Capillary-based microreactor for high throughput catalyst screening in Lewis acid and strong Brønsted acid catalyzed reactions

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Capillary-based microreactor for high throughput catalyst screening in Lewis acid and strong Brønsted acid catalyzed reactions

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The microreactor technique has received considerable research attention due to its promising applications in organic chemistry. Compared to traditional organic synthesis, the employment of microreactor has several advantages. First, the small diameter of the microchannel can reduce the reagent mixing time to milliseconds, allowing fast heat transfer and thermal equilibrium. Second, higher yield and better selectivity are often observed for reactions carried out in a microreactor. Most importantly, reaction optimization and catalyst library generation can be rapidly achieved by the microreactor with reagents on a small scale.

In the past few years, our group has been developing a capillary-based microreactor system that is capable of high throughput catalyst screening. This system consists of HPLC apparatus, syringe pumps and capillary tubings, which are all commonly used in the chemistry laboratory. Compared with the traditional chip-based microreactor, our system is easy to operate, and simple to modify. Additionally, it couples with gas chromatography (GC) or high-performance liquid chromatography (HPLC) for online analysis, providing near-real-time reaction monitoring.

One of the applications we explored with our microreactor system was the homogeneous catalysis reaction. The first reaction tested was lanthanide-triflate catalyzed allylation of benzaldehyde with tetraallyltin. With GC online analysis, the reaction was successfully carried out in our microreactor system. The optimized reaction condition, 10% catalyst load/60 min

reaction time in room temperature, was much milder compared with any published bench top conditions. The screening of 8 different catalysts for the reaction was accomplished within 2 hours, which led to a significantly shortened optimization time.

The online enantiomeric separation analysis method was developed for a strong chiral Brønsted acid catalyzed asymmetric cyanide addition. Six chiral columns and various separation conditions were involved in the method development. Due to the incompatible issue between the reaction solvent and column bonded phases, a GC method was optimized and chose as our interfaced online analysis method.

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1.0 INTRODUCTION

1.1 BACKGROUND

The microreactor technique has received considerable research attention due to its promising applications in organic chemistry. [1-4] Compared to traditional organic synthesis, the employment of a microreactor has several advantages. First, the small diameter of the microchannel can reduce the reagent mixing time to milliseconds, allowing fast heat transfer and thermal equilibrium. Second, higher yield and better selectivity are often observed for those reactions carried out in microreactors. Most importantly, reaction optimization and catalyst library generation can be rapidly achieved by the microreactor with a small scale of reagents. For industrial chemical productions, the microreactor reactions provide much larger space-time yields than bench top reactions.

A typical microreactor consists of a series of 10-1000μm-wide channels which can be designed to various geometries, providing spatial and temporal control over small amounts of fluid and reagent streams. The microreactor chip is usually fabricated based on well-developed semiconductor and microelectronic fabrication methods. Different materials such as silicon, glass, quartz, metal and polymer are currently utilized to produce the microreactor chips, with glass and silicon being the most frequent.

Control of the microreactor is accomplished with the help of two major mechanisms: Pressure-driven flow and electrokinetic flow [5]. Pressure-driven flow describes the movement of a reagent stream driven by the pressure difference between a channel's inlet and outlet. Positive pressure is provided by syringe pumps, which can infuse or withdraw fluids at different flow rates. The advantage of pressure-driven flow is obvious as it can couple with any liquid and device without limitation. However, the accuracy of the flow rate can be problematic if the rate decreased to a certain level. The high pressure resulting from the resistance in the microchannels can also be problematic for the microreactor system in some cases.

The second mechanism employed is electrokinetic flow [6, 7], which results from a potential bias between the inlet and the outlet of the microchannels. Generally speaking, there

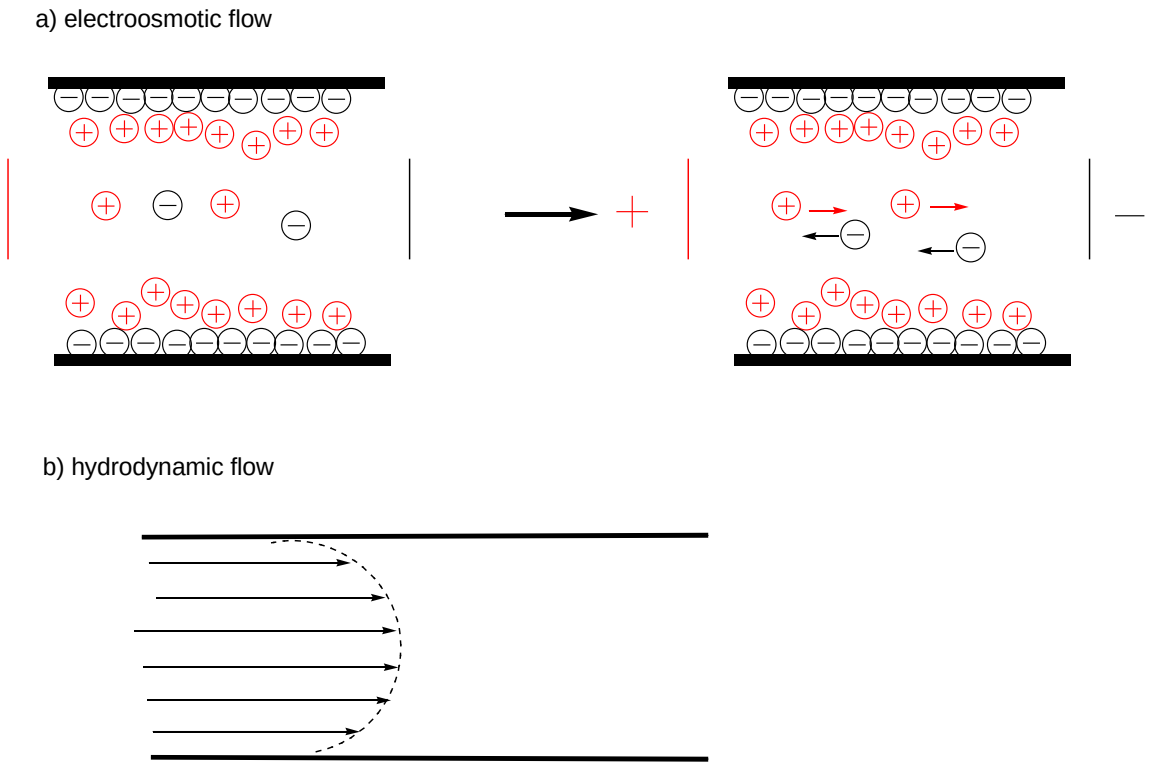


Figure 1. Electroosmotic flow vs. pressure-driven flow

are two different mechanisms for the electrokinetic flow: one is the direct movement of ions in solution towards the opposite charged electrode, and the other is electroosmotic flow, rising from

the double-layer near the charged surface. The velocity of electroosmosis is proportional to the potential applied. Hence, precise control of the fluid is achievable even at a very low flow rate. Compared with pressure-driven flow, the velocity across the channel are uniform in an electroosmotic flow process, resulting in less dispersion of the reagents. However, only polar solvents can be used for this mechanism, including water, methanol, acetonitrile and dimethylformamide [8]. Limited materials which can develop charges in the surface are suitable for this mechanism.

The future trend in the development of microreactors is to achieve an easier operation and a simpler set-up. Our group has been developing capillary-based microreactors for years. Shi *et al.* introduced a simple microreactor system consisting of Teflon® tubing and syringe pumps with small syringes [9]. All the instruments and tools can be found in a regular laboratory and are commercially available. This type of microreactor is easy to build, with flexible device geometry and solution junctions. Its flow profile is the same as that of microchannels. Instead of Teflon®, poly(vinyl chloride) (PVC) tubing was also used [10]. Another example of this type of system was demonstrated by Ismagilov and co-workers for screening the hydrolysis of a complex molecule. All of the examples mentioned above demonstrated that the capillary-based system worked as well as the chip-based one. Moreover, the capillary-based system could tolerate most common organic solvents, the geometry and solvent junctions could be modified whenever needed, all components could be easily found in an organic laboratory, and the system was simple to build even for beginners.

1.2 MICROREACTOR APPLICATIONS

It has recently been discovered that the application of microreactors in the synthetic chemistry could be advantageous in many aspects. Since separate reagents could be brought together through different feeder channels to the main channel, reagents could be mixed and reacted on their way to a reservoir for collection and analysis. This microreactor approach could reduce the reaction time along with the quantity of waste produced. Additional benefits of the microreactor in synthetic chemistry also includ system safety, as the quantity of toxic compounds was minimized, and evidence suggested that reactions performed using this methodology could be cleaner and give higher yields than the same reaction using a typical solution-phase approach.

Microreactors have been applied in catalyst discovery for its high-throughput screening. Various organic reactions were investigated using microreactors. Generally, there were two approaches to carry out catalysis reactions in the microreactor. One involved immobilization of catalyst to a resin or the surface of the microchannel, where the reagent stream passed through. The other used homogeneous catalysts in the reagent stream. Both methods had their unique advantages. Immobilized catalysts could be recycled and reused and many studies were done with this type of packed-bed reactor. On the other hand, homogeneous catalysts in the reaction mixture made the microreactor an excellent tool for high-throughput catalyst screening and reaction optimization.

1.2.1 Supported catalytic reactions

Supported catalysts have been utilized in microreactors for quite a long time. In recent years, new techniques were introduced to further improve the reaction efficiency of microreactors.

Greenway and co-workers [11] used flow injection techniques to study the Suzuki reaction in their microreactor device using a supported catalyst. Periodic injections of aryl halide into the flow of phenylboronic acids resulted in an improved conversion (67%) of cyanobiphenyl at room temperature. Another advantage of this application was that no additional base was required when the reaction was carried out in the microreactor. The reasons for this, as the author suggested, could be that the electric field in the microreactor caused the ionization of water at metal surface or that a basic environment might be generated near the surface of the microreactor.

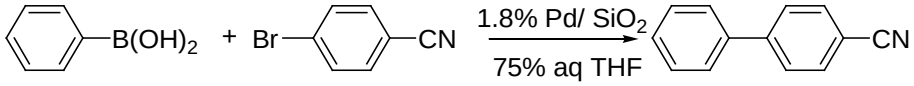


Figure 2. Greenway's Suzuki reaction

Wilson and co-workers [12] demonstrated an application of the dehydration of hexane-1-ol in a microreactor with a catalytically-active wall of microchannels. The catalyst, sulphate zirconia, was dusted in the surface of the glass plate which greatly increased the device's surface area. Compared to the 30% conversion in the industrial process, the conversion with the microreactor was much higher, ranging from 85% to 95% without any detectable byproduct.

Plugs of glass wool [13] or resins were reported as the support for various catalysts. The reaction of *p*-bromoanisole and phenylmagnesium bromide was studied by O'Sullivan *et al.* [13], in which the nickel catalyst was linked to a Merrifield resin.

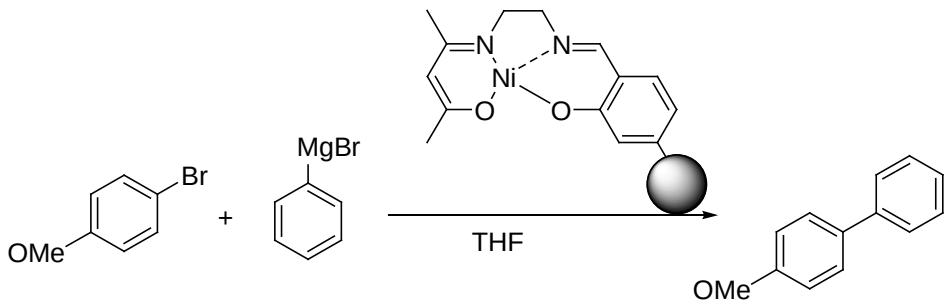


Figure 3. O'Sullivan's nickel-catalyzed reaction of *p*-bromoanisole and phenylmagnesium bromide

However, there was a problem associated with Merrifield resin: solvent-caused swelling. It caused extreme back pressure in the microreactor channels. Thus less catalyst-resin could be used in this type of system, which limited the conversion of the reaction. Other types of media were tested for resin-based microreactors. For example, silica was more robust than polymeric resin. The drawback of silica media was that salts tend to build up on the surface and eventually deactivate the catalyst.

Ping and co-workers [15] used microreactors to develop a general device for the Suzuki reaction. A thin layer of gold patched over the microchannel was employed to absorb microwave irradiation and functioned as a heater. The reaction could achieve 58-99% conversions within 60s. Further improvement was made by anchoring 4 % Pd(0) on polystyrene beads to the surface of the microchannels, which was a more effective and practical way to pack catalyst in the device.

1.2.2 Homogeneous catalysis

Homogeneous catalysis involves reactions where the catalyst is in the same phase as the reactants. Since the use of a microreactor effectively minimizes the amount of reagents and

catalysts/ligands due to its reduced size, the system has been found especially useful in catalyst screening for homogeneous catalysis.

An example of this reaction carried out in a continuous flow microreactor was first reported by Hessel and co-workers in 2000 [16], in which they investigated the isomerization of 1-hexene-3-ol. The catalytic reaction was accomplished by using a pulse injection technique. The pulses of water and n-heptane mixed perfectly in the microreactor and the liquids emulsified and behaved as reacting segment. A library of 8 different catalyst/ligand combinations and 10 similar substrates was screened in the system and the best conversion was observed in the presence of $RuCl_3$/ 3,3′,3″-Phosphinidynetris(benzenesulfonic acid).

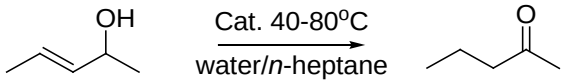


Figure 4. Hessel's isomerization of 1-hexene-3-ol

Moberg and co-workers reported the first application of asymmetric catalysis in a microreactor in 2003 [17]. An enantioselective silylcyanation of benzaldehyde was catalyzed by lanthanide(III)-pyBox complexes in a borosilicate microreactor. A detailed comparison between the bench top results and the microreactor results was discussed, which implied the usefulness of a microreactor for optimizing the reaction condition. Additionally, different lanthanide catalysts, additives and applied voltages were tested to achieve optimized conditions, where a 95-99% conversion of the final yield with 52% enantioselectivity was achieved.

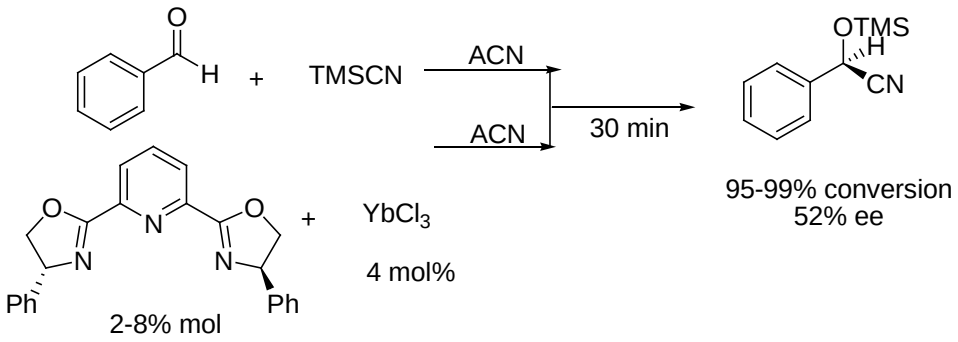


Figure 5. Haswell's enantioselective silylcyanation

In 2005, Seeberger and co-workers developed a modular microreactor system, with extended applications to several important homogeneous and heterogeneous reactions in organic synthesis[18]. The system was able to withstand pressure up to 100 bar. A set of 59 measurements was performed by the microreactor in total of 34 hr, which was significantly shorter than the 65 hours required for a similar optimization in bench top.

Table 1. Reactions applied in Seeberger's microreactor

Reaction	Reactant 1	Reactant 2	catalyst	product	solvent	Residence time(min)	Yield in the microreactor
Acylation	2-phenylethanol	Ac_2O	DMAP	2-phenylethyl acetate	Pyridine	15	95
Alkylation	PhOH/ KOH	$PhCH_2Br$	Bu_4NI	$PhCH_2OPh$	DMF	1	100
Alkylation	PhOH/ KOH	$PhCH_2Br$	Bu_4NI	$PhCH_2OPh$	$CHCl_3$/ H_2O	60	93
Cycloaddition	2,3-Dimethylbuta-1,3-diene	Maleic anhydride	-	DBFD	NMP	30	98
Olefination	Triethyl phosponoacetate	PhCHO	TBD	Ethyl cinnamate	MeCN	10	91
Nitroaldol addition	$MeNO_2$	PhCHO	TBD	2-Nitro-1-phenyl-ethanol	i-PrOH	10	76
Aldol condensation	Acetone	PhCHO	NaOH	Benzylidene-acentone; dibenzylidene-acetone	EtOH	7	59; 22
C-C coupling	PhI	Ethyl acrylate	Pd/C	Ethyl cinnamate	NMP	30	99

Lee and co-workers investigated the oxidation of cyclohexene in a capillary based microreactor [19]. Compared to a chip based microreactor, this capillary microreactor was easier to fabricate. Various reaction conditions, including catalyst, applied potential, applied current and reaction time, were tested for the epoxidation reaction. A conversion of 2-hydroxy-cyclohexanone (70%) was observed in the microreactor, higher than in the bench-top.

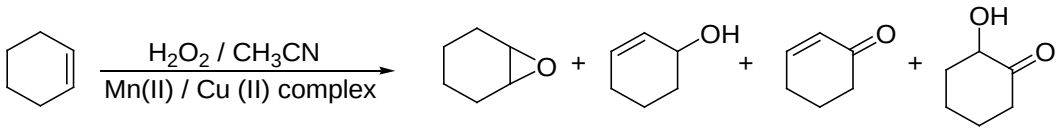


Figure 6. Lee's oxidation

A falling film microreactor was developed by Hessel and co-workers in 2005 to screen rhodium/chiral diphosphine catalysts for the asymmetric hydrogenation of (Z)-methyl acetamidocinnamate and five similar substrates [20]. 17 chiral phosphine ligands were tested for the best enantioselectivity in the reaction. The falling film technique was employed to facilitate the gas-liquid phase contact. In their system, only 0.1 μg of the Rh catalyst was used each run, and the results were comparable to those in bench top experiments.

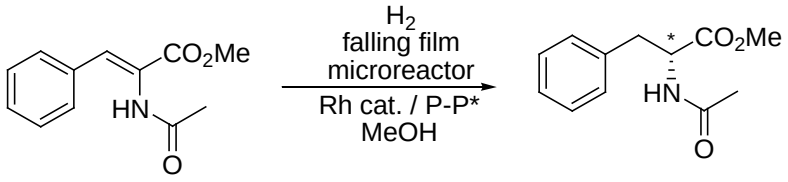


Figure 7. Hessel's hydrogenation with falling film

Harsh conditions become possible in the microreactor due to a better control of the reaction parameters. In 2008, de Bellefon and co-workers reported a gas-liquid oxidation of cyclohexane, performed at high temperature (>200 ^{o}C) and pressure (up to 25 bar) in a chip-based microreactor [16]. The microfluidic system even allowed for reaction conditions that were

far above the flammability limit. A reaction selectivity as high as 88% was observed with optimized reaction conditions.

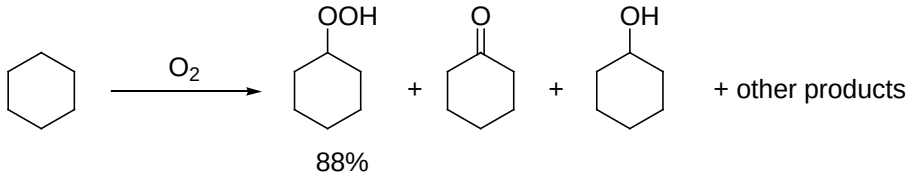


Figure 8. de Bellefon's oxidation of cyclohexane

For most microfluidic system, only one reaction is running at any time. In our group, a capillary based, serial loading, high throughput microreactor was developed for homogeneous catalyst screening. Separate reaction zones with different catalysts were loaded serially into the capillary, and were then injected into GC or HPLC for online analysis. Up to 54 reaction zones containing different catalysts can exist simultaneously in the capillary reactor. Shi explored the Stille cross-coupling reaction with known palladium-based precatalysts and phosphine or arsine ligands in the microreactor [9]. The results mostly agreed with the results from traditional bench top reactors, validating that reactions run in this type of microreactor and under conventional conditions in a similar manner.

Later, high-throughput catalyst screening for an intramolecular Friedel-Crafts addition was explored by Hui *et al*. in this capillary-based microreactor,[19] The effects of catalyst loading, reaction time, and reaction temperature were evaluated with minimal material investment. $Er(OTf)_3$ showed best efficiency at promoting the cyclization reaction.

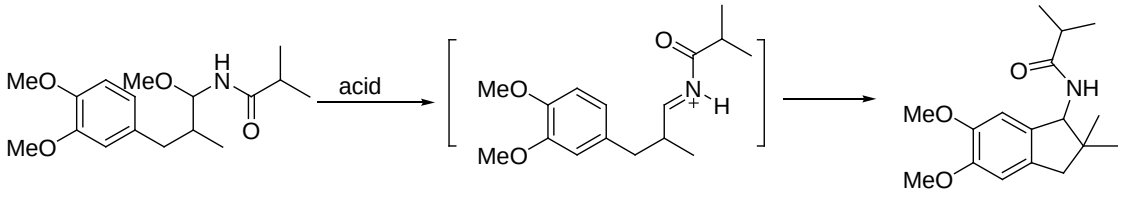


Figure 9. Fang's intramolecular Friedel-Crafts addition

1.2.3 Motivation

It was demonstrated that a flow-through microreactor could be used to screen additives and catalysts. This feature makes it a promising tool for the study of reaction optimization in organic chemistry. However, limitations exist for most systems. Firstly, most continuous flow microreactors process only one sample at a time, which is unsuitable for long time reactions. As a result, the reactions that have been explored in the microreactor are relatively fast. The second factor that prevents the broad application of the microreactor is the material (typically glass or silicon) used in them. It is well known that a glass surface is quite reactive that may even act as a catalyst in some cases, and silicon does not tolerate most commonly used organic solvents. The last problem is that current microreactors are not capable of performing large numbers of combinatorial synthesis and screening experiments. For example, if a complicated combinatorial synthesis were performed in a chip based microreactor, a prohibitively large array of pumps, tubes, multiple connectors and chips with microchannels would be required for the system.

Therefore, a microreactor system with the following characteristics would be extremely valuable in organic synthesis: large capacity, high throughput, low cost and simple construction. We have developed a novel capillary-based microreactor system in our lab that employs these characteristics and successfully carried out the high-throughput screening of slow, homogeneous catalysts. This microreactor consists of apparatus that could easily be found in the organic laboratory: syringe pumps, an autosampler heater, capillaries and GC/HPLC. The reaction zones of different reactants and catalysts are combined and loaded into the capillary reactor, react in parallel and are injected serially for online analysis. The system has unique benefits for advanced organic synthesis compared to the chip-based reactor. First of all, the capillary-based reactor does not require a fabrication process. The capillaries needed are commercially available in

various diameters and materials. Secondly, with capillaries, it is easy to build or rearrange the system with the help of standard HPLC connectors. Any flow inside the capillary is isolated from the atmosphere, and the capillary's inner surface is inert to most reactions. Lastly, the capillary tubing is suitable for either electroosmotic flow or pressure driven flow mechanics.

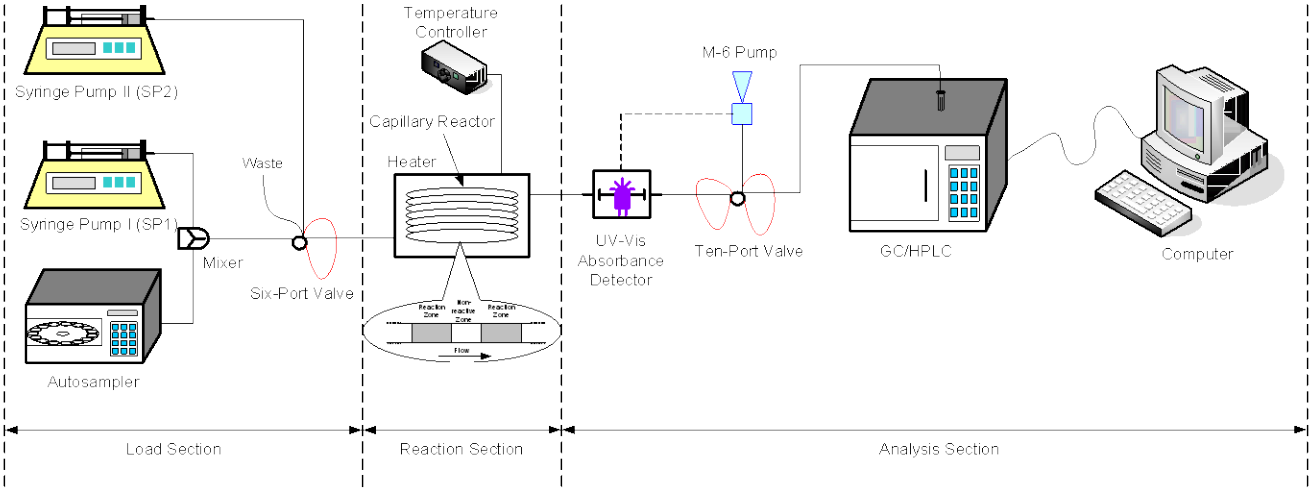


Figure 10. The setup of our microreactor

Figure 10 shows a schematic diagram of the microreactor [21]. The system includes three sections: loading, reaction and analysis. The catalysts are first combined with reagents in the loading section, and are then pushed into the capillary reactor. Reactions take place inside the capillary reactor of the reaction section at a controlled temperature. After a specific time (controlled by SP2), the samples are injected serially into GC for online analysis in the analysis section. Each of these three sections is described in more detail below.

Injection. Samples of a catalyst and reagents were loaded into sampling vials and placed into the autosampler tray. The autosampler took a 20 µl sample solution from the vials and pumped it out at a flow rate of 15 µl/min. The other reagents were pumped out by syringe pump 1. For equal mixing, the flow rate of syringe pump 1 was set at the same rate as the autosampler's. After exiting the mixer (Y connector), the samples entered a 6-port valve, where a loop volume of 1.9

μl was used. The loop contents were pushed into the capillary reactor with pure solvent from syringe pump 2 at 20μl/hr. By switching between loading and injecting positions, the 6-port valve separated the reaction zones of reagents and catalysts from each other using the pure solvent from SP2.

Reaction. The reaction section was built from a 100 μm ID(inside diameter), 6.23 m-long Teflon® tubing. Different residence times were achieved by controlling the flow rate of SP2. A heating/cooling media such as oil/ice bath was also employed when necessary.

Detection. The monitoring of reaction zones was achieved by an Ocean Optical absorbance detector. The online analysis was triggered by the absorbance detector. A 10-port valve was employed to store samples in one loop while the content of the other loop was injected into GC/HPLC for separation.

The microreactor in our laboratory was designed specifically for synthetic chemistry. Therefore, we devoted its use to synthesis-related fields, like combinatorial synthesis and catalyst screening. The major focus of this project was catalyst screening for the discovery of new catalysts and the generation of a library of potential catalysts by high-throughput screening. In addition, our microreactor may also be applied in the study of reaction kinetics and reaction optimization. Serial sets of data, such as reaction parameters or kinetic process, can be obtained with our microreactor.

In summary, the purpose of our project was to facilitate the exploration of methodologies in organic chemistry through the application of our microreactor technology. With minimal reagent consumption, we were able to accomplish the reaction study and the generation of a library of catalysts in a considerably short time.

2.0 LANTHANIDE-CATALYZED REACTION AS CASE STUDY IN CAPILLARY-BASED MICROREACTOR

Shi *et al*[9] and Fang *et al*[21] have made preliminary optimization of experimental conditions for the reactor system. After successful catalyst screening was done for the Stille reaction and the intramolecular Friedel-Crafts addition, we turned our interests to one of the major fields in organic synthesis - carbon-carbon bond-forming reaction in aqueous media. We first chose a typical reaction in aqueous phase, which was widely studied in the literature. Reaction conditions were then optimized, and a comparison between the microreactor results and the bench top results was demonstrated.

2.1 EXPERIMENTAL SECTION

Materials. ACS grade acentonitrile (As solvent), tetraallytin (97%), lanthanum (ш) trifluoromethanesulfonate, scandium (ш) trifluoromethanesulfonate, ytterbium (ш) trifluoromethanesulfonate, 4-phenyl-1-buten-4-ol (97%), and 2-ethyl-naphthalene (99%) were purchased from Aldrich (Milwaukee, WI); benzaldehyde (97%) was bought from Acros.

Sample solution preparation: Catalyst reaction solution: benzaldehyde (0.025 M) and 2-ethyl-naphthalene (0.025 M) were dissolved in the reaction solvent (ACN:H_2O 4:1) with different

loadings of the catalyst. Tetraallyltin solution: tetraallyltin (0.025 M) was dissolved in the aqueous solvent with naphthalene (0.025 M).

Instrument Waters 515 HPLC pump, HP 1050 Autosampler, Thermo Scientific FOCUS GC Gas Chromatograph; Harvard Apparatus 11 plus syringe pumps, DH-2000 UV-Vis NIR lightsource.

GC method: column: Rxi^{TM}-5ms: 30m×0.032 mm ID×0.25μm film thickness.

	Rate (^{o}C/min)	Temperature (^{o}C)	Holding time (min)
Initial		100	0.1
Ramp	120	250	0.1

Oven run-time: 1.450 min
Maximum Temperature: 300 ^{o}C
Pre-run timeout: 30 min
Equilibration time: 0.1 min

2.2 RESULTS AND DISCUSSION

2.2.1 Test reaction criteria and reagent arrangement

Due to the small diameter of the capillary used in our system, not all reactions are suitable for the microreactor. Some criteria we used for test reactions are as follows:

1) O_2 tolerable. Because the capillary-based microreactor uses most HPLC connectors to connect each component, it is not strictly isolated from the atmosphere. Even though we can achieve the isolation with airtight connectors and other accessories, at the preliminary stage, we prefer reactions that can tolerate O_2, avoiding byproducts or other pathways.

2) Insensitive to moisture. As indicated above, the microreactor is not isolated from the atmosphere. Also, the trace of water inside the syringe or the capillary tubing may also affect the reaction due to the small amount of reagents used in the microreactor.

3) No precipitates form during the reaction. Precipitation will clog the valves and capillaries severely and the cleaning is very time-consuming.

Therefore, we chose a scandium (Ⅲ) trifluoromethanesulfonate catalyzed allylation reaction of benzaldehyde with tetraallyltin [23].

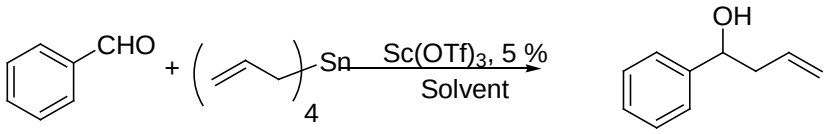


Figure 11. $Sc(OTf)_3$ catalyzed allylation

Based on Iwao et al., this reaction can be carried out in different aqueous phase and no byproduct is observed in any condition. But they did not mention whether there were precipitates or not. So first of all, a test was done in a bench top reactor to observe the reaction solution in order not to clog the capillary during the process. The reaction was carried out in small vials with different ACN/H_2O ratios, from pure ACN to Pure H_2O. The clearest solution was ACN/H_2O 4:1 solution. Thus ACN/H_2O (4:1) was chosen as our reaction solvent.

Another part to consider when setting up the microreactor is the arrangement of different reagents; in our case, different combinations resulted in completely different solutions. Experiments showed that the mixture of benzaldehyde and tetraallytin, without any catalyst, formed precipitates. The mixture of catalyst and benzaldehyde is clear. Hence, the final arrangement of reagents in the solution is as follows: the autosampler is loaded with the catalyst and benzaldehyde solution, SP1 is with the tetrallyltin solution, and SP2 is with THF to separate the reaction zones and pushes them into the reactor capillary. At the flow rate of 20 μL/ hr in SP2, the residence time of reaction zones in the capillary reactor is 120 min. When the reaction

zones come out of the capillary reactor, they then go through the UV detector, forming peaks due to the absorbance differences between reaction zones and solvent zones (Figure 12).

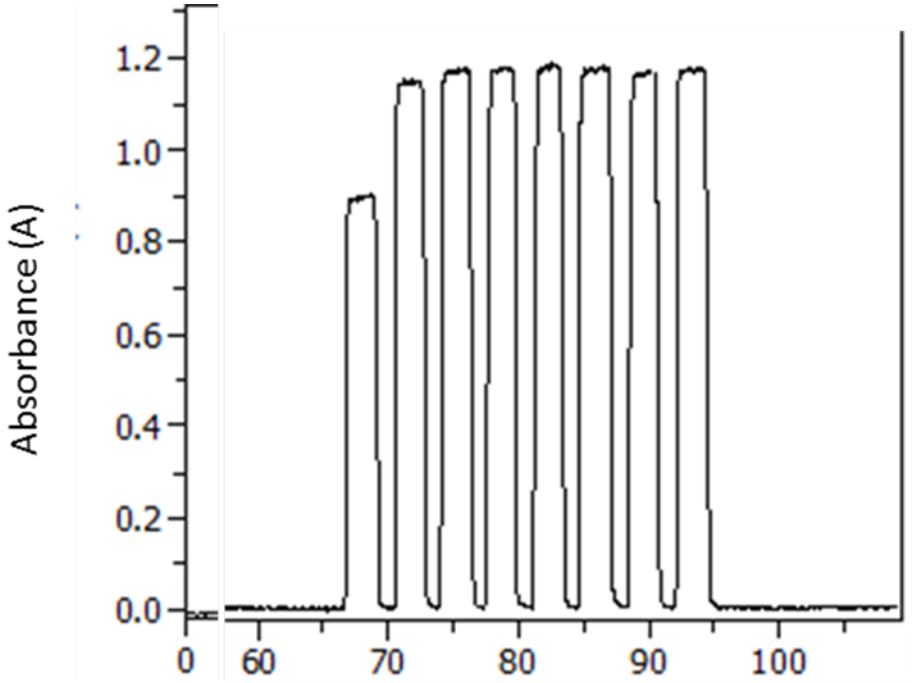


Figure 12. UV monitoring of reaction zones through microreactor

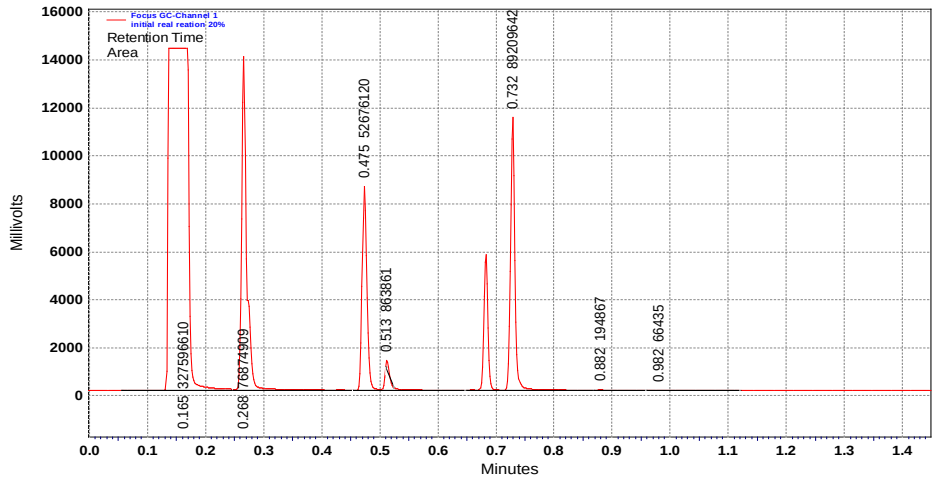


Figure 13. GC chromatogram of the reaction zone: t_R= 0.268 is benzaldehyde; t_R=0.475, naphthalene; t_R=0.513, 4-phenyl-1-buten-4-ol the product; t_R= 0.732, 2-ethyl-naphthalene.

After reaction zone pass the UV monitor, the M6 pump injects the reaction mixture into the GC for analysis (Figure 13), and all these actions are automatically controlled by a software.

2.2.2 Materials for capillary-microreactor

For our system, a fused silica capillary was first used as the capillary reactor. It is inexpensive, compatible with HPLC connectors and available in various insider diameter. The first several experiments with catalysts were good. Later when the 120-min experiment was repeated in the microreactor, its results varied from time to time. As well known, the surface of the fused silica capillary is quite active and can act as catalysts in some cases. Thus in our reaction, it may interfere with the Lewis-acid catalyzed reaction. To prove that the capillary tubing may play a role in the irreproducible results, a reaction without any catalysts was carried out in the microreactor. As seen in the Figure 14, there were many unknown peaks in the GC chromatogram, which confirmed our speculation.

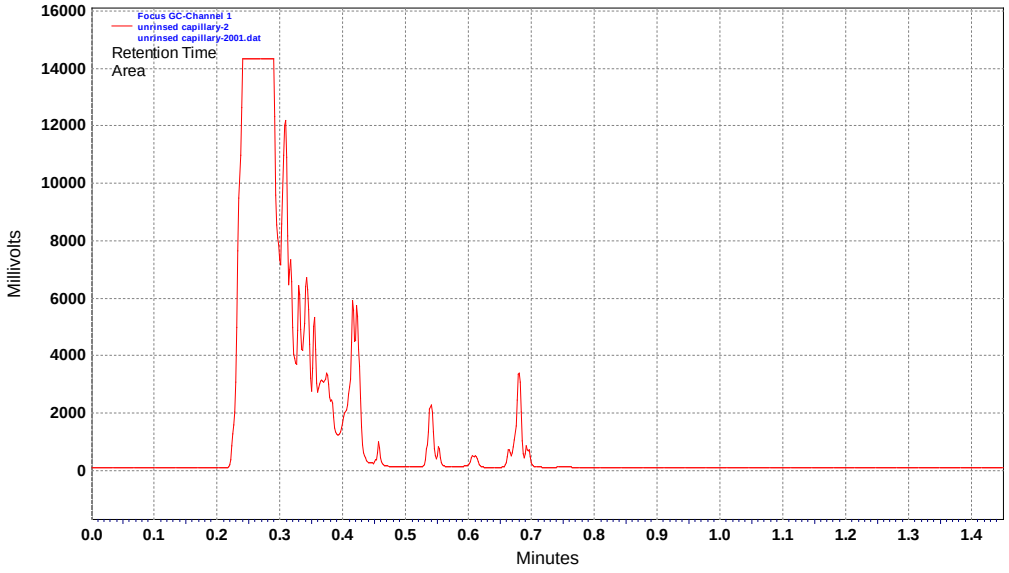


Figure 14. GC chromatogram of uncatalyzed-reaction mixture**.**

To eliminate such influence, we tried to rinse the surface of the capillary with a base solution. The following method was used: 1M NaOH solution was used to flush the capillary for an hour and a half (15μL/ min), then the capillary was washed with pure water until the pH is 7,

following up with THF for half an hour. After the procedure, we ran the reaction in microreactor again. This time, GC chromatogram showed reasonable peaks, indicating that the base rinse procedure works well for our capillary. The only drawback was that after 2 or 3 runs, the capillary needs to be rinsed again.

Meanwhile, since the fused silica capillary tubing interferes with our reaction, we also test the use of the Teflon® tubing as the capillary reactor in our system, whose surface is more inert and will not interfere with our reaction. With the same setup we used before, we found that all the reaction zones seemed to come out together (Figure 15). It seemed that the reaction zone/THF zone pattern was disturbed and resulted in one combined peak of all individual peaks in the Teflon® tubing. The interaction between Teflon® and THF is sophisticated, the only conclusion we can only presume is that THF can not be used in the purpose of separating zones in Teflon® tubing.

Then we changed the solvent in SP2 from THF(tetrahydrofuran) to pure reaction solvent (ACN: H_2O 4:1), UV and GC results are shown in Figure 15. No combined peak in the UV results and the reaction happened in the way that we expected.

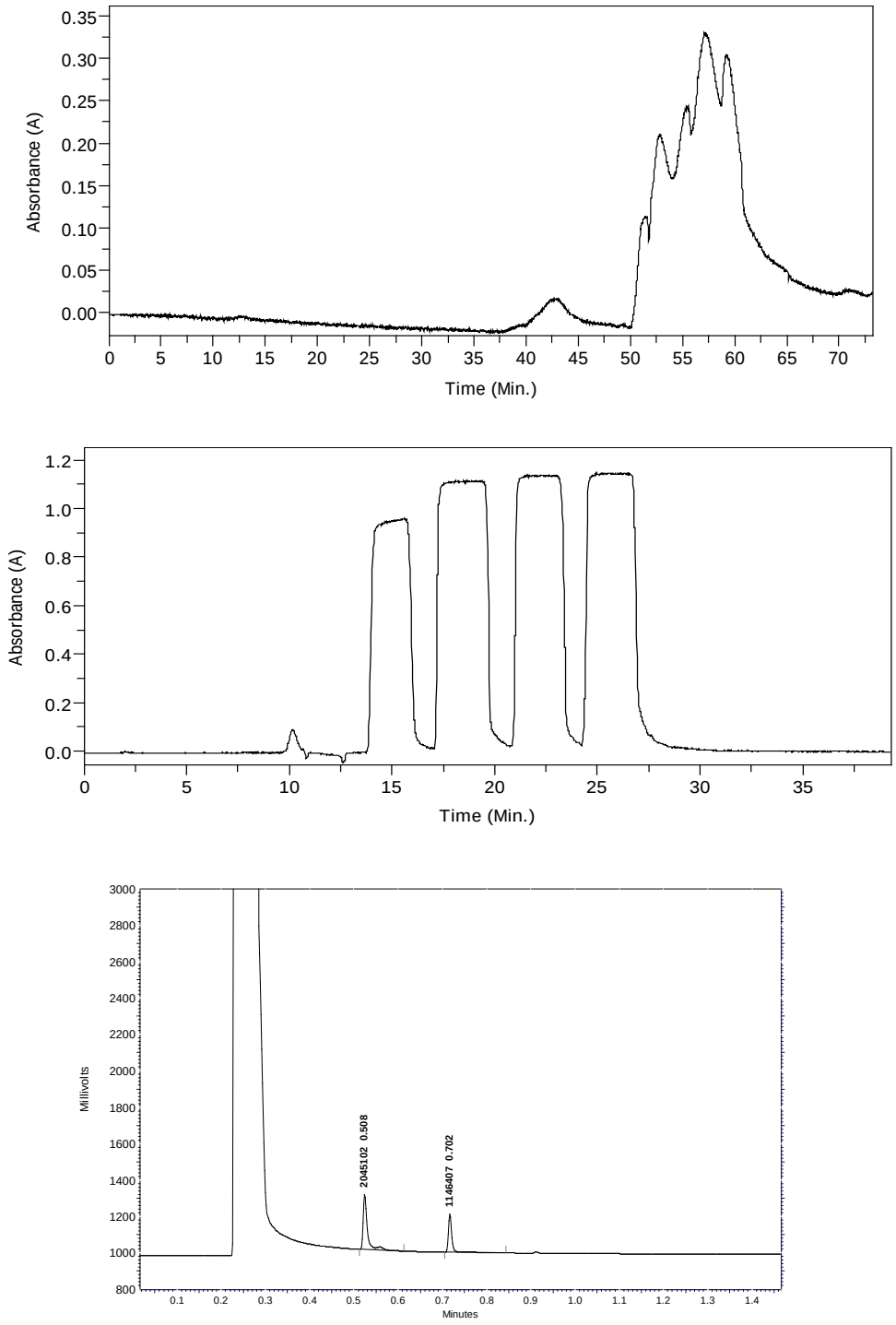


Figure 15. Upper: THF's effect in Teflon® tubing: six individual peaks combined to one large peak; Middle:the UV/vis result when aqueous ACN solution was used in SP2; lower: The GC result of reaction mixture without catalysts in Teflon® tubing.

In conclusion, the choice of capillary materials is not universal in all cases. The properties of catalysts and interaction of reaction solvents should be considered. In our case, the interaction of metal-catalyzed reaction and the surface of the fused silica glass capillary affected our experimental results. So in another strong Brønsted acid catalyzed reaction project, we chose the Teflon® tubing due to the same consideration.

More to add, when we changed the capillary material to Teflon®, the reaction zones were no longer separated if THF was used in syringe pump 2(SP2). Hence pure reaction solvent was used in SP2 to help maintaining the separated pattern. The initial purpose of using a different solvent to separate reaction mixture may not be a good method while pure reaction solvent works very well in most cases.

2.2.3 Reaction study

Based on Iowa et al., in the bench top, the allylation of benzaldehyde with tetraallyltin usually takes 3- 14 hour at 25-60 ^{o}C. Two different internal standards are used in our reactor: 2-ethyl-naphthalene is added into catalyst solution which is also the internal standard for the yield calculation and naphthalene is added to the tetraallyltin solution. The second standard naphthalene was employed to reflect the mixing ratio of starting substance and tetraallyltin in the reaction mixture.

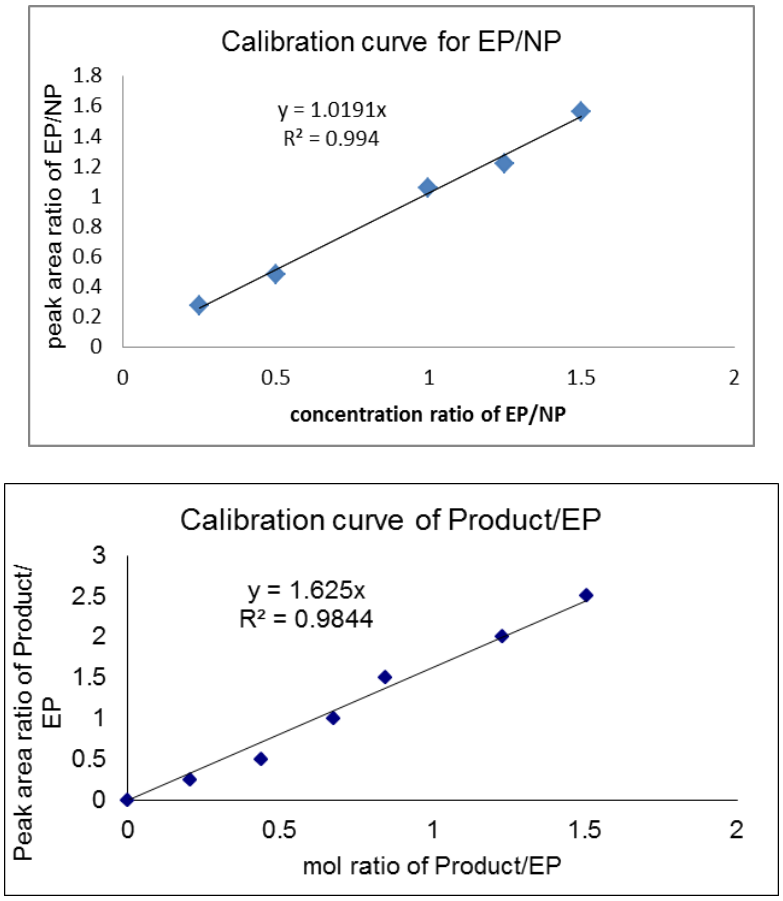


Figure 16. Upper: Calibration curve of 2-ethyl-naphthalene (EP)/naphthalene (NP); Lower: calibration curve of 2-ethyl-naphthalene (EP)/ product.

First the reaction was studied in bench top since we used a new solvent for the reaction. As shown in Figure 17, when $Sc(OTf)_3$ was used as the reaction catalyst, the reaction yield reached to 100% in around 90 min in the bench top, This helped us to set the residence time in the microreactor as 120 min at the beginning for complete conversion.

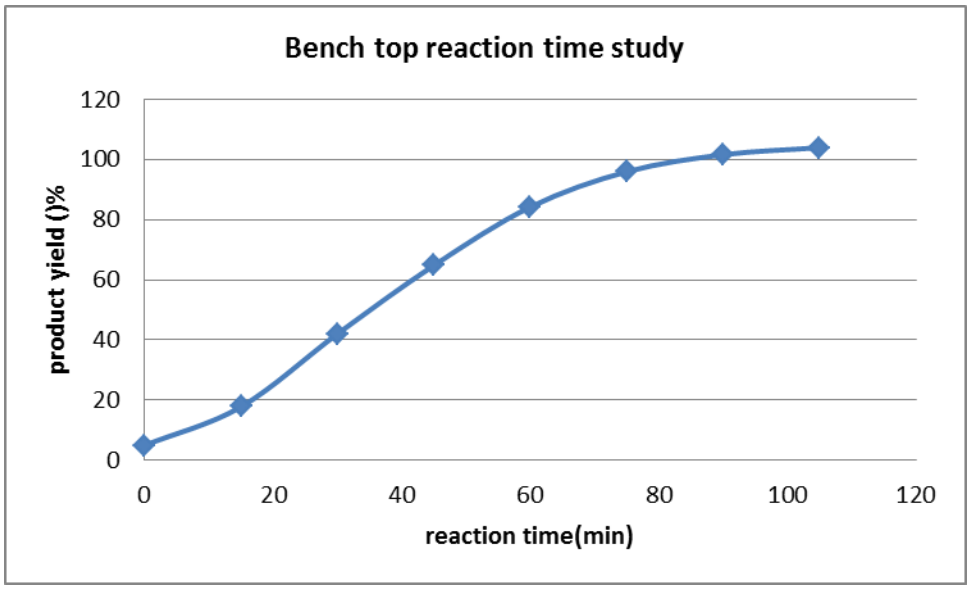


Figure 17. Bench top reaction time study

Figure 18 compares the reaction yields of the bench top and the microreactor. At initial stage (5.5 min), bench top reaction reached 31%, while the reactor only gave around 5%; but at the time of 120 min, they all reached 98%. The results reflected the reaction acted in a similar way to both in the bench top and in the microreactor.

Table 2. Yield comparison between the bench top and the microreactor

	Reaction time (min)	
	5.5	120
Bench top yield (%)	47.7	98.74
Microreactor yield (%)	4.89	98.55

The effect of catalyst loads on the reaction yield was first tested. As shown in Figure 19, the reaction yield increased in proportion to the catalyst loadings, from 1% to 10 %, until the reaction reached to maximum yield and then the yield became independent of catalyst loading (15%). Based on the catalyst mechanism, too little catalyst will not be enough for activate all the

reagents, while when the catalyst loading went over 10%, the reaction yield reached to maximum 100%, so increasing catalyst loading did not affect the yield any more.

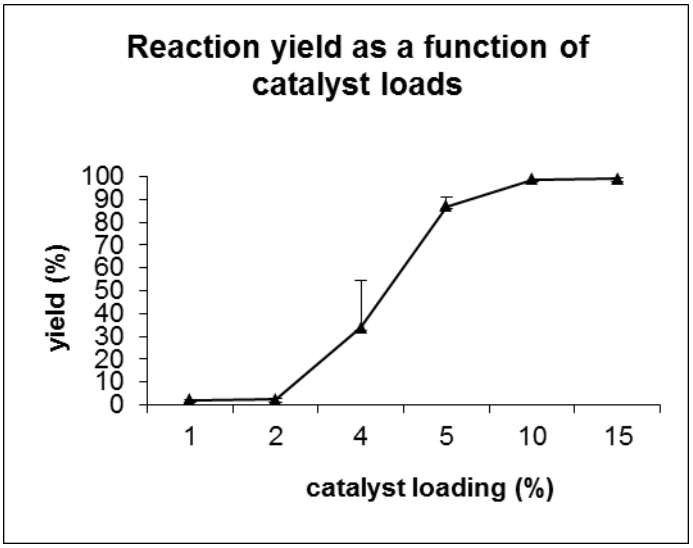


Figure 18. The effect of different catalyst loads in microreactor. Plotted data are mean ± standard deviation (n=3) 0.005 M benzaldehyde and 0.005 M 2-ethyl-naphthalene (internal standard) in CH_3CN/H_2O (4/1) with 0.5 mol equiv of tetraallyltin with various $Sc(OTf)_3$ concentration at 25 ^oC for 2 h

Another effect, the reaction temperature, was also studied for the allylation reaction. As most metal catalyzed reaction, the temperature has a positive effect on the reaction yield because it can accelerate the reaction rate markedly. In our experiment, three different temperatures were screened for the reaction efficiency. Compared to bench top reaction of 6 hr reaction time at 60 ^oC, the reaction yield reached to around 100% at 40 ^oC within 30 min. and reaction at 0 ^oC is much less efficient, only 14% product was detected in the reaction mixture. Also, these results also indicated that less time and much mild reaction condition were needed for the same yield in the microreactor than in the bench top.

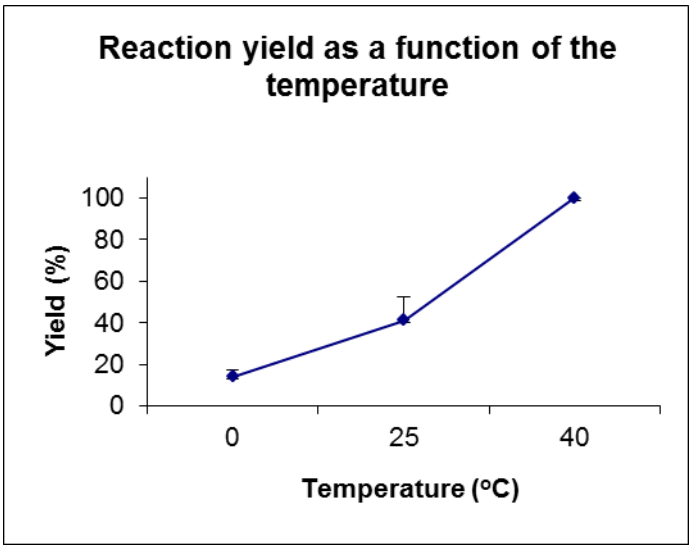


Figure 19. Reaction yield as a function of temperature. Plotted data are mean ± standard deviation (n=3) 0.005M benzaldehyde and 0.005M 2-ethyl-naphthalene (internal standard) in CH_3CN/H_2O (4/1) with 0.5 mol equiv of tetraallyltin and 0.15 mol equiv of $Sc(OTf)_3$ at various temperatures for 0.5 h.

The result above indicated the reaction was much faster when it was carried out by the microreactor than in the bench top, so we further test the reaction yield as a function of the reaction time. According to literature, the allylation of keton and aldehyde with tetraallyltin varied from several hours to days in different conditions. To get an optimum reaction time for the screening efficiency, I chose $Sc(OTf)_3$ catalyzed allylation as a test reaction for a standard reaction time. Figure 21 showed that at room temperature, the reaction reached to around 100% in 60 min. further increasing the reaction time has little effect on the reaction yield. Hence, the reaction condition was chose as in room temperature, 60 min residence time. Compared to reference bench top condition, it is much mild in the microreactor.

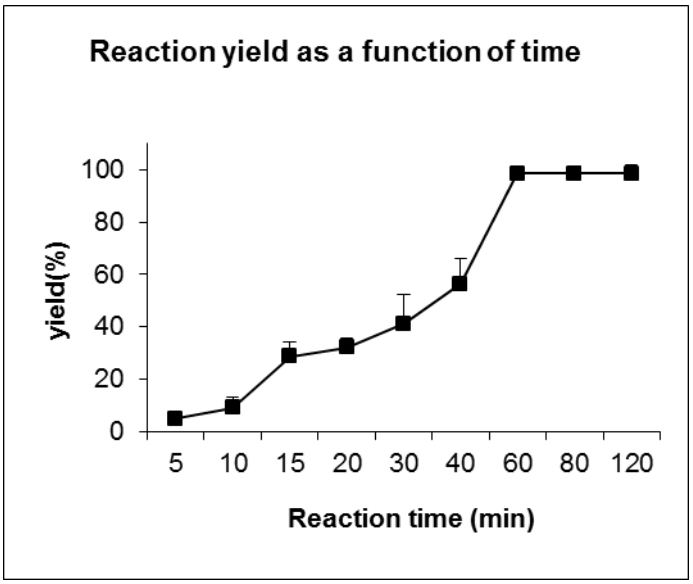


Figure 20. The reaction yield as a function of time. Plotted data are mean ± standard deviation (n=3). 0.005M benzaldehyde and 0.005M 2-ethyl-naphthalene (internal standard) in CH_3CN/H_2O (4/1) with 0.5 mol equiv of tetraallyltin and 0.15 mol equiv of $Sc(OTf)_3$ at 25^oC for various time.

Later, various catalysts were screened for this reaction. Results show in Table 2. In room temperature, a library of 8 different catalysts was screened for the allylation of benzaldehyde with tetraallyltin. We drew several conclusions from the data: The highest yield was achieved by using $Sc(OTf)_3$ as catalyst, followed by $Cu(OTf)_2$ and $Bi(OTf)_3$. Low yields were observed for the reactions using BF_3•Et_2O, TMSOTf and $Y(OTf)_3$ as catalyst. This may due to their sensitivity to the moisture, and aqueous phase is not a good reaction solvent for those catalysts.

Table 3. Product formation from various catalysts in an aqueous phase**.**

Entry	Catalyst	Yield(%)
1	$Sc(OTf)_3$	49.4 ± 4.33
2	$Cu(OTf)_2$	37.9 ± 4.63
3	$Y(OTf)_3$	3.7 ± 0.92
4	$Bi(OTf)_3$	36.6 ± 0.57
5	$Sm(OTf)_3$	27.2 ± 5.05
6	TMSOTf	6.4 ± 1.26
7	$BF_3{\cdot}Et_2O$	2.2 ± 0.35
8	$BiCl_3$	11.2 ± 2.63

Yields of substrate are determined by GC. Yield = mean ± std (standard deviation) (n =3). 0.005M benzaldehyde and 0.005M 2-ethyl-naphthalene (internal standard) in CH_3CN/H_2O (4/1) with 0.5 mol equiv of tetraallyltin and 0.15 mol equiv of various catalysts at 25^oC for 60 min.

When we extended the reaction in our reactor with other lanthanide catalysts, lanthanum trifluoromethanesulfonate and yttrium trifluoromethanesulfonate, both reaction yields went beyond 100% if we calculated them based on the calibration curve we made earlier.

At this point, the purity of the product peak was questioned by the unusual high yield. The product peak in the chromatogram contained more than expected product 4-phenyl-1-buten-4-ol. So the reactions was carried out in bench flasks with $Yb(OTf)_3$ and $La(OTf)_3$. At the end of the reaction, we used the TLC to compare the reaction mixture with standard product (Figure 22). Instead of the expect product, the reaction mixture showed another spot at R_f = 0.8. So the peak in chromatogram around t_R=0.513 was not the expected 4-phenyl-1-buten-4-ol.

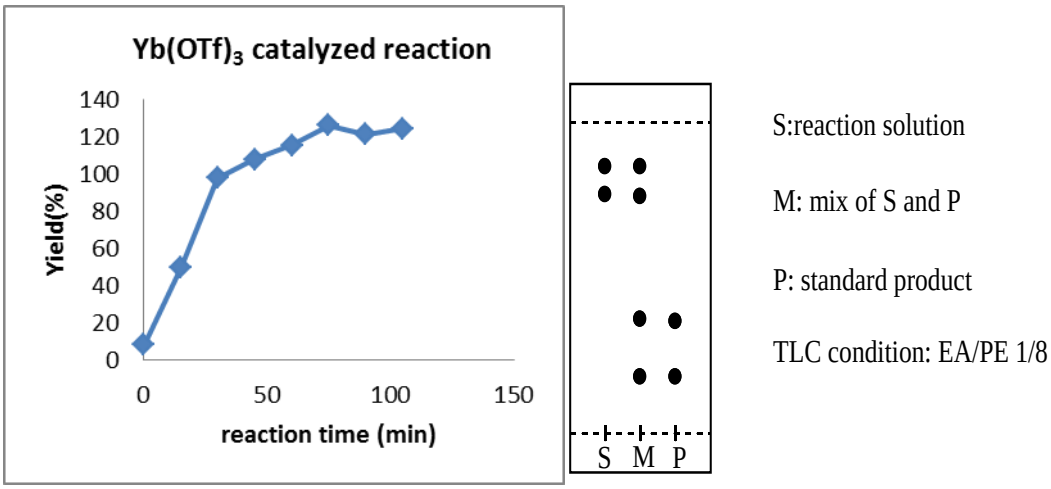


Figure 21. GC and TLC results of Yb $(OTf)_3$ catalyzed reaction

In the literature, there were some cases that 4-phenylbut-3-en-2-ol could be found in the reaction mixture [24]. Considering the unexpected product peak was completely overlapped with target product peak in GC, we think it might be the 4-phenylbut-3-en-2-ol. This assumption was further confirmed with MS due to the different fragmentation patters of the two compounds. The product peaks from $La(OTf)_3$ and $Yb(OTf)_3$ showed the spectrum on the left instead of the right one (Figure 22).

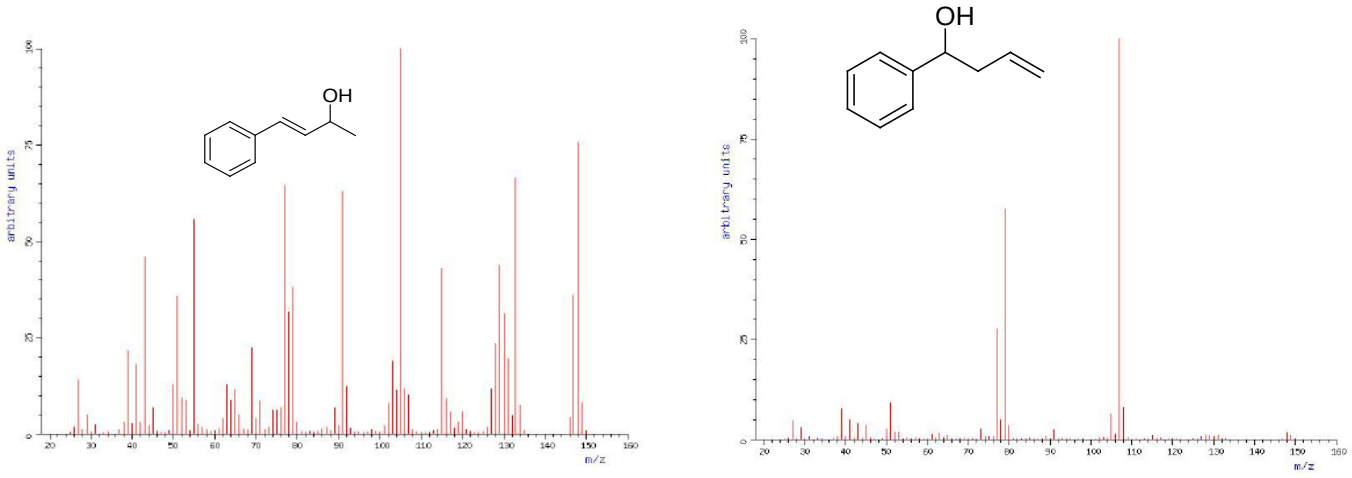


Figure 22. Mass Spectrum for the isomer (left) and target product(right).

In conclusion, The Lewis acid-catalyzed allylation of benzaldehyde with tetraallyltin has been successfully applied in the microreactor, and an improved reaction condition (r.t, 60 min) is

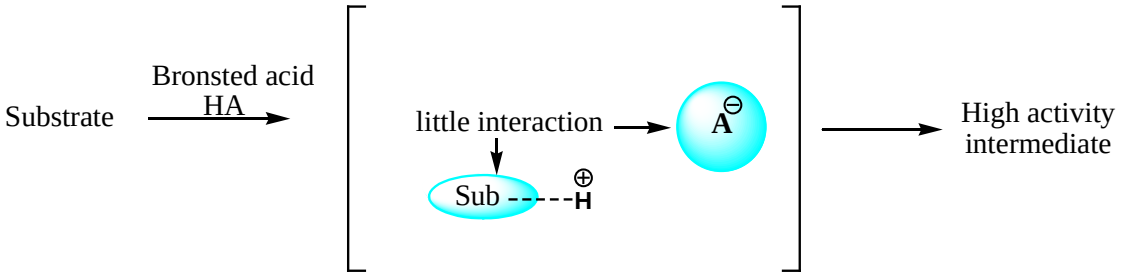
achieved by using our system. The effects of catalyst loading, temperature, reaction time are studied for the best yield. The reaction is good to be carried out at higher temperature (40 ^{o}C) and only 30 min reaction time is needed to achieve maximum yield. 8 Lewis acids are screened for the reaction.

3.0 ENANTIOMERIC SEPARATION METHOD DEVELOPMENT FOR STRONG CHIRAL BRØNSTED ACID CATALYZED CYANIDE ADDITION REACTION

Chiral Brønsted acid catalyst has attracted a lot of research attention due to its versatile applications in synthetic chemistry [25]. Conventionally, it was only considered as a proton-giving catalyst, which functions through a protonated substrate (Sub-H^+) with an unfavorable interaction to form highly active intermediates, and its conjugate base (A^-) is not involved (Figure 23). Chemists devote to develop "superacids", which can generate unstable, highly reactive intermediates during the reactions. However, according to the research on chiral Brønsted acid catalysts in the last decade, the conventional mechanism is not accurate. A chiral environment must be formed during the process in order to give a chiral product, and hydrogen-bonding between the conjugate base (A^-) and the substrate (Sub-H^+) appears to be a key factor in this catalytic mechanism (Figure 23). The chiral transformation proceeds under the chiral environment provided by the conjugated base.

The first example of chiral Brønsted acid catalyst was demonstrated in the enantioselective Strecker reaction by Jacobsen and co-workers [26], since then numerous works have been reported on the chiral Brønsted acid catalysis. These results indicated that a chiral Brønsted acid could discriminate enantiotopic faces between imine substrates through hydrogen bonds, which led to a novel approach in the chiral catalysis without any use of chiral metal (Lewis acid) catalysts.

a). conventional mechanism



b). modern mechanism

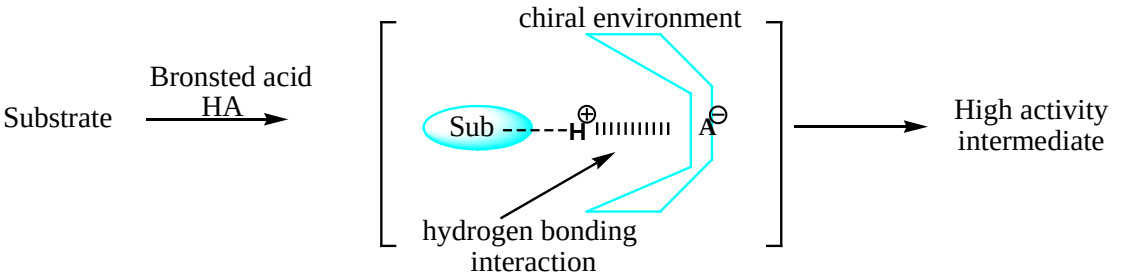
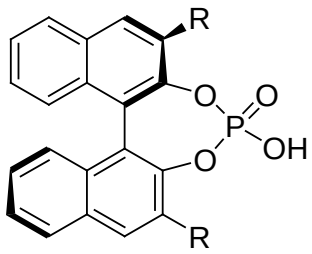


Figure 23. Brønsted acid catalysis in organic reaction[25]

Our small-dimension, capillary-based microreactor can be a useful tool for the screening of chiral catalysts as well as reaction conditions. Currently, there are only a few examples of enantioselective reactions that have been carried out in the reactor system, and none of them is coupled with online analysis. For applications of our microreactor in asymmetric reactions, developing online enantiomeric separation methods is critical to provide the near-real-time reaction monitoring.



R	R
a: H	**h**:2,4,6-*i*-$Pr_3C_6H_2$-
b: C_6H_5 -	**i**: 4-MeC_6H_4 -
c: 4-PhC_6H_4 -	**j**:4-$CF_3C_6H_4$ -
d: 4-naphthylphenyl	**k**:4-*t*-BuC_6H_4 -
e: 9-anthryl	**l**:-naphthyl
f: 3,5-dimesitylphenyl	**m**: 3,5-*t*-$Bu_2C_6H_3$ -
g: 3,5-dephenylphenyl	**n**: 2,4,6-$Me_3C_6H_2$ -

Figure 24. BINOL-derived monophosphorie acids as chiral Brønsted acid catalysts

3.1 EXPERIMENTAL SECTION

Materials 1-(benzyloxy)hexyl acetate, 1-methoxy-3-phenylpropyl acetate, 1-(benzyloxy)-3-phenylpropyl acetate, (E)-(4-methoxybut-3-enyl)benzene and coordinate products 2-(benzyloxy)heptanenitrile, 2-methoxy-4-phenylbutanenitrile, 2-(benzyloxy)-4-phenylbutanenitrile, 2-(methoxymethyl)-4-phenylbutanenitrile were prepared by Lu, a student from Professor Floreancig's group. TMSCN was distilled before used. And DCM was desiccative by refluxing in CaH_2. Brønsted acid catalysts (Figure 25) were synthesized by Professor Floreancig's group as well.

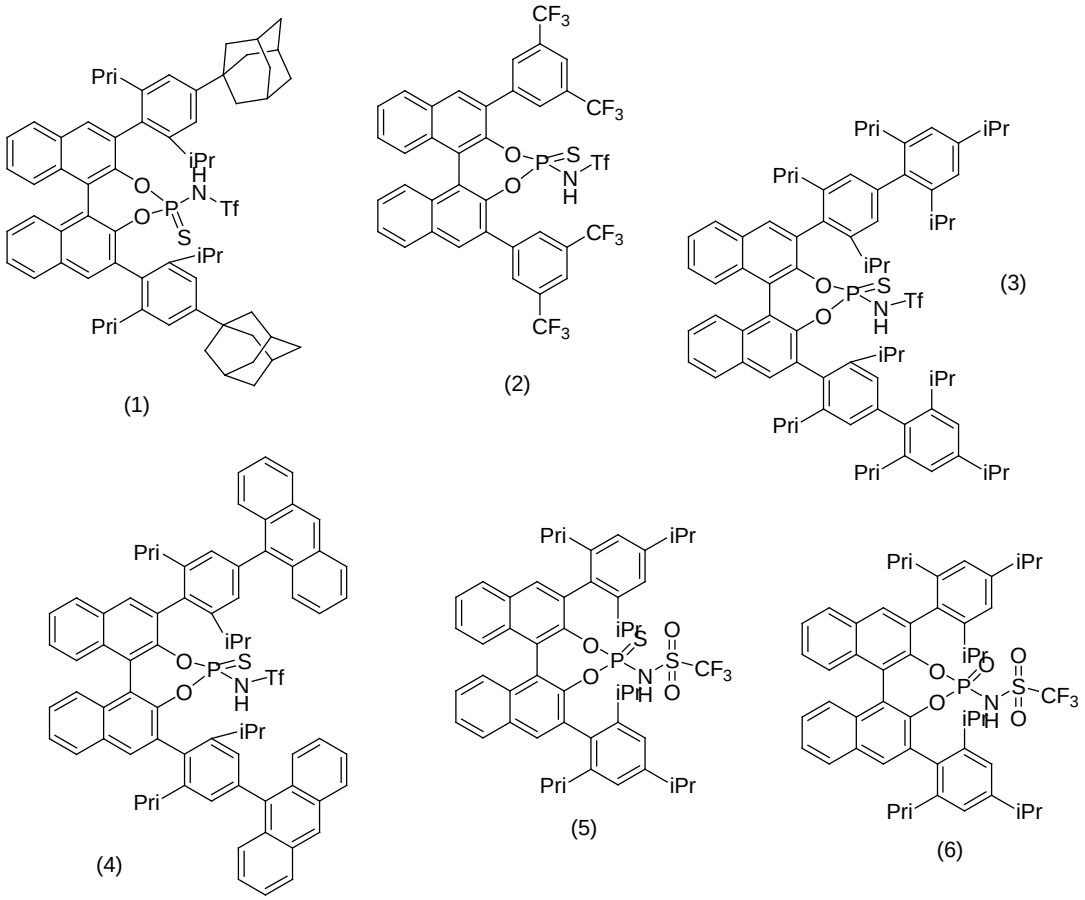


Figure 25. Brønsted acid catalysts

GC methods: Astec CHIRALDEXTM G-TA, 30m×0.25mmID ×0.12μm film thickness.

	Temperature(^{o}C)	Holding time(min)
Initial	110	30

Oven run-time: 30 min

Maximum temperature: 180 ^{o}C

Equilibration time: 0.1 min

Solution preparation: TMSCN and 2,4,6-trimethylphenol (0.04mol/L) solution: TMSCN was dissolved in DCM with 2,4,6-trimethylphenol; the substrate (0.01 mol/L) was dissolved with 1 mL DCM as well as the catalyst (1-5%).

3.2 RESULTS AND DISCUSSION

The reaction we chose to test is a strong chiral Brønsted acid catalyzed asymmetric cyanide addition reaction, as shown in Figure 26. The reason we are interested in this particular reaction is that the cyano group is a versatile building block which can be transferred into amino acid and other valuable substrates. Similar substrates with different substituent groups were tested in our microreactor.

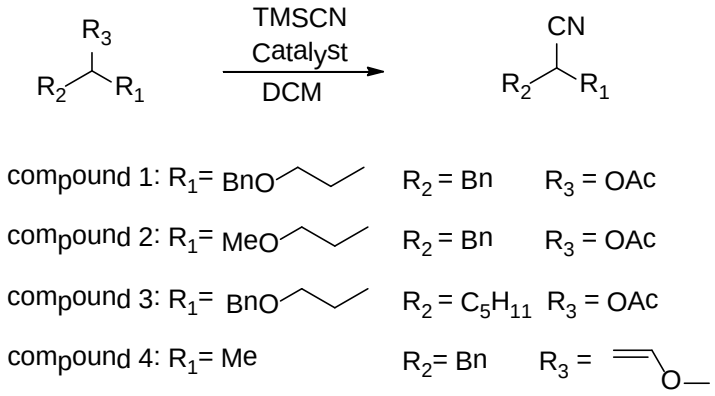


Figure 26. Test reactions for strong chiral Brønsted acid catalyzed reactions

3.2.1 Online analysis method development.

The most difficult part in this method is the separation of two isomer products. Both HPLC and GC chiral columns were tested to accomplish this goal. We started with the development of HPLC methods, which involved five different chiral columns. Various separation conditions were tested, using either reverse phase or normal phase. However, no separation was achieved in these columns, as shown in the Table 4. In all the conditions, the best resolution we can get is Rs=1.4 with extremely tailing effects by using cyclobond 1 200 DM. Then compound 4 was

Table 4. HPLC results for interested products with different columns

Mobile Phase	Compound 1	Compound 2	Compound 3	Compound 4
Hexane :IPA	Cellulose-1 (9 :1): R_s= 0 Celluose-2(9 :1) R_s=0 Chiralpak (7 :3) R_s=0.1	Cellulose-1: (9 :1) R_s= 0 Cellulose-2(9 :1) R_s=0 Chiralpak (7 :3) R_s=0	Cellulose-1: (9 :1) R_s= 0 Cellulose-2(9 :1) R_s=0 Chiralpak (7 :3) R_s=0	Cellulose-3 (99 :1) **R_s=2.5** Chiralpak (95 :5) **R_s=2.5**
Hexane : EtOH	Chiralpak (6 :4) R_s=0	Chiralpak (6 :4) R_s=0	Chiralpak (6 :4) R_s=0	
ACN : IPA	Cellulose-1 : (0 : 1) R_s=0.5 Cellulose-2 R_s=0.2	Cellulose-1 : (0 : 1) R_s=0.42 Cellulose-2 R_s=0.1	Cellulose-1 : (0 : 1) R_s=0.2 Cellulose-2 R_s=0	
ACN :MeOH	Cellulose-1 (1 :9) R_s=0 Cellulose-2 R_s=0	Cellulose-1 (1 :9) R_s=0 Cellulose-2 R_s=0	Cellulose-1 (1 :9) R_s=0 Cellulose-2 R_s=0	
ACN:H_2O	Chiralpak (4 :6) R_s=0	Chiralpak (4 :6) R_s=0	Chiralpak (6 :4) R_s=0	
ACN + 20mM NH_4HCO_3 + 0.1 % DEA	Cellulose-1 (8 :2) R_s=0 Cellulose-2 R_s=0	Cellulose-1 (8 :2) R_s=0 Cellulose-2 R_s=0	Cellulose-1 (8 :2) R_s=0 Cellulose-2 R_s=0	
MeOH + 20mM NH_4HCO_3 + 0.1 % DEA	Celloluse-1 (6 :4) R_s=0.2	Celloluse-1 (6 :4) **R_s=0.85**	Celloluse-1 (6 :4) R_s=0.3	
H_2O/1-PrOH/MTBE	Cyclobond 1200 DM (97.5/2/0.5) **R_s=1.4**	N /A	N /A	
H_2O/EtOH/MTBE	N /A	Cyclobond 1200 DM (90/9.5/0.5) R_s=0.5	N /A	

introduced, and resulted in similar product in the reaction. In this case a good resolution for the two enantiomers within 20min was achieved in Lux Cellulose-3 column. However, due to the incompatible issue between column stationary phase and reaction solvent (dichloromethane), we cannot use this as our interfaced online analysis method.

Since the interested compounds are all small molecules, and GC has no limitations for reaction solvent, a GC chiral column- G-TA column- was also investigated for the interfaced online analysis method. Primary screening showed that an enantiomeric separation for one of the compounds' isomers was achieved using this chiral column (Figure 27).

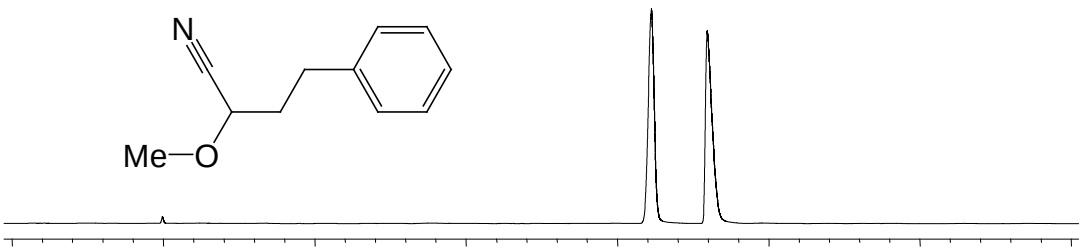


Figure 27. GC separation method of 2-methoxy-4-phenylbutanenitrile: G-TA column (30m ×250 um), flow=10 ml/min, oven T (^{o}C) =110. injector/ detector T (^{o}C)= 250.

Further effort was directed to reduce the separation time for this enantiomeric separation method. There are three parameters we can adjust to alter the retention time of the isomers in GC: oven temperature, carrier gas flow rate and column length. Our first attempt was temperature programming. Increasing temperature programs with various starting points from 50 ^{o}C to 180 ^{o}C were tested, with a ramp of 5 ^{o}C/min. However, from t =14 min, the baseline began to drift badly to the end of the chromatogram. And product peaks were not observed (Figure 28). Reversing the gradient was also tested for our situation. The decreasing gradient program began from 130 ^{o}C, ended at 90 ^{o}C with an oven ramp of -5^{o}C/min. The resolution of the enantiomers decreased, and could not be used for quantity analysis. Increasing the flow rate also resulted in

loss of resolution, due to less effective radial mass transfer, and it also required a high split flow rate which was not achievable for our current GC instrument. Last parameter that might be adjusted is the column length, which means cutting the column to a shorter length. Since this is an irreversible change, we decided to keep the column length. As a result of the above efforts, the final GC method is as follows: flow=10 ml/min, Oven Temperature (^{o}C) =110. injector/detector temperature (^{o}C) =250.

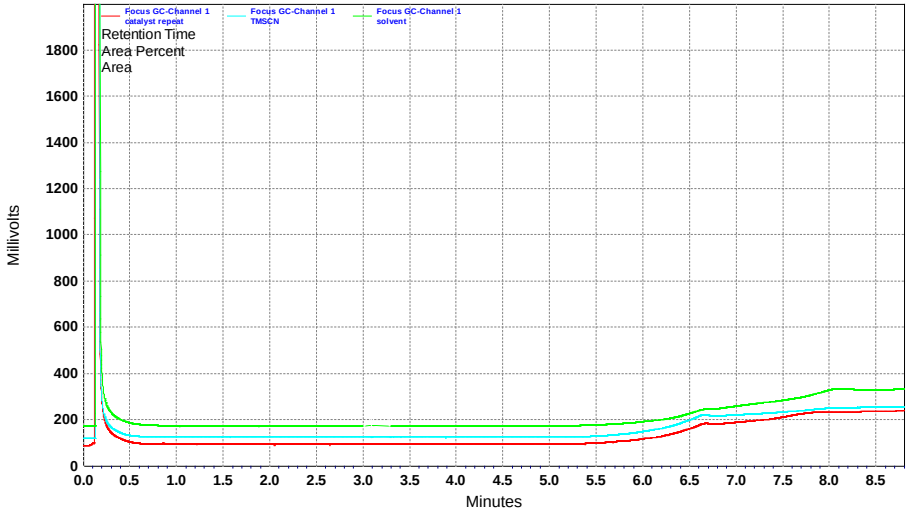


Figure 28. Gradient temperature programing in GC method caused base-line drifting

Figure 29 depicts the stationary phase structures of 6 different chiral columns we screened for the enantiomeric separation of our product. We got excellent resolutions of product isomers in Cyclobond 1 2000DM and G-TA column, both of which are the cyclodextrin-derivative functionalized column. These results indicate that cyclodextrin bonded phases are powerful tools for small molecules with similar structure like our target products.

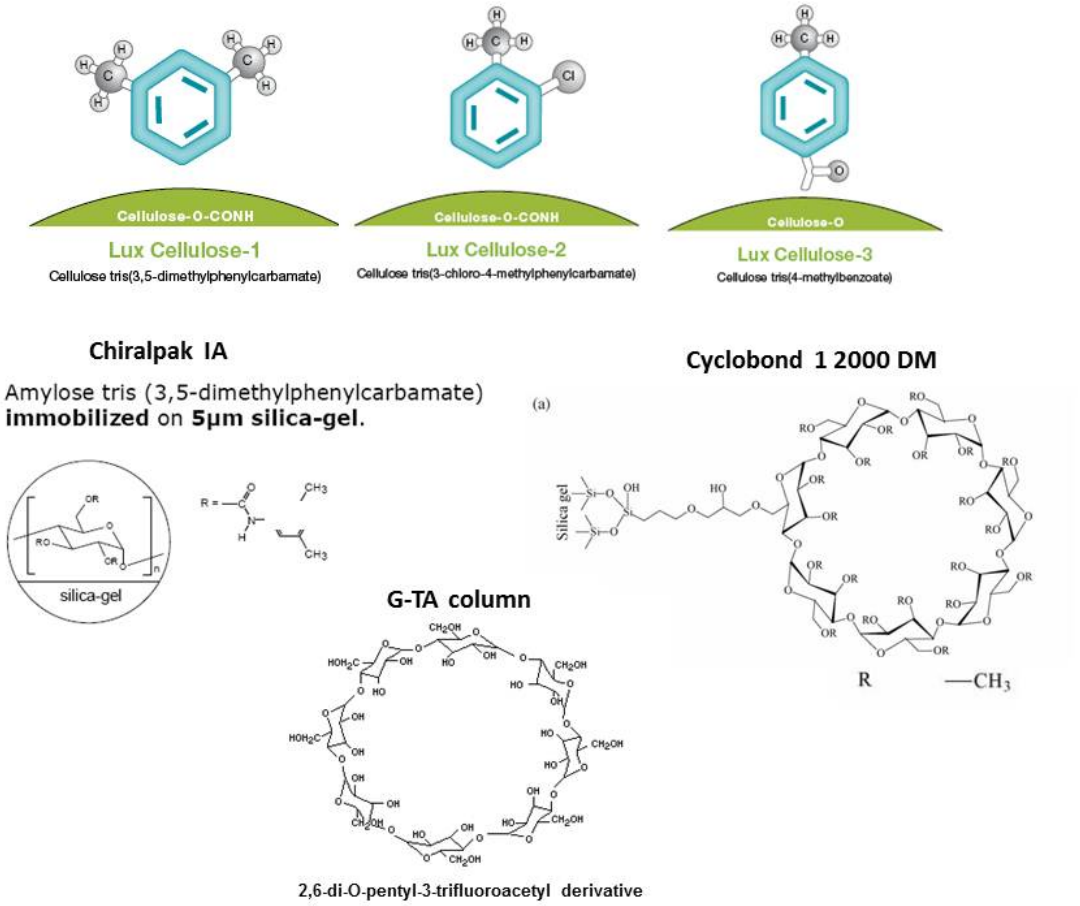


Figure 29. The stationary phase of five chiral columns used for product-isomer separations[28].

4. FUTURE PLAN

4.1 LANTHANIDE-CATALYZED REACTION

Lewis acid catalysis is widely used in organic synthesis, due to the advantage of its reactivity and selectivity. However, the traditional Lewis acids, such as $TiCl_4$, $AlCl_3$, BF_3, are used more than stoichiometric amount in many of those reactions. And they are sensitive to moisture, can be easily decomposed or deactivated in the presence of the trace amount of water. Recent year, the lanthanide triflate catalyst has been used as catalysts in various reactions because of its water-compatible character. They are considered to be a promising star in Lewis acid catalysis. And in most cases, just a catalytic amount of the rare-earth metal triflate is needed for the reaction.

Even though we encountered some problems due to the properties of the test reaction, above experiments and results proved that the idea and the setup of our microreactor works well in general. Teflon® capillary tubing is used as the capillary reactor in our system, various catalysts and reaction conditions have been screened. Next step, similar reactions can be applied and investigate in our system, not only the type of catalysts and reaction conditions, but also reaction mechanism study. By changing the flow rate of the syringe pump, we can get near-real-time reaction monitor for different reaction stage.

4.2 CHIRAL BRØNSTED ACID CATALYZED ASYMMETRIC CYANIDE ADDITION

The Lewis acid catalyzed chiral reaction has been well investigated and widely used in organic synthesis, while Brønsted acid chiral catalyzed reaction has just become a new strategy to introduce enantioselectivity. Since the first example of Brønsted acid catalyst, many developments have been achieved by scientists. And according to the recent research, the structure of Brønsted acid is more than a conjugate base; it also provides chiral environments for the intermediate. Various derivatives bring different enantioselectivities for the reactions. The pioneering work done by Jacobsen/Sigman and Terada/Uragichi has brought intense research interests to this area.

Due to the structures of the targeting products, we encountered difficulties in the enantiomeric separation method development of the product. Six chiral columns, various conditions have been screened and a GC method with G-TA column is developed and can be interfaced as online analysis method. Further efforts will be focused on applications of asymmetric reactions in our capillary-based, high throughput microreactor system. The study of effects of diverse starting reactants, various bases, different temperatures and flow rates can be performed for reaction optimizations. The parameters of each component need further adjustments to make the microreactor work smoothly and efficiently.

4.3 MCR SYSTEM

MCR refers to “Multi-component reaction”, the reaction consisted of three or more components to form a single product. Hence the multi-component reaction is able to give a highly selective product in major yield[27] Examples can be found in Alkyne trimerisation, Mannich Reaction, Strecker amino acid synthesis and many other reactions. It provides a method to combine two or more steps together, skipping the wash up, and environment friendly.

Right now, our microreactor is capable of processing one-step, homogeneous catalyst reaction. By adding new reagent resource after one conversion, we can accomplish the catalyst screening of multi-step reaction in one device (Figure 30). Meanwhile, the new source can also be a quenching solution, for the study of some reaction mechanisms.

Furthermore, the catalyst in the microreactor can be used several times by immobilizing on the surface of the capillary reactor. With continuous flow in sequence of different capillary reactors, multi-catalyst reaction can also be investigated in microreactor.

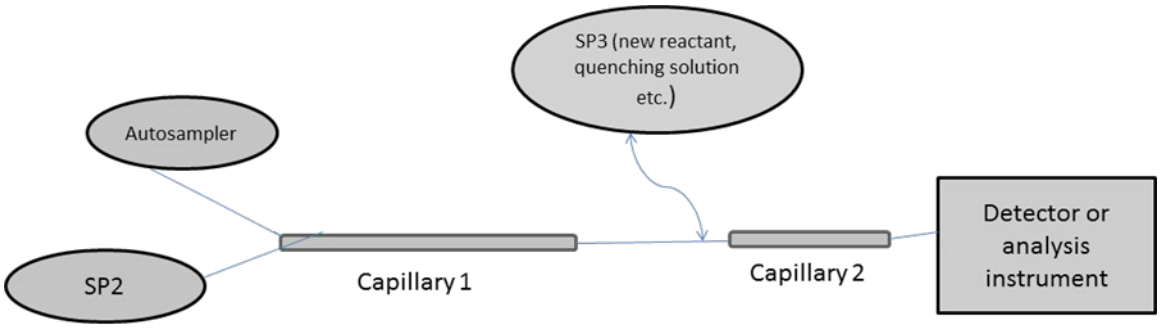


Figure 30. Future conceptualization of multi-step, multi-catalyst screening system.

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d) http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Sigma/ General _Information/chiraldex_handbook.pdf.

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