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Solid dosing in High-Throughput Experimentation: generalization of mass enhancer technologies for submilligram scale

Taline Kerackian^{1,2} · Géraud Chacktas^{1,3} · Didier Durand³ · Eugénie Romero¹

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Abstract

The emergence of High-Throughput Experimentation (HTE) as a powerful tool for reaction discovery and optimization is changing the way organic chemists are designing their experiments. It is a fantastic way to largely investigate a reaction, in a minimum of time and reagent consumption. However, HTE needs to be accessible to a wide audience for a full implementation in academic and industrial sectors. In that context, developing accessible solid dosing methodologies for submilligram dispensing is necessary. This paper aims at proposing robust mass enhancers solutions for nanomole scale dosing applicable to HTE campaigns.

Keywords High-Throughput Experimentation · Catalysis · Mass enhancer

Introduction

Discovery of robust new chemical reactions is critical to manage efficiently public health, societal problems and human welfare but also ensure chemical and pharmaceutical industry development and address scientific challenges. However the discovery and optimization of such reactions can be extremely time and money consuming, thus reducing the time dedicated to those steps is crucial for accelerating Drug Discovery and Development (DDD) [1].

Some technologies have emerged to overcome these limitations and accelerate DDD: High-Throughput Experimentation (HTE) has been shown to drastically speed up reaction discovery as well as optimization and has been identified as the best way to generate accurate and standardized large data sets from experimental workflow [2–4].

HTE has revolutionized the way researchers are designing and performing their experiments. It is a miniaturization and parallelization of reaction conditions, allowing a large number of experiments to be performed with high reproducibility, minimal material consumption, leading to a reduction of time, waste and thus cost. [5]. HTE platforms developed for synthetic organic chemistry have evolved dramatically during the last decade, for a large majority in the USA, from standard screening protocols performed at micromole scale in a 96-well plate format [2], to HTE campaigns being currently performed at nanomole scale in 1536-well plates [6, 7]. HTE has proven to be complementary with flow technologies. It allows the optimisation of reactions which can be then applied directly to flow protocols [8, 9]. HTE has also been identified as the best way to generate reliable large data sets to feed Machine Learning/Artificial intelligence, leading to the development of accurate predictive models [10–12]. Several industry laboratories have deployed resources to establish HTE facilities [2]. HTE has been strongly seized and empowered by some of these companies, leading to robust and consistent techniques for a wide variety of chemical reactions commonly used by organic chemists, especially in catalysis where the solvent, catalyst and ligand combination are key elements [13].

Among technologies developed for accurate and universal HTE set-up, liquid handling is one of the most efficient way to dispense chemicals in a precise and reproducible manner. However, some reagents can display low solubility in

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solvents highly limiting the use of liquid dispensing. For solid dispensing, if some robotic instrumentation for gravimetric solid dispensing are commercially available, it is quite expensive and by consequence not easily accessible to most laboratories, furthermore the precision of these instrumentations are not good enough at very low scale (submilligram scale and below) when considering the limitation of most precision balances (0.1 mg precision) [14]. In order to face this challenge and to propose accuracy in solid dosing of very low loading using automated instrumentation or manual dispensing, researchers from Abbvie® came out with the coated beads technology as mass enhancer [15–19]. Glass has been a support of choice for materials – heterogeneous catalysts for example – because of its inert character and high availability [20–22]. As mass enhancer, it consists of glass or polystyrene beads coated with a solid using mechanical force, in order to increase the mass to be weight and so allow a more precise measure, in accordance with our traditional precision balances (0.1 mg precision). The solid powder will coat the surface of the beads via van der Waals forces. These so called Chembeads (CB) have been applied to a range of chemical compounds – photocatalysts, metal complexes – but also inorganic bases as potassium or cesium carbonate, inorganic bases being one of the biggest dispensing challenge in HTE due to their low solubility in organic solvents. This technology has been extended to enzymes – EnzyBeads – propulsing HTE into the field of biocatalysis [19].

In only few years, Chembeads have been accepted by the HTE community and are now commonly used in such platforms. Some coated Chembeads have been commercialized, as the first protocol for Chembeads preparation involved the use of a specific mixer system: a Resodyn® Resonant Acoustic Mixer (RAM) (RAMLab II).

Earlier this year, researchers from Abbvie® have described a more accessible general protocol for Chembeads preparation. They compared the beads coating in terms of

targeted loading and reproducibility, with several technics: RAM mixer (60 k€), vortex mixer (200–600€), hand mixing (0€). It appears that all methods are quite robust, making Chembeads preparation widely accessible. They also evaluated the loading charge for 3 sizes of beads, and concluded that 5% loading w/w was optimal, with possibility to charge up to 20% w/w depending on the solid considered. In the same study, the authors have shown the good quality of Pd precatalysts Chembeads (XPhos Pd G3, DavePhos Pd G3, MorDalPhos Pd G3) in terms of efficiency in reaction compared to non-supported Pd precatalysts [19].

If this technology seems promising, reproducible, and essential for the generalization of HTE in industrial but also academic ecosystems, some improvements remain necessary. As an example, from an academic point of view, the use of precatalysts is not systematic as their price is at least twice the price of a homemade mixture Pd/Ligand (Fig. 1). A more in depth evaluation of mixed Chembeads is still needed. In addition, even though the coating is homogeneous along the glassbeads, a non-negligible amount of solid is coated on the glass vial, which implies a lower loading than the expected charge, and the necessity of a systematic evaluation of Chembeads loading in order to know the exact charge coated. Finally, the evaluation of the accuracy of non-automated calibrated dosing instruments should also be studied.

In this paper, we were willing to answer the remaining interrogations around mass enhancer technologies for submilligram scale solid dosing. We will evaluate intensively the possibility of Chembeads coated with mixtures of solids, as metal and ligands, for accurate dispensing of submilligram scale in HTE experiments. The compability of Chembeads in different types of chemistry (under thermal, photo or electro activation) will be checked. Also, in an attempt to circumvent the mass loss due to coating of reagent on glass vial in CB preparation, we have investigated the use of inorganic carriers as alternative mass enhancers and evaluated

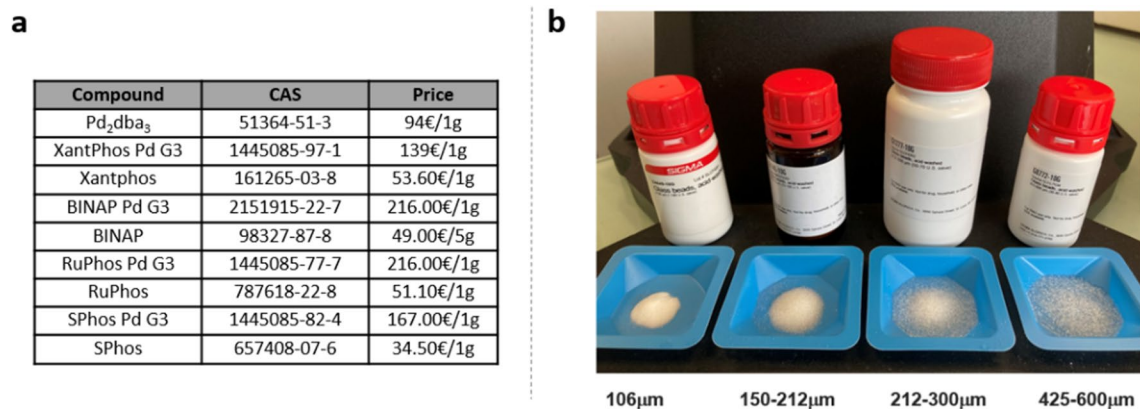


Fig. 1 **a**) Price comparison of Pd G3 precatalysts and ligands (Sigma Aldrich prices in 2023); **b**) Comparison of glass beads diameters

their efficiency on reactions involving thermal, photo or electro activation, with the establishment of a catalogue of mass enhancers that could answer all challenges in mind. Finally, the readily accessible calibrated dosing instruments will be evaluated and commented.

Discussion

HTE is a growing technology and needs to be easily accessible for an efficient deployment. With this objective in mind, the investigation of mixed CB will be carried out in different types of chemistry. Indeed four reactions will be investigated: i) a Suzuki–Miyaura cross-coupling, one of the most common reaction performed in HTE in industry, for the evaluation of CB under thermal conditions [2], where a list of 4 ligands will be supported, associated with Pd₂dba₃, ii) a Sonogashira reaction allowing the investigation of a mixture of metals coated on CB, iii) a nickel/photoredox catalyzed reaction for the efficiency under photoirradiation [23], and iv) an electroreductive cross-coupling [24], as the first use of CB in electrosynthesis. All CB and mixed CB have been prepared following the reported procedure under simple hand mixing [19], and the coating charges have been systematically evaluated by double weight method (see SI). Most experiments have been performed in duplicate, triplicate or quadruplicate, for reproducibility evaluation. Most reactions have been investigated under HTE campaigns, and were reproduced in batch for isolation and characterisation of product. Both HTE or batch reactions were evaluated based either on the Total Wavelength Chromatogram (TWC) or the Total Ion Chromatogram (TIC), by calculating the ratio of the area under curve (AUC) of the product/AUC of the internal standard.

Evaluation of mixed CB on a Suzuki–Miyaura cross-coupling reaction

With the evaluation of complex mixed Chembeads in thermal conditions in mind, we decided to start with a robust palladium catalyzed reaction, a Suzuki–Miyaura Cross-Coupling, as model reaction (Fig. 2.a). As standard conditions, the coupling of 2-bromo-6-methoxynaphthalene with 3-(trifluoromethyl)benzeneboronic acid was performed using Pd₂dba₃ (5 mol%), XantPhos (10 mol%) and potassium phosphate, in THF at 100 °C, to give 2-methoxy-6-[3-(trifluoromethyl)phenyl]naphthalene as the product.

The reaction was evaluated in quadruplicate in a HTE campaign (10 μmol scale), by comparing results obtained with: a) Pd₂dba₃ and Xantphos by liquid dosing of stock solution; b) individual CB coated with Pd₂dba₃ (5% w/w) and individual CB coated with Xantphos (6.31% w/w); c) mixed CB coated with a mixture of Pd₂dba₃ and Xantphos

(ratio 1:2 with 5% w/w in Pd₂dba₃). The evaluation was performed on 4 sizes of glass beads, from 100 to 600 μm diameter (Fig. 2.b).

The CB respectively coated with Pd₂dba₃, Xantphos, and a mixture of Pd₂dba₃/Xantphos were then evaluated on the Suzuki–Miyaura reaction, and compared to the liquid dispensing (Fig. 2.b). As an important note, the CB have been weighted in each vial using a precision balance (0.1 mg precision).

For the evaluation of Mixed CB in regards of glass beads diameters (Fig. 2.b), the results have shown a good reproducibility in all systems, with an impressive precision on the system involving the palladium and the ligand coated separately on individual CB. Nevertheless, mixed CB have shown a similar outcome, as precise as the liquid handling, and a perfect reproducibility (quadruplicate). The size on glass beads seems to have a minimal impact on the yield of the reaction, regardless of the dosing system studied, and a good reproducibility. For the rest of the investigation, the glass beads with a diameter of 212–300 μm were used for all CB preparations.

In order to further investigate the mixed CB on this thermal system, we evaluated the approach in an HTE experiment with three other ligands. RuPhos, BINAP and SPhos have been coated with Pd₂dba₃ to generate corresponding mixed CB, characterized (see SI) and evaluated on the model reaction (Fig. 2.c). The mixed CB system was compared to a liquid dosing system, in triplicates. Mixed CB have proven to be highly reproducible with a minimal variation on the ratio product/IS. Surprisingly, we also observed an increased ratio product/IS when the reaction was performed with CB, compared to liquid dosing. This could be explained by a more efficient and strong stirring of the reaction, especially in HTE vials (1 mL total, 100 μL of reaction solvent), due to the presence of glass beads. Another explanation could be found in the progressive solubilization of the powders mixture coated on glass beads during the reaction. In addition, even though BINAP turns out to have a lower coating charge than expected, the mixture was perfectly homogeneous with a good reproducibility, thus no impact or bias could be observed in screening experiments.

Evaluation of mixed CB on a Sonogashira coupling reaction

In an attempt to extend the scope of mixed CB application, we evaluated a new mixed CB system involving two metals, Pd((PPh)₃)₂Cl₂ and CuI, in a Sonogashira coupling reaction (Fig. 3.a). 2-Bromo-6-methylpyridine and 1-hexyne reacted in presence of Pd((PPh)₃)₂Cl₂ and CuI as catalysts, potassium carbonate as a base, in THF at 60 °C under inert atmosphere, to give 2-(1-hexyn-1-yl)-6-methylpyridine as the product.

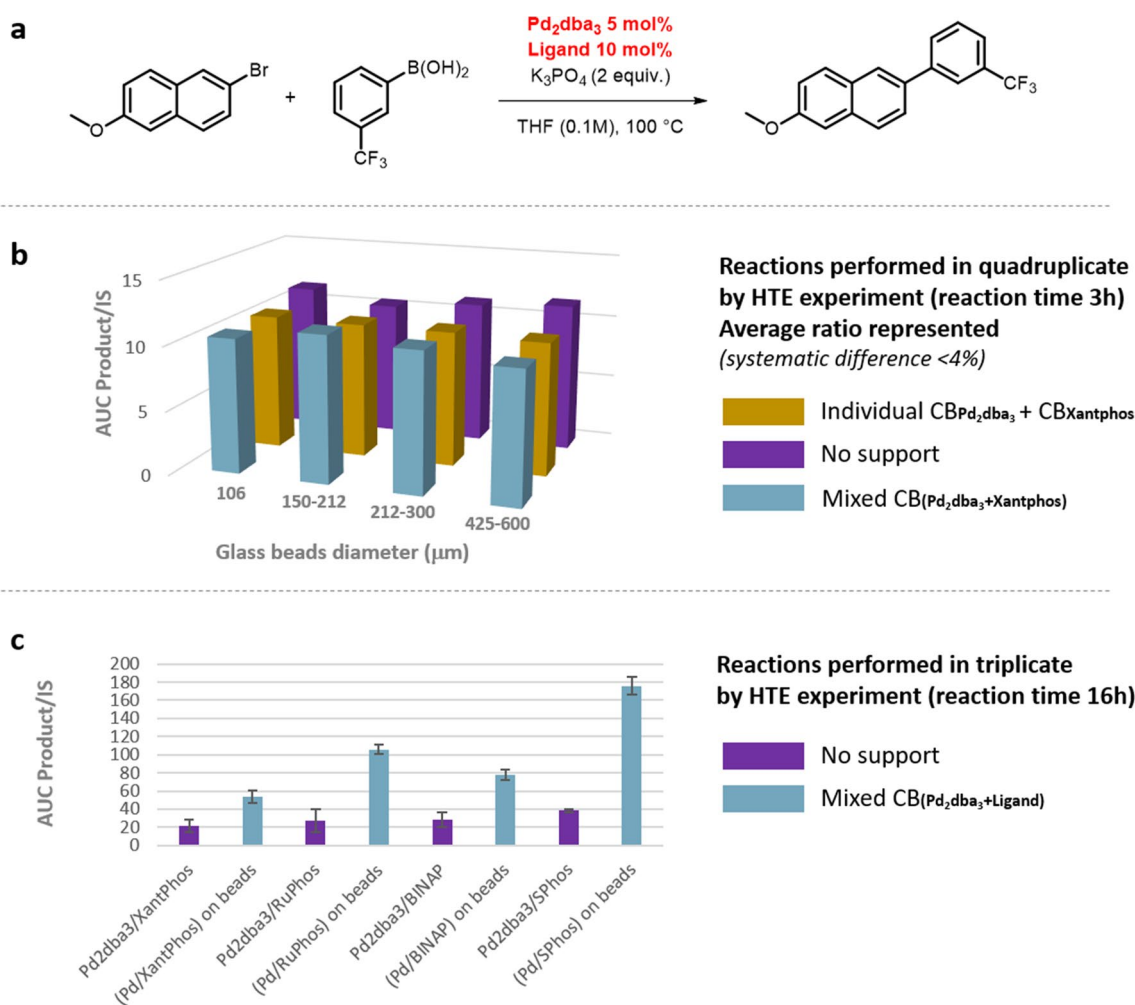


Fig. 2 **a**) Suzuki–Miyaura cross-coupling for the evaluation of mixed CB under thermal conditions; **b**) Evaluation by HTE of mixed Chembeads $\text{Pd}_2\text{dba}_3/\text{Xantphos}$, in comparison with individual Chembeads (coated with Pd_2dba_3 or Xantphos) and stock solution dispensing in a Suzuki–Miyaura cross-coupling reaction. Reaction performed in quadruplicate with 4 different sizes of glass beads. Ratio of product

vs internal standard are presented (Area under curve (AUC) of product/AUC of Internal Standard); **c**) Evaluation by HTE of the Suzuki–Miyaura reaction involving BINAP, SPhos and RuPhos ligands, with 3 different dosing systems, in triplicate. Ratio of product vs internal standard are presented (Area under curve (AUC) of product/AUC of Internal Standard)

Mixed CB have been prepared with a coating target of 5% w/w $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and a ratio 1:2 of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and CuI respectively. The reaction has been performed in an HTE campaign, in triplicate, by comparing mixed CB dosing and classical stock solution liquid dosing. The results have shown the robustness of both systems with a similar outcome for both liquid and CB dosing (Fig. 3.b). These results are confirming the efficiency of mixed CB system for complex mixtures of solids such as metals.

Evaluation of mixed CB on a dual Ni/photoredox catalyzed reaction

The compatibility of two metals on mixed CB has been further investigated on a third reaction, where the possibility of

mixed CB supporting a mixture of three solids has also been evaluated. A dual catalyzed reaction allowing the allylation of aldehyde was selected (Fig. 4.a) [23], *P*-anisaldehyde and allyl acetate reacted in presence of $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ as photocatalyst, a catalytic source of $\text{NiBr}_2 \cdot \text{glyme}$, 1,10-phenanthroline as a ligand, *N,N*-diisopropylethylamine (DIPEA) as a base, in acetonitrile at room temperature under the irradiation of blue LEDs, to give 1-(4-methoxyphenyl)-3-buten-1-ol as the product. In order to validate this complex system, we have prepared mixed CB coated with $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$, $\text{NiBr}_2 \cdot \text{glyme}$ and 1,10-phenanthroline, with a ratio of respectively 1:10:15 (target 5% w/w of $\text{NiBr}_2 \cdot \text{glyme}$) as well as individual CB. The reaction has been performed in duplicates involving 3 dispensing systems: with individual CB, with mixed CB, and without CB (No support).

Fig. 3 a) Sonogashira coupling for the evaluation of mixed CB involving two metals; b) Results obtained with an HTE campaign for the evaluation of dosing systems (mixed CB vs liquid dosing). Ratio of product vs internal standard are presented (Area under curve (AUC) of product/AUC of Internal Standard)

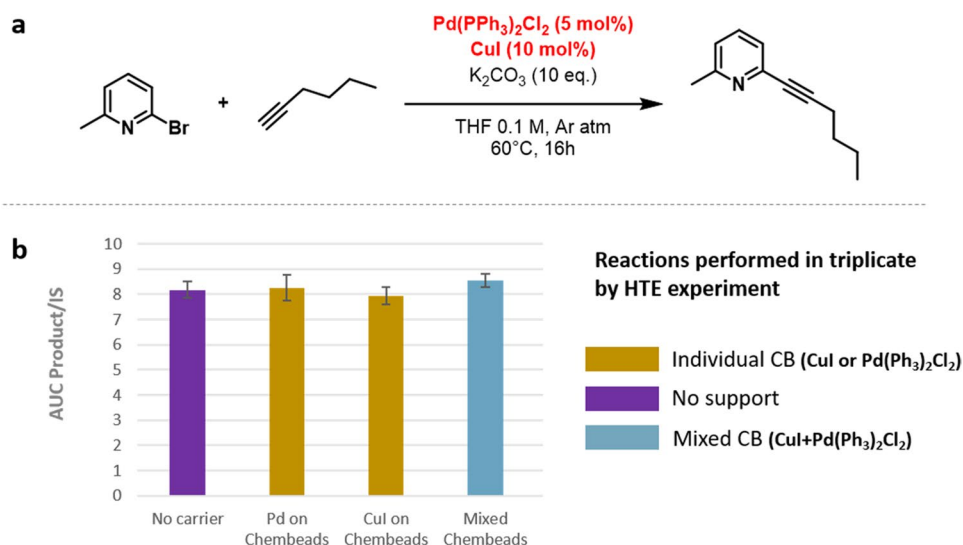
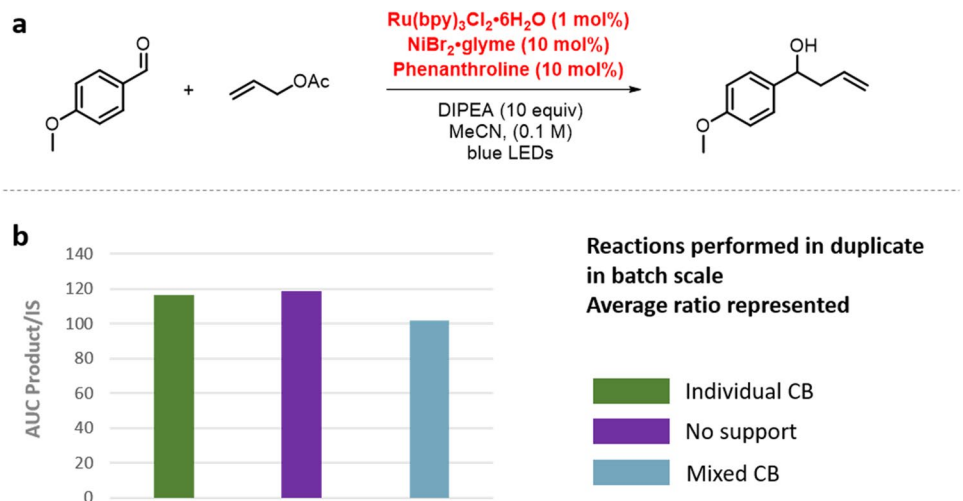


Fig. 4 a) Allylation of aldehyde by dual catalysis as model reaction for mixed CB supporting 3 compounds; b) Results obtained in duplicate with 3 dosing systems (liquid dosing, individual coated CB or mixed CB). Ratio of product vs internal standard are presented (Area under curve (AUC) of product/AUC of Internal Standard)



The results have shown a similar efficiency in all systems, with a comparable ratio (AUC product/AUC Internal Standard), regardless of the dosing system used (Fig. 4.b). A negligible reduction of the yield is observed for individual CB. These results are confirming the robustness of mixed CB systems, even with highly complex mixtures of compounds.

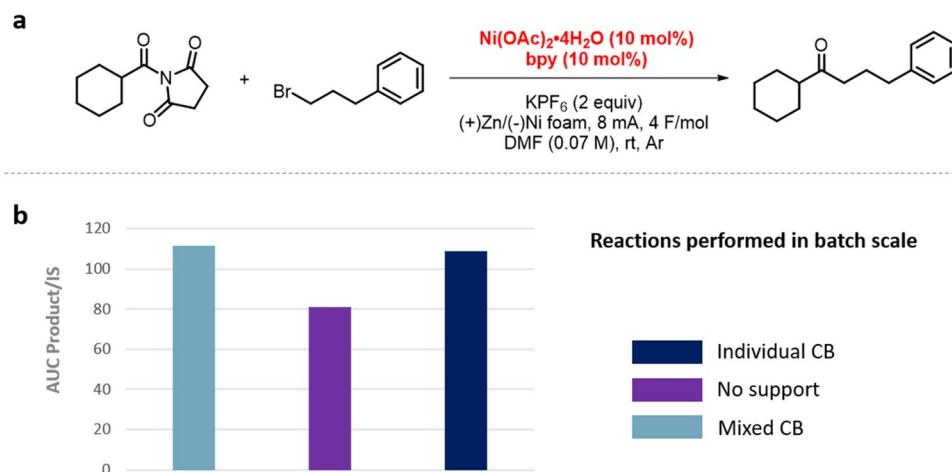
Evaluation of mixed CB on an electroreductive reaction

To pursue the evaluation of mixed CB, we decided to evaluate the compatibility of individual and mixed CB on an electrochemical system [24]. In fact, the deployment of commercially available HTE reactors applied to electroactivation [25] should soon conduct to the use of CB in electrosynthesis. To do so, we have performed a cross electrophile coupling between an *N*-acyl imide and an alkyl bromide, under nickel catalysis in electrosynthesis

(Fig. 5.a). 1-(Cyclohexanecarbonyl)pyrrolidine-2,5-dione and 1-bromo-3-phenylpropane reacted in presence of a catalytic source of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, 2,2'-bipyridine as a ligand, potassium hexafluorophosphate as electrolyte in DMF under inert atmosphere, to give 1-cyclohexyl-4-phenylbutan-1-one as the product. The reaction has been evaluated on an ElectraSyn 2.0 IKA® system, i) without supported chemicals, ii) with individual coated CB (coating target 5% w/w) and iii) with mixed CB coated with a mixture of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ and 2,2'-bipyridine in a ratio of 1:1 (coating target 5% w/w of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$).

Results proved the compatibility of CB with electrosynthesis (Fig. 5.b). If no difference were observed between individual and mixed CB, an increased yield is observed for CB systems compared to the reaction without supported compounds. This observation might be explained by the importance of mass transfer in electrochemical reactions. The presence of a non-negligible amount of glass beads in

Fig. 5 a) Electroreductive cross-coupling as model reaction for mixed CB; b) Results obtained with 3 dosing systems (liquid dosing, individual nickel coated CB or mixed CB). Ratio of product vs internal standard are presented (Area under curve (AUC) of product/AUC of Internal Standard)



the vial could improve the stirring and homogeneity of the system, giving a more efficient reaction.

With all these results in hands, and as a complementary study in regards of the literature [15–19], we have described the robustness of mixed CB as mass enhancer for the dosing of compounds, compatible with mixture of metals, or with complex mixtures up to 3 components supported on the same glass beads. As a specific note, we were not able to test complex mixtures involving inorganic bases, as specific recommendations from Abbvie® for the coating of such compounds involve non-accessible instrumentation for our lab (RAM mixing system) [19].

Despite these comforting results, one major drawback of CB remains: the targeted loading charge. When preparing CB in glass vials, a difference is observed between the targeted loading charge and the observed/measured loading charge (see SI). This is easily explained by the fact that a part of the solid is coated on the vial wall (Fig. 6). As a consequence, a systematic analysis of the exact loading charge is necessary after each CB preparation, in order to determine the correct coating charge and so the correct amount of CB needed. As an answer to this issue, we are proposing to evaluate two other mass enhancer systems, using inorganic carriers, Silica or Celite®. These new systems will be called SiO₂ or Celite® ChemCarrier (CC).

Evaluation of inorganic ChemCarriers as mass enhancers

Due to the coating of solid on glass vial during chembeads preparation, lowering the expected chemical loading, we decided to study the possibility of using SiO₂ (mesoporous, < 50 μm particle size) and diatomaceous earth Celite® as mass enhancer. In fact, the use of solids supported on inorganic carriers has become more and more common in organic synthesis due to their high efficiency in improving the speed and the yield of reactions under mild conditions [26]. As another example of inorganic carriers interest, both Silica and Celite® are already commonly used as material to support catalysts in heterogeneous catalysis [27–30] or in flow chemistry [31–34]. Based on this observation, both Silica and Celite® are promising mass enhancers, or ChemCarriers, for submilligram dosing with the hope of a perfect coating charge objectively expected due to their porosity and their affinity with reagents in comparison with glass surfaces.

We decided to investigate Silica and Celite® CC on each reaction previously investigated for mixed CB evaluation (Fig. 2, 3 and 5). All Silica and Celite® CC have been prepared with a systematic 5% w/w loading target. As an important note, and as expected, the loading charge was systematically identical to the

Fig. 6 Pictures of CB, SiO₂ CC and Celite® CC for the coating of Xantphos (targeted coating charge of 5% w/w for Silica and Celite® and 6.31% w/w for CB)



- A. Xantphos on Silica**
B. Xantphos on Celite®
C. Xantphos on glass beads
 212–300 μm

targeted charge (less than 1% w/w deviation), which confirmed our hypothesis and could answer the limitation met with CB systems (see SI for CC preparations).

The results obtained on each reaction type are highly encouraging, with competitive outcomes obtained with inorganic CC systems. On the Suzuki–Miyaura reaction (Fig. 7.a), Celite® and Silica CC systems have shown a slight increase of the yield compared to CB system or standard protocol (no support). On the Sonogashira coupling reaction (Fig. 7.b), Pd(PPh₃)₂Cl₂ was coated on CB (results reported in Fig. 3), on Silica CC and Celite® CC, with a 5% w/w targeted charge. Those carriers were evaluated and compared to the reaction without carrier. Ratios Product/IS are highly comparable, with a slight increase of the yield for the reaction without any support. With considering this negligible variation, the robustness of all carriers systems, inorganic as well as glass supported ones, seems evident. Finally, on the electrochemistry electrophile cross-coupling (Fig. 7.c), we have investigated mixed Celite® CC and mixed Silica CC systems, in comparison with mixed CB and standard protocol. Inorganic CC are as good as standard protocol without support. Nevertheless, mixed CB have shown a better yield, which might be explained again by a more efficient stirring at the electrodes surface.

These results, associated with the excellent coating charge, are confirming the high potential of inorganic

carriers as mass enhancer for submilligram dosing of reagents. If Silica and Celite® CC can easily compete with CB systems, even on mixed coating system, it remains important to evaluate their efficiency with specific reagents such as inorganic bases. In that case, the thinness of the powder might be a limiting parameter for a correct coating of inorganic CC, and so might necessitate high performance grinding system as a Resodyn acoustic mixing instrument.

As a final study of this paper, and as mentioned earlier, we had to weigh CB on each vial (batch or HTE) using a precise balance. The reason of this long and complicated procedure was the lack of reproducibility and precision of available non-robotized dispensing systems. We thus decided to perform a meticulous study of these commercially available systems.

Solid dosing calibrated instruments

The development of such carrier technologies are very powerful, and need to be supported by suitable calibrated solid dosing systems. Some robotic platforms are commercially available and highly efficient with milligram to gram scale dosing [14]. For non-automated HTE platforms, calibrated dispensers development is still needed. Calibrated scoops are commercially available dispensers. Their efficiency was evaluated. Based on preliminary studies performed in our laboratory (Fig. 8) [35], calibrated scoops have shown low precision and reproducibility

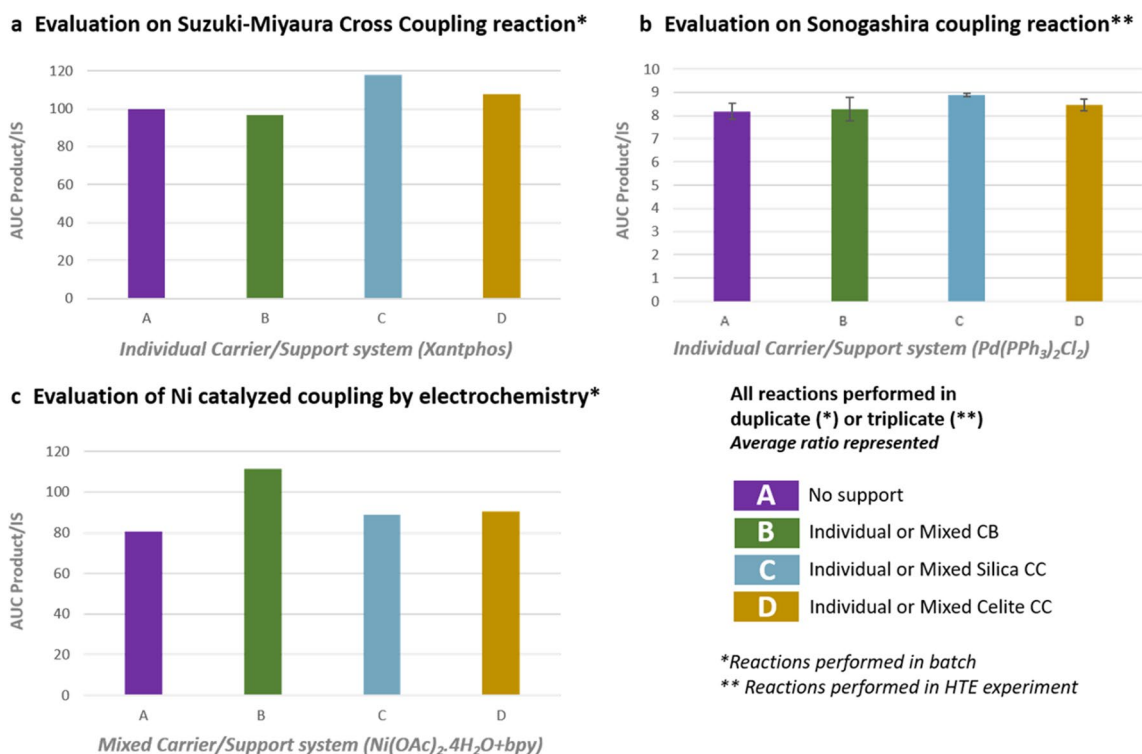


Fig. 7 Results obtained for Silica and Celite.® CC on different reactions, in comparison with liquid dosing and CB systems. Ratio of product vs internal standard are presented (Area under curve (AUC) of product/AUC of Internal Standard)

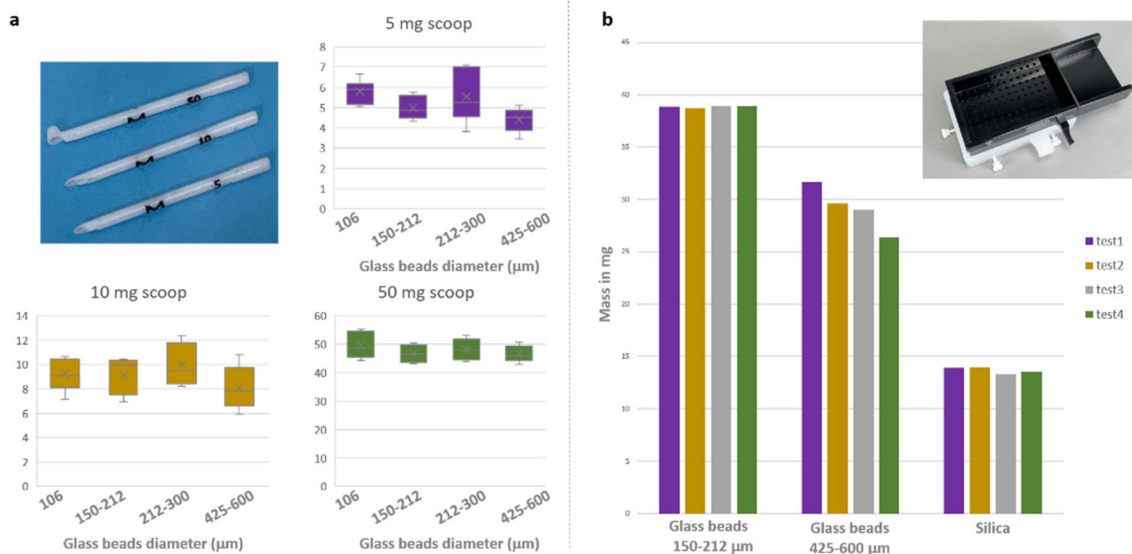


Fig. 8 a) Evaluation of solid dosing by commercial 3D printed scoops; b) Evaluation of solid dosing using 96 well dispenser from V&P Scientific

at low scale. In the case of micromole scale reactions, the error range identified is too high for a good standardization and interpretation of our HTE results, due to a significant variation of catalytic charges. However, with the merging of 3D-printers for the development of technical instrumentations, specific multi-channel solid dispensers are currently under study/design by the HTE community. As an initiative to validate the use of such instruments, we have evaluated the multi dispensers of solid carriers (CB and inorganic CC) with a 96 well dispenser from V&P scientific, originally designed for stir bars dispensing [36]. If the dispensed mass is carrier dependant, this strategy brought important data about the reproducibility of such techniques. The reproducibility is excellent for Silica ChemCarriers and Chembeads with a small diameter (150–212 μm), as both present the same aspect (i.e. thin powder) (Fig. 8). However, the reproducibility is not satisfying for Chembeads with larger glass beads diameter (>400 μm).

Nevertheless, the results are encouraging and suggest the high interest – if not necessary – in the development of specific solid dispensers.

Conclusion

In complement with the reported literature on Chembeads preparation and applications, this study aims at proving the robustness of this technology in many activation modes. As complementary methods, we have evaluated the possibility of using inorganic ChemCarriers such as silica and Celite® to improve the coated charge efficiency. In a near future, the deeper evaluation of such inorganic ChemCarriers, as well as their parameters such as the

grain size or the stability over time could help understanding the limitations of the technology and its full implementation. Nevertheless, as a valuable dosing tool for submilligram scale, we are convinced by the impact Chembeads and ChemCarriers will have on the deployment and accessibility of High-Throughput Experimentation to the highest number of organic chemists, in industrial but also academic area.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s41981-023-00304-x>.

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Declarations

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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