

Automated, Capsule-Based Suzuki–Miyaura Cross Couplings

Guillaume Coin, Tuo Jiang, Samuele Bordi, Paula L. Nichols, Jeffrey W. Bode,* and Benedikt M. Wanner*

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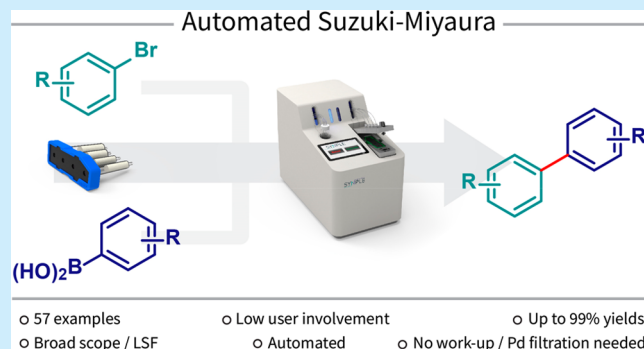
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ABSTRACT: The development of an automated process for Suzuki–Miyaura cross couplings is described, in which the complete reaction, workup, and product isolation are effected automatically with no user involvement, aside from loading of the starting materials and reaction capsule. This practical and simple method was successfully demonstrated to provide the desired biaryl products using a range of aryl bromides and boronic acids and is also effective for the late-stage functionalization of aryl halides in bioactive molecules.



Over the past few decades, organic synthesis has undergone significant development, as evidenced by the emergence of new synthetic technologies and methodologies. In parallel, the basic techniques used to effect chemical reactions are shifting from traditional flask-based approaches to safer, standardized systems. By exploiting advances in synthesis hardware and computational power, these new synthetic technologies offer the potential to minimize time-consuming and repetitive synthesis tasks. Despite currently being limited to a small number of robust chemical reactions, chemical synthesis automation offers opportunities for researchers to focus their efforts on value adding tasks, controlling costs, improving safety, and accelerating chemistry-based research.^{1–7}

Recently, we described the use of a simple console with preinstalled highly optimized reaction specific automated sequences, which performs automated organic reactions and uses prepacked reaction capsules containing all of the reagents and purification materials needed for the transformation, workup, and product isolation (Figure S1).^{8,9} In line with our goal of expanding the capabilities of this highly robust, enabling technology, we now report a fully automated, capsule-based approach to Suzuki–Miyaura cross couplings (Figure 1). This millimole scale process is easy to use and effective for a broad



Figure 1. Automated Suzuki–Miyaura cross coupling.

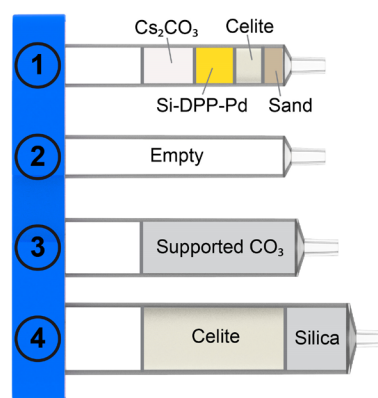


Figure 2. Content of the capsule for the automated Suzuki–Miyaura cross coupling.

scope of substrates and requires no filtration of the palladium catalyst and no tedious workup.

The palladium-catalyzed Suzuki–Miyaura cross coupling has been extensively studied and used in a myriad of applications, such as drug, agrochemical, polymer, and material synthesis.^{10–15} By enabling the selective formation of new carbon–carbon bonds, it represents one of the most powerful organic synthesis tools, due to its broad substrate scope and the

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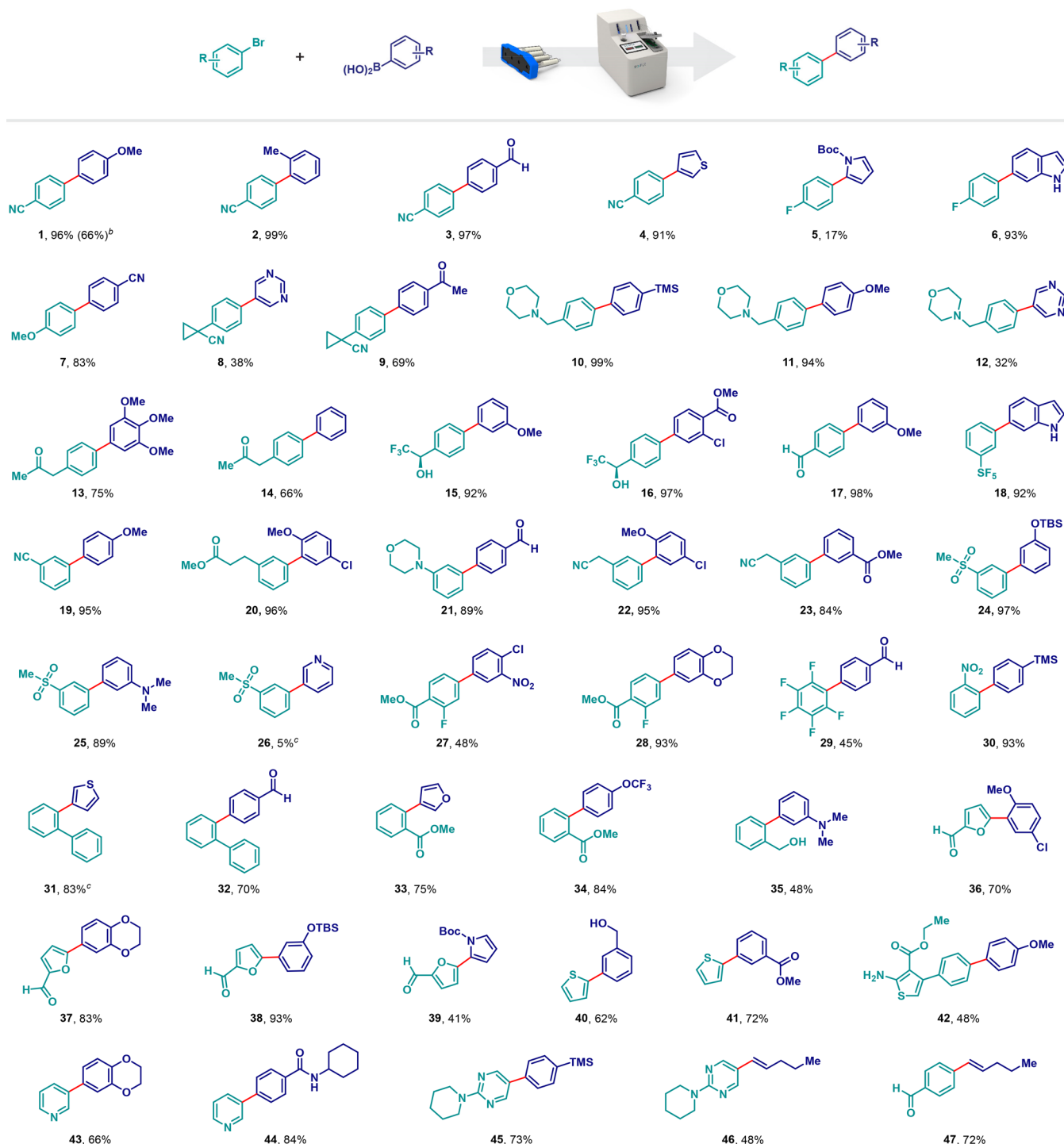


Figure 3. Scope of the automated Suzuki–Miyaura cross coupling. Reaction conditions: 3.5 h, 60 °C, 0.2 M, 0.8 mmol scale, vial content of aryl bromide (0.8 mmol), boronic acid (0.96 mmol), DME (1.6 mL), EtOH (1.6 mL), and H₂O (0.8 mL), capsule content of Si-DPP-Pd (5 mol %, 0.3 mmol/g), Cs₂CO₃ (1.2 mmol), supported CO₃ (1.9 mmol, 0.5 mmol/g), silica (1 g), Celite (2 g). ^bFrom the aryl chloride. ^cNMR yield using 1,3,5-trimethoxybenzene as an internal standard.

wide availability of safe-to-handle organoboronic acids and organohalides.^{16–21}

Given the synthetic power and widespread applicability of Suzuki–Miyaura cross couplings, particularly in discovery research, a user-friendly, automated implementation of this reaction could be of significant value. To the best of our knowledge, only a few examples of automated devices that can perform Suzuki–Miyaura cross couplings have been re-

ported.^{22–26} In most cases, however, the devices either operate on a nanomole scale or are used for reaction optimization or they have been demonstrated with only specific molecules. While powerful for their intended applications, none of these technologies were specifically designed to give easy access to novel molecules on a millimole scale.

The first step in our development process involved identification of reaction conditions compatible with the

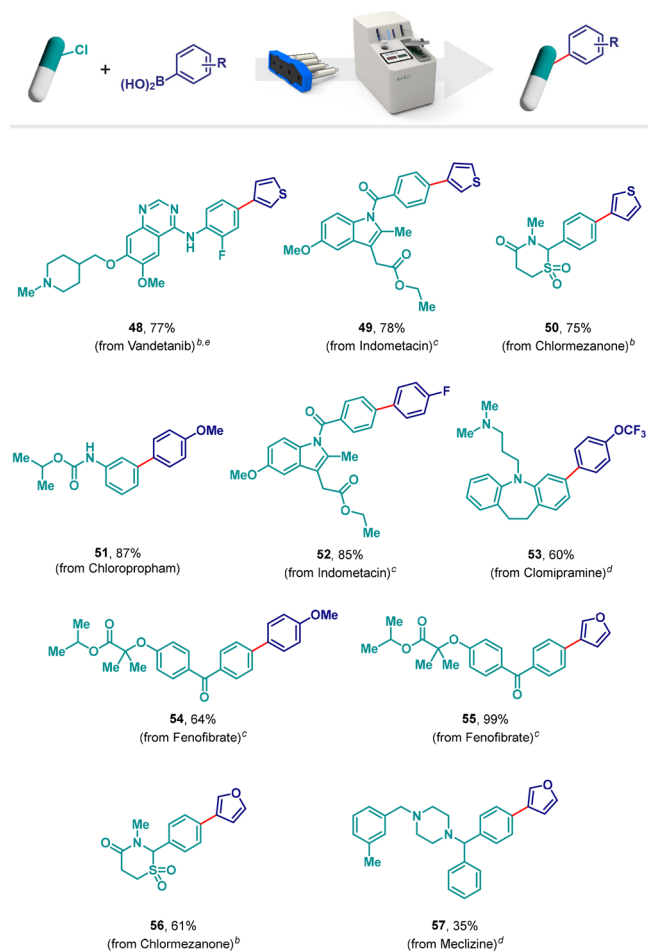


Figure 4. Rapid late-stage functionalization of bioactive molecules. Reaction conditions: 12 h, 60 °C, 0.2 M, 0.8 mmol scale, vial content of aryl chloride (0.8 mmol), boronic acid (0.96 mmol), DME (1.6 mL), EtOH (1.6 mL), and H₂O (0.8 mL), and capsule content of Si-DPP-Pd (5 mol %, 0.3 mmol/g), Cs₂CO₃ (1.2 mmol), supported CO₃ (1.9 mmol, 0.5 mmol/g), silica (1 g), Celite (2 g).^bDME replaced by DMF. ^cDME replaced by THF. ^dFrom the HCl salt aryl chloride; 1.5 equiv of DIPEA was added for the *in situ* freebasing. ^eFrom the aryl bromide.

established synthesis console. Initially, the utility of two common homogeneous catalysts, Pd(PPh₃)₄ or Pd₂(dba)₃, was investigated. Regrettably, even under mild conditions (<70 °C), we observed the formation of palladium black, which could potentially leach into the internal fluidic system. Such contamination would require a corrosive wash cycle to remove the palladium black, which, although tolerable, was not ideal. As an alternative to homogeneous catalysts, we explored the use of commercially available heterogeneous palladium catalysts. Disappointingly, the polystyrene-bound palladium catalyst (PS-PPh₃-Pd), equivalent to the homogeneous catalyst tetrakis(triphenylphosphine)palladium [Pd(PPh₃)₄], had limited application due to solvent compatibility restrictions.

Fortunately, an alternative supported palladium catalyst, Si-DPP-Pd (silica-supported diphenyl phosphine palladium), showed promise, offering good reactivity and a broad range of compatible solvents (DME, THF, DMF, EtOH, and H₂O).^{27–29} To minimize leaching of palladium black from the compartment, thereby preventing contamination of the console, two layers of sand and Celite were incorporated into the compartment below the catalyst (Figure 2 and Figure S2).

In addition to the palladium catalyst and ligands, the base and reaction solvent also play key roles in the Suzuki–Miyaura reaction. A screen of the bases commonly used in Suzuki–Miyaura reactions revealed that Cs₂CO₃ was best suited for use in the console due to its higher solubility in polar organic solvents, compared to that of Na₂CO₃ or K₂CO₃. With respect to the reaction solvent, it has previously been shown that Si-DPP-Pd displays good activity with EtOH as the solvent.²⁷ However, upon development of a console process, reactivity is not the only consideration. The solvent system must also avoid precipitation of the starting materials, products, and reagents. As such, we identified a solvent system that offered both optimal reactivity and solubility: 2:2:1 DME/EtOH/H₂O, with DME supporting the solubilization of most aryl bromides and H₂O being beneficial for both the reaction itself and the solubilization of the boronic acid and base.

For a fully integrated and automated synthesis process, the workup and product isolation steps are also critical. Because the palladium catalyst was immobilized and prepacked in one of the capsule compartments, filtration of the reaction mixture to remove the catalyst was unnecessary. However, the water and the salts derived from the base and side products still needed to be removed. We employed a pad of silica, combined with a pad of Celite, as an alternative to the usual liquid–liquid extraction workup, as it could effectively trap both the water and water-soluble components. The excess boronic acid was efficiently trapped by circulating it through a capsule compartment containing a solid-supported tetraalkyl amine carbonate (supported CO₃) base. Unfortunately, unreactive aryl bromide or homocoupling side reaction products could not be removed from the crude reaction due to their similarity to the desired diaryl product. As such, these impurities needed to be removed by flash chromatography to obtain high-purity material (>95%).

With the compartment contents optimized for both the reaction and workup/product isolation stages, a complete workflow was established, which was translated into a script to drive the hardware for automatically performing Suzuki–Miyaura reactions (Figure S3). This script controls all three stages of the automated process: (i) reaction, (ii) removal of water and salts, and (iii) scavenging of excess boronic acid. Prior to initiation of this script, the starting aryl bromide and boronic acid are added to the reaction vial of the console, along with 1,2-dimethoxyethane, ethanol, and water in a 2:2:1 ratio. After complete dissolution of the starting materials, the script for the automated Suzuki–Miyaura sequence is loaded by scanning the Suzuki–Miyaura capsule, containing a preprogrammed RFID chip, using the scanner on the console. Upon starting, the full program of operations required for the reaction and product isolation is automatically initiated; no further user input is required.

To effect stage i of the automated sequence, the system circulates the solution of starting materials (1 mL/min) through compartment 1 of the capsule, which contains 1.5 equiv of Cs₂CO₃, 5 mol % Si-DPP-Pd, and two short layers of Celite and sand (Figure 2). For this step, the system also automatically heats both the capsule and the vial at 60 °C. Although formation of the Ar–Ar bond can be dependent of the substrate, circulation of the reaction mixture through compartment 1 for 3.5 h provided optimal conversion in most cases. Following this 3.5 h period, the capsule and the reaction media are cooled to room temperature. After compartment 1 is washed with EtOAc, stage ii of the process is initiated and the reaction solution is automatically loaded onto the Celite/silica in compartment 4,

allowing the removal of water and the salts generated during the reaction. Compartment 4 is further rinsed with EtOAc prior to initiation of the final stage of the automated process, stage iii. In this stage, the solution is circulated through compartment 3, containing a solid-supported carbonate, which scavenges any excess of boronic acid that might still be present in the crude reaction mixture. After compartment 3 is finally rinsed with EtOAc, the desired Ar–Ar product is delivered as a solution into the reaction vial, with a purity of >90% if the conversion of the aryl bromide is quantitative (see Figure S4 for a selection of crude NMR and LC-MS data).

Following optimization of the machine automation, we sought to demonstrate that the standardized method was robust and reproducible as with manual chemistry there are inevitably subtle variations in how different chemists perform the same procedure, which can sometimes affect the reaction outcome. Standardized automation offers the potential to overcome this variability and ensure that the same result is achieved regardless of where or by whom the process is carried out.^{30,31} Pleasingly, a study with two sets of substrates (**1** and **42**) demonstrated that this console-based Suzuki–Miyaura method was indeed robust and consistent. In both cases, the reactions were highly reproducible, with comparable yields obtained each time (Figure S5).

Using this console and standardized capsules for automated Suzuki–Miyaura cross couplings (Figure S4), the substrate scope was subsequently investigated (Figure 3). Aryl bromides with both electron-donating and electron-withdrawing functional groups at the *meta* or *para* positions (**1**–**26**) generally reacted well, with good to excellent yields (66–99%). The presence of steric hindrance at the *ortho* position of the aryl bromide ring, such as a phenyl group, slightly decreased the yields to 70–80% (**31** and **32**). Heteroaryl bromides, including furan, pyridine, and pyrimidine, showed a good aptitude for generating the desired biaryl compound (**36**–**45**). The limitations with respect to the aryl boronic acid substrates were also probed.

Aryl boronic acids bearing electron-donating groups resulted in the formation of the desired products in excellent yields (selected examples being **1**, **11**, and **15**), whereas electron-withdrawing groups led to a slight decrease in yield (selected examples being **8**, **26**, and **27**). Electron-rich heteroaryl boronic acids, such as thiophenes, furans, or indoles, gave product yields ranging from 75% to 93% (**4**, **6**, **18**, **31**, and **33**). In the case of more electron-poor heteroaryl boronic acids, such as pyridines or pyrimidines, the yields obtained (<40%) were less satisfactory (**5**, **8**, **12**, **26**, and **39**). Interestingly, allyl boronic acids generated the desired product in moderate to good yields, from 48% to 72% (**46** and **47**). This method also enabled the synthesis of drug intermediates, such as compound **15**, which is one of the building blocks for LX1031.³²

Overall, we found that a multitude of aryl bromides and boronic acids with different substitution patterns and functional groups were well tolerated, including alcohols (**15**, **16**, **35**, and **40**), aldehydes (**3**, **17**, **21**, **29**, **32**, and **36**–**39**), amides (**44**), sulfones (**24** and **25**), aryl fluorides (**5**, **6**, and **27**–**29**), esters (**16**, **20**, **23**, **27**, **28**, **33**, **34**, and **41**), ketones (**9**, **13**, and **14**), nitro aryls (**27** and **30**), silyl ethers (**24** and **38**), trimethylsilyls (**10**, **30**, and **45**), pentafluorosulfanyl (**18**), nitriles (**1**–**4**, **7**–**9**, **19**, **22**, and **23**), and basic heterocycles, such as morpholine or piperidine (**10**–**12**, **21**, and **45**).

The utility of this technology was further demonstrated with the late-stage functionalization of biologically active molecules

(Figure 4). The automated reaction and product isolation processes generally proceeded with moderate to excellent yields obtained (35–99%). In nearly all cases, the Suzuki–Miyaura cross couplings were effected using aryl chlorides instead of aryl bromides (except in the case of **48**) due to their greater presence in these drugs. In such cases, the reaction time was extended from 3.5 to 12 h. The reaction time could easily be edited using the reaction menu on the console. Notably, replacement of 1,2-dimethoxyethane with dimethylformamide or tetrahydrofuran as a cosolvent offered improved solubility for these substrates but did not affect the reactivity, with the desired products being generated in moderate to excellent yields. This demonstrates the versatility of this method and the ability of this system to cover a large substrate scope.

In summary, we have developed a capsule-based, standardized, automated, easy-to-use process for the Suzuki–Miyaura cross coupling of a wide range of aryl bromides (and aryl chlorides) and boronic acids, which could also be applied to the late-stage modification of highly functionalized bioactive molecules. In total, more than 50 different cross coupling products were prepared in good to excellent yields, demonstrating that the method is highly reproducible, tolerant of a large range of functional groups, and flexible in terms of cosolvent choice, thus offering the potential to further expand the scope. With this approach, tedious workups and removal of the palladium catalysts have been avoided by encapsulating the reagents inside the capsules, making the entire process more efficient in terms of time and cost than manual synthesis. Such an automated, user-friendly method will be extendable to other types of cross couplings or palladium-catalyzed transformations, which would enable researchers to employ this synthesis automation tool for an even greater proportion of their work.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c01057>.

Experimental procedures, synthesis and characterization of compounds, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Benedikt M. Wanner – Synple Chem AG, 8310 Kempththal, Switzerland; orcid.org/0000-0002-3524-1053; Email: wanner@synplechem.com

Jeffrey W. Bode – Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich, Switzerland; orcid.org/0000-0001-8394-8910; Email: bode@org.chem.ethz.ch

Authors

Guillaume Coin – Synple Chem AG, 8310 Kempththal, Switzerland; Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich, Switzerland; orcid.org/0000-0002-8703-585X

Tuo Jiang – Synple Chem AG, 8310 Kempththal, Switzerland

Samuele Bordini – Synple Chem AG, 8310 Kempththal, Switzerland

Paula L. Nichols – Synple Chem AG, 8310 Kempthal, Switzerland; Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, 8093 Zürich, Switzerland

Complete contact information is available at:
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Notes

The authors declare the following competing financial interest(s): B.M.W., P.L.N., and J.W.B. are listed as inventors of a patent (WO Patent WO2017121724A1, 2016) related to this technology and are co-founders of Synple Chem AG.

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