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1 **A spatially orthogonal hierarchically porous acid-base catalyst for cascade and antagonistic**
2 **reactions**

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21
22 **Abstract**

23 Complex organic molecules are of great importance to academic and industrial chemistry and typically
24 synthesised from smaller building blocks by multistep reactions. The ability to perform multiple
25 (distinct) transformations in a single reactor would greatly reduce the number of manipulations
26 required for chemical manufacturing, and hence the development of multifunctional catalysts for such
27 one-pot reactions is highly desirable. Here we report the synthesis of a hierarchically porous
28 framework, in which the macropores are selectively functionalised with a sulfated zirconia solid acid
29 coating, while the mesopores are selectively functionalised with MgO solid base nanoparticles. Active

30 site compartmentalisation and substrate channelling protects base catalysed triacylglyceride
31 transesterification from poisoning by free fatty acid impurities (even at 50 mol%), and promotes the
32 efficient two-step cascade deacetylation-Knoevenagel condensation of dimethyl acetals to cyanoates.

33

34 Catalysis is a cornerstone of green chemistry, enabling energy and resource efficient synthesis of fine
35 and specialty chemicals through selective transformations which minimise by-product and waste
36 formation, eliminate the necessity for auxiliaries, and facilitate product separation. Multistep synthesis
37 of complex molecules is fraught with limitations arising from the costly and time-consuming isolation
38 and purification of intermediates, and hence ripe for substantial improvements in energy and atom
39 efficiency. The ability to perform one-pot cascade processes involving one or more catalysts for
40 multistep synthesis is particularly attractive, offering fewer unit operations, reduced solvent and energy
41 inputs and associated product losses,^{1,2} and unlocking new processes utilising impure feedstocks³ or
42 intermediates that are difficult to isolate.⁴⁻⁶ Integrated product formation during the simultaneous
43 conversion of mixed feedstocks over different catalysts is another area where scientific and
44 technological advances are required to reduce constraints on feedstock purity and by-product
45 isolation.⁷

46 Multistep sequential reactions are ubiquitous in cell biology, wherein the transport of chemical
47 intermediates between enzymes directs product formation via substrate channelling over inter-enzyme
48 distances up to 10 nm.⁸ Such coordination between active sites requires efficient molecular diffusion,
49 and attempts to replicate substrate channelling in homogeneous or heterogeneous catalysis has proved
50 challenging, requiring precise control over the spatial distribution and connectivity of the catalytic
51 species to optimise diffusion paths. In this context, tandem catalysis is defined as a process in which
52 sequential reactant transformations occurs by at least two distinct mechanisms, with all catalytic
53 species present at the beginning of the reaction.⁹ For homogeneous transformations, single catalysts
54 operating by auto-tandem or assisted tandem approaches are prone to by-product formation or require

55 a perturbation in reaction conditions to trigger subsequent steps.⁹ Auto-tandem catalysis is considered
56 the more attractive approach since the temporal separation of catalytic steps¹⁰ (wherein conversion of
57 an intermediate awaits full conversion of the substrate) may reduce by-product formation. In contrast,
58 orthogonal tandem catalysis involves multiple, non-interfering catalytic sites that can diversify
59 accessible transformations,¹¹ however negative interactions between incompatible catalytic species (or
60 substrates/reactively-formed intermediates and active sites) has hindered this approach (**Figure 1**).
61 Methodology to segregate/compartmentalise active sites for so-called spatially orthogonal catalysis is
62 hence of significant interest in organic synthesis, and a hot topic in porous materials design.

63 Cooperative effects in bifunctional catalysts may be classified into systems wherein: multiple active
64 sites are randomly distributed throughout the catalyst;¹²⁻¹⁵ multiple active sites located in different
65 parts of a catalyst but operate independently;^{16,17} or multiple active sites in immediate proximity
66 participating in same reaction.¹⁸⁻²⁰ However, despite their elegance, none of these synthetic strategies
67 can control the sequence in which reactants interact with individual active sites. Such control is critical
68 for antagonistic reactions wherein one component of a reaction mixture may interfere with the reaction
69 of other components, and a key feature of biological catalysis (substrate channelling).

70 Bifunctional acid-base catalysts have been widely studied in recent years,²¹ with spatial segregation
71 exploited to incorporate these chemically incompatible sites in a single material.^{16,22-24} Core-shell
72 nanostructures have proven popular in efforts to control the reaction sequence,^{25,26} but rely on
73 incorporating one catalytic function over the external surface of e.g. porous silica spheres,²⁷ resulting
74 in low active site densities. More sophisticated analogues have employed acid-functionalised
75 mesoporous cores encapsulated by base-functionalised mesoporous shells,²⁴ or yolk-shell systems with
76 basic amine cores and silica sulfonic acidic shells to increase active site loadings in the shell.²⁸
77 However, all such spatially orthogonal catalysts utilise organic acids-bases of limited thermal stability
78 (typically <200 °C),²⁹ and their intrinsic microporosity or mesoporosity^{17,30} is problematic for the
79 transformation of bulky biomass-derived substrates. Efforts to coat (basic) Mg-Al layered double

80 hydroxide cores with porous (acidic) Al-MCM shells²⁵ are compromised by entrained alkali from
81 NaOH during synthesis, and limited accessibility of base sites between microporous layers.

82 Solid acids and bases catalyse diverse organic transformations:³¹⁻³⁵ esterification, isomerisation,
83 dehydration, Friedel-Crafts acylation/alkylation, ring-opening, and hydrocarbon cracking for the
84 former; transesterification, aldol-condensation, Michael and Henry addition, double-bond migration,
85 and dehydrogenation for the latter. Solid bases are particularly efficient for the transesterification of
86 triacylglycerides (TAGs) with methanol under mild conditions to produce fatty acid methyl esters
87 (FAMEs), the key component of biodiesel.³⁶ However, free fatty acids (FFAs), which typically
88 constitute 1-20 wt% of non-edible or waste oleaginous feedstocks,³⁷ rapidly poison base active sites.
89 One solution is to introduce an acid catalysed esterification pretreatment to transform these
90 problematic FFAs into additional FAME, prior to transesterification of the TAG component.³⁸
91 Nonetheless, this approach necessitates rigorous separation of the acid catalyst and/or neutralisation
92 of the resulting TAG/FAME product stream to avoid subsequent base catalyst deactivation, lowering
93 overall process atom and energy efficiency.³ Tandem acid-base catalytic cascades are important for
94 fine chemical and natural product synthesis,³⁹ with transformations spanning hydrolysis-condensation
95 for the synthesis of benzylidene malononitrile from benzaldehyde dimethylacetal,¹⁷ to Michael
96 addition-aldol condensation for the synthesis of alkaloid intermediates in Alzheimer's treatments.⁴⁰ In
97 biomass valorisation, cascades include the synthesis of fructose from cellulose by hydrolysis-
98 isomerisation,⁴¹ 5-HMF or alkyl-levulinate synthesis from glucose by respective isomerisation-
99 dehydration or condensation-isomerisation. Cooperative aldol condensation via base catalysed
100 condensation and subsequent acid catalysed dehydration is also known.¹⁴ Early attempts at such one-
101 pot cascades used physical mixtures of solid acid and base catalysts,^{30,42} or co-derivatised materials in
102 which active sites were randomly distributed⁴³ and/or partially sacrificed during the catalyst
103 synthesis.⁴⁴ Subsequent efforts to partition acid and base functions have employed isolated polymer
104 capsules for enolization-acylation,⁴⁵ or non-penetrating dendritic star polymers to encapsulate or

105 isolate separate active sites for iminium, enamine, and hydrogen-bond formation in asymmetric
106 synthesis.⁴⁶

107 We recently reported the fabrication of a spatially orthogonal hierarchically porous catalyst,
108 conceptually illustrated in **Figure 1**,⁴⁷ for which the cascade selective aerobic oxidation of cinnamyl
109 alcohol to cinnamic acid overcomes the limitations outlined above. Selective detemplation and post-
110 functionalisation of a macroporous SBA-15 silica framework permitted the exclusive confinement of
111 Pd nanoparticles (active for allylic alcohol oxidation to aldehydes) within macropores and Pt
112 nanoparticles (active for allylic aldehyde oxidation to acids) within the mesopores. However, this route
113 required macropore hydrophobisation to differentiate the surface chemistry of the two pore networks,
114 increasing the complexity of the synthesis and hindering transformations in polar environments.

115 Here we adopt a different methodology, using a metallosurfactant to template (and thereby directly
116 introduce a catalytic function into) the mesopores from the outset, obviating the need for additional
117 surface derivatisation and ensuring spatial compartmentalisation of chemically distinct active sites.
118 This approach is demonstrated for the synthesis of a spatially orthogonal (inorganic) acid-base catalyst,
119 SZ/MgO/MM-SBA-15, comprising nanoparticulate MgO within mesopores and a conformal sulfated
120 zirconia (SZ) monolayer coating macropores, and its application for the one-pot transesterification of
121 fatty acid contaminated bio-oils and cascade reactions.

122

123 **Results**

124 **Synthesis of spatially orthogonal acid-base pore framework.** A hierarchical macroporous-
125 mesoporous SBA-15, containing spatially segregated acid (sulfated zirconia) and base (MgO
126 nanoparticles) catalytic sites, was synthesised by adapting our previously reported dual templating
127 strategy⁴⁷ (**Figure 2**) to incorporate one chemical function directly into the lyotropic liquid crystal
128 template (rather than by post-functionalisation). The ability of Pluronic P123 to coordinate Mg²⁺
129 cations through the polyethylene oxide head groups⁴⁸ was exploited through the addition of magnesium

130 nitrate to a lyotropic liquid crystal ordered mesophase (**Figure 2a**), which acted as a soft template for
131 subsequent infiltration by a silica network grown through the acid hydrolysis of
132 tetramethoxyorthosilane. Monodispersed 400 nm polystyrene nanospheres in a crystalline matrix were
133 introduced during the early stage of silica network condensation as a macropore-directing hard
134 template. Sub-ambient extraction of the polystyrene nanospheres from the resulting hybrid organic-
135 inorganic framework with toluene to create a macropore array (**Figure 2b**) was confirmed by
136 thermogravimetric analysis and porosimetry. These mild extraction conditions achieved 95 % removal
137 of the polystyrene macropore template, while retaining 98 % of the P123 mesopore template (see
138 **Supplementary Figure 1**); no mesopores were detectable by N₂ physisorption (see **Supplementary**
139 **Figure 2a**). The macropore network was then selectively functionalised by zirconium isopropoxide,
140 which in turn was hydrolysed to form a Zr(OH)₄ conformal monolayer⁴⁹ (**Figure 2c**) and sulfated to
141 introduce Brønsted acidity (**Figure 2d**). Nitrogen porosimetry confirmed that the mild conditions
142 employed in these latter steps preserved the P123 mesopore template throughout the silica framework
143 (see **Supplementary Figure 2a**). A final calcination served to burn out the surfactant template (see
144 **Supplementary Figure 3**), thereby creating an open mesopore network of 4 nm channels, evidenced
145 by the emergence of a type-IV adsorption-desorption isotherm with H1 hysteresis and associated
146 narrow mesopore size distribution (see **Supplementary Figure 2a-b**), and to transform Mg and Zr
147 species entrained within the meso- and macropores respectively into their corresponding oxides. Hg
148 porosimetry and SEM (see **Extended Data Figure 1**) confirmed the formation of a hexagonal close-
149 packed array of 350 nm macropores within the final material, interconnected by 50 nm windows, which
150 we denote SZ/MgO/MM-SBA-15. Note that framework contraction following thermal processing
151 shrinks macropore dimensions relative to their polystyrene hard template, as previously reported.⁵⁰

152 Low angle powder X-ray diffraction (XRD) confirmed the formation of a *p6mm* hexagonal
153 arrangement of ordered mesoporous channels (see **Supplementary Figure 4**), as previously reported
154 for macroporous SBA-15, however wide angle XRD provided no evidence of magnesium or zirconium

155 containing crystalline phases, indicating that both elements were present in highly dispersed forms.
156 Surface chemical analysis by X-ray photoelectron spectroscopy (XPS) was consistent with the
157 formation of sulfated zirconia, and fitting of the O chemical environment revealed components
158 characteristic of the silica framework and a stoichiometric sulfated zirconia adlayer (see
159 **Supplementary Figure 5**). Quantitative comparison of Mg 2p XP spectra obtained using
160 monochromated Al K α (1486.69 eV) versus Ag L α (2984.3 eV) excitation sources (see **Supplementary**
161 **Figure 6**), confirmed that Mg lies deep within the SZ/MgO/MM-SBA-15 framework as anticipated
162 for mesopore localisation. SZ/MgO/MM-SBA-15 was amphoteric (see **Extended Data Figure 2**),
163 with an acid site density of 0.13 mmol.g⁻¹ and mixed Brønsted:Lewis character (0.75:1) from
164 propylamine and pyridine titration respectively (see the **Methods** for further details), and a base site
165 density of 45 μ mol.g⁻¹ from CO₂ titration. These values, and corresponding acid and base strengths
166 obtained from temperature programmed desorption, are in accordance with literature for sulfated
167 zirconia monolayers⁴⁹ and MgO nanoparticles⁵¹ subject to similar calcination treatments, and provide
168 good evidence for the introduction of spatially orthogonal (non-interacting) acid-base functions. Note
169 the relative acid:base site density does not mirror the relative macropore:mesopore surface areas. This
170 likely reflects the different syntheses by which they are incorporated: Zr was introduced by a liquid
171 phase atomic layer deposition route which conformally coats the available macropore surface area; in
172 contrast, Mg is introduced through a metallosurfactant route in which the maximum metal content in
173 the mesopores is restricted by the stability of the liquid crystal templating phase on cation chelation.

174 Note that the present strategy is fundamentally different from other approaches to create spatially
175 orthogonal catalysts. Post-functionalisation methodologies require additional synthetic steps to
176 chemically differentiate regions of pre-formed porous solids (whether interior versus exterior of
177 mesopores,¹⁶ or mesopore versus macropore networks⁴⁷). Assembly of molecular precursors (e.g.
178 hydrogelators) into interpenetrated networks necessitates the careful synthesis of components
179 possessing unique structural motifs that only self-sort, and not co-assemble,¹² and does not offer

180 control over the sequence in which reactants/intermediates in a cascade encounter different active sites.
181 These limitations restrict the range of catalytic functions that can be incorporated, and scope of
182 chemical transformations accessible, by such approaches. In contrast, here we directly introduce
183 chemical functionality into the organic mesophase (precursor to the inorganic mesopore network) at
184 the start of the synthesis, through simple cation chelation. This strategy can be generalised to introduce
185 diverse metal cations into the mesopores of hierarchical bimodal porous architectures, and eliminates
186 complex and restrictive (synthetic) measures otherwise necessary to prevent interactions between
187 chemical functions navigating to different destinations through pre-formed porous solids.

188

189 **Visualisation of spatially orthogonal acid-base functions.** The spatial distribution of Mg and Zr
190 within SZ/MgO/MM-SBA-15 was mapped by scanning transmission electron microscopy (STEM)
191 and energy dispersive X-ray spectroscopy (EDX). High-angle annular dark-field scanning
192 transmission electron microscopy (HAADF-STEM) (**Figure 3a**) revealed enhanced contrast of
193 macropore perimeters relative to mesoporous domains, which we attribute to stronger scattering from
194 zirconia within the sulfated adlayer.⁵² An EDX linescan across a mesopore domain bridged by two
195 macropores (**Figure 3b**) also indicated the highest Zr and S concentrations occurred close to the
196 macropore perimeters, whereas Mg was concentrated within the mesopores. Spatial
197 compartmentalisation of Mg within the mesopores, and of Zr at the macropore perimeter, is more
198 clearly evidenced by superposition and quantification of corresponding EDX elemental maps of a well-
199 defined mesopore domain (**Figure 3c-e**). The atomic ratio of Zr:Mg averaged across the two regions
200 indicated in **Figure 3d** is 12 times higher at the macropore boundaries than within the mesopore
201 domain (**Figure 3f**), consistent with the selective coating of macropores by SZ. Note that areas where
202 MgO appears to spillover at the vertices of the central mesopore domain in **Figure 3d** correspond to
203 mesopore channels that encircle the macropores (apparent in **Figure 3c**).

204

205 Evidence that acid and base sites were respectively associated with SZ and MgO spatially
206 segregated within macropores and mesopores, was obtained by the subsequent reactive grafting of
207 ligand-stabilised Pt NPs as imaging contrast agents. Colloidal solutions of Pt NPs (see **Supplementary**
208 **Figure 7**) synthesised with either 4-aminothiophenol or 3-mercaptopropionic acid ligands
209 (coordinated to the metal surface through thiols) were reacted with SZ/MgO/MM-SBA-15 to
210 selectively titrate acid or base sites respectively (see the **Methods** for further details). STEM imaging
211 and EDX elemental mapping revealed that the amine base functionalised Pt NPs only accumulated at
212 the perimeter of macropores, while carboxylic acid functionalised Pt NPs were confined within
213 mesopores (see **Extended Data Figure 3a-f**).

214

215 **Antagonistic acid-base catalysis.** A spatially orthogonal hierarchical catalyst offers a unique
216 approach to biodiesel production from FFA contaminated oleaginous feedstocks: namely a one-pot
217 process in which acid catalysed esterification pretreatment of an FFA containing bio-oil feedstock
218 occurs in the macropores, with the resulting (neutral) TAG/FAME mix diffusing into mesopores of
219 the same particle to undergo base catalysed transesterification. This concept is demonstrated for the
220 transesterification of tributyrin, a model TAG, in the presence of hexanoic acid, a model FFA, over
221 SZ/MgO/MM-SBA-15, SZ/MM-SBA-15 (acid functionalised macropores) and MgO/MM-SBA-15
222 (base functionalised mesopores) analogues and a physical mixture thereof. Physicochemical
223 characterisation of these monofunctional materials revealed similar textural and acid/base properties,
224 compositions, and spatial localisation of functions within macropore/mesopore networks (see
225 **Extended Data Figures 1 & 2, Supplementary Figure 8, and Supplementary Tables 1 & 2**).

226 Sulfated zirconia and MgO are independently active solid acid and base catalysts respectively for
227 hexanoic acid esterification with methanol³⁵ and tributyrin transesterification with methanol (**Figure**
228 **4**),³⁶ however neither SZ/MM-SBA-15 nor MgO/MM-SBA-15 can efficiently effect the counterposing
229 reaction (see **Supplementary Figure 9**). In contrast, SZ/MgO/MM-SBA-15 is active for both

230 reactions, exhibiting similar rates for hexanoic acid esterification and tributyrin transesterification to
231 those obtained over SZ/MM-SBA-15 and MgO /MM-SBA-15 respectively. The co-existence of SZ
232 and MgO catalytic functions within a single catalyst particle is achieved without detriment to the
233 performance of either, strongly evidencing their segregation within macropores (acid) and mesopores
234 (base).

235 The unique advantage of a spatially orthogonal acid-base catalyst become apparent when tributyrin
236 transesterification is attempted in the presence of hexanoic acid (as observed in **Figure 5a** and
237 **Supplementary Figure 10** and **Supplementary Table 3**). Transesterification is strongly poisoned by
238 FFA addition over MgO/MM-SBA-15, a physical mixture of SZ/MM-SBA-15 with MgO/MM-SBA-
239 15, and a non-porous MgO functionalised SZ (see **Extended Data Figure 4**), due to neutralisation of
240 MgO base sites. The latter observations highlight that acid sites in a different particle, or co-located at
241 the surface of the same particle (see **Supplementary Figure 11**), offer no protection for base sites. In
242 contrast, SZ/MgO/MM-SBA-15 is resistant to 50 mol% (28 wt%) FFA addition (**Figure 5a**). This
243 resistance to FFA poisoning reflects that: base sites are overwhelmingly located in the mesopores
244 (**Figure 3** and **Extended Data Figure 3**); and mesopores are only accessible through the macropores,
245 the latter being acid-functionalised and hence neutralising the FFA by esterification (see
246 **Supplementary Figure 10e**) before it can enter the mesopore). Such a molecular transport process,
247 the movement of reactants from the bulk solution into macropores and subsequently from macropores
248 to mesopores, constitutes substrate channelling (**Figure 5b**).

249

250 **Molecular transport: NMR relaxation-exchange correlation.** A key element of substrate
251 channelling is control over the sequence in which reactants/products access different active sites. NMR
252 relaxation and diffusion experiments are powerful methods for the non-invasive investigation of
253 adsorption and transport phenomena occurring within optically-opaque porous catalysis materials.⁵³⁻⁵⁵
254 Low-field ¹H relaxation-exchange correlation measurements were applied here to elucidate the

255 dominant diffusive pathways present throughout our hierarchically porous MM-SBA-15 framework.
256 The NMR pulse sequence for these experiments (see **Supplementary Figure 12**) is detailed in the
257 **Supplementary Discussion**, and comprises two correlated measurements of the transverse nuclear
258 spin relaxation time constant T_2 either side of a mixing time of length t_{mix} . As the T_2 of spin-bearing
259 liquids confined to porous media is partially defined by the surface-to-volume (S/V) of the confining
260 pore structure ($1/T_2 \propto S/V$, see **Supplementary Discussion**), this method is sensitive to the diffusive
261 exchange of species between pores of different size, as well as between confined liquid within the pore
262 structures and unrestricted bulk liquid outside of the material. Importantly, the use of low-field
263 experiments facilitates the accurate measurement of T_2 by minimising undesired transverse relaxation
264 effects resulting from magnetic susceptibility differences at the solid-liquid interface, which scale with
265 magnetic field strength. An unfunctionalised framework was chosen to decouple molecular transport
266 from surface chemistry, and water chosen as a probe molecule due to its high ^1H density, comparatively
267 rapid self-diffusivity, and because its surface relaxation characteristics were optimal in differentiating
268 the range of pore structures present (see **Supplementary Discussion**).

269 Relaxation-correlation data of our unfunctionalised framework in excess water was obtained at
270 multiple mixing times between 50 ms and 2.5 s (**Figure 6**). Peak intensities indicate the relative
271 probability of the system exhibiting a given combination of T_{2A} and T_{2B} time constants, which
272 characterise the T_2 relaxation properties of the system before and after t_{mix} , respectively. Peaks along
273 the $T_{2A} = T_{2B}$ diagonal therefore indicate water populations which remain within a given S/V during
274 t_{mix} , while off-diagonal cross-peaks identify populations which undergo diffusive exchange during this
275 time; the exchange pathways of these populations is found by identifying peaks with mutual relaxation
276 coordinates. **Figure 6a** reveals four on-diagonal peaks, labelled A-D in order of decreasing T_2 . The
277 existence of four separate spin populations was further confirmed *via* a separate T_1 - T_2 correlation
278 measurement (see **Supplementary Figure 13**).⁵⁶ Given our knowledge of the MM-SBA-15 pore
279 network, and the sensitivity of T_2 to pore environments of different S/V , these peaks may be readily

280 assigned to water located: (A) between MM-SBA-15 particles, (B) in macropores, (C) in mesopores,
281 and (D) in micropores. Observation of a small micropore population is in accordance with reported
282 microporosity in the pore walls of SBA-15,⁵⁷ and in agreement with pore size modelling in
283 **Supplementary Figure 2c**. These peak assignments were further supported by separate measurements
284 of water in mesoporous SBA-15 (data not shown) which exhibited peaks A, C and D only.

285 The low-intensity cross-peaks in **Figure 6a** were reproducible at short t_{mix} and are assigned to the
286 diffusive exchange of water between micropores and both mesopores (peaks CD and DC) and
287 macropores (BD and DB); the short t_{mix} time associated with the appearance of these cross-peaks
288 confirms a short-range exchange process.⁵⁸ **Figure 6b-d** reveals additional cross-peaks (BC and CB)
289 at slightly longer t_{mix} . Importantly, these cross-peaks identify exchange between mesopores and
290 macropores, confirming the proposed pore connectivity (**Figure 5b**). **Figure 6c-d** report correlation
291 data for long mixing times, which are required to observe long-range diffusive processes. **Figure 6c**
292 suggests the onset of observable exchange between the macropore population and water outside of the
293 MM-SBA-15 material is on the order of 1.5 s; this observation is supported by **Figure 6d** which shows
294 clear AB and BA cross-peaks at $t_{mix} = 2.5$ s. Crucially, there is no evidence of exchange between
295 mesopores and water outside of the material (AC or CA cross-peaks), which if occurring is expected
296 to be observable within the range of t_{mix} values investigated; indeed the clear persistence of cross-peaks
297 characterising mesopore \leftrightarrow macropore exchange (BC and CB) at long mixing times confirms that
298 significant exchange processes involving the mesopore water population are readily observable using
299 this approach. In summary, these results demonstrate that molecules in the bulk medium can only
300 access active sites in the mesopores of our spatially orthogonal catalyst by first passing through
301 macropores; a necessary condition for substrate channelling.

302

303 **Cascade deacetalisation-Knoevenagel condensation.** The catalytic advantage of our spatially
304 orthogonal acid-base SZ/MgO/MM-SBA-15 material was also explored for the one-pot, two-step

305 cascade transformation of benzaldehyde dimethyl acetal (BDMA) to benzylidene cyanoacetate (BCA)
306 (**Figure 7a**). Benzaldehyde formed in the acid catalysed deacetalisation step may subsequently
307 undergo a base catalysed Knoevenagel condensation with ethyl cyanoacetate to yield BCA. **Figure**
308 **7b-c** compares the performance of SZ/MgO/MM-SBA-15 with SZ/MM-SBA-15 (acid functionalised
309 macropores) and MgO/MM-SBA-15 (base functionalised mesopores) analogues, and a physical
310 mixture thereof.

311 Only catalyst configurations possessing acid sites were active for BDMA conversion (**Figure 7b**),
312 while only those possessing base sites exhibited significant activity for benzaldehyde condensation
313 with ethyl cyanoacetate (**Figure 7c**). The spatially orthogonal SZ/MgO/MM-SBA-15 showed
314 comparable deacetalisation activity to SZ/MM-SBA-15 (see **Supplementary Table 4**), and
315 comparable activity to MgO/MM-SBA-15 for the Knoevenagel condensation (see **Supplementary**
316 **Table 5**). These similarities are also apparent in their 6 h conversions (**Figure 7**) demonstrating that
317 our synthetic strategy successfully incorporated acid and base functions into the hierarchical porous
318 framework without compromising the performance of either. In the Knoevenagel condensation alone
319 (**Figure 7c**), both SZ/MgO/MM-SBA-15 and pure base MgO/MM-SBA-15 catalysts are 89 % to BCA,
320 despite the presence of water (to mimic the cascade conditions). This compares favourably with amine
321 functionalised silicas which achieve >95 % selectivity to BCA in organic solvents⁵⁹ or under
322 solventless operation⁶⁰ to suppress hydrolysis of the cyanoester and avoid benzoic acid by-product
323 formation.⁶⁰

324 A physical mixture of the SZ/MM-SBA-15 and MgO/MM-SBA-15 monofunctional catalysts,
325 possessing the same number of acid and base sites as SZ/MgO/MM-SBA-15, proved inefficient for
326 the overall cascade, only achieving 26 % BCA yield from BDMA. This is close to the value (23 %)
327 predicted if the probabilities of BDMA and reactively-formed benzaldehyde colliding with requisite
328 acid and base sites for their respective deacetalisation and condensation in the physical mixture were
329 simply half those for reactions employing SZ/MM-SBA-15 and MgO/MM-SBA-15 alone (see

330 **Supplementary Note 1).** Agreement between the observed and predicted BCA yields, wherein the
331 latter neglects any potential acid-base synergy, indicates minimal interaction between discrete acid and
332 base catalyst particles in the physical mixture. In contrast, SZ/MgO/MM-SBA-15 achieved 68 % BCA
333 evidencing strong synergy between spatially orthogonal acid and base sites within the same catalyst
334 particle. We attribute this synergy to the proximity of acid and base functions in SZ/MgO/MM-SBA-
335 15, and hence increased probability that benzaldehyde reactively-formed from BDMA over SZ coated
336 macropores will rapidly diffuse and encounter MgO nanoparticles within the mesopores, at which to
337 couple with the cyanoester (i.e. substrate channelling). Similar performance enhancements for the
338 spatially orthogonal acid-base SZ/MgO/MM-SBA-15 catalyst were also observed for anisaldehyde
339 dimethyl acetal (ADMA) and 2-furaldehyde dimethyl acetal (FDMA) substrates (see **Extended Data**
340 **Figure 5**), demonstrating a promising substrate scope.

341 The preceding examples highlight the versatility of spatially orthogonal catalysts for two
342 mechanistically distinct applications. In the first, substrate channelling ensures that FFA molecules are
343 neutralised (by esterification) in macropores, preventing them poisoning base sites within mesopores
344 which therefore remain active for transesterification. In the second, cascade deacetalisation and
345 Knoevenagel condensation is facilitated by locating base sites close to acid sites, thereby minimising
346 diffusion paths for the reactively-formed benzaldehyde intermediate.

347

348 **Conclusions**

349 A strategy is reported for the fabrication of spatially orthogonal acid-base catalysts, in which pore
350 hierarchy and metallosurfactant templating is exploited to segregate chemically incompatible catalytic
351 sites. An acidic sulfated zirconia monolayer is grown within the macropores of a hierarchical SBA-15
352 silica framework, and basic magnesium oxide nanoparticles introduced into the connected mesopores.
353 Low-field NMR relaxation-exchange correlation measurements strongly evidence that the hierarchical
354 nature and connectivity of the porous framework enables substrate channelling from a bulk reaction

355 medium into macropores and subsequent molecular transport from macropores to mesopores. This
356 architecture is uniquely suited to suppressing free fatty acid poisoning of triacylglyceride
357 transesterification (pertinent to biodiesel production from low-grade feedstocks), and cooperative acid-
358 base catalysis in the cascade synthesis of chemical intermediates. The combination of our route to
359 spatially orthogonal porous materials and existing metallosurfactant templating literature provides
360 opportunities to create diverse families of dual site catalysts for one-pot selective transformations.

361

362 **Methods**

363 **Polystyrene colloidal nanospheres.** Monodispersed non-crosslinked polystyrene spheres were produced
364 following literature methods.⁶¹ 105 cm³ of styrene (99.9 %, Sigma Aldrich) was washed five times with 0.1 M
365 sodium hydroxide solution (1:1 vol ratio of NaOH solution:styrene) and subsequently five times with distilled
366 water (1:1 vol ratio) to remove polymerisation inhibitors. The purified styrene was added to 850 cm³ of N₂
367 degassed de-ionised water at 80 °C, prior to the dropwise addition of 50 cm³ of 0.24 M potassium persulfate
368 (99+ %, Fisher) aqueous solution during 300 rpm agitation. After 22 h the solution turned white due to the
369 formation of polystyrene colloidal nanospheres, which were recovered and processed into a crystalline matrix
370 by centrifugation at 8,000 rpm/7,441 g for 1 h in a Hereus Multifuge X1centrifuge with a Thermo Fiberlite F15-
371 8x50cy Fixed-Angle Rotor. The resulting highly ordered polystyrene crystalline matrix was finally ground to a
372 fine powder in a mortar and pestle for use as a macropore-directing hard template.

373

374 **Hierarchically ordered Mg functionalised SBA-15.** A modified true liquid crystal templating approach⁶² was
375 used to prepare a Mg functionalised hierarchical SBA-15 silica framework. 2 g of Pluronic P123 (Sigma-
376 Aldrich) was sonicated with 2 g of HCl acidified water (pH 2) at 40 °C to form a lyotropic H₁ liquid crystalline
377 phase, to which 0.5 g of magnesium nitrate hexahydrate (98%, Sigma-Aldrich) was added. The resulting Mg²⁺
378 containing organic mesophase was then treated with 4.08 cm³ tetramethoxysilane (99%, Sigma-Aldrich) and
379 stirred rapidly for 5 min at 800 rpm to form a homogeneous liquid. Immediately following this change in
380 physical state the 400 nm polystyrene colloidal crystals (6 g ground to a fine powder) were added with agitation
381 at 100 rpm for 1 min to homogenise the mix. The resulting viscous mixture was heated under 100 mbar vacuum

382 at 40 °C for 2 h to remove methanol released during the hydrolysis. The solid was finally aged in air at room
383 temperature for 24 h to complete condensation of the silica network.

384

385 **Stepwise template extraction and macropore SZ functionalisation.** Polystyrene template was extracted from
386 the 10 g of the hard-soft templated silica by stirring in 100 cm³ toluene (99 %, Sigma-Aldrich) at -8 °C for 1
387 min. The resulting solid was recovered by vacuum filtration and briefly washed with cold toluene. This
388 extraction protocol was repeated four times to achieve complete removal of the polystyrene hard template. 1 g
389 of the resulting macroporous silica (still containing P123) was then stirred in 30 cm³ anhydrous hexane at 70
390 °C under flowing N₂ (1 cm³.min⁻¹), prior to addition of 0.6 cm³ zirconium isopropoxide (98 %, Fisher) This
391 mixture was stirred 24 h, and 800 mg of the zirconium functionalised solid subsequently recovered by vacuum
392 filtration. Zirconium isopropoxide functional groups were converted to hydroxyls via a hydrolysis step in which
393 800 mg of the previously isolated solid was dispersed with mild stirring in 25 cm³ deionised water for 15 minutes
394 before separation by filtration and drying overnight at 80 °C. Sulfation was achieved by the addition of 30 cm³
395 of a 0.2 M solution of ammonium sulfate (99 %, Fisher) in isopropanol (98 %, Fisher), with the mixture stirred
396 for 2 h, and the solid recovered by vacuum filtration and finally calcined at 400 °C (ramp rate of 1 °C.min⁻¹) for
397 10 h to remove the P123 mesopore template and form Mg and Zr oxides. The final material contained 2 wt%
398 Zr, 1 wt% Mg, and 1.2 wt% S as determined by bulk elemental analysis (see **Supplementary Table 2**).

399

400 **MgO/SZ control catalyst.** A MgO/SZ control catalyst was prepared by wet impregnation of a non-porous SZ
401 (MEL chemicals X201720/01, 99 %). The SZ was first calcined in air at 550 °C for 3 h (ramp rate of 5 °C min⁻¹).
402 2 g of Mg(NO₃)₂.6H₂O (Aldrich, 98 %) was dissolved in 10 cm³ of milli Q water and added to 0.5 g of
403 calcined SZ in a 50 cm³ 3-neck round bottomed flask and stirred at 200 rpm for 2.5 h at room temperature. The
404 flask was then heated at 80 °C overnight, and the resulting dry powder calcined in air at 550 °C for 3 h (ramp
405 rate of 5 °C min⁻¹) and the final sample stored in a vacuum desiccator. The Zr:Mg mass ratio determined by
406 XRF was 1.60 ±0.01.

407

408 **Platinum nanoparticle synthesis.** Solvents were reagent grade and obtained from Fisher Scientific unless
409 otherwise specified. Near monodisperse platinum nanoparticles of 3.6 ± 0.8 nm diameter were prepared using
410 a procedure adapted from Mazumder and Sun.⁶³ Synthesis was carried out using standard Schlenk techniques
411 under a nitrogen atmosphere. Pt(acac)₂ (50 mg, 0.13 mmol, Alfa Aesar) was added into a 3-neck round-bottom
412 flask. The system was evacuated and refilled with N₂ (repeated three times). Oleylamine (OAm) (15 cm³, Acros
413 Organics, 80-90%) was added into the flask, and the mixed solution was heated to 100 °C while stirring for 20
414 min. Borane triethylamine complex (200 mg, 1.74 mmol, Aldrich, 97%) in 3 cm³ OAm was then added into
415 the Pt-OAm solution. The temperature was raised to 120 °C for 60 min. The reaction was cooled to room
416 temperature, before addition of 30 cm³ of ethanol, precipitating nanoparticles which could then be extracted by
417 centrifugation (8000 rpm, 8 minutes, 50 cm³ plastic centrifuge tube, prewashed with ethanol). The product was
418 then dispersed in hexane. Ligand exchange was performed as follows. 4-Aminothiophenol (20 mg in 1 cm³
419 chloroform solution, Sigma Aldrich) was added to approximately 5 mg of platinum nanoparticles prepared as
420 above (by Pt wt.) dispersed in HPLC grade hexane (5 cm³, Fisher) and stirred overnight at room temperature.
421 The particles were isolated by centrifugation and washed with ethanol or acetone to remove excess 4-
422 aminothiophenol and oleylamine. The same procedure was applied to 3-mercaptopropionic acid exchange but
423 replacing the 4-aminothiophenol with 3-mercaptopropionic acid (Sigma Aldrich).

424

425 **Reactive grafting of functionalised Pt nanoparticles.** Functionalised Pt nanoparticles were incorporated into
426 the SZ/MgO/MM-SBA-15 catalyst through a reactive grafting from hexane: 3.6 cm³ of 0.017M functionalised
427 Pt nanoparticles in hexane were added to 2.5 mg of the SZ/MgO/MM-SBA-15 catalyst and stirred for 10 min
428 at 60 °C. The grafted catalyst was then filtered using a 0.2 µm syringe filter and washed three times with 3.6
429 cm³ aliquots of hexane, dried and stored in a vacuum desiccator.

430

431 **Materials characterisation.** Nitrogen porosimetry was undertaken on a Quantachrome Autosorb IQTPX
432 porosimeter with analysis using ASiQwin v3.01 software. Samples were degassed at 150 °C for 12 h before
433 recording N₂ adsorption/desorption isotherms. BET surface areas were calculated over the relative pressure
434 range 0.02-0.2. Mesopore properties were calculated using either the BJH method applied to the desorption

435 branch of the isotherm or fitting the desorption isotherm to the DFT (density functional theory) kernel within
436 the software package appropriate for hexagonal close-packed cylindrical pores typical of SBA-15. Mercury
437 intrusion porosimetry was performed using a Quantachrome Poremaster 60 with a 0.5cc penetrometer to
438 determine macropore window size.⁶⁴ Sample was inserted into the weighed penetrometer (0.064 g) and the cell
439 filled with mercury at low pressure. The sample was then inserted into the high-pressure chamber and intrusion
440 porosimetry run up to 50000 psi. Data was analysed using Porowin v4.03. Thermogravimetric analysis was
441 conducted using a Mettler-Toledo TGA/DSC 2 STAR* system at 10 °C min⁻¹ under flowing N₂/O₂ (80:20 v/v
442 20 cm³ min⁻¹) fitted with a Pfeiffer ThermoStar mass spectrometer.

443 Powder X-ray diffraction patterns were recorded using a Bruker D8 diffractometer employing a Cu K_α (1.54
444 Å) source fitted with a Lynx eye high-speed strip detector. Low-angle patterns were recorded for 2θ = 0.3-8°
445 with a step size of 0.01°. Wide-angle patterns were recorded for 2θ = 10-80° with a step size of 0.02°. High-
446 resolution XPS was recorded using a Kratos Axis HSi spectrometer fitted with an Al K_α (1486.6 eV)
447 monochromated source and a charge neutraliser with a pass energy of 40 eV. Dual excitation XPS was recorded
448 using a Kratos SUPRA XPS fitted with monochromated Al (1486.7 eV) and monochromated Ag (2984.3 eV)
449 X-ray sources and an electron flood gun charge neutraliser with a pass energy of 20 eV. Mg 2p XP spectral
450 intensities obtained using monochromated Al K_α (1486.69 eV) versus Ag L_α (2984.3 eV) excitation sources
451 were quantified using inelastic mean free paths of 4.6 and 8.1 nm respectively to assess the vertical distribution
452 of magnesium.⁶⁵ All measurements were recorded at a pressure below 10⁻⁹ Torr. All spectra were calibrated to
453 adventitious carbon (284.8 eV). Peak fitting was performed using CASA v2.3.18PR1.0. All peaks were fit with
454 a Shirley background and a Gaussian-Lorentzian(30) lineshape.

455 Transmission electron microscopy (TEM) imaging was performed using a JEOL 2100F FEG TEM with a
456 Schottky field-emission source, equipped with an Oxford INCAx-sight Si(Li) detector for energy-dispersive
457 spectroscopy (EDX). High-resolution (scanning) transmission electron microscopy (S)TEM images were
458 recorded on either a FEI Titan³ Themis G2 operating at 300 kV fitted with 4 EDX silicon drift detectors and
459 multiple STEM detectors (sub-nm probe size), or a JEOL 2100F FEG STEM operating at 200 kV and equipped
460 with a spherical aberration probe corrector (CEOS GmbH) and a Bruker XFlash 5030 EDX. Samples were
461 prepared for microscopy by dispersion in methanol and drop-casting onto a copper grid coated with a holey
462 carbon support film (Agar Scientific). Images were analysed using ImageJ 1.41 software.

463 CHNS analysis was performed using a Thermo Flash 2000 CHNS analyser calibrated against a
464 sulphanilamide standard. Samples were prepared in tin capsules using vanadium pentoxide as an accelerant.
465 ICP-OES analysis was performed using a Thermo iCAP 7000 calibrated against a series of standards between
466 0.1 and 100 ppm. Samples (20 mg) were digested using a CEM SP-D discover microwave in a mixture of
467 ammonium fluoride (100 mg) and nitric acid (5 cm³) prior to fluoride neutralisation with boric acid (3% solution,
468 1 cm³) and hydrochloric acid (1 cm³). Acid digestion mixtures were diluted to 10 % prior to analysis and
469 measurements were repeated 3 times against 3 distinct wavelengths per element.

470

471 **Acid/base site characterisation.** Brønsted/Lewis acid character was determined from pyridine adsorption by
472 dropping 0.5 cm³ of pyridine on 10 mg of sample, and subsequent removal of physisorbed pyridine by in vacuo
473 drying at 40 °C/100 mbar in a Heraeus Vacutherm vacuum oven overnight. DRIFT spectra were recorded using
474 a Thermo Nicolet iS50 spectrometer and LN₂ cooled MCT detector, processed using OMNIC 9.2.98 software,
475 and background subtractions using the spectra of untreated parent samples. Relative Brønsted:Lewis character
476 was determined from the ratio of absorbances at 1545-1535 cm⁻¹ and 1445 cm⁻¹ respectively.⁶⁶ Temperature-
477 programmed decomposition of n-propylamine to propene and NH₃ via the Hoffman elimination reaction was
478 used to quantify acid loadings:⁶⁷ 0.5 cm³ of n-propylamine was added to 10 mg of sample, and physisorbed n-
479 propylamine subsequently removed in vacuo by drying at 40 °C/100 mbar in a Heraeus Vacutherm vacuum oven
480 overnight. Thermogravimetric analysis of n-propylamine treated samples was performed under flowing N₂ (20
481 cm³.min⁻¹) with a ramp rate of 10 °C.min⁻¹ using a Mettler-Toledo TGA/DSC 2 STAR* system fitted with a
482 Pfeiffer ThermoStar mass spectrometer. The m/z = 41 signal was monitored to identify the temperature range
483 over which n-propylamine decomposed over acid sites and hence accompanying mass loss over this range and
484 therefore mols of n-propylamine initially adsorbed at acid sites. CO₂ titrations were performed using a
485 Quantachrome ChemBET 3000. Samples were outgassed at 400 °C under flowing helium (20 cm³ min⁻¹) for 1
486 h prior to pulse chemisorption using a fixed volume injection loop. Temperature-programmed desorption (TPD)
487 of CO₂ saturated samples was subsequently performed 10 °C min⁻¹ under flowing He (20 cm³ min⁻¹) monitoring
488 the m/z = 44 signal.

489

490 **Low-field NMR relaxation-exchange correlation measurements.** Approximately 0.25 g of an
491 unfunctionalised MM-SBA-15 architecture was soaked in excess deionised water (produced onsite at the
492 Australian Resources Research Centre, Perth, Australia) for at least 48 h before analysis. Low-field NMR
493 relaxation data were acquired using an Oxford Instruments Geospec spectrometer equipped with a parallel plate
494 0.3 T permanent magnet (corresponding to a ^1H (proton) NMR frequency of $\nu_0 = 12.7$ MHz) and 53 mm Q-
495 sense probe; all measurements were performed at room temperature (25 ± 2 °C) and under ambient pressure.
496 Both $T_2 - T_2$ and $T_1 - T_2$ correlation measurements were performed; an extensive description of these
497 measurements, together with detailed background theory relating the measured T_1 and T_2 nuclear spin relaxation
498 times to material pore size characteristics, is provided in the **Supplementary Discussion**.

499

500 **Catalytic testing.** Deacetalisation-Knoevenagel cascade reactions were performed in a 25 cm³ round-bottom
501 flask using a Radleys StarFish reactor with 25 mg of catalyst, 5 mmol BDMA (99 %, Sigma-Aldrich), 50 mmol
502 ethyl cyanoacetate (99 %, Sigma-Aldrich), 5 mmol deionised water, 5 cm³ toluene (99 %, Sigma-Aldrich) and
503 1 mmol nonane (99 %, Sigma-Aldrich) as an internal standard. Alternatively, ADMA (98.5 %, Sigma-Aldrich)
504 or FDMA (97 %, Sigma-Aldrich) were used instead of BDMA. Knoevenagel condensation was performed using
505 5 mmol benzaldehyde (99 %, Sigma-Aldrich) instead of BMDA, and in the presence of 5 mmol deionised water
506 to mirror the cascade reaction conditions (wherein water is required to hydrolyse the C-O bond in BDMA in the
507 first step). Reactions were performed at 50 °C under a N₂ atmosphere. 0.25 cm³ aliquots were periodically
508 sampled, filtered to remove catalyst, diluted with toluene, and analysed by gas chromatography using a Varian
509 450 GC and ZB-5 column (30 m x 0.53 mm x 1.50 µm). Average rates were calculated over the first 10 min of
510 reaction.

511 Esterification, transesterification, and simultaneous esterification/transesterification reactions over
512 hierarchical porous catalysts were performed in a 100 cm³ ACE round-bottom pressure flask, fitted with a
513 sampling dip-tube, using 25 mg of catalyst in 60 cm³ methanol and 0.1 mmol dihexylether as an internal standard
514 (99 %, Sigma-Aldrich) and either 5 mmol tributyrin (98 %, Fisher) 5 mmol hexanoic acid (99 %, Sigma-Aldrich)
515 or a mixture of 5 mmol tributyrin and 5 mmol hexanoic acid. Reactions were performed at 90 °C under air at
516 autogeneous pressure. 1 cm³ aliquots were periodically sampled, filtered to remove catalyst, and analysed by

517 gas chromatography using a Varian 3800 GC and ZB-50 column (30 m x 0.25 mm x 0.25 μm). Average rates
518 were calculated over the first 30 min of reaction.

519 Transesterification and simultaneous esterification/transesterification reactions over MgO/SZ and SZ
520 nanoparticle catalysts were performed in 100 cm³ 2 neck round-bottom flasks fitted with Findensers and suba-
521 seal septa. Flasks were charged with 100 mg of catalyst in 60 cm³ methanol (Univar, 99.8 %) and 0.1 mmol
522 dihexylether as an internal standard (99 %, Sigma-Aldrich), and either 5 mmol tributyrin (Aldrich 98.5 %) or a
523 mixture of 5 mmol tributyrin and 5 mmol hexanoic acid Aldrich 99 %). Reactions were performed at 60 °C
524 under air with 500 rpm of agitation using a 25 mm stirrer bar. 0.5 cm³ aliquots were periodically sampled,
525 filtered to remove catalyst, and analysed by gas chromatography using a Perkin Elmer Clarus 590 GC and ZB-
526 1HT column (30 m x 0.32 mm x 0.1 μm).

527

528 **Data availability**

529 The data that support the findings of this study are available from the corresponding author upon reasonable
530 request.

531

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682

683 **Author contributions**

684 A.F.L. and K.W. conceived the work. A.F.L. M.A.I., C.M.A.P. and K.W. planned the experiments. M.A.I. and
685 A.C.L. synthesised materials. S.K.B. and S.J. synthesised Pt nanoparticles. M.A.I., A.C.L. and J.M. performed
686 catalytic testing. M.A.I., C.M.A.P., L.J.D., N.S.H., D.J. and N.R. undertook materials characterisation. N.R. and
687 M.L.J. analysed NMR data. M.A.I., C.M.A.P., N.R., M.L.J., K.W. and A.F.L. wrote the manuscript.

688

689 **Competing Interest**

690 The authors declare no competing interests.

691

692 **Additional information**

693 **Extended data** is available for this paper at

694 **Supplementary information** is available for this paper at

695 **Correspondence and requests for materials** should be addressed to A.F.L..

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697

698 **Figure 1: Substrate channelling in hierarchical pore networks.** Limitations of conventional versus
699 spatially orthogonal approaches to catalytic cascades; the latter affords intrinsic control over the
700 reaction sequence and prevents negative interactions between (e.g. chemically incompatible) active
701 sites.

702

703 **Figure 2: Synthetic route to a spatially orthogonal, acid-base hierarchically porous framework.**

704 **a**, A P123-templated silica mesophase containing Mg^{2+} cations is formed around an ordered array of
705 polystyrene colloidal nanospheres. **b**, Polystyrene hard template is extracted to form a macropore
706 network. **c**, A $Zr(OH)_x$ conformal adlayer is deposited throughout the macropores. **d**, Sulfation of
707 $Zr(OH)_x$ conformal adlayer. **e**, Calcination to remove P123 soft template, and form MgO nanoparticles
708 (NPs) entrained within mesopores and a SZ adlayer selectively coating macropores.

709

710 **Figure 3: Spatial distribution of Mg and Zr within hierarchically porous SBA-15 framework. a,**

711 HAADF-STEM image exhibiting bright macropore perimeters. **b**, EDX linescan across a mesopore
712 domain bound by macropores. **c**, HAADF-STEM image of a single mesopore region bound by
713 macropores. **d**, Superposition of EDX elemental maps for image **c** with macropore and mesopore
714 domains indicated. **e**, Elemental quantification of Mg and Zr distribution across image **d**. **f**, Area
715 averaged Zr:Mg atomic ratio within macropore and mesopore domains indicated in **d**.

716

717 **Figure 4: Antagonistic reactions in biodiesel production.** (left) base catalysed transesterification of
718 tributyrin with methanol, and (right) acid catalysed esterification of hexanoic acid to FAME.

719

720 **Figure 5: Substrate channelling: esterification and transesterification over acid/base catalysts.**

721 **a**, Average rate of tributyrin transesterification over SZ/MgO/MM-SBA-15, a 1:1 by weight physical
722 mixture of MgO/MM-SBA-15 and SZ/MM-SBA-15, or MgO/MM-SBA-15, in the absence and

723 presence of hexanoic acid. **b**, Schematic of proposed substrate channelling mechanism: (i) TAG+FFA
724 mixture enters macropores; (ii) FFA undergoes esterification over SZ (**Acid**) sites and is neutralised in
725 macropores; unreacted TAG diffuses and undergoes transesterification over MgO (**Base**) sites within
726 mesopores. Reaction conditions: 25 mg of catalyst (except for physical mixture where 25 mg of each
727 monofunctional catalyst was used), 5 mmol tributyrin (or 5 mmol hexanoic acid, or a mixture of 5
728 mmol tributyrin and 5 mmol hexanoic acid), 60 cm³ methanol, 0.1 mmol dihexylether as an internal
729 standard, 90 °C under air (autogenous pressure). Error bars represent S.D. of the mean (n=3).

730

731 **Figure 6: NMR relaxation-exchange correlation data. a-d**, Low-field ¹H relaxation-exchange
732 correlation plots for water in unfunctionalised MM-SBA-15 with various t_{mix} times. Normalised peak
733 intensities are defined by the colour bars, which follow a linear scale. On-diagonal peaks A, B, C and
734 D are assigned to water populations: (A) outside the hierarchical pore framework, (B) within
735 macropores, (C) within mesopores, and (D) within micropores, while off-diagonal cross-peaks indicate
736 diffusive-exchange between these sites on the time-scale of t_{mix} . The reduction in peak resolution at
737 short T_2 arises from longitudinal (T_1) relaxation processes during t_{mix} .

738

739 **Figure 7: Cascade deacetalisation and Knoevenagel condensation over acid/base catalysts. a**, acid
740 catalysed deacetalisation of BDMA to BZALD and subsequent base catalysed Knoevenagel
741 condensation to BCA. **b**, BDMA conversion and BCA yield from BDMA after 6 h reaction over
742 SZ/MgO/MM-SBA-15, SZ/MM-SBA-15, MgO/MM-SBA-15, a 1:1 by weight physical mixture of
743 SZ/MM-SBA-15 and MgO/MM-SBA-15, or without catalyst. **c**, Benzaldehyde (BZALD) conversion
744 and BCA yield after 6 h reaction over SZ/MgO/MM-SBA-15, SZ/MM-SBA-15, MgO/MM-SBA-15,
745 a 1:1 by weight physical mixture of SZ/MM-SBA-15 and MgO/MM-SBA-15, or without catalyst.
746 Reaction conditions: 25 mg of catalyst (except for physical mixture where 25 mg of each
747 monofunctional catalyst was used), 5 mmol BDMA or BZALD, 50 mmol ethyl cyanoacetate, 5 mmol

748 deionised water, 5 cm³ toluene, 1 mmol nonane as an internal standard, 50 °C under N₂. Error bars
749 represent S.D. of the mean (n=2).

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