J. Chem. Sci. (2020)132:111
https://doi.org/10.1007/s12039-020-01822-0

REGULAR ARTICLE

Development of a continuous process: a perspective for Mitsunobu reaction

GIRISH BASAVARAJU[a,b,*] and RAVISHANKAR RAJANNA[b]
[a]Process Engineering, Syngene International Ltd., Bengaluru, India
[b]Department of Chemical Engineering, Dayananda Sagar College of Engineering, Bengaluru, India
E-mail: girish.basavaraju@gmail.com; ravishankar70@gmail.com

MS received 18 May 2020; revised 6 July 2020; accepted 6 July 2020

Abstract. The developments around flow processing technology have paved the way for new avenues and perspectives to consider in the field of organic chemistry and engineering. In this study, customized flow equipment was utilized to develop and optimize the Mitsunobu reaction. The flow reactor was a prototype of a simple tubular reactor based on the plug flow reactor concept. The experimentation methodology was designed through the statistical design of experiments approach to minimize the number of experiments. The molar ratios of cyclohexanol (**1**) and o-cresol (**2**) and interaction effects of triphenylphosphine, diisopropyl azodicarboxylate were studied in detail. The reaction profile of flow experiments agreed with the batch conditions adding noteworthy improvements to the overall reaction time, selectivity, and yield towards the desired product 1-(cyclohexyloxy)-2-methylbenzene (**3**). The Mitsunobu reaction in batch condition would take on an average of 3 to 5 h, which was effectively accomplished in 30 to 45 mins in this flow reactor. The generated mathematical model is in good agreement with the reaction conditions. We believe that the process could be executed continuously without a break, readily scaled to kilogram quantities in a short time without further development.

Keywords. Continuous flow chemistry; Mitsunobu reaction; tubular reactor; design of experiments (DoE).

1. Introduction

The Mitsunobu reaction is widely practised in the synthetic chemistry area to achieve alkyl aryl ethers transformation.[1–3] The reaction is quite successful in coupling a broad selection of alcohol and phenol substrates.[4] These reactions, in general, are slow and offer specific advantages such as stereospecificity, mild reaction conditions, and scope of the chemistry.[5] The chemical bonds such as C-O, C-N, C-S, C-C could be built with diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD) under redox conditions.[2,4] The azodicarboxylates, in general, are explosive compounds that undergo decomposition in the presence of elevated temperature,[6] poses a safety risk in case of large-scale operations, especially under batch conditions. On the other side, azodicarboxylates simplify easy workup and purification during downstream processing.[2,3] The Mitsunobu reaction is highly acquainted with batch processing methods for several decades. In the last few years, there have been significant development and technological advancements being investigated to reap the benefits to improve safety, minimize cost, improve selectivity, and overall simplifying the efforts. To mention a few advancements, continuous or flow technologies are emerging as a front runner in the early and late phase drug development.[7–14] Today most of the commodity chemicals are being manufactured through continuous processing technologies and proved profitable, however very recently small-scale off-the-shelf equipment is available for research and development.[15,16] The processes developed through the flow approach in the lab could be readily transferred to the production facilities with minimal modifications.[17–23]

Design of experiments (DoE) is another area of expertise to develop the experimental plan, to advance a rational and relationship of factors and their outputs

*For correspondence

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-020-01822-0) contains supplementary material, which is available to authorized users.

Published online: 19 August 2020

or responses to conclude a meaningful outcome.[24–28] The outcome would have a cause and effect relationships across known and unknown variables, response prediction with statistical significance. So, the statistical methodologies are increasingly deployed across pharmaceutical research and development and process data analytics in the manufacturing environment.[29,30]

In the present study, a customized flow reactor was developed to investigate a simple Mitsunobu reaction (Scheme 1) and made an effort to transform a known batch procedure into a continuous process. The synthesis of 1-(cyclohexyloxy)-2-methylbenzene (**3**) was conducted using cyclohexanol (**1**) and o-cresol (**2**) in presence of diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP) and tetrahydrofuran (THF) as a solvent. A DoE methodology was used to illustrate the reaction and effects of each parameter. The reaction was examined in batch and the learnings were utilized to develop, optimize, and intensify under flow conditions using a customized flow reactor. The benefits and opportunities were discussed.

2. Experimental

2.1 *Chemicals*

The chemicals cyclohexanol (**1**), o-cresol (**2**), triphenylphosphine (TPP), diisopropyl azodicarboxylate (DIAD), and solvent tetrahydrofuran (THF) were obtained from Sigma Aldrich and Spectrochem, Mumbai.

2.2 *Batch reactor setup*

A schematic representation of a batch reactor setup is shown in Figure 1. All the batch experiments were performed in a jacketed reactor setup equipped with a 50 mL reactor fitted with a coiled condenser. The pitch blade turbine was used as an agitator for conducting experiments. The head of the reactor had 4 ports, of which one was used for the temperature probe (T), other for the agitator shaft, a third one for the condenser along with nitrogen vent and fourth was for dosing reagents. A detailed experimental procedure is available in the supporting information.

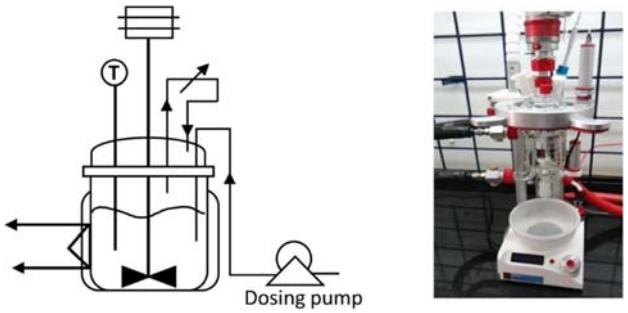


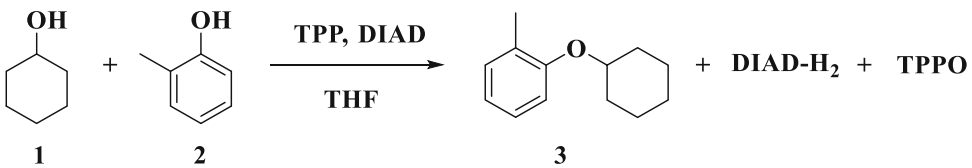
Figure 1. Schematic and actual image of the batch reactor.

2.3 *Continuous flow process design-tubular reactor setup*

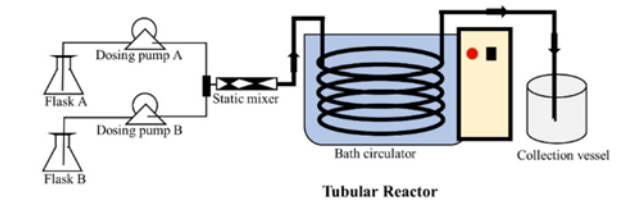
The tubular flow reactor was constructed using perfluroalcoxy alkane (PFA) tubes with internal diameter 3.175 mm (supplied by Swagelok, India) coiled with a definite volume of 15 mL rolled into a disc form, connected with a T- joint and a static mixer (supplied by Cole-Parmer, India) and immersed into a bath circulator (ministat-125, supplied by Huber, Germany). Two pumps A and B (QG50, supplied by FMI, Inc.) were used to pump the reaction mixture at a definite flow rate. The open bath circulator was used to control the temperature of the flow reactor. The schematic and actual image of the experimental setup is shown in Figure 2. The detailed experimental procedure is available in the supplementary information.

2.4 *Analytical method development*

The reaction was performed at 1 g scale like the regular experiment, after completion of the reaction, the mixture was diluted with water and extracted in ethyl acetate. The organic layer was separated and concentrated using a rotavapour. The product is treated with petroleum ether to precipitate triphenylphosphine



Scheme 1. Reaction scheme for Mitsunobu reaction.[34]



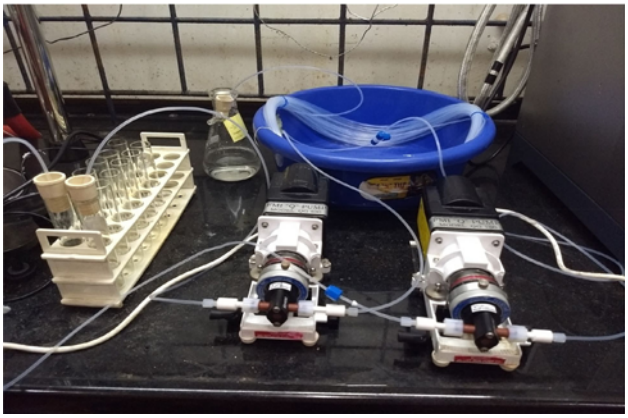


Figure 2. Schematic and actual image of the tubular reactor.

oxide and filtered. The bed was washed with petroleum ether twice and the filtrate was concentrated to dryness. Further purification of the product was done through prep-HPLC to achieve samples for analytical standards. The synthesized compound (**3**) along with cyclohexanol (**1**) and o-cresol (**2**) were used to develop an analytical method through HPLC.

3. Results and Discussion

The synthesis of 1-(cyclohexyloxy)-2-methylbenzene (**3**) was studied as a representative procedure for the Mitsunobu reaction (Scheme 1). Initially, screening experiments were performed under batch conditions at 100 to 250 mg scale to understand the behavior of the reaction profile. The scope of the work was more focused and limited to continuous flow process development. The design of experiments (DoE) methodology was adopted to design the experimentation matrix for continuous flow process development. The following factors such as the *molar ratio of cyclohexanol (**1**) and o-cresol (**2**), the equivalence of TPP, the equivalence of DIAD and reaction temperature* were considered. The solvent THF volumes were kept constant at 15 V based on the batch size. The design was a *two-level half-factorial design with 3 center points*, arriving at a total of 11 experiments, and the design was limited to main effects. These experiments were designed to understand the effect of the parameters individually and in pairs as well. For each experimental parameter, high value and a low value was assigned based on the details obtained from the screening experiments. The factors were codified as (−1), (+1), and '0' for minimum, maximum, and as center point average values respectively to ease the computations and analysis. The experiments were performed as per the run order of the design matrix, which was already randomized in the design to minimize noise. The three center points were added to the design to estimate the curvature effects if any. The data presented for each experimental run was of final yield and the same data was used to build the model.

Batch experiments were performed at 100-250 mg scale with temperature around 25 to 40 °C. the selectivity was around 28 to 35% at the crude stage and yields were of the order 40 to 45%. These experiments were quite sluggish and require 3 to 5 h towards completion. Commonly, it is well known that the side products and impurities would form such as bi-product and PPh3 while using DIAD. We have observed precipitation during workup, which may be of hydrazine adduct. The by-product estimation has not been carried out by analytical technique. The crude was extracted using ethyl acetate followed by pet ether to get an isolated product. The batch experiments provided a good insight towards reaction behavior and kinetics using this data, continuous process development using customized flow reactor was undertaken.

3.1 *Discussion on tubular reactor*

The experiments were conducted in a tubular reactor of diameter 3.175 mm with a total reactor volume of 15 mL. The residence time was around 30 min for all experiments with a total flow rate of 0.5 mL/min. Three different temperatures were considered for experimentation such as 30 °C, 45 °C, and 60 °C. The molar ratios of cyclohexanol (**1**) and o-cresol (**2**) were of the order 1.1, 1.2, and 1.3 respectively. The TPP was varied from 1.0, 1.15, and 1.3 equivalence and DIAD from 1.0, 1.15, and 1.3 equivalence. Using the above factors and range, a design matrix (Tables 1–3) was developed and performed experiments accordingly.

Table 1. Experimental design details for continuous flow reactor experiments.

Study type	Factorial	Runs	11
Design type	2 level factorial	Blocks	No blocks
Design model	Reduced 2FI	Center point	3

Table 2. Details of factor levels used for DoE design for continuous flow reactor experiments.

Factor	Name	Units	Type	Subtype	Minimum	Maximum	Coded Values		Mean
A	Molar ratio (1:2)	Ratio	Numeric	Continuous	1.1	1.3	− 1.0 = 1.1	1.0 = 1.3	1.20
B	triphenylphosphine	Eq.			1.0	1.3	− 1.0 = 1.0	1.0 = 1.3	1.15
C	DIAD	Eq.			1.0	1.3	− 1.0 = 1.0	1.0 = 1.3	1.15
D	Temperature	°C			30	60	− 1.0 = 30	1.0 = 60	45.0

Table 3. Experimental design with results.

		Factors				*Response*
Std	Run	Molar ratio (1 and 2)	Triphenyl phosphine, Eq.	DIAD, Eq.	Temperature, °C	*Yield %*
11	1	1.20	1.15	1.15	45	*45.44*
7	2	1.10	1.30	1.30	30	*36.10*
9	3	1.20	1.15	1.15	45	*41.94*
2	4	1.30	1.00	1.00	60	*42.08*
4	5	1.30	1.30	1.00	30	*69.99*
8	6	1.30	1.30	1.30	60	*51.51*
5	7	1.10	1.00	1.30	60	*49.60*
10	8	1.20	1.15	1.15	45	*42.42*
3	9	1.10	1.30	1.00	60	*32.37*
1	10	1.10	1.00	1.00	30	*31.95*
6	11	1.30	1.00	1.30	30	*70.69*

The results were charted in the experimental template to identify the significant factors and their effects on the formation of 1-(cyclohexyloxy)-2-methylbenzene (**3**). From the experiments, we observed the increase in the molar ratio of cyclohexanol (**1**) and o-cresol (**2**) along with an increase in DIAD would increase in selectivity and the overall yield of 1-(cyclohexyloxy)-2-methylbenzene (**3**). Similarly, an increase in TPP equivalence along with an increase in temperature would decrease the yield of 1-(cyclohexyloxy)-2-methylbenzene (**3**) by significant numbers. All these factors were critical in deciding the yield of 1-(cyclohexyloxy)-2-methylbenzene (**3**). Factors A, C, D, and AD were shown to be highly significant factors by the model. Factor B in the selected range has little effect on the conversion and selectivity of (**3**). The contour and surface plots for 1-(cyclohexyloxy)-2-methylbenzene (**3**) were obtained from DoE analysis and represented in Figure 3. Additionally, the ANOVA table was prepared and the model was found to be significant.

3.2 *Optimization and model fitting*

An optimization exercise was undertaken with setting a goal as maximize 1-(cyclohexyloxy)-2-methylbenzene (**3**) keeping all other factors within the boundary conditions. *A yield of 70.70% (**3**), could be achieved with a 1.3 molar ratio (1:2), the temperature of 30* °C*, 1.27 equivalence of TPP, and 1.12 equivalence of DIAD with the desirability of more than 98%.* The predicted Vs actual values were in good agreement. The model equation was derived from the compound (**3**) and presented. Graphical optimization results keeping 1.3 equivalence of DIAD and temperature 30 °C was presented in the supporting information.

4. Conclusions

DoE methodology was effectively used to develop and optimize the flow process in this customized tubular reactor setup. The reaction profile of flow experiments agreed with the batch conditions adding noteworthy improvements to the overall reaction time, selectivity, and yield towards the desired product (**3**). *The Mitsunobu reaction in batch condition would take on an average of 3 to 5 hours under these conditions, which was effectively achieved around 30 to 45 mins*. Factor B in the selected range has little effect on the conversion and selectivity of (**3**). The experiments revealed the increase in the molar ratio of cyclohexanol (**1**) and o-cresol (**2**) along with an increase in DIAD would increase in selectivity and the overall yield of (**3**). Similarly, an increase in TPP equivalence

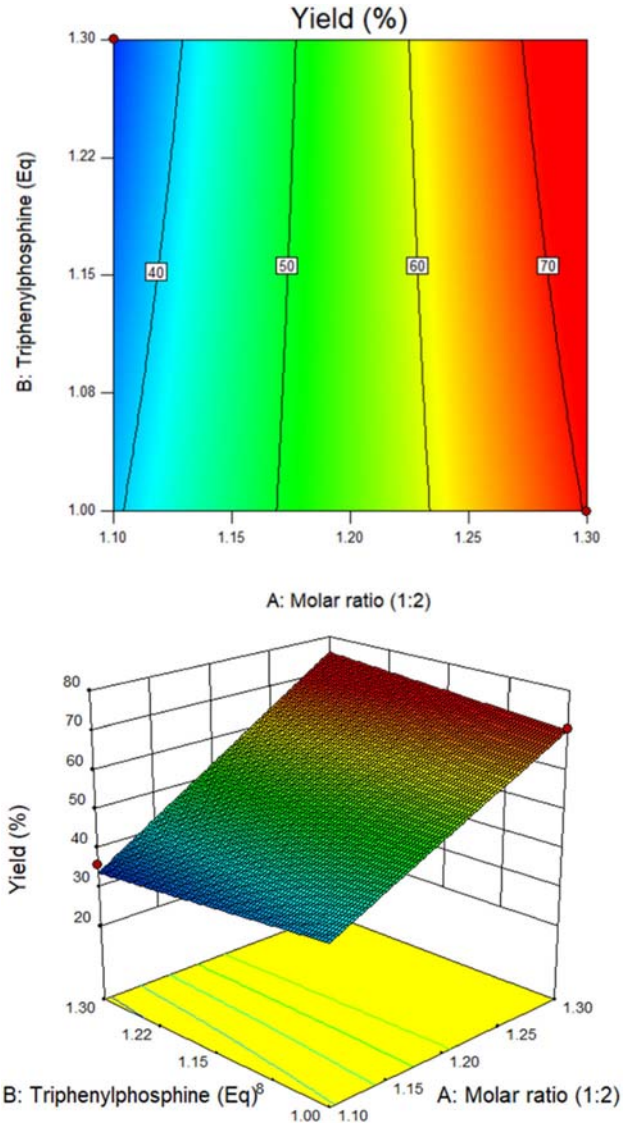


Figure 3. 1-(cyclohexyloxy)-2-methylbenzene (3) DoE analysis for the tubular reactor experiments (a) Contour plot and (b) Surface plot.

along with an increase in temperature would decrease the yield of (**3**) by significant numbers. The reaction model was in good agreement with the reaction conditions. The initial feasibility and development of the flow process for the Mitsunobu reaction were successfully demonstrated using customized reactor setup, which could be further studied using precise equipment to fine-tune the process conditions for improved selectivity and yield. The demonstrated methods could be used effectively to leverage the benefits of continuous process techniques over batch processes. We believe the process could be executed continuously without a break, readily scaled to kilogram quantities in a short time without further development.

Acknowledgements

The authors would like to acknowledge Dr. Jegadeesh Thampi and Dr. Narendra Ambhaikar (Chemical Development, Syngene International Ltd.) for providing adequate support, guidance, and motivation throughout the work.

Funding

This work was supported by Syngene International Ltd., Bengaluru, India, and all the necessary approvals are in place to publish the same.

Data transparency

Authors confirm that the paper now submitted is not copied or plagiarized version of some other published work.

Compliance with ethical standards

Competing interest The authors declare that they have no competing interests.

Availability of data and materials The data supporting the results and conclusion are included in this article. Any queries regarding data may be directed to the corresponding author.

Supplementary Information (SI)

The supplementary data (experimental procedure, data analysis, and model equations, etc.) associated with this article are available at www.ias.ac.in/chemsci.

References

1. Lepore Salvotore D and Yuanjun H 2003 Use of sonication for the coupling of sterically hindered substrates in the phenolic Mitsunobu reaction *J. Org. Chem.* **68** 8261
2. Oyo M 1981 The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products *Synthesis* **1981** 1
3. Oyo M and Masaaki Y 1967 Preparation of esters of carboxylic and phosphoric acid *via* quaternary phosphonium salts *Bull. Chem. Soc. Jpn.* **40** 2380
4. Kumaraswamy K C, Bhuvan Kumar N N, Balaraman E and Pavan Kumar K V P 2009 Mitsunobu and related reactions: Advances and applications *Chem. Rev.* **109** 2551
5. Gu Y, Azzouzi A, Pouilloux Y, Jérôme F and Barrault J 2008 Heterogeneously catalyzed etherification of glycerol: new pathways for transformation of glycerol to more valuable chemicals *Green Chem.* **10** 164
6. Berger A and Wehrstedt K D 2009 Azodicarboxylates: Explosive properties and thermal hazards *12th Annual Symposium, Mary Kay O'Connor process safety center*

beyond regulatory compliance: Making safety second nature at Texas A&M University, College Station, Texas
7. Caron S and Thomson N M 2015 Pharmaceutical process chemistry: Evolution of a contemporary data-rich laboratory environment *J. Org. Chem.* **80** 2943
8. Otman B, Deal M, Farrant E, Tapolczay D and Wheeler R 2008 Continuous flow microwave-assisted reaction optimization and scale-up using fluorous spacer technology *Org. Process Res. Dev.* **12** 1007
9. Roberge D M, Ducry L, Bieler N, Cretton P and Zimmermann B 2005 Microreactor technology: A revolution for the fine chemical and pharmaceutical industries? *Chem. Eng. Technol.* **28** 318
10. Norbert K, Gottsponer M, Zimmermann B and Roberge D M 2008 Enabling continuous-flow chemistry in microstructured devices for pharmaceutical and fine-chemical production *Chem. Eur. J.* **14** 7470
11. Bogdan A R, Poe S L, Kubis D C, Broadwater S J and McQuade D T 2009 The continuous-flow synthesis of Ibuprofen *Angew. Chem. Int. Ed.* **4**8 8547
12. Herath A, Dahl R and Nicholas D P Cosford 2010 Fully automated continuous flow synthesis of highly functionalized imidazo[1,2-a] heterocycles *Org. Lett.* **12** 412
13. Ryan L H and Jensen K F 2009 Microchemical systems for continuous-flow synthesis *Lab Chip.* **9** 2495
14. Klaus J, Hessel V, Löwe H and Baerns M 2004 Chemistry in microstructured reactors *Angew. Chem. Int. Ed.* **43** 406
15. Delville M M E, Nieuwland P J, Janssen P, Koch K, van Hest J C M and Rutjes F P J T 2011 Continuous flow azide formation: Optimization and scale-up *Chem. Eng. J.* **167** 556
16. Karolin G, Gustafsson T and Seeberger P H 2009 Developing continuous-flow microreactors as tools for synthetic chemists *Synlett* **15** 2382
17. Aiichiro N, Kim H, Usutani H, Matsuo C and Yoshida J-I 2010 Generation and reaction of cyano-substituted aryllithium compounds using microreactors *Org. Biomol. Chem.* **8** 1212
18. Andreas H, Filipponi P, Piccioni L, Meisenbach M, Schenkel B, Venturoni F and Sedelmeier J 2016 A simple scale-up strategy for organolithium chemistry in flow mode: From feasibility to kilogram quantities *Org. Process Res. Dev.* **20** 1833
19. Chaoyu Z, Zhang J and Luo G 2016 Kinetic study and intensification of acetyl guaiacol nitration with nitric acid-acetic acid system in a microreactor *J. Flow. Chem.* **6** 309
20. Zoé A, Cabassud M, Gourdon C and Tochon P 2008 Heat exchanger/reactors (HEX reactors): Concepts, technologies: State-of-the-art *Chem. Eng. Process. Process Intensif.* **47** 2029
21. Kaspar K, van Weerdenburg B J A, Verkade J M M, Nieuwland P J, Rutjes F P J T and van Hest J C M 2009 Optimizing the deprotection of the amine protecting *p*-methoxyphenyl group in an automated microreactor platform *Org. Process Res. Dev.* **13** 1003
22. René B, van den Broek SA M W, Nieuwland P J, Koch K and Rutjes F P J T 2012 Optimisation and scale-up of α-bromination of acetophenone in a continuous flow microreactor *J. Flow. Chem.* **2** 87
23. Fabry D C, Sugiono E, Rueping M and Meunier F C 2016 Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems *React. Chem. Eng.* **1** 165
24. Antimo G, Mancino V, Filipponi P, Mostarda S and Cerra B 2016 Concepts and optimization strategies of experimental design in continuous-flow processing *J. Flow. Chem.* **6** 167
25. Nunn C, DiPietro A, Hodnett N, Sun P and Wells K M 2018 High-throughput automated design of experiment (DoE) and kinetic modeling to aid in process development of an API *Org. Process Res. Dev.* **22** 54
26. Ahmad A, Muhammad I A, Muhammad Y, Hayat K and Ul Hassan Shah M 2013 A comparative study of alkaline hydrolysis of ethyl acetate using design of experiments *Iran J. Chem. Chem. Eng.* **32** 33
27. Asprey S P and Macchietto S 2000 Statistical tools for optimal dynamic model building *Comput. Chem. Eng.* **24** 1261
28. Franceschini G and Macchietto S 2008 Model-based design of experiments for parameter precision: State of the art *Chem. Eng. Sci.* **63** 4846
29. Atkinson A C, Barbara Bogacka B and Bogacki M B 1998 D-and T-optimum designs for the kinetics of a reversible chemical reaction *Chemom. Intell. Lab. Syst.* **43** 185
30. Gupta A and Chandrajit B 2015 Residence time distribution study for continuous column packed with tea waste biomass *Integ. Res. Adv.* **2** 5
31. Danckwerts P V 1953 Continuous flow systems: distribution of residence times *Chem. Eng. Sci.* **2** 1
32. Anderson N G 2001 Practical use of continuous processing in developing and scaling up laboratory processes *Org. Process Res. Dev.* **5** 613
33. Frank K, Wolff T, Thomas S and Seidel-Morgenstern A 2003 Concentration and residence time effects in packed bed membrane reactors *Catal. Today* **82** 25
34. El-Deeb, Yussif I, Tian M, Funakoshi T, Matsubara R and Hayashi M 2017 Conversion of cyclohexanones to alkyl aryl ethers by using a Pd/C–ethylene system *Eur. J. Org. Chem.* **2017** 409