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Continuous Flow Synthesis of β-Aminoketones as Masked Vinyl Ketone Equivalents

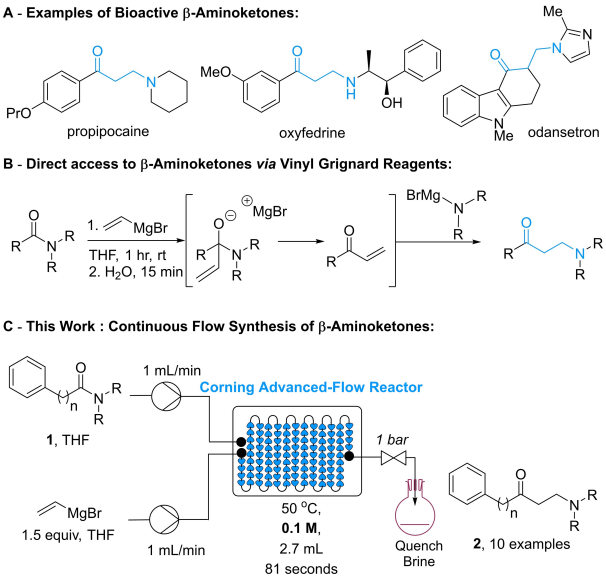
Ruairi Bannon,[a] Megan Smyth,[b] Thomas S. Moody,[b, c] Scott Wharry,[b] Philippe M. C. Roth,[d] Guillaume Gauron,[d] and Marcus Baumann*[a]

Herein we report the efficient synthesis of β-aminoketones *via* addition of a vinyl Grignard reagent into amides followed by trapping of the vinyl ketone intermediate with the magnesium-amide by-product. The reaction was successfully translated from a batch process into continuous flow mode to increase its efficiency, safety and scalability. Different set-ups were evaluated to minimize/overcome clogging issues arising from magnesium salt precipitates. Ultimately, the resulting β-aminoketones were obtained in high yields and productivities with residence times of less than 90 seconds at elevated temperatures of 50 °C. Importantly, the β-aminoketone products are valuable building blocks that can be unmasked to reactive vinyl ketones *via* a Cope elimination process.

Introduction

β-Aminoketones are versatile synthetic entities that can be found in multiple biologically active compounds including drugs and natural products (Scheme 1A).[1] The most classical entry into this motif uses the Mannich reaction[2] between enolizable compounds and imines, however, due to the prevalence of β-aminoketones a variety of alternative methods have been reported in recent years. These include variants catalyzed by ammonium chloride,[3] a metal-free addition of amines to ynones in the presence of pinacolborane,[4] or the Wacker oxidation of protected allylic amines.[5] Moreover, a serendipitous discovery reported by Gomtsyan highlights the possibility to generate β-aminoketones *via* the addition of vinyl Grignard species into amides in which the magnesium amide by-product was observed to engage in a 1,4-addition reaction to the vinyl ketone intermediate upon work-up (Scheme 1B).[6,7]

This process is noteworthy as it formally inserts the ethyl fragment into the amide bond providing access to the β-aminoketone motif with excellent atom economy. In addition, this approach holds interest as the vinyl ketone can potentially be regenerated *via* a Cope elimination which represents an attractive unmasking strategy liberating highly reactive vinyl ketone species *in situ* (*vide infra*) which would enable further applications in industrial settings. One limitation of the method relates to the scalable use of Grignard reagents in batch reaction vessels due to limitations in terms of heat and mass transfer that may lead to side reactions (i.e., double addition of vinyl Grignard species) as well as safety concerns due to the exothermicity of this metalation process. Continuous flow[8] applications have recently showcased how such problems can be overcome thus offering safe and scalable means to execute Grignard reactions at a larger scale. The improved heat and mass transfer resulting from miniaturized flow set-ups have enabled several applications of Grignard species exploiting tubular reactors, microplate reactors as well as continuous stirred tank reactors.[9] Plate reactors are particularly attractive as the high surface area to volume ratio enables the effective dissipation of heat while advanced mixing elements provide for



Scheme 1. Relevance and synthetic access to β-aminoketones.

[a] *R. Bannon, Dr. M. Baumann*
School of Chemistry, University College Dublin, Belfield D04 N2E2, Ireland
E-mail: marcus.baumann@ucd.ie
[b] *Dr. M. Smyth, Dr. T. S. Moody, Dr. S. Wharry*
Technology Department, Almac Sciences, Craigavon BT63 5QD, U.K.
Homepage: https://baumannresearchgroup.com/
[c] *Dr. T. S. Moody*
Arran Chemical Company, Roscommon N37 DN24, Ireland
[d] *Dr. P. M. C. Roth, Dr. G. Gauron*
Corning Reactor Technologies, Corning SAS, 77215 Avon Cedex, France

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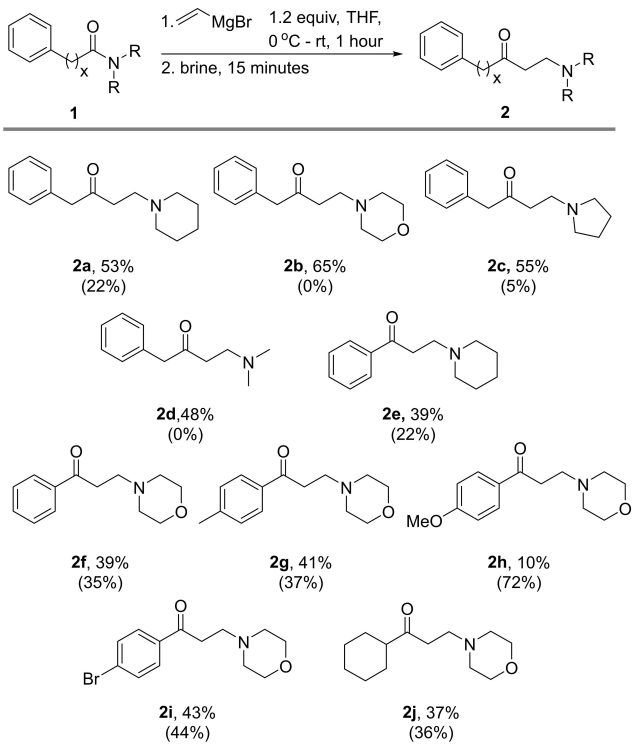
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turbulent mixing at high flow rates that favors short residence times and therefore high productivities.[10–12] Cognizant of these advantages we wished to develop a continuous flow process for the effective generation of β-aminoketones utilizing the direct synthesis from amides and vinyl Grignard species which would provide access to masked vinyl ketone equivalents that were required as key building blocks in one of our synthesis campaigns (Scheme 1C).

Results and Discussion

Initial Batch Approach

Our study commenced by subjecting a series of phenylacetamides and benzamides (**1 a**–**j**) to the protocol reported by Gomtsyan[6] using batch conditions. As shown in Scheme 2 this afforded a series of β-aminoketone products in yields averaging 50 %. The Grignard solution (1.2 equiv. in THF, 0.1 M, 1.5 mmol scale) was thereby added dropwise to a cooled solution of the amide substrate followed by a quench with brine after 1 hour reaction time. Phenylacetamides afforded the desired products **2 a**–**d** in acceptable yields which may be explained by the presence of the enolizable benzylic position. Benzamides gave slightly lower yields of the desired products **2 e**–**i** especially in the case of electron-donating aryl substituents (i. e., **2 h**) with up to 70 % substrate recovery along with side products containing vinyl groups. Similarly, saturated systems such as **2 j** could be generated in modest yields along with small amounts of double addition products. A small selection of amines including dimethylamine, piperidine, morpholine and pyrrolidine were thereby found to render the β-aminoketone products in comparable yields. A higher amount of starting material was recovered when performing the reactions on benzamides **1 e–i** (35–72 %) compared to phenylacetamides **1 a–d** (0–22 %) which may indicate the reduced reactivity of the former towards nucleophilic attack by the Grignard species. In addition to observing modest yields due to competing double addition and enolization pathways, the formation of precipitates was noticed in most cases which would warrant precautions when translating this batch process into a more scalable flow approach.



Scheme 2. Summary of batch results. Starting material recovered in parentheses.

Continuous Flow Strategy in Tubular Reactor

Initial experiments in flow mode used substrate **1 b** in combination with a standard set-up whereby two streams (stream A: substrate **1 b** in THF, 0.2–0.4 M; stream B: vinyl-Grignard in THF, 0.22–0.48 M) are mixed in a T-piece prior to entering a tubular flow reactor as depicted schematically in Table 1.

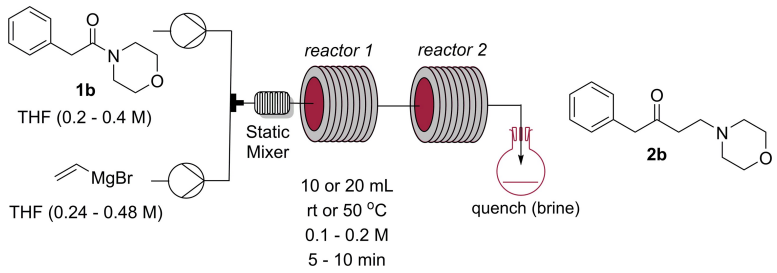
Using narrow polymer tubing (PTFE, 1/16-inch outer diameter) quickly showed that blockages due to precipitates were inevitable (entry 1, one 10 mL reactor, 1.1 equiv. Grignard reagent). When using wider-diameter tubing (PTFE, 1/8-inch outer diameter) in combination with a static mixer to prevent the settling of precipitates,[13] clogging-related issues could be prevented, however, formation of gas pockets was observed in the tubing likely due to solvent boiling resulting from the exothermic process (entry 2). To prevent the formation of gas pockets which would result in non-uniform residence times within the tubular reactor, the concentration was reduced maintaining a temperature of 50 °C in both reactors which gave a slight improvement in yield (entry 3). Next, two reactor zones held at different temperatures were introduced while the residence time was slightly increased (entry 4). The first zone (rt, ca. 22 °C) allowed for dissipation of the reaction heat, whereas the second zone (50 °C) allowed for complete consumption of the reactants within a short time without issues arising from solvent boiling or precipitate formation. This approach allowed operation of the set-up for extended periods of time, affording comparable yields of the desired product.

Next, we performed a steady state study to evaluate the effect of different flow rates on the conversion of substrate over longer periods of time to investigate process robustness. This study was aimed at identifying the time it takes for the reaction to reach the maximum yield under those specific conditions and whether this performance is maintained over the course of the reaction.

As summarized in Figure 1, this study exploited the conversion of substrate **1 a** into β-aminoketone **2 a**. Three different flow rates (i. e., 8 mL/min, 4 mL/min and 3 mL/min) were trialed which translated into residence times of 2.5 min, 5.0 min and 6.66 min respectively (panels A–C). Using the shortest residence time of 2.5 min showed that β-aminoketone product **2 a** is formed in ^{1}H-NMR yields up to 58 %. The large variation can be explained both by the delay in reaching steady

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Table 1. Optimization study using tubular flow reactor set-up.



Entry[a]	tRes	Concentration	Temperature	^{1}H-NMR yield of **2b**
1	10 min	0.2 M	rt	0% (blockage)
2	5 min	0.2 M	50 °C	56%
3	5 min	0.1 M	50 °C	61%
4	6.66 min	0.1 M	Reactor 1: rt Reactor 2: 50 °C	61%

[a] Reactions performed on a 2 mmol scale.

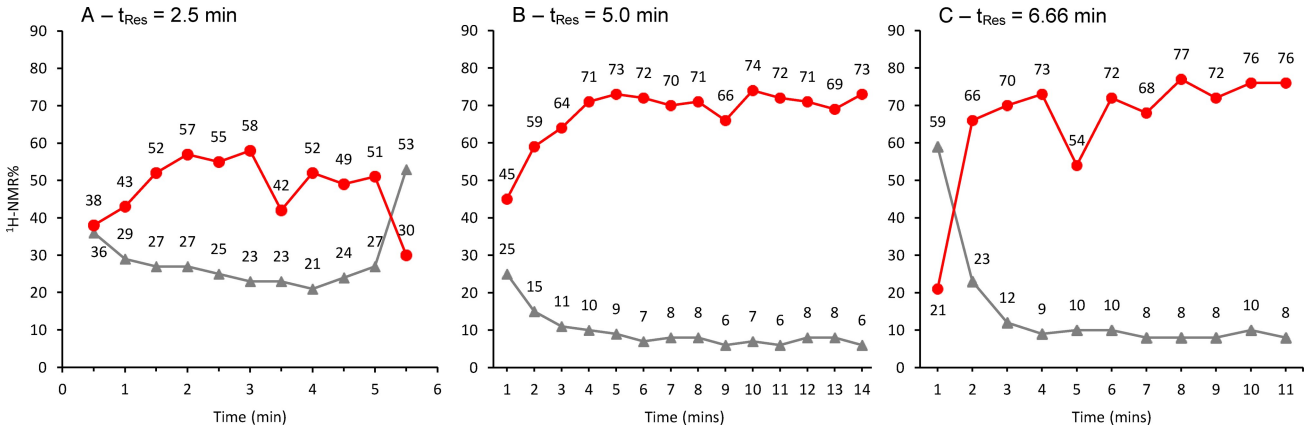


Figure 1. Steady state study using two reactor zones (T_1 = rt, T_2 = 50 °C). ● Formation of β-aminoketone **2a**. ▲ starting material **1a** remaining. Each data point was determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

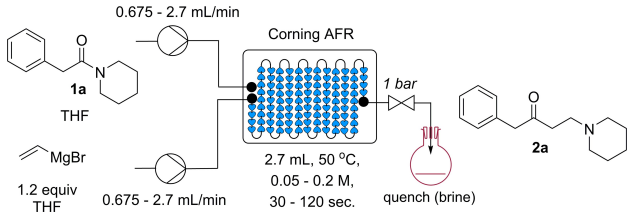
state (0–2 min) and the effect of switching syringes when using syringe pumps as part of this set-up. Using a longer residence time of 5.0 min or 6.6 min shows that higher conversions exceeding 70% can be achieved while steady state is reached within 3–4 minutes. This study therefore indicates that flow processing increases the product yield by about 20% compared to the batch reaction. Importantly, significant rate acceleration is observed in flow, indicating the effect of improved mixing combined with the ability to safely perform this reaction at elevated temperatures. Using a simple flow set-up comprising of two tubular reactors held at different temperatures (i.e., rt and 50 °C) is thereby advantageous in managing the reaction heat and controlling precipitate formation which are key features in realizing a robust flow process that can deliver larger quantities of β-aminoketone products.

Continuous Flow Strategy in Corning® Advanced-Flow Reactor

Having established the advantages of performing this transformation in flow mode, we wished to exploit a plate-type reactor in combination with syringe pumps utilising a Corning® lab-scale reactor. The use of a plate-type reactor would thereby increase the heat transfer through the larger surface area, whereas the heart-shaped mixing elements within this plate increase mixing which facilitate reduced residence times.[10] The small volume of the Corning® Advanced-Flow reactor (AFR) of 2.7 mL enables the use of higher flow rates (typically above 2 mL/min) to achieve effective micro-mixing and consequently higher productivity because of shortened residence times. As shown in Table 2, substrate **1a** was used for the optimization study which was initiated at a concentration of 0.05 M to avoid precipitation issues. With a reactor temperature of 50 °C and a flow rate of 2.7 mL/min (t_{Res} 60 seconds) a low yield of only 21% was observed for product **2a** with significant amounts of substrate remaining (entry 1). Increasing the concentration to

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Table 2. Optimization study using micro-plate reactor.



Entry	Flow rate	t_{Res}	^{1}H-NMR yield[d] **1a**:**2a**	Selectivity for **2a**
1[a]	2.7 mL/min	60 s	65% : 21%	60%
2[b]	2.7 mL/min	60 s	27% : 49%	67%
3[b]	5.4 mL/min	30 s	38% : 43%	69%
4[b]	3.8 mL/min	45 s	33% : 51%	76%
5[b]	2.0 mL/min	81 s	18% : 58%	71%
6[b]	1.35 mL/min	120 s	Reactor clogging	
Microreactor plate with hydrophobic coating used for entries **7**–**10**				
7[b]	1.35 mL/min	120 s	42% : 46%	79%
8[b,e]	3.8 mL/min	45 s	31% : 55%	80%
9[b,e]	2.0 mL/min	81 s	16% : 64%	76%
10[c,e]	2.0 mL/min	81 s	0% : 70%[f]	70%

[a] 0.05 M. [b] 0.1 M. [c] 0.2 M. [d] Using 1,3,5-trimethoxybenzene as an internal standard. [e] Using 1.5 equiv. of vinyl Grignard reagent. [f] Isolated yield.

0.1 M did not lead to reactor clogging and afforded a higher product yield of 49% along with 27% of substrate (entry 2). The selectivity for formation of product **2a** (expressed as its yield based on recovered substrate) increased to 67%. Doubling the flow rate to 5.4 mL/min (t_{Res} 30 seconds) afforded a yield of 43% confirming that faster flow rates lead to better mixing despite a small reduction on the yield (entry 3). Conversely, residence times of 45 seconds and 81 seconds generated the desired products in yields of 51% and 58%, respectively (entries 4 and 5). However, increasing the residence time to 120 seconds led to precipitate formation which caused reactor clogging (entry 6).

At this stage we turned to using a new Corning® AFR possessing a hydrophobic coating which should reduce adherence of particles on the internal surface and therefore delay clogging issues. Indeed, this allowed the use of longer residence times (120 seconds entry 7) without clogging issues giving a yield of 46%. Combining a slight increase of the Grignard reagent (1.5 equiv. instead of 1.2 equiv.) with shorter residence times (45 seconds, entry 8) as well as medium residence times (81 seconds, entry 9) gave marginal improvements when compared to the non-coated reactor plate (entries 4 and 5). Importantly, the coated surface allowed doubling the concentration to 0.2 M without clogging issues which gave the best result when using a residence time of 81 seconds (isolated yield: 70%, entry 10).

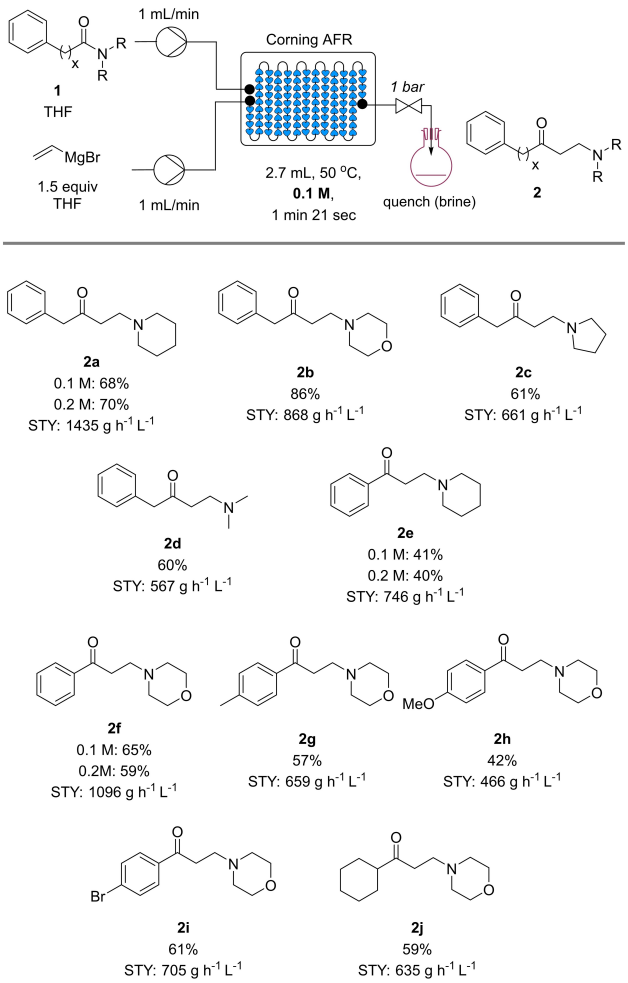
Comparing the use of the microplate reactor to the initial tubular reactor set-up thus shows advantages due to the better mixing achieved at high flow rates in combination with the ability to increase the concentration without reactor clogging when using the internally coated plate.

Subsequently, this set-up was applied to produce a series of β-aminoketone products as shown in Scheme 3. Using the standard conditions (81 seconds, 50 °C, 0.1 M) generated the desired products in good yields of up to 86%. The resulting scalability is noteworthy as indicated by the calculated space-time yields (STY) typically exceeding 500 $g\,h^{-1}L^{-1}$.[14] A significant improvement was achieved when comparing the STY of compound **2e** from the original batch report (yield: 54% in 6 hours)[6] which was calculated as 7.47 $g\,h^{-1}L^{-1}$ whereas the flow set-up gives a STY of 746 $g\,h^{-1}L^{-1}$ (yield: 41% in 81 seconds) marking a 100-fold increase in productivity. Moreover, the application of the hydrophobic coating has given promising results allowing higher concentrations to be used for several substrates without clogging issues (i.e., 0.2 M for **2a**, **2e**, **2f**), however, for products such as **2b** this was not possible due to lower solubility leading to eventual reactor clogging.

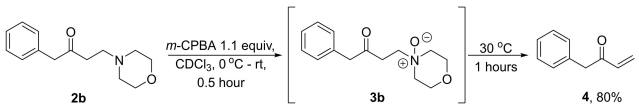
To demonstrate the value of these β-aminoketone products we explored the conversion of product **2b** into vinyl ketone **4** (Scheme 4). This can be achieved *via* *N*-oxide formation and *in situ* Cope elimination[15–17] thus presenting an attractive strategy to generate these highly reactive vinyl ketones *in situ* by unmasking of the initial β-aminoketone products.

To affect the desired Cope elimination, substrate **2b** was dissolved in $CDCl_3$ to allow for reaction monitoring by ^{1}H-NMR. *m*-CPBA (1.1 equiv.) was used as the oxidant and the reaction mixture was initially stirred for 30 minutes with cooling to allow for the *in situ* formation of the *N*-oxide species **3b**. Under these conditions the Cope elimination product forms readily at room temperature which may be due to the acidic nature of the α-proton favoring the characteristic syn-periplanar elimination

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Scheme 3. Product scope using microplate flow reactor.



Scheme 4. Unmasking of β-aminoketone **2 b** *via* Cope elimination strategy.

process.[18] Warming the reaction mixture to 30 °C ensures vinyl ketone **4** in a yield of 80 % after 1 hour.

The facile formation of α, β-unsaturated ketones *via* unmasking of the initial β-aminoketone is an attractive feature as these entities are highly reactive and toxic compounds which can interact with enzymes and DNA as good Michael acceptors.[19,20] Being able to access vinyl ketones *via* a more stable and less toxic amine allows for safer handling and prevents the need to store large quantities which over time may degrade or polymerize. Within the literature, compound **4** can undergo a series of chemical reactions including conjugate addition,[21] cross metathesis,[22] and enzymatic transformation to access chiral alcohols.[23]

Conclusions

In summary, we report the successful development of a continuous flow approach exploiting the addition of vinyl Grignard reagent to a variety of amides affording β-aminoketone products. The initial tubular flow reactor set-up demonstrated the advantages of improved heat transfer and micromixing in flow mode with good results being obtained when two temperature zones were employed (i.e., rt and 50 °C) under steady state conditions. Exploiting a Corning® Advanced-Flow reactor gave further improvements due to more efficient mixing leading to shorter residence times and higher yields. One challenge for such organometallic reactions remains the likelihood of reactor clogging due to precipitate formation, however, the use of a prototype plate reactor with an internal hydrophobic coating indicated that increased concentrations can be accommodated in several cases without clogging issues observed. Overall, the high space-time yields resulting from the microplate flow reactor set-up show that this approach offers clear advantages for industrial exploitations due to improved scalability and reaction efficiency. The resulting β-aminoketone products can be unmasked *via* a mild Cope elimination process by *in situ* generation of the *N*-oxide affording highly reactive vinyl ketones as versatile building blocks.

Supporting Information Summary

The authors have cited additional references within the Supporting Information (Ref. [24]).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: β-aminoketone · Continuous flow synthesis · Grignard reaction · Reactor fouling · Vinyl ketone

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[1] M. M. Hammouda, K. M. Elattar, *RSC Adv.* **2022**, *12*, 24681–24712.
[2] M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.
[3] S. R. Waghmare, M. D. Deokate, P. D. Lokhande, *Org. Prep. Proced. Int.* **2022**, *54*, 65–78.
[4] R. Fu, Y. Liu, T. Wu, X. Zhang, Y. Zhu, J. Luo, Z. Zhang, Y. Jiang, *Chem. Commun.* **2022**, *58*, 3525–3528.
[5] M. Garbacz, S. Stecko, *Org. Biomol. Chem.* **2022**, *21*, 115–126.
[6] A. Gomtsyan, *Org. Lett.* **2000**, *2*, 11–13.
[7] A. Gomtsyan, R. J. Koenig, C. H. Lee, *J. Org. Chem.* **2001**, *66*, 3613–3616.
[8] a) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* **2020**, *24*, 1802–1813; b) A. Bonner, P. Naik, R. Crawford, M. Baumann, *Curr. Opin. Green Sustain. Chem.* **2024**, *47*, 100907; c) C. A. Hone, C. O. Kappe, *Chem.– Methods* **2021**, *1*, 454–467; d) L. Capaldo, Z. Wen, T. Noël, *Chem. Sci.* **2023**, *14*, 4230–4247; e) M. Guidi, P. H. Seeberger, K. Gilmore, *Chem. Soc. Rev.* **2020**, *49*, 8910–8932; f) L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062–4098; g) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.
[9] a) E. Riva, S. Gagliardi, M. Martinelli, D. Passarella, D. Vigo, A. Rencurosi, *Tetrahedron.* **2010**, *66*, 3242–3247; b) J. C. Pastre, P. R. D. Murray, D. L. Browne, G. A. Brancaglion, R. S. Galaverna, R. A. Pilli, S. V. Ley, *ACS Omega* **2020**, *5*, 18472–18483; c) M. J. Pedersen, T. L. Holm, J. P. Rahbek, T. Skovby, M. J. Mealy, K. Dam-Johansen, S. Kiil, *Org. Process Res. Dev.* **2013**, *17*, 1142–1148; d) M. E. Kopach, K. P. Cole, P. M. Pollock, M. D. Johnson, T. M. Braden, L. P. Webster, J. M. Groh, A. D. McFarland, J. P. Schafer, J. J. Adler, M. Rosemeyer, *Org. Process Res. Dev.* **2016**, *20*, 1581–1592; e) D. Kaldre, S. Stocker, D. Linder, H. Reymond, A. Schuster, J. Lamerz, S. Hildbrand, K. Püntener, M. Berry, J. Sedelmeier, *Org. Process Res. Dev.* **2024**, *28*, 1576–1586.
[10] M. Yang, L. Yang, J. Zheng, N. Hondow, R. A. Bourne, T. Bailey, G. Irons, E. Sutherland, D. Lavric, K.-J. Wu, *Chem. Eng. J.* **2021**, *412*, 128565. Note: The internal surface area of the tubular reactor used in our study was calculated as 3,144 mm^2 which is significantly smaller than that of the Corning plate reactor use (13,000 mm^2).
[11] K.-J. Wu, V. Nappo, S. Kuhn, *Ind. Eng. Chem. Res.* **2015**, *54*, 7554–7564.
[12] P. Watts, C. Wiles, *J. Chem. Res.* **2012**, *36*, 181–193.
[13] A. Ghanem, T. Lemenand, D. Della Valle, H. Peerhossaini, *Chem. Eng. Res. Des.* **2014**, *92*, 205–228.
[14] P. De Santis, L.-E. Meyer, S. Kara, *React. Chem. Eng.* **2020**, *5*, 2155–2184.
[15] A. C. Cope, T. T. Foster, P. H. Towle, *J. Am. Chem. Soc.* **1949**, *71*, 3929–3934.
[16] R. D. Bach, D. Andrzejewski, L. R. Dusold, *J. Org. Chem.* **1973**, *38*, 1742–1743.
[17] a) E. Ciganek, J. M. Read Jr, J. C. Calabrese, *J. Org. Chem.* **1995**, *60*, 5795–5802; b) E. Ciganek, *J. Org. Chem.* **1995**, *60*, 5803–5807.
[18] R. D. Bach, C. Gonzalez, J. L. Andres, H. B. Schlegel, *J. Org. Chem.* **1995**, *60*, 4653–4656.
[19] D. Mulliner, D. Wondrousch, G. Schüürmann, *Org. Biomol. Chem.* **2011**, *9*, 8400.
[20] R. Benigni, C. Bossa, *Chem. Rev.* **2011**, *111*, 2507–2536.
[21] a) H. Oh, J. Park, S. H. Han, N. K. Mishra, S. H. Lee, Y. Oh, M. Jeon, G.-J. Seong, K. Y. Chung, I. S. Kim, *Tetrahedron* **2017**, *73*, 4739–4749; b) J. S. Yadav, S. Abraham, B. V. S. Reddy, G. Sabitha, *Synth* **2001**, *2001*, 2165–2169; c) N. Alotaibi, R. Babaahmadi, M. Pramanik, S. Das, B. M. Kariuki, E. Richards, T. Wirth, R. L. Melen, *Eur. J. Org. Chem.* **2024**, *27*, e202400022.
[22] a) Y. Deng, C.-P. H. Yang, A. B. Smith Iii, *J. Am. Chem. Soc.* **2021**, *143*, 1740–1744; b) S.-G. Kim, T.-H. Park, B. J. Kim, *Tetrahedron Lett.* **2006**, *47*, 6369–6372.
[23] Y.-C. Liu, Y. Liu, Z.-L. Wu, *Org. Biomol. Chem.* **2015**, *13*, 2146–2152.
[24] N. Alotaibi, R. Babaahmadi, M. Pramanik, S. Das, B. M. Kariuki, E. Richards, T. Wirth, R. L. Melen, *Eur. J. Org. Chem.* **2024**, *27*, e202400022.

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