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High-throughput experimentation for the application in oxidation reactions: solid dispensing approach for miniaturised reactions

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The traditional reaction screening method means testing reagents such as bases, ligands, and catalysts using trial-and-error approaches, which is tedious, and fewer reagents can be evaluated. However, by developing a method that can be used to dispense solid chemical reagents at a nanomole scale for high-throughput reaction screening (HTS), a combination of multiple reagents can be screened rapidly until optimal reagents can be identified. As a proof of principle, a solid dispensing method developed using silica (SiO_2) as an inert carrier of reagents was utilised to screen four bases and twelve ligands for the copper-catalysed oxidative esterification of benzaldehyde and the oxidation reaction of styrene. Using high-throughput screening together with the developed solid dispensing method, about 96 reactions of copper-catalysed oxidative esterification of benzaldehyde with ethyl bromide and benzyl bromide were screened, and one reaction of oxidation of styrene until an optimal combination of reagents was found.

1. Introduction

Several interrelated variables, such as stoichiometry, reaction time, temperature, solvent, and concentration, must be investigated before even the simplest reactions can be performed. Each of the variables can impact the outcome of a chemical reaction differently. For instance, an oxidation reaction must consider the choice and amount of oxidant, catalyst, and other reaction components. A chemist can only screen a limited number of reaction conditions when performing reactions for a certain period, especially *via* sequential conventional (traditional) approaches. In sequential conventional approaches, one variable is screened while other variables are fixed (kept constant), which ignores critical interactions between variables of interest.[1]

In addition, conventional methods are considered time-consuming, costly, and tedious due to the lack of automation for designing screening sets and reactions on a miniature scale and the limitation of advanced intermediates available to synthesise targeted materials. High-throughput experimentation (HTE) is increasingly used across the academic and pharmaceutical industries to solve these challenges.[2]

High-throughput experimentation uses advanced tools and techniques to execute and analyse multiple (large number) reactions simultaneously using less effort per experiment than the sequential conventional methods.[3] HTE aims to develop optimal conditions for specific chemical reactions when employed rapidly. Using HTE, (i) existing chemical reactions can be rapidly improved, (ii) there could be discoveries of new chemicals and methods that can remain unexplored due to the use of limited sequential traditional methods and lack of development, and (iii) new reaction parameters can be developed.[4,5]

The available advanced technology and the benefits of using HTE influenced the growth and application of HTE in diverse fields, including biology, medicinal chemistry, catalysis, and drug discovery.[6–8] Robotic-enabled high-throughput reaction screening can be used in catalysis using different methods, including combinatorial approaches. Multiple reaction conditions can be screened to optimise reactions to obtain desired compounds. However, the success of an HTE efficiency depends on a high-throughput reaction setup and analysis.[9] It is important to use a miniaturised reaction scale to ensure that only minimal precious starting materials are used when executing arrays of reaction conditions.[10]

Reaction miniaturisation requires a suitable technology to dispense reagents effectively and efficiently for high-throughput reaction screening (HTRS). Commercially available technologies for dispensing solids are expensive, and in some cases, it is challenging to use different materials because the dispensing head cannot be cleaned. Therefore, there is still a challenge to effectively dispense a nanomole quantity of reagents for HTRS with accuracy and efficiency.[10,11] Furthermore, batch-scale chemistry relies on

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the manual weighing method using an analytical balance. However, such a method is unreliable in nanomole-scale chemistry. Stock solutions of reagents can be prepared in the reaction solvent, but reagents must be soluble in the reaction solvent to have an unbiased reaction screening.[12,13]

Considering this challenge, we were motivated to work towards solving the causes of problems associated with dispensing nanomole quantities of reagents by developing a solid dispensing technology. This approach ensures that the developed dispensing method can dispense various chemical reagents. Recently, we developed a solid dispensing method whereby a nanomole scale of chemical reagents (guest particles) was coated on SiO_2 (host article/inert carrier) for reaction screening in the context of HTE.[14]

The SiO_2-based solid dispensing method requires a solvent for the coating process, where chemical reagents adsorb to the surface of SiO_2 *via* van der Waals interaction.[15] Fine particles of SiO_2 reduce the van der Waals interaction between the chemical reagents, resulting in improved flowability. Once the coating particles reduce the bonding force between the coated reagents and inert carrier, the number of chemical reagents coated on the inert carrier does not significantly affect the flowability. Hence, the flowability of the materials is improved significantly even with a separate coating on the surface of the inert carrier.[16,17]

Using 3D-printed volumetric transfer scoops, SiO_2 with coated chemical reagents can be dispensed into reactions without using an analytical balance. Hence, the materials will be easy to handle at the nanomole scale. We propose that this solid dispensing method could be a lower-cost alternative to preparing stock solutions of reagents for HTE to determine the optimised reaction systems. In this work, we report the extension of the SiO_2-based solid dispensing method's efficiency and accuracy by dispensing solid chemical reagents for the oxidation reaction of styrene and oxidative esterification of benzaldehyde.

2. Materials and methods

2.1. Materials

All reagents were purchased from Merck/Sigma-Aldrich and used as received, without further purification. The reagents used include styrene (≤99%), benzaldehyde (≥99%), ethyl bromide (C_2H_5Br, 99%), benzyl bromide (C_6H_7Br, 98%), *tert*-butyl hydroperoxide (TBHP, 70% in H_2O), and copper(II) sulphate pentahydrate ($CuSO_4{\cdot}5H_2O$, ≥98%). Bases used are sodium hydrogen carbonate ($NaHCO_3$, 99.5%), potassium carbonate (K_2CO_3, 99%), cesium carbonate (Cs_2CO_3, 97%), and sodium carbonate (Na_2CO_3, 99.5%). The solvents include acetone ($(CH_3)_2CO$) (99.9%), acetonitrile (MeCN, ≥99.8%), and dichloromethane (DCM, ≥99.8%). Decane ($C_{10}H_{22}$, ≥99%) and dodecane [$CH_3(CH_2)_{10}CH_3$] (≥99%) were used as internal standards. The inert carrier is silica (SiO_2, pore size 60 Å, 230–400 mesh particle size, 40–63 μm particle size). Various pyridine-based ligands with different electronic and steric properties were investigated, see Table 1.

Table 1 Pyridine ligands used for the oxidation reaction of benzaldehyde

Labels	Pyridine ligands
P1	2,2′-Bipyridyl, ≥99%
P2	1,10-Phenanthroline, ≥99%
P3	3-Aminopyridine, 99%
P4	2-Chloro-5-nitropyridine, 99%
P5	4-Dimethyl-aminopyridine, 99%
P6	2-Hydroxyl-3-nitropyridine, 98%
P7	2-[*N*,*N*-Bis(trifluoromethyl-sulfonyl)amino]pyridine, 96%
P8	2-Phenyl-pyridine, 98%
P9	2-Chloro-6-methoxy-pyridine, 98%
P10	2,6-Diacetyl-pyridine, 99%
P11	4,4′-Bipyridyl, 98%
P12	Pyridine, ≥99%

2.2. General method for model reactions

2.2.1. Oxidation of styrene. Before the reaction, styrene (1 mmol, 1.0415 g) and palladium on carbon (Pd/C) (5 mol%) were each coated onto approximately 5 g of SiO_2 to form a homogeneous mixture.

The reaction was performed by dispensing 0.5 g of styrene coated on SiO_2, 193 μL *tert*-butyl hydroperoxide (TBHP, 70% in H_2O) (2 mmol), and 195 μL decane (1 mmol) to 10 mL of acetonitrile (MeCN) in a carousel tube. Then 0.5 g of Pd/C on SiO_2 was dispensed into the reaction as a catalyst. Solid reagents were dispensed into the reaction using volumetric transfer scoops, and the stock solutions were dispensed using a 100–1000 μL pipette. The reaction mixture was heated under reflux at 80 °C for 6 hours in a Radleys Carousel 12 plus reaction station coupled with a magnetic stirrer. Sampling was done at 0 (initial) and 6 (final) hours to compare the conversion of styrene to products. Gas chromatography-flame ionisation detection (GC-FID) was used to monitor the progress of the reaction, and gas chromatography-mass spectrometry (GC-MS) was used to identify products.

2.2.2. Oxidative esterification of benzaldehyde. The copper-catalysed oxidation reactions of benzaldehyde were carried out in the 96-aluminium block. The 96-aluminium block consists of rows A–H and columns 1–12 (see Fig. 1). Four (4) bases and twelve (12) pyridine-based ligands were investigated in a high-throughput manner. Bases (0.2 mmol) were labelled C1–C4; see Table S4 in the SI. Benzaldehyde (nucleophile, 0.2 mmol, labelled **1**), ethyl bromide (0.24 mmol, labelled **2a**), and benzyl bromide (0.24 mmol, labelled **2b**) were used as substrates, see Table S2 in SI. Copper(II) sulphate pentahydrate ($CuSO_4{\cdot}5H_2O$, 10 mol%) was used as a catalyst, *tert*-butyl hydroperoxide (TBHP in 70% H_2O) (2 equiv.) as an oxidant, and dodecane (1 equiv.) as an internal standard.

Twelve (12) pyridine ligands (labelled P1–P12) were separately coated on SiO_2 (inert carrier). During the coating process, 10 mol% of each ligand was added to approximately 10 g of SiO_2 dissolved in acetone [$(CH_3)_2CO$], which was subsequently evaporated overnight. A homogeneous final mixture was ground into a fine powder using a mortar and

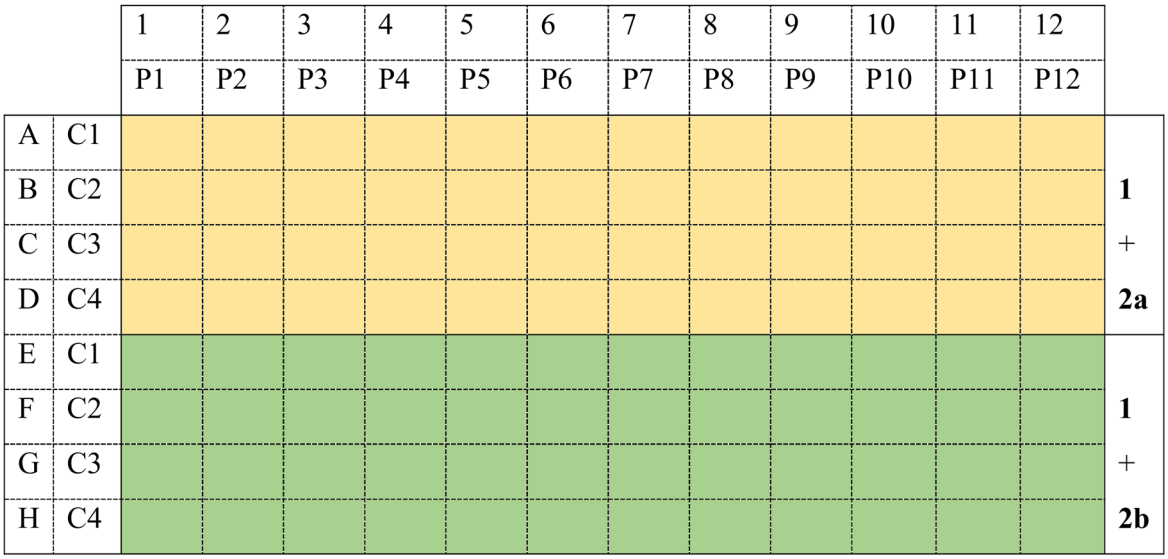

Fig. 1 Layout of the 96-aluminium block in a high-throughput evaluation of the oxidative esterification of benzaldehyde. The 96-aluminium block consists of twelve columns labelled 1–12 and eight rows labelled A–H. Twelve ligands (P1–P12) were dispensed in each column (1–12). Four bases (C1–C4) were dispensed in each row (A–H); see orange and green colours. The right-hand side shows where the reactions between substrates **1** and **2a** occur (orange colour, top) and where the reactions between substrates **1** and **2b** (green colour, bottom) were carried out. A combination of row and column labels indicates the individual reaction/reactor's name, *e.g.*, C5, where C refers to the row, and 5 refers to the column.

pestle. The 12 ligands were given labels P1–P12, see Table S5 in SI.

5 mol% of $CuSO_4{\cdot}5H_2O$ was added to 10 g of SiO_2 in acetone. The mixture was evaporated overnight, and the resulting powder was ground to a fine powder in a mortar and pestle. A 0.2 g transfer scoop was used to dispense solid reagents into the 96-well block (Table S6 in SI).

In a typical procedure, twelve ligands on SiO_2 (P1–P12) were dispensed into all 96 reactions (reactors/vials A1–H12), as shown in Fig. 1. After that, bases were dispensed in reaction vials in the following order:

- Sodium hydrogen carbonate, $NaHCO_3$ (C1): 0.0168 g into reaction vials A1–A12 and E1–E12 (rows A and E).
- Potassium carbonate, K_2CO_3 (C2): 0.0276 g into reaction vials B1–B12 and F1–F12 (rows B and F).
- Cesium carbonate, Cs_2CO_3 (C3): 0.0652 g into reaction vials C1–C12 and G1–G12 (rows C and G).
- Sodium carbonate, Na_2CO_3 (C4): 0.0202 g into reaction vials D1–D12 and H1–H12 (rows D and H).

The Opentrons 2 (OT-2, liquid handling robot) was used to dispense the following stock solution:

- Benzaldehyde (**1**): A 100 μL into all 96 reaction vials A1–H12 (rows A1–H12).
- Ethyl bromide (**2a**): 100 μL was dispensed into reaction vials A1–D12 (rows A–D).
- Benzyl bromide (**2b**): 100 μL was dispensed into reaction vials E1–H12 (rows E–H).
- Dodecane: 100 μL into all 96 reaction vials A1–H12 (rows A1–H12).
- *Tert*-Butyl hydroperoxide (TBHP): 100 μL into all 96 reaction vials A1–H12 (rows A1–H12).
- Acetonitrile (MeCN): 400 μL into all 96 reaction vials A1–H12 (rows A1–H12), topping all reaction mixtures to 800 μL.

In addition, $CuSO_4{\cdot}5H_2O$ on SiO_2 was added to all 96 reaction mixtures using a 0.2 g transfer scoop. Table S2 in the SI indicates a list of solid reagents and stock solutions used in reactions. The 96-aluminium block was closed with two rubber gaskets, a perfluoroalkoxy (PFA) sheet, and a cover, sealing all reactions. Reaction were performed at approximately 80 °C for 3 hours. Sampling was done at 0 (initial) and 3 (final) hours. The progress of reactions was monitored by analysing reaction samples with GC-FID and GC-MS to monitor the progress of reactions and confirm products. Reaction with the highest conversion of a substrate to products was considered to have the optimum conditions.

Calibrated volumetric scoops were used to transfer solid reagents coated on SiO_2 into reaction vials. Each scoop was level-filled with reagents coated onto SiO_2 to deliver a consistent volume into the reaction vials. The volumetric scoops were intended to deliver reproducible nanonole quantities suitable for miniaturised HTS. During dispensing/transfer, each scoop was gently tapped to remove air gaps and minimise variability, and excessive reagent mass was removed by scraping along the top edge of the scoop.

3. Results and discussion

In our previous work (https://doi.org/10.1016/j.rechem.2025.102598), we demonstrated that reagents can be coated homogeneously on SiO_2, indicating that this solid dispensing method (based on SiO_2) can make weighing nanomole quantities of reagents accurate and effective. The

method is further applied to oxidation reactions below to test its applicability in different catalytic systems.

3.1. Oxidation reaction of styrene

The accuracy and efficiency of the SiO_2-based solid dispensing method were evaluated using the oxidation reaction of styrene. The oxidation of styrene was carried out using styrene coated on SiO_2, palladium on carbon (Pd/C) coated on SiO_2, and *tert*-butyl hydroperoxide (TBHP), as illustrated in Fig. 2.

The oxidation reaction of styrene (performed using styrene on SiO_2, Pd/C on SiO_2, and TBHP as an oxidant) resulted in the formation of four (4) products: styrene oxide, phenylacetaldehyde, benzaldehyde, and benzoic acid. Fig. 2 indicates that after styrene oxide was formed, it was further oxidised to phenylacetaldehyde and benzaldehyde as the reaction proceeded. After that, benzaldehyde was also oxidised to benzoic acid after the reaction was carried out for 6 hours in one entry. The GC-MS confirmed all the products, refer to Fig. S3 to S11. The conversion of styrene to products was calculated at a specific time interval. Thus, the maximum conversion of styrene obtained was 72.54% at 80 °C after 6 hours. See the styrene conversion and the catalyst's selectivity toward the products in Table 2.

The data in Table 2 shows that the selectivity of benzaldehyde (major product) was highest (66.03%) among the products, indicating that a large amount of styrene oxide formed during the reaction was further oxidised to the benzaldehyde product. At the same reaction conditions, the selectivity of styrene oxide and phenylacetaldehyde was 22.29% and 7.73%, respectively. Lastly, benzoic acid had a selectivity of 1.65% selectivity, indicating that only a trace amount of benzaldehyde was oxidised to form benzoic acid (see Eqn. S1 in SI). The literature suggests that the vinyl C–H styrene bonds are very reactive and readily oxidise to products at high temperatures.[18] Hence, the results obtained are consistent with the literature.

Catalytic oxidation of styrene was evaluated because of its importance in the chemical and petrochemical industries. This catalytic reaction mainly produces styrene oxide (and benzaldehyde), an important intermediate for synthesising drugs, plasticisers, pharmaceuticals, perfumes, and agrochemicals. Achieving high selectivity of one product is crucial, especially in heterogeneous catalysis. The conventional method of oxidation of styrene uses organic peracids as an oxidant. However, peracids have poor selectivity, are expensive, and produce undesirable products.[18–20] The oxidation reaction of the styrene using TBHP as an oxidant is an alternative method.[21] The Pd/C catalysts and TBHP (oxidant) used in this reaction were more selective toward benzaldehyde (66.03%) than styrene oxide (22.59%). Therefore, this shows that the solid dispensing method effectively dispenses styrene and Pd/C into the reaction.

3.1.1. The role of the solid dispensing method. The solid dispensing method plays an important role in the oxidation reaction of styrene. The method addressed the challenge of dispensing solid reagents at a nanomole scale into the reaction. In this case, styrene and Pd/C were effectively dispensed into the reaction using SiO_2 as an inert carrier. During dispensing, the reagents (styrene and Pd/C) were desorbed (released) from the inert carrier (SiO_2) upon contact with the reaction solvent, and the reaction took place while SiO_2 was not reacting. The 20 mg transfer scoop accurately dispensed 20 mg of reagents coated on SiO_2, allowing the

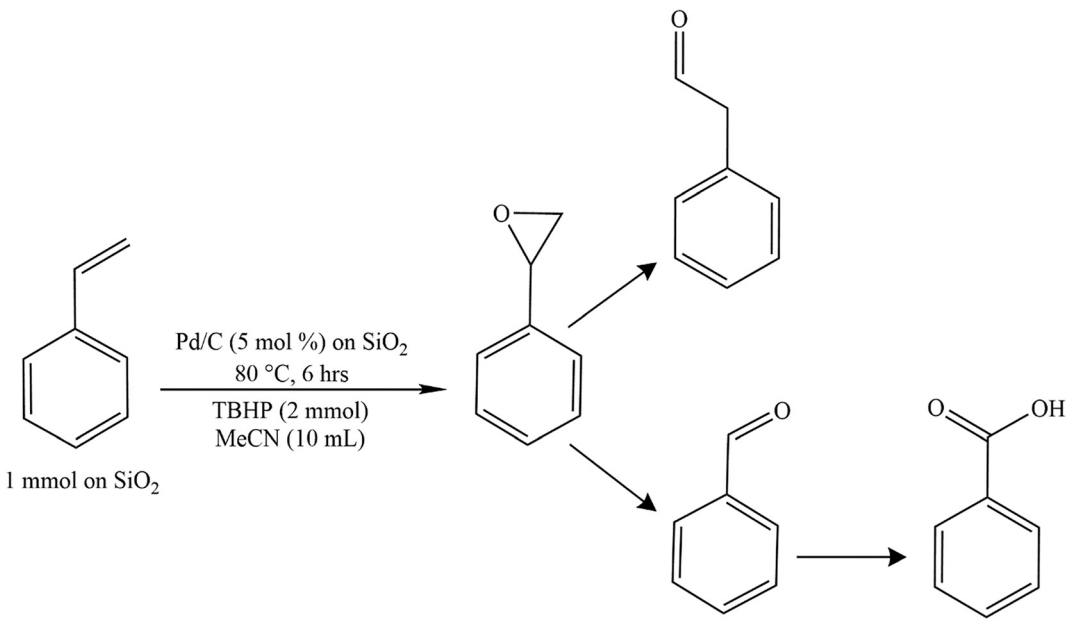

Fig. 2 Reaction scheme of the oxidation reaction of styrene.

Table 2 The conversion of styrene to products and selectivity of the Pd/C on SiO_2 catalyst toward products

Entry	Substrate	Catalyst	Products	Overall yield%	Selectivity%
1	Styrene on SiO_2	Pd/C on SiO_2	Styrene oxide	72.54	22.59
			Phenylacetaldehyde		9.73
			Benzaldehyde		66.03
			Benzoic acid		1.65

dispensing method to be used for miniaturised reactions without needing an analytical balance or expensive robotic system.

3.2. Oxidative esterification of benzaldehyde

The solid dispensing method was further evaluated on oxidation reactions of benzaldehyde. The coupling of benzaldehyde (**1**) with ethyl halide (**2a**) and benzyl bromide (**2b**) was investigated (see Fig. 3).

The reagents were split into several reactions for screening and analysed using GC-FID and GC-MS. Only $CuSO_4{\cdot}5H_2O$ and ligands were coated on SiO_2, whereas TBHP, bases, and substrate were used without being coated on SiO_2. About 96 reaction conditions were screened, and the best one was identified as optimum.

The oxidation reactions of benzaldehyde with ethyl bromide resulted in ethyl benzoate and benzoic acid formation, as shown in SI: GC-MS spectrum in Fig. S12 to S15. On the other hand, the oxidation reactions of benzaldehyde with benzyl bromide formed benzyl benzoate (refer to the GC-MS spectrum in Fig. S16 to S18). The reaction with the highest product formation at the shortest interval was identified as the best. The amount of substrate in the samples before and after the reaction was used to determine the conversion of substrates to products (refer to Table 3). Substrate conversions were calculated based on Eqn. S1 in SI. Each reaction is labelled in the 96-aluminium block to distinguish it from others, *e.g.*, reaction A8 (C1P8) is based in row A and column 8, and B1L8 indicates a combination of a base (C1) and ligand (P8) used in a particular reaction (refer to Fig. 1).

3.2.1. Oxidative esterification of benzaldehyde (1) with ethyl bromide (2a). The conversions for the oxidation reactions of benzaldehyde with ethyl bromide to form ethyl benzoate and benzoic acid are depicted in Table 3 for reactions A1–D12 (vial in rows A–D). Reaction A8 (C4P8) had the highest conversion of 65% of products. Comparatively, conversions of 60%, 58%, and 54% were obtained for reactions D4 (C4P4), B1 (C2P1), and C11 (C3P11), respectively. Reactions A8 (C1P6), B6 (C2P6), and A2 (C1P2) had low conversions of 2%, 3%, and 9%, respectively. Thus, combining Na_2HCO_3 (C1) and 2-phenyl-pyridine (P8) provides the least favourable reaction conditions. On the other hand, the combination of Na_2CO_3 (C4) and 2-hydroxyl-3-nitropyridine (P6) provides optimal reaction conditions.

3.2.2. Oxidative esterification of benzaldehyde (1) with benzyl bromide (2b). The conversions for the oxidation reactions of benzaldehyde with benzyl bromide to form benzyl benzoate are shown in Table 3 for reactions E1–H12 (vials in rows E–D). Reaction H6 (C4P6) had the best (optimal) conversion of 94% for forming benzyl benzoate. Also, conversions of 92%, 91%, and 90% were obtained for reactions F1 (C2P1)/F11 (C2P11), H8 (C4P8), and G4 (C3P4)/F12 (C2P12). Additionally, reactions E4 (C1P4) and E10

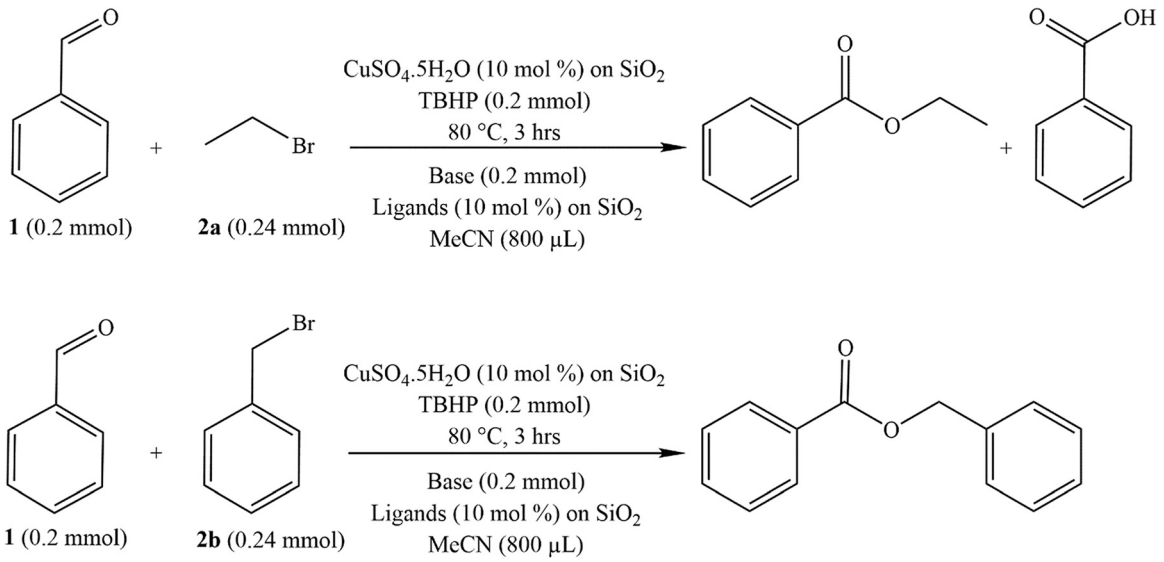

Fig. 3 Reaction scheme for the oxidative esterification of benzaldehyde (**1**) with ethyl bromide (**2a**) and benzyl bromide (**2b**).

Table 3 Conversions of substrates to products in reaction vials in the 96-aluminium block. Green colour represents the substrate's highest conversion, yellow moderate, orange low, and red the lowest conversion

		2 P1	2 P2	3 P3	4 P4	5 P5	6 P6	7 P7	8 P8	9 P9	10 P10	11 P11	12 P12	
A	C1	43%	9%	33%	33%	27%	14%	30%	2%	21%	15%	18%	33%	
B	C2	58%	26%	15%	31%	30%	3%	24%	10%	38%	21%	11%	11%	1
C	C3	39%	29%	30%	35%	24%	10%	30%	17%	49%	51%	54%	13%	+
D	C4	49%	39%	43%	60%	31%	65%	50%	51%	34%	47%	45%	12%	2a
E	C1	31%	23%	31%	11%	82%	34%	52%	33%	26%	14%	39%	64%	
F	C2	92%	66%	42%	83%	84%	75%	84%	77%	84%	78%	92%	90%	1
G	C3	50%	61%	41%	90%	66%	64%	54%	55%	71%	72%	83%	14%	+
H	C4	73%	58%	61%	82%	84%	94%	86%	91%	57%	62%	85%	72%	2b

(C1P10)/G12 (C3P12) had low conversions of 11% and 14%, respectively. Thus, Na_2CO_3 (C4) and 2-hydroxyl-3-nitropyridine (P6) are the optimal reagents, whereas Na_2-HCO_3 (C1) and 2-chloro-5-nitropyridine (P4) are the least favourable reagents for this reaction.

The selectivity of ethyl benzoate and benzoic acid is indicated in Tables 4 and 5, respectively. Reactions B7–B12, C6, and D4–D12 had 100% selectivity of ethyl benzoate, whereas only reactions B1 and B2 had 0% (see Table 4). In contrast, reactions A1–A12 had a higher selectivity of benzoic acid than other reactions in Table 5, and only reactions A1 and A2 had 100% selectivity of benzoic acid. Therefore, the $CuSO_4{\cdot}5H_2O$ catalyst and TBHP oxidant were more selective toward ethyl benzoate than benzoic acid. Eqn. S2 in SI was used to calculate selectivity of the products.

The results indicate that using aryl halide (**2b**) in the reactions gave higher conversions than when an alkyl halide (**2a**) was used, which is supported by low substrate

Table 4 Selectivity of ethyl benzoate for reactions A1–D12 (rows A–D) in the 96-aluminium block. Green represents the substrate's highest selectivity, yellow moderate, orange low, and red the lowest selectivity

		1 P1	2 P2	3 P3	4 P4	5 P5	6 P6	7 P7	8 P8	9 P9	10 P10	11 P11	12 P12	
A	C1	0%	0%	21.56%	20.13%	19.86%	22.37%	33.80%	19.93%	53.28%	24.76%	23.65%	41.06%	
B	C1	53.28%	53.33%	59.94%	59.39%	65.61%	69.67%	100%	100%	100%	100%	100%	100%	1
C	C3	90.84%	84.17%	90.39%	93.88%	93.21%	100%	90.99%	93.42%	88.54%	89.54%	92.35%	82.06%	+
D	C4	45.98%	45.53%	50.87%	100%	100%	100%	100%	100%	100%	100%	100%	100%	2b

Table 5 Selectivity of benzoic acid for reactions E1–H12 (rows E–H) in the 96-aluminium block. Green represents the substrate's highest selectivity, yellow moderate, orange low, and red the lowest selectivity

		1	2	3	4	5	6	7	8	9	10	11	12	
		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	
E	C1	100%	100%	78%	79.87%	80.14%	77.63%	66.19%	80.07%	46.72%	75.24%	76.35%	58.94%	
F	C2	46.72%	0.47	40.06%	40.61%	34.39%	30.33%	0%	0%	0%	0%	0%	0%	1
G	C3	9.16%	15.83%	9.61%	6.12%	6.79%	0%	9.01%	6.58%	11.46%	10.46%	7.65%	17.94%	+
H	C4	54.02%	54.47%	49.13%	0%	49.94%	44.73%	0%	0%	0%	0%	0%	0%	2a

conversions to products obtained when substrate **2a** was used and high conversions when substrate **2b** was used. Even though several bases and ligands were used, the results indicate that any of these bases and ligands can be used for the oxidation reaction of benzaldehyde.

The copper-catalysed oxidation reaction of benzaldehyde was chosen as a model reaction because it is considered an eco-friendly approach; it offers flexible use of aldehydes as acyl precursors compared to acyl groups and provides better atom economy. Advancements in synthetic esterification methods are important because esters are present in many natural products, agrochemicals, pharmaceuticals, polymers, and cosmetics. Numerous alternative methods, such as N-heterocyclic carbene-catalysed direct oxidation reaction of aldehydes and noble-metal-catalysed cross dehydrogenative coupling, require using an expensive catalyst, sophisticated ligands, a significant excess of coupling partners, and pre-activation of acyl surrogate. Therefore, the solid dispensing method was utilised to carry out copper-catalysed oxidation reaction of benzaldehyde to synthesise aryl and alkyl esters to address the mentioned challenges.[22,23]

Although oxidation reactions of styrene and benzyldehyde can take place slowly under ambient conditions, such autoxidation reactions are typically kinetic-limited, uncontrolled, and reagent-dependent, particularly at short reaction times and in miniaturised HTS. The use of oxidants such as TBHP offers control over the oxidation step, ensures consistent conversions and reproducible oxidation rates, prevents side reactions, and enables reliable assessment of catalytic performance under standardised conditions in the HTE workflow.[24–26]

3.2.3. The role of the solid dispensing method. The solid dispensing method was used to address challenges associated with dispensing reagents for the miniaturised oxidation reactions of aldehyde to ester. The ligands on SiO_2 and $CuSO_4{\cdot}5H_2O$ on SiO_2 were effectively and accurately dispensed into reactions to enable miniaturised reactions to be performed in a high-throughput approach (HTA). The ligands and Cu-based catalyst were readily desorbed/released from SiO_2 upon contact with the reaction solvent. Using 20 mg transfer scoops made weighing small amounts of reagents more accurate, efficient, and rapid since there was no need to use an analytical balance. As a result, this work demonstrates that the SiO_2-based method can be applied to different catalytic systems: the Cu-catalysed system in this work and the Pd-catalysed system in our previous work.

In this work, all reagents were coated onto SiO_2 under controlled, repeatable conditions, and the method's reproducibility was confirmed through multiple experiments that yielded consistent reaction outcomes. These results support the conclusion that dispensing reagents onto SiO_2 is qualitative and that variability in dispensing or coating density is minimal. Therefore, this study focuses on demonstrating the application and generalisation of the solid phase SiO_2-based method across different catalytic systems.

Although several liquid-handling platforms, such as positive-displacement systems (*e.g.*, Mosquito) and acoustic droplet ejection (ADE) technology, are commonly used in HTE, solid dispensing platforms offer methodological and practical advantages.[13,27] Liquid dispensing platforms inherently require reagents to be soluble and stable in the solvent of choice, which can bias towards readility-soluble compounds while excluding poorly soluble, unstable, or hydrophobic reagents from the screening.[13,28,29] It is important to note that a solvent is not entirely eliminated in a solid dispensing platform, particularly as solvents are used during the initial preparation step to coat reagents onto SiO_2, however, the solvent is subsequently evaporates prior to dispensing. In contrast to liquid handling, solid dispensing allows the introduction of solvent-independent reagents into reactions, enabling a less biased and broader assessment of

chemical space, particularly in early-age condition screening and heterogeneous catalysis.[2,10,28,29]

Moreover, reagents coated or immobilised on inert carriers, such as SiO_2, generally have improved stability, which enhances reproducibility across extended screening workflows compared to the liquid handling platforms,[30] where stock solutions are susceptible to concentration drift, precipitation, and degradation over time, and often necessitate frequent preparation.[13,28,29] In addition, volumetric accuracy in liquid dispensing can be compromised by factors such as viscosity, wettability, and solvent carryover, whereas these issues are inherently minimised in solid dispensing.[27,31,32] Practically, solid dispensing offers increased accessibility, reduced reliance on proprietary consumables and specialised instrumentation, frequent calibration, and lower operational costs, rendering it particularly attractive for limited resources or academic laboratories. Furthermore, previous studies have shown that solid dispensing is a flexible and scalable alternative to liquid dispensing HTE approaches, as it is compatible with both manual and automated workflows and can achieve reproducible sub-milgram dispensing.[2,10,28,29]

The literature reports that reagents coated on inert carriers, such as polystyrene or glass beads, can be reproducibly dispensed using robotic powder or solid dispensing systems or volumetric dispensing devices, across multiple reaction wells with minimal operator intervention.[2,10,30] This is attributed to the physical stability of the coated reagents on an inert carrier and the robustness of the transfer procedure, which enables automation with accuracy, reproducibility, and consistency while increasing throughput. Thus, the SiO_2-based method can be rapidly and reproducibly integrated into automated HTS of diverse reaction conditions.

The accuracy, precision, and reproducibility of the solid phase SiO_2-based dispensing method have been established in prior work. In a previous study, more than 192 reaction conditions were screened in a high-throughput format, and optimal combinations of phosphine ligands and base conditions were identified for Suzuki–Miyaura and Mizoroki–Heck reactions, using both traditional manual weighing and SiO_2-based methods. Consistent results were obtained from both methods, validating the qualitative accuracy of the SiO_2-based method. Furthermore, phosphine ligands and palladium salt were successfully and homogeneously coated onto SiO_2, and volumetric transfer scoops were used to consistently deliver reproducible small-scale quantities of solid reagents into a 96-well block without the use of an analytical balance.[14]

The performance of the solid dispensing was evaluated across a chemically diverse set of compounds in both prior and current work, highlighting that the dispensing approach is not strongly compound-dependent within reaction screening. A broad range of reagents with a variety of physicochemical properties, including base composition, ligands of different electronic and steric properties, and metal salts, were successfully coated onto SiO_2 and dispensed reproducibly for miniaturised high-throughput reactions. Homogeneous coating and consistent reaction outcomes were observed across all applications of the solid dispensing method, despite differences in coordination ability, molecular weight, and polarity, demonstrating the method's robustness to compound properties when suitable coating solvents and preparation conditions are used. Accordingly, the solid-phase SiO_2-based dispensing method is broadly applicable and generally sufficient for early-stage reaction screening across different catalytic systems, as highlighted by both prior and current results.[14]

Conclusions

This study demonstrates the application of a low-cost SiO_2-based method for dispensing solid reagents at a nanomole scale to address the challenges of accurate, efficient dispensing. This method enables high-throughput reaction screening, allowing the use of minimal solid reagents for miniaturised reactions. This method allows the use of automation, the Opentrons (OT-2) liquid-handling robot, and manual transfer scoops. The SiO_2-based solid-dispensing method was used to evaluate the oxidation of styrene, with Pd/C and TBHP as the optimal catalyst and oxidant, respectively.

In addition, the solid dispensing method was utilised to evaluate the oxidative esterification of benzaldehyde with ethyl bromide and benzyl bromide in a high-throughput manner using a 96-aluminium block. The 96-aluminium block enabled screening of four bases and twelve ligands, and optimal reagents were identified. The optimal reagents are Na_2CO_3 (C4) and 2-hydroxyl-3-nitropyridine (P6). Therefore, this method allows multiple reactions to be rapidly screened and optimised.

Author contributions

Professor Reinout Meijboom conceived the project and designed the experiments. Fulufhelo Radzilani performed experiments, analysed, and interpreted the data. Dr Orpah Zinyemba contributed to the preparation of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data used for this research is reported in the manuscript and the supplementary information (SI), where instrumental techniques, detailed Methodology, equipment, and GC-MS chromatograms, mass spectra, and product structures are provided. See DOI: https://doi.org/10.1039/d5re00471c.

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References

1 A. Cook, R. Clément and S. G. Newman, Reaction Screening in Multiwell Plates: High-Throughput Optimization of a Buchwald–Hartwig Amination, *Nat. Protoc.*, 2021, **16**, 1152–1169, DOI: 10.1038/s41596-020-00452-7.

2 M. C. Martin, G. M. Goshu, J. R. Hartnell, C. D. Morris, Y. Wang and N. P. Tu, Versatile Methods to Dispense Submilligram Quantities of Solids Using Chemical-Coated Beads for High-Throughput Experimentation, *Org. Process Res. Dev.*, 2019, **23**, 1900–1907, DOI: 10.1021/acs.oprd.9b00213.

3 M. Shevlin, Practical High-Throughput Experimentation for Chemists, *ACS Med. Chem. Lett.*, 2017, **8**, 601–607, DOI: 10.1021/acsmedchemlett.7b00165.

4 J. R. Schmink, A. Bellomo and S. Berritt, Scientist-Led High-Throughput Experimentation (HTE) and Its Utility in Academia and Industry, *Aldrichimica Acta*, 2013, **46**, 71–80.

5 J. Lee, J. R. Schmink and S. Berritt, Introduction of Low-Barrier High-Throughput Experimentation in the Undergraduate Laboratory: Suzuki - Miyaura Reaction, *J. Chem. Educ.*, 2020, **97**, 538–542, DOI: 10.1021/acs.jchemed.9b00794.

6 Z. Jaman, A. Mufti, S. Sah, L. Avramova and D. H. Thompson, High Throughput Experimentation and Continuous Flow Validation of Suzuki–Miyaura Cross-Coupling Reactions, *Chem. – Eur. J.*, 2018, **24**, 9546–9554, DOI: 10.1002/chem.201801165.

7 Z. Jaman, D. L. Logsdon, B. Szilágyi, T. J. P. Sobreira, D. Aremu, L. Avramova, R. G. Cooks and D. H. Thompson, High-Throughput Experimentation and Continuous Flow Evaluation of Nucleophilic Aromatic Substitution Reactions, *ACS Comb. Sci.*, 2020, **22**, 184–196, DOI: 10.1021/acscombsci.9b00212.

8 P. P. Pescarmona and P. A. Jacobs, A High-Throughput Experimentation Study of the Epoxidation of Alkenes with Transition-Metal-Free Heterogeneous Catalysts, *Catal. Today*, 2008, **137**, 52–60, DOI: 10.1016/j.cattod.2008.01.015.

9 R. Grainger and S. Whibley, A Perspective on the Analytical Challenges Encountered in High-Throughput Experimentation, *Org. Process Res. Dev.*, 2021, **25**, 354–364, DOI: 10.1021/acs.oprd.0c00463.

10 N. P. Tu, A. W. Dombrowski, G. M. Goshu, A. Vasudevan, S. W. Djuric and Y. Wang, High-Throughput Reaction Screening with Nanomoles of Solid Reagents Coated on Glass Beads, *Angew. Chem., Int. Ed.*, 2019, **58**, 7987–7991, DOI: 10.1002/anie.201900536.

11 M. N. Bahr, M. A. Morris, N. P. Tu and A. Nandkeolyar, Recent Advances in High-Throughput Automated Powder Dispensing Platforms for Pharmaceutical Applications, *Org. Process Res. Dev.*, 2020, **24**, 2752–2761, DOI: 10.1021/acs.oprd.0c00411.

12 S. Lin, S. Dikler, W. D. Blincoe, R. D. Ferguson, R. P. Sheridan, Z. Peng, D. V. Conway, K. Zawatzky, H. Wang, T. Cernak, I. W. Davies, D. A. DiRocco, H. Sheng, C. J. Welch and S. D. Dreher, Mapping the Dark Space of Chemical Reactions with Extended Nanomole Synthesis and MALDI-TOF MS, *Science*, 2018, **361**, 1–7, DOI: 10.1126/science.aar6236.

13 D. Perera, J. W. Tucker, S. Brahmbhatt, C. J. Helal, A. Chong, W. Farrell, P. Richardson and N. W. Sach, A Platform for Automated Nanomole-Scale Reaction Screening and Micromole-Scale Synthesis in Flow, *Science*, 2018, **359**, 429–434, DOI: 10.1126/science.aap9112.

14 F. Radzilani, K. Potgieter, O. Zinyemba and R. Meijboom, Miniaturised Cross-Coupling Reactions: Solid Dispensing Approach for High-Throughput Screening, *Results Chem.*, 2025, **17**, 102598, DOI: 10.1016/j.rechem.2025.102598.

15 R. Pfeffer, R. N. Dave, D. Wei and M. Ramlakhan, Synthesis of Engineered Particulates with Tailored Properties Using Dry Particle Coating, *Powder Technol.*, 2001, **117**, 40–67, DOI: 10.1016/S0032-5910(01)00314-X.

16 M. Ramlakhan, C. Y. Wu, S. Watano, R. N. Dave and R. Pfeffer, Dry Particle Coating Using Magnetically Assisted Impaction Coating: Modification of Surface Properties and Optimization of System and Operating Parameters, *Powder Technol.*, 2000, **112**, 137–148, DOI: 10.1016/S0032-5910(99)00314-9.

17 J. Yang, A. Sliva, A. Banerjee, R. N. Dave and R. Pfeffer, Dry Particle Coating for Improving the Flowability of Cohesive Powders, *Powder Technol.*, 2005, **158**, 21–33, DOI: 10.1016/j.powtec.2005.04.032.

18 S. Sharma, S. Sinha and S. Chand, Polymer Anchored Catalysts for Oxidation of Styrene Using TBHP and Molecular Oxygen, *Ind. Eng. Chem. Res.*, 2012, **51**, 8806–8814, DOI: 10.1021/ie201953y.

19 P. R. G. N. Reddy, B. G. Rao, T. V. Rao and B. M. Reddy, Mesoporous Ce–Zr Mixed Oxides for Selective Oxidation of Styrene in Liquid Phase, *Appl. Petrochem. Res.*, 2020, **10**, 67–76, DOI: 10.1007/s13203-020-00246-8.

20 A. Aberkouks, A. A. Mekkaoui, B. Boualy, S. El Houssame, M. Ait Ali and L. El Firdoussi, Selective Oxidation of Styrene to Benzaldehyde by Co-Ag Codoped ZnO Catalyst and H2O2 as Oxidant, *Adv. Mater. Sci. Eng.*, 2018, **2018**, 7, DOI: 10.1155/2018/2716435.

21 O. A. Alimi, T. B. Ncongwane and R. Meijboom, Design and Fabrication of a Monolith Catalyst for Continuous Flow Epoxidation of Styrene in Polypropylene Printed Flow Reactor, *Chem. Eng. Res. Des.*, 2020, **159**, 395–409, DOI: 10.1016/j.cherd.2020.04.025.

22 N. Dagar, S. Singh and S. R. Roy, Copper Catalyzed-TBHP/DTBP Promoted C(sp2)–H Bond Scission of Aldehydes: An Approach to Transform Aldehyde to Esters, Asian, *J. Org. Chem.*, 2021, **10**, 2238–2245, DOI: 10.1002/ajoc.202100319.

23 S. K. Rout, S. Guin, K. K. Ghara, A. Banerjee and B. K. Patel, Copper Catalyzed Oxidative Esterification of Aldehydes with Alkylbenzenes via Cross Dehydrogenative Coupling, *Org. Lett.*, 2012, **14**, 3982–3985, DOI: 10.1021/ol301756y.

24 M. Sankar, E. Nowicka, E. Carter, D. M. Murphy, D. W. Knight, D. Bethell and G. J. Hutchings, The Benzaldehyde Oxidation Paradox Explained by the Interception of Peroxy Radical by Benzyl Alcohol, *Nat. Commun.*, 2014, **5**, 1–6, DOI: 10.1038/ncomms4332.

25 M. A. Andrade and L. M. Martins, Selective Styrene Oxidation to Benzaldehyde Over Recently Developed Heterogeneous Catalysts, *Molecules*, 2021, **26**(6), 1680, DOI: 10.3390/molecules26061680.

26 A. N. Campbell and S. S. Stahl, Overcoming the "Oxidant Problem": Strategies to Use O2 as the Oxidant in Organometallic C-H Oxidation Reactions Catalyzed by Pd (and Cu), *Acc. Chem. Res.*, 2012, **45**, 851–863, DOI: 10.1021/ar2002045.

27 J. Jenkins and M. Cook, Mosquito Ò : An Accurate Nanoliter Dispensing Technology, *SLAS Technol.*, 2004, **9**, 257–261, DOI: 10.1016/j.jala.2004.04.020.

28 B. Mahjour, Y. Shen and T. Cernak, Ultrahigh-Throughput Experimentation for Information-Rich Chemical Synthesis, *Acc. Chem. Res.*, 2021, **54**(10), 2337–2346, DOI: 10.1021/acs.accounts.1c00119.

29 J. A. Selekman, J. Qiu, K. Tran, J. Stevens, V. Rosso, E. Simmons, Y. Xiao and J. Janey, High-Throughput Automation in Chemical Process Development, *Annu. Rev. Chem. Biomol. Eng.*, 2017, **8**, 525–547.

30 N. A. Mugheirbi, P. O'Connell, D. R. Serrano, A. M. Healy, L. S. Taylor and L. Tajber, A Comparative Study on the Performance of Inert and Functionalized Spheres Coated with Solid Dispersions Made of Two Structurally Related Antifungal Drugs, *Mol. Pharmaceutics*, 2017, **14**, 3718–3728, DOI: 10.1021/acs.molpharmaceut.7b00482.

31 Y. Wang, S. Shaabani, M. Ahmadianmoghaddam, L. Gao, R. Xu, K. Kurpiewska, J. Kalinowska-Tluscik, J. Olechno, R. Ellson, M. Kossenjans, V. Helan, M. Groves and A. Dömling, Acoustic Droplet Ejection Enabled Automated Reaction Scouting, *ACS Cent. Sci.*, 2019, **5**, 451–457, DOI: 10.1021/acscentsci.8b00782.

32 E. K. Sackmann, L. Majlof, A. Hahn-Windgassen, B. Eaton, T. Bandzava, J. Daulton, A. Vandenbroucke, M. Mock, R. G. Stearns, S. Hinkson and S. S. Datwani, Technologies That Enable Accurate and Precise Nano- to Milliliter-Scale Liquid Dispensing of Aqueous Reagents Using Acoustic Droplet Ejection, *J. Lab. Autom.*, 2016, **21**, 166–177, DOI: 10.1177/2211068215602191.