

Chemical Development of NBI-75043. Use of a Flow Reactor to Circumvent a Batch-Limited Metal–Halogen Exchange Reaction

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Abstract:

The discovery route and subsequent scale-up routes for NBI-75043 are presented. When traditional batch chemistry was found to limit the scale of a key reaction, a flow reactor was designed and optimized to provide an alternate method of production.

Introduction

Four types of histamine receptors have been characterized in humans (H1–H4).¹ The H1 receptor is the primary receptor involved in allergic rhinitis symptoms and motion sickness. H1 antagonists such as diphenhydramine hydrochloride block histamine binding in peripheral tissues, thereby reducing symptoms of allergic rhinitis.² One side effect of diphenhydramine results from its penetration of the blood–brain barrier resulting in CNS depression. Accordingly, selective H1 antagonists with good blood–brain barrier penetration are thought of as likely candidates for next-generation sleep therapies.³ NBI-75043 (Figure 1) is a highly selective and potent H1 antagonist that was under evaluation for safety and efficacy in the treatment of insomnia.

Background: Early lots of NBI-75043 were produced by the Medicinal Chemistry department following the route shown in Scheme 1. Deprotonation of benzo[*b*]thiophene **2** using *n*-BuLi followed by alkylation with 2-*N,N*-dimethylaminoethyl-1-bromide provided **3**; subsequent bromination of this intermediate afforded compound **4**. After metal–halogen exchange, the resulting 2-lithio derivative was treated with acetic anhydride to produce the corresponding 2-acylbenzothiophene **5**. Reaction of **5** with *in situ* generated 2-lithiopyridine resulted in tertiary alcohol **6** which in turn was dehydrated to alkene **7** and subsequently hydrogenated to give **8** as a racemic mixture. The

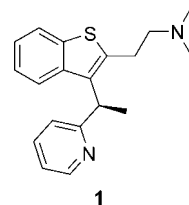
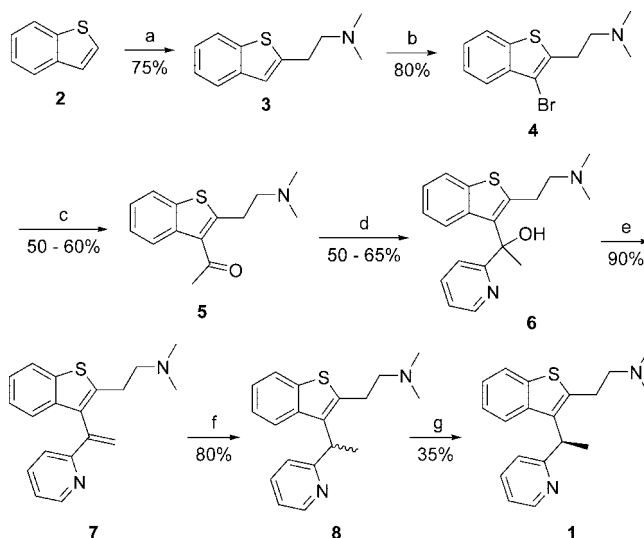


Figure 1. NBI-75043.

Scheme 1. Medicinal Chemistry Route^a for NBI-75043



^a Reagents and conditions: (a) 1. *n*-BuLi, -78°C ; 2. 2-*N,N*-dimethylaminoethyl-1-bromide hydrobromide; (b) bromine, HOAc; (c) 1. *n*-BuLi, -78°C , TMEDA, 2. Ac_2O ; (d) 2-pyridyllithium; (e) TFA, c. H_2SO_4 ; (f) H_2 , Pd/C, MeOH; (g) D-tartaric acid; aq NaOH, EtOAc; L-tartaric acid.

desired product, **1**, was obtained through resolution of this racemate. Crystallization of the undesired isomer with D-tartaric acid enriched the remaining solution with the desired isomer. After neutralization and extraction, crystallization of the L-tartaric acid salt produced the desired compound.

There were two areas of immediate concern for scale-up of this route. The acetylbenzothiophene **5** was difficult to purify, and the reaction of **5** with 2-lithiopyridine was run under high dilution ($\sim 0.04\text{ M}$) conditions.⁴ The completion of the synthesis

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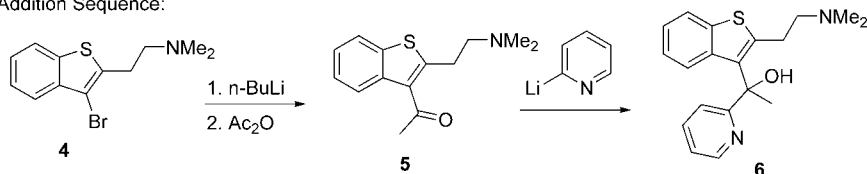
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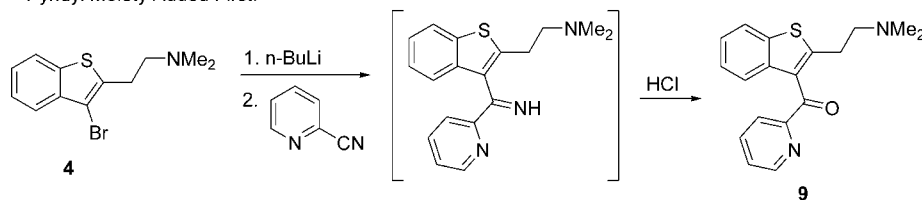
- (4) (a) Gardiner, J. M.; Crewe, P. D.; Smith, G. E.; Veal, K. T.; Pritchard, R. G.; Warren, J. E. *Org. Lett.* **2003**, *5* (4), 467–470. (b) Hari, Y.; Obika, S.; Sakaki, M.; Morio, K.; Yamagata, Y.; Imanishi, T. *Tetrahedron* **2002**, *58*, 3051–3063. (c) Lima, P. G.; Sequeria, L. C.; Costa, P. R. R. *Tetrahedron Lett.* **2001**, *42*, 3525–3527. (d) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257–260.

Scheme 2. Avoiding the use of 2-pyridyllithium

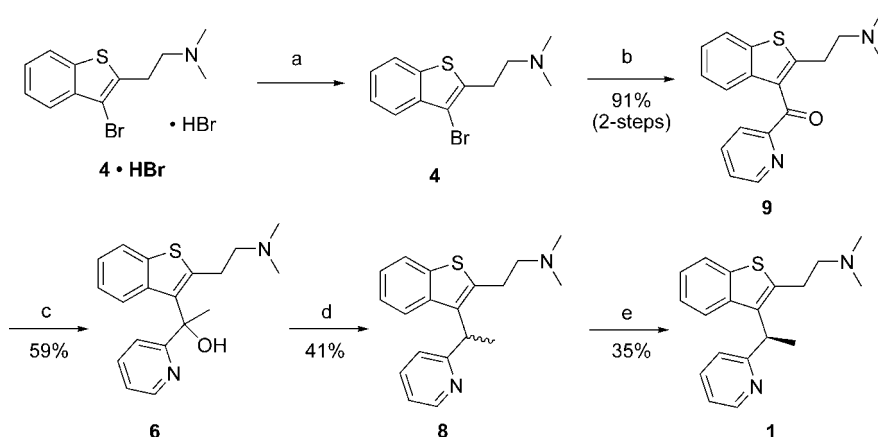
Original Addition Sequence:



Pyridyl Moiety Added First:



Scheme 3. Initial scale-up route^a



^a Reagents and conditions: (a) MTBE, aq NaOH; (b) *s*-BuLi, TMEDA; 2-cyanopyridine, PhMe, $-78\text{ }^{\circ}\text{C}$; 6 N HCl; (c) MeLi, PhMe, $-78\text{ }^{\circ}\text{C}$; (d) TMS-Cl, NaI, MeCN; (e) D-tartaric acid; aq NaOH, EtOAc; L-tartaric acid.

was considered straightforward with alcohol **6** being the last crystalline intermediate prior to isolation of the final salt.⁵

Results and Discussion:

Initial Scale-up Route. The decision was made to outsource the synthesis of the hydrobromide salt of bromobenzothiophene **4**, and this material was used as the starting point for future syntheses. Taking advantage of the crystalline nature of alcohol **6**, we decided to use this intermediate as a convergence point for future routes.

Two major changes were implemented to the original route. First, the order of addition of the pyridyl and methyl functionalities to the benzothiophene was reversed. Where the earlier route used the addition of a pyridyl anion to a methyl ketone, we chose to add a methyl anion to a pyridyl ketone as shown in Scheme 2. Cyanopyridine was added to the 2-lithiated benzothiophene intermediate which, after workup with HCl, hydrolyzed the intermediate imine resulting in ketone **9**. Addition of methyl lithium to **9** produced the desired intermediate alcohol **6**. By avoiding the use of 2-pyridyllithium⁶, high

dilution conditions and the resulting high workup volumes required were avoided. Second, rather than repeating the steps of dehydration and hydrogenation as in the earlier route, direct removal of the hydroxyl group was performed by treatment with *in situ* generated TMS-I.⁷

Even though these improvements allowed us to scale up and provide necessary quantities of NBI-75043 for preclinical studies (Scheme 3), the approach still suffered from low-yielding steps and intermediates that were difficult to purify. Chromatography of ketone **9** failed to afford any purity improvement due to instability of this intermediate. It was found that exposure of ketone **9** to UV or visible light resulted in rapid degradation. It was determined that the ketone should not be held for extended times and converted to the alcohol as rapidly as practical. Attempts at larger-scale halogen–metal exchange reactions resulted in lower yields of ketone **9** with yields in the 22–28% range on 2.1–2.6 mol scales. It was clear additional route improvements would be required going forward.

(5) Gross, T. D.; Schaab, K.; Ouellette, M.; Zook, S.; Reddy, J. P.; Shurtleff, A.; Saccaan, A. I.; Alebic-Kolbah, T.; Bozigan, H. *Org. Process Res. Dev.* **2007**, *11*, 365–377.

(6) Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4335–4338.

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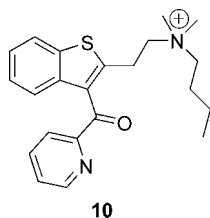


Figure 2. Quaternized product.

Second Scale-Up Route. During the evaluation of the halogen–metal exchange reaction, different types of organolithium reagents were explored. It was found that *n*-BuLi performed acceptably on a small scale. In larger-scale reactions, the quaternary ammonium salt **10** (Figure 2) was detected as a new impurity. Compound **10** is formed as a result of the reaction of *n*-butyl bromide (formed as a reaction byproduct during the metal–halogen exchange) with the dimethyl amine side chain of compound **9**. The explanation for its formation is that, as the scale increased from ~50 mmol to ~200 mmol, the reaction and workup times increased correspondingly. The reaction mixture was difficult to analyze, giving inconsistent results, and impurity levels could only be determined after the workup. As expected, use of *s*-BuLi for the halogen–metal exchange resulted in a lower amount of the corresponding impurity. Use of *t*-BuLi (2 equiv) showed significantly better results with no quaternization observed and therefore was used in the manufacturing campaigns.

The halogen–metal exchange reaction was performed by addition of a toluene solution of compound **4** to a cooled solution of *n*-BuLi and TMEDA in toluene. Other solvents such as THF were investigated; the best results were obtained using toluene. The addition rate was controlled carefully to maintain an internal temperature less than $-70\text{ }^{\circ}\text{C}$ in order to obtain the best yields and consistent results. Because of the exothermic nature of this addition, it took approximately 3 h from the start of addition of compound **4** to the start of addition of 2-cyanopyridine on a 2 mol scale.

Conversion of **9** to **6** was found to proceed easily with either methylolithium or methylmagnesiumbromide. Work-up of the magnesium salts resulting from the use of methylmagnesiumbromide was problematic, and it was decided to use methyl-lithium for this conversion.

The direct reductive dehydroxylation was found to be unreliable for scale-up and was again replaced with a two-step process. The alcohol was first dehydrated to olefin **7** by treatment with methanesulfonic acid in dichloromethane. This procedure was more convenient and productive when compared with the original $\text{H}_2\text{SO}_4/\text{TFA}$ procedure. Hydrogenation using palladium catalysis proved inconsistent, presumably due to the susceptibility to catalyst poisoning by either the sulfur or amine groups in the molecule. After a screening effort, this reduction was conveniently accomplished with hydrogen in the presence of Adam's catalyst. The final improvement for the second scale-up route (Scheme 4) was the direct crystallization of the desired isomer from the reaction mixture. At larger scale, this crystallization proceeded without yield loss while omitting enrichment by initial crystallization of the undesired isomer. This route was utilized to produce the early requirements of a multikilo batch.

Experiments were performed in order to explore the limits of time and temperature that could be tolerated on larger scale. The results from these experiments are summarized in Table 1. Following our small-scale procedure where addition of compound **4** was controlled at or below $-70\text{ }^{\circ}\text{C}$, ~70% of compound **9** was obtained along with ~10% of des-bromo compound **3** (entries 1, 2). Increasing the solvent volume and adding compound **4** at or below $-60\text{ }^{\circ}\text{C}$ resulted in a dramatic decrease in the amount of product formed and a corresponding increase in the amount of des-bromo side product **3** (entry 3). Reducing solvent volumes decreased these effects; however, they remained unacceptably high (entry 4). Repeating the starting conditions on a slightly larger scale (entry 5) resulted in product and side product in the expected range.

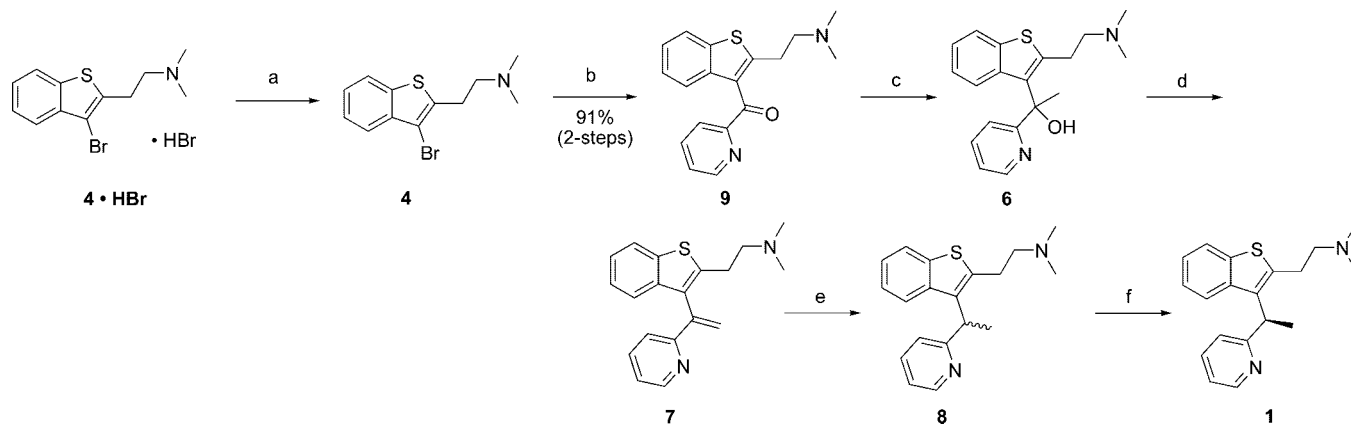
The addition of compound **4** was quite exothermic, and it was calculated that large-scale addition (5–6 kg) would require ~4 h. Repeating the experimental conditions and slowly adding compound **4** over 4 h resulted in an unacceptably low yield of product and a high level of the des-bromo side product (entry 6). We carried out an experiment where the solvent volume was doubled with the extended addition time (entry 7). It was expected that a larger precooled solvent volume would provide a larger heat sink and that we would be able to add compound **4** at a faster rate. This experiment resulted in a product:des-bromo ratio similar to that of our small-scale results, and these conditions were deemed acceptable with which to proceed to larger scale. To aid cooling, both solutions of compound **4** and 2-cyanopyridine were precooled prior to charging to the reactor. The kilo-scale batches showed a modest lowering in the yield along with a slight increase in the amount of the side product (entries 8, 9). While these conditions were sufficient to provide material on a 6 kg scale, it was clear from the data that alternate chemistry would be required for any larger-scale campaigns.

Final Scale-up Route. Due to the cryogenic conditions required for the lithiation chemistry, we also explored using Grignard chemistry to accomplish the conversion at more moderate temperatures. The Grignard reagent formed from compound **4** was found to be unreactive with 2-acetylpyridine by itself or in the presence of zinc chloride. Deuterium quench of the reagent failed to demonstrate any deuterium incorporation while compound **4** was consumed. Attempts at Friedel–Crafts reaction with benzothiophene **3** showed no reaction in the presence of various Lewis and protic acids (CeCl_3 , H_2SO_4 , AlCl_3 , AgOTf , and $\text{Et}_3\text{B/C}_6$).

Attempts at adding 2-acetylpyridine to lithiated compound **4** failed to produce the desired product. Lithiation followed by the addition of 2-acetylpyridine in the presence of catalytic $\text{Ti}(\text{O}i\text{Pr})_4$ formed the desired alcohol **6**. Repeating these conditions with ZnCl_2 as the Lewis acid resulted in ~50% of des-bromo side product (**3**) and ~50% of alcohol **6**. 2-Methyl-THF gave similar results to THF as expected. Use of toluene as the solvent resulted in larger amounts of the des-bromo side product in the presence of $\text{Ti}(\text{O}i\text{Pr})_4$. Our best conditions (*t*-BuLi, THF, catalytic $\text{Ti}(\text{O}i\text{Pr})_4$) provided a 67% yield of alcohol **6**.

With an alternate approach to alcohol **6** in hand, we sought to improve the reduction of olefin **7**. An obvious approach was to attempt asymmetric hydrogenation with the expectation of

Scheme 4. Second scale-up route^a



^a Reagents and conditions: (a) MTBE, aq NaOH; (b) *s*-BuLi or *t*-BuLi, TMEDA; 2-cyanopyridine, PhMe, -78°C ; 6 N HCl; (c) MeLi, PhMe, -78°C ; (d) MsOH, DCM; (e) PtO_2 , EtOH, 30°C , H_2 120 psi; (f) L-tartaric acid.

Table 1. Cyanopyridine addition

| 4 | conditions | | 9 | 3 | yield |
|----------|--------------|-------------------|-----|------|-------|
| (wt) | | | (%) | (%) | (%) |
| 1 16 g | 15 volumes | THF −70 °C | 71 | 6 | 85 |
| 2 16 g | repeat | | | 7 | 93 |
| 3 16 g | 20 volumes | THF −60 °C | 9 | 47 | |
| 4 25 g | 15 volumes | THF −60 °C | 29 | 29 | |
| 5 27 g | 15 volumes | THF −70 °C | 72 | 9.50 | 86 |
| 6 25 g | 4 h addition | | 13 | 54 | |
| 7 25 g | 4 h addition | double THF volume | 72 | 8 | |
| 8 5.7 kg | batch 1 | | 56 | 15 | 90 |
| 9 6.4 kg | batch 2 | | 57 | 21 | |

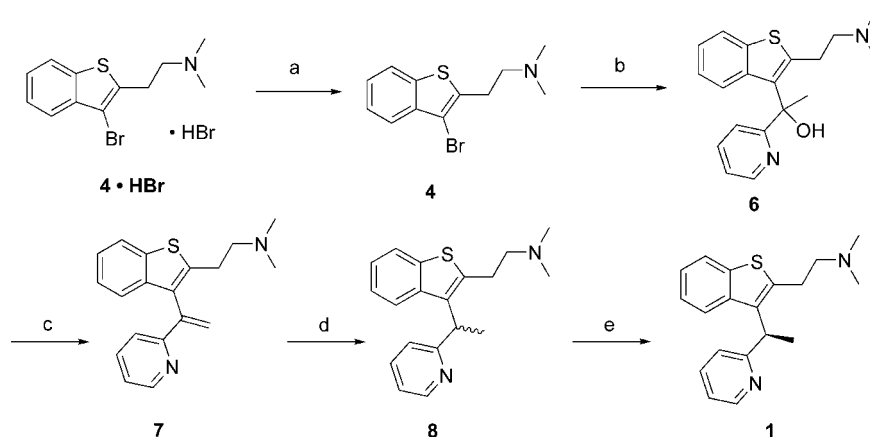
producing an enantio-enriched mixture of **8**. Reaction screening (a total of 45 experiments) using different Ru, Rh and Ir catalysts was performed as a first pass. One combination resulted in 100% conversion with 78% ee of the undesired enantiomer. The reaction was further optimized using this ligand while efforts went towards preparing the ligand with the opposite (desired) chirality. Using purified (column chromatographed) olefin **7**, substrate to catalyst (S/C) ratios of 1000:1 could be achieved while the ratio dropped to 100:1 when using starting material isolated/purified through an extractive workup (as would be preferred for scale-up). Running the reduction on a 5-g scale with an S/C ratio of 100 using the ligand with the correct chirality, full conversion was observed with an ee of 60% of the desired isomer. A single crystallization with L-tartaric acid improved the ee to 95% in 56% isolated yield (from olefin **7**). Along with these route improvements, a change was made in the counterion for the final salt formation from L-tartrate to benzenesulfonate. Use of L-tartaric acid was still required for the enantio-enrichment. The final salt formation was accomplished with a neutralization of the L-tartrate salt and formation of the benzenesulfonate salt. With the latest route improvements, we were prepared to manufacture again with our final scale-up route (Scheme 5). These improvements to the route bought a short amount of time to afford us the opportunity to generate the required quantities of API for additional studies more reliably and productively. Given the instability of lithiated compound **4**, it was clear that additional improvements to the preparation of alcohol **6** were needed for the future.

Flow Reactor Development: Small-scale experiments indicated that both the halogen–metal exchange and anion addition to acetylpyridine reactions were extremely rapid and quite reproducible. Obvious limitations on larger scale would be due to the exothermic nature of these two steps and the time required for reagent addition to maintain low internal temperature. Having chemistry that worked effectively only on small scale, we chose to explore this methodology using a solution afforded by engineering.⁸ Focusing on the final scale-up route, we investigated the application of flow reactor technology to our scale-limited lithiation sequence.

A schematic of our first-generation flow reactor is shown in Figure 3. The reactor was constructed using 1/4 in. stainless steel tubing, 3 peristaltic pumps and 3/8 in. Teflon tubing. The entire steel portion of the reactor was submerged in a dry ice/acetone bath with Teflon lines running to and from the reactor. A solution of *t*-BuLi and TMEDA in THF was prepared and cooled in a -78°C bath. This solution was combined via a T-connection with a solution of compound **4** in THF with an in-line thermocouple and through a static line mixer. As the solution exited the mixer, it passed an in-line thermocouple and into a coil of tubing (residence time control) to allow the mixture to age briefly. A third stream of 2-acetylpyridine and $\text{Ti}(\text{O}i\text{Pr})_4$ in THF was introduced *via* a T-connection along with a thermocouple. This mixture passed through a second static line mixer and hold coil. As the solution exited the hold coil, temperature was recorded prior to quenching in a stirred flask of methanol. The flow rates of the pumps were calibrated in order to determine approximate starting values (Figure 4). The actual settings were to be determined experimentally both by monitoring the temperature at various points in the reactor and by periodic sampling of the reaction. Flow was adjusted until the temperature remained in-range and stable which would

(8) Recent publications citing the benefits of flow reactor technology include: (a) Ehrfeld, W.; Hessel, V.; Lowe, H. *Microreactors - New Technology for Modern Chemistry*; Wiley-VCH: Weinheim, 2000. (b) Delhaye, L.; Stevens, C.; Merschaert, A.; Delbeke, P.; Br  ne, W.; Tilstam, U.; Borghese, A.; Geldhof, G.; Diker, K.; Dubois, A.; Barberis, M.; Casarubios, L. *Org. Process Res. Dev.* **2007**, *11*, 1104–1111. (c) Bogaert-Alvarez, R. J.; Demena, P.; Kodersha, G.; Polomski, R. E.; Soundararajan, N.; Wang, S. S. Y. *Org. Process Res. Dev.* **2001**, *5*, 636–645. (d) Brechtelsbauer, C.; Ricard, F. *Org. Process Res. Dev.* **2001**, *5*, 646–651. (e) Choe, J.; Kim, Y.; Song, K. H. *Org. Process Res. Dev.* **2003**, *7*, 187–190.

Scheme 5. Final scale-up route^a



^a Reagents and conditions: (a) MTBE, aq NaOH; (b) *t*-BuLi, TMEDA; 2-acetylpyridine, Ti(OiPr)₄, THF, −78 °C; (c) MsOH, DCM; (d) [RuI₂(*p*-cymene)]₂, SL-M004-2, MeOH, 30 °C, H₂ 260 psi; (e) L-tartaric acid; salt break; PhSO₃H.

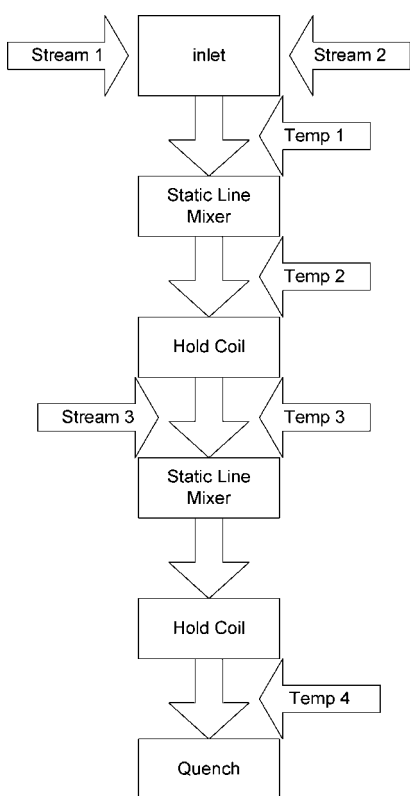


Figure 3. First-generation flow reactor schematic.

indicate steady-state conditions. The presence of bromide **4** in the sample would indicate the rate of stream 1 addition was too fast, too slow a *t*-BuLi addition or inadequate resonance time for the halogen–metal exchange. Excess 3,3-dimethyl-2-methyl-1-(2-pyridyl)-butan-2-ol **11** (the product of *t*-BuLi addition to 2-acetylpyridine) would indicate too high a flow rate of *t*-BuLi. The relative proportions of des-bromo side product, the desired product, and 2-acetylpyridine would give insight into the proper flow rate for the third pump.

The results of our initial run are shown in Table 2. Our starting flow rates appeared too high as evidenced by the high and variable temperatures observed at the initial mixing of the streams. Slowing the flow rates both lowered the temperature and the variability previously observed. However, the temper-

ature was still above our target of −65 °C. Closer examination of the data revealed that the temperature at the end of the static line mixer (temp 2, Table 2) remained constant, indicating that the system had stabilized by the time the stream exited the mixer. The initial variability in temperature was attributed to both the heat of reaction and cooling of the room temperature stream of compound **4** that was introduced. Thus, two 1/8 in. cooling coils were added to the output of pumps 1 and 2 prior to combining the streams (Figure 5). The smaller tubing provided a large surface area to volume ratio which aided in efficient cooling.

The results of the pump setting and thermal results from the subsequent run are summarized in Table 3, and analyses of in-process testing are summarized in Table 4. The modified reactor was submerged in a −78 °C bath, and once the temperature had stabilized (entry 1), the pumps were started (entry 2). The reactor was run for 2 min, and then the reaction mixture was sampled and the pumps were stopped (entries 3, 4). Analysis of the sample (Table 4, 206-A) showed a high level of 2-acetylpyridine and its *t*-BuLi adduct, which indicated over-addition from pump 3. The speed of pump 3 was reduced and the process repeated (Table 3, entries 5–7), and the analysis of the second sample (Table 4, 206-B) showed greatly reduced levels of 2-acetylpyridine, and none of the *t*-BuLi adduct was detected. The starting bromide **4** was detected, and the pump 2 flow rate was reduced; then the sequence was repeated. Analysis of the third sample (Table 4, 206-C) showed alcohol **6** was present at the levels typical of small-scale batch runs and des-bromo side product at or slightly below typical levels. In two runs with such a setup, we had equaled our best results observed in small scale with batch reactors. We next sought to investigate the limits of productivity possible for our reactor system. We expected the halogen–metal exchange to be rapid, and therefore the hold coil (hold coil 3) after the first static line mixer (Figure 5) was removed, and the reactor system was run using the best previous settings. Steady-state conditions were achieved as evident by low and stable temperature readings at all of the measured points. Analysis of in-process samples showed consumption of starting bromide **4** and presence of ~13% of product **6**, ~50% of des-bromo side product and

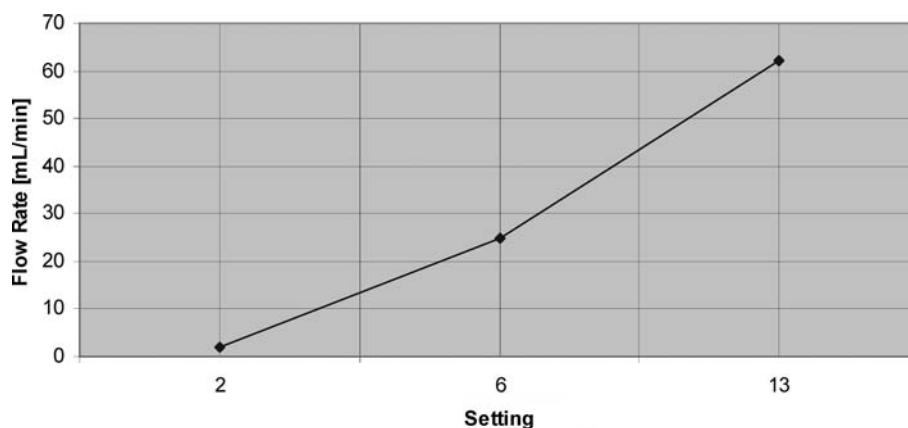


Figure 4. Pump calibration.

Table 2. First-generation flow reaction

| time | temp 1 (streams 1, 2 mixed °C) | temp 2 (end of mixer °C) | temp 3 (Ac-pyr addition °C) | pump 1 setting(<i>t</i> -BuLi) | pump 2 setting(4) | pump 3 setting(ac-pyr) |
|------|-----------------------------------|-----------------------------|--------------------------------|------------------------------------|-----------------------|---------------------------|
| 3:27 | -15.6 | -76.0 | -72.0 | 12.5 | 2 | 5 |
| 3:29 | -6.1 | -73.0 | -72.6 | 12.5 | 2 | 5 |
| 3:32 | -7.5 | -73.0 | -72.8 | 12.5 | 2 | 5 |
| 3:33 | -11.4 | -73.6 | -68.2 | 12.5 | 2 | 5 |
| 3:34 | -12.9 | -73.8 | -68.2 | 12.5 | 2 | 5 |
| 3:40 | -13.2 | -74.8 | -67.2 | 12.5 | 2 | 5 |
| 3:40 | -48.1 | -76.7 | -71.5 | 3.75 | 2.5 | 2.5 |
| 3:45 | -45.1 | -78.2 | -76.6 | 3.75 | 2.5 | 2.5 |
| 3:50 | -57.1 | -78.4 | -76.4 | 3.75 | 2.5 | 2.5 |

~26% of **11**. Our interpretation of these results was that the halogen–metal exchange had completed, but there was insufficient time for the elimination of *t*-BuBr; therefore, the remaining *t*-BuLi reacted with 2-acetylpyridine, and the 2-lithiobenzo[*b*]thiophene was quenched. This was clear evidence

that the hold coil was necessary for the elimination of *t*-BuBr, and it was replaced. No further modifications were performed on the reactor.

Previous experiments were run with pump 1 (supplying *t*-BuLi) at or near its maximum speed. The speed of this pump

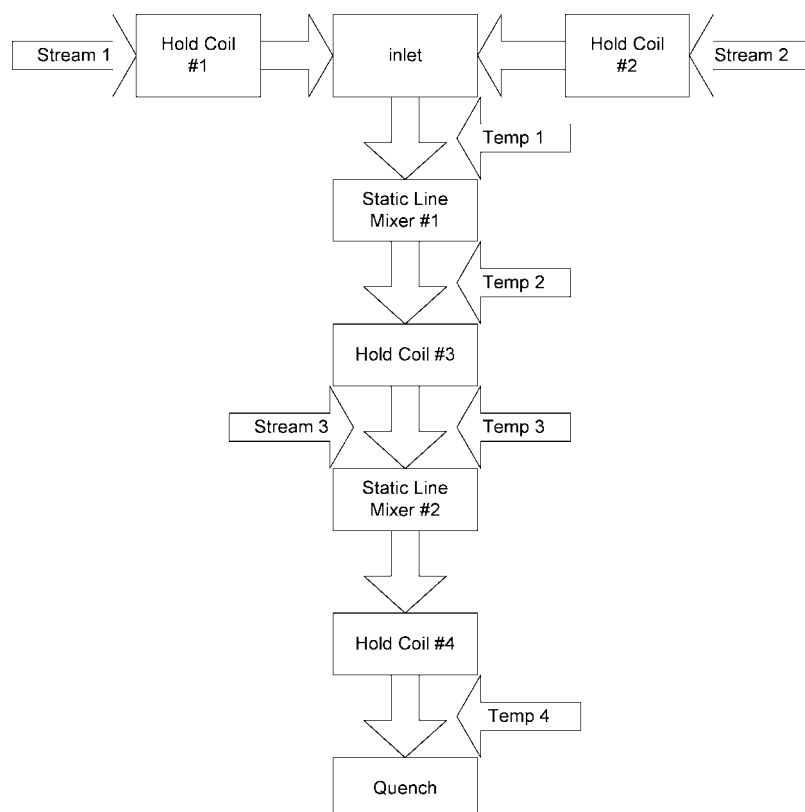


Figure 5. Second-generation flow reactor schematic.

Table 3. Second-generation flow reactor, run 1

| entry | time | pump | | | temperature (°C) | | | | sample |
|-------|------|------|-----|-----|------------------|-------|-------|-------|--------|
| | | 1 | 2 | 3 | 1 | 2 | 3 | 4 | |
| 1 | 3:22 | 0 | 0 | 0 | -78.7 | -79.0 | -77.0 | -79.8 | |
| 2 | 3:22 | 12.5 | 5 | 5 | | | | | |
| 3 | 3:24 | | | | -71.9 | -75.8 | -62.8 | -79.6 | 206-A |
| 4 | 3:24 | 0 | 0 | 0 | | | | | |
| 5 | 3:56 | 12.5 | 5 | 2.5 | -78.3 | -78.4 | -77.8 | -77.6 | |
| 6 | 3:59 | | | | -70.0 | -76.1 | -76.4 | -77.2 | 206-B |
| 7 | 4:00 | 0 | 0 | 0 | | | | | |
| 8 | 4:31 | | | | -78.2 | -78.2 | -77.4 | -77.4 | |
| 9 | 4:32 | 12.5 | 2.5 | 2.5 | | | | | |
| 10 | 4:35 | | | | -69.3 | -74.3 | -77.2 | -77.2 | 206-C |
| 11 | 5:29 | 0 | 0 | 0 | -78.2 | -78.1 | -77.5 | -77.5 | |
| 12 | 5:29 | 12.5 | 2.5 | 2.5 | | | | | |
| 13 | 5:31 | | | | -75.1 | -74.3 | -77.3 | -77.3 | |
| 14 | 5:33 | | | | -71.9 | -74.5 | -77.3 | -77.3 | |
| 15 | 5:40 | | | | -73.3 | -77.7 | -77.3 | -77.3 | |
| 16 | 5:45 | | | | -73.6 | -74.9 | -77.2 | -77.2 | |
| 17 | 5:50 | | | | -73.4 | -76.5 | -77.3 | -77.3 | |
| 18 | 5:52 | 0 | 0 | 0 | -73.9 | -74.9 | -77.3 | -77.3 | |

Table 4. Sample analysis from second-generation flow reactor, run 1

| sample | HPLC area % | | | | |
|--------|-------------|--------|-------|-------|-------|
| | cpd 12 | cpd 11 | cpd 6 | cpd 3 | cpd 4 |
| 206-A | 49.3 | 11.3 | 18.6 | 11.5 | 0.0 |
| 206-B | 5.9 | 0 | 33.7 | 13.9 | 28.6 |
| 206-C | 0 | 8.8 | 66.2 | 16.5 | 0.0 |

| | |
|-----|---------------------------|
| 12: | 2-acetylpyridine |
| 11: | 12/ <i>t</i> -BuLi/adduct |
| 6: | product alcohol |
| 3: | des-brominated |
| 4: | bromobenzthiophene |

Table 5. Second-generation flow reactor, run 2

| entry | time | pump | | | temperature (°C) | | | | sample |
|-------|------|------|-----|-----|------------------|-------|-------|-------|--------|
| | | 1 | 2 | 3 | 1 | 2 | 3 | 4 | |
| 1 | 4:22 | 0 | 0 | 0 | -78.2 | -78.2 | -78.1 | -77.7 | |
| 2 | 4:22 | 6 | 3 | 3 | | | | | |
| 3 | 4:31 | | | | -74.6 | -79.5 | -74.9 | -77.9 | 003-A |
| 4 | 4:32 | 12 | 6 | 6 | | | | | |
| 5 | 4:33 | | | | -48.6 | -72.8 | -60.0 | -77.3 | 003-B |
| 6 | 4:34 | 9 | 4.5 | 4.5 | | | | | |
| 7 | 4:35 | | | | -64.8 | -74.6 | -68.3 | -77.4 | 003-C |
| 8 | 4:35 | 3 | 1.5 | 1.5 | | | | | |

Table 6. Sample analysis from second-generation flow reactor, run 2

| sample | HPLC area % | | | | |
|--------|-------------|--------|-------|-------|-------|
| | cpd 12 | cpd 11 | cpd 6 | cpd 3 | cpd 4 |
| 003-A | 10.3 | 0 | 26.7 | 13.8 | 35.5 |
| 003-B | 25.1 | 0 | 44.9 | 16.7 | 7.6 |
| 003-C | 5.6 | 0 | 63.0 | 20.8 | 5.6 |

| | |
|-----|---------------------------|
| 12: | 2-acetylpyridine |
| 11: | 12/ <i>t</i> -BuLi/adduct |
| 6: | product alcohol |
| 3: | des-brominated |
| 4: | bromobenzthiophene |

was varied in the next experiment, and the results are shown in Tables 5 and 6. Reducing the rate of pump 1 by 50% or increasing the rates of pumps 2 and 3 by 100% both resulted

Table 7. Second-Generation Flow Reactor, Run 3

| entry | time | pump | | | temperature (°C) | | | | sample |
|-------|------|------|-----|-----|------------------|-------|-------|-------|--------|
| | | 1 | 2 | 3 | 1 | 2 | 3 | 4 | |
| 1 | 2:30 | 0 | 0 | 0 | -78.2 | -78.8 | -77.8 | -77.4 | |
| 2 | 2:31 | 7 | 3 | 3 | | | | | |
| 3 | 2:35 | | | | -53.7 | -74.9 | -61.7 | -77.7 | 004-A |
| 4 | 2:36 | 9 | 4 | 4 | | | | | |
| 5 | 2:38 | | | | -41.8 | -72.8 | -70.9 | -77.3 | 004-B |
| 6 | 2:38 | 3 | 1.5 | 1.5 | | | | | |
| 7 | 2:43 | 0 | 0 | 0 | | | | | |
| 8 | 3:11 | | | | -78.2 | -78.2 | -77.7 | -77.5 | |
| 9 | 3:11 | 6 | 2 | 2 | | | | | |
| 10 | 3:44 | | | | -78.2 | -78.1 | -77.3 | -76.7 | 004-C |
| 11 | 3:44 | 0 | 0 | 0 | | | | | |
| 12 | 4:11 | 12 | 6 | 6 | -78.2 | -78.2 | -77.7 | -77.6 | |
| 13 | 4:12 | 12 | 6 | 7 | | | | | 004-D |
| 14 | 4:13 | | | | -63.7 | -72.4 | -48.8 | -76.2 | |
| 15 | 4:14 | 0 | 0 | 0 | | | | | |

Table 8. Sample analysis from second-generation flow reactor, run 3

| sample | HPLC area % | | | | |
|--------|-------------|--------|-------|-------|-------|
| | cpd 12 | cpd 11 | cpd 6 | cpd 3 | cpd 4 |
| 004-A | 59.1 | 0 | 2.3 | 10.2 | <1 |
| 004-B | 4.6 | 13.5 | 53.2 | 14.9 | 0.0 |
| 004-C | 0 | 34.1 | 14.5 | 23.5 | 0.0 |
| 004-D | 7.3 | 0 | 70.5 | 17.8 | 1.6 |

| | |
|-----|---------------------------|
| 12: | 2-acetylpyridine |
| 11: | 12/ <i>t</i> -BuLi/adduct |
| 6: | product alcohol |
| 3: | des-brominated |
| 4: | bromobenzthiophene |

in unacceptable mixtures (Table 5, entries 1–5; Table 6, samples 003-A, 003-B). Reducing the speed of pump 1 while increasing the speed of pumps 2 and 3 gave a similar reaction profile (Table 6, sample 003-C) at a higher temperature than previous reactions (Table 5, entry 7). A much slower flow rate was attempted (Table 5, entry 8), but at reduced speed, the solution had a greater residence time in the supply lines and cavitations in pump 1 caused us to discontinue this run. Bubbles that formed in the lines and pump head led to inconsistent reagent supply to the reactor.

Our next set of experiments is summarized in Tables 7 and 8. Running the reactor with the pumps at approximately half the flow rate of our best conditions, we observed an initial temperature above -60 °C for the halogen–metal exchange. Samples were taken, and we were surprised to find a high level of product in one of them (Table 8, sample 004-B). We suspected that the reaction might be tolerant of higher temperatures for a brief period of time, but this was our first such observation. The pumps were run at slow speed (Table 7, entry 6) to try to minimize the measured temperature stream. Once again, cavitations were observed in pump 1, and therefore the reaction was suspended (Table 7, entry 7) while the tubing leading from the cooled *t*-BuLi solution to the pump and from the pump to the flow reactor was covered with pipe insulation. Insulating the supply lines stabilized the solution, and no bubbles were observed in the lines. After sampling (Table 8, sample 004-C) and final pump adjustments, we allowed the reactor to reach steady state and took a final sample. Analysis of this sample (Table 8, sample 004-D) exceeded all of our expecta-

Table 9. Second-generation flow reactor, run 4

| entry | time | pump | | | temperature (°C) | | | | sample |
|-------|-------|------|---|---|------------------|-------|-------|-------|--------|
| | | 1 | 2 | 3 | 1 | 2 | 3 | 4 | |
| 1 | 10:54 | 0 | 0 | 0 | -77.6 | -78.3 | -78.2 | -76.9 | |
| 2 | 10:55 | 12 | 6 | 7 | | | | | |
| 3 | 11:00 | | | | -69.5 | -76.0 | -78.7 | -76.0 | 053-A |
| 4 | 11:00 | 0 | 0 | 0 | | | | | |
| 5 | 11:36 | | | | -77.2 | -77.3 | -77.8 | -77.4 | |
| 6 | 11:37 | 12 | 6 | 6 | | | | | |
| 7 | 11:41 | | | | -69.3 | -76.8 | -75.8 | -77.4 | 053-B |
| 8 | 11:41 | 0 | 0 | 0 | | | | | |
| 9 | 12:25 | | | | -77.2 | -77.3 | -77.8 | -77.4 | |
| 10 | 12:25 | 12 | 6 | 7 | | | | | |
| 11 | 12:30 | | | | -66.5 | -74.9 | -75.8 | -77.3 | 053-C |
| 12 | 12:35 | | | | -66.1 | -74.3 | -75.3 | -77.4 | 053-D |
| 13 | 12:40 | | | | -69.4 | -73.8 | -75.0 | -77.4 | 053-E |
| 14 | 12:45 | | | | -68.8 | -73.5 | -74.6 | -77.3 | |
| 15 | 12:45 | 0 | 0 | 0 | | | | | |

Table 10. Sample analysis from second-generation flow reactor, run 4

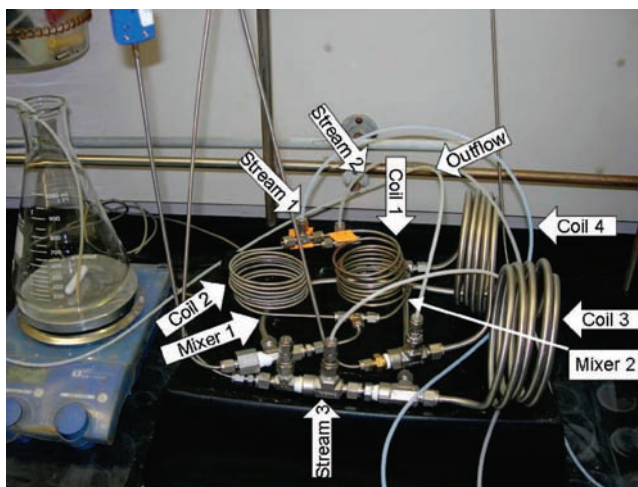
| sample | HPLC area % | | | | |
|--------|-------------|--------|-------|-------|-------|
| | cpd 12 | cpd 11 | cpd 6 | cpd 3 | cpd 4 |
| 053-A | 25.8 | 0 | 65.1 | 9.1 | 0 |
| 053-B | 20.9 | 0 | 51.3 | 9.4 | 18.4 |
| 053-C | 20.3 | 0.0 | 65.4 | 9.2 | 5.1 |
| 053-D | 18 | 0.0 | 76.3 | 6.1 | 0 |
| 053-E | 19.1 | 0 | 74.9 | 5.9 | 0 |

12: 2-acetylpyridine
 11: 12/*t*-BuLi/adduct
 6: product alcohol
 3: des-brominated
 4: bromobenzthiophene

tions. We observed the highest level of product of any reaction we had run. The reaction was repeated in a final set of experiments (Tables 9, 10) to verify the observations. Thus, after cooling, the reactor was run repeating our best conditions and was sampled (Table 9, entries 1–3). Analysis of this sample (Table 10, sample 053-A) found the same level of product, less debromination, and a slightly elevated level of 2-acetylpyridine when compared to the previous run. The speed of pump 3 (2-acetylpyridine supply) was slightly reduced, the reactor run and sampled (Table 9 entries 6–7). This sample was found to contain a reduction in the amount of product formed, a slight reduction in the amount of 2-acetylpyridine, the same level of des-bromination, and a large amount of starting bromide (Table 10, sample 053-B). It was clear that a small adjustment to one pump had a large effect on the entire system. The initial pump settings were used and the reactor run continuously with periodic sampling (Table 10, samples 053-C to 053-E) until the feed reagents were exhausted (Table 9, entries 10–14). In sample 053-C, a small amount of starting bromide was observed; however, as the reactor reached steady state, the starting bromide was no longer detected. The last two samples (Table 10; samples 053-D, 053-E) showed a high level of product and a low level of des-bromination. 2-Acetylpyridine was used in excess in the batch process to ensure consumption of the 2-lithio species; it was therefore known from experience that it would purge during isolation of the product. The sampling data was reprocessed without integrating the 2-acetylpyridine peak, and the results are shown in Table 11. More than 92% of the starting material

Table 11. Sample analysis from second-generation flow reactor, run 4 corrected for 2-acetylpyridine

| sample | HPLC area % | | | |
|--------|-------------|-------|-------|-------|
| | cpd 11 | cpd 6 | cpd 3 | cpd 4 |
| 053-D | n/a | 92.6 | 7.4 | 0 |
| 053-E | n/a | 92.7 | 7.3 | 0 |

**Figure 6.** Actual flow reactor.

was converted to product, and there were no variations (within experimental error) in the peak area of the final two samples, again demonstrating steady-state conditions were achieved.

Conclusions

In the route development of NBI-75043, we identified and developed a novel Ti(OiPr)₄-catalyzed addition of a metalated species to 2-acetylpyridine to afford a key intermediate and simultaneously avoided unstable intermediates. As the exothermic nature of the key halogen–metal exchange reaction limited batch size, we demonstrated the use of continuous flow reactor technology to successfully execute this chemistry. In two experimental runs with a custom-built reactor (Figure 6), we were able to equal the best results from batch-wise runs. In two additional experimental runs, we achieved higher conversion than had been previously observed and confirmed these results in a subsequent run. In the process, we have demonstrated the ease and practicality of this valuable tool in process chemistry.

Experimental Section

Compound 9 [2-(2-dimethylamino-ethyl)-benzo[*b*]thiophen-3-yl]-pyridin-2-yl-methanone. To 100 g (277 mmol) of [2-(3-bromo-benzo[*b*]thiophen-2-yl)ethyl]dimethylamine HBr (compound 4 HBr) in 500 mL of water was added 300 mL of 1N sodium hydroxide solution. The mixture was extracted twice with 1 L of MTBE. The combined organic phases were dried and concentrated *in vacuo* affording 72 g of freebase. The free base was diluted with 500 mL of anhydrous toluene and charged to a 3 L three-neck flask equipped with a mechanical stirrer, thermocouple, addition funnel, and nitrogen inlet. To the solution was charged 38.5 mL (257 mmol, 1 equiv) of TMEDA, and the mixture was chilled with a dry ice–acetone bath. To the mixture was carefully charged 193 mL (270 mmol, 1.05

equiv) of *s*-BuLi in cyclohexane dropwise, keeping the internal temperature <−60 °C. After the addition, which took approximately 30 min, the mixture was stirred at −78 °C for 15 min. To the solution was charged 29.4 g (283 mmol, 1.1 equiv) of 2-cyanopyridine in 50 mL of anhydrous toluene. During the addition the internal temperature was kept <60 °C and took approximately 15 min. The mixture was stirred at −78 °C for 30 min, and the reaction was complete as evidenced by HPLC. The reaction was quenched by the careful dropwise addition of a 100 mL 6 N HCl/200 mL methanol solution. During the addition of the first 150 mL, the internal temperature was kept <−50 °C at which time the solution turned orange. The final 150 mL was added keeping the internal temperature <−40 °C. The mixture was allowed to warm to 0 °C. The mixture was transferred to a separatory funnel and the organic phase separated. The organic phase was extracted with 400 mL of 1 N HCl. The combined aqueous phases were stirred at ambient temperature until no imine was observed by HPLC. Additional 6 N HCl may be required to accelerate the hydrolysis. Following complete hydrolysis of the imine, the mixture was brought to pH 10 with the careful addition of 50% sodium hydroxide. The mixture was extracted 3 times with 600 mL of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo*. This afforded 78 g of a dark oil, which was approximately 80% pure. The major impurity was the debrominated starting material. The product was used without further purification for the next step.

Compound 6 1-[2-(2-dimethylamino-ethyl)-benzo[*b*]-thiophen-3-yl]-1-pyridin-2-yl-ethanol. *MeLi Addition to Compound 9.* In a 2 L three-neck Morton flask equipped with a mechanical stirrer, thermocouple, and addition funnel with a nitrogen inlet was charged 75 g (242 mmol) of ketone **9** in 500 mL of anhydrous toluene. The mixture was chilled using a −78 °C bath and stirred. To the solution was charged dropwise 160 mL (254 mmol, 1.05 equiv) of methyllithium in cyclohexane. The addition was kept at a rate to keep the reaction temperature <−60 °C and took approximately 30 min. The mixture was stirred for an additional 15 min and judged complete by HPLC. The reaction was quenched with a solution of 200 mL 6 N HCl/400 mL methanol, keeping the reaction temperature <−45 °C during the addition. The mixture was allowed to warm to ambient temperature and the organic phase separated. The organic phase was extracted with 500 mL of 1 N HCl. The combined aqueous phases were neutralized with 50% sodium hydroxide solution and extracted three times with 600 mL of ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated. The crude product was diluted with 600 mL of warm acetonitrile and seeded with authentic product. The mixture was stirred at ambient temperature for 3 h and then chilled in an ice bath. The slurry was filtered using a Büchner funnel, and the filter cake was washed with cold acetonitrile. After drying *in vacuo* at 45 °C this afforded 46 g of alcohol **10** in a 59% yield as a light-tan powder.

2-Acetylpyridine Addition to Compound 4. TMDEA (3.8 kg, 33 mol) was dissolved in THF (8 kg) and dried over activated molecular sieves (1 kg). The solution was filtered and transferred to a 400 L Hastelloy reactor followed by a THF (2 kg) rinse. Additional THF (132 kg) was charged and agitation started.

The jacket was set to −85 °C. While the reactor was cooling, a 50 L round-bottom flask was charged with compound **4** (6 kg, 21 mol) and THF (22 kg). The flask was placed under a nitrogen atmosphere, agitated, and cooled to <−65 °C. In a second flask, THF (10 kg) and 2-acetylpyridine (2.8 kg, 23 mol) were mixed. To the 400 L reactor was charged *t*-BuLi (11.9 kg in heptane, 25 wt %, 46 mol), maintaining an internal temperature <−70 °C. The solution of compound **4** was charged to the reactor while maintaining an internal temperature <−70 °C. The reaction was monitored by HPLC for the disappearance of compound **4**. Once complete, Ti(Oi-Pr)₄ (0.4 kg, 1.4 mol) was charged to the 2-acetylpyridine solution; the solution was agitated and charged to the 400 L reactor while maintaining an internal temperature <−70 °C. The reaction was sampled, and the amount of 2-acetylpyridine was found to be >1%. The reaction was resampled and judged complete as the difference in area % for compound **3** in the two samples was less than 2%. The reaction was quenched by the addition of methanol (2.4 kg) while maintaining an internal temperature <−70 °C. The reactor was warmed to 0 °C, and then water (48 kg) and isopropyl acetate (44 kg) were charged while maintaining an internal temperature <20 °C. Agitation was stopped, and the layers were split. The aqueous layer was extracted again with isopropyl acetate (44 kg). The combined organic layers were washed with water (3 × 48 kg) until the pH of the wash was found to be <9. The organic layer was concentrated by distillation until 192 kg of distillate was collected. Acetonitrile (48 kg) was charged and the reactor concentrated to ~20 L while maintaining an internal temperature <45 °C. This process was repeated, and then additional acetonitrile (48 kg) was charged, and the reactor was agitated for 2 h at 20 °C. The contents were filtered through a Büchner funnel with Whatmann #5 filter paper and blown dry with nitrogen for 20 min. The filter cake was transferred to a tray dryer and dried at 45 °C until constant weight was obtained to produce 3.35 kg, 49%; 99.6% HPLC purity.

Compound 8 Dimethyl-{2-[3-(1-pyridin-2-yl-ethyl)-benzo[*b*]thiophen-2-yl]-ethyl}-amine. *Direct Dehydroxylation Route:* In a 500 mL round-bottom flask, alcohol **6** (46 g, 141 mmol, 1.0 equiv) was slurried in 200 mL of anhydrous acetonitrile. To the mixture was charged sodium iodide (42.3 g, 282 mmol, 2 equiv) followed by trimethylsilyl chloride (36 mL, 282 mmol, 2 equiv). The mixture was stirred at ambient temperature for 1 h and the precipitate collected by filtration using a Büchner funnel. The filter cake was split into two 37 g lots and diluted with 100 mL of acetonitrile in a 350 mL pressure flask. To the slurry was charged sodium iodide (27.9 g, 186 mmol) and trimethylsilyl chloride (23.6 mL, 186 mmol). To the mixture was added 1 drop of water, and the pressure vessel was sealed and heated in an oil bath at 95 °C for 3 h. The mixture was cooled and the reaction checked for completeness by HPLC. If starting material remained, the reaction was heated until complete. The completed reaction mixture was poured into a 500 mL Erlenmeyer flask and treated with an aqueous solution of sodium thiosulfate until the solution was light yellow. The solution was neutralized with 50% sodium hydroxide solution and extracted with 500 mL of ethyl acetate. The organic phase was dried over anhydrous MgSO₄ and

concentrated *in vacuo*. The crude product was chromatographed using a Biotage 75 eluting with 95:5 dichloromethane/methanol. When pure product was observed, the eluent was changed to 9:1 dichloromethane/methanol. The pure fractions were combined and concentrated, affording 17.9 g of compound **8** in a 41% yield.

Achiral Hydrogenation. A solution of compound **7** (3.4 kg, 11.0 mol) in absolute ethanol (20 kg) was charged to a glass lined (GL) 200 L reactor under a nitrogen blanket followed by a slurry of Darco G60 charcoal (0.7 kg) in absolute ethanol (10 kg). The reactor was agitated and heated to 50 °C for 2 h. The reactor cooled to 25 °C, and the contents were filtered through a bag filter followed by a 0.45 μ m polish filter to remove trace contaminants prior to hydrogenation. The cake was washed with absolute ethanol (15–20 kg). The filtrate and wash were charged to a 200 L pressure reactor under nitrogen. A slurry of PtO₂ (0.07 kg) in absolute ethanol (10.0 kg) was charged to the reactor. With gentle agitation, the reactor was thoroughly flushed with nitrogen followed by hydrogen. The reactor was pressurized to 120 psig hydrogen and heated to 45–50 °C internal temperature. The agitation was increased to the best gas mix mode, the temperature was maintained at 45–50 °C and the hydrogen pressure at 120 psig. Samples were taken every 6 h and checked (HPLC). The end point was reached when compound **7** was <0.5% by HPLC analysis. The hydrogenation could take more than 70 h. The agitation was slowed, the reactor cooled to 25 °C, the hydrogen pressure released, and the reactor thoroughly flushed with nitrogen. The contents were filtered through a bag filter, and the filtrate was discharged to a 200 L reactor. The pressure reactor was flushed with a small amount of absolute ethanol and the flush drained to the same reactor. Charcoal (3.3 kg) and silica gel (7.0 kg) were charged to the 200 L reactor, and the contents were agitated at 30 °C for 2 h.

The contents of the 200 L reactor were filtered through a bed of silica gel (7 kg) in a Nutsche filter, and the cake was rinsed with absolute ethanol until no more product eluted (as determined by HPLC or TLC). The filtrate was concentrated by vacuum distillation at 40 °C to dryness to afford 2.9 kg, 9.34 mol, 85% yield of compound **8** with >98% HPLC purity.

Compound 1 (NBI 75043) Dimethyl-2-[3-((R)1-pyridin-2-yl-ethyl)-benzo[b]thiophen-2-yl]-ethyl}-amine. *Two-Step Resolution.* To a 2-L round-bottom flask was charged 97 g (312 mmol) of compound **8** followed by 312 mL of ethanol. The mixture was heated to near reflux, and a hot solution of 46.9 g (312 mmol, 1 equiv) of D-tartaric acid in 312 mL of ethanol was added. The mixture was seeded and stirred at ambient temperature for 4 h. The precipitate was filtered, and the filter cake was washed with ethanol. The mother liquor was concentrated *in vacuo* and the semisolid diluted with 500 mL of water. The mixture was brought to pH 10 with 50% sodium hydroxide and extracted twice with 500 mL of ethyl acetate. The combined organic phases were concentrated *in vacuo*, affording 54 g of oil. The oil was diluted with 175 mL of ethanol and heated to near reflux. To the mixture was charged a solution of 26.1 g (174 mmol, 1 equiv) of L-tartaric acid in 175 mL of hot ethanol. The hot solution was filtered through Celite, seeded, and stirred at ambient temperature for 10 h. The solid was

filtered and washed with 200 mL of ethanol. The filter cake was diluted with 350 mL of ethanol and heated until the solution was homogeneous. The mixture was seeded and stirred at ambient temperature for 8 h. The precipitate was collected by filtration using a Büchner funnel, and the filter cake was washed with 200 mL of ethanol. The filter cake was dried *in vacuo* at 45 °C for 36 h (constant weight), affording 50.0 g of NBI-75043 in a 69% enantiomeric yield. Chiral purity determined by chiral HPLC was 95.6% ee with an overall HPLC purity of 98.7%.

One-Step Resolution. Compound **8** (2.25 kg, 7.2 mol) was dissolved in absolute ethanol (7 kg) in a small vessel under nitrogen. The solution was charged to a 400 L GL reactor under nitrogen followed by a rinse of absolute ethanol (3 kg). Agitation was started and the reactor heated to 75 °C (internal temperature). A solution of L-tartaric acid (1.1 kg, 7.3 mol, 1.01 equiv) in absolute ethanol (10 kg) was charged to the reactor. The solution was stirred until a clear solution was obtained. With gentle agitation, the reactor was cooled to 55 °C at a rate of 15 °C/h. A suspension of NBI-75043 L-tartrate seed crystals (2–5 g) in absolute ethanol (0.05 kg) charged. The reactor was cooled to 45 °C over one hour; additional seeds were charged if the first charge dissolved. The reactor was cooled to 20 °C at a rate of 15 °C/h and then agitated at 20 °C for 4 h. The resulting crystals were filtered through a Nutsche filter. The cake was washed twice with absolute ethanol (5 kg). The cake was dried in a vacuum oven at 45 °C to constant weight to give 1.5 kg, 3.3 mol, 45% yield, 99.7% HPLC purity.

Compound 7 Dimethyl-2-[3-(1-pyridin-2-yl-vinyl)-benzo[b]thiophen-2-yl]-ethyl}-amine. To a 200 L GL reactor was charged 3.5 kg of compound **6** and DCM (10 kg). Agitation was started. Methanesulfonic acid (10.3 kg, 10.3 equiv) was added gradually at such a rate as to allow a gentle reflux. The mixture was stirred at reflux for 5 h and monitored by HPLC. The reaction was judged complete when the starting material was <0.5 area % by HPLC analysis. The reaction was cooled to room temperature, and then DCM (70 kg) was charged. NaOH (64 kg, 2 M) was charged while maintaining the temperature <30 °C until the pH of the aqueous layer measured >9. Agitation was stopped, and the phases were split. The aqueous layer was extracted with DCM (23 kg); the emulsion was kept with the aqueous layer. The combined organic layers were washed with 15% brine (58 kg). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum at ~45 °C to yield 3.4 kg (100% yield) of compound **7** as a dark amber oil. HPLC purity: 94.3%.

Flow Reactor. *Pumps.* Masterflex Console Drive, model 7520-60; head model 77390-00

Static Line Mixers. Koflo Corporation, Stratos tube mixer, series 250; –0.250 in. O.D., 7 in. length, 21 elements; 11.5 in. length, 34 elements.

Reactor Construction. See Figures 5 and 6 for schematic and photo, respectively. The reactor was constructed from 316 stainless steel 1/8 in. and 1/4 in. tubing with Swagelok fittings and tees to connect the parts; 1/8 in. stainless steel thermocouples were used to monitor temperature at various points in the reactor. Reagent streams were plumbed with 3/8 in. PTFE tubing from the supply flasks to the pumps and from the pumps

to the reactor. Two of the pumps were connected to two coils of 1/8 in. tubing with a diameter of ~3 in. and a volume of 7 mL (hold coils no. 1 and no. 2). These coils were connected with a T-fitting to a short length of 1/8 in. tubing (~3 in.) and then to a second T-fitting containing a thermocouple (no. 1). At this T-fitting, the O.D. was changed to 1/4 in. and the fitting was connected to the 7 in. static line mixer and then to another T-fitting with a thermocouple (no. 2). Next was a 1/4 in. O.D. hold coil (no. 3) with a diameter of ~5 in. and a volume of 39 mL. At the end of the coil no. 3 was a T-fitting with tubing from the third pump and a T-fitting with a thermocouple (no. 3). Attached to the T-fitting was the second (11.5 in.) static line mixer which was connected to a 1/4 in. O.D. hold coil (no. 4) with a volume of 39 mL. A final T-fitting contained a thermocouple (no. 4) and was connected to 3/8 in. PTFE tubing running to the quench vessel.

Reagent Preparation. A dry flask was charged with TMEDA (40 mL, 0.27 mol) and THF (250 mL). The flask was placed under a nitrogen atmosphere and cooled in a $-78\text{ }^{\circ}\text{C}$ bath. *t*-BuLi (200 mL, 0.34 mol, 1.7 M) was added slowly, maintaining an internal temperature $<-65\text{ }^{\circ}\text{C}$. This flask was connected to pump no. 1. In a second dry flask, compound **4** (50 g, 0.18

mol) was dissolved in THF (200 mL) and connected to pump no. 2. In a third flask, THF (200 mL), 2-acetylpyridine (21.7 mL, 0.19 mol), and $\text{Ti}(\text{O}i\text{Pr})_4$ (3.9 mL, 0.013 mol) were mixed and connected to pump no. 3.

The flow reactor was placed in a large container (the bottom 18 in. of a 30-gal plastic drum was used) and covered with $\text{CO}_{2(\text{s})}$ and acetone. While the reactor was cooling, the outflow tubing was placed in a stirred container of methanol (500 mL). Once the temperature reading stabilized, the pump speeds were set and the pumps switched on. The reactions were sampled, and the pumps were switched on and off and adjusted as shown in Tables 3, 5, 7, and 9.

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