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Article

Asymmetric Organocatalysis and Continuous Chemistry for an Efficient and Cost-Competitive Process to Pregabalin

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Cite This: *Org. Process Res. Dev.* 2021, 25, 2795−2805

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ABSTRACT: Herein, we present the scale up development of an innovative synthetic process to pregabalin. The process is underpinned by two enabling technologies critical to its success; continuous chemistry allowed a safe and clean production of nitroalkene, and asymmetric organocatalysis gave access to the chiral intermediate in an enantioenriched form. Crucial to the success of the process was the careful development of a continuous process to nitroalkene and optimization of the organocatalyst and of the reaction conditions to attain remarkably high turn-over frequency in the catalytic asymmetric reaction. Successful recycle of the organocatalysts was also developed in order to achieve a cost-competitive process.

KEYWORDS: *Pregabalin, organocatalysis, continuous chemistry, asymmetric catalysis*

INTRODUCTION

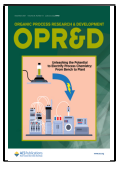
Developed by Pfizer and commercialized under the brand name Lyrica, pregabalin ((*S*)-3-aminomethyl-5-methylhexanoic acid, **1**)[1] is one of the blockbuster drugs[2] of the last decades. This structurally simple *S*-configured γ-amino-acid is a central nervous system inhibitor, useful for the treatment of different conditions, such as seizure disorders, neuropathic pain, fibromyalgia, and epilepsy.[3] Different routes amenable to the manufacture of pregabalin have been developed by Pfizer. The first process entailed resolution of the racemic γ-amino-acid by crystallization with (*S*)-mandelic acid.[4] Later, a synthetic sequence based on an asymmetric hydrogenation step catalyzed by a rhodium bisphosphine complex was proposed.[5] Further research toward the development of a process led to the disclosure of two very efficient enzymatic protocols, involving an early stage lipolase resolution,[6] and an ene-reductase reduction.[7] The resolution approaches (via diastereoisomer crystallization or lipolase) employ very simple and straightforward synthetic sequences (based on the conjugate addition of cyanide to an alkylidene malonate) for the preparation of the racemates, resulting in a very economical overall process. However, these methods can reach maximum 50% overall yield; in the lipolase process, this drawback is alleviated by the earliness of the resolution step, and by off-enantiomer recycle, making it in all respect a classic in green/industrial chemistry.[8] Conversely, the intrinsic higher efficiency of the asymmetric reduction approaches (hydrogenation and enzymatic) is counterbalanced by less straightforward substrate syntheses; both processes require relatively difficult-to-access α,β-unsaturated nitrile substrates.[5,7] Besides these four sequences developed at Pfizer, the commercial value of pregabalin, combined with its simple structure, has prompted a very rich literature describing innovative synthetic routes to this γ-amino-acid and/or its precursors in the enantioenriched form.[9]

In this context, we were interested in a noninfringing and economically competitive approach to manufacture generic pregabalin. We were aware of the high competition in the area and of the efforts needed in developing a successful route.

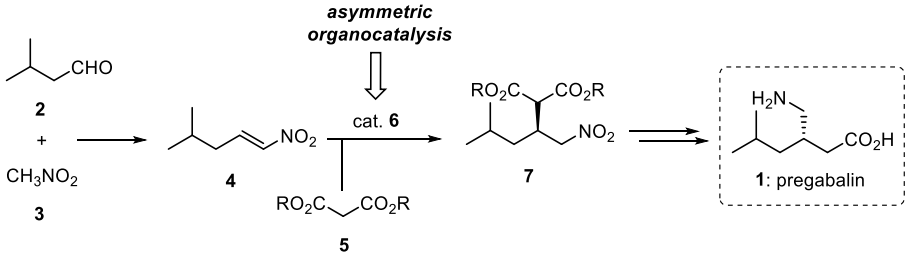
At Dr. Reddy's, when devising efficient and cost-effective processes for the manufacture of generic active pharmaceutical ingredient (API), we look at a number of parameters, e.g., intellectual property (IP) (i.e., freedom to operate), regulatory, production costs, raw material costs, site of manufacture, timelines, sustainability, and scalability. Following a first assessment, we narrowed down the selection to few routes that were either based on biocatalysis[10] or organocatalysis.[11] A common key to all these routes was the employment and development of innovative synthetic technologies. After careful evaluation, we focused on the sequence outlined in Scheme 1. Raw materials (*iso*-valeraldehyde **2**, nitromethane **3**, and malonates **5**) are bulk chemicals available at low prices, and the key intermediate **7**, if obtained in a sufficiently enantioenriched form, can be readily converted to the target enantiopure γ-amino-acid with simple downstream chemistry. Finally, the asymmetric conjugate addition of malonates **5** to nitroalkene **4**, the key step of the sequence, can be performed with an enantiopure chiral catalyst **6**. Literature precedents indicated bifunctional organocatalysts featuring a tertiary amine moiety flanked by a hydrogen bond donor as promising catalyst candidates.[12]

While having a strong literature support for all steps of the sequence, two major issues in the implementation of the

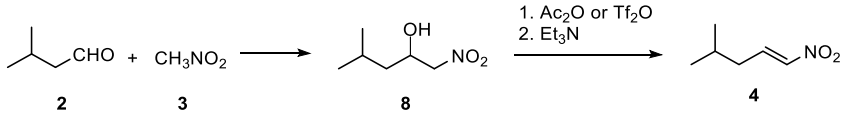
Received: October 15, 2021
Published: December 1, 2021



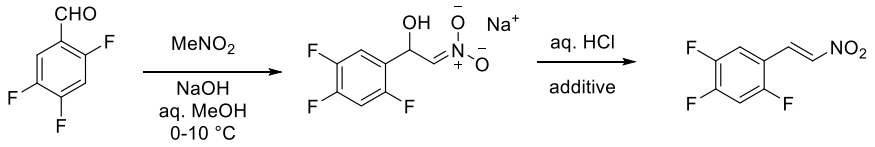
Scheme 1. Synthetic Sequence Leading to Pregabalin 1 Based on the Catalytic Asymmetric Conjugate Addition of Malonates 5 to Nitroalkene 4



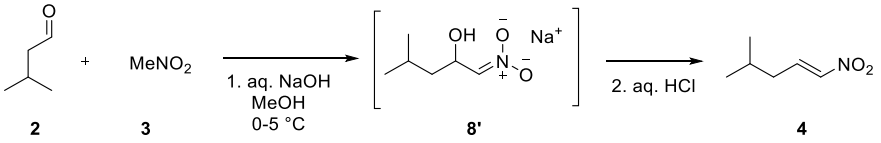
Scheme 2. Preparation of Initial Batches of Nitroalkene 4



Scheme 3. Route to Nitrostyrene Derivative Reported by Merck



Scheme 4. Route to Nitroalkene 4 Reported in the Literature



sequence sketched in Scheme 1 in a competitive manufacture process were recognized:

- an efficient preparation of nitroalkene **4** was dependent on a scalable process, along with the safety concerns related to the utilization of nitromethane **3**, its nitronate salt, and the isolation of the product;
- the economic viability of the whole process could be hampered by the non-negligible cost of bifunctional catalysts **6**. This class of catalysts has been applied to the small-medium scale preparation of pregabalin and/or its precursors;[12] however, reported results were generally discouraging from the catalyst activity point of view.

Herein, we present the scale up development of the organocatalytic step in the synthetic process to pregabalin **1** sketched in Scheme 1.[13] Key to success was the solution of the above mentioned issues: (i) flow technology[14] was exploited in a lab set-up for the continuous, safe, and clean production of nitroalkene **4**; (ii) an operationally simple method was developed to recover the catalyst at the end of the organocatalytic reaction — the recycled catalyst proved to be competent in the catalytic reaction without loss of activity.

RESULTS AND DISCUSSION

The first batches of nitroalkene **4** were prepared via dehydration of the Henry product **8** after derivatization with either acetic anhydride or triflic anhydride (Scheme 2).

This was a short-term solution to generate material to help the development of the organocatalytic step. In fact, there are several issues with this first synthesis for production; the main two, without delving into the chemistry, are the cost of reagents and the fact that acetic anhydride is a controlled substance.

While the novelty of the route came from the organocatalysis, the route was deemed inoperable without a low hazard method of forming the nitroalkene **4**. Further, since **4** is synthesized from **2** and **3** via the basic salt of nitromethane, both the starting materials and the intermediates present operational challenges.[15]

Besides the issues mentioned, the initial preparation of nitroalkene **4** via the route shown in Scheme 2 had a few drawbacks: (a) the product is a liquid and, therefore, it cannot be purified by crystallization; (b) Accelerated Rate Calorimetry showed that it is unstable at moderately high temperature, showing an exothermic onset temperature of 174.9 °C and eventually rupturing the test cell; (c) its initial purification by distillation or chromatography is not scalable; (d) a two-stage process using acetic or triflic anhydride is undesirable. Moreover, the product **4** showed to be prone to undergo oligo/polymerization over time and those oligomers proved to be potential poisons for the subsequent organocatalytic step. Preliminary studies showed that presence of aldehyde **2** and nitromethane **3** did not affect the next step to an appreciable extent; however, traces of either acid or base were detrimental to the efficiency of the organocatalyst.

This prompted us to investigate and develop an efficient and economically viable process that would be simple to perform, produce crude **4** in high purity, so that purification could be

https://doi.org/10.1021/acs.oprd.1c00394
Org. Process Res. Dev. 2021, 25, 2795−2805

avoided, and free of impurities and contaminants that would affect the following step.

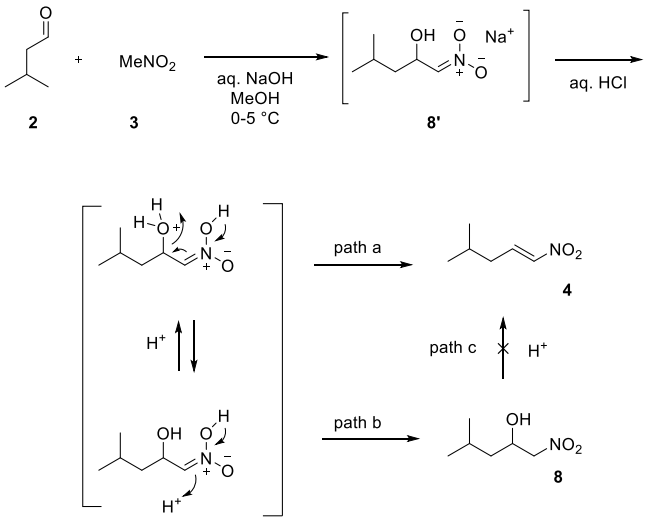
Merck reported an efficient route to a nitroolefin (Scheme 3), a key fragment in the synthesis of a DPP-4 inhibitor;[12f] dehydration of the Henry product via acidic quench furnished the desired product in high yield. The target nitrostyrene is a crystalline solid and it precipitated during formation.

Some literature reports[16] on the preparation of our target nitroolefin showed similar conditions, where the Henry intermediate **8′** would be quenched in aqueous HCl to generate **4**, albeit details on its purification were scarce (Scheme 4).

There were indications that the isolated yield was low (~28% for a similar compound as reported in ref 16b.), hence we expected to have to address the yield as well as the aforementioned issues.

When the process under the conditions in ref 16b. was run, it was not possible, in our hands, to attain full conversion from **8′** to **4** and isolate the clean product in good yields. We reasoned that, as presented in ref 12f., the intermediate **8′** could undergo two different pathways (Scheme 5); path a

Scheme 5. Formation of Nitroalkene 4 during the Aqueous Quench



would yield target product **4**, whereas C-protonation would lead to nitroalcohol **8** (path b) that would not undergo dehydration to provide **4** under acidic conditions (path c).

In contrast with ref 12f, where they optimized the preparation of aromatic nitroalkenes, we observed no beneficial effect with the use of the additives (e.g., $MgCl_2$ and $ZnCl_2$) on our aliphatic nitroalkene of interest. However, we deducted that the local concentration of acid must be high enough to promote dehydration and the intermediate **8′** must not be in a moderately acidic environment; the dehydration pathway is a very fast process and therefore, to achieve the highest possible yield, the mixing must be at least as fast as the kinetics.

The published process generally consisted of the addition of sodium hydroxide to a mixture of nitromethane and aldehyde in methanol. In our hands, this resulted in the formation of a very thick slurry that was challenging to stir − a significant problem, especially on scale, given that the next phase was to pour this slurry into an excess of concentrated acid. After some initial experiments, a more practical process using a mixture of methanol and water (to ensure solubility) was developed.

However, there were still concerns over the safety of the process; in fact, besides the Accelerated Rate Calorimetry on pure **4**, with an exothermic onset temperature of 174.9 °C, the crude sample of **4** showed a minor event at 59.5 °C (31 kJ/kg) with a significant exothermic event onset at 194.6 °C (1627 kJ/kg) (see Supporting Information). Furthermore, nitromethane **3** is classed as a flammable liquid, this raw material is regularly handled in bulk, but is referenced in as being sensitive to shock and strong heat (it explodes at 230 °C) - severe shock can cause it to detonate;[17] the Angus Chemical Company is a manufacturer of nitroalkanes and provides recommendations as to storage and handling of nitromethane.[18] Finally, nitronate salt raises an additional concern for safety: nitromethane reacting with strong bases such as sodium hydroxide or potassium hydroxide is referenced in Bretherick's.[19] The dry salt should not be isolated as it can be explosive, however it is relatively stable when solvated.

The potential hazards of this process can, therefore, be mitigated by minimizing the inventory and quickly reacting product **4** onwards into the following organocatalytic reaction.

Additionally, as detailed above, the final acidic quench to generate **4** was proving challenging to scale up, mainly because of mixing.

In order to address all of these points, the use of flow chemistry was evaluated. After initial batch reactions with in-situ infrared, it was evident that the individual process steps were all sufficiently fast that flow chemistry would be viable.

The chemistry detailed below is for a process carried out at an isovaleraldehyde **2** input flow of 0.8 g/min using high-performance liquid chromatography pumps, syringe pumps, and coils of capillary tubing submerged in a water bath. At this early stage, success has been achieved using a 5 mol % excess of nitromethane and a 15 mol % excess of NaOH. Dehydration has been forced using 4.0 equivalents of HCl versus NaOH and results in a reasonable separation of a light product-rich phase with little yield loss to the cloudy aqueous heavy phase.

The reaction to form the alkaline salt of nitromethane, if carried out at around 15 °C, needs about 10s residence time. Henry reaction of nitronate salt and **2** is substantially complete in 100 s at 20 °C. The final quench and dehydration to form nitroalkene **4** are exothermic and the concentration of the HCl needs to be set to prevent salts from crashing out of solution and causing blockage problems. More concentrated HCl is beneficial, and high intensity mixing immediately at the joining of the two streams is important for high conversion and good yield. The degree and consistency of this mixing is a key engineering focus. Following the final step, two liquid phases form, with the lighter organic phase containing most of **4**. Finally, the crude nitroalkene stream is neutralized with potassium bicarbonate followed by a water washing. In fact, crude **4** is used as is in the next step and it is crucial to prevent the presence of any residual base that would have any detrimental effect on the downstream organocatalysis chemistry.

To start with, a small-scale test reactor was assembled, and this proved remarkably successful, affording a roughly 60% yield of **4** in around 75% purity. **4** can be purified by distillation; however, as previously described, there are significant stability issues. Therefore, the preference was to use the crude material in the organocatalytic step − fortunately this proved successful and after washing with a weak base (bicarbonate), the crude olefin works in the organocatalytic reaction.

https://doi.org/10.1021/acs.oprd.1c00394
Org. Process Res. Dev. 2021, 25, 2795−2805

The arrangement of the lab set-up is outlined in Figure 1 and this is translated into reality in Figure 2.

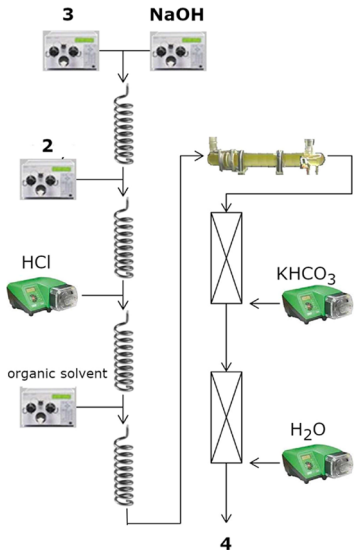


Figure 1. Schematic outline of the equipment arrangement.

The laboratory installation (Figure 2) consisted of the first four pumps in the sequence with all the reactors. For the proof of concept and production of about 300 g of crude nitroalkene, a continuous gravitational separator was used and effectively separated the two phases; as depicted in Figure 1, an organic solvent could be optionally added to aid phase separation if needed. Washing with potassium bicarbonate and then further washing with water to remove any residual salts was done batch-wise at this stage.

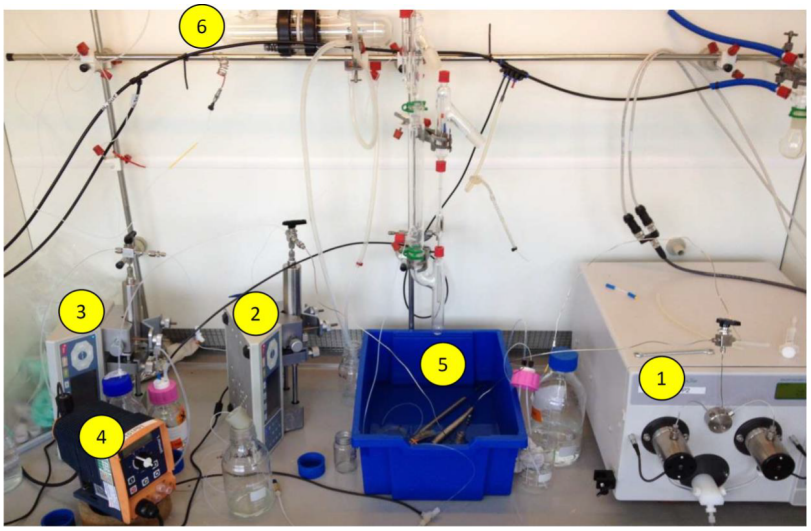
The nitronate reactor was made from 0.5 and 1.0 mm capillary tubing in SS316 and the coupling with the aldehyde **2** was carried out in a much longer length of 0.5 and 1.0 mm capillary. For the dehydration with HCl, a 1/8″ OD PTFE tube was used, packed with static mixers.

3 was fed as a 10%w/w solution, 18%w/w methanol with the remainder water. **2** is mostly insoluble in water, but completely miscible with methanol; hence, a water/methanol combination was used to give a homogenous mix of components in the reactor. Methanol was used both for reaction and cleaning the system. NaOH was fed as a 25% solution in water. HCl was used as a 18%w/w in water.

At full scale, to achieve an output of 60mt/year, with a single flow set-up, it was calculated that an input flow rate of **3** of about 8 kg/h is required. This equates to the first reactor volume of 0.3 L and the second reactor volume of 3.3 L. As a guide, it is likely that a fully scaled up reactor system would use a 25 mm diameter static mixer around 600 mm in length to carry out the first reaction stage. The second stage would be 6 m total length if the diameter was maintained. This longer 6 m length would be realized as a "serpentine" of three lengths of 2 m each.

Several use tests of crude **4** have been carried out and have been successful. The downstream organocatalytic step is believed insensitive to levels of nitroalcohol or nitromethane. However, levels of acid or base will interfere resulting in reduced selectivity and, hence, the desired product yield. Residual acid will deactivate the organocatalyst, while residual base will reduce the enantioselectivity of the step as it promotes a racemic Michael reaction. Therefore, the control of the bicarbonate feed/neutralization and the water washing is a critical factor in the implementation of the process.

Development of the Organocatalytic Step. The enantioselective Michael addition of malonates to nitroolefins has become one of the benchmark reactions for bifunctional organocatalysts,[11,12] thus there were precedents in the literature to support our approach. However, most reported reactions employing low catalyst loadings are conducted on nitrostyrene and derivatives because of their higher reactivity

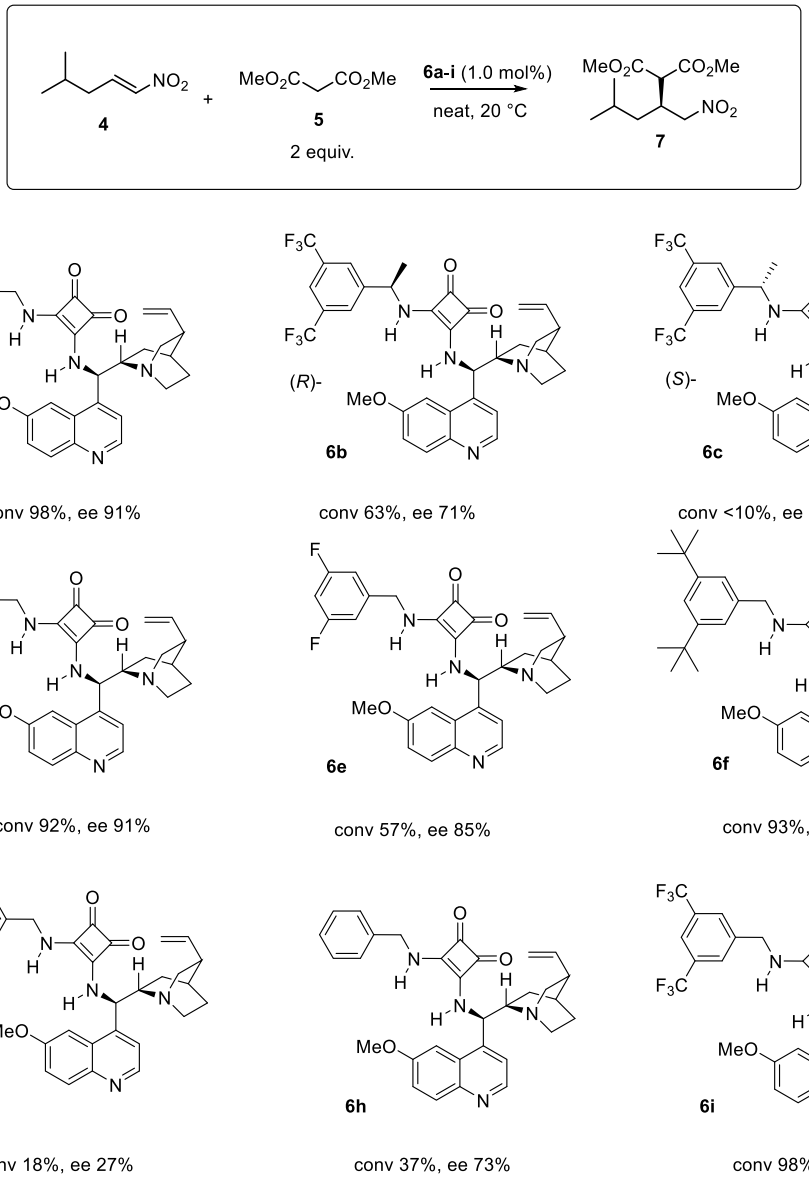


1. Nitromethane **3** pump
2. NaOH pump
3. Isovaleraldehyde **2** pump
4. HCl pump
5. 3x reactors
6. Gravitational separator

Figure 2. Three stage reaction laboratory arrangement.

https://doi.org/10.1021/acs.oprd.1c00394
Org. Process Res. Dev. 2021, 25, 2795−2805

Scheme 6. Representative Catalysts Screened for the Optimization of the Benzylamine Fragment. Conditions: dimethyl malonate 5 (2 equiv), nitroalkene 4 (0.5 mmol), catalyst 6a–6i (1 mol %), neat, 18 h



and stability. Therefore, at the outset of the project we anticipated that the main challenges with this reaction would rely on enantioselectivity, reactivity, and on achieving an economically viable catalyst loading.

Based on the literature, a preliminary screening of a broad range of organocatalysts and reaction conditions in the addition of dimethyl malonate **5** to nitroalkene **4** was undertaken; in particular, Takemoto-like catalysts, *β*-isocupreidine, and bifunctional (thio)ureas or squaramides derived from Cinchona alkaloids, were tested in a range of solvents and temperatures. Not surprisingly, *epi*-9-deoxy-9-amino-*Cinchona*-derived squaramides outperformed other structures in terms of activity and stereoselectivities, yielding the desired adduct **7** with high enantioselectivities (>80% ee). Instead, a less expected yet promising result was the relatively high turnover number (ca. 200) displayed by the quinidine catalyst **6a** (Scheme 6) already in the first experiments, performed under solvent-less[20] conditions. After identifying squaramides derived from *Cinchona* alkaloids as the catalysts of choice, the results of an additional screening showed that a methoxy group on the quinoline ring (i.e., quinidine derivative versus cinchonine one) and a benzylamine derived squaramide (as opposed to an aniline derived one) were critical for the reactivity. Based on this, additional known or novel organocatalysts were tested; the variations were done with a rationale to identify the crucial fragments in the benzylamine part of the catalyst for the reactivity and enantioselectivity (see Scheme 6 for selected results, using pure **4**). The substituents on the aromatic moiety proved important; as expected, catalyst **6a** bearing trifluoromethyl groups at the 3 and 5 positions[21] displayed the best reactivity and enantioselectivity. **6d** bearing chloro substituents at the same positions had a similar performance but was discarded because of the higher cost. All other catalysts, with different types of substituents, performed worse and the introduction of an additional chiral centre also provided worse results (**6b** and **6c**).

Reports in the literature[12f,g] suggested that the readily obtained desmethyl quinidine (**DMQD**) or its metalated

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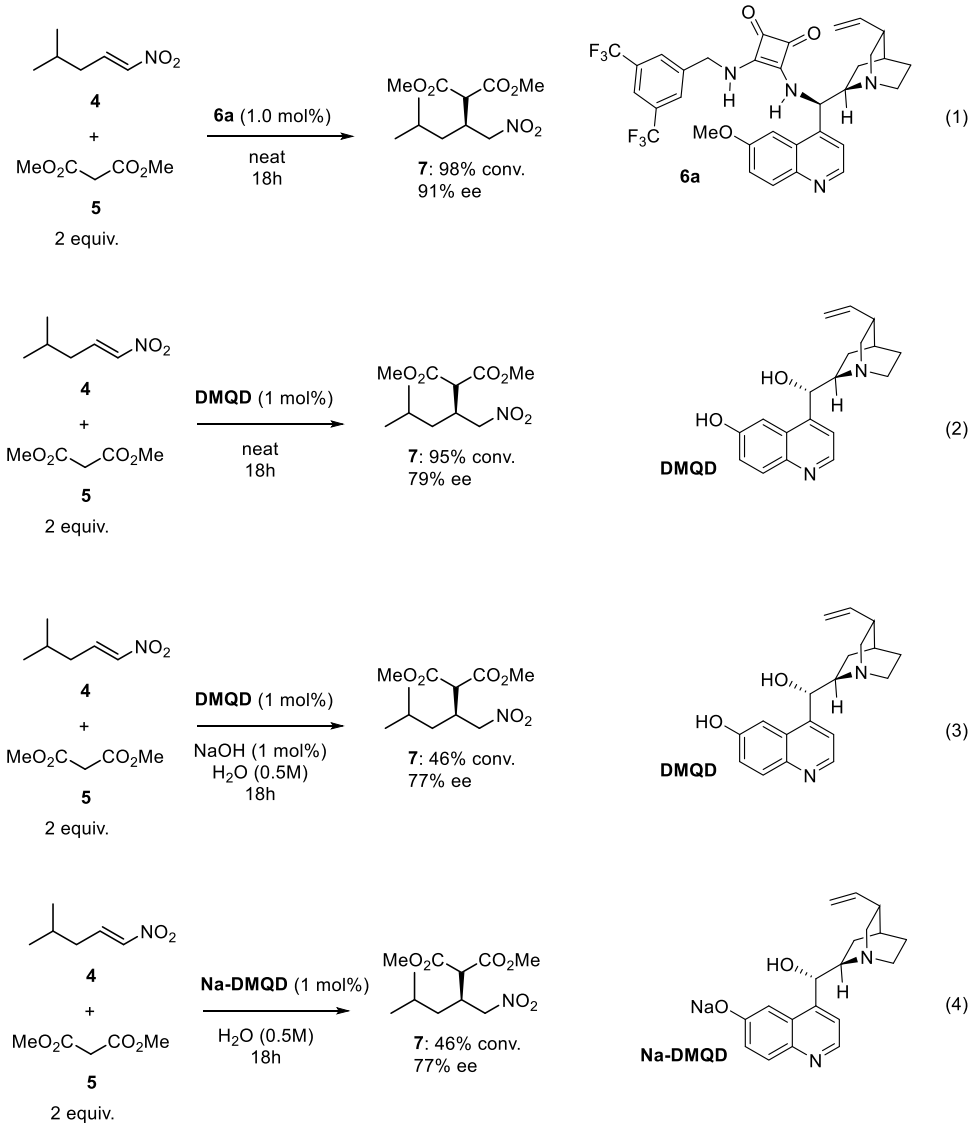
Org. Process Res. Dev. 2021, 25, 2795–2805

Scheme 7. Comparison of the Performance of DMQD, Na-DMQD, and 6a



version (**Na-DMQD**) could be very interesting candidates as catalysts; their use, in fact, would have had a high impact on the cost of the process. Unfortunately, they did not prove to be efficient catalysts neither under our conditions, nor under the aqueous conditions that had been employed for the addition of malonates to nitrostyrenes with the parent quinine derivative;[12g] they showed lower reactivity and enantioselectivity when compared to catalyst **6a** in our reaction of interest, using pure **4** (Scheme 7, compare eqs 2–4 with eq 1).[22]

Because of the modular nature of the catalyst, it is worth highlighting that there is a high number of possible variations that could be envisaged, offering the possibility of identifying a better catalyst in terms of reactivity and enantioselectivity, and of cost impact on the process. However, because of the project demands and the need to transition from an initial screening phase into the optimization and development phase, the decision was made to focus on the best catalyst found at the time as it offered sufficient activity and selectivity to be economically viable. Eventually, catalyst **6i**, derived from hydroquinidine (Scheme 6), was preferred to **6a**. In fact, it displayed a higher reactivity than **6a** (94% vs 86% conversion at 0.5 mol % loading) while maintaining the same enantioselectivity (91%) when using unpurified nitroalkene **4**. Additionally, the replacement of the vinyl fragment with the ethyl one enabled a better synthesis of the catalyst from the process chemistry point of view (*vide infra* for the preparation of the catalyst **6i**). It is worth noting that **6i** provided full conversion in 18 h at a catalyst loading as low as 0.2 mol % when purified nitroalkene **4** was used. From a process chemistry point of view, the reaction set-up is extremely simple and does not need any special equipment; the addition of catalyst followed by **5** and then **4**, and stirring at room temperature, provides the desired crude product that can be used directly in the next step, after treatment of the reaction mass to recover the catalyst.

A set of experiments showed that 1.5 equivalents of malonate **5** was the minimum needed to consistently attain full conversion in 24 h at 0.5 mol % of catalyst; however, it was chosen to proceed by using 2.0 equivalents, to be in the best design space. A screening of reaction temperatures showed negligible effect on the ee; however higher temperatures, albeit increased the initial reaction rate, had a detrimental effect on the eventual conversion. This was ascribed to the increased formation of small amounts of unidentified oligomers of

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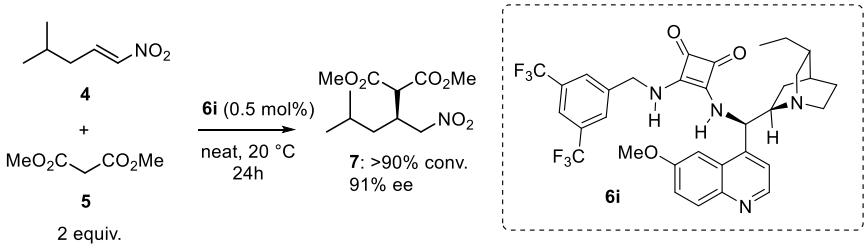
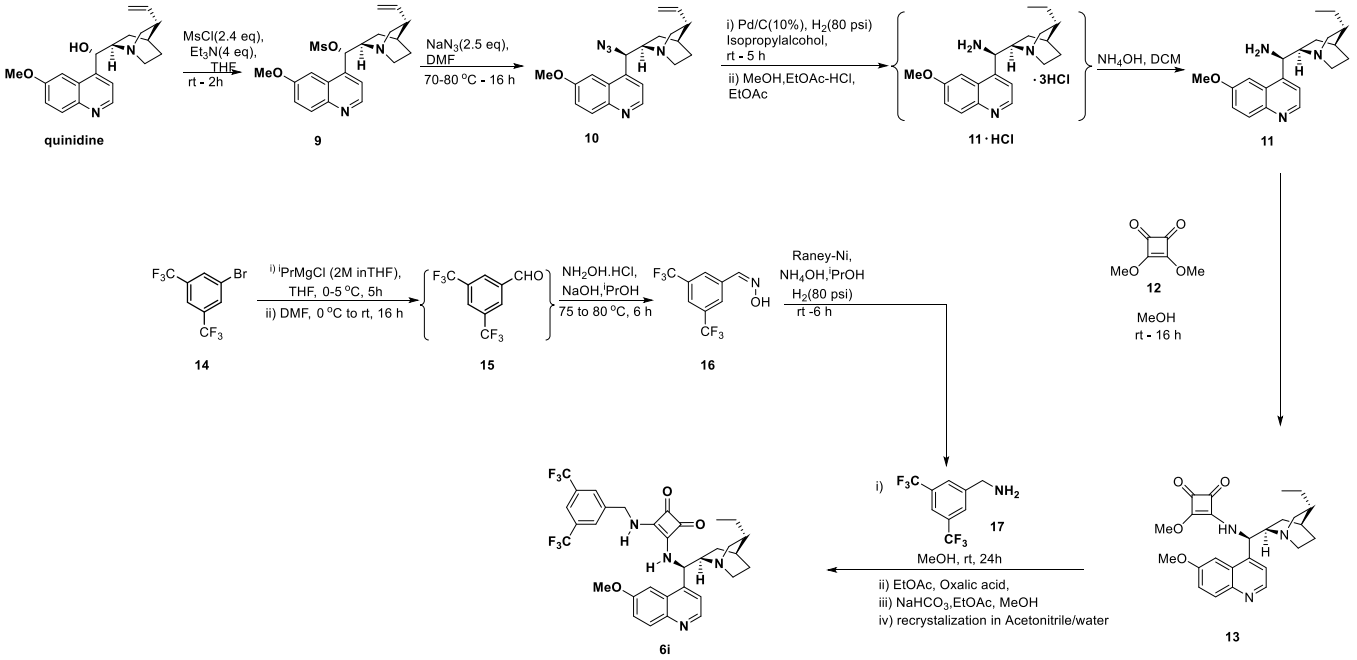
Scheme 8. Conditions Chosen for Further Development on Scale



Scheme 9. Cost-Efficient Convergent Synthetic Route for Organocatalyst 6i



nitroalkene **4** that could inhibit the activity of the catalyst. Additionally, it was noted that the catalyst **6i** is deactivated upon stirring with pure nitroalkene **4**; it is, therefore, critical to add malonate **5** to the catalyst prior to the addition of **4**. Therefore, the chosen conditions to deliver a robust process and reproducible results used 2.0 equivalents of **5**, 0.5 mol % of **6i**, with no solvent at 20 °C, for 24 h (Scheme 8).

Synthesis of Organocatalyst 6i. A cost-efficient convergent synthetic route for organocatalyst **6i** was developed to be performed on scale (Scheme 9). The route is based on the synthesis of **11** reported by Melchiorre,[23] delivering **11** in a 68% overall yield. **11** was then coupled with dimethyl squarate **12** yielding intermediate amine **13**. On the other hand, amine **17** was prepared starting from bromide **14**, in 58% overall yield.

Bromide **14** was reacted with ^{i}PrMgCl in THF and then quenched with DMF to generate intermediate aldehyde **15**, that was taken in the next step without isolation. Hydroxylamine hydrochloride was added to the crude solution of **15** to yield **16** under heating. Final reduction produced the desired amine **17**. Finally, **13** and **17** were coupled by simple stirring in methanol at room temperature over 24 h. Crude **6i** was purified by a simple procedure: salt generation with oxalic acid in ethyl acetate, isolation of the salt, and salt breaking in a mixture of methanol and ethyl acetate *via* $NaHCO_3$. The resulting crude material was then recrystallized in acetonitrile/water to furnish pure **6i** as an off-white solid in 76% yield. The overall synthesis of **6i** was reproduced in a lab fume hood to produce **6i** on a scale of 50 g, before progressing to further development.[24] The synthesis plan was based on the procedure used to prepare the library of organocatalysts; in fact, a large quantity of **13** was prepared and coupled to different amines to produce a library of **6**.

Recycle of the Organocatalyst. Despite the very low catalyst loading for an organocatalyzed reaction, the cost contribution to the overall process that the catalyst **6i** bore was still very high for a low-cost API such as pregabalin. Additionally, pregabalin is a high-volume API and, therefore, the goal was also to have as little impact as possible on the environment and, consequently, on the limited world supply of natural quinidine. The set target for a competitive process was to recycle a minimum of 50% catalyst. While a number of options was tested, three main ones were investigated in more detail given the potential higher impact and expectations.

Size Exclusion Membranes. Organic Solvent Nanofiltration (OSN) is a relatively new molecular separation technology used for separating solutes present in an organic solvent.[25] OSN is used to separate compounds on the basis of molecular size and geometry roughly in the molecular weight range 100−2000 Da. Although OSN is still a relatively young technology, it has been developed and applied to process chemistry. By enabling the molecular separations in organic solvent at ambient temperatures, in fact, it offers unique advantages over conventional separations methods and became

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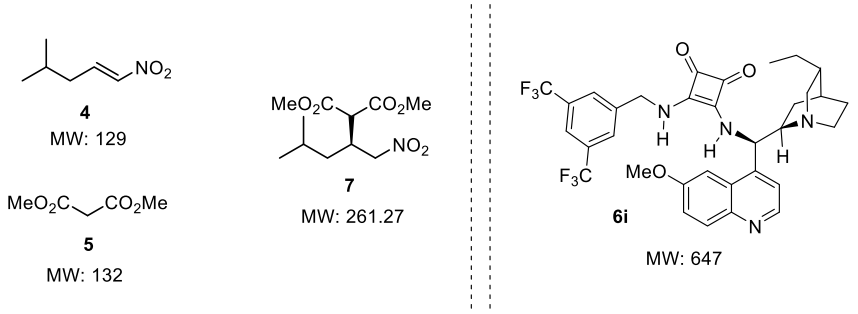

Figure 3. Molecular weight of the components of the crude mass in the organocatalytic step.

attractive to the chemical and pharma industries. Furthermore, the nanofiltration can be made continuous and it has been demonstrated on scale under GMP conditions. OSN relies on the differences in molecular size and geometry of the solutes and has already been demonstrated to recycle organocatalysts;[25b,c,26] based on the reported precedents, and given the difference in molecular weights between the starting materials and products with the catalyst (Figure 3), OSN seemed one of the best options with the highest chances of success.

Retention studies were carried out. The individual filtrations were run in a Sterlitech cell HP4750 with an Evonik Duramem 300 (T1) membrane (MWCO = 300), at an operating pressure of 40 bar and a flow rate of 200 mL/h. Starting materials **4** and **5** were not retained by the membrane, whereas product **7** and catalyst **6i** had, respectively, 37 and 90% rejection. Based on this data, modeling calculations[27] showed that a membrane cascade technology[25a] was needed for an efficient recycle and product recovery; however, the number of units and the volumes of solvent rendered the OSN process noneconomically viable for this particular application. More importantly, the crude reaction mass contained oligomers that would accumulate in the retentate and poison the catalyst recovered by filtration; this posed an additional problem from the process point of view.

Organotextile. During the development of the process, Prof. List's group reported a facile and permanent immobilization of organocatalysts on the textile nylon using ultraviolet light.[28] The prepared textile-immobilized organocatalysts displayed stability, activity, and recyclability for various organic transformations and maintained their enantioselectivity over more than 250 cycles. This immobilization technique proved very attractive for the recycle and reuse of the organocatalyst **6i** in our process; unfortunately, immobilization studies showed that the catalyst was not stable when irradiated with UV light to be anchored on the textile nylon.[29] This approach was therefore not pursued further, while more studies are carried out to address the immobilization issue.

Catch and Release Resin. Given the basic functionalities on the catalyst, the use of an acidic resin to catch and release the catalyst was a rational and low-tech solution to the problem. The resin had to not affect and bind the other reagents and had to be relatively inexpensive; on this basis, the readily available Dowex Marathon MSC proved to be a successful candidate. The process appeared also simple from an operational point of view: once the reaction was complete, the resin was added, the crude product washed off, and then the catalyst released by washing the resin with a base. Catalyst binding studies, on the batches of Dowex Marathon MSC analyzed, showed that 1 mL of resin were needed to bind 29 mg of catalyst. In batch mode, >95% of the catalyst would bind to the resin within 4 h, whereas it would be released by treatment with ammonia within 1.5 h.

As a proof of concept, before catalyst **6i** was adopted, the process was tested in the lab on a reaction starting from 0.75Kg of crude **4** with 15 g of cat **6a**, in two parallel experiments that showed reproducibility. Methanolic ammonia was used to release the catalyst from the resin; pH was first adjusted to acidic with HCl and then back to pH ∼ 8 with NaOH. The catalyst was taken up in DCM and then recrystallized from IPA/toluene as a white solid in 59% assayed recovery. The recovered catalyst could be successfully recycled and proved to work as well as pristine catalyst.

■ CONCLUSIONS

Following a thorough analysis of a range of factors relevant to Dr. Reddy's business, the most cost-effective process with freedom-to-operate selected used a novel asymmetric organocatalytic route generating pregabalin **1** without the need for resolution. At the outset of the project, based on the precedents and on our experience, it was recognized that a high-performing organocatalytic step had to be developed to achieve a successful process. The low TOFs very often displayed by organocatalysts would not render the process amenable to manufacture. Associated with this, the high loadings reported for this kind of reactions would have made it not economically viable, along with the worldwide availability of raw materials to sustain such a high-volume drug. It was also appreciated that, given the volumes of materials involved, it was still needed to recycle the catalyst even if we were to develop a high-performing organocatalytic step.

The preparation of nitroalkene **4** was performed in a continuous process as flow chemistry proved able to address the mixing issues, along with the control of reactive and unstable intermediates. The continuous process to generate crude **4**, that could be used directly in the next stage, has been demonstrated in a lab set-up carried out continuously at an output flow of **4** of 60 g/h and the process showed to be robust. Quality of product stream is maintained high by adopting a clear start-up and shutdown sequence; this means that a high quality, low risk process could be implemented on scale. Hazard is managed by using a continuous process which maintains low inventories of all intermediates, has high heat transfer capabilities, high level of process control, incorporate substantial heat sink in the process, and provides consistent high intensity mixing.

The organocatalytic step[30] was developed following a screening of organocatalysts; it proved to work efficiently with very mild conditions, i.e., catalyst loading as low as 0.2

https://doi.org/10.1021/acs.oprd.1c00394
Org. Process Res. Dev. 2021, 25, 2795−2805

mol %, in the absence of solvent and at room temperature. The synthesis of the organocatalyst **6i** was straightforward to develop by reproducing reported protocols and implementing known chemistry. Furthermore, an efficient and easy recycle of the organocatalyst was demonstrated to meet the requirements that were set at the beginning of the project; more advanced recycle strategies have been investigated and, albeit promising on paper, did not prove efficient enough at the current stage of development. The downstream chemistry to provide pregabalin **1** is based on reported procedures.

EXPERIMENTAL SECTION

Preparation of 4 by Continuous Mode Process. The feed solutions were prepared according to the following mass ratios and allowed to equilibrate to 21 °C. They were then charged to appropriate pumping devices connected to the reactor described hereafter. Feed 1: Nitromethane **3** (1.0) in a mixture of methanol (1.8) and water (7.2). Feed 2: Sodium hydroxide (1.0) in water (3.0). Feed 3: Isovaleraldehyde **2**. Feed 4: Concentrated hydrochloric acid (1.0) and water (1.0). Flow process: Stage 1: Feed 1 is pumped at 5.97 mL/min through 1.0 m of 1/16″ × 0.40″ tube followed by 2.0 m of the 1/16″× 0.40″ tube cooled to 20 °C. Feed 2 is pumped at 1.498 mL/min through 1.0 m of the 1/16″× 0.40″ tube. Feeds 1 and 2 are then mixed in a T-piece, cooled to between 5 and 20 °C are then passed through the following sequence of reactor segments, 1.0 m of the 1/16″× 0.20″ tube followed by 0.5 m of the 1/16″× 0.40″ tube and then 1.0 m of the 1/16″× 0.40″ tube, all cooled to between 5 and 20 °C. The total residence time is 5−15 s. Feed 3 is pumped at 1.000 mL/min through 2.0 m of the 1/16″× 0.40″ tube cooled to between 5 and 20 °C and into Stage 2. Stage 2: The output of Stage 1 is mixed with Feed 3 through a T-piece and cooled to between 5 and 20 °C before passing through the following sequence of reactor segments, 5.2 m of the 1/16″× 0.20″ tube followed by 7.45 m of the 1/16″× 0.40″ tube, 8.0 m of 1/16″× 0.40″ tube and then 0.3 m of the 1/16″ × 0.40″ tube, all cooled to between 5 and 20 °C. Total residence time in Stage 2 is 90−120 s. Feed 4 is pumped at 8.5 mL/min through 1.0 m of 1/16″× 0.40″ tube at between 5 and 25 °C and into Stage 3. Stage 3: The output of Stage 2 is mixed with Feed 4 through a T-piece at ambient temperature before passing through the following sequence of reactor segments, 0.3 m of 1/8″× 0.092″ tube containing 12 plastic mixing elements followed by 1.0 m of the 1/16″× 0.40″ tube. After 5−120 s residence time, the mixture exits the reactor after which the crude product [(*E*)-4-methyl-1-nitropentene **4**] can be separated as a light layer. Purification of crude (*E*)-4-methyl-1-nitropentene **4**: The crude product stream was transferred to a separator and the slightly milky acidic aqueous phase was separated from the clear yellow organic phase. The organic phase was diluted with dichloromethane (3 mL/mL organic phase) and the resulting mixture was washed with 10% w/v aqueous potassium hydrogen carbonate (0.25 mL/mL organic phase) followed by saturated aqueous brine (0.2 mL/mL organic phase). The resulting milky organic phase was concentrated on a rotary evaporator at 100 mbar and 40 °C to give a milky solution which was filtered (Whatman 541 filter paper) to give the title compound as a pale yellow liquid.

General Procedure for the Preparation of 7. 4-methyl-1-nitropentene **4** (145 g; 90% purity; 1.01 mol) was added to a mixture of dimethylmalonate **5** (265 g, 2.0 mol) and catalyst **6** (0.5 mol %) and the resulting mixture was stirred. The crude product was obtained as a ∼40 wt % solution in dimethylmalonate (390 g; 90% ee) that was used directly in the next stage.

Preparation of ***15****.* In a 3 L 4-neck round bottomed flask (RBF), 1,3-[bis-(trifluoro methyl)]-5-bromo-benzene (100.0 g, 0.341 moles) and THF (1000 mL) were charged at rt under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C. Isopropyl magnesium chloride (179.1 mL, 0.3583 moles) was added dropwise to the reaction mixture over a period of 45−60 min. (Brown color clear solution was observed). Then the resulting reaction mixture was stirred for 5−6 h at 0−5 °C. DMF (78.8 mL, 1.0239 moles) was added dropwise to the reaction mixture over a period of 30−45 min at 0−5 °C. Then the resulting reaction mixture allowed to reach rt, and stirred for 16−18 h at rt. After the completion of the reaction, the reaction mixture was quenched with 1 N HCl solution (300 mL) and extracted with ethyl acetate (2 × 150 mL). The combined organic layers was washed with water (3 × 500 mL), brine (2 × 500 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure to furnish **15** (73.5 g, 88.9%) as a yellow color crude liquid. The obtained crude material (73.5 g, 89% yield) was taken for next step without any purification.

Preparation of ***16****.* In a 3 L 4-neck RBF, **15** (71.0 g, 0.2932 moles), 5% aqueous IPA (1065 mL), hydroxyl amine hydro chloride (40.7 g, 0.5865 moles), and sodium hydroxide (23.4 g, 0.5865 moles) were charged at RT under a nitrogen atmosphere. Then the resulting reaction mixture was heated to 75−80 °C and stirred for 5−6 h. After the completion of the reaction, the reaction mixture was cooled to rt and concentrated under reduced pressure. Resulted semisolid was diluted with water (350 mL) and extracted with ethyl acetate (2 × 350 mL). The combined organic layer was washed with water (350 mL), brine solution (2 × 350 mL), and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure to furnish **16** (73 g, 96.82%) as a pale yellow semisolid. The obtained crude material was taken for the next step without any purification.

Preparation of ***17****.* **16** (71.0 g, 0.2761 moles), isopropyl alcohol (350 mL), NH_4OH solution (350 mL), and Raney nickel (21 g) were charged at RT in a 2 L hydrogenation Parr shaker. Degas the vessel with the nitrogen followed by hydrogen gas. Stir the reaction mass using a Parr shaker under hydrogen pressure (70−80 psi) at 25−35 °C for 6−8 hrs. After the completion of the reaction, reaction mixture was filtered through Celite bed and washed with ethyl acetate (700 mL) and water (350 mL). Layers were separated, organic layer washed with brine solution (2 × 350 mL) and concentrated under reduced pressure to furnish crude **17** as a brown liquid. The crude product was purified by high vacuum fractional distillation and collected pure fractions at oil bath temp. 120−145 °C and vapor temp. 45−70 °C to furnish the **17** (45 g, 67.04%) as a low melting white solid (45 g, 67% yield).

Isolation and Purification of ***6i****.* In a 3 L 4-neck RBF equipped with a condenser, crude **6i** (70 g, 0.1082 moles) and ethyl acetate (700 mL) were charged at RT under a nitrogen atmosphere. Oxalic acid dihydrate (40.9 g, 0.3250) was dissolved in ethyl acetate (350 mL) and was slowly added to the reaction mixture at rt for 30−45 min (solid precipitation was observed after 25 to 30% addition) and stirred for 30−45 min at rt. Filtered the solid product and washed with ethyl acetate (2 × 70 mL) and dried at rt for 2 h to furnish **6i** as oxalate salt (101 g), as a yellow solid. In a 5 L 4-neck RBF

https://doi.org/10.1021/acs.oprd.1c00394
Org. Process Res. Dev. 2021, 25, 2795−2805

equipped with a condenser, **6i** as oxalate salt (101 g) and 10% MeOH in ethyl acetate (700 mL) were charged at rt. Then, 10% $NaHCO_3$ (700 mL) solution was added slowly at rt (pH: ~7.5 to 8.0). The resulting reaction was stirred at rt for 30−45 min (a pale brown clear solution was obtained). Separated the organic layer and washed with brine solution (2 × 350 mL). The resulting organic layer was concentrated under reduced pressure. The resulting crude material was diluted with acetonitrile (350 mL). Then the resulting reaction mixture was heated to 50−55 °C (clear solution was observed). Water (700 mL) was added dropwise to the mixture over a period of 1−2 h at 50−55 °C (Pale brown solid formation was observed after ~50% addition of water). The resulting reaction mixture was stirred at 50−55 °C for 30−45 min. The resulting reaction mixture was cooled to rt, and stirred at rt for 45−60 min. The resulting reaction mixture was cooled to 5−10 °C, and stirred for 30−45 min. Filter the solid product and washed with mixture of acetonitrile and water (1:1) (2 × 50 mL) and dry at rt for 24 h to furnish **6i** (51 g, yield: 75.5%) as an off-white solid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00394.

NMR spectra of products **4** and **7**, intermediates, and catalyst **6a**, and advanced reaction calorimetry study (PDF)

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The manuscript was written through contributions of all authors. All authors have participated in the development of the project and have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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