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Scalability of Visible Light Induced Nickel Negishi Reactions: A Combination of Flow Photochemistry, use of Solid Reagents and in-line NMR Monitoring.

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ABSTRACT: The scale up of light induced nickel catalyzed Negishi reactions is reported herein, with output rates reaching multigram quantities per hour. This level of throughput is suitable to support preclinical medicinal chemistry programs in late lead optimization, where tens of grams to hundreds of grams of final product is needed. Adjusting reaction times and concentrations was critical in achieving this robust output. This example demonstrates how visible photochemistry and use of solid metal reagent can be used, and how the progress of the reaction can be followed by in-line NMR monitoring.

INTRODUCTION

Using light to accelerate a chemical reaction is one of the most promising opportunities to access new chemical transformations in a more effective and sustainable way.¹ However, for larger scale reactions, the logarithmic decrease in light transmission versus pathlength of the liquid medium, defined by the Lambert-Beer Law, limits photochemical transformations.² Therefore, in large batch reaction vessels, the reaction mixture is inefficiently irradiated and low reaction rates may be obtained. These limitations can be avoided by changing from traditional batch processes to continuous flow approaches. The large surface to volume ratio ensures efficient irradiation of the entire reaction mixture. This results in significantly intensified protocols and allows scaling up of these novel chemistries.³

However, developing photochemistry, especially at pilot/industrial scale where significant productivity is required, continues to be a challenge.⁴ In general, photochemical processes are not used in industry because thermal driven batch protocols are considered to be superior in terms of affordability and convenience.⁵ In addition, solid reagents cannot be utilized due to their likelihood to cause reactor clogging.^{5c}

Recently, we published a new visible light induced photosensitizer free nickel catalyzed Negishi reaction for C(sp³)-C(sp²) cross coupling. This new protocol presents a broader scope than traditional Negishi reaction and dual catalytic processes in terms of halogenated derivatives that can be used.⁶ In view of the medicinal chemists' need nowadays for new methodologies to enrich drug candidates with (sp³) motifs,⁷ we consider it a valuable reaction and therefore we aimed to test its scalability in pilot scale photoreactor.

RESULTS AND DISCUSSION

To start with, we selected compound **3** (Table 1), an example that was already scaled up with our Vapourtec reactor⁸ using a 10 mL coil of fluorinated ethylene propylene (FEP). This reactor provided a throughput of 800 mg/h, very convenient for Drug Discovery purposes.⁶ However, due to size limitations of the reactor, the higher productivities necessary for the preparation of clinical candidates for preclinical biological studies cannot be reached.⁹ Therefore, an appropriate pilot scale designed reactor was selected to increase productivity. In collaboration with CORNING SAS, Corning G1 photoreactor was chosen to perform the experiments.¹⁰

The photoinduced Negishi cross-coupling is a two-step reaction that requires the formation of the organozinc reagent in flow followed by coupling with the aryl halide. The first step of the reaction, formation of organozinc reagent, is key for the overall outcome of the reaction and involves the use of solid zinc. We sought a method to capture organozinc formation in real time, in order to optimally minimize reaction times.

NMR spectroscopy is a great technique for monitoring organic reactions due to its high degree of functional group specificity.11 Despite being one of the most powerful analytical techniques, the use of the NMR integrated into processes12 has been scarcely reported and mainly used in by-pass configurations, flow cells in high field NMR machines or micro coils for microfluidic applications.¹³ Nowadays, apart from our previous work⁶, NMR spectra for organozinc reagents are scarcely presented in literature. This is due to their instability in open air. However, with the use of NMR-inline monitoring, we expected that we could directly monitor the conversion of the starting material in organozinc reagent before flowing into the photoreactor. Effectually, we observed that the singlet of the benzylic CH2 of trifluoromethoxy benzyl bromide 1 has a distinct upfield shift (or a distinct right shift) when we form the organozinc reagent (Figure 1).

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The protons corresponding this signal are shielded due to the higher electron density at the carbon bonded the metal. The same effect is observed even in ¹⁹F NMR, but the difference between 2 and 4 in ppm is lower (-57,04 and -57.27 ppm) (see Figure S1 supporting information). Thus, we selected ¹H NMR analysis to monitor the reaction. We calculated the concentration of the outcoming organozinc solution by integrating the aromatic hydrogens with respect to solvent tetrahydrofuran (THF) hydrogens. Our flow NMR cell was made from PTFE tube connected with Teflon connectors at both ends. In this way we could support the 4 bars of pressure inside the NMR.

Figure 1. NMR monitoring for the formation of 2.



In the initial setup, the zinc column was fed from gear pump 1 controlled from MFC1 (Mass-flow controller). At the exit of the zinc column, a Magritek benchtop NMR was connected for in-line monitoring of the organozinc formation. The NMR output line was fed directly into the photo reactor. A second gear pump controlled from MFC2 fed Methyl 4-bromobenzo-ate 3 and catalyst into the photoreactor. Moreover, by monitoring the energy the pump uses under a stable flow rate, we could observe abrupt pressure drops, which can be caused by fouling that could lead to clogging. To assure a stable flow rate the entire system was used under a pressure of 3.5-4 bars using a back-pressure regulator (BPR) at the exit of the photoreactor (Scheme 1).

Scheme 1. Schematic overview of the initial flow set-up



This set up was designed for our preliminary experiments, with the aim of adjusting the components for reaction optimization. Our previously reported conditions⁶ provided full conversion to compound **4** (Table 1, entry 1). When the instrument was run at atmospheric pressure, several bubbles were observed in the line, probably due to the partial evaporation of THF (boiling point 68 °C). This likely contributed to the lower conversion of 79% (Table 1, entry 2). Decreasing the temperature to 40 °C was not beneficial, as conversion was

reduced to 90% (Table 1, entry 3). Maintaining both the temperature at 60 °C and the pressurized system while reducing the residence time to 15 minutes provided the best combination of yield and throughput (Table 1, entry 5).

F3C0 1	Br −Zn ← F ₃ CO MeOOC 3	Zn-Br 2 Br 2 mol% + Ni catalyst	F ₅ CO 4
Entry	t _R (min)	T (°C)	Conversion (%)
1	20	60	100

5 15 60	100
4 12 60	70
3 20 40	90
2 20 ^a 60	79
1 20 60	100

^aNo pressure in the system. **Reaction conditions:** Methyl 4bromobenzoate (1 eq., 15 mmol); 4-(trifluoromethoxy)benzyl bromide (2 eq., 30 mmol); Nickel catalyst (0.02 eq., 0.3 mmol); dtbbpy (0.03 eq., 0.45 mmol). t_R (Residence time)

With the optimized conditions, the reaction was run for 6.5 h. Conversion was analyzed by GCMS sampling every 30 minutes (Figure 2). In-line NMR analysis showed a stable concentration of organozinc solution over time with slight variation between 4 to 5% during the run (see Figure S3 supporting information). There were no traces of benzyl bromide in the NMR spectra.

According to the results obtained in Table 1, entry 2, where the reaction was run in the absence of back pressure regulator, the presence of bubbles had a detrimental effect on the reaction. We decided to introduce some nitrogen bubbles in the reaction by moving the inlet frit of compound 3 (limiting reagent) out of the solution. The conversion of the corresponding fraction was reduced to 93%. Beyond that fraction, the overall conversion remained 98% for the rest of the process and the final isolated yield was 93%. 36.6 g of product were obtained after purification, increasing seven times the productivity, from o.8 g/h to 5.6 g/h (Table 2).

Table 2. Comparison of productivity Experiment 1

	CO CO CO CO CO CO CO CO CO CO	
	Vapourtec	Corning G1
Yield	93%	93%
Time	20 min	15 min
Reactor size	10 mL	40 mL
Throughput	0.8 g/h	5.6 g/h

The mass flow controllers were used not only to control the gear pumps but also to directly monitor the flow rates, thereby giving indirect information about what is happening in both reactors, Zn column reactor and the photoreactor. After the run we observed that while in the catalyst feed (MFC2) the report showed a stable and linear graph in time, the benzyl bromide feed presented various instabilities (Figure 3 and Figure S4 supporting information). The monitoring graph showed a linear line parallel to the (X) axis. A fouling is at least at the

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beginning also linear. It is in the course of time that fluctuations became more frequent, however only in the benzyl bromide feed (MFC1). This suggested us that these instabilities could be originated by zinc consumption over time. Nevertheless, productivity was not affected. The mass flow controller gave a very sensitive measurement of the flow rates in time; one every 1/10 of a second. Thus, even though we had small spikes every tenth of a second the effect produced in conversion is insignificant. This observation showed us that the system needed further optimization.

Figure 2. Monitoring of the conversion of starting material in product



Figure 3. Pump monitoring showing fluctuations over time.



To avoid the potential back flow into the zinc column caused by zinc consumption, a modified set up able to keep the zinc column under higher pressure than the photoreactor was put in place with several additions to the system. A needle valve was placed just after the NMR in order to maintain the first part of the reaction under 4 bars of pressure. This was monitored with a pressure sensor. To observe the exact flow rate entering the photoreactor after the zinc column, a mass flow meter (MFM) was added. In order to monitor the lower pressure in the photoreactor, a new pressure sensor was added at its entrance which was controlled from the BPR (Back Pressure Regulator) at the exit of the photoreactor (Scheme 2). Taking advantage of the fact that Mini CORI-FLOW[™] MFC/MFM (Mass Flow Meter) can also measure the density in-line, the density of the solution was measured before and after the zinc column. As expected, the density of the organozinc solution was higher than the starting material

solution. In this way density can be used as an additional parameter of control when NMR monitoring does not provide suitable information about this first step of the reaction.

To test this new set up, the coupling between benzyl zinc bromide **5** and 2-amino-5-iodopyrimidine **7** was used as a model. The free amino group in this example makes it an especially useful product, suitable for further derivatization.^{7a}

As in the previous example, the original conditions provided full conversion (Table 3, entry 1). Reducing the residence time to 15 minutes also provided full conversion (entry 2). Shortening the reaction times further was insufficient for full conversion of starting material (entry 3). Increasing the concentration of **5** to 1 M had the same result as using 0.5 M, but due to solubility issues of **7** pure DMF was used to dissolve the catalyst feed reagents (entry 6). Three equivalents of benzyl bromide were necessary to obtain full conversion (entry 5). In the absence of light, only 34% of isolated product was obtained (entry 7).

The final scale up reaction was performed using the conditions of entry 6 in Table 2 as it could be run at higher concentration increasing significantly the productivity of the reactor to 3.4 g/h, more than 10 times larger than our initial report using a reactor only 4 times larger (Table 4).⁶



Scheme 2. Schematic overview of the optimized flow set-up

Table 3. Optimization of the conditions Experiment 2



E.	$t_R(min)$	T (°C)	Eq. 5	Light	[7](M)	Con. (%)
1	20	60	3	On	0.375	100
2	15	60	3	On	0.375	100
3	12	60	3	On	0.375	>95
4	15	60	2	On	0.375	>95
5	15	60	2.5	On	0.375	>95
6	15	60	3	On	0.750	100(94) ^a
7	15	60	3	Off	0.750	34 ^a

^aIsolated yield, DMF used as solvent. **Reaction conditions:** 2amino-5-iodopyrimidine (1 eq., 15 mmol); benzyl bromide (3 eq., 45 mmol); Nickel catalyst (0.02 eq., 0.3 mmol); dtbbpy (0.03 eq., 0.45 mmol).

Table 4. Productivity of the rea

Vapourtec Corning G1		Vapourtec	Corning G1
Yield 93% 94%	Yield	93%	94%
Time 20 min 15 min	Time	20 min	15 min
Reactor size 10 mL 40 mL	Reactor size	Reactor size 10 mL	
Conc. RM 0.375 M 0.750 M	Conc. RM	0.375 M	0.750 M
Throughput 0.3 g/h 3.4 g/h	Throughput	0.3 g/h	3.4 g/h

In order to avoid chromatographic purification on this Discovery Process scale reaction, it was decided to perform a recrystallization in water after an aqueous work up.¹⁴⁻¹⁶ To remove zinc salts, extraction with aqueous ammonia solution (pH=9) was required. Then the organic phase was separated and concentrated to perform the recrystallization in water affording the desired product as a white crystalline solid (see Figure S6 supporting information).

In this second experiment, NMR monitoring provided clear information about the formation of the benzyl zinc bromide under more concentrated conditions. The singlet corresponding to the benzylic protons was shifted downfield when benzyl zinc bromide 6 was formed. The integration of aromatic protons provided information about the concentration of the outcoming organozinc reagent, in this case varying between 8.5%-9.8% (see Figure S7 supporting information). The concentration remained stable in time without important variations. The density sensors showed similar results as the NMR monitoring. There was a clear difference between the density of the benzyl bromide solution (0.959 g/mL) and the benzyl zinc bromide solution (1.022 g/mL) and this difference remained stable over the run. Under the new reaction conditions, the report showed stable flow rates in both feeds. Moreover, the system seems to get more stable over time. Even though some nitrogen bubbles were intentionally introduced into both feeds at different points in time, minor alterations were observed (see Figure S8 supporting information).

CONCLUSION

In conclusion, visible light induced nickel catalyzed Negishi reaction can be scaled up in guantities that would support the preparation of potential drugs for preclinical experiments. This protocol provides an example of how the use solid reagents and photochemistry can be scaled up using flow chemistry. NMR monitoring provided an excellent readout for the organozinc formation. In-line density monitoring has been identified as an alternative when NMR is not suitable. Herein we proved this two-step reaction works in gram scale with productivities that ranges from 3.4 to 5.6 g/h (ideally from 82 to 270 g/day). The nickel loading was kept at 2 mol%. The optimized system and the controlled parameters give autonomy to the chemist and reproduce situations that can be found in a production plant. Future work for a completely automated system can bring the process to direct industrial production and will be matter of future publications.

EXPERIMENTAL SECTION

General information

The reactions were conducted in a standard Corning © Advanced-Flow[™] G₁ Photo reactor equipped with 5 glass fluidic modules connected in series (8.2 ml volume each). Each module was illuminated from both sides by a multiple wavelength LED (Light Emitting Diode) panel (>100mW/cm2). The chosen wavelength was 405 nm and the intensity was adjusted to 100%. The temperature of the fluidic modules was regulated by a LAUDA® Proline RP45 thermostat using ethylene glycol as thermofluidic (transparent at 405 nm), the LED panels were cooled by a second LAUDA® Proline RP45 thermostat. The liquids were pumped with micro gear pumps (HNP Mikrosysteme MZR[®]- 7255), which were controlled directly by Mini CORIFLOWTM M14 mass flow controllers using the software flowplot for monitoring (Bronkhorst High-Tech B.V). The pressure was regulated with a back-pressure regulator from Zaiput flow technologies. In-line NMR analysis was carried out with a 43 MHz SpinsolveTM NMR spectometer from Magritek, the flow cell was a PTFE tube (OD 5 mm, ID 4mm). For the preparation of the organozinc reagent SolventPlusTM Omnifit column (bore: 35 mm, length: 150 mm, AF (1× adjustable & 1× fixed endpiece); Omnifit, cat. no. 006SCC-35-15-AF. The needed parts are the glass tube, two 30 μ m \times 35 mm polytetrafluoroethylene (PTFE) frits, one fixed end piece as a bed support and one adjustable end piece (plunger) to adjust the bed height.

(https://www.dibaind.com/wpcontent/uploads/2015/01/2015 01_1_OFLW_CAT.pdf).

GC measurements were performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and auto sampler, J&W HP-5MS column (20 m x 0.18 mm, 0.18 μ m) from Agilent Technologies coupled to a 5973N FID Flame Ionization Detector. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification.

Activation of the Zn column:

A solution 1.0 M trimethylchlorosilane (TMSCl) and 0.24 M 1bromo-2-chloroethane was prepared under nitrogen (N_2) atmosphere in a dried flask by dissolving 6.25 mL of TMSCl and 1.25 mL of 1-bromo-2-chloroethane in 50 mL of dried tetrahydrofuran (THF). 25 mL of this solution were passed through the 35 mm internal diameter Omnifit column containing Zn (150 g) using the MFC1 at room temperature and 4 mL /min flow rate.

Methyl 4-[[4-(trifluoromethoxy)phenyl]methyl]benzoate (4). A solution of 4-(trifluoromethoxy) benzyl bromide 1 (254 mmol; 2 eq.+50 mmol) in 608 mL of THF was pumped through a column containing activated zinc at room temperature at 1.35 mL /min using the MFC1. The outcoming solution of the organozinc compound was analyzed by in line NMR monitoring and once the organozinc reagent started to flow, inserted into the photoreactor. The outcoming solution was combined with a solution of methyl 4-bromobenzoate 3 (1 eq. 127 mmol), NiCl₂ glyme (0.02 eq., 2.54 mmol), dtbbpy (0.03 eq., 3.81 mmol) in 407 mL of THF and 101 mL of DMF in Corning G1 Photoreactor at 1.35 mL /min each line (t_{R=} 15 min; coil volume= 40 mL) at 60 °C irradiating with 405nm blue LEDs. The

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system was maintained under 3.5-4 bars of pressure with a back-pressure regulator. The out coming of the reactor was collected in fractions of 80 mL each. The collected fractions were concentrated by evaporating the THF and then diluted with ethyl acetate and added to a separatory funnel containing 1 L of ammonium chloride saturated aqueous solution. The organic layer was separated, dried with MgSO₄, filtered and then the solvents evaporated. Purification by flash chromatography using Heptane: Ethyl acetate from 100:0 to 75:25 afforded 36.6 g of 4 as a transparent liquid, 93% isolated yield. ¹H NMR $(CDCl_3, 500 \text{ MHz}): \delta = 7.97 \text{ (d, J} = 8.4 \text{ Hz}, 2\text{H}), 7.22-7.27 \text{ (m, J)}$ 10 2H), 7.09-7.21 (m, 4H), 4.03 (s, 2H), 3.90 ppm (s, 3H). ¹³C NMR 11 $(CDCl_3, 126 \text{ MHz}): \delta = 166.9, 147.8, 145.7, 138.9, 130.2, 130.0,$ 12 128.9, 128.4, 121.5, 121.0, 52.1, 41.2 ppm. ¹⁹F NMR (CDCl₃, 471 13 MHz): $\delta = -57.93$ ppm (br s, 1F). HRMS (ESI-TOF) m/z: Calcd [M+H]+ for C₁₆H_{14F3}O₃ 311.0895; Found 311.0897. 14 15

5-Benzylpyrimidin-2-amine (8). A solution of benzyl bromide 5 16 (351 mmol; 3 eq.+ 100 mmol) in 451 mL of THF was pumped 17 through a column containing activated zinc at room temper-18 ature at 1.35 mL /min using the MFC1. The outcoming solution 19 of the organozinc compound was analysed by NMR in line 20 monitoring and once the organozinc reagent started to flow, 21 inserted into the photoreactor. The outcoming solution was 22 combined with a solution (B) of 2-amino-5-iodopyrimidine 7 23 (1 eq. 117 mmol), NiCl₂ glyme (0.02 eq., 2.34 mmol), dtbbpy 24 (0.03 eq., 3.51 mmol) in 351 mL of DMF in Corning G1 Photoreactor at 1.35 mL/min each line (t_{R} = 15 min; coil volume= 40 25 mL) at 60 °C irradiating with 405 nm blue LEDs. The zinc re-26 actor was maintained under 4 bars of pressure controlled from 27 the needle valve and the photoreactor was maintained at 3.5 28 bars of pressure from the BPR. The out coming of the reactor 29 was collected in fractions of 80 mL each. The collected frac-30 tions were concentrated by evaporating the THF and then di-31 luted with dichloromethane and added to a separatory funnel 32 containing 1 L of aqueous ammonium solution (pH= 9). The 33 organic layer was separated, dried with MgSO4, filtered and 34 then the solvents evaporated. The rests were dissolved in min-35 imum quantity of dichloromethane and the product was crystallized in water as 20.4 g of **8** a white crystalline solid, 94%36 isolated yield. ¹H NMR (CDCl₃, 400 MHz): δ = 8.15 (s, 2H), 7.27-37 7.36 (m, 2H), 7.22 (s, 1H), 7.17 (s, 2H), 4.96 (br s, 2H), 3.80 ppm 38 (s, 2H). ¹³C NMR (CDCl₃, 101 MHz): δ = 158.4, 139.8, 128.7, 128.6, 39 126.5, 123.9, 103.6, 35.7 ppm. HRMS (ESI-TOF) m/z: [M+H]+ 40 Calcld for C₁₁H₁₂N₃: 186.1031; Found 186.1029. Melting point: 41 121.86 °C. 42

ASSOCIATED CONTENT

Supporting Information. 1H, 19F and 13C NMR spectra, control graphs and reaction details are available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Beeler, A. B.; Introduction: Photochemistry in organic synthesis Chem. Rev. 2016, 116, 9629-9630; (b) Turro, N.; Schuster, G.; Photochemical reactions as a tool in organic syntheses. Science 1975, 187, 302-312.

Parnis, J. Mark; Oldham, Keith B.; Beyond the (2) Lambeert- Beer Law. J. Photochem. Photobio. 2013, 267, 6-10.

(a) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, (3) P. H. The Hitchhiker's Guide to Flow Chemistry Chem. Rev. 2017, 117, 11796-11893; (b) Gilmore, K.; Seeberger, P. H. Continuous Flow Photochemistry. Chem. Rec. 2014, 14, 410-418.

(a) Politano, F.; Oksdah-Mansilla, G.; Light on the hori-(4)zon: Current research and future perspectives of flow-photochemistry Org. Proces Res. Dev. 2018, 22, 1045-1062; (b) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. Chem. Rev. 2016, 117, 10276-10341; (c) Su, Y.; Kuijpers, K.; Hessel, V.; Noël, T. A convenient numbering-up strategy for the scale-up of gas-liquid photoredox catalysis in flow. React. Chem. Eng. 2016, 1, 73-81; (d) Zhao, F.; Cambié, D.; Janse, J.; Wieland, E. W.; Kuijpers, K. P. L.; Hessel, V.; Debije, M. G., Noël, T. Scale-up of a Luminescent Solar Concentrator-Based Photomicroreactor via Numbering-up. ACS Sustainable Chem. Eng. 2018, 6, 422-429; (e) Elliot, L. D.; Berry, M.; Harji, B.; Klauber, D.; Leonard, J.; Booker-Milburn, K. Org. Process Res. Dev. 2016, 20, 1806-1811.

(5) (a) Malet-Sanz, L.; Susanne, F. Continuous Flow Synthesis. a Pharma Perspective. J. Med. Chem. 2012, 55, 4062-4098; (b) Rasheed, M.; Wirth, T. Intelligent Microflow: Development of Self-Optimizing Reaction Systems. Angew. Chem. Int. Ed. 2011, 50, 357-358; (c) Wegner, J.; Ceylan, S.; Kirschning, A. Ten Key Issues in Modern Flow Chemistry. Chem. Commun. 2011, 47, 4583.

Abdiaj, I.; Fontana, A.; Gomez, M. V.; De la Hoz, A.; Alcazar, J. Visible-Light-Induced Nickel-Catalyzed Negishi Cross-Couplings by Exogenous-Photosensitizer-Free Photocatalysis. Angew. Chem. Int. Ed. Engl. 2018, 57, 8473-8477.

(a) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. (7)K. Pharmacological Significance of Synthetic Heterocycles Scaffold: A Review. Adv. Biol. Res. (Rennes). 2011, 5, 120-144; (b) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. What Do Medicinal Chemists Actually Make? A 50-Year Retrospective. J. Med. Chem. 2011, 54, 6405-6416; (c) Tsukamoto, T. Tough Times for Medicinal Chemists: Are We to Blame? ACS Med. Chem. Lett., 2013, 4, 369-370.

For Further Information about Instrument Used Visit (8) the Web: www.Vapourtec.Com>.

Alcázar, J. Sustainable Flow Chemistry in Drug Discov- (\mathbf{q}) ery in Sustainable Flow Chemistry. Vaccaro, L., Ed.; Wiley-VCH Verlag GmbH & Co.; Weinheim, 2017, pg.: 135-164.

Elgue, S.; Aillet, T.; Loubiere, K.; Conté, A.; Dechy-Cab-(10)aret, O.; Prat, L.; Horn, C. R.; Lobet, O.; Vallon, S. Flow Photochemistry: A Meso-Scale Reactor for Industrial Applications. Chim. Oggi 2015, 33, 58-61.

(a) Nordon, A.; McGill, C. A.; Littlejohn, D. Process (11) NMRSpectrometry. Analyst 2001, 126, 260-272; (b) Sans, V.; Porwol, L.; Dragone, V.; Cronin, L. A Self Optimizing Synthetic Organic Reactor System Using Real-Time in-Line NMR Spectroscopy. Chem. Sci. 2015, 6, 1258-1264; (c) Jones, C. J.; Larive, C. K. Could Smaller Really Be Better? Current and Future Trends in High-Resolution Microcoil NMR Spectroscopy. *Anal. Bioanal. Chem.* **2012**, *4*02, 61–68; (d) Goldbach, M.; Danieli, E.; Duchateau, L. L. A. Preparation of Grignard reagents from magnesium metal under continuous flow conditions and on-line monitoring by NMR spectroscopy. *Tetrahedron Lett.* **2016**, 57, 122-125.

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60

(12) Giraudeau, P.; Felpin, F.-X. Flow Reactors Integrated within-Line Monitoring using Benchtop NMR Spectroscopy. *React. Chem. Eng.* **2018**, *3*, 399-413.

(a) Bart, J.; Kolkman, A. J.; Vries, A. J. O. De; Koch, K.; (13) Nieuwland, P. J.; Janssen, H. J. W. G.; Van Bentum, J. P. J. M.; Ampt, K. A. M.; Rutjes, F. P. J. T.; Wijmenga, S. S.; et al. A Microfluidic High-Resolution NMR Flow Probe. J. Am. Chem. Soc. 2009, 131, 5014-5015; (b) Fratila, R. M.; Gomez, M. V.; Sýkora, S.; Velders, A. H. Multinuclear Nanoliter One-Dimensional and Two-Dimensional NMR Spectroscopy with a Single Non-Resonant Microcoil. Nat. Commun. 2014, 5, DOI: 10.1038/ncomms4025. (c) Nordon, A.; Diez-Lazaro, A.; Wong, C. W. L.; McGill, C. A.; Littlejohn, D.; Weerasinghe, M.; Mamman, D. A.; Hitchman, M. L.; Wilkie, J. Consideration of Some Sampling Problems in the On-Line Analysis of Batch Processes by Low-Field NMR Spectrometry. Analyst 2008, 133, 339-347; (d) Buser, J. Y.; McFarland, A. D. Reaction Characterization by Flow NMR: Quantitation and Monitoring of Dissolved H 2 via Flow NMR at High Pressure. Chem. Commun. 2014, 50, 4234-4237; (e) Gomez, M. V.; Verputten, H. H. J.; Díaz-Ortíz, A.; Moreno, A.; de la Hoz, A.; Velders, A. H. On-Line Monitoring of a Microwave-Assisted Chemical Reaction by Nanolitre NMR-Spectroscopy. Chem. Commun. 2010, 46, 4514; (f) Gökay, O.; Albert, K. From Single to Multiple Microcoil Flow Probe NMR and Related Capillary Techniques: A Review. Analytical and Bioanalytical Chemistry 2012, 402, 647-669; (g) Dalitz, F.; Cudaj, M.; Maiwald, M.; Guthausen, G. Process and Reaction Monitoring by Low-Field NMR Spectroscopy. Prog. Nucl. Magn. Reson.

Spectrosc. **2012**, *60*, 52–70; (h) Vargas, M. A.; Cudaj, M.; Hailu, K.; Sachsenheimer, K.; Guthausen, G. Online Low-Field 1H NMR Spectroscopy: Monitoring of Emulsion Polymerization of Butyl Acrylate. *Macromolecules* **2010**, *43*, 5561–5568; (i) Maiwald, M.; Fischer, H. H.; Kim, Y. K.; Albert, K.; Hasse, H. Quantitative High-Resolution on-Line NMR Spectroscopy in Reaction and Process Monitoring. *J. Magn. Reson.* **2004**, *166*, 135–146.

(14) (a) Schoenmakers, P. Chromatography in Industry. Annu. Rev. Anal. Chem. 2009, 2, 333–357; (b) Brown, P. R.; Grushk, E. Advances in Chromatography, (2nd ed.); Miller, J. M., Ed.; 1994, Wiley-VCH: New York.; (c) Heftmann, E. Chromatography, (3rd ed).; 1974, New York.; (d) Braithwaite, A.; Smith, F. J. Chromatographic Methods, (4th ed.); 1985, London; (e) Mandík, L. Applications of Gel Permeation Chromatography in the Paint Industry. Prog. Org. Coatings 1977, 5, 131–198.

(15) (a) Walters, I. A. S. A Convenient One-Pot Negishi Coupling of Amino-Heteroaryl Chlorides and Alkyl Bromides. *Tetrahedron Lett.* **2006**, *47*, 341–344; (b) Otzen, T.; Wempe, E. G.; Kunz, B.; Bartels, R.; Lehwark-Yvetot, G.; Hänsel, W.; Schaper, K. J.; Seydel, J. K. Folate-Synthesizing Enzyme System as Target for Development of Inhibitors and Inhibitor Combinations against Candida Albicans - Synthesis and Biological Activity of New 2,4-Diaminopyrimidines and 4'-Substituted 4-Aminodiphenyl Sulfones. *J. Med. Chem.* **2004**, *47*, 240–253.

(16) (a) Joachim Ulrich. *The Crystallization Technology Handbook*, 2nd ed.; A. Marsmann, Ed.; American Chemical Society: **2001**, New York.; (b) *Crystallization: Basic Concepts and Industrial Applications*, 1st ed.; Beckmann, W., Ed.; **2013**, Wiley-VCH.

