Key Differences between Flow Chemistry and Traditional Chemical Analysis

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Flow chemistry is a modern technique used for synthesis that utilizes pumps, tubing, and reactor coils rather than traditional round-bottomed flasks found in batch applications, allowing for faster reactivity, increased mass/heat transfer, increased safety, and more. This paper discusses these details, providing arguments for further adoption, practicalities, and potential disadvantages of flow chemistry. Chemical engineering concepts are covered with specific examples from the literature, that relate to reaction kinetics, plug-flow modelling, reaction analysis (online and inline), and more. As the modern laboratory attempts to diversify its skillsets and adopt optimal workflows, flow chemistry is a vital consideration that this paper highlights. These analyses will hopefully inspire today's engineers and scientists to adopt the flow chemistry technique on a larger scale, exhausting significantly less resources and thus opening the door to a future of economic viability and sustainability in science.

Introduction

A fundamental aspect of chemical engineering is optimizing modern processes to contribute to the sustainability of our developing world[1]. Many chemical practices exhaust large amounts of global resources, which not only reduces the sustainability of the process, but also places future generations at risk of losing essential materials. In an attempt to combat this scarcity by developing more efficient processes, flow chemistry was developed. Flow chemistry is a modern chemical methodology that works by conducting reactions in tiny tubes continuously, rather than in batch vessels[2]. The significance of flow in various industries has been studied thoroughly in recent years, demonstrating its economic viability, safety, and efficiency when compared to conventional chemical practices[3].

In this paper, known methods in the literature will be compared to introduce synthesis and analysis in flow processes. This will be done by evaluating the mechanism of flow chemistry by establishing a contrast between its unique features and those of batch processes. Various mathematical concepts and formulae that govern flow chemistry will also be explored through analyzing recent research and case studies. Similarly, various safety distinctions between batch and flow are highlighted to effectively compare both methods' adaptability on a larger scale. Hopefully, in recognizing these significant differences, today's engineers and scientists can recognize the value of implementing flow chemistry on a larger scale, guiding the fields to sustainability.

Costs and Adaptability in Modern Labs

Reactions in flow reduce production costs by allowing for smaller reactant volumes to be used as samples are analyzed in-situ[4]. On the contrary, batch reactions require larger reactant volumes to compensate for larger samples needed for analysis. Moreover, increasing product throughput in batch requires more reactant, further increasing costs. This contrasts to flow, which only requires an increased reactor residence time (and hence faster flow rates) to increase product throughput as it is a continuous process[5]. This increased reaction rate in flow has been observed in Comas-Barcelo's research into the copper catalysed synthesis of 1,4-di-substituted pyrazoles via the cycloaddition reaction of sydnones and terminal alkynes (Figure 1)[6]. At a reaction temperature of 140°C, conversions of $24-100\%$ were reached for a range of substituted pyrazoles. This reactivity increase is as a result of heating the reaction medium to a temperature higher than the boiling point of the toluene solvent, which is impossible to achieve in traditional batch setups. As a result, this conversion took only 5 minutes, which is very fast when compared to batch synthesis. Such an increased rate can also be modelled by observing the shorter reaction time in Table 1.

Furthermore, the increased rate of flow reactions allows for a higher product throughput compared to batch reactions. This is because they require less reaction time. Also, since they occur in a closed system, flow reactions experience heat loss notably less than do batch reactions, thus increasing their thermal efficiency. This makes them more energetically viable to scale up in various industries[7]. Additionally, mixing is far greater in smaller tubes than in batch, especially for scale-up

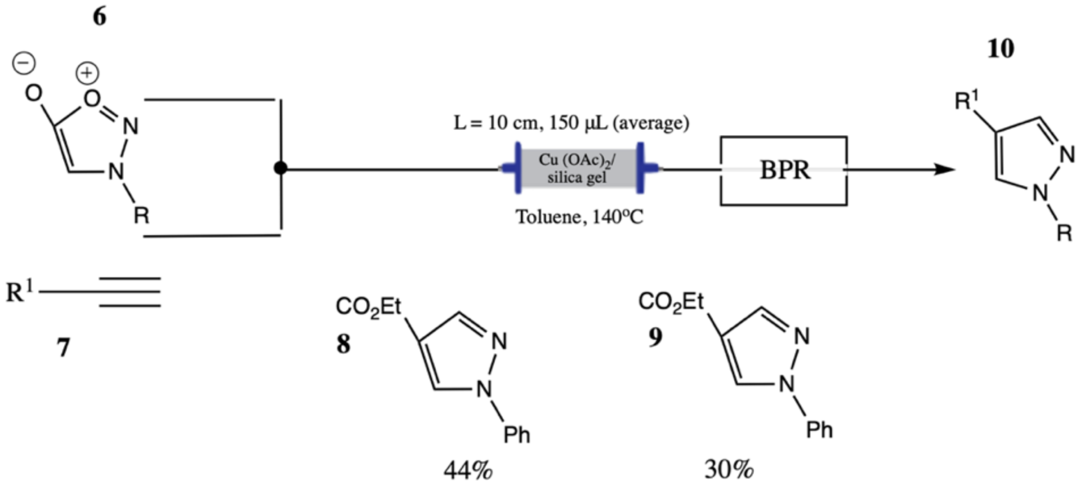

Fig. 1 Continuous flow synthesis of 1,4-di-substituted pyrazoles via cycloaddition of sydnones and terminal alkynes[6].

Table 1 Increased rate of reaction in flow when compared to conventional batch[3]

	Round-bottom flask	Microreactor	Flow reactor	Stirred-tank reactor
Mixing time	1-10	0.001-0.2	0.02-0.2	1-20
Heat transfer time		0.01-0.5	10-150	300-600
Liquid space time		0.1-100	2-200	10-2000

reactions – this is when a plug flow model is assumed[8]. This can be modelled by the set of equations below[9]:

$$u\frac{dC_i}{dz} = r_i \tag{1}$$

$$\tau = \frac{z}{u} \tag{2}$$

$$\frac{dC_i}{d\tau} = r_i \tag{3}$$

1 Reactivity and Applications

1.1 Flash Chemistry

Because of flow chemistry's various advantages over batch, there are many reactions that can only occur in flow – some of which, such as extremely fast chemistry, fall under the terminology of "flash chemistry". Today, flash chemistry is a field of chemical analysis in which extremely fast reactions are conducted under highly controlled conditions to form highly selective products. In Yoshida's research, Yoshida describes various features specific to flow processes that may limit throughput if conducted in batch. For example, **1** (Figure 2) could be generated from styrene oxide using t-BuLi or s-BuLi in the presence of tetramethyl ethylenediamine (TMEDA) at –98°C in a conventional batch reactor. However, the use of s-BuLi in the absence of TMEDA caused decomposition even at –98°C. A flow microreactor enables us to conduct the transformation at cheaper maintenance temperatures such as –70°C. Furthermore, these reaction times in flow can be as low as 0.003s, which is necessary to avoid side-product formation and product degradation - this is practically impossible to reach in batch but can be achieved in flow using precise pumps. Scaling batch reactions may also pose some issues as convective heat transfer depends on the impeller and liquid level, in addition to the size of the flask. Similarly, in both high-and low-temperature reactions, flow chemistry is useful as it facilitates smaller temperature gradients derived from the large surface area of its chips and tube reactors[10].

Another group who has replicated this flash chemistry methodology is the Kappe group, who synthesized propionic acids in flow with less than 4 seconds residence time[11]. This is shown in Figure 3.

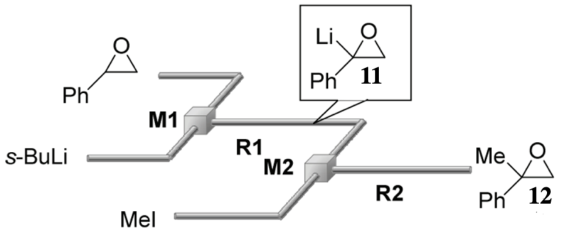

Fig. 2 Generation of styrene oxide using s-BuLi10[10].

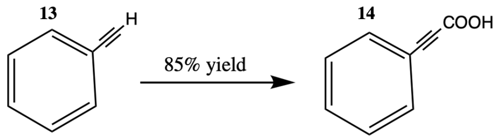

Fig. 3 Synthesis of propionic acids in flow with less than 4 seconds residence time[11].

1.2 Role of kinetics

1.2.1 Molar flow rate Molar flow rate in flow can be described using the equation $F_A = F_{A0}(1-X)^{12}$. The reduced operating time allows for a smaller reactor to be used[4]. This relationship has been demonstrated by the sample Levenspiel plot in Figure 4, whereby reaction rate is inversely proportional to reactor volume.

The graph can be summarized by the equation $V = F_{A0}\frac{1}{-r_A}X$. V represents the reactor volume, F_{A0} is the molar flow rate per unit time entering reactant A, X is the conversion of reactant A, and $-r_A$ is the rate of disappearance of reactant A per unit volume per unit time. The Levenspiel plot is a representation of the continuous flow reactor and is often used in chemical reaction engineering to determine the volume of a reactor[12].

1.2.2 Plug-flow and steady state Traditionally, in flow, the concentration of the starting product decreases as the reaction progresses. Conversely, if ideal plug-flow behavior (constant density) is assumed, length dependency allows for the concentration to remain unchanged at a certain point in the reaction under what is called "steady state conditions". In Figure 5, the fundamental characteristic of steady state conditions is demonstrated through the horizontal line, indicating a consistent reaction concentration and output. However, in order to obtain steady state conditions in a reaction, many residence times of reaction material must be wasted, adding costs to the process8. This can be a potential drawback of adopting flow chemistry.

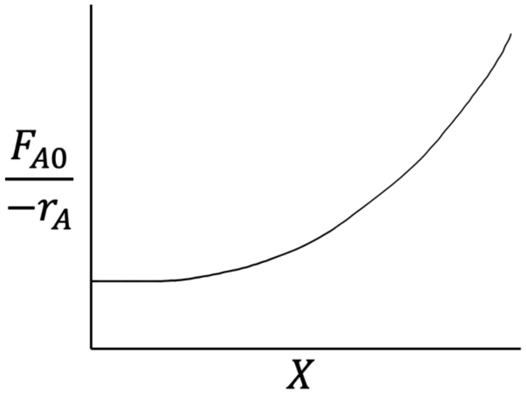

Fig. 4 A plot showing the molar flow rate and how it changes with respect to X (conversion of reactant A) and -rA (rate of disappearance of reactant A per unit volume per unit time)[12].

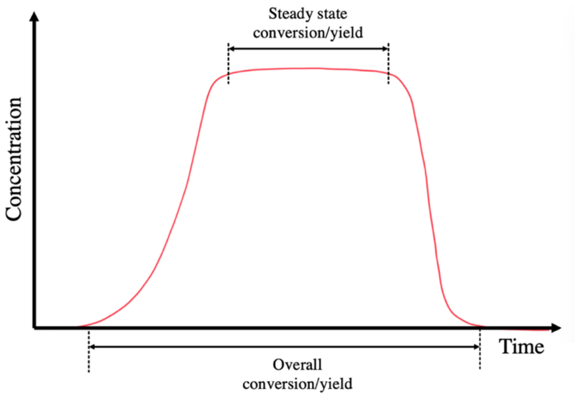

Fig. 5 Steady state condition[8].

1.2.3 Turbulent flow Since the beginning of continuous flow's history around a 100 years ago, it has required a particularly rapid rate of reaction, which can be achieved through turbulent flow. This allows for rapid and continuous mixing, which can be determined by calculating the Reynolds number, Re, as shown in the equation below, where v = average flow velocity, d = tube diameter, ρ = fluid density, and η = fluid viscosity[9].

$$Re = \frac{vd\rho}{\eta} \tag{4}$$

2 Safety

2.1 Capacity to reach higher temperatures

Modern protocols have engineered reactions in flow to be sustainable and environmentally friendly by increasing the reaction rate and thus decreasing the operating times in the reactors[4]. Reaction rates are increased because of the ability to increase the reactor temperature beyond the boiling point of the solvent, allowing faster conversion. Furthermore, temperatures higher than the solvent autoignition temperature can be reached without flammability restrictions, as flow reactions occur inside tubes that often do not contain oxygen[6]. This also improves the safety of flow processes. In contrast, batch reactions pose significantly more risk as they are exposed to the laboratory environment, so reaching or exceeding autoignition temperatures can cause an explosion. This flexibility of temperature control has, for example, allowed for the methyl ester to be selectively and reproducibly reduced to the aldehyde in Newton's research. This couldn't be done in batch with this level of control[13].

2.2 Reduced exposure to toxic compounds

Conducting flow reactions in a closed system makes flow safer to implement on a large scale in different industries, particularly in agriculture as it often includes highly nitrated compounds, which are highly toxic if inhaled. In batch reactions, however, the lack of sealed tubing does not prevent the exposure of such compounds, therefore posing potential hazards to experimenters[14]. This means that certain reactions simply cannot be conducted in batch without the implementation of various measures to reduce risk. Implementing such measures could add to the cost of the process, making batch less economically viable at times. Such measures are crucial to note, especially today as resources are becoming scarcer, and scientists are searching for methods that are not only more economically viable, but also more sustainable.

2.3 Thermal runaway reactions

Similarly, extremely exothermic reactions can lead to thermal runaway reactions in batch processes. A thermal runaway reaction occurs if the heat produced exceeds the heat removed. Other potential causes of runaway reactions in batch are exceeding the existing cooling capacity of the reactor, changing operating conditions, or using inappropriate materials[5]. However, because reactions in flow occur continuously, small amounts are reacted together at a time, so the risk of thermal runaway reactions is greatly mitigated[3]. Also, operating conditions are specified and unchanged from the start in flow reactions, further reducing the risk of thermal runaway reactions.

The specification of reaction conditions from the beginning of the reactive process makes scaling up the reaction a simple and systemic process. Baumann et al. used a Vapourtec E-series flow system with a UV-150 photo-reactor in the synthesis of Ibuprofen[15]. The acylation of isobutylbenzene **1** with chloropropionyl chloride was done in the presence of $AlCl_3$ (Figure 6). The intermediate 3 was subjected to conditions to yield a ratio of 7:81:12 of intermediate 3, ibuprofen 4, and Norrish product 5 respectively. At a 1 $mmol$ scale, 3.65 $mmolh^1$ of target compound 4 was generated. In this study, precise reaction conditions for the chemical transformation were easily found and could be accurately employed to scale up the production of Ibuprofen[6].

2.4 Scaling up

Critically, scaling up reactions in batch may pose safety risks due to the presence of large quantities of toxic substances. For example, the chemical synthesis of hydantoins, drugs used to treat seizures[18], involves heating an aqueous solution of potassium cyanide, which presents many health hazards like headaches and dizziness[19]. Such side effects are compounded when scaled up to industrial production.

3 Reaction Analysis

3.1 Online analytical techniques

The products formed during flow processes can be analyzed through a number of different inline and online techniques – the former involves a sensor being placed in the process vessel to analyze the substances in question, whereas the latter is connected to the vessel, conducting sampling automatically[20]. Online techniques most commonly used are High Performance Liquid Chromatography (HPLC) and Gas Chromatography/Mass Spectroscopy (GC/MS)[21]. The pressure in HPLC spectroscopy allows small particles with a large surface area to interact between the stationary phase and the molecules flowing past it. This results in effective separation of the mixture's components due to the different degrees of interaction with the absorbent particles[22]. For example, the weaker the affinity (Van der Waals forces) between the component and the mobile phase, the higher the rate at which the component moves through the column with the mobile phase. Consequently, different affinities cause different elution rates for the different components in addition to the separation of the components as they flow through the column. In Wegner's research, Larhed and co-workers' succeeded in yielding 10 $mmol$ (Figure 7) of disubstituted styrene by using common HPLC tubing as micro reacting channels[16].

Gas chromatography (GC) spectroscopy, on the other hand, works by gradually heating the mixture to separate it into its

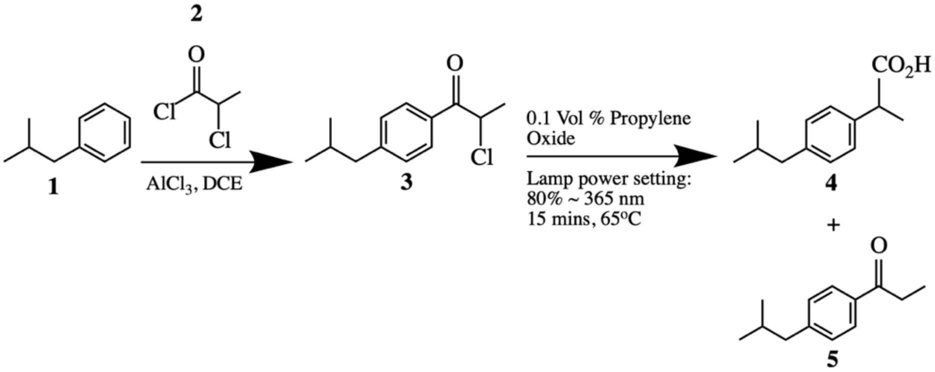

Fig. 6 Friedel Craft's acylation of isobutylbenzene[6].

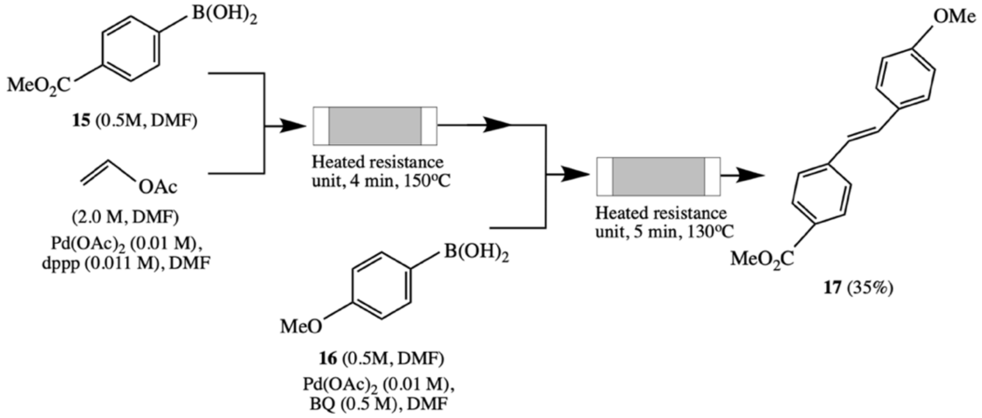

Fig. 7 Flow vinylation of boronic acids22[16].

individual components. The heated gases are then carried through a column with an inert gas such as argon, and the relative mixture composition is quantified. As the separate substances emerge from the column opening, they are often coupled with a mass spectrometer and hence flow into this instrument. Mass spectroscopy, as the name suggests, identifies substances by mass[23]. It is commonly coupled with HPLC or GC. Mass spectroscopy works by first ionizing the molecules of interest, then, the ion is accelerated towards negatively charged plates, then into a magnetic field, where it is deflected. Ions with a high charge and small mass are deflected the most. Finally, the ion enters a machine, where it is detected electrically[24]. Because mass spectrometers generally report their mass values to at least four decimal places[25], they are considered to be very precise in identifying products from complex mixtures. This is demonstrated in Browne's research (Figure 8), where the mass spectrometer detected the explosive diazotized intermediate[17].

3.2 Inline analytical techniques

Inline techniques analyze samples of the flowing material by placing a sensor in the process vessel; infrared (IR) spectroscopy and ultraviolet (UV) spectroscopy are commonly used inline analytical techniques. IR spectroscopy works by shining a beam of infrared light, exciting bonds within molecules of certain compounds. These molecules then absorb light that is directed towards a filter and onto a detector, which is used for the measurement and identification of the molecule or changes within it[26]. Though this method is widely used, it is less accurate if there are multiple species due to the presence of overlapping peaks that measure the absorption of side products, solvents, and metals[27]. IR spectroscopy was useful in Muller's research, where it enabled the rapid formation of the diazo species in flow[28].

On the other hand, data generated by UV spectroscopy works by directing UV light towards a sample, which thus ab-

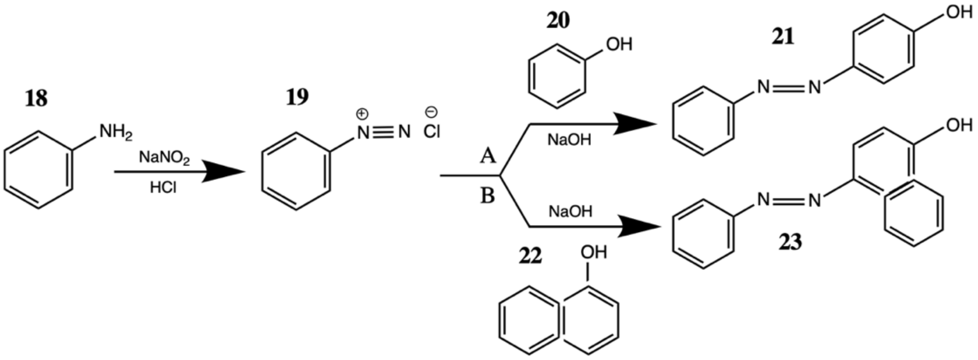

Fig. 8 Explosive diazotized intermediate[17].

sorbs energy – the absorbances at different wavelengths are characteristic of particular molecules and are used for composition analysis[29]. These wavelengths can be used to determine the elemental composition of the sample.

Modern day flow processes also use packed columns in distillation and gas absorption. In Figure 9, packed columns were used by Ley to utilize hydrogenation in imines[7]. This, too, exemplifies how the adoption of flow can resolve traditional problems, in this case the use of solids in flow systems, to provide viable syntheses of important pharmaceuticals and natural products.

4 Drawbacks of Flow Chemistry

Despite flow chemistry's many advantages, it is equally important to note its potential drawbacks. Though flow chemistry is, by definition, a continuous process[30], only certain amounts of reactant can be pumped at a time. Due to the tubes' small size, these amounts are similarly small, which leads to restricted flow capacity. This, however, can be overcome by installing more pumps, thus increasing throughput – this is referred to as 'numbering up'. Moreover, heterogeneous reaction mixtures can often be difficult to process in flow due to solid clogging in the reaction tubing[31]. This can be an issue, particularly from a synthetic chemistry standpoint. Such limitations are less prevalent in batch processes as they are not restricted to small tubes, and thus are more flexible. Though there is no direct solution to this problem, it can be avoided by using CSTRs in flow that can handle solids[32]. Equally important to note is that while all labs have batch equipment, only some have flow equipment, making the implementation of flow processes, especially on a large scale, an expensive procedure[33]. Having said that, investing in flow equipment is vastly economical in the long-term due to its high efficiency when compared to traditional batch processes[3], meaning less resources are exhausted. This, in effect, positively contributes to achieving sustainability in engineering and science.

5 Conclusion

Through examining flow chemistry's many distinctive qualities, it can be concluded that its implementation in today's chemical practices can revolutionize the functionality of various industries. This has been used in several synthetic strategies, including reactions relating to thermochemical, photochemical, electrochemical, heterogeneous, polymer synthesis and more[7]. Furthermore, flow chemistry can be readily coupled with online/inline analytical techniques, allowing for fast reaction composition quantification and reaction optimization. Beyond the additional advantages in providing safer alternatives and more efficient reaction pathways when compared with batch, flow chemistry significantly cuts costs for complex processes. We hope that this paper inspires future generations to adopt flow chemistry at a large scale to achieve global sustainability.

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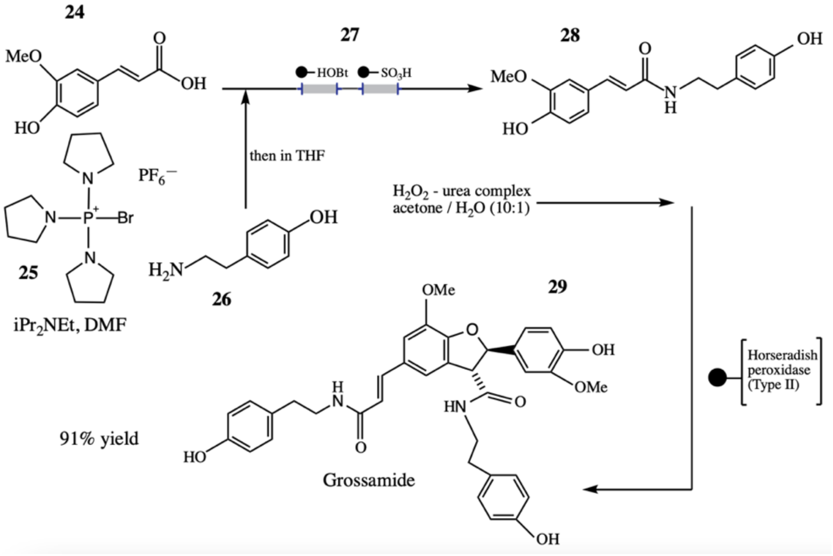

Fig. 9 Hydrogenation in imines[7].

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