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Process Intensification via Reaction Telescoping and a Preliminary Cost Model to Rapidly Establish Value

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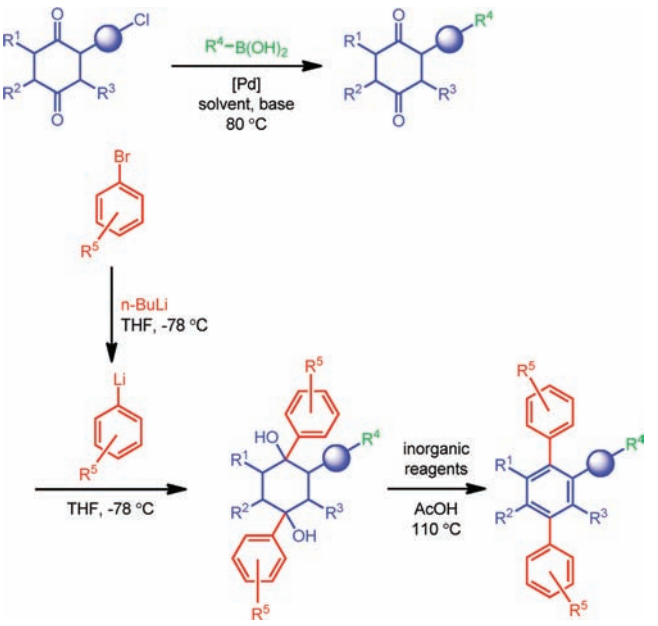
ABSTRACT: Process intensification via reaction telescoping has recently been demonstrated in our research laboratories. The improved process is significantly streamlined; 1 intermediate isolation vs 2, 24 workup and purification unit operations vs 49, and a batch cycle time of 116 h vs 177 h are the key improvements realized. A preliminary cost model was developed to establish the value generated, which predicts a >50% reduction in the total cost to manufacture 1 kg of the product. This cost model can serve as a preliminary method for rapidly establishing the value of process intensification in the manufacture of fine and specialty chemicals.

The field of process intensification has enjoyed tremendous growth in the past decade.[1−3] It has become a "buzzword" amongst researchers in academia and industry.[4] In this article, we detail a simple case study of process intensification via reaction telescoping that has been recently demonstrated in our process development laboratories. The improved process is significantly streamlined; the process improvements realized have the potential to reduce manufacturing cost and cycle time, and increase production capacity. The specific chemical structures for this project are proprietary, and have been genericized in this report.

The original manufacturing route that was being practiced at a 20-L reactor scale is depicted in Scheme 1. The synthetic process consisted of three discrete steps: (1) a palladium-catalyzed Suzuki−Miyuara cross-coupling, (2) cryogenic organolithiation chemistry in THF, and (3) a final aromatization step conducted in acetic acid.

Block flow diagrams for the three steps in the original manufacturing route appear in Figure 1. The purity specification of the final product was high (>99.8% HPLC area purity) which led to the development and implementation of extensive purification sequences. Thus, although successfully practiced on the 20-L reactor scale for quite some time, the original manufacturing route was cumbersome and time-, material-, and labor-intensive. This ultimately resulted in a high cost of manufacture. The business demand for this product was already high at the time the present work was initiated, and this demand was projected to increase by a factor of >10 by 2013. Our process development team was engaged in early 2011 to streamline the overall manufacturing route, and an ambitious target for the process development work was set with an aggressive timeline. Success was defined as the development of a scalable process that lead to a 50% reduction in the cost to manufacture 1 kg of the final pure product while maintaining or improving the yield and purity.

Scheme 1. Original manufacturing route



We were chartered to demonstrate the improved process on a 1-L reactor scale in a time frame of two months.

The aggressive timeline for the project prevented us from making fundamental changes to the chemical route and technology involved. Thus, at the outset it was decided that we would focus our efforts on streamlining the unit operations and intensifying the process while retaining the fundamental chemistry and technology. A detailed study of the process block flow diagrams for the original manufacturing route (Figure 1) brought to light numerous opportunities for process development work. A few of these are highlighted below.

1. The route consisted of three discrete steps with two intermediate isolation and purification sequences. Significant process intensification could be achieved if we were to couple two of the three steps in a sequential "one-pot" process and eliminate an isolation/purification sequence.
2. The high-purity specification had led to the incorporation of tedious purification sequences. For example, seven trituration/filtration sequences were included in the third-step process which added 14 unit operations for purification. Similar purification sequences were also being utilized in the first two steps.

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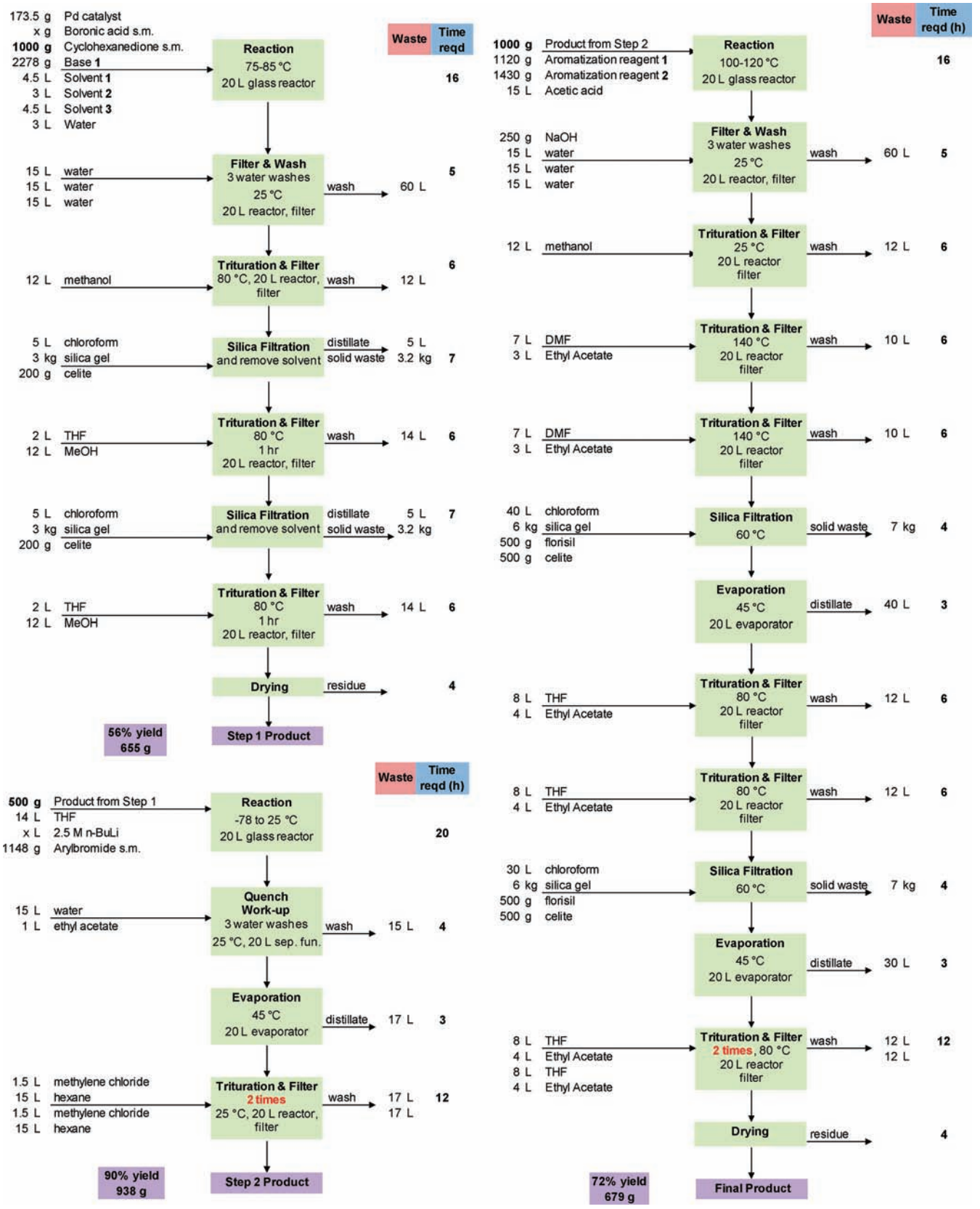

Figure 1. Process block flow diagrams for the original manufacturing route, practiced on a 20-L reactor scale.

It was thus desired to develop a single "true" crystallization to replace the triturations in each of the three steps.[5]

3. Silica gel filtration was also being utilized for purification and polishing in Steps 1 and 3. This was considered

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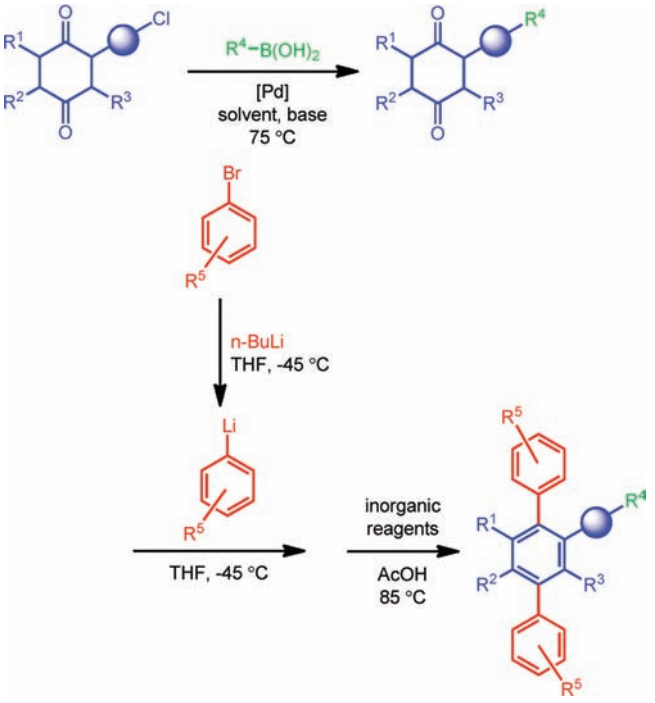
Scheme 2. Improved process



impractical for manufacturing at larger scale. It was again desired to replace these silica gel operations with efficient crystallization processes.

4. The cryogenic reaction conditions (−78 °C) for Step 2 were a significant concern. Cryogenic organolithiation chemistry is difficult to scale up in batch mode principally due to the handling of large volumes of hazardous alkyllithium reagents and the challenges associated with cryogenic technology at scale; these reactions are well-suited for continuous processing.[6] The aggressive timeline prevented us from exploring this avenue, and so the development work was focused on relaxing the cryogenic conditions and operating at relatively "warmer" temperatures.

Process development was initiated, and the first phase was completed within the stipulated two months. The chemical scheme for the improved process appears in Scheme 2, and the detailed process block flow diagrams in Figure 2. The various process improvements realized are self-evident on comparison with the original manufacturing route (Scheme 1 and Figure 1). Only the major improvements which led to the significantly intensified new process will be highlighted here.

The improved process has been demonstrated successfully on a 1-L reactor scale, and has been extrapolated to the 20-L reactor scale for comparison to the original manufacturing route. The final product was obtained in 48% overall yield (combined yield for three steps) and exceeded the purity specifications. The purity was >99.8% (HPLC analysis), and neutron activation analysis (NAA) indicated an inorganic analysis of ≤20 ppm for I, Br, Cl, Na, K, and Pd.

The original manufacturing route involved three triturations and two silica gel filtrations for purifying the Step 1 intermediate. A thorough investigation of the impurities formed from the original process revealed the presence of a major impurity originating from the cyclohexanedione starting material. A purification step for this starting material was incorporated in the new process prior to conducting the reaction. A "true" crystallization was then developed to replace the triturations.[5] These improvements allowed us to purify the Step 1 intermediate up to specification with only one silica gel filtration and one crystallization, as compared to two silica gel filtrations and three triturations in the original route. The yield for Step 1 increased to 63% from 56% for the original route.

Through independent optimization of Step 2, we were able to increase the cryogenic temperature to −45 °C from the original −78 °C. The reaction worked well with similar results up to −20 °C, but the reaction pathway completely switched at 0 °C to quantitatively furnish the alkylation product formed by the reaction between the initially formed aryllithium and *n*-butylbromide intermediates. Thus, it was decided to maintain the reaction temperature at −45 °C to provide a safe operating process window.

Step 2 of the process involves cryogenic organolithiation chemistry in THF and the final Step 3 is an aromatization process with inorganic reagents and acetic acid. The chemistry in these two steps is completely different, and convention would dictate that these steps should be carried out independently with isolation of the intermediate product. However, we theorized that we could use the complete exclusivity of both chemistries to our advantage and combine these two discrete steps into a sequential "one-pot" process. This theory was validated in initial experiments, and rapidly optimized to the final improved process for Steps 2 + 3 (Scheme 2 and Figure 2). The cryogenic organolithiation chemistry is carried out at −45 °C in THF, with the initial formation of the aryllithium intermediate by reaction between *n*-BuLi and the arylbromide starting material and subsequent bis-attack of the aryllithium to the cyclohexanedione product from Step 1. This furnishes the lithium salt of the bis-alcohol intermediate as the reaction mixture is allowed to warm up to room temperature. This salt is protonated by addition of acetic acid, which becomes the cosolvent for the final aromatization step. The inorganic aromatization reagents are added, the temperature increased to 80 °C, and the mixture is refluxed for two hours. This "one-pot" process works smoothly and, quite serendipitously, the final product precipitates out of the solution and a simple filtration furnishes the crude final product with an organic purity of 99.6%.

The purification process for the final product was subsequently optimized. The crude product is dissolved in hot toluene and filtered to remove the inorganic salts, and the pure product is then allowed to crystallize from this hot toluene solution (Figure 2). The yield for this "one-pot" process is 77% (compared to 65% for Step 2 + Step 3 in the original process) and the final product is obtained with >99.8% HPLC purity. Tremendous process intensification has been achieved through the improved process for Steps 2 and 3: the original manufacturing route involved one intermediate isolation, two aqueous extractions, nine triturations, and two silica gel filtrations for these two steps whereas the improved process now involves no intermediate isolation and only one solvent wash and one crystallization to furnish the final product with better overall yield and well within the organic/inorganic purity specifications.

Preliminary comparative cost analyses for the original and improved processes were created to establish the value generated from the development work.[7] Several assumptions were made to allow for a quick analysis, these are detailed below; these assumptions were kept constant for the analysis of both the original and improved processes.

1. The parameters considered for the analyses are batch cycle times (which translate to labor costs), raw material costs, and waste disposal costs.

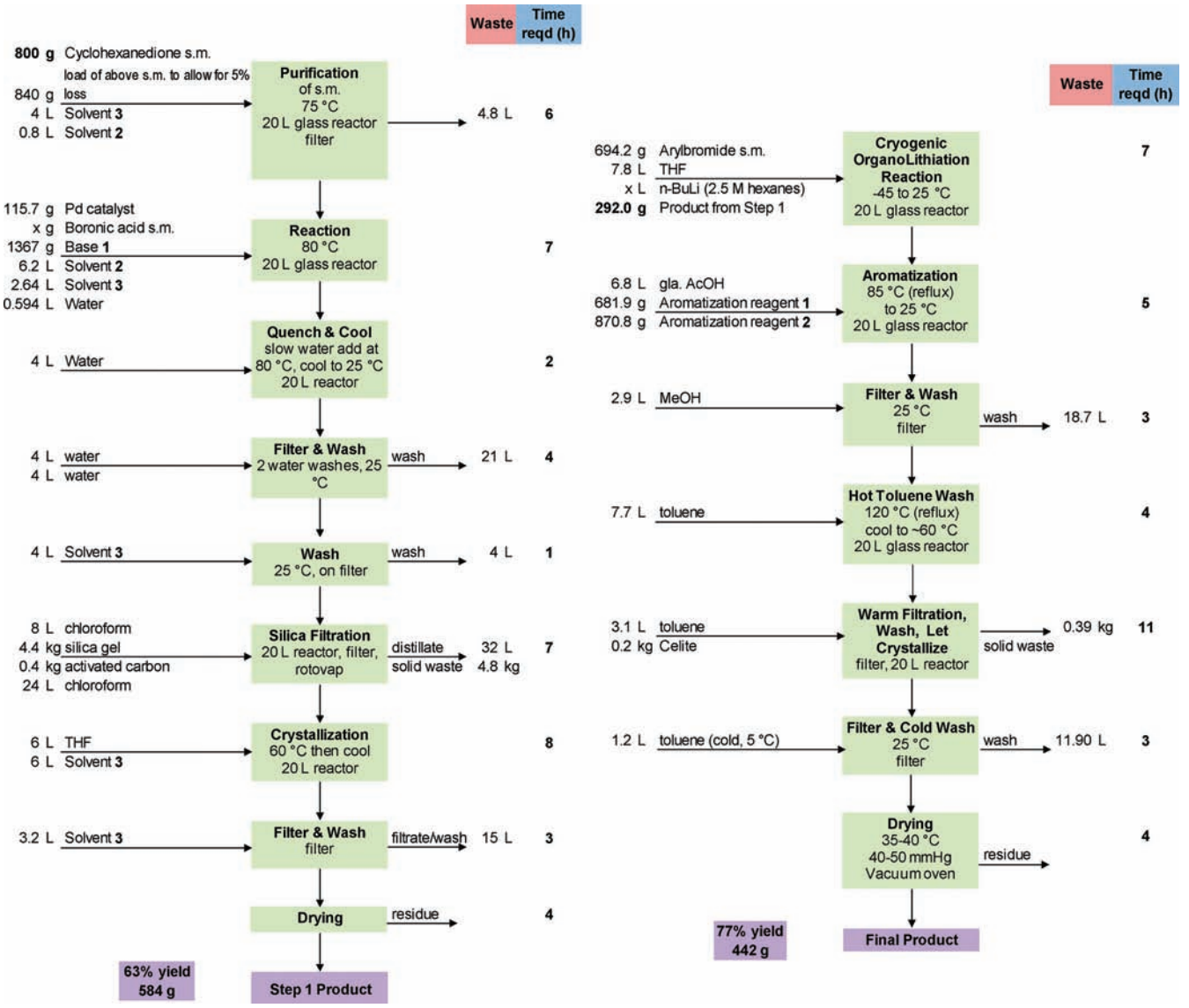


Figure 2. Process block flow diagrams for the improved process, demonstrated on a 1-L reactor scale, extrapolated to a 20-L reactor scale.

2. Batch cycle times are calculated on the assumption that one operator is required, and all steps and unit operations are conducted in a sequential manner.
3. The cryogenic organolithiation step is scale limiting for both the original and improved processes, and the scale is also limited by the availability of only 20-L reactors.
4. On the basis of the above scale-limiting considerations and to maximize productivity, one batch from the original process is defined as [Step 1 → Step 2 → Step 3], affording 637 g pure final product per batch. One batch from the improved process is defined as [Step 1 → (2 × Step 2 + 3)], affording 884 g pure final product per batch.
5. Unit labor cost = $100/h, based on an annual $200,000 salary/benefits package and a (250 days/year and 8 h/day) work schedule.
6. A waste disposal cost of $2 per kg of waste is assumed. This may be conservative for a commercial process, but at small scale this process might be operated at a location where off-site disposal is required.
7. Constant times are empirically assigned for all unit operations (representative for a 20-L scale): filtration - 2 h, wash on filter - 1 h, heated trituration - 4 h, crystallization - 8 h, silica gel filtration - 4 h, quench - 1 h, extraction - 1 h, solvent evaporation - 3 h, and drying - 4 h. The time requirements assigned for the individual unit operations in the process block flow diagrams for the original and improved processes (Figures 1 and 2) are based on these assumptions.

Usage rates and prices of raw materials were combined to obtain the cost of raw materials (Tables 1 and 2). Prices were obtained for two different production scales: "lab" pricing for a 5-kg scale and "commercial" pricing for a 1-MT scale. The labor costs associated with both processes were computed on the basis of the batch cycle times and the assumed unit labor cost. The process block flow diagrams (Figures 1 and 2) also include details of the waste produced from each unit operation, and these were used to compute the waste disposal costs. All costs were normalized by the batch sizes to arrive at costs per kg of product.

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Table 1. Cost of raw materials for one batch of final product in the original manufacturing route

		1-MT scale			5-kg scale		
	qty reqd per batch product	price per kg ($)	source	cost ($) for 1 batch	price per kg ($)	source	cost ($) for 1 batch
Reactants, Reagents							
Pd catalyst	132.5 g	4800.0	Calculation	635.8	19700.0	Aldrich	2609.5
boronic acid s.m.	– g	–	Internal	55.2	363.0	SciFinder	167.1
cyclohexanedione s.m.	763.5 g	11.2	Aldrich/10	8.6	76.5	SciFinder	58.4
base **1**	1739.2 g	1.3	SRI Yearbook	2.3	32.9	SciFinder	57.1
2.5 M *n*-BuLi	– L	–	Calculation	7.9	103.6	SciFinder	160.5
arylbromide s.m.	1148.2 g	219.0	Aldrich/10	251.5	530.0	SciFinder	608.5
aromatization reagent **1**	1050.7 g	33.1	SRI Yearbook	34.8	168.2	SciFinder	176.7
aromatization reagent **2**	1341.5 g	3.7	SRI Yearbook	4.9	23.3	Aldrich	31.2
Solvents, Purification Media							
solvent **1**	3.4 L	1.1	SRI Yearbook	3.8	30.0	SciFinder	81.0
solvent **2**	2.3 L	5.5	Internal	12.6	120.5	Aldrich	239.3
solvent **3**	3.4 L	0.6	SRI Yearbook	1.9	55.3	SciFinder	149.8
water	93.9 L	0.0	–	0.0	0.0	–	0.0
MeOH	38.7 L	0.2	SRI Yearbook	8.1	5.2	SciFinder	159.4
chloroform	73.3 L	0.4	SRI Yearbook	29.3	5.4	Internal	584.3
silica gel	15.8 kg	2.2	SRI Yearbook	34.5	172.0	Aldrich	2724.2
Celite	1243.5 g	0.9	Internal	1.1	41.8	Aldrich	52.0
THF	47.1 L	2.5	SRI Yearbook	119.1	21.7	Aldrich	906.1
ethyl acetate	21.6 L	1.1	SRI Yearbook	23.4	11.5	Aldrich	223.5
CH_2CI_2	3.0 L	0.5	SRI Yearbook	1.4	15.8	SciFinder	62.8
hexanes	30.0 L	0.7	SRI Yearbook	19.5	9.1	SciFinder	179.9
AcOH	14.1 L	0.6	SRI Yearbook	9.0	8.3	SciFinder	122.1
NaOH	234.5 g	2.6	Aldrich/10	0.6	26.0	Aldrich	6.1
DMF	13.1 L	1.4	SRI Yearbook	18.0	7.6	SciFinder	94.6
florisil	938.1 g	27.0	Aldrich/10	25.3	270.0	Aldrich	253.3

Table 2. Cost of raw materials for 1 batch of final product in improved process

		1-MT scale			5-kg scale		
	qty reqd per batch product	price per kg ($)	source	cost ($) for 1 batch	price per kg ($)	source	cost ($) for 1 batch
Reactants, Reagents							
Pd catalyst	115.7 g	4800.0	Calculation	555.4	19700.0	Aldrich	2279.3
boronic acid s.m.	– g	–	Internal	57.9	363.0	SciFinder	175.1
cyclohexanedione s.m.	840.0 g	11.2	Aldrich/10	9.4	76.5	SciFinder	64.3
base **1**	1366.9 g	1.3	SRI Yearbook	1.8	32.9	SciFinder	44.9
2.5 M *n*-BuLi	– L	–	Calculation	9.1	103.6	SciFinder	184.6
arylbromide s.m.	1388.4 g	219.0	Aldrich/10	304.1	530.0	SciFinder	735.8
aromatization reagent **1**	1363.7 g	33.1	SRI Yearbook	45.1	168.2	SciFinder	229.4
aromatization reagent **2**	1741.6 g	3.7	SRI Yearbook	6.4	23.3	Aldrich	40.5
Solvents, Purification Media							
solvent **2**	7.0 L	5.5	Internal	38.6	120.5	Aldrich	731.5
solvent **3**	19.8 L	0.6	SRI Yearbook	10.9	55.3	SciFinder	865.0
MeOH	5.8 L	0.2	SRI Yearbook	1.2	5.2	SciFinder	24.0
chloroform	32.0 L	0.4	SRI Yearbook	12.8	5.4	internal	255.1
silica gel	4.4 kg	2.2	SRI Yearbook	9.6	172.0	Aldrich	756.8
Celite	400.0 g	0.9	Internal	0.4	41.8	Aldrich	16.7
THF	21.5 L	2.5	SRI Yearbook	54.5	21.7	Aldrich	414.8
AcOH	13.6 L	0.6	SRI Yearbook	8.7	8.3	SciFinder	118.2
activated carbon	0.4 kg	3.2	Aldrich/10	1.3	32.0	Aldrich	12.8
toluene	23.8 L	0.8	SRI Yearbook	19.0	12.5	SciFinder	257.4

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Table 3. Costs to manufacture 1 kg final product from original and improved processes

estimated cost in dollars	original process	improved process	% reduction in cost by improved process
labor cost	27800	13100	53
waste disposal cost	1150	330	71
raw material cost (1 *MT pricing*)	2100	1300	37
raw material cost (*5 kg pricing*)	15200	8200	46
total cost (***1 MT pricing***)	**31000**	**14700**	**53**
total cost (***5 kg pricing***)	**44200**	**21600**	**51**

Table 4. Original vs improved processes

original process	improved process
2 intermediate isolations	**1** intermediate isolation
standard chemistry	**novel one-pot** chemistry
49 total unit operations	**24** total unit operations
36% overall yield	**48%** overall yield
−78 °C cryogenic reaction step	**−45 °C** cryogenic reaction step
batch cycle time = **177 h**	batch cycle time = **116 h**
high total cost to make 1 kg product	**>50% reduction in total cost** to make 1 kg product

All costs were then combined to compute the total cost of manufacturing 1 kg pure final product from both the original and improved processes. These numbers for both processes are tabulated in Table 3, along with the % reduction in the costs from the improved process over the original process. Irrespective of the pricing mode considered, success was realized in the project, and >50% reduction in the total cost to manufacture 1 kg of product was demonstrated through the improved process (Table 3).

In conclusion, we have reported herein a simple case study of process intensification via reaction telescoping in a development project. The improved process is significantly intensified compared to the original process; these improvements are highlighted in the comparative analysis in Table 4. A preliminary cost model has been developed to establish the value generated from the process intensification; it is thought that this cost model can serve as a preliminary method for rapidly establishing the value of process intensification in the manufacture of fine and specialty chemicals.

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(1) Process intensification is a term loosely used in the literature. We define process intensification simply as measures which significantly increase the productivity of a chemical process. Process intensification in this work has been primarily achieved by incorporating reaction telescoping, aided by sound overall process development work.

(2) Two of the most widely studied tools for process intensification are microreaction technology and microwave technology, see: (a) Wiles, C.; Watts, P. *Micro Reaction Technology in Organic Synthesis*; CRC Press, Taylor & Francis Group: Boca Raton, FL, 2011. (b) Loupy, A., Ed. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2006.

(3) For books which have been published recently in the field of process chemistry and development, see: (a) Yasuda, N., Ed. *The Art of Process Chemistry*; Wiley-VCH: Weinheim, 2010. (b) Harrington, P. J. *Pharmaceutical Process Chemistry for Synthesis: Rethinking the Routes to Scale-Up*; John Wiley & Sons, Inc.: NJ, 2011.

(4) A simple Scifinder exercise illustrates this phenomenon. A search generated on the term "process intensification" yields 85 hits for the year span 1933−1990 (57 years), 144 hits for the year span 1991−2000 (10 years), and a staggering 749 hits for the year span 2001−2010 (10 years)!

(5) A trituration is simply a hot solvent wash where the crude product does not dissolve. A "true" crystallization involves complete dissolution of the crude product followed by precipitation/crystallization of the desired pure product.

(6) (a) Gross, T. D.; Chou, S.; Bonneville, D.; Gross, R. S.; Wang, P.; Campopiano, O.; Ouellette, M. A.; Zook, S. E.; Reddy, J. P.; Moree, W. J.; Jovic, F.; Chopade, S. *Org. Process Res. Dev.* **2008**, *12*, 929–939. (b) Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312–3315. (c) Usutani, H.; Tomida, Y.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2007**, *129*, 3046–3047. (d) Nagaki, A.; Takabayashi, N.; Tomida, Y.; Yoshida, J.-I. *Org. Lett.* **2008**, *10*, 3937–3940.

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