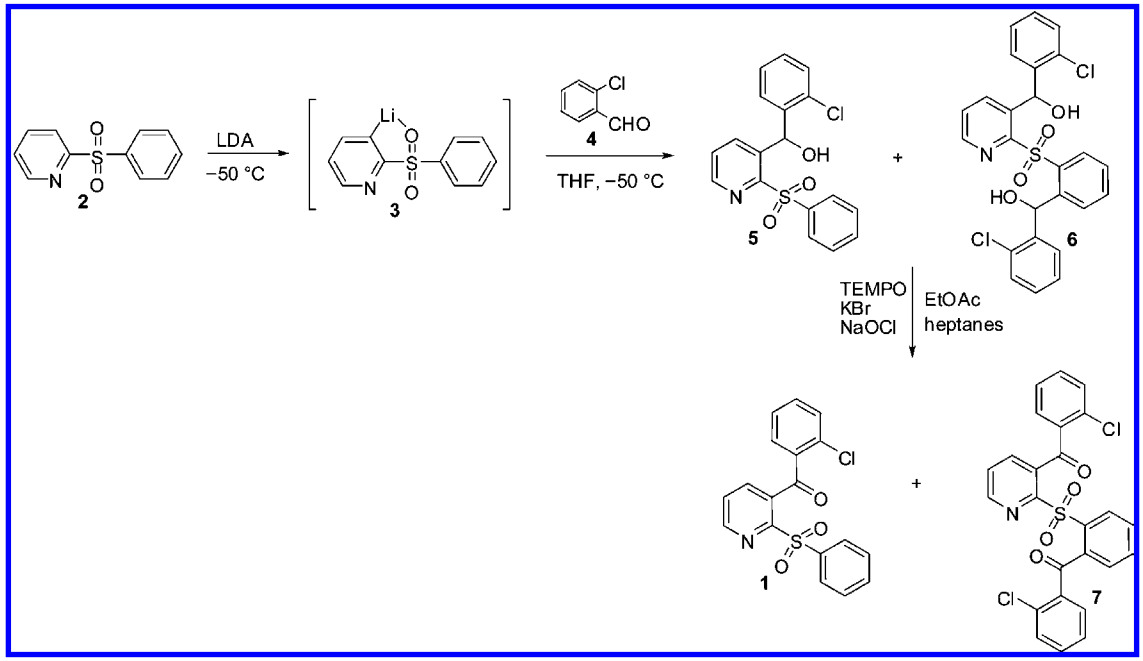
Scheme 2. **Synthesis of (2-chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanone, 1**



achieve productive transformations, and contamination of isolated products with TEMPO can be problematic.[5] For these reasons, there is still a need to develop and utilize similar oxidation catalysts that operate at much lower catalyst levels. In the course of research, we therefore developed a second-generation process where the lithiation step was operated at −10 °C and the Anelli−Montanari oxidation was performed with 1 mol % of the highly active AZADO catalyst.

Results and Discussion

Ortho metalations are well-known in the literature but can present significant operational hazards due to the potential formation of highly unstable benzyne intermediates.[6] Consequently, the thermal hazards of the target ortho lithiation reaction were characterized by the collection of ARC data. In this case, the adiabatic heat rise from the lithiation, condensation, and quench were measured at 33, 50, and 53 °C, respectively. For the initial 50-gal scale pilot-plant campaign, it was expected that these exotherms could be readily controlled by the dosage rate of process streams and managing the utilities.[7] While the heats of reaction were large compared to most conventional processes, they were relatively low in comparison to ortho lithation processes for similar substrates. A key requirement for long-term commercial manufacture was to show anion stability in the 2−5 h range which would allow for long-term operation of this process on a 2000-gal scale.

In Situ Lithium Diisopropylamide (LDA) Preparation. For initial evaluation of the chemistry on lab scale, a ∼0.65 M solution of LDA (lithium diisopropylamide) in THF/hexanes was produced by standard protocol.[8] A series of ortho metalation reactions were then run using conditions similar to what would ultimately be employed for scaling up under cryogenic conditions (Table 1). Each reaction was carried out at between −75 and −60 °C by adding a THF solution of 2-benzenesulfonylpyridine, **2**, to LDA.[9] The results of these experiments highlight the importance of proper LDA stoichiometry as an additional 0.05 equiv of LDA in the reaction causes formation of considerably more bis-alcohol impurity **6** as the kinetics of the secondary metalation become more favorable later in the reaction pathway when alcohol **5** is the dominant species (Table 1, entry 2). Both of the scale-up reactions performed well, but there was higher than expected levels of residual starting

(3) Process mass intensity is defined as the total mass of all materials (kg) used to produce 1 kg of active pharmaceutical ingredient (API). The process mass intensity calculation is based on compound **1**. For leading references see: (a) Dunn, P. J.; Wells, A. S.; Williams, M. T. *Green Chemistry in the Pharmaceutical Industry*, 1st ed.; Wiley-VCH: New York, 2010. (b) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521. (c) Constable, D. J. C.; Curzons, A. D.; Freitas dos Santos, L. M.; Geen, G. R.; Kitteringham, J.; Smith, P.; Hannah, R. E.; McGuire, M. A.; Webb, R. L.; Yu, M.; Hayler, J. D.; Richardson, J. E. *Green Chem.* **2001**, *3*, 7. (d) Eissen, M.; Hungerbûhler, K.; Dirks, S.; Metzger, J. *Green Chem.* **2003**, *5*, G25.

(4) (a) Backvall, J. E., Ed. *Modern Oxidation Methods*; Wiley-VCH: Weinhem, 2004. (b) Zanka, A. *Chem. Pharm. Bull.* **2003**, *51*, 888. (c) Fritz-Langhals, E. *Org. Process Res. Dev.* **2005**, *9*, 577. (d) Rossi, F.; Corcella, F.; Caldarelli, F. S.; Heidempergher, F.; Marchionni, C.; Auguadro, M.; Cattaneo, M.; Ceriani, L.; Visentin, G.; Ventrella, G.; Pinciroli, V.; Ramella, G.; Candiani, I.; Bedeschi, A.; Tomasi, A.; Kline, B. J.; Martinez, C. A.; Yazbeck, D.; Kucera, D. J. *Org. Process Res. Dev.* **2008**, *12*, 322. (e) Hewitt, B. D. WO/1995/9516698, 1995. CAN 123:314263.

(5) 2010 Aldrich pricing = $6/g (25 g quantity).

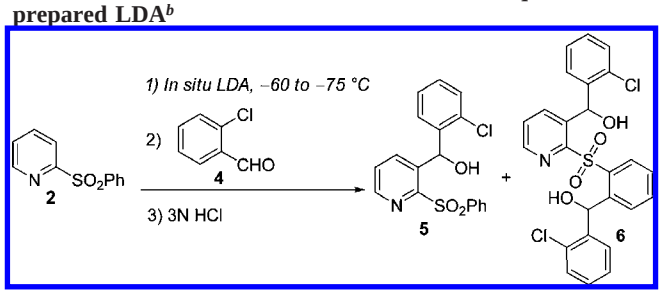
(6) (a) Rawalpally, T.; Ji, Y.; Shankar, A.; Edwards, W.; Allen, J.; Jiang, Y.; Cleary, T. P.; Pierce, M. E. *Org. Process Res. Dev.* **2008**, *12*, 1293. (b) Hickey, R. M.; Allwein, S. P.; Nelson, T. D.; Kress, M. H.; Sudah, O. S.; Moment, A. J.; Rodgers, S. D.; Kaba, M.; Fernandez, P. *Org. Process Res. Dev.* **2005**, *9*, 764. (c) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33* (49), 7495.

(7) In the event of a catastrophic utilities failure the process energetics are not sufficient to bring the reactor temperature up to the boiling point of the solvent system (THF/hexanes) used for the lithiation chemistry.

(8) (a) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934. (b) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773. (c) Enders, D.; Pieter, R.; Renger, B.; Seebach, D. *Org. Synth.* **1978**, *58*, 113.

(9) Pre-cooling of solutions containing **2** is not recommended due to precipitation risk.

Table 1. **Ortho metalation reactions with 1.05 equiv in situ prepared LDA[b]**



entry	scale (g)	**5** (%)	**2** (%)	**6** (%)
1	5	93.8	2.1	2.1
2	5[a]	83.3	5.7	6.3
3	50	88.3	7.0	1.3
4	100	88.4	8.0	1.4
5	5	92.4	3.2	1.3
6	5	91.2	3.7	2.5

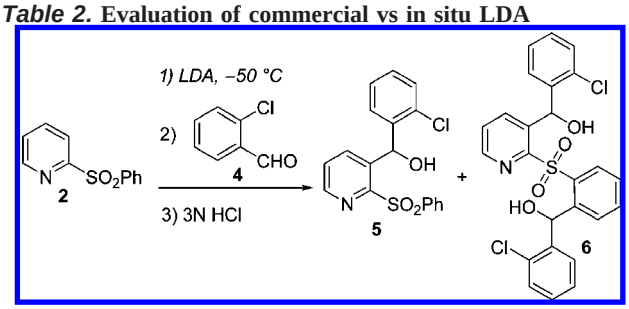
[a] 1.10 equiv of LDA. [b] All HPLC data reported in tables are uncorrected area % at 250 nm.

material **2** and low levels of the bis-product **6**; it was suspected that this was due to an undercharge of LDA.[10]

As we prepared to adapt this chemistry to 50-gal scale, the lithiation/condensation operation temperature was recentered at −50 °C due to commercial manufacturing constraints. Process modeling data showed that by assuming a reactor temperature of −50 °C, a jacket temperature of −60 °C, and an estimated heat of reaction of 100 kJ/mol for lithiation of **2**, the minimum addition time on a 2000-gal scale would be about 3 h. Consequently, one of the goals of the pilot-plant campaign was to evaluate longer addition times to see if there were any adverse effects to the process. Unfortunately, precooling the THF solution containing **2** was not an option because the solid would precipitate.

Evaluation of Commercial LDA. The use of *n*-butyllithium solutions on large scales is replete with hazards and requires specialized handling procedures.[11] In fact, all formulations of *n*-butyllithium have been classified as pyrophoric by the DOT. A further hazard associated with direct use of *n*-butyllithium is liberation of butane during processing, which requires appropriate venting controls. A potentially attractive option is the use of commercial LDA, which is significantly less hazardous,[12] and is available on large scale from FMC Lithium as a 2.0 M solution in a mixture of THF/heptanes/ethylbenzene. However, there are some known liabilities of commercial LDA as these solutions undergo decomposition to LiH and the corresponding imine, the rate of which is primarily impacted by storage temperature. Thus, it is not surprising that there are several reports of inconsistent performance with commercial LDA,

Table 2. **Evaluation of commercial vs in situ LDA**



entry	LDA (equiv)	LDA Source	conversion to **5** (%)	remaining **2** (%)	conversion to **6** (%)
1	1.05	in situ	85.8	7.1	0.69
2	1.10	in situ	80.8	6.5	3.4
3	1.30	in situ	69.9	12.1	7.9
4	1.00	commercial	66.2	10.8	1.2
5	1.10	commercial	82.4	5.5	1.7
6	1.15	commercial	82.7	6.2	1.6
7	1.20	commercial	76.2	6.5	2.9
8	2.0	commercial	48.8	15.8	8.2
9	3.0	commercial	11.7	25.4	12.7
10[a]	1.05	commercial	87.7	3.6	2.4

[a] 500 g scale run.

especially when an aged source is used.[13] In comparison, *n*-butyllithium solutions are stable at ambient temperature, but are much more sensitive to moisture-based degradation. However, in our case the overall improved safety profile with commercial LDA was a significant driver to thoroughly evaluate that option. A fresh supply of commercial LDA was evaluated head to head with in situ prepared LDA (Table 2). The commercial LDA was diluted with THF to produce a 0.65 M solution comparable in concentration to the in situ produced LDA.

The results achieved using commercial LDA were similar, although not identical, to using in situ prepared LDA and demonstrated a close correlation between LDA stoichiometry and the amount of bis-addition product **6** (Table 2). With these results in hand, commercial LDA was evaluated on a 500 g scale, and the results showed excellent conversion albeit with elevated levels of bis-byproduct **6** compared to when in situ LDA was employed (Table 2, entry 10 vs entry 1). To overcome solubility issues we also evaluated an inverse addition protocol at double the normal dilution which gave very similar results to the standard addition mode. Anion stability was tested at −50 °C, by aging the mixture for 5 h prior to quenching with aldehyde **4**, which produced one of the best results to date. The stoichiometry of aldehyde **4** was shown to be not as crucial as the LDA charge since excess aldehyde was oxidized to 2-chlorobenzoic acid which was removed in the aqueous workup. For standard conditions, a slight excess of aldehyde (1.05 equiv) was employed because if there were elevated levels of bis-anion present, this would also result in unreacted starting material. With the data showing that fresh commercial LDA performs as well as in situ generated LDA when scaled, the

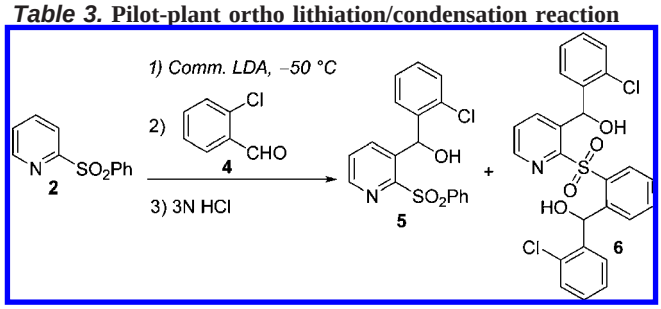
(10) In this case, the scale-up runs were performed with *n*-butyllithium which had been used for several prior experiments.

(11) (a) Dezmelyk, E. W.; Reed, R. S. *Ind. Eng. Chem.* **1961**, *53* (6), 68A. (b) Schwindeman, J. A.; Woltermann, C. J.; Letchford, R. J. *Chem. Health Saf.* **2002**, (May/June), 6.

(12) Commercial LDA is nonpyrophoric, as determined by the Department of Transportation (DOT). The official test for pyrophoricity is detailed in the DOT regulations. Code of Federal Regulations, 49 CFR 173, Appendix E.

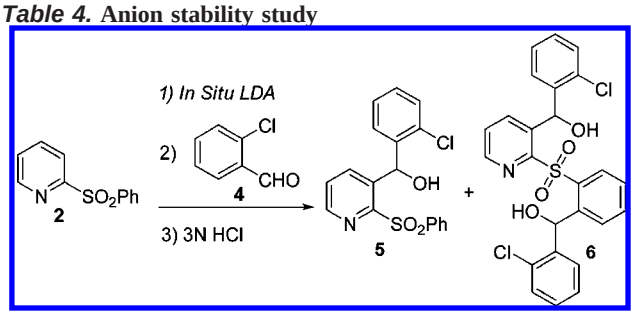
(13) (a) Smith, I. H.; Alorati, A.; Frampton, G.; Jones, S.; O'Rourke, J.; Woods, M. W. *Org. Process Res. Dev.* **2003**, *7*, 1034. (b) Collum, D. B.; Singh, J. K.; Hoepkar, P. C.; Gupta, L. *J. Org. Chem.* **2009**, *74* (5), 2231. (c) Morrison, R. C.; Hall, R. W.; Rathman. T. L. U.S. Pat. 4,595,779, 1986.

Table 3. **Pilot-plant ortho lithiation/condensation reaction**



batch	addition time of **2** (min)	addition time of **3** (min)	LDA (equiv)	conversion to **5** (%)	remaining **2** (%)	conversion to **6** (%)
1	27	40	1.05	78	9.9	2.6
2	21	39	1.15	75	7.6	4.6
3	58	60	1.12	78	4.7	5.0
4	117	120	1.10	77	7.8	6.8
5	17	27	1.12	87	4.5	4.2

Table 4. **Anion stability study**



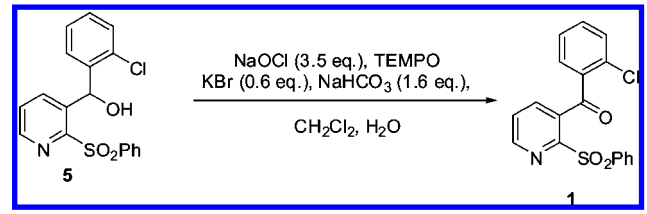
entry	reaction temperature (°C)	conversion to **5** (%)	remaining **2** (%)	conversion to **6** (%)
1	−70	89	5.7	1.0
2	−50	87	11	1.0
3	−40	93	6.8	0.1
4	−20	90	8.0	0.8
5	−10	92.1	6.8	0.6
6	0	88.0	10.3	0.7

decision was made to move ahead with commercial LDA for the pilot plant campaign. A total of five lots were run in the pilot plant with each using a 3.5 kg charge basis of 2-benzenesulfonyl pyridine **2**, the crude product solutions were quenched with 3 N HCl, and then carried directly into the oxidation and crystallization steps for production of **1** (Table 3). As expected, the process streams with the faster feed rates resulted in improved conversion and purity, but notably all feed rates examined produced satisfactory results.

Second-Generation Lithiation/Condensation Studies. While the results from the pilot-plant scale lithiation/condensation reaction were acceptable, an attractive green chemistry improvement would be to operate this chemistry at warmer temperatures. With this objective in mind, a significant goal of this new study was to ascertain the stability of the anion **3** at milder temperatures. Thus, the initial study on 2-g scale involved preparation of the LDA at −70 °C and addition of **2**, followed by adjustment to the desired temperature (Table 4). The anion solution was then held for 2 h at the selected temperature, followed by addition of aldehyde **4**.

The results of the anion study revealed considerable stability, even up to 0 °C. However, when the anion temperature was raised further to room temperature, degradation of the anion

Scheme 3. **Standard condition for Anelli−Montanari oxidation**



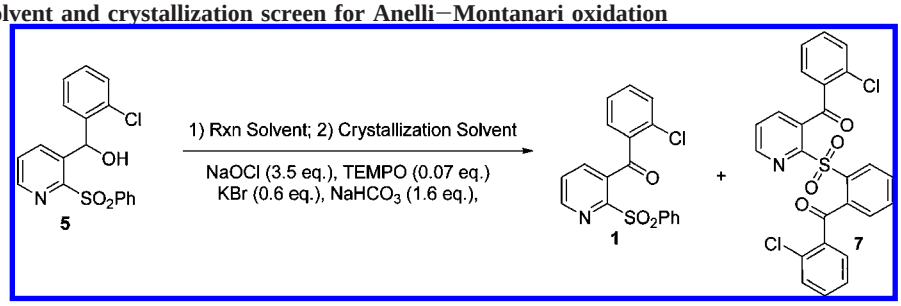
was observed with only a mixture of starting materials (**2** and **4**) observed. Thus, it was evident that the process could be carried out at a much higher temperature, thereby eliminating the need for extreme cryogenic conditions. The next step was to determine whether the anion of **3** could be generated at warmer temperatures. Thus, generation of the LDA was carried out at −10 °C, followed by addition of **2** and quenching with 2-chlorobenzaldehyde. The crude product was formed with 87% conversion and barely detectable levels of bis-addition product **6**. From this data it was surmised that the bis-anion was significantly less stable at warmer temperature. While the quantity of remaining starting material was higher than desired, there was not a considerable difference between this temperature and some of the lower-temperature reactions (cf. −50 °C, Table 4, entry 2).

Oxidation Reaction Development. With improved conditions developed for the lithiation/condensation step, our attention was directed toward the oxidation step. The crude alcohol/THF solution was initially solvent-exchanged to dichloromethane, which is the most prevalent solvent for the Anelli−Montanari oxidation.[14] Initial experiments used 0.07 equiv of TEMPO and 3.5 equiv of 12 wt % aqueous sodium hypochlorite in a solution of dichloromethane and crude alcohol **1** (Scheme 3). These conditions gave complete conversions without formation of impurities other than those indigenous to the ortho metalation reaction such as ketone **7**. Sodium bicarbonate was used to lower the pH of the bleach to 8.5−9.5 and to buffer any acid formed in the reaction, because sodium hypochlorite is unstable at a lower pH. Additional water generally does not affect the reaction rate of the biphasic system, and oxidations are usually complete within 1 h. We also examined two literature alternatives to the current process. The first method, employing trichloroisocyanuric acid, potassium bromide, and TEMPO in acetone and water delivered only a 2:1 ratio of starting material to product after 21 h, even after heating to 50 °C for the last 2 h. The second method, using sodium hypochlorite and acetic acid, showed only 1.7% conversion to product after 19 h; thus, both of these approaches were abandoned.

Since **1** is freely soluble in dichloromethane, a greener solvent was desired for crystallization of **1**. The result of solubility studies revealed that **1** was sparingly soluble in toluene (14 mg/mL) which made it a potentially attractive crystallization solvent. Ultimately, the goal was to replace dichloromethane entirely in both the reaction and isolation. For the oxidation reaction we found that toluene performed equivalently to dichloromethane, and as the reaction progressed in toluene, compound **1** precipitated from the reaction and could be isolated

(14) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970.

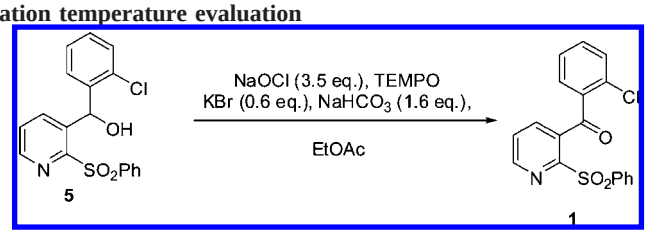
Table 5. **Reaction solvent and crystallization screen for Anelli−Montanari oxidation**



entry	rxn solvent	xtal solvent	crude **1** (%)	crude **7** (%)	yield **1** (%) isolated	purity **1** (%) isolated	**7** (%) in product
[a]1	CH_2Cl_2	EtOAc/heptane	98	0.3	90	99.9	n.d.
[a]2	toluene	toluene	98	n.d.	86	99.8	n.d.
[a]3	EtOAc	EtOAc/heptane	99	n.d	90	100	n.d.
4	CH_2Cl_2	EtOAc/heptane	91	2.0	85	99.1	0.43
5	EtOAc	EtOAc/heptane	78	1.5	84	99.0	0.39
[b]6	EtOAc	EtOAc/heptane	90	2.4	90	97.2	1.2

[a] Purified **5** used. [b] 500-g scale-up.

Table 6. **Anelli−Montanari oxidation temperature evaluation**



entry	start temp (°C)	end temp (°C)	addition time (min)	remaining **5** (%)	reaction conversion to **1** (%)
1	2	16	25	0.3	79
2	7	17	20	n.d.	89
3	10	21	20	0.9	86
4	15	27	15	0.8	78
5	22	36	30	2.1	79
6	23	38	30	2.3	83

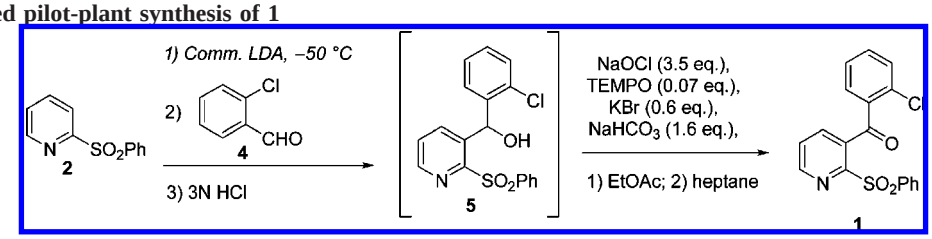
without additional workup. However, the reaction mixture became very thick as the product precipitated, and we were concerned that poor mass transfer could negatively affect completion as the process was scaled. Additionally, filtration of the biphasic mixture to isolate **1** was found to be very slow on lab scale which would not translate well to plant scale. Additional solvent screens were run for the reaction and crystallization (Table 5).

The process screen revealed that ethyl acetate was an effective solvent for both reaction and crystallization; with purified alcohol **5** as a substrate a 99% conversion was observed within an hour, and an isolated yield of 90% was achieved. As the reaction progressed in ethyl acetate, the product precipitated. However, the isolated yield was about 10% lower due to loss of product to filtrate. Heptane was found to be an effective antisolvent, and after the reaction was complete in EtOAc, the mixture was warmed to ambient temperature and 8 volumes of heptanes were added. Under these conditions it was possible to telescope crude alcohol **5** directly to **1** in 84−90% yield with 97−99% chemical purity (Table 5, entries 5, 6). In contrast to the toluene crystallization, the biphasic filtration in the ethyl acetate/heptane/water system was exceptionally rapid, occurring within a few minutes. With respectable small-scale results in hand, we tested the telescoped process on a 500-g scale of 2-benzenesulfonylpyridine **2**. The ortho metalation proceeded as expected, with 3.6% residual starting material and 2.4% bis-impurity **6** (Table 2, entry 10). The oxidation reaction also ran as expected with less than 1% alcohol **5** remaining after one hour and the isolated yield (90%) was the best to date; however, the purity of the isolated solid was lower than expected with 2.8% total impurities including 1.2% bis-adduct **7** (Table 5, entry 6). We were able to reslurry the product in 1:1 ethyl acetate/heptane and recovered 94% of **1** with 99.4% purity. This indicated that the initial filter cake wash might not have been very effective, possibly due to channeling.

During the oxidation reaction we observed that the addition of bleach was exothermic; therefore, the reaction contents are usually cooled before the addition. Throughout most of the development phase, we cooled the alcohol **5** solution to 0−5 °C which allowed rapid bleach addition while maintaining a pot temperature of <15 °C on small scale. To potentially save on heating and cooling time on production scale, we evaluated warmer temperatures for the oxidation (Table 6). The amount of remaining **5** could be driven below 1% except when the oxidation process was started at room temperature and allowed to exotherm to 35−40 °C (Table 6, entries 5, 6). Most likely, the decreased conversion is due to NaOCl degradation which is common at higher temperatures.

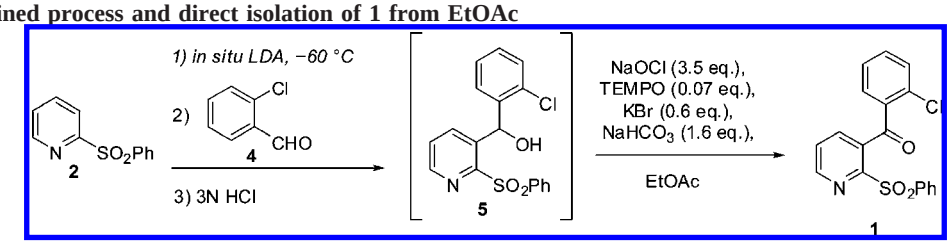
Both of the reactions that commenced between 10−15 °C showed a steady exotherm from the outset of the bleach feed, with maximum end temperatures of 21−27 °C (Table 6, entries 3, 4). With the success of these experiments, we decided that

Table 7. **Telescoped pilot-plant synthesis of 1**



entry	conversion to **1** (%)	remaining **2** (%)	conversion to **6** (%)	yield (kg) isolated	yield (%) isolated	purity **1** (%) isolated	**2** (%) in product	**7** (%) in product
1	72	10.3	2.8	4.4	76	98.2	3.4	1.2
2	72	8.7	7.1	4.8	84	94.1	2.8	6.1
3	76	5.0	5.2	5.1	88	96.8	1.4	3.1
4	75	6.4	5.1	5.0	87	93.7	1.1	5.0
5	82	3.9	4.2	5.2	92	96.4	0.6	3.3
ave	75	6.9	4.9	24.5 (net)	85	95.8	1.9	3.7

Table 8. **Streamlined process and direct isolation of 1 from EtOAc**



entry	scale **2** (g)	crude **1** (%)	crude **2** (%)	crude **7** (%)	yield (%) isolated	purity **1** (%) isolated	**2** (%) in product	**7** (%) in product
1	5	83	4.6	5.8	75	98.2	0.50	0.91
2	50	82	5.1	1.5	82	99.0	0.50	0.21
3	100	83	6.2	1.1	81	99.2	0.57	0.24
4	400	92	1.9	2.3	87	97.8	0.67	0.85
5	400	90	2.2	2.7	85	97.7	0.91	0.94

the oxidation step in the pilot plant would start at ∼15 °C and the exotherm would be limited to not more than 20 °C by jacket temperature control. Prior to the start of the pilot-plant campaign we also evaluated a reduced TEMPO catalyst load from the standard level of 7 mol %. Unfortunately, reduction of the catalyst level to 3 mol % resulted in only a ∼50% conversion, and addition of kicker charges of TEMPO did not increase the conversion, so we decided to stay with the standard catalyst load of 7 mol %.

Pilot-Plant Synthesis of 1. The telescoped process for the 500-g scale synthesis of **1** was run in the pilot plant on a 50-gal scale. A total of 25 kg of **1** were produced in five lots with average 95.8% purity (Table 7). The initial run resulted in a high level of residual starting material **2** (10.3%) that gave correspondingly higher amounts in the isolated product. The LDA stoichiometry was increased in the next lot and the bis-byproduct **6** was significantly elevated (Table 7, entry 2). The Anelli−Montanari oxidation performed as expected, efficiently converting crude alcohol **5** and bis-alcohol impurity **6** to the desired product **1** and bis-diketone **7** within one hour. The main difference between the pilot-plant runs and supporting-laboratory runs was that the oxidation step was run at a warmer starting temperature of 14 °C, and an exotherm to 20 °C was observed during the bleach addition. The main issue encountered was variable impurity levels on pilot scale, with respect to the bis-adduct **7**. Fortunately, while the chemical purity of **1** was low for an API starting material, a rework was not necessary. Forward-processing of **1** to the penultimate intermediate involves a S_NAr reaction that converts the bis-ketone **7** to a byproduct that is completely removed during the workup. Thus, all lots of **1** produced in this campaign were converted to the penultimate intermediate, none of which contained any impurities related to the purity profile of **1**.

Second-Generation Studies. Although the yield goals were achieved for the pilot-plant campaign, the higher than expected impurity levels and process variability needed to be addressed before outsourcing the process to contract manufacturing organizations. After the pilot-plant campaign was complete, a survey of methods to purify **1** was performed. We found that bis-impurity **7** could be reduced by a factor of 5 with a 92% recovery with an ethyl acetate reslurry at 0−5 °C. Numerous other solvent systems were studied, but ethyl acetate was by far the most effective. With this data in hand, the next logical step was to evaluate heptane removal from the precipitation/isolation step in the standard process. For these studies we used 1.05 equiv of in situ generated LDA, and series of experiments were run while progressively increasing the scale (Table 8). The final two experiments were performed on a 400-g scale of **2** in 22 L equipment. In both cases, after the reaction was complete the mixture was cooled to 0−5 °C and the entire contents of the biphasic mixture were filtered to isolate **1** without the addition of heptanes. Under these conditions, the two 400-g scale-up runs averaged 86% yield of isolated product with 97.8% chemical purity, a 2−3% improvement in purity from that in the pilot-plant campaign. Analysis of the filtrate revealed a 6−7% soluble product loss which was about 4−5% worse than filtrate loss observed in the pilot plant. The overall mass yield of **1** for the streamlined process was the same as for the

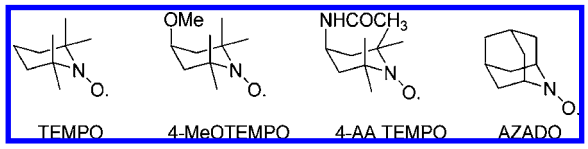
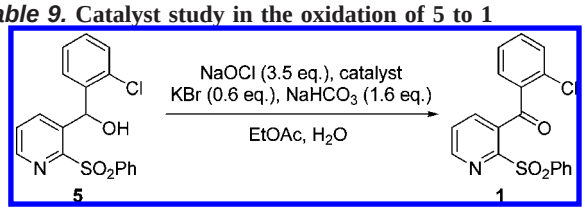


Figure 1. **TEMPO alternatives.[16]**

Table 9. **Catalyst study in the oxidation of 5 to 1**



loading amount (equiv)	yield of **1** (%)[a]			
	TEMPO	4-MeO-TEMPO	4-AA-TEMPO	AZADO
0.07	93	98	90	94
0.01	53	62	47	99
0.005	25[b]	54	46	97

[a] Combined yield of product, which precipitated, plus extraction of organic layer. [b] No precipitate.

pilot-plant campaign. However, the potency-corrected yield for the second-generation approach was ~3% higher due to improved purity of the product. The overall improvements in yield and quality appear to be mainly due to higher-purity ortho lithiation/condensation reactions. Most notably, bis-impurity **7** in all experiments was reduced to <1% by the crystallization. The streamlined process can not only accommodate a wider variability in the ortho lithiation reaction but also significantly reduces the process mass intensity by 25%. Ultimately, these conditions will be recommended to contract manufacturing organizations targeting the production of **1**.

Alternative Oxidant Screens. Despite the successes of the TEMPO system, an opportunity existed to investigate alternatives with improved catalytic activity (Figure 1). TEMPO, 4-acetamido-TEMPO, 4-methoxy-TEMPO, and AZADO[15] were evaluated in the sodium hypochlorite oxidation of **5** to **1** (Table 9).

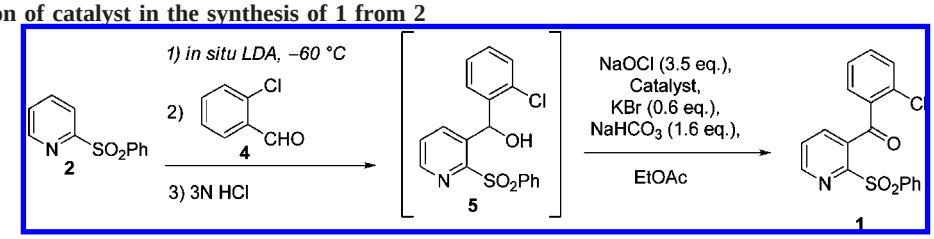
At loadings of 0.07 equiv, the four organocatalysts exhibited similar catalytic activity. On decreasing the loading to 0.01 equiv, the efficiency of the TEMPO-based catalyst was reduced, while AZADO maintained its high activity. When the catalyst loading was decreased to 0.005 equiv, the efficiency of the TEMPO-derived catalysts were further reduced (with TEMPO proving to be the least efficient), while a 97% conversion was still achieved with AZADO. However, at this lower loading of AZADO less product precipitated out of the reaction solution (76% vs 94−99%) than with the corresponding experiments which were conducted using the higher catalyst loadings, and on extracting the mother liquor a further 21% of **1** was isolated. In this case the crystallization mixture was ~20% more dilute which likely contributed to the higher loss of yield of product to filtrate. While the experiment was not repeated with the typical substrate concentration, we decided to continue further experimentation with 0.01 equiv AZADO. Enhanced reactivity of AZADO has been postulated to be due to reduced steric hindrance near the nitroxyl group (Figure 1).[13] These same four oxidation catalysts were then used in the two-step process for the preparation of **1** from **2**. Experiments were conducted using ~2 g of **2** in which either 0.07 equiv of TEMPO, 4-MeO-TEMPO, or 4-acetamido-TEMPO or 0.01 equiv of AZADO were employed (Table 10). As expected, similar yields of **1** were achieved on employing a 0.01 equiv loading of AZADO in comparison to a 0.07 equiv loading of TEMPO.

Borax (sodium tetraborate, $Na_2B_4O_7$) has been described as an environmentally friendly alternative to KBr by Augustine.[17] Two experiments were conducted using 0.6 equiv of borax as a 2% aqueous solution. With 7 mol % TEMPO this afforded **1** in 74% yield, while the use of 1 mol % of AZADO and borax gave **1** in 86% yield. However, the isolated ketone **1** contained borax as an impurity which coprecipitated from the reaction medium, making this a less attractive option. The final refinement we evaluated was performing the fully telescoped process with 1 mol % AZADO where the lithiation step was operated at −10 °C. In this case the process was scaled up to 5 L scale (using 200 g of **2**) with an overall yield of 71% being achieved (Scheme 4). With further optimization it is anticipated that the yield of the process could match the TEMPO-based process.[18] The AZADO catalyst is presently available in small quantities from Aldrich (250 mg @ $187.50). While bulk quantities for commercial scale do not appear available without custom manufacture, it is hoped that the successes reported here and elsewhere will produce a commercial market for the highly active AZADO catalyst.[19]

Process Impurities. Both 2-benzenesulfonyl pyridine **2** and alcohol **5** can be found in varying amounts in isolated **1** due to incomplete reactions. The synthesis of **2** for all studies was prepared in high yield and purity by the Trankopach reaction.[20] The principal process impurity observed was bis-ketone **7** which was formed by the reaction of monolithiated **2** with excess LDA followed by the subsequent reactions. The dilithiated species where the second lithiation occurs on the other benzene ring then reacts with 2-chlorobenzaldehyde to produce diol **6** that undergoes oxidation to the diketone **7**. The bis-adduct was found to be significantly more insoluble in water than **1** and of interest; secondary reactions with the parent pyridine ring were not observed. Compounds **8** and **9** are positional isomers of **1** and can be traced back to contamination of 2-chlorobenzaldehyde with the 3- and 4-chloro isomers (Figure 2). We prepared the 3- and 4-chloro isomers of **1** without any significant issues using the telescoped TEMPO process, and both analogues behaved similarly to the 2-chloro isomer. These standards were used to show that production batches of **1** typically contained non-detectable levels of isomers **8** and **9**.

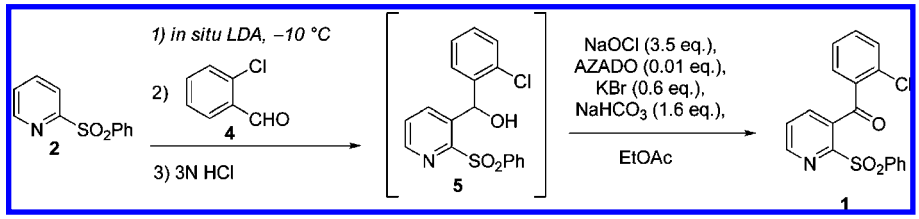
(15) Shibuya, M.; Tomizawa, I.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *126*, 8412.
(16) Criminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245.
(17) (a) Prakash, I.; Tanielyan, S. K.; Augustine, R. L.; Furlong, K. E.; Scherm, R. C.; Jackson, H. E. U.S. Pat. 6,825,384, 2004. CAN 142: 6014. (b) Tanielyan, S. K.; Augustine, R. L.; Prakash, I.; Furlong, K. E.; Scherm, R. C.; Jackson, H. E. WO/2004/067484, 2004. CAN 141: 190314. (c) Tanielyan, S.; Augustine, R.; Meyer, O.; Korell, M. U.S. Pat. 7,030,279, 2006. CAN 144: 393182.
(18) Preliminary experiments indicate that 2-methyl THF may be a viable alternative to THF for the lithiation chemistry.
(19) When running the oxidation step in the clinical pilot plant in 2005, AZADO was not available.
(20) Kopach, M. E.; Trankle, W. G. *Org. Process Res. Dev.* **2007**, *11*, 913.

Table 10. **Variation of catalyst in the synthesis of 1 from 2**



catalyst	loading (equiv)	yield (%)
TEMPO	0.07	74−80
4-methoxy-TEMPO	0.07	63
4-acetamido-TEMPO	0.07	69
AZADO	0.01	78

Scheme 4. **Preparation of the ketone 1 using AZADO methodology**



Conclusions

A highly selective ortho lithiation/condensation/oxidation telescoped process to produce 25 kg of **1** was demonstrated in our pilot plant. Commercial LDA was used for the lithiation step which operated at −50 °C. The efficient Anelli−Montanari oxidation using catalytic TEMPO (7 mol %) was used to oxidize the intermediate ketone to **1**. A second-generation process was also developed which delivered the target compound in improved purity using ethyl acetate as both oxidation and crystallization solvent. Significantly, this improved process had a 25% reduced process mass intensity relative to that of the piloted route. In addition, we developed an alternative process option where the lithiation chemistry can be performed at −10 °C and the Anelli−Montanari oxidation can be run with the highly efficient AZADO catalyst.

Experimental Section

General. For non-pilot-plant and kilo-lab operations solvents were distilled prior to use as follows. Tetrahydrofuran was freshly distilled over sodium benzophenone ketal; ethanol was distilled from magnesium ethoxide and stored over activated 3 Å molecular sieves; ethyl acetate was distilled over potassium carbonate; diisopropylamine was freshly distilled over calcium hydride. High performance liquid chromatography (HPLC) analysis was performed on a Waters Alliance 2690 separations module with a Waters 486 tunable absorbance detector using a Zorbax RX-C8 (25 mm × 4.6 mm × 5 mm) column using a flow rate of 1.0 mL/min, a wavelength of 250 nm, at a temperature of 23 °C. Mobile phases (A and B) were 0.1% H_3PO_4 in H_2O and acetonitrile, respectively. HPLC retention times were as follows: compound **1** = 11.2 min; compound **2** = 9.3 min; compound **4** = 10.5 min; compound **5** = 10.7 min; compound **6** = 11.8 min; compound **7** = 12.2 min; compound **8** = 11.6 min; compound **9** = 11.6 min.

(2-Chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanone, 1. *Preparation A: Pilot-Plant Synthesis with Commercial LDA.* Tetrahydrofuran (17 L) was charged to a 30-gal glass-lined cryo-rated vessel and cooled to −55 °C. Commercial LDA (2.1 *M*, 6.8 kg, 8.4 L) was charged and the vessel temperature readjusted to −55 °C. A solution of compound **1** (3.5 kg) in THF (11 L) was added over 17 min at <−50 °C. The mixture was stirred for 2.5 h at −55 °C, and then a solution of aldehyde **4** (2.39 kg) in THF (4 L) was added over 27 min at <−50 °C. The solution was stirred at −50 °C for 2 h at which time HPLC analysis showed 4.5% of compound **2** remaining. Aqueous 3 N HCl (29.4 kg) was added to the reaction over 13 min while allowing the contents to warm to 10 °C. The contents were warmed to 20 °C, and the layers were allowed to separate. The lower aqueous layer was back extracted with ethyl acetate (21 L), the combined organic layers were washed with 8.5 wt % $NaHCO_3$ (25 kg), and the resulting organic solution was vacuum distilled with a maximum jacket temperature of 55 °C to a volume of 15−20 L. Ethyl acetate (35 L) was added, and the solution was reconcentrated to a volume of 15−20 L. Ethyl

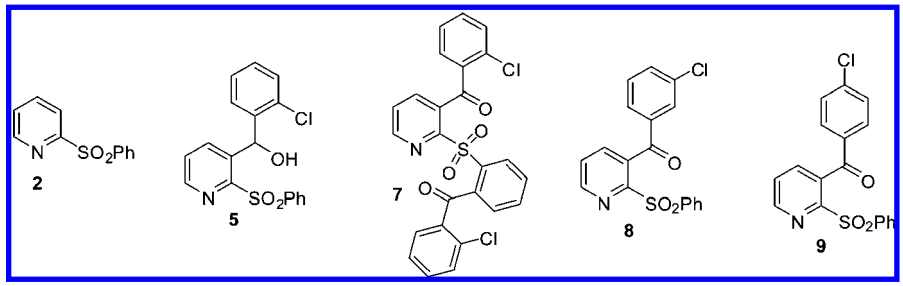


Figure 2. **Impurities identified in the preparation of 1.**

acetate (15 L), aqueous 10% potassium bromide solution (11.2 kg), and 2,2,6,6-tetramethyl-1-piperidine-*N*-oxide (TEMPO) (180 g) were added to the 50-gal vessel, and the mixture was cooled to 15 °C. A solution of 12% aqueous sodium hypochlorite (31 L), sodium bicarbonate (1.7 kg), and water (18 kg) was added to the biphasic mixture over 45 min, while allowing the reaction temperature to heat to 20 °C. After the reaction mixture stirred for 1 h at 20−25 °C, HPLC analysis of an aliquot showed <1% of compound **5** remaining. Heptane (28 L) was added to the product mixture over 30 min. The mixture was then aged for 3 h at 20 °C, the slurry was filtered, and the cake was washed with heptanes (10 L), followed by water (10 L) and then heptanes (10 L). The product **1** was dried under vacuum at 55 °C for 44 h to produce 5.2 kg (92% yield) of **1** with a potency of 96.4%. ν_{max}/cm^{-1} (KBr) 3445, 1682, 1298, 1159; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, ddd, *J* 7.8, 7.2, 1.6), 7.45−7.56 (5H, m), 7.59−7.65 (1H, m), 7.74 (1H, dd, *J* 7.6, 1.6), 7.81 (1H, dd, *J* 8.0, 1.6), 7.98−8.04 (2H, m), 8.78 (1H, dd, *J* 4.4, 1.6); δ_C (75.5 MHz, $CDCl_3$) 126.4, 126.8, 128.9, 129.2, 131.5, 133.1, 133.8, 133.9 (8 × CH), 134.2, 134.8 (2 × C), 136.7 (CH), 137.1, 138.6 (2 × C), 150.5 (CH), 155.1, 191.5 (2 × C). HRMS (ES^+) Exact mass calculated for $C_{18}H_{13}{}^{35}ClNO_3S$ [$(M + H)^+$], 358.0305. Found 358.0298, *m/z* (ES^+) 359.9 {[($C_{18}H_{13}{}^{37}ClNO_3S$) + H^+], 40%}, 358.0 {[($C_{18}H_{13}{}^{35}ClNO_3S$) + H^+], 100%}. Process Mass intensity = 53.4 kg/kg **1**.

Preparation B: Second-Generation Kilo-Lab Process with EtOAc Crystallization. Tetrahydrofuran (2.0 L) and diisopropylamine (335 mL) at −75 °C were treated with 1.6 M *n*-butyllithium in hexanes (1.28 L) over 30 min at <−60 °C. The resulting light-yellow solution was stirred at −60 to −70 °C for an additional 30 min; then a solution of compound **1** (400.5 g) in THF (1.2 L) was added over 20 min at <−60 °C. A greenish-yellow suspension formed during the addition, and the mixture was stirred for 2.5 h at −60 °C. A solution of compound **4** (272.3 g) in THF (400 mL) was added over 30 min at <−60 °C. The solution was stirred at −60 °C for 1 h at which time HPLC analysis showed 3.6% of compound **1** remaining. Aqueous 3 N HCl (2.8 L) was added over 30 min while allowing the contents to warm to 2 °C (the cooling bath was removed about halfway through the addition). The contents were stirred until the temperature warmed to 8 °C over 30 min. Stirring was stopped, the layers were separated, and the lower aqueous layer was extracted with ethyl acetate (4 L). The combined organic layers were stirred with saturated sodium bicarbonate solution (1 L) for 15 min, and the layers were allowed to separate. The organic solution was vacuum distilled (bath temperature was 48 °C) to a volume of ∼1 L. Ethyl acetate (4 L) was added, and the solution was reconcentrated to a volume of 2 L. Ethyl acetate (2 L), aqueous 10% potassium bromide solution (1.3 L), and then 2,2,6,6-tetramethyl-1-piperidine-*N*-oxide (TEMPO) (20.8 g) were added, and the mixture was cooled to 3 °C. A mixture of 12% aqueous sodium hypochlorite (3.6 L), sodium bicarbonate (192.2 g), and water (2.2 L) was added to the biphasic solution over 1 h while allowing the reaction temperature to rise to 22 °C. After stirring the reaction mixture for 1 h at 20−25 °C, HPLC analysis of an aliquot showed 0.73% of compound **5** remaining. The mixture was cooled to 0 °C and stirred for 3 h. The slurry was filtered through polypropylene cloth on a 24 cm stainless steel single-plate filter (the entire filtration took 50 s), and the filter cake was washed with cold ethyl acetate (2 L) followed by water (2 L). The product, **1** was dried under vacuum at 45 °C overnight to constant weight. The quantity of compound **1** produced was 571.8 g (87% yield) with a potency of 97.8%.

Preparation C: In Situ Prepared LDA at −10 °C with AZADO Oxidation. Tetrahydrofuran (1.0 L) and diisopropylamine (169 mL, 1197.8 mmol, 1.3 equiv) were cooled to −10 °C, and 1.75 M *n*-butyllithium (553 mL, 967.5 mmol, 1.05 equiv) was added over 30 min at −10 to 0 °C. The reaction mixture was stirred for 0.5 h at −10 °C. A solution of **2** (202.0 g, 921.4 mmol, 1.0 equiv) in THF (600 mL) was added over 20 min, at −10 and 0 °C. The mixture was then stirred at −10 °C for 2 h. 2-Chlorobenzaldehyde (110 mL, 977 mmol, 1.15 equiv) was added over 15 min. The mixture was stirred for 1 h at −10 °C. Aqueous 3 N HCl (1.4 L) was added over 30 min as the reaction mixture was allowed to warm to ∼10 °C. The layers were separated. The aqueous layer was extracted with ethyl acetate (2.0 L), and the combined organic layers were stirred with saturated aqueous sodium bicarbonate (2.0 L) for 15 min. The layers were separated, and the organic layer was washed with brine (2.0 L), dried with $MgSO_4$, and concentrated under reduced pressure to a volume of 1.0 L. Ethyl acetate (1.0 L) was added, and aqueous KBr (10% w/w) solution (660 mL) was added, followed by AZADO (1.4025 g, 9.2 mmol), and the reaction mixture was cooled to 0 °C. A mixture of 9.3 wt % aqueous sodium hypochlorite (2.58 kg), sodium bicarbonate (123.85 g, 1474.2 mmol), and water (750 mL) was added over 1 h while allowing the reaction mixture to warm to room temperature. Following stirring at room temperature for 3 h, a thick precipitate was observed. The mixture was cooled to −5 °C and maintained at this temperature for 2 h. The resultant slurry was filtered through a sintered glass funnel, and the cake was rinsed with cold ethyl acetate (500 mL), water (500 mL), and ethyl acetate (500 mL) to yield the ketone **1** (233.66 g, 71%) as a white solid with a purity of 98.2%.

(2-Chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanol, 5. A solution of sodium borohydride (0.91 g, 24.1 mmol) in ethanol (50 mL) was added over 15 min to a solution of the ketone **1** (8.48 g, 23.7 mmol) and ethanol (250 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (100 mL) was added with stirring to quench the reaction, and the crude reaction mixture was concentrated under reduced pressure to yield a white aqueous residue. Ether (100 mL) was added, and the layers were separated. The aqueous layer was washed with ether (2 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried, filtered, and concentrated under reduced pressure to give the alcohol **5** (5.64 g) as a white solid. Purification (of 2 g) by recrystallisation at 65 °C from a mixture of ethyl acetate and *tert*-butyl methyl ether (added at 40 °C) gave **5** (1.76 g) as a white solid, mp 135−138 °C; (Found: C, 59.74; H, 3.87; N, 3.67; S, 9.09; Cl, 10.03. $C_{18}H_{14}ClNO_3S$ requires C, 60.08; H, 3.92; N, 3.89; S, 8.91; Cl, 9.85%); ν_{max}/cm^{-1} (KBr) 3547, 3050, 1442, 1293, 1153; δ_H (300 MHz) 4.27 (1H, br s, OH, exchanges with D_2O), 6.87 (1H, s, C*H*OH), 7.25−7.35 (4H, m), 7.41 (1H, ddd, *J* 7.8, 6.2, 2.6), 7.57 (2H,

2 × overlapping dd *J* 7.9, 7.4), 7.67 (1H, ddd, *J* 7.4, 4.4, 1.0), 7.84 (1H, d, *J* 8.0), 8.05−8.11 (2H, 2 × overlapping d, *J* 8.6), 8.53 (1H, dd, *J* 4.3, 1.8); δ_C (75.5 MHz) 66.1 (CH, C*H*OH), 126.0, 126.3, 127.5, 128.00, 128.01, 128.2, 128.5 (7 × CH), 131.0 (C), 132.9, 136.7 (2 × CH), 137.6, 137.7 (2 × C), 147.2 (CH), 155.4 (C); HRMS (ES^+) Exact mass calculated for $C_{18}H_{15}{}^{35}ClNO_3S$ [$(M + H)^+$], 360.0462. Found 360.0465, *m/z* (ES^+) 362.0 {[$(C_{18}H_{14}{}^{37}ClNO_3S) + H^+$], 33%}, 360.0 {[$(C_{18}H_{14}{}^{35}ClNO_3S) + H^+$], 100%}.

2-{[2-(2-Chlorobenzoyl)phenyl]sulfonyl)pyridin-3-yl}(2-chlorophenyl)methanone, 7. Tetrahydrofuran (40 mL) and diisopropylamine (6.6 mL, 46.8 mmol, 2.55 equiv) were cooled to −70 °C, and *n*-butyllithium (1.8 M, 22 mL, 39.6 mmol, 2.16 equiv) was added over 30 min at <−70 °C. The reaction mixture was stirred for 30 min at −70 °C. A solution of sulfone **2** (4.02 g, 18.3 mmol, 1.0 equiv) was added in THF (12 mL) over 20 min, at <−70 °C. The reaction mixture was then stirred at −70 °C for 3.5 h. 2-Chlorobenzaldehyde (4.3 mL, 38.4 mmol, 2.1 equiv) was added over 15 min to the reaction mixture at <−70 °C. The reaction mixture was stirred for 1 h at −70 °C. Aqueous 3 N HCl (30 mL) was added over 30 min as the reaction mixture was allowed to warm to ∼10 °C, and the layers were separated. The aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were stirred with saturated aqueous sodium bicarbonate (20 mL) for 15 min. The layers were separated, and the organic layer was washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure to yield the alcohol (6.41 g) as an orange oil. By HPLC analysis the mixture was found to contain 61.9% of the alcohol **5**, 1.5% of **2**, 31.6% 2-chlorobenzaldehyde, 4.4% of the bis-impurity. Ethyl acetate (50 mL) was added followed by aqueous KBr solution (10% w/w, 13.1 g, 0.6 equiv) and TEMPO (204 mg, 1.30 mmol, 0.07 equiv), and the reaction mixture was cooled to 0 °C. A mixture of aqueous sodium hypochlorite (180 g of standard lab bleach, titrated as 2.5%, 3.5 equiv), sodium bicarbonate (2.46 g, 29.1 mmol, 1.6 equiv) was added over 1 h while allowing the reaction mixture to warm to room temperature and stir for 17 h. The mixture was filtered to give the bis-adduct **7** (0.59 g) as a white solid which was 94% pure by HPLC, mp 209−212 °C; ν_{max}/cm^{-1} (KBr) 3000, 1681, 1579, 1433, 1292; δ_H (300 MHz, $CDCl_3$) 7.17−7.52 (10H, m), 7.65 (1H, ddd, appears as an overlapping td, *J* 7.5, 7.4, 1.3), 7.69−7.77 (1H, m), 7.82 (1H, dd, *J* 7.8, 1.6), 8.43 (1H, dd, *J* 7.8, 1.3), 8.58 (1H, dd, *J* 4.7, 1.6); δ_H (75.5 MHz, $CDCl_3$) 125.7, 126.5, 126.6, 129.4, 130.7, 131.00, 131.01, 132.5, 132.6, 132.9, 133.23, 133.24, 133.3 (13 × CH), 133.5, 133.9, 134.8, 135.6, 135.8 (5 × C), 137.9 (CH), 138.0, 140.1 (2 × C), 149.7 (CH), 158.1, 191.3, 193.5 (3 × C); HRMS (ES^+): Exact mass calculated for $C_{25}H_{16}{}^{35}Cl_2NO_4S$ [$(M + H)^+$], 496.0178. Found 496.0166, *m/z* (ES^+) 500.0 {[$(C_{25}H_{15}{}^{37}Cl_2NO_4S) + H]^+$, 22%}, 497.9{[$(C_{25}H_{15}{}^{37}Cl^{35}ClNO_4S)+H]^+$,80%},496.0{[$(C_{25}H_{15}{}^{35}Cl_2NO_4S) + H]^+$, 100%}.

(3-Chlorophenyl)[2-(phenylsulfonyl)pyridin-3-yl]methanone, 8. The general procedure described for the preparation of **1** was used, except 3-chlorobenzaldehyde was used in place of 2-chlorobenzaldehyde for the condensation reaction. These conditions produced compound **8** as a tan solid in 72% yield with 94% purity. Purification of compound **8** by flash chromatography on silica gel using 20% cyclohexane in *tert*-butyl methyl ether produced a white solid in 97% purity, mp 147−150 °C; ν_{max}/cm^{-1} (KBr) 3081, 1677, 1573, 1430, 1322; δ_H (300 MHz, $CDCl_3$) 7.45 (1H, t, *J* 7.9), 7.50−7.71 (6H, m), 7.74 (1H, dd, *J* 7.8, 1.6), 7.80 (1H, dd, appears as overlapping t, *J* 1.9, 1.8), 7.97−8.06 (2H, m), 8.83 (1H, *J* 4.6, 1.6); δ_C (75.5 MHz, $CDCl_3$) 126.5, 128.2, 129.2, 129.3, 129.6, 130.2, 134.0, 134.1 (8 × CH), 135.2, 135.3 (2 × C), 136.8 (CH), 138.1, 138.5 (2 × C), 151.0 (CH), 155.6 (C), 196.9 (C); HRMS (ES^+): Exact mass calculated for $C_{18}H_{13}{}^{35}ClNO_3S$ [$(M + H)^+$], 358.0305. Found 358.0300, *m/z* (ES^+) 359.9 {[$(C_{18}H_{12}{}^{37}ClN_3O_4) + H]^+$, 33%}, 358.0 {[$(C_{18}H_{12}{}^{35}ClN_3O_4) + H]^+$, 100%}, 326 (2%).

(4-Chlorophenyl)[2-(phenylsulfonyl)pyridine-3-yl]methanone, 9. The general procedure described for the preparation of **1** was used, except 4-chlorobenzaldehyde was used in place of 2-chlorobenzaldehyde for the condensation reaction. These conditions produced compound **9** as a tan solid in 82% yield with 92.5% purity; mp 164−165 °C; (Found C, 60.28; H, 3.35; N, 3.97; S, 9.00; Cl, 10.10. $C_{18}H_{12}ClNO_3S$ requires C, 60.42; H, 3.38; N, 3.91; S, 8.96; Cl, 9.91); ν_{max}/cm^{-1} (KBr) 3615, 1676, 1289, 1155; δ_H (400 MHz, $CDCl_3$) 7.47 (2H, d, *J* 8.4), 7.50−7.56 (2H, m), 7.57 (1H, dd, *J* 7.6, 4.4), 7.59−7.66 (1H, m), 7.73 (1H, dd, *J* 7.6, 1.6), 7.76 (2H, ddd, *J* 8.4, 2.4, 1.6), 7.98−8.04 (2H, m), 8.80 (1H, dd, *J* 4.4, 1.6); δ_C (100 MHz, $CDCl_3$) 126.4, 129.1, 129.2, 129.3, 131.3, 134.1 (6 × CH), 135.0, 135.5 (2 × C), 136.8 (CH), 138.5, 140.7 (2 × C), 150.8 (CH), 155.5, 191.9 (2 × C); HRMS (ES^+): Exact mass calculated for $C_{18}H_{13}ClNO_3S$ [$M + H]^+$ 358.0305. Found 358.0301; *m/z* (ES^+) 359.9 {[$(C_{18}H_{12}{}^{37}ClNO_3S) + H^+$], 28%}, 358.0 {[$(C_{18}H_{12}{}^{35}ClNO_3S) + H^+$], 66%}.

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Supporting Information Available

^1H and ^{13}C NMR characterization data for key compounds **1**, **5**, **7**, **8**, and **9** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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