ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: B. Mahajan, T. Mujawar, S. ghosh, S. Pabbaraja and A. K. Singh, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC06127D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC06127D

COMMUNICATION

Micro-Electro-Flow Reactor (μ-EFR) System for Ultra-Fast Arene Synthesis, and Manufacturing of Daclatasvir

5r5Received 00th August 20xx,
Accepted 00th August 20xx

DOI: 10.1039/x0xx00000x

Bhushan Mahajan, [1,#] Taufiqueahmed Mujawar,[1] Subhash Ghosh, Srihari Pabbaraja, [#] Ajay K. Singh[#]

World Health Organization (WHO) has listed daclatasvir (DCV), symmetrical arene as one of the essential medicines for the human health system. DCV manufacturing is carried out usually in non-continuous or "batch" approach at multiple locations that are severely limited by long production times (3-10 days) causing non-affordability (highly expensive), and disruption of potential chain supply. Here, we report the total process system including development of novel electro-flow reactor containing patterned electrodeposited Ni or Pt nanoparticle over the copper electrode for C-C coupling reaction in a co-reductant/oxidant-free, the ultra-fast process for symmetrical substituted/unsubstituted biphenyl synthesis. This method was further extended to new generation commercial batch synthetic route to continuous flow ultra-fast daclatasvir synthesis in 33.2 min. We envision that μ-EFR system platform is substantial enabling advances in continuous-μ-flow fine chemicals manufacturing, multistep reaction sequence, reaction devising equipment, and real-time extraction.

Worldwide, more than 2.25 percent (170 million) of the world's population are infected with hepatitis C virus (HCV).[1] HCV is a primary cause of chronic liver disease and can lead to liver cancer.[2] After several efforts, DCV has been synthesized and demonstrated the potential exists to exterminate a chronic viral disease using a new class of direct-acting antiviral agent (DAA's) that inhibit the HCV protein NS5A.[3] Several successful drugs for HCV protein NS5A inhibitor have recently emerged, including the protease inhibitor (DCV, velpatasvir, and ledipasvir) and frequently used in the combination therapy for the treatment of HCV genotype 1, 3, or 4 infections with or without cirrhosis.[4] Protease inhibitor contains a biaryl core moiety derived from L-proline and substituted imidazoles of the general structure (Fig. 1).[3b] The central part of DCV has been a biaryl unit which forms the key starting material for DCV synthesis. Though a large number of batch/flow protocols for the synthesis of symmetrical and unsymmetrical biaryls exists, Ullmann coupling is the most preferable one and utilized in academia and industry.[5] The first Ullmann coupling goes back to 1901,[6] wherein aryl iodides are used and the coupling reaction was promoted by excess amount of copper at high temperatures.[7] The recent developments during the decade in the C-C coupling reaction has allowed the use of aryl bromides or chlorides as reactants in the presence of a co-reductant such as Zn powder, formic acid, organosilicon reductant and dihydrogen under mild conditions for the preparation of biphenyls/substituted symmetrical or unsymmetrical biphenyls.[8] To minimize the use of co-reductant, several novel transition metal (Pd, Ir, Ru, Rh, Pt) catalytic reaction, under both homogeneous and heterogeneous conditions are employed.[9]

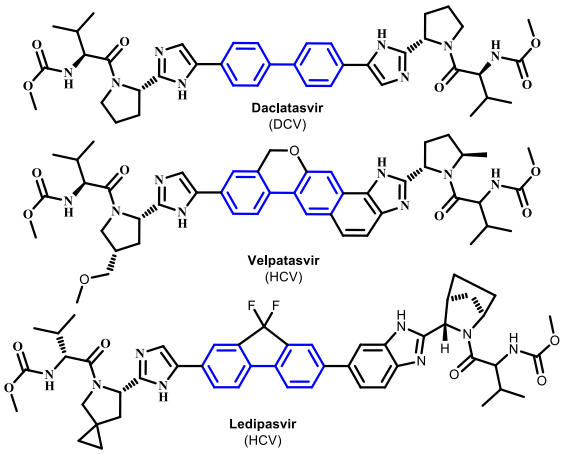


Fig. 1 Prevalence of the arenes skeleton in pharmaceutical compounds.

Among the novel metal catalysts, nickel catalysts are inexpensive and exhibit high reactivity towards less reactive electrophiles such as aryl bromide/chloride, thus offering an alternative approach for coupling reaction.[9b,10] On the other hand, batch process homo/heterogeneous catalytic reaction system provides the insufficient reactant collision resulting in longer reaction times (4-48 h) to form the biphenyl moiety.[7,11] To reduce the co-reductant/oxidant wastage in the chemical reaction, electrochemistry represents the most suitable electron transfer process where solid surface cathode or anode directly interacts with catalyst and changes the oxidation state.[12] However, electrochemistry is a surface phenomenon and allows the unique activation of reagents enabling selectivity and transformations which are not possible by other techniques. Batch process electro-organic reactions have a low surface to volume ratio and inefficient mixing resulting in the longer reaction times to complete the reaction with

[*] Mr. B. Mahajan, Mr. T. Mujawar, Dr. S. Ghosh, Dr. P. Srihari, Dr. A. K. Singh
Division of Organic Synthesis and Process Chemistry,
CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India.
[#] Academy of Scientific and Innovative Research (AcSIR), CSIR-Human Resource Development Centre (CSIR-HRDC) Campus, Ghaziabad 201002, Uttar Pradesh, India
E-mail: srihari@iict.res.in; ajaysingh015@gmail.com;
[+] These authors contributed equally to this work.
Supporting information for this article is available on the

off quality product and hence inappropriate for the automation.[13] It is still challenging to demonstrate a high surface to volume ratio, micro-patterned porous nanoparticle electrode, reducing the distance between electrodes for more efficient electron transfer chemistry with excellent performance. In the recent years, continuous-flow microfluidic devices owing to the intrinsic advantages such as fast heat and mass transfer, an improved safety profile, potential for process automation and process integration have emerged as one of the most significant man-made tools for process intensification.[13d,e,14] Therefore, fabrication of suitable continuous-flow electro-flow microfluidic reactors are highly urgent for the ultra-fast core moiety synthesis.

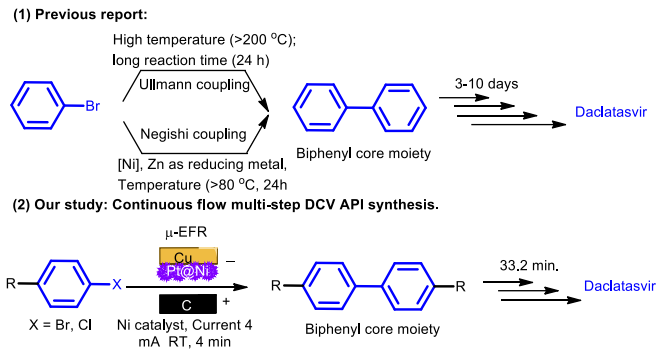


Fig. 2 (**a**) Previous batch-reactor methods for the synthesis of antiviral daclatasvir API; (**b**) current continuous flow multi-step daclatasvir synthesis; (**1**) second generation commercial route; (**2**) modified new commercial route.

DCV has been listed one among the essential medicines for human health systems by WHO.[15] The first generation synthetic route for the synthesis of DCV is outlined in Scheme S1. The synthesis had a drawback wherein the problem was associated with noble Pd metal-assisted coupling reaction of bromide resulting in epimerization and by-product formation during imidazole synthesis. However, long-term manufacturing process (DCV manufacturing is done usually at multiple locations in non-continuous or "batch" approach which often requires long production times 3-10 days and generally involves high cost for the transportation causing disruption of the potential chain supply) causing non-affordability (highly expensive; price is similar to diamond) for common-man.[16-17] Thus, there is a need for an efficient approach to further expand the scope of the Ultra-fast synthesis of DCV in continuous mode, including the electro-micro flow chemistry, for unexplored dimensions. To prove our working hypothesis, we used a general two-step protocol (Fig. 2) in each optimization: (i) design of the reactor and reaction sequence (selecting the reagents, solvents, and catalysts for making the core biphenyl moiety; (ii) various parameter boundaries (time, temperature, catalyst loading) towards optimization for DCV synthesis. To realize the concept of an electrochemistry and DCV API synthesis process, we present the total process system including development of electro-flow reactor containing patterned electrodeposited Ni/Pt metal over the copper electrode for C-C coupling reaction and further extended to multi-step continuous flow ultra-fast DCV synthesis which was achieved within 33.2 min (Fig. 2).

Our initial plan was to design the μ–EFR and screen the catalyst for coupling reactions. Accordingly, μ–EFR was designed which consists of a long-serpentine tunnel sandwiched in a solid block of a graphite and metal anode and three PTFE sheets with the identical dimension of groove channels. The metal holder was tightly pressed

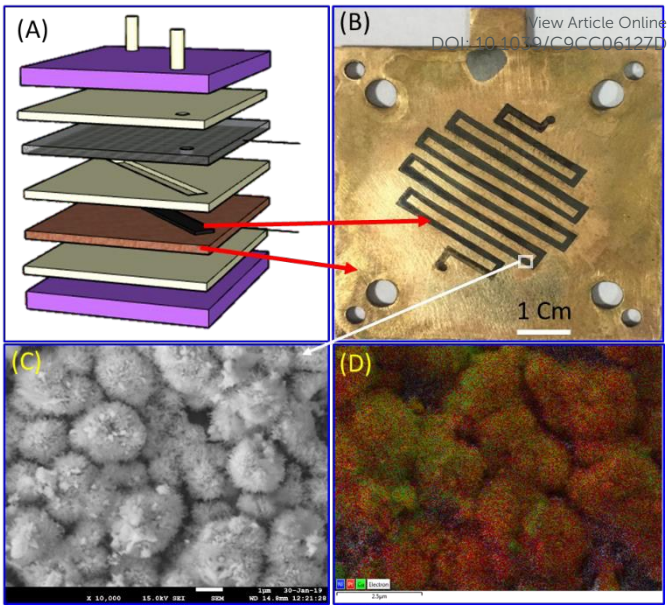


Fig. 3 (A) Micro-electro flow reactor; (B) original image of the Pt@Ni@Cu micro-pattern electrode; (C)top view: low and high resolution SEM image respectively; (D) top view elemental Pt, Cu, Ni and mix mapping respectively.

by the screw to seal the device with no leaks (Fig. 3A). The middle part of the serpentine patterned nickel nanoparticle coated over the copper plate was fabricated by electrodeposition method (details in SI section 2). The particle size of Ni nanoparticles and thickness were controlled by electrodeposition time, applied current, and Ni salt concentration, respectively, to obtain a homogenous nanoparticle size with a uniform thickness. The scanning electron microscopy (SEM) images in (Fig. S2&S3), revealed that the nickel nanoparticle is in the range of 10–100 nm and the thickness is 4 μm, which can be controlled by varying the deposition time. To prepare the Pt@Ni@Cu electrode, stock electrolytic solution containing mixture of Pt(IV) chlorides, diammonium hydrogen phosphate, disodium hydrogen phosphate, ammonium chloride, and water, was pumped with fix flow rate of 100 μL min^{-1} for 2h at 70 °C under current density of 0.3 A/dm^2, which typically led to the generation of a black coloured patterning, and then washed with water thoroughly to remove any unreacted salt and nanoparticle. It should be noted here that the Pt@Ni nano texturing on the Cu smooth surface of flower-shaped Pt@Ni bundles with nano-scale intervals led to a hierarchically structured surface, which enhances the high-electron transfer significantly. The dimensions of the Pt@Ni coated electrode channel are 2000 μm in width, 20-25 μm in height and 100 cm in length and those of the PTFE channel are 2000 μm,1000 μm, and 10 cm, respectively, for the width, height and length (Fig. S5). Polytetrafluoroethylene (PTFE) channel sandwiched by two electrodes with matching dimension of microchannel were placed between metal holder, the set was aligned by inserting metal pins through the holes at the film corners. Finally, the metal holder was tightly pressed by screw to seal the device with no leak (Fig. S5a, and S7).

We proceeded further by monitoring the model C-C coupling reaction of a solution containing bromobenzene(**1a**)/ $NiCl_2$.glyme/ bipyridine/ LiCl/ DMA, which was taken in the syringe and connected with above designed μ-EFR as described in (Fig. S8) to synthesize biphenyl. The solution, in a stoichiometric molar ratio of 10 (**1a**/ $NiCl_2$.glyme), was passed through a μ–EFR (reactor volume 200

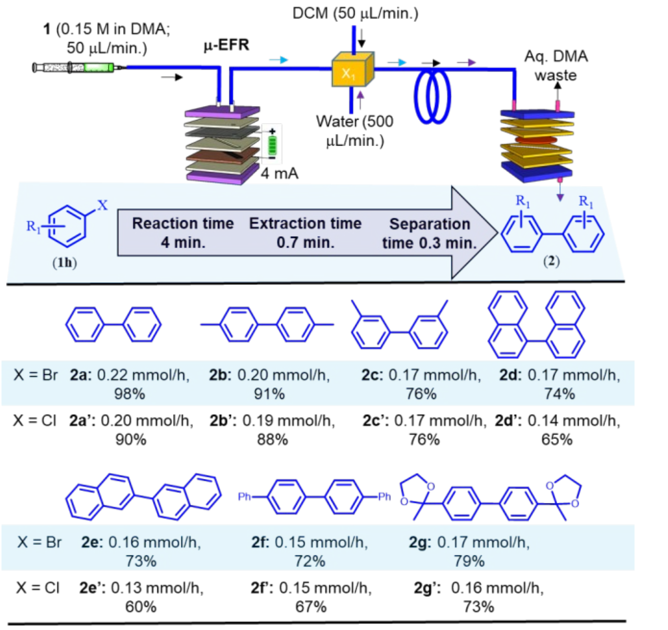


Fig. 4 Synthesis of symmetrical biaryls: Reaction condition: stock solution of 1 contained bromobenzene (0.15 M in DMA), $NiCl_2$.glyme (10 mol%), bipyridine (10 mol%), LiCl (4 eq.), current (4 mA), reaction time 4 min. RT; (') represent that X= chloro group; yields are based on isolated yields.

μL) containing Ni@Cu anode and graphite cathode held at 25 °C with current 4 mA at a flow rate of 50 μL min^{-1} (residence time = 4 min), which typically led to the generation of a brownish coloured solutions with 5% yield of the desired product **2a** (Table S1, entry 1). The use of various electrode combination of Ni/C, Ni foam/C, Cu/C, Pt/C, C/C, and Pt@Ni@Cu furnished **2a** (0–98%) (Table S1, entries 2–6). Notably, only the Pt@Ni@Cu anode was found to be the best system suitable for the ultra-fast biphenyl generation reaction (Table S1, entry 6). Assured of the feasibility of the μ-EFR with Pt@Ni@Cu anode system for use in C-C coupling reaction, we next examined the solvent effect. The use of either dimethylacetamide (DMA) or dimethylformamide (DMF) as a solvent led to complete conversion and excellent selectivity within 4 min, whereas tetrahydrofuran (THF), dimethylsulphoxide (DMSO), acetonitrile (MeCN), and water were not successful to produce the product in desired yield. Ligand screening experiments shows that the inexpensive combination of $NiCl_2$·glyme and a bipyridyl ligand (L_1) provides the most effective catalyst system for the transformation on bromobenzene (Table S1, entries 12-19). Optimized micro-electrolysis reaction conditions, 98% yield of **2a** was obtained in 4.0 min of residence time at 4 mA constant current, resulting in ca. 0.22 mmol h^{-1} (0.82 g/day) productivity (Table S1, entry 6), while 4-7 h residence time was needed in batch electrolysis reaction under similar reaction condition. It was also observed that there was no electrode (Pt@Ni) degradation or leaching even after continuous running of experiments for 4 days.

In order to reduce the number of tedious workup steps, we were interested in the fully integrated serial process of reaction and in-line purifications, post-synthesis work-up for the selective removal of waste chemicals (LiCl, bipyridyl, $NiCl_2$.diglyme/solvent). Since, the high boiling point of (165 °C) DMA becomes problem for isolating the product, we wanted to replace the high boiling solvent with a low boiling solvent after the μ–EFR reaction. We used our previously designed continuous flow liquid–liquid extractor,[13b,c,14b,18] to isolate the synthesized **2a** in DCM from the DMA mixture (details in Supporting information). After the successful development of an integrated process for the synthesis of biphenyl, we were interested in testing the scope and limitation of this strategy. Figure 4 represents the integrated serial process with 4 mA constant current that can deliver various biphenyl products in excellent yields over 90% at 25 °C for activated substituted bromobenzene (**2a**) in 5 min. of total process time: 4.0 min for electrolysis reaction, 0.7 min, and 0.3 min for water mixing and extraction in DCM, respectively (Table S2, entry 1). Aside from aryl bromides, other aryl chlorides are much more difficult to activate. Therefore, we were interested to check the reactivity of aryl chlorides and when the same was tested under the μ-EFR standard conditions, 92% yield of **2a** was obtained in 5.0 min of residence time. This versatile system when further tested with a range of substrates containing electron-donating and electron-withdrawing substituents (**1b**–**1g**), were well tolerated, providing the required arenes in good yields and resulting in productivity of 0.15-0.22 mmol/h. It is worth to mention that this system has emerged as a superior alternative for the conventional batch photochemical, thermal, electrochemical processes wherein the noble metal-catalysed, copper-catalysed, and nickel-catalysed reactions requires a longer reaction times (2–48 h) and when excess amount of catalyst, co-reductant/oxidant are used, the reaction ends up with huge wastage of mixtures resulting in tedious work-up procedure for the selective isolation of desired product[19] (Table S3).

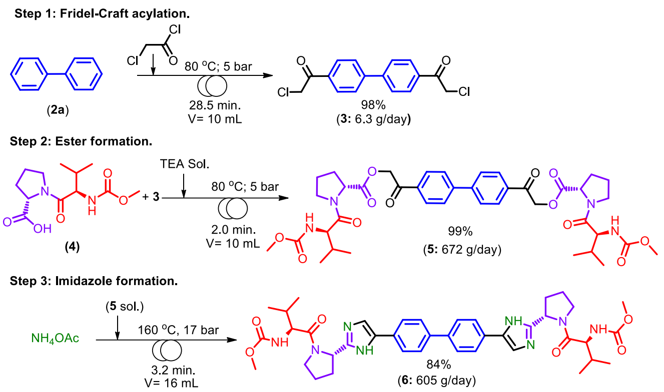


Fig. 5 New generation continuous micro-flow ultra-fast Daclatasvir API synthetic route: Reaction condition step 1: stock solution 2a (0.16 M in DCE), chloroacetyl chloride and aluminium chloride (0.4 M in DCE with 1:1 molar ratio); Step 2: mixture of **3** (0.25 M in MeCN) + 9 (0.5 M in MeCN), TEA (1.3 M in MeCN); Step 3: **5** (0.16 M in MeCN), NH_4OAc (8.6 M in water). Yields are based on isolated yield.

Next, we were interested in demonstrating the practicability of our present integrated μ–EFR platform for the synthesis of DCV. Batch synthesis would have required several operations over 3-10 days to complete the DCV synthesis (Scheme S2).[20] Encouraged by our ultra-fast biphenyl synthesis (5 min), we wanted to optimize and adapt the commercial new generation synthetic route to an ultra-fast continuous flow system in order to stream line manufacturing of the DCV API. For the continuous flow Friedel-Craft biphenyl acylation step (Fig. 5), we found that 98% yield of **3** in 28 min of residence time at 80 °C and 5 bar pressure in the presence of chloroacetyl chloride and $AlCl_3$ catalyst (Table S4, entry 5), resulting in ~0.85 mmol h^{-1} productivity. It is worth to mention that the conventional batch for the identical reaction showed lower yields (90%) and longer reaction time (4.5 h) to furnish the same product. After the development of a continuous-flow process for the synthesis of **3**, we were interested in optimizing and adapt the esterification strategy. The plug and play methodology was applied for the coupling reaction of **3** and **4** to

obtain **5** as summarized in (Table S5). The reaction performance generally depended on the residence time of **3** at fixed flow rate of base triethylamine (TEA). In the range of molar ratio of 2.25 (TEA/**3**), the optimized reaction resulted in 99% conversion (Table S5, entry 3) within 2 min of residence time at 80 °C temperature and 5 bar pressure, resulting in ~36 mmol h^{-1} productivity of **5**. We next focused our attention on the cyclization reaction, which involves the treatment of compound **5** with ammonium acetate to form DCV in excellent yield (~84%) (Fig. 5, step 3) in 3.2 min residence time at 160 °C temperature and 17 bar pressure, resulting in ~34 mmol h^{-1} productivity using the continuous flow platform (Table S6, entry 3). In contrast, the conventional batch process required a longer reaction time (3-10 days) to attain overall ~22-45% yield, while continuous flow process enhanced the overall yield 77% in 33.2 min of residence time.[20] Such a striking contrast highlights the additional power of the continuous flow system that results when it is combined with multi-component reaction. Additional, integrated continuous one-flow multi-step DCV synthesis work is under progress in our lab.

In conclusion, we have developed an integrated total process system including development of electro-flow reactor containing patterned electrodeposited Ni/Pt metal over the copper electrode for C-C coupling reaction. The examination of the haloarenes to multistep sequences afforded ultra-fast DCV API synthesis with improved yield. An advanced μ–EFR platform in continuous flow chemistry, and with an additional plug and play research, ultimately enables the continuous synthesis of modern small molecule pharmaceuticals, including enantiopure APIs. More importantly, the developed system detailed here would enable the future automation of research laboratory and chemical industry to produce on-demand ultra-fast structural complex APIs (DCV, velpatasvir, and ledipasvir) and commodity chemicals synthesis in the areas of drug discovery, natural products, materials synthesis, and biology.

A.K.S. thanks Department of Science and Technology, New Delhi (Govt. of India) (DST), New Delhi, for the INSPIRE Faculty Award and Early Career Research Award. Financial assistance received from CSIR (HCP-0011), DST and Science and Engineering Research Board (SERB) project no. DST/INSPIRE/04/2016/000247 and ECR/2017/000208 are gratefully acknowledged. We gratefully acknowledge Director, CSIR-IICT for his support and encouragement. CSIR-IICT, Hyderabad, has filed a patent on the process reported herein. CSIR-IICT manuscript communication no. IICT/Pubs./2019/214.

Note and References

1 (a) Mohd Hanafiah, K.; Groeger, J.; Flaxman, A. D.; Wiersma, S. T. *Hepatology* **2013**, *57*, 1333; (b) Shepard, C. W.; Finelli, L.; Alter, M. J. *Lancet Infect. Dis.* **2005**, *5*, 558.

2 Feld, J. J.; Gehring, A. J. *Nat. Rev. Gastroenterol. Hepatolo.* **2019**, *16*, 77.

3 (a) Gesty-Palmer, D. *Sci. Transl. Med.* **2012**, *4*, 119ec16; (b) Hughes, D. L. *Org. Process Res. Dev* **2016**, *20*, 1404.

4 Sun, J.-H.; O'Boyle Ii, D. R.; Fridell, R. A.; Langley, D. R.; Wang, C.; Roberts, S. B.; Nower, P.; Johnson, B. M.; Moulin, F.; Nophsker, M. J.; Wang, Y.-K.; Liu, M.; Rigat, K.; Tu, Y.; Hewawasam, P.; Kadow, J.; Meanwell, N. A.; Cockett, M.; Lemm, J. A.; Kramer, M.; Belema, M.; Gao, M. *Nature* **2015**, *527*, 245.

5 Simonetti, M.; Cannas, D. M.; Larrosa, I. In *Adv. Organomet. Chem.*; Pérez, P. J., Ed.; Academic Press, 2017; Vol. 67.

6 Ullmann, F.; Bielecki, J. *Berichte der deutschen chemischen Gesellschaft* **1901**, *34*, 2174.

7 Mondal, S. *ChemTexts* **2016**, *2*, 17.

8 (a) Karimi, B.; Kabiri Esfahani, F. *Chem. Commun.* **2011**, *47*, 10452; (b) Yurino, T.; Ueda, Y.; Shimizu, Y.; Tanaka, S.; Nishiyama, H.; Tsurugi, H.; Sato, K.; Mashima, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 14437.

9 (a) Khan, F.; Dlugosch, M.; Liu, X.; Banwell, M. G. *Acc. Chem. Res.* **2018**, *51*, 1784; (b) Lv, L.; Qiu, Z.; Li, J.; Liu, M.; Li, C.-J. *Nat. Commun.* **2018**, *9*, 4739; (c) Dhital, R. N.; Kamonsatikul, C.; Somsook, E.; Bobuatong, K.; Ehara, M.; Karanjit, S.; Sakurai, H. *J. Am. Chem. Soc.* **2012**, *134*, 20250.

10 (a) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sitler, T. C. *J. Org. Chem.* **2006**, *71*, 409; (b) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. *Nat. Chem.* **2016**, *8*, 1126.

11 (a) Zeng, M.; Du, Y.; Qi, C.; Zuo, S.; Li, X.; Shao, L.; Zhang, X.-M. *Green Chem.* **2011**, *13*, 350; (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588; (c) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525.

12 (a) Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 13088; (b) Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117*, 13230; (c) Ghorai, D.; Finger, L. H.; Zanoni, G.; Ackermann, L. *ACS Catal.* **2018**, *8*, 11657.

13 (a) Singh, R.; Lee, H.-J.; Singh, A. K.; Kim, D.-P. *Korean J. Chem.l Eng.* **2016**, *33*, 2253; (b) Mahajan, B.; Aand, D.; Singh, A. K. *Eur. J. Org. Chem.* **2018**, *2018*, 2831; (c) Aand, D.; Karekar, S.; Mahajan, B.; Pawar, A. B.; Singh, A. K. *Green Chem.* **2018**, *20*, 4584; (d) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. *Science* **2016**, *352*, 61; (e) Bédard, A.-C.; Adamo, A.; Aroh, K. C.; Russell, M. G.; Bedermann, A. A.; Torosian, J.; Yue, B.; Jensen, K. F.; Jamison, T. F. *Science* **2018**, *361*, 1220; (f) Heider, P. L.; Born, S. C.; Basak, S.; Benyahia, B.; Lakerveld, R.; Zhang, H.; Hogan, R.; Buchbinder, L.; Wolfe, A.; Mascia, S.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F. *Org. Process Res. Dev* **2014**, *18*, 402; (g) Diab, S.; Gerogiorgis, D. I. *Org. Process Res. Dev* **2017**, *21*, 924; (h) Zhang, P.; Russell, M. G.; Jamison, T. F. *Org. Process Res. Dev.* **2014**, *18*, 1567; (i) Diab, S.; Gerogiorgis, D. I. *Comp. Chem.Eng.* **2018**, *111*, 102.

14 (a) Aand, D.; Mahajan, B.; Pabbaraja, S.; Singh, A. K. *React. Chem. Eng.* **2019**; (b) Vishwakarma, N. K.; Singh, A. K.; Hwang, Y.-H.; Ko, D.-H.; Kim, J.-O.; Babu, A. G.; Kim, D.-P. *Nat. Commun.* **2017**, *8*, 14676; (c) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796; (d) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384 (e) Lévesque, F.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1706; (f) Mándity, I. M.; Ötvös, S. B.; Fülöp, F. *ChemistryOpen* **2015**, *4*, 212; (g) Mándity, I. M.; Ötvös, S. B.; Szőllősi, G.; Fülöp, F. *Chem. Rev.* **2016**, *16*, 1018; (h) Mascia, S.; Heider, P. L.; Zhang, H.; Lakerveld, R.; Benyahia, B.; Barton, P. I.; Braatz, R. D.; Cooney, C. L.; Evans, J. M. B.; Jamison, T. F.; Jensen, K. F.; Myerson, A. S.; Trout, B. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 12359; (i) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502.

15 (a) You, Y.; Kim, H. S.; Park, J. W.; Keum, G.; Jang, S. K.; Kim, B. M. *RSC Adv.* **2018**, *8*, 31803; (b) Shawn K. Pack, P. G., Michael J. Smith, Jason Hamm *US7728027B2*, *2008*.

16 Freeman *https://www.amfar.org/articles/around-the-world/treatasia/2017/when-drugs-cost-as-much-as-diamonds/* **2017**.

17 Carneiro, P. F.; Gutmann, B.; de Souza, R. O. M. A.; Kappe, C. O. *ACS Sustain. Chem. Eng.* **2015**, *3*, 3445.

18 Singh, A. K.; Ko, D.-H.; Vishwakarma, N. K.; Jang, S.; Min, K.-I.; Kim, D.-P. *Nat. Commun.* **2016**, *7*, 10741.

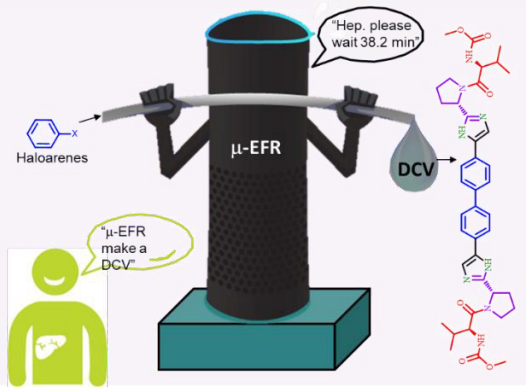
19 (a) Nadri, S.; Azadi, E.; Ataei, A.; Joshaghani, M.; Rafiee, E. *J. Organomet. Chem.* **2011**, *696*, 2966; (b) Li, J.-H.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2003**, *68*, 9867; (c) Pinxterhuis, E. B.; Visser, P.; Esser, I.; Gualtierotti, J.-B.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 9452; (d) Buter, J.; Heijnen, D.; Vila, C.; Hornillos, V.; Otten, E.; Giannerini, M.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 3620; (e) Wang, Z.-J.; Wang, X.; Lv, J.-J.; Feng, J.-J.; Xu, X.; Wang, A.-J.; Liang, Z. *New J. Chem.* **2017**, *41*, 3894; (f) Dzhevakov, P. B.; Topchiy, M. A.; Zharkova, D. A.; Morozov, O. S.; Asachenko, A. F.; Nechaev, M. S. *Adv. Synth. Catal.* **2016**, *358*, 977; (g) Zhang, L.; Wang, A.; Miller, J. T.; Liu, X.; Yang, X.; Wang, W.; Li, L.; Huang, Y.; Mou, C.-Y.; Zhang, T. *ACS Catal.* **2014**, *4*, 1546; (h) Karimi, B.; Vafaeezadeh, M.; Akhavan, P. F. *ChemCatChem* **2015**, *7*, 2248; (i) Rahil, R.; Sengmany, S.; Le Gall, E.; Léonel, E. *Synthesis* **2018**, *02*, 146; (j) Lakshmidevi, J.; Appa, R. M.; Naidu, B. R.; Prasad, S. S.; Sarma, L. S.; Venkateswarlu, K. *Chem. Commun.* **2018**, *54*, 12333.

20 Medikonduri, S. S., Rammohan; Indukuri, Venkata Sunil Kumar; Kalindi, Srihari Raju; Chava, Satyanarayana *World Intellectual Property Organization* **2017**, *021904 A1*.

View Article Online
DOI: 10.1039/C9CC06127D

COMMUNICATION

Graphical Abstract



Electro-micro flow reactor containing Pt@Ni@Cu anodes materials for the reductant free biaryl synthesis and further extented to DCV synthesis.