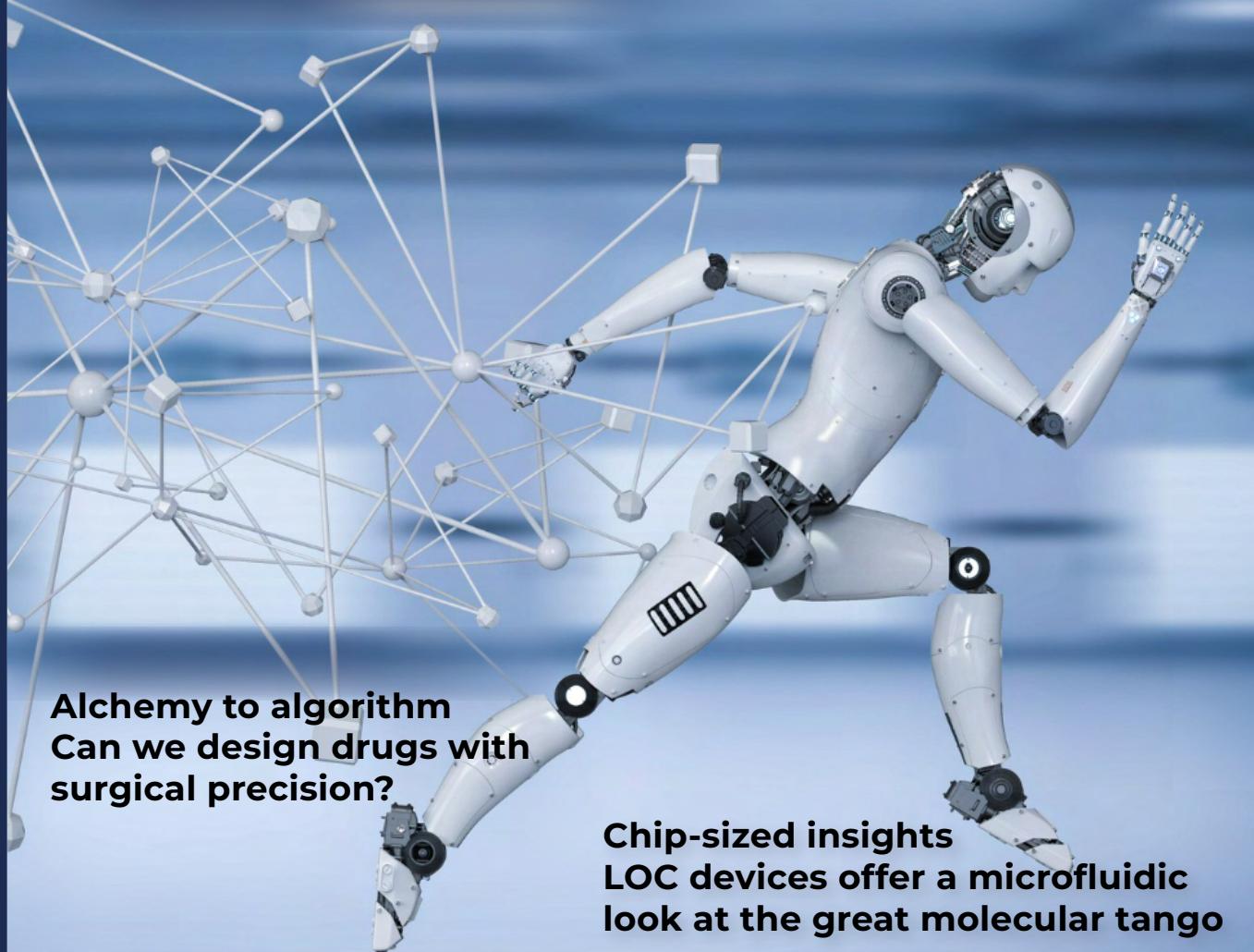


THE FUTURE OF CHEMICAL SYNTHESIS

Excerpts from an interview with

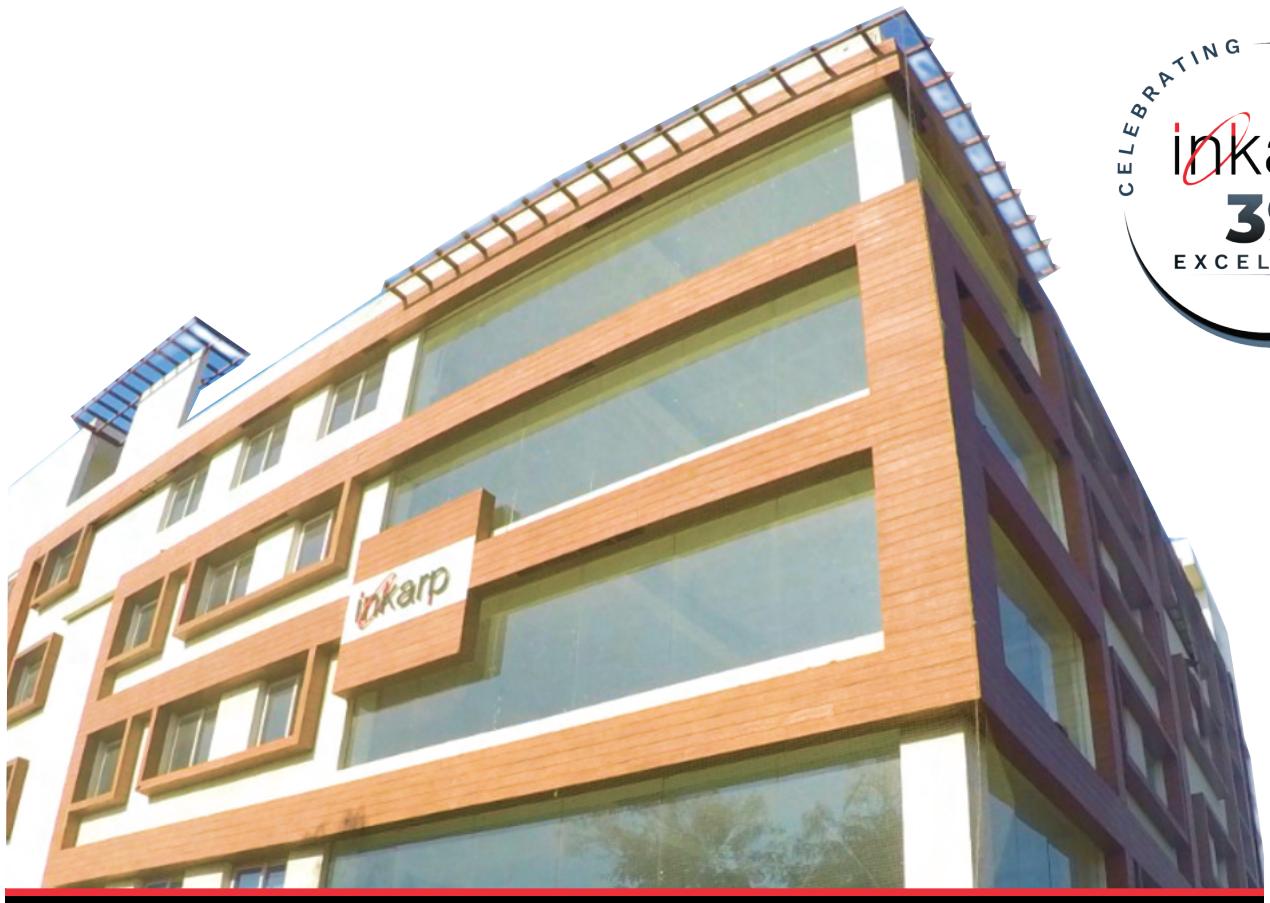
Mr. S. Balu

(CMD Inkarp group of companies)



**Alchemy to algorithm
Can we design drugs with
surgical precision?**

**Chip-sized insights
LOC devices offer a microfluidic
look at the great molecular tango**



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From the editor

Dear CatalystCue readers,

Warm greetings to all of you!

It's with immense joy and a sense of shared vision that I welcome you to this edition of **CatalystCue**. As someone who has witnessed the pulsating rhythm of the science and technology sectors for years, the introduction of this platform feels like a significant milestone for us at Inkarp Instruments and, I believe, for everyone passionate about our industry.

The inception of CatalystCue was born out of a vision: to bridge the exciting, ever evolving world of scientific advancements with the eager minds that yearn to know, innovate, and grow. Every page you turn in this magazine is curated with that intent, bringing insights from the field, reflections from experts, and, most importantly, stories of innovation and passion.

In this issue, apart from diving deep into the latest industry advancements, I've also indulged in reflecting on our shared journey. And in doing so, I've realized that while technology and innovation are our tools, it's the human spirit, the insatiable curiosity, that drives us forward.

From enlightening interviews to taking a closer look at products that are setting new industry standards, CatalystCue aims to ignite your passion, inspire your projects, and offer you fresh perspectives.

As we set forth on this new journey together, I would love to hear from you. Your feedback, ideas, and stories are the heartbeat of CatalystCue. They help us ensure that with each issue, we're not just sharing information but fostering a vibrant community of innovators.

Here's to a future filled with discovery, collaboration, and boundless inspiration. Welcome to CatalystCue, our collective ode to the wondrous world of science and technology.

Best regards,

Arun Mathrubootham
Director
Inkarp Instruments Pvt. Ltd.

AUGUST 2024

Volume 01 Issue 01

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Alchemy to algorithm: Computational approaches to 'warhead' prediction in targeted covalent inhibitors

Historically, covalent drugs were not the preferred choice due to their undesirable toxicity issues. However, in the recent years, covalent inhibition has seen major developments. In contrast to their non-covalent counterparts, TCIs react with one given amino acid residue in a target protein and produce stable, covalent modification which is irreversible. However, enhancement on TCI efficiency is most dependent on the choice of the warhead – the functional group, which is involved in the formation of covalent bond. This critical component should have the right measure of reactivity to produce strong target inhibition and right measures of selectivity so that off-target interactions and subsequently side effects will be kept to a minimum. Earlier, the selection of chemical warhead was based on the existing scientific knowledge. However, the accessible chemical space is immensely larger, and the complexity of protein interactions involved necessitate a more sophisticated approach.

This article delves into various computational techniques that assist in the design of TCIs with optimized warhead functionalities.

1. A two-pronged in-silico approach: Computational modelling approach deals with TCI selectivity in a step-by-step manner, which is basically a two-step process.

a) Non-covalent binding prediction: These simulations help to judge as to how well a TCI is accommodated into target protein binding site. Since docking involves the precise determination of the interactions between the warhead and amino acid residues, it can reveal possible covalent bonding locations.



Can we design drugs with surgical precision?

AutoDock Vina and Glide softwares use complex scoring functions that estimate the binding affinity as well as the pose of the TCI in the active site of the protein. This first pass of the screening focuses on identifying warheads that have the correct binding orientation that suggests that an actual covalent bond could be forged with the specific amino acid.

Key considerations here include:

• Electrostatic Interactions:

These interactions play a very crucial role in binding affinity and selectivity because they determine the strength of hydrogen bonds and salt bridges between the inhibitor and active site residues.

• Hydrophobic Interactions:

Docking programs compare the levels of compatibility in the two substrates; the polar inhibitor and the polar receptacles in the active site. A greater hydrophobic interaction is a driving force that makes the binding site preferable to the ligand than other sites.

• Steric Considerations:

Evaluation of the shape and size of the inhibitor relative to the active site ensures a good fit and avoids steric clashes with surrounding residues, which could lead to decreased affinity.

Cover story

Although docking simulations are mainly based on force field calculations, they do not consider entire covalent bond formation in detail.

b) Quantum Mechanics/Molecular Mechanics (QM/MM) Calculations: QM/MM simulations address this limitation by providing a more precise description of the covalent bond formation process by treating the warhead and its immediate environment quantum mechanically, while representing the rest of the system classically. This makes it possible to understand the reaction pathway with special reference to the formation of covalent bond as well as the energy changes during the reaction process.

- **Warhead reactivity:** QM/MM enables one to study the electronic structure of the warhead and its ability to form a covalent link with the target amino acid residue.

- **Reaction mechanism:** These simulations can help explain the basic sequence of events of the covalent bond formation process and the actual attack by the warhead together with the bond rearrangement.

- **Energetic landscape:** If one looks at the energy profile of the reaction, it is possible to understand which processes are hindered by potential energy barriers to covalent bond formation. This knowledge will be useful in enhancing the conception of proper warhead design towards reasonable covalent bond synthesis.

- **Minimizing off-target interactions:** It is possible to predict off-target binding sites of a warhead by using the energetics of warhead-protein interactions. This lets in changes to the warhead structure in a way that reduce reactivity to other proteins hence lowering side effects.

2. Free Energy Perturbation (FEP) calculations: While QM/MM predominantly deals with the warhead fragment only, FEP calculations give the overall idea of binding affinity. This technique mimics the change process of a non-covalent inhibitor to its covalently bound form and the free energy change for each process can be evaluated. FEP calculations could help outline the inherent energy contrasts between on-target and off-target modes that would generally

lead towards quantification of binding strength as well as warhead selectivity and low off-target reactivity.

3. Machine Learning (ML) models: Thanks to the power of big data; the use of ML applied to databases from docking, QM/MM, and FEP simulations can also help in warhead prediction. From these large databases, trained ML models can predict the reactivity and selectivity of new and efficient warhead designs. Machine learning models can also be trained to apply online methods to examine vast databases of potential warhead structures for the most favourable interactions related to covalent bond formation and selectivity.

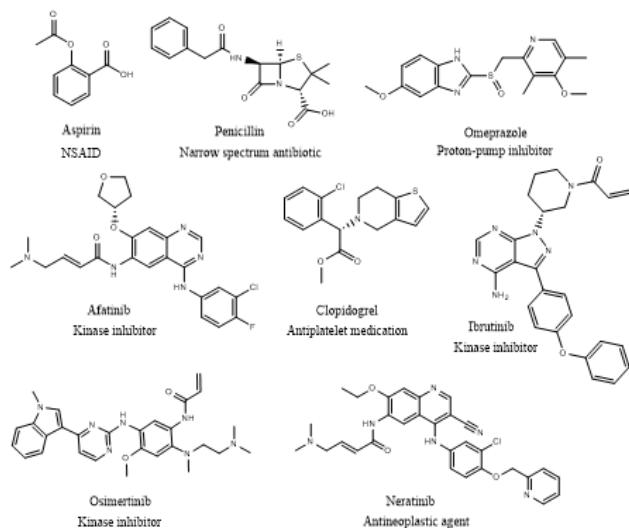
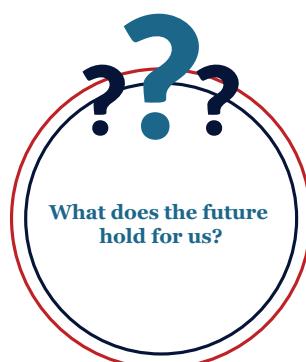


Figure: Few of the FDA approved covalent inhibitors

The field of computational warhead prediction is constantly evolving, with exciting advancements on the horizon:



- **Incorporating Protein Dynamics:** The methods operating today can be questionable as they assume protein structures to be in a fixed state. But proteins naturally have conformational freedom which can alter the interaction between the warhead and the

protein. In the future models, it may be possible to incorporate protein dynamics simulation to increase accuracy of the predicted behaviour of the warhead in the context of binding pocket environment.

- **Cellular context integration:** TCI depends much on the cellular environment. Some influences may include the presence of other molecules, the differences in the pH levels, and effects of cellular enzymes. The inclusion of such factors into computational models will strengthen that of warhead design and selectivity prediction of TCIs, which should ultimately translate into *in vivo* efficacies.

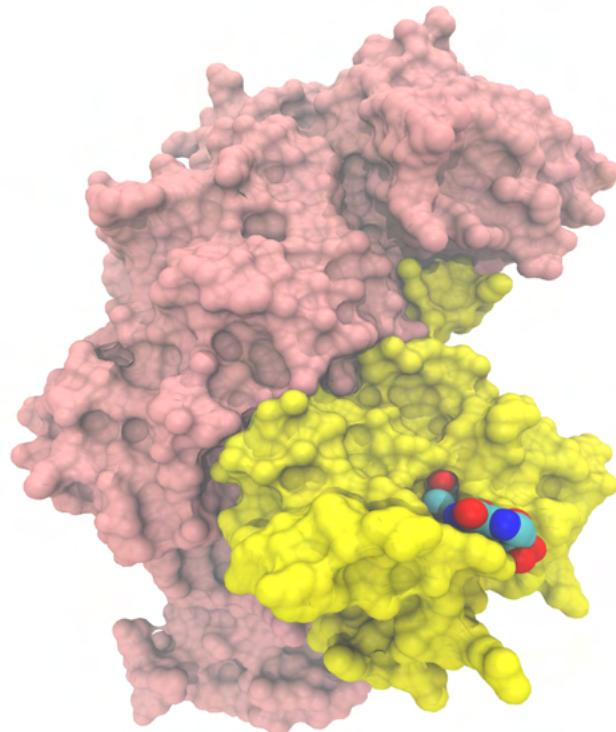
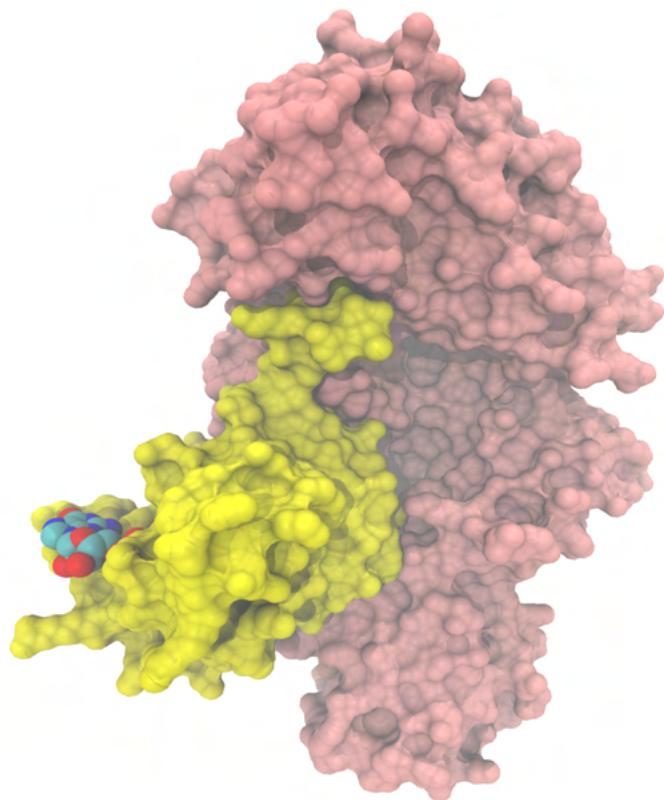
- **AI-driven design:** Modern advancements such as artificial intelligence has the capability of greatly enhancing warhead identification. AI algorithms can discover the chemical space beyond human experience and knowledge and suggest new warhead actions with the best reactivity and selectivity. This has a great potential for synthesizing very effective and selective TCIs with almost no toxic effects.

Conclusion

Nowadays, the field of warhead prediction in TCIs is rapidly shifting due to the emergence of computational methods. Also, the combined application of elaborate methodologies allows researchers to advance the knowledge of warhead action mechanisms and the effects observed on TCI efficiencies. Such an approach opens possibilities for the design of highly active and selective TCIs that will have reduced side effects.

Thus, with the progress of the field due to developments in protein dynamics simulations, integration of cellular context, and the use of AI in design, a new generation of TCIs with unprecedented therapeutic value is approaching.

-CC



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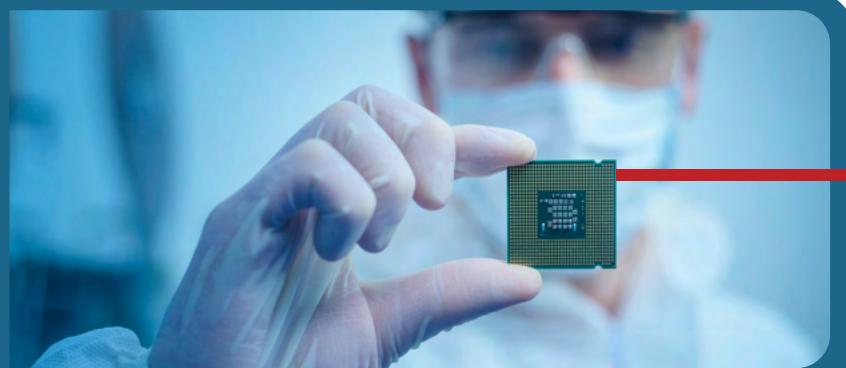


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AUGUST 2024



Chip-sized insights

LOC devices offer a microfluidic look at the great molecular tango

A plethora of biological processes depend heavily on the complex interplay between ligands and proteins. The hunt for new drugs is critically dependent upon our ability to understand this molecular tango, measure it most accurately and characterize these interactions. Known techniques such as Surface Plasmon Resonance (SPR), Isothermal Titration Calorimetry (ITC), X-ray crystallography, and Nuclear Magnetic Resonance (NMR) spectroscopy are being used to analyse these interactions. While these approaches offer invaluable information, there are frequent limitations in terms of sample amount, throughput, and scalability. Thus, new tools and methods must be explored that will help in streamlining protein-ligand interaction studies workflow.

What?

Lab-on-a-chip technology packs functionality of an entire laboratory within a small gadget that is as big as a pen drive. This palm-sized device engraved with small networks, that controls the act of fluids even down to the molecular level can explain the physiological functioning of humans.

LOC platforms appear to hold great promise in various applications, including human diagnostics, DNA analysis, and, to a lesser extent, even chemical synthesis. Complex chemical and biological tests are miniaturised using LOC devices which are built on a microfluidic substrate.

Lab-on-a-chip devices can be exploited to our benefits in comprehending ligand-protein interactions.

Why?

Reduced sample volumes: LOC platforms utilize much smaller sample volumes as compared to conventional methods thus enabling research with limited availability of proteins or ligands.

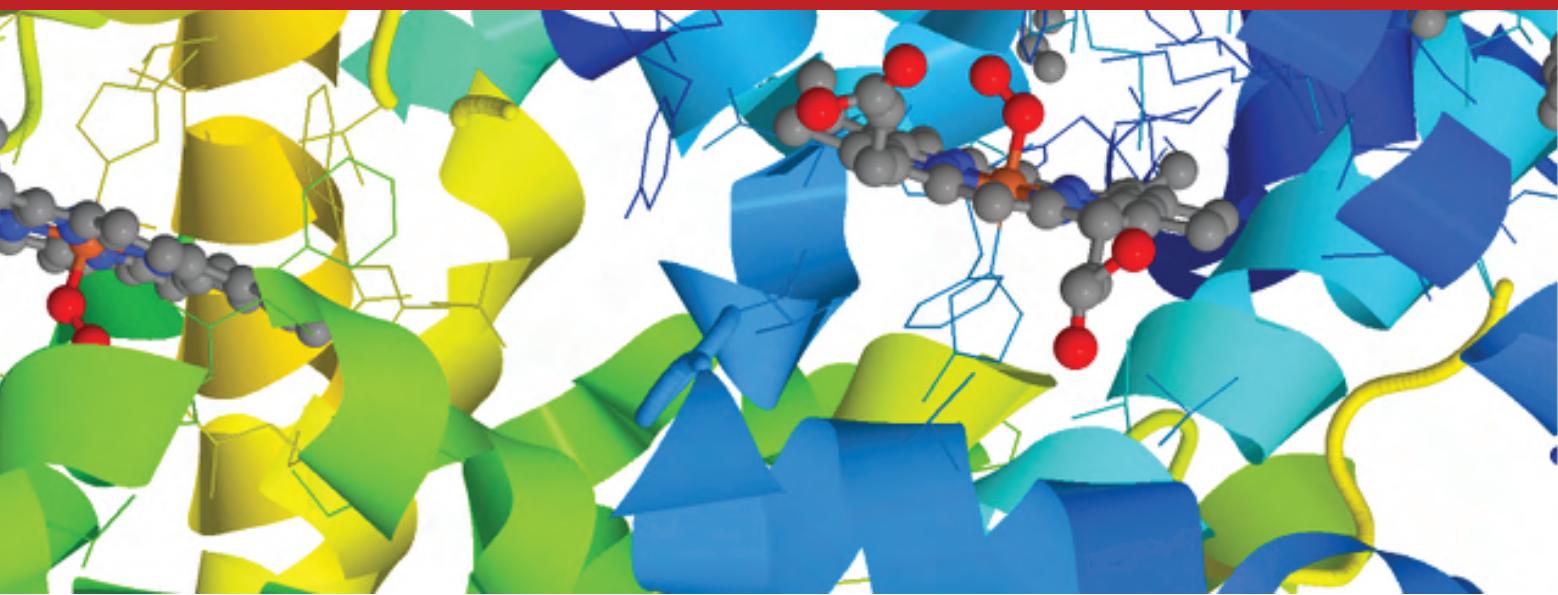
Increased throughput: By using the parallelization of experiments made possible by microfluidic channels present in LOC devices, high-throughput screening can be carried out through vast compound libraries for potential therapeutic candidates.

Integration with microfluidics: Compared to its conventional counterparts, LOC platforms are highly compatible with microfluidic techniques for on-chip sample preparation and separation. This minimized the aspect of handling the documents manually as well as any errors and this enhances efficiency.

Automation: LOC devices run on microfluidic principles, which can produce high precision and repeatable analysis with minimal interferences from humans.

Where?

Miniaturised biophysical assays: Miniature versions of known biophysical processes like surface plasmon resonance (SPR) and isothermal titration calorimetry (ITC) can be scaled down using the LOC technology,



which makes it possible to realize minimum sample consumption for quick and efficient screening of protein-ligand interactions.

High-throughput screening (HTS): Such devices enable screening of extensive compound libraries against a target protein in a high-throughput manner. Microfluidic channels that allow multiple samples to be processed in parallel are used, thus speeding up the search process for lead candidates with suitable binding affinity and specificity.

Integrated assays: On a same chip, protein immobilisation, ligand screening, and signal detection can all be combined using LOC platforms. One can imagine how this integration of LOC platforms could streamline the process and lower the possibility of artefacts from transferring samples between different platforms.

Kinetic and thermodynamic analysis: In addition to affinity measurements, functionalities for detecting binding kinetics and thermodynamics are being developed for advanced LOC devices. This would offer a condensed but thorough understanding of the encounter.

The flip side!

Even though there are some drawbacks like the complexity of the assays, high cost of fabrication and

perfect compatibility with other workflows; they are not dealbreakers!

Or are they?

It would be useful to note that potential further developments of LOC technology for protein-ligand interactions show great promise. These investigations will give established knowledge a brand-new perspective. Some exciting possibilities include-

Multiplexed assays: It is seen that the enhancement of high-throughput screening by developing multiple proteins/ligand interaction analysing LOC devices will be highly beneficial.

Point-of-care applications: LOC technology might give portable and easily operated devices to analyse protein-ligand interactions directly at care-on places or point of care which might revolutionize the personalized medicine strategies.

Turn this tango into a ballet!

The subject of protein-ligand interactions can be characterized as an actively developing field. The essence of LOC technology, 'miniaturization, automation and integration' of functions holds promises of revolutionizing this field. Indeed, by discussing the current limitations and future possibilities of LOC devices, more useful resources for developing new therapeutic and diagnostic algorithms may be created.

-CC

Mr. S. Balu

CMD Inkarp Instruments Pvt Ltd



In 1985, Mr. S. Balu embarked on a remarkable journey with just two employees, founding Inkarp Instruments. Today, Inkarp has transformed into a powerhouse, spread across India, partnering with over 40 principals.

This August, we celebrate a milestone as Inkarp Instruments steps into its 40th year. Join us as we delve into Mr. Balu's inspiring story and celebrate Inkarp's incredible growth.

What sparked your initial interest in the scientific instruments field?

S. Balu: The chance to support scientists and be part of their journey excites me. I saw a great opportunity to bring useful solutions to researchers and institutions, helping them achieve their goals. This mix of curiosity and the desire to make a difference inspired me to start Inkarp.

Looking back on your journey, what piece of advice would you give to your younger self starting out in this industry?

S. Balu: Oh! (Laughs) Well, I'm 80+ today, and if I could give advice to my younger self, the first thing I would say is that I should have started this journey much earlier. Age can be a hurdle now, but looking back, I realize the importance of time.

I would also tell my younger self, to embrace failures as learning opportunities. Every setback is a step forward in disguise. Building a strong, supportive network is crucial. Surround yourself with people who inspire and challenge you. Don't be afraid to take risks and always stay curious. The journey will be tough, but persistence and passion will make all the difference.



“Inkarp will continue to be a company that brings solutions for all research needs, and we will keep priding ourselves on our service deliverable.”

What kind of impact do you hope Inkarp will leave on the scientific community?

S. Balu: I hope Inkarp is remembered as a catalyst for scientific discovery, a company that provided the tools and support needed for researchers to push the boundaries of human knowledge. Our legacy should be one of innovation, integrity, and unwavering support for the scientific community.

Inkarp will continue to be a company that brings solutions for all research needs, and we will keep priding ourselves on our service deliverable, which is our unique selling point. The priority and importance we give to our product managers and customer service champs to know the products inside and out, with principal training, will add immense value to the growth of the company and its people.

Imagine a scientist 20 years from now using one of Inkarp's instruments. How would their experience be different from today?

S. Balu: See, three decades ago, scientific instruments were bulky and required a lot of manual input. Over time, we've seen these instruments become smaller, more efficient, and more automated.

“

Being there for my customers, no matter what, has been key to my journey.

”

If you ask me how 20 years in the future would look like, I envision the instruments to be even more advanced. They will be incredibly intuitive, seamlessly integrating with AI to provide real-time data analysis and insights. The user experience will be highly interactive, with augmented reality interfaces guiding researchers through complex procedures. The pace of technological progress is speeding up, and we can expect even more groundbreaking innovations soon.

Looking back, what was the biggest gamble you took with a new instrument, and how did it pay off?

S. Balu: Ah! One of the biggest gambles was investing heavily in the development of a next-gen centrifuge i.e., Kubota, when the market was still nascent. I took a bold move, and it paid off by positioning Inkarp as a preferred partner in the field, attracting top-tier customers and setting a new standard for precision and reliability.

Can you share a story of a scientific breakthrough that you believe wouldn't have been possible without one of our instruments?

S. Balu: Absolutely, I'd love to share this story. Fuji, a brand well-known in India for their cine film rolls, wasn't initially recognized for their scientific instruments. Despite many Indian companies approaching Fuji to market their Molecular Imager, it was only Inkarp that secured the rights. This was a significant win for us, especially since we had prior experience marketing a Molecular Imager from a US brand against stiff competition from other US brands.

The Fuji systems were attractively priced, and we had strong connections with prestigious institutes, notably the Centre for Cellular and Molecular Biology (CCMB), which helped us secure a breakthrough. We formed a highly motivated team with experienced members. Their dedication and expertise played a crucial role in our success.

Within a few years, we managed to sell 60 systems, each priced at over USD 70,000+. Our customers included some of the top institutes in India, such as CCMB, IISc, JNU, Delhi University, TIFR, TNAU, Anna University, and Mysore University. This success not only demonstrated the quality and reliability of Fuji's Molecular Imager but also highlighted the effectiveness of our team and strategy.

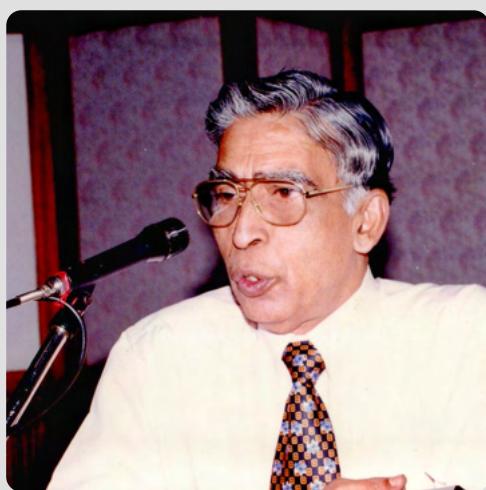
Our success in marketing these systems also led to us acquiring the marketing rights for other major international brands' systems.

This collaboration and our approach to customer relations have enabled significant scientific breakthroughs in these institutes, facilitating advanced research and discoveries that might not have been possible otherwise. It's a testament to how the right partnerships and a respectful approach to customer needs can drive innovation and progress in the scientific community.

How does Inkarp foster a culture of creativity and collaboration among its employees?

S. Balu: Gone are the days when company directors would not interact with front-line employees! Today, I'm proud to see many companies, including my own, where leadership genuinely values every employee's input, regardless of their position. We call it an Open-Door Policy, and it holds high value for both leadership and employees, creating a sense of harmony.

We many a times have brainstorming sessions and an inclusive work environment where everyone's voice is heard. This approach helps us foster a thriving culture of creativity and collaboration.





Down the memory lane

Interview

Do you think this increases communication and transparency between leadership and all levels of the company?

S.Balu: Honestly, with the new generation of leadership coming into Inkarp, we've seen a lot of positive changes. Time changes many things. The way our leaders work with employees now is quite different. They often see themselves as equals with their team members, which brings good acceptance and fosters a strong sense of community.

In your experience, what are the most important qualities for success in this fast-paced industry?

S. Balu: I believe in today's scientific research; it's not just about having the right product. Honestly, anyone can provide a product. The real key is how well we support the research, train the scientists, and understand their needs. We need to be with them throughout their research journey.

At Inkarp, we take pride in doing just that. We focus on being adaptable, curious, and flexible. We always learn, explore new ideas, and bounce back from challenges. But most importantly, we build strong relationships with our customers, offering continuous support and collaboration. Our dedication to understanding and helping our customers makes a real difference and sets us apart in the industry.

What is the ultimate vision you have for Inkarp's impact on scientific progress?

S. Balu: The ultimate vision for Inkarp is to be one of the leaders in scientific innovation, providing solutions that help researchers make world-changing discoveries. We want to be a trusted partner in scientific progress, offering the best solutions and support to our customers. On a personal level, I'm also passionate about creating jobs and supporting new entrepreneurs. I want Inkarp to be a place where talented people can grow, innovate, and build successful careers.

What does a "typical day" look like for you as the company's founder?

S. Balu: (In exclamation) I'm over 80 now, and my typical day is quite different from what it used to be!

“

“Our dedication to understanding and helping our customers makes a real difference and sets us apart in the industry.”

”

I'm deeply involved in my hobby of share trading, which keeps me busy from 8:30 to 3:30. I do get involved in the business, but only when the current leadership feels my input is necessary. Otherwise, I'm enjoying my time with my family and my hobby. I also love going on road trips occasionally and really enjoy those moments!

What are some of the most valuable lessons you've learned in this journey?

S. Balu: One of the biggest lessons I've learned is the power of perseverance. The road can be tough, but staying focused on your vision and pushing through challenges is crucial. Building genuine relationships with customers and employees creates a foundation of trust and respect that's priceless.

The words "support" and "service" are more than just words. In this business, during my times, a lot of the credit goes to the scientists who helped me with many the solutions for me to grow my network and credibility. I was good at networking and could quickly call another scientist to clear up technical doubts.

I was always available for my customers when they needed me. I took ownership of their research and went above and beyond to make sure they got the support they needed. Being there for my customers, no matter what, has been key to my journey.

Enantioselective asymmetric hydrogenation using chiral phosphorous ligands

Safe hydrogenations on solid supported Rh catalysts in ThalesNano H-cube reactor

Catalytic asymmetric hydrogenation is one of the most efficient and convenient methods for synthesizing optically active compounds, e.g. amino acids, chiral amines, and itaconic acids, which are widely used in the pharmaceutical and fine chemical industries. Chiral phosphorus ligands, such as novel phosphine-phosphoramidite and phosphine-phosphite (P-OP) ligands have been widely applied for asymmetric hydrogenation. Unsymmetrical hybrid phosphine-phosphoramidite compounds have recently emerged as a new class of chiral ligand for highly efficient asymmetric catalysis.

Due to the different phosphorus binding sites, this type of ligand can offer a unique electronic environment around the central metal, which results in significantly improved enantioselectivities in some cases. The immobilization of the catalyst can be carried out on natural and mesoporous Al_2O_3 in the presence of phosphotungstic acid (PTA). Phosphotungstic acid is a heteropoly acid that provides high stability to the catalysts and prevents

leaching in the asymmetric reduction of different substrates in heterogeneous batch and high throughput microfluidic based flow reactors.

Hydrogenation on the H-Cube® flow hydrogenation system using solid-supported Rh catalysts bearing chiral phosphorus ligands was performed.

The catalyst PTA/ Al_2O_3 /[Rh(COD)(chiral ligand)] was tested in the chiral hydrogenation of (Z)- α -acetamidocinnamic acid methyl ester (Figure 2).



Figure 2: Hydrogenation of (Z)- α -acetamido-cinnamic acid methyl ester

The H-Cube® reactor was used for asymmetric hydrogenation under flow conditions. This system provides safe and rapid optimization of the reaction conditions (flow rate, temperature, pressure, solvent, substrate concentration) using only a few mg of substrate.

Application showcase

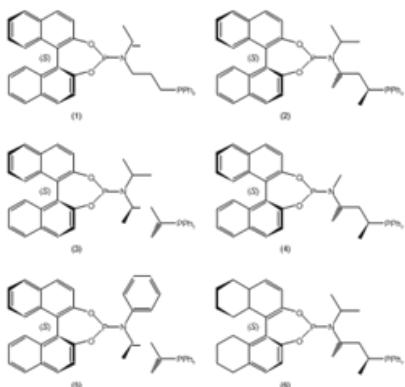


Figure 1: Structures of chiral phosphine-phosphoramidite ligands

Standard Experimental Protocol

PTA/Al₂O₃/[Rh(COD)(2)] was filled into a CatCart® column. The substrate was stirred in the solvent to prepare a 0.05 mol/dm³ solution and the solution was fed into the reactor using a flow rate of 0.1 mL/min at room temperature. The conversions of the hydrogenation reactions of (Z)- α -acetamidocinnamic acid methyl ester and the enantiomeric excesses of the product were determined by chiral GC using a Hewlett Packard HP 4890 D, equipped with CHIRASIL-L-VAL column (25 m x 0.25 mm, df = 0.12 μ m), N₂ as carrier gas, a split/split less injector at 250°C, and an FID at 250°C. Temperature program: 2 min at 140°C; 2°C/min from 140°C to 180°C; 40 min at 180°C. Retention times were 12.3 min for (R), 13.2 min for (S)-product, and 22.1 min for (Z)- α -acetamidocinnamic acid methyl ester. The productivity of a catalyst can be described by the turnover number (or TON) and the catalytic activity by the turnover frequency (TOF), which is the TON per time unit. The results of solvent effects are displayed in Table 1 and the monitoring of catalyst stability over time is detailed in Table 2.

Solvent	Conversion (%)	TOF (h ⁻¹)	e.e. (%)
CH ₂ Cl ₂	65.8	15.8	90.9
EtOAc	>99	24.1	99.3
MeOH	>99	24.1	99.4

Table 1. Results of solvent effects in the asymmetric hydrogenation of (Z)- α -acetamidocinnamic acid methyl ester with (PTA/Al₂O₃/[Rh(COD)(2)])

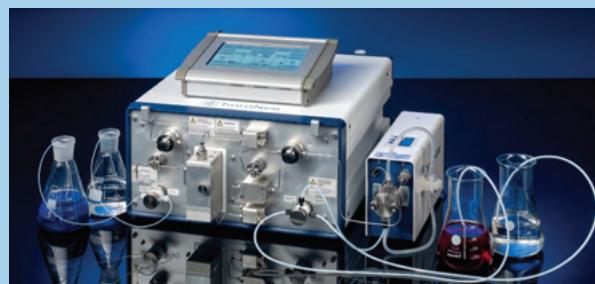
Reaction time (min)	Conversion (%)	TOF (h ⁻¹)	e.e. (%)
First sample	65.8	25.2	98.5
60	>99	25.2	99.7
120	>100	25.2	99.7
210	92	23.2	99.7
240	86.3	21.7	99.7
300	64.5	16.2	99.6
360	69	17.4	99.6
540	43.5	11	99.6
570	35.5	9	99.6
630	39.1	9.9	99.5
700	28.4	7.2	99.5
780	29.5	7.4	99.5

Table 2. The stability of the catalyst over time in the asymmetric hydrogenation of (Z)- α -acetamidocinnamic acid methyl ester with (PTA/Al₂O₃/[Rh(COD)(2)])

Conclusion

It was found that high enantioselectivity can be achieved in asymmetric hydrogenation when using the bidentate phosphine-phosphoramidite ligands.

The advantage of these ligands is that there is little or no decomposition in common polar protic solvents. The immobilization of the catalyst can be carried out on Al₂O₃ in the presence of phosphotungstic acid.



Safe hydrogenation at high pressures & temperatures, with active cooling for selective reactions



Check out the list of catalysts in CatCart!

Application showcase



Synthesis of triazole library

Automated synthesis using ISYNTH workflow in Chemspeed FLEX Isynth

PharmBioTec's department of Drug Discovery focuses on the synthesis of small, drug-like molecules for a broad range of therapeutic targets. Usually, many compounds are needed to identify active species, or to improve the activity/pharmacokinetic profile of an initial hit. Instead of employing time and labor-intensive bench work, PharmBioTec has chosen another path, that of automation. Towards this end PharmBioTec has acquired the most flexible platform for organic synthesis on the market: Chemspeed's ISYNTH.

This modular robotic platform enables library synthesis and work-up in easy-to-use disposable reactors. It is suited for low and high temperatures, for handling liquids / solids and working under inert or reactive gas pressure atmosphere.

Workflow



Objectives

- Synthesize a library of 32 triazoles in a fully automated protocol, including work-up and sampling, starting from commercially available boronic acids and alkynes
- Compare yields obtained in the manual and automated procedures

Experimental Set-up

1. ISYNTH, a software-driven robotic platform containing:
2. Solid Dispensing Unit
3. 4-Channel Liquid Handling Unit
4. 20 mL Disposable Glass Reactors
5. Phase-separation cartridges for automated work-up

Application showcase

Results

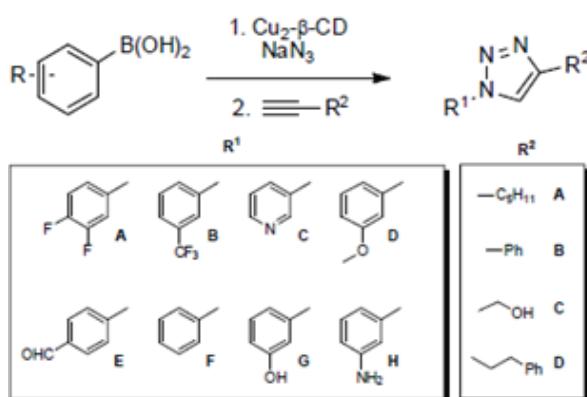
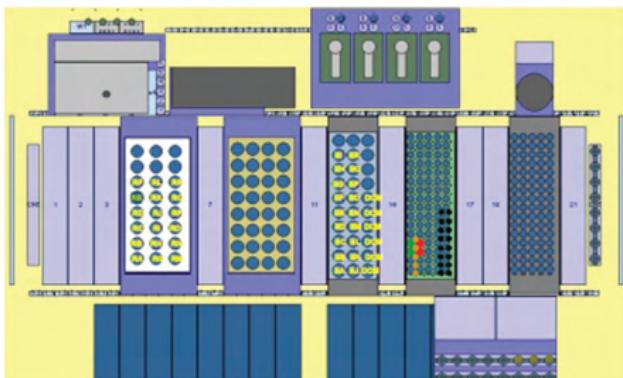


Figure 1: Overview of prepared compounds



A: RA-RR (Reaction-Zone)
B: EA-ER (Extraction-Zone)
C: DCM
Cu-CD-Complex, Sodium Azide, Alkynes, HPLC-Samples, MgSO_4

Figure 2: Schematic layout of the experiment, showing storage positions of raw materials and reaction wells.

All reaction steps, including work-up, were performed in the ISYNTH platform.

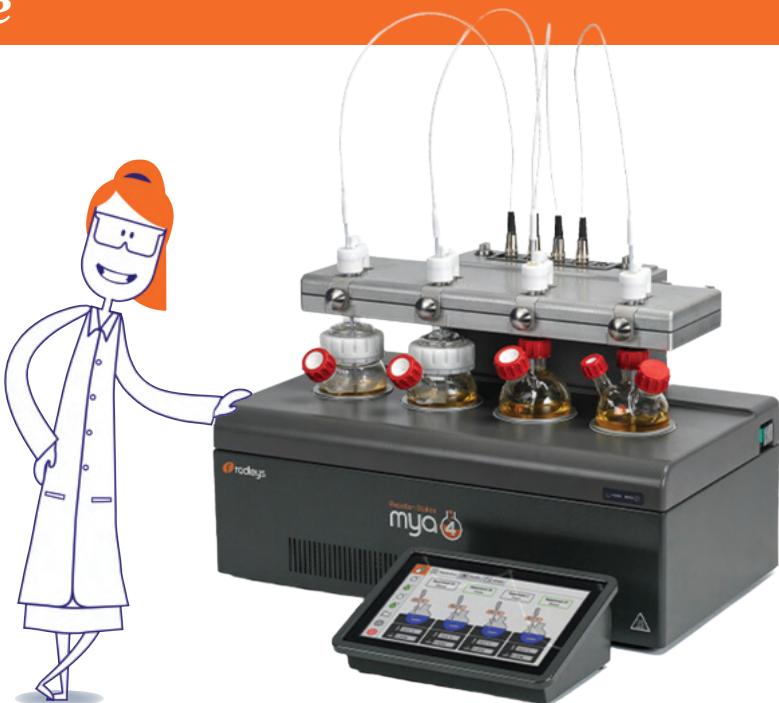
Crude products were purified by preparative HPLC if their purity was below 95%. The average yields obtained were above 30% and comparable to manual procedure.

Conclusion

A library of 32 triazoles was synthesized on the ISYNTH platform, with an average purity of 96% (after HPLC). Generation of such libraries is achieved at the same time as it takes for a single compound manually.



Rapid optimization of a Buchwald–Hartwig amination using Design of Experiments (**DoE**)



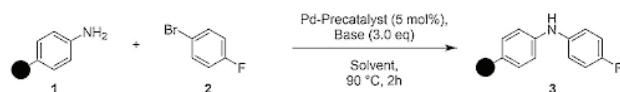
Catalyst screening and DOE optimization for Buchwald–Hartwig amination via Mya4 parallel reaction station

Buchwald–Hartwig couplings are an important tool for the synthesis of aromatic amines. Since its discovery, palladium catalysed cross coupling of amines with aryl halides have been extensively used in medicinal chemistry, materials science, heterocyclics and natural product synthesis. Although, the underlying catalytic process and mechanistic details of C–N couplings have been extensively documented over many years, identifying suitable reaction conditions remains tedious and time consuming.

A major reason for the slow development of Buchwald–Hartwig amination is its sensitive nature towards the catalyst, ligand, additives and even the solvent, thus limiting its reproducibility.

In this study, reaction conditions of C–N coupling were optimized using Radleys Mya4 Reaction Station.

The rapid identification of Buchwald–Hartwig amination conditions was required for the synthesis of building block 3. Initially, a literature review of potential reaction conditions was conducted, and a shortlist of different options was prepared. This shortlist of conditions was subsequently screened on a Radleys Mya 4 Reaction Station using minimum quantities of material, leading to the identification of a set of “hit” conditions. We also screened several greener reaction solvents as alternatives to 1,4-dioxane, leading to the identification of t-BuOH as an effective replacement.



Finally, this new process was optimizing using “Design of Experiments” (DoE) software, allowing us to fully explore multiple reaction parameters and variables in as few experiments as possible. In this way, we avoided the fallacy of a “false optimum”, which is often encountered when changing one factor at a time. The desired product was isolated in high yield from our highly optimized process.

Application showcase

Catalyst/base screening

The high throughput screening capabilities of the Radleys Mya 4 Reaction Station allowed for the rapid screening of all sixteen of our shortlisted catalyst-base combinations for this reaction. In this way, a full suite of reaction data was generated, including the UPLC-MS analysis of all 16 reactions, within 2 hours.

The results of this screening process revealed that the use of K_3PO_4 with Xphos Pd G3 gave the highest conversion to product (Table 1). Notably, the use of KO-t-Bu led to bis-addition impurities.

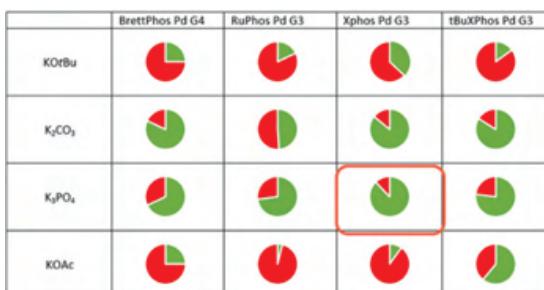


Table 1: Product conversions

Dioxane solvent swap - safety and sustainability

As a known carcinogen¹, the use of 1,4-dioxane as a reaction solvent raises significant environmental, health and safety (EHS) concerns, highlighting the need for more benign alternatives. A set of greener, sustainable solvents were screened against the best conditions identified from the catalyst-base screening exercise. The solvents used in this experiment were chosen based on well-documented solvent selection guides for greener, more sustainable solvents.^{1,2} Pleasingly, t-BuOH gave comparable results to 1,4-dioxane and was selected for further optimization work (Table 2).

Solvent	% Product Conversion
1,4-Dioxane - Control	88
Toluene	84
2-MeTHF	87
TBME	80
t-BuOH	90
CPME	80
TPGS-750-M	62
DMC	73

Table 2: Alternative solvents screened as potential replacements for 1,4-dioxane

*CPME: Cyclopentyl methyl ether, TPGS: DL- α -Tocopherol methoxypolyethylene succinate, DMC: Dimethyl carbonate. Reactions conducted in a sealed tube.

Optimum conditions identified when changing one factor at a time: Xphos Pd G3 (5 mol%), K_3PO_4 (3 eq.) t-BuOH (0.4 M conc.), reflux, 2 h – 90% product.

Design of Experiments - DoE

Finally, the reaction was subjected to further optimization using DoE software from Design Expert. This work focused on several key reaction parameters, including catalyst loading, equivalents of base, temperature and concentration. The results of these experiments were used to build a surface response plot (Figure 1), as well as a statistical model of the Buchwald–Hartwig reaction, leading to further improvements in the yield of the reaction (98% yield), as well as avoiding the potential for a “false optimum”, which can be encountered when changing just one factor at a time.

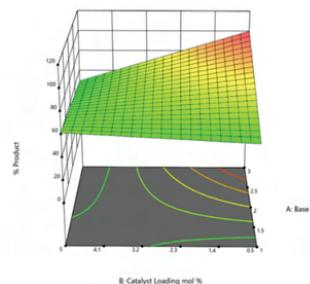


Figure 1: 3D surface response with respect to catalyst loading and equivalency of base.

Conclusion

In summary, the rapid optimization of a Buchwald–Hartwig amination reaction was achieved using the Radleys Mya 4 Reaction Station together with DoE software from Design Expert. Further improvements to the reaction were made by replacing 1,4-dioxane with t-BuOH, which represents a much safer and sustainable reaction solvent.

The use of DoE allowed for the generation of a statistical model of the reaction based on multiple factors, as well as the identification of important two-factor interactions. In this way, the model allowed the prediction of optimum conditions for maximizing yield, resulting in 98% conversion to product 3.

Mid IR-Spectroscopic Reaction Monitoring



A flow-through mid-IR spectroscopic method for real-time reaction monitoring using Bruker Alpha II FT-IR spectrometer

The spectroscopic monitoring of chemical reactions in the mid-IR is an established method to determine optimal reaction conditions, to identify the endpoint of a reaction or to gather information about the reaction order and path. At the laboratory scale a reaction can be monitored via a series of manual measurements, for example by frequently drawing and measuring samples. This is, however, very laborious and error prone. Furthermore, it can happen that the sample disintegrates on its way to the spectrometer due to temperature change, air contact etc. Additionally, the measurement intervals are much longer in this case, which reduces the temporal resolution significantly. The measurement in a flow-through setup, that passes the reaction medium constantly over an ATR-crystal in a closed cycle, constitutes an efficient alternative (figure 1).

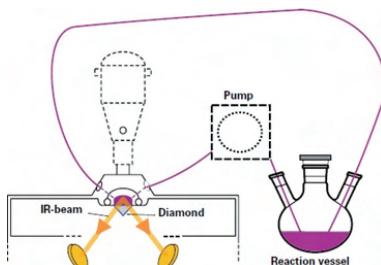


Figure 1: Schematic of the measurement setup

As reaction media can be chemically aggressive or might contain particles, the ATR (Attenuated Total Reflection) technique usually is the more robust and therefore, better approach than transmission. During the whole reaction, spectra are recorded software controlled at regular intervals. The Bruker ALPHA II FT-IR spectrometer in combination with the temperature-controlled diamond ATR-unit and a specially designed flow-through cell is a cost effective, robust and compact combination for the monitoring of reactions with a temporal resolution of up to five seconds.

Application showcase

Instrumentation

The example measurement was performed with the Bruker ALPHA II FT-IR spectrometer in combination with a temperature-controlled diamond ATR unit. The temperature at the ATR measurement element can be set to values between room-temperature and 120°C.

The diamond of the ATR-unit is brazed in tungsten carbide and the O-ring material is Kalrez. This results in an extremely high tolerance to all kinds of chemicals. In our demonstration experiment the reaction medium was passed continuously over the diamond crystal. The automated measurement and the evaluation were performed by the function "Reaction Monitoring" of the OPUS spectroscopy- software.

Example measurement: Monitoring of an esterification

As an example reaction, we show the monitoring of the synthesis of ethyl acetate from glacial acetic acid and ethanol. The reaction mixture was stirred over a period of 3.75 h at 40°C. Finally, the temperature was raised to 60°C and held there for two more hours.

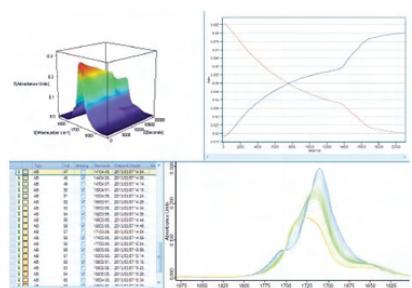


Figure 2: OPUS-analysis of the reaction process.

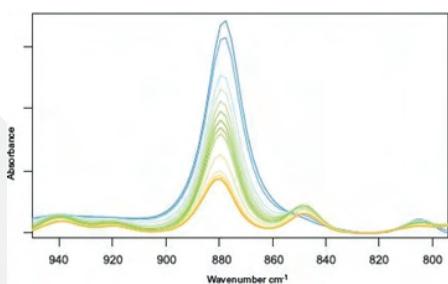
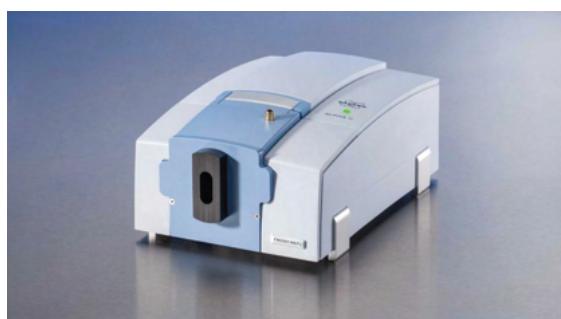


Figure 3: Band of the carbonic acid dimer.

During the whole reaction automated measurements were performed every five minutes. Figure 2 shows the OPUS evaluation view for time resolved

measurements which contains four different fields. The field on the upper left shows the zoomed carbonyl band (C=O stretching vibration) in its temporal evolution in 3D-view, on the lower right the same is shown in 2D. The carbonyl band of the acetic acid is located around 1710 cm⁻¹, the band of the ethyl acetate is around 1740 cm⁻¹. It is clearly visible how the band of the carbonic acid declines and how the one of the esters is rising. For the evaluation of the temporal changes of the ester concentration the intensity at 1747 cm⁻¹ was used. The change of the carbonic acid was evaluated by using the intensity at 879 cm⁻¹ (figure 3).

The latter band results from the carbonic acid dimers that are formed by hydrogen bonding. The evaluation result is shown in figure 2. The red curve shows the formation of the ester and the blue curve the decrease of the carbonic acid. Also clearly visible is the increase of the reaction rate in the last third of the diagram due to the temperature rise from 40 to 60°C.



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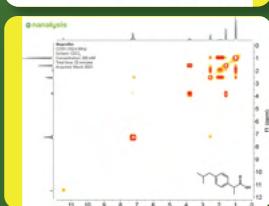
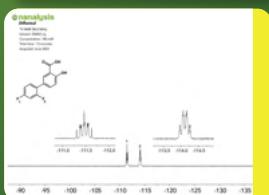
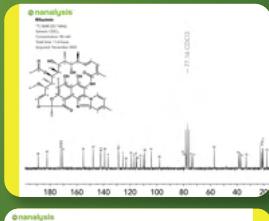


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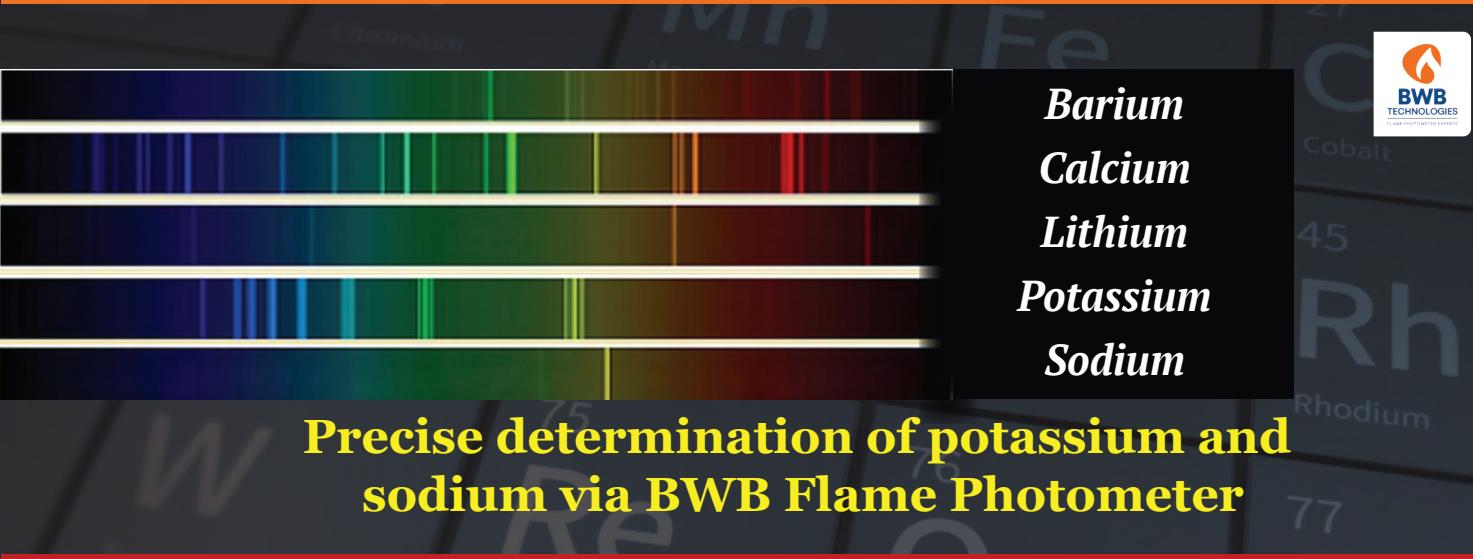
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Application showcase



Precise determination of potassium and sodium via BWB Flame Photometer

A reliable technique for quality control

Flame photometry is a technique for measuring the concentration of certain elements based on the intensity of light they emit when excited in a flame. Elements suitable for this analysis must ionize readily in aqueous solutions and have low excitation energies. This makes Group 1 (alkali metals) and Group 2 (alkaline earth metals) ideal candidates. Among these, potassium (K) and sodium (Na) are particularly important for various industries such as pharmaceuticals, food and beverage production, and environmental monitoring. The BWB Technologies Flame Photometer is a state-of-the-art instrument designed for precise and consistent measurement of these elements.

BWB Flame Photometer Features

The BWB Flame Photometer offers several key features for efficient and reliable analysis:

- **Multi-channel detection:** Enables simultaneous measurement of multiple elements, improving analysis speed.
- **User-friendly interface:** Simplifies operation and data management on the BWB Flame Photometer.

- **Advanced calibration:** Supports both single-point and multi-point/multi-ion calibration for increased accuracy on the BWB instrument.
- **High sensitivity:** Detects low concentrations of elements, ensuring wider applicability for the BWB Flame Photometer.
- **Built-in air compressor:** Reduces noise and minimizes lab space requirements for the BWB instrument.
- **Optional automatic fluid handling system:** Automates analysis and increases lab productivity with the BWB Flame Photometer.
- **Access control technology:** Ensures compliance with Good Laboratory Practices (GLP), Laboratory Information Management Systems (LIMS), and multi-user access features for the BWB Flame Photometer.

Methodology

Instrument startup and stabilization: The BWB Flame Photometer is powered on, and the flame ignited. It is allowed to stabilize for 45 minutes to ensure optimal performance.

Standard preparation: A series of standards is prepared from a 10ppm stock solution of sodium and

Application showcase

potassium. Concentrations ranging from a blank (0 ppm) to 0.10 ppm are created in increments of 0.02 ppm using a dilution process. Deionized water is used for dilution.

Calibration: The standards are aspirated into the BWB Flame Photometer in ascending concentration order for multi-point/multi-ion calibration.

Sample analysis: The instrument is switched to read mode, and the sample solution is aspirated for measurement using the BWB Flame Photometer.

Considerations for low concentration analysis

For samples with low sodium and potassium concentrations, diluting both the sample and standards with up to 20% xylene can theoretically improve signal strength by raising the flame temperature in the BWB Flame Photometer. However, this dilution needs to be factored into the results as it reduces the water content and may push the sample below the instrument's detection limit. Further experimentation is recommended to determine the optimal water-to-xylene ratio for optimal signal enhancement without compromising accuracy when using the BWB Flame Photometer.

Benefits of BWB Technologies Flame Photometer

High precision and accuracy: The BWB Flame Photometer delivers reliable measurements for quality control and regulatory compliance.

Efficiency: Automated features and multi-channel detection on the BWB Flame Photometer increase sample throughput and reduce analysis time.

User-friendliness: The BWB Flame Photometer boasts an intuitive interface and straightforward procedures, simplifying training and operation.

Versatility: The BWB Flame Photometer is suitable for a wide range of applications beyond potassium and sodium analysis.

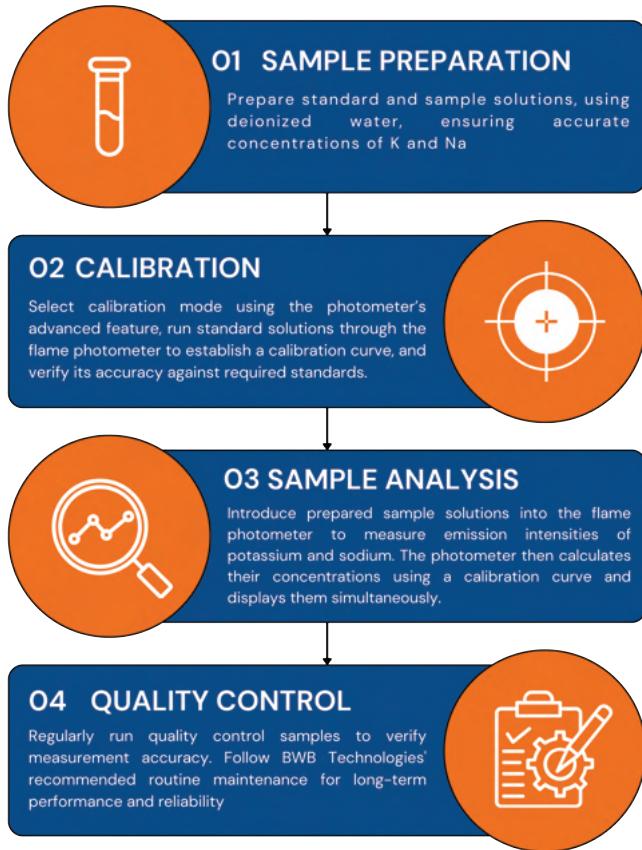
Conclusion

The BWB Technologies Flame Photometer is a valuable tool for laboratories requiring precise and efficient analysis of potassium and sodium. Its advanced features and reliable performance make it ideal for ensuring product quality and compliance across various industries. By following the outlined procedures, users can achieve accurate and reproducible results, enhancing their analytical capabilities with the BWB Flame Photometer.



The BWB XP Flame Photometer

Procedure



Safe reprocessing of used surgical instruments



A potential approach for safe and efficient ultrasonic cleaning in Bandelin's SONOREX ultrasonic bath.

The reprocessing of medical instruments with ultrasound enables a fast instrument cycle and gentle intensive cleaning by disinfection and cleaning. The usual damage and wear of the instruments by manual "brushing" is thus excluded. In the dental field, SONOREX ultrasonic baths are used for instrument preparation and impression mould cleaning. Due to the insert cups specially developed for this application, impression mould cleaning and instrument disinfection with different cleaning preparations can be carried out simultaneously in one unit.

The SONOREX ultrasonic baths use the effect of cavitation. They contain piezoelectric transducers under their oscillating tank bottoms, which cause mechanical oscillations. As a result, microscopically small bubbles are continuously formed in the bath liquid, which release energy upon imploding and generate microcurrents. During the cleaning process, it causes contamination to 'blast off' from the surfaces and hard-to-reach places.

Which instruments can be reprocessed with ultrasound?

- General instruments such as scissors, needle holders, tweezers, forceps, trocars, scalpels.
- Micro-instruments from neurosurgery and ophthalmology.
- MIS instruments such as dismountable tubular shaft instruments, microclamps, etc.
- Endoscope accessories such as biopsy forceps, slings, valves.
- ECG, EEG electrodes.

Advantages of instrument reprocessing in an ultrasonic bath

- Fast instrument circulation.
- Time reduction of the chemical disinfection to 5 minutes.
- Protection of the instruments.
- Short contact of the instruments with disinfection and cleaning liquids.
- No risk of corrosion.
- Economical use of water, chemicals and energy.
- High cleaning effect in hard-to-reach places, such as boreholes, joints or grooves, without mechanical damage.

Application showcase

Which ultrasonic bath do I choose?

- Size of the cleaning objects determines the tub size and thus the type of appliance.
- Dimensions of the hanging baskets must be observed.
- To avoid overloading the unit, it is advisable to choose the next larger unit. This also gives scope for further applications.



What to consider when using the ultrasonic bath

- The items to be cleaned must not lie directly on the bottom of the tub.
- Do not stack instruments and do not overload baskets.
- Open articulated instruments, e.g. forceps or scissors, completely and disassemble if necessary.

Is heating required?

Unit without heating

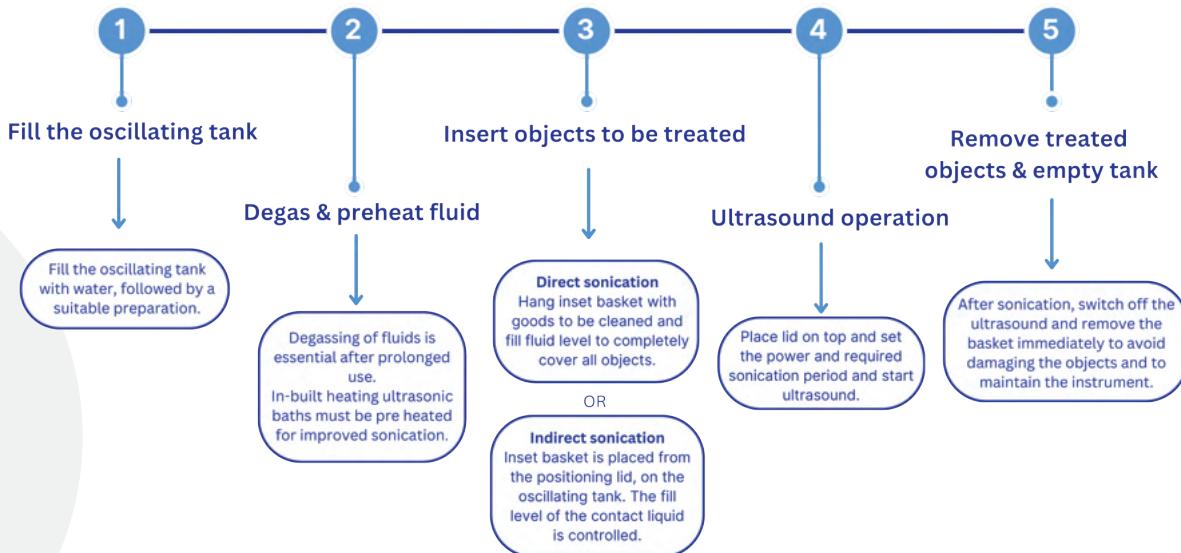
- For simultaneous disinfection and cleaning after dry filing.
- Disinfectant liquids must not be warmed up.
- At temperatures above 40°C, there is a risk of protein coagulation.

Unit with heating:

- For cleaning after wet filing or for basic cleaning.
- Impurities are removed more quickly.

- Instruments must be completely covered with solution.
- Air from cavities must escape recommended liquids.
- STAMMOPUR concentrates were specially developed for disinfection and cleaning in the ultrasonic bath.
- The corresponding microbiological reports are available for the disinfection time reduction in the ultrasonic bath.
- Flammable liquids such as alcohols and aggressive cleaning liquids such as acids and salt solutions are not permitted for use.
- Disinfection or cleaning is not possible with water alone, that is, without suitable additives.

Operation process-Bandelin ultrasonic baths





Automated solvent recovery

Sustainable practices using Heidolph Distimatic rotary evaporator

The COVID-19 crisis and the resulting increased demand for disinfectants such as isopropanol or ethanol have already led to bottlenecks in some regions and to a rise in solvents prices on the world market. Therefore, solvent recycling is not only a sustainable but also a considerable way of reducing operating costs in the own laboratory and at the same time increasing efficiency.

Solvent recovery by means of an evaporation process is a common laboratory work process, for which often a rotary evaporator is used. Even if this is a suitable and sample-conserving lab device for this process, the manual operation (the so-called batch operation) is less than efficient if larger solvent volumes must be purified.

Evaporating flasks only hold a limited volume and must be refilled or replaced, which leads to long heating times of the cold medium before the process starts again. The capacity of receiving flasks is also limited and requires regular emptying during operation. To do this, the entire system must be ventilated, and a running process must be stopped.

Evaporation in batch operation is a dynamic process during which the conditions in the entire system are constantly changing.

In addition, the vacuum must be manually readjusted several times to achieve consistently high performance. Consequently, a laboratory employee is often busy for several minutes adjusting the process parameters, filling and emptying the flasks or changing them if necessary. This is a cost factor that reduces the possible savings. Hundreds of customers worldwide have already achieved a significant efficiency increase in solvent recycling by using an automated module that independently controls the filling and emptying of the evaporator and receiving flasks.

At the labs of the Faculty of Macromolecular Chemistry, University of Bayreuth (Germany), very small quantities with similar contents were very often evaporated, as usual in chemistry laboratories. The doctoral students and laboratory assistants working in this laboratory spent a significant amount of time performing the typical work steps on the rotary evaporator to purify small amounts of a few hundred millilitres of solvents.

Mr. Lothar Benker, responsible for the equipment pool in this work group, recognized the potential of automation and instructed the doctoral students in the respective work group to collect the small quantities into 5 to 20L containers and not to bother with manual processing. A Heidolph Distimatic system with a rotary evaporator automates overnight processing of a filled container after workday activation, saving hours of precious time.

Capturing sunshine to fight climate change: The challenges of photocatalytic CO₂ reduction

Tuning the photoreactor for selective CO production in Luzchem ICH photoreactor

Photocatalytic CO₂ reduction (PCR) has emerged as a potential game-changer in tackling climate change and energy scarcity. PCR offers a clean and sustainable alternative to traditional fuel sources by harnessing sunlight to convert the ever-increasing atmospheric CO₂ into valuable fuels like methane or methanol.

However, despite its promise, PCR faces significant hurdles before reaching widespread commercial application. The main challenge lies in the inherent stability of the CO₂ molecule. Breaking the strong bond between carbon and oxygen requires a significant energy input, limiting the overall efficiency of the process.

Furthermore, the success of PCR hinges on the development of highly efficient photocatalysts. These materials play a crucial role in capturing CO₂ molecules, activating them using sunlight, and ultimately converting them into desired fuels.

Ideally, the photocatalyst should possess several key attributes

- High CO₂ adsorption: The ability to effectively capture and hold onto CO₂ molecules on its surface is essential.
- Strong light absorption: Efficient utilization of sunlight is crucial for driving the photocatalytic reaction.
- Selective product formation: The catalyst should favour the production of specific fuels like methane or methanol, minimizing unwanted byproducts.

Beyond the catalyst itself, the design of the photoreactor, the chamber where the reaction takes place, is also critical. The reactor needs to optimize the interaction between light, CO₂, and the catalyst for maximum CO₂ conversion. Current research efforts are primarily focused on overcoming these limitations by engineering novel photocatalysts and optimising reaction conditions.

Application showcase

Traditionally, research has optimized individual components like photosensitizers, catalysts, and sacrificial electron donors in photocatalytic CO_2 reduction systems. However, it has been recently known that the choice of solvent and additives play significant role in the system's photoredox properties, impacting overall efficiency.

This research introduces a novel Co(II) catalyst designed for CO_2 reduction, emphasizing the use of earth-abundant elements for cost-effectiveness and sustainability. The catalyst is paired with a well-established, earth-abundant photosensitizer to create a fully sustainable system. Furthermore, the study focuses on controlling the selectivity of the Co(II) catalyst. This is crucial for directing the reaction towards desired products, such as valuable carbon-based fuels, rather than solely producing hydrogen gas.

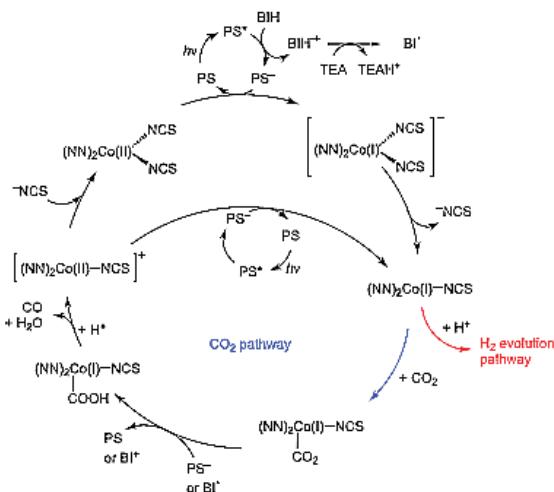


Figure 1: Proposed mechanism for the photoinduced reduction of carbon dioxide with the presented system.

Experimental

The novel cobalt(II) complex 1 was synthesized in dry methanol (MeOH) by mixing in a 2:1 ratio, the chelating diamine ligand, 1-benzyl-4-(quinolin-2-yl)-1H-1,2,3-triazole (BzQuTr) and the cobalt precursor $\text{Co}(\text{NCS})_2(\text{py})_4$. The reaction was performed under an argon atmosphere at room temperature. The resulting complex 1 was obtained after evaporation of the solvent, as a lilac precipitate in good yield (60%).

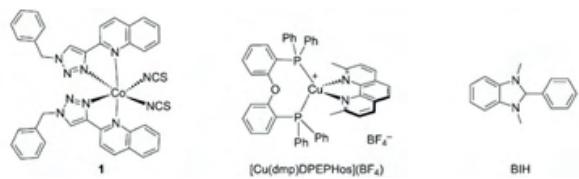


Figure 2: Chemical structures of Co(II) complex 1 as the novel catalyst, the heteroleptic Cu(I) complex as photosensitizer, and the benzimidazolidine derivative BIH as the sacrificial electron donor.

This cobalt complex, designed for CO_2 conversion was structurally characterized using mass spectrometry and elemental analysis. Further confirmations were done using UV-Vis spectroscopy in the chosen solvent (DMA), which revealed its light absorption properties. Cyclic voltammetry explored its electrochemical behavior, suggesting its potential suitability for CO_2 reduction reactions (CO_2RR).

Photo driven CO_2 reduction

The efficiency of the catalyst in photoreduction of CO_2 was analysed. The heteroleptic Cu(I) complex, $[\text{Cu}(\text{dmp})\text{DPEPhos}](\text{BF}_4)^-$, was selected as a photosensitizer for the development of earthabundant systems. In addition, the benzimidazolidine derivative, BIH (1,3-dimethyl-2-phenylbenzo[d]imidazolidine) was chosen as a sacrificial electron donor, because of its high reducing power. The tests were performed in glass vials (20 mL) equipped with a screw-cap septum. The solutions were prepared under air and CO_2 (or argon) was bubbled inside for at least 10 minutes. TEA or TEOA was distilled twice before use. Experiments were performed in a photoreactor from Luzchem (model: LZC-ICH2) equipped with two lamps at 420 nm (fluorescent lamps of 8 W each) and four mini-stirrers. On each stirrer, two samples were irradiated at the same time, for a total of eight simultaneous reactions. The solutions contained the photosensitizer (1 mM or 0.5 mM), catalyst 1 (different concentrations were studied), and BIH (usually 10 mM or 20 mM). The temperature of the reactor was controlled with an in-built ventilator, $T = (25 \pm 5)^\circ\text{C}$. Every test was repeated at least twice. The photon flux was evaluated with actinometry, and it was $0.025 \mu\text{E s}^{-1}$.

Application showcase

Therefore, an apparent photoluminescent quantum yield could be estimated to be upto 2.4%, after 4h, according to the equation-

$$\Phi = \frac{\text{CO moles}}{\text{incident photons} \times (1 - 10^A)} \times 100$$

Where A is the initial absorption value of the photocatalytic system at the irradiation wavelength.

TON and TOF were calculated according to the following equations-

$$\text{TON}_{\text{CO}} = \frac{n_{\text{CO}}}{n_{\text{catalyst}}}$$

$$\text{TON}_{\text{H}_2} = \frac{n_{\text{H}_2}}{n_{\text{catalyst}}}$$

$$\text{TOF} = \frac{\text{TON}}{t_{\text{reaction}}}$$

Where n is the number of moles of the products and of the catalyst and t is the time of the reaction.

HFIP, %	CO, μmol	H_2 , μmol	TON _{CO}	TON _{H₂}	Sel _{CO}
1	4.6	3.1	184	126	59%
2	4.9	2.1	198	83	70%
5	6.0	4.7	231	189	55%

Table 1: Photocatalytic CO_2 reduction tests with different concentrations of HFIP- In a 20 mL flask, 5 mL of a solution with the following concentrations, PS (0.5 mM), BIH (20 mM), complex 1 (0.005 mM) and the indicated amounts of HFIP was irradiated for 4h.

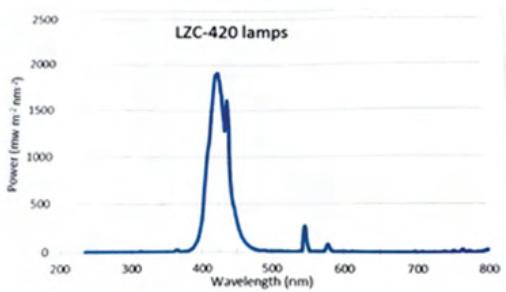


Figure 3: Emission spectrum of the Luzchem lamp at 420 nm.

Conclusion

A fully earth-abundant system was employed for CO_2 RR. Initial experiments with a DMA/TEOA solvent mix yielded both CO and hydrogen from CO_2 . To favour CO formation within the reactor, the reaction conditions were meticulously adjusted.

This optimization achieved a dominant CO pathway (97% selectivity) through a specific modification to the reaction environment within the photoreactor. Further optimization efforts within the reactor maximized CO production efficiency (TON of 86) after extended light exposure to 15 hours. While introducing a supplemental proton source (HFIP), later enhanced CO evolution (TON up to 230) within 4 hours, it also decreased selectivity within the photoreactor.

References

- 1) Fang, S., Rahaman, M., Bharti, J. et al. Photocatalytic CO_2 reduction. *Nat Rev Methods Primers* 3, 61 (2023). *Doi:10.1038/s43586-023-00243-w*.
- 2) Gracia LL, Henkel P, Fuhr O, Bizzarri C. Selectivity control towards CO versus H_2 for photo-driven CO_2 reduction with a novel Co(II) catalyst. *Beilstein J Org Chem.* 17;19 (2023). *Doi: 10.3762/bjoc.19.129*.
- 3) S. R. Lingampalli, Mohd Monis Ayyub, and C. N. R. Rao. *ACS Omega*, 2, 6 (2017) 20172740-2748. *Doi: 10.1021/acsomega.7b00721*



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An ideal workhorse for R&D success

Organic synthesis is exciting but is your lab up for it?

The goal of any pharmaceutical development is to design a quality product to consistently produce the intended performance of the chemical entity. API development is gaining increased attention with time. It has the potential to be controlled and modified by identifying and addressing the issues at a very early stage. This journey starts with the synthesis of high-quality small molecules, which are an indispensable element of pharmaceutical research and development. Small molecules have consistently contributed to medical breakthroughs, however, there are still major hurdles in their synthesis.

It is well known that small molecule synthesis is extremely meticulous, not to mention excessively time consuming. This tedious process can be a true test against one's patience and perseverance! From weighing out reactants to separation, purification and characterisation, there is a constant battle against time, demanding unwavering dedication from the chemist. The tedium doesn't stop here- often the desired product is formed in minuscule quantities, requiring the entire process to be repeated several times.

Fret not! This guide will equip you with the knowledge to upgrade to a high-powered laboratory that promotes your creativity, maximizes efficiency, and makes those late nights a little less... well, late.

Finding the right balance

METTLER TOLEDO

Weighing is one of the most crucial necessities in pharma R & D and has a wide array of applications, for instance, in sample/standard preparation, formulation, interval weighing, and much more. The **Mettler Toledo analytical Balances** offer high stability and precision.



Why Mettler Toledo

- High degree of accuracy and precision.
- Offer a weighing capacity from 22 g to 520 g and readability ranging from 0.001 mg to 1 mg.
- Perfectly suitable for highly sensitive applications.



Turn your lab into the ultimate workhorse of productivity and efficiency

DLAB

Perhaps the most exciting segment in chemical synthesis is performing successful reactions without any nitty-gritties. Chemical synthesis is incomplete without a reliable magnetic stirrer or let's say 6 stirrers! The **DLAB 4/6 Channel LCD Digital Hotplate Magnetic Stirrers** with independent control of start/stop, temperature, speed and display provide increased efficiency for a variety of scenarios like parallel synthesis or reaction optimisation.



Why DLAB

- Integrated spacious 4/6 channel in one instrument.
- Corrosion resistance with ceramic coated aluminium work plate.
- Enhanced experimental safety.
- Extended motor life with stirring speed of 200-1500rpm.
- Compatible with different heating blocks and reaction vessels.



And what is the safest, fastest and efficient way of heating? No, not those messy and unsafe oil baths! The **Radleys Heat-On Block System** provide safer, cleaner and uniform heating of reaction flasks. Think interchangeable blocks for ultimate flexibility, allowing you to scale your reactions with ease.



Why Radleys

- Two 3mm temperature probes provide uniform heating up to 260°C.
- Exceptionally rapid heating.
- The PTFE coating reduce surface temperatures up to 50%, reducing burn risks and is corrosion resistant.
- Choose from over 50 styles and sizes from tubes and flasks of 1 ml to 5 litres.
- Unique well design eliminates cracking of reaction flasks.

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Let us move on to characterisation. Honestly, waiting for the product to be characterised is as time consuming as performing the reactions itself, or even more! Generally, these instruments are confined to a specific facility and the wait is quite wearying. Here is where some serious firepower comes in. Imagine having the ability to quickly verify the structure of your synthesized compounds right at your workstation. **Nanalysis 100Pro benchtop NMR** is a complete game-changer for synthesis labs.



Why Nanalysis

- Accessible, affordable with minimal maintenance.
- Non destructive analysis- reclaim your sample after analysis.
- Multi-channel 100 MHz benchtop NMR spectrometer engineered for simple and fast acquisition of high-performance 1D and 2D NMR data.
- Multi nuclei configurations available- $^1\text{H}/^{13}\text{C}$, $^1\text{H}/^{31}\text{P}$, and $^1\text{H}/^{19}\text{F}$.
- Encompasses a strong permanent magnet and a 100 MHz (2.35 T) frequency.
- Run samples at sub milli-molar concentrations in standard 5mm NMR tubes.
- Set up queuing of a series of experiments to be acquired automatically- 1D, T_1 , T_2 , COSY, TOCSY, JRES, DEPT, HSQC, HMBC, etc.



Incorporate the Nanalysis 100Pro benchtop NMR and get real-time feedback, accelerate your research and save precious time.



Tech corner

Another essential tool for confirming molecular identity and purity- mass spectroscopy. The **Advion Interchim expression® CMS** (Compact Mass Spectrometer) integrates with the simplest technique to fastest direct probe analysis requiring no sample preparation. The CMS is specially designed to cater to detection of compounds in organic and analytical labs.

Why Advion Interchim



The Expression Compact Mass Spectrometer enables:

- TLC-MS for direct MS analysis of TLC spots (TLC-MS)
- Stand-alone system for direct injection measurements (e.g., for reaction monitoring)
- Direct analysis of solids & liquids with ASAP probe
- Direct analysis of air and moisture sensitive solids & liquids with iASAP probe
- Head space sample analysis with vAPCI
- A range of normal phase flash chromatography systems for normal phase Flash-MS
- As a MS detector for any HPLC system and UPLC system (LC-MS)



So bid adieu to those moments of despair waiting for days at length to optimise reactions and getting external analysis. By incorporating these instruments, you can transform your small molecule synthesis lab from a functional space into a true powerhouse of discovery.

Investing in the right equipment is an investment in your research- contact Inkarp Instruments Pvt Ltd. to upgrade your laboratory. In the meantime, keep calm, synthesize on, and may your next molecule be life altering!



Troubleshooting tips for optimum instrument longevity and efficiency: Expert's advice



**ThalesNano
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Hydrogenation
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The ThalesNano H-Cube® is a flow reactor designed for safe and efficient catalytic hydrogenation reactions in the laboratory. The H-Cube® generates hydrogen gas on-demand through electrolysis of water, eliminating the need for bulky and potentially hazardous hydrogen cylinders.

Features:

On-demand hydrogen generation: Offers a continuous and reliable source of hydrogen gas, eliminating the need for external cylinders.

Temperature and pressure control: Enables researchers to conduct hydrogenation reactions at a wide range of temperatures and pressures, allowing for optimization based on specific reaction requirements.

Fast reaction times: Streamlines workflows by facilitating rapid hydrogenation compared to traditional methods.
User-friendly design: Simplifies operation with an intuitive interface, making it accessible to a broad range of researchers.

Safety features: Provides a safer laboratory environment by removing the risks associated with high-pressure hydrogen gas cylinders.

The H-Cube is a powerful tool offering remarkable capabilities and precision. However, like any sophisticated equipment, proper handling and maintenance are crucial for maximizing its lifespan and ensuring optimal performance.

We bring to you the troubleshooting tips and tricks for ThalesNano H-Cube from our highly experienced service engineers- so pay attention!

Tech corner

No reaction or low conversion rates?

- ! **Check catalyst condition:** Ensure the catalyst is fresh and properly loaded. Replace if necessary.
- ! **Flow Rates and Pressure:** Verify that the flow rates and pressure settings match the requirements of your specific reaction.
- ! **Hydrogen supply:** Confirm that the hydrogen supply is uninterrupted and at the correct pressure.

Clogged reactor?

- ! **Backflush the system:** Use the backflush function to clear any blockages in the reactor.
- ! **Filter check:** Inspect and clean the filters regularly to prevent particle buildup.
- ! **Reactor maintenance:** Periodically dismantle and clean the reactor components as per the maintenance schedule.

Temperature fluctuations?

- ! **Solvent purity:** Use high-purity solvents to avoid contamination and clogging of the pump.
- ! **Tubing inspection:** Check tubing for kinks, leaks, or blockages that might affect flow rates.

Hydrogen leaks?

- ! **Inspect Seals and Fittings:** Regularly inspect seals, gaskets, and fittings for signs of wear or damage.
- ! **Proper assembly:** Ensure all components are correctly assembled and tightened according to the manufacturer's specifications.

Software or interface issues?

- ! **Firmware updates:** Keep the H-Cube's firmware up to date to benefit from the latest features and fixes.
- ! **System reboot:** Restart the system if the interface becomes unresponsive.
- ! **Technical support:** Contact Inkarp Instruments support for assistance with persistent software issues.

Flow rate inconsistencies?

- ! **Temperature stability:** Check if the reactor is maintaining set temperature. If not replace heat cartridge.
- ! **Heat exchanger check:** Verify that the heat exchanger is functioning properly and not clogged.

Reactor overpressure?

- ! **Pressure relief valve:** Ensure the pressure relief valve is functional and correctly set.
- ! **Flow restriction:** Identify and remove any flow restrictions in the system.
- ! **System venting:** Properly vent the system before starting the reaction to avoid pressure buildup.

By following these troubleshooting tips, users can ensure optimal performance and longevity of their ThalesNano H-Cube, leading to more consistent and reliable results for years to come.

Prioritizing safety and longevity of hazardous liquids

Safely transport, store and manage metering, dispensing, decanting or disposal of inflammable liquids.



Safety first:

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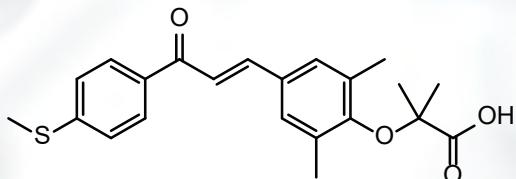
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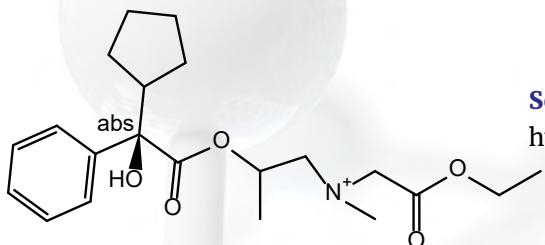
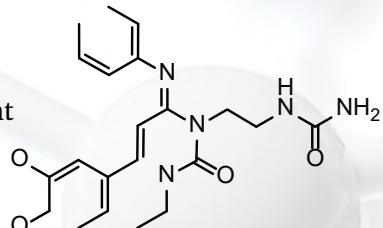


Recent novel FDA approved drugs



Elafibrinor is a peroxisome proliferator activated receptor agonist used to treat primary biliary cholangitis in adults with intolerance of inadequate response to ursodeoxycholic acid.

Ensifentrine is a phosphodiesterase inhibitor used for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults.



Sofipironium bromide is an anticholinergic to treat primary axillary hyperhidrosis (excessive sweating).

Crovalimab is a monoclonal antibody (complement c5 inhibitory humanized recycling monoclonal antibody (rg-6107)) used for the treatment of paroxysmal nocturnal haemoglobinuria.

Imetelstat is an oligonucleotide telomerase inhibitor used for the treatment of myelodysplastic syndromes with transfusion-dependent anaemia.

Tarlatamab is a monoclonal antibody (Bi-specific T-cell engager) used for the treatment of extended-scale small cell lung cancer.



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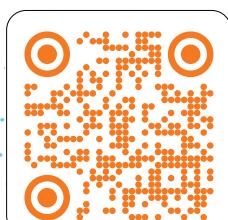
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