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Organogel media for on-bead screening in combinatorial catalysis

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Abstract—Poly(vinylidene fluoride) (PVdF) forms thermoreversible gels with a number of dipolar aprotic solvents. Gels were prepared containing chromogenic substrates, subject to transformation by polymer-bound catalysts. When the catalysts were mixed with inactive beads and applied to the surface of the gels, the active beads were identifiable through colour changes. Active beads could also be visualised by thermographic imaging. These methods hold promise for catalyst discovery from split-and-mix combinatorial libraries.

High-throughput or combinatorial methodologies are gaining importance in catalysis research.[1] Parallel synthesis and screening accelerates catalyst development and allows consideration of structures which might be ignored in the standard, iterative protocol. Most of this work involves spatially separated catalysts, prepared and studied in discrete reaction vessels. However, an interesting and complementary alternative is provided by 'split-and-mix' combinatorial chemistry (SMCC). Split-and-mix solid phase synthesis allows the preparation of very large libraries of resin-bound catalysts, among which the prospects of finding exceptional and unexpected properties should be high. Unfortunately, locating these library members is nontrivial. The compounds must be tested while still on the bead and the assay must be highly parallel. Realistically, it is necessary to screen visually under conditions that allow picking of active beads. Screening for catalysis is complicated by product diffusion away from catalytic centres. A visual signal (e.g., a colour change) may thus be delocalised, preventing the identification of active beads. Solutions to this problem have been published,[2] but all have limitations and improved/complementary methods are still sought.

One approach which shows promise is the use of gel-based reaction media.[2d,3] The catalyst beads are suspended in or placed on the gel, reactants diffuse in, and the reaction takes place on active beads. Because the gel limits diffusion over long distances, the products can be confined to the neighbourhood of the bead. The reaction must be chromogenic, or otherwise visually detectable, but the method is otherwise fairly versatile. The gel is clearly a critical component of the procedure. In one variant, due to Miller, it is synthesised by polymerisation of specially designed precursors around the library beads.[2d] Work from our group, in contrast, has exploited commercially available agarose, which is simply dissolved in hot water and allowed to set.[3]

The agarose-based method is experimentally convenient, but limited to the aqueous solvent systems required to dissolve the polysaccharide. The scope of our strategy could be increased significantly if suitable nonaqueous gels (organogels) could be identified. We now report a simple thermoreversible organogel system, which serves this purpose, extending the methodology to polar nonaqueous solvents.

A gel for use with our screening method should fulfil a number of criteria. Firstly the gelling agent should be readily accessible. Secondly, it should form gels with a range of solvents. Thirdly these gels should have suitable physical properties, being capable of supporting the library and allowing bead picking under a microscope. Fourthly, it should be unlikely to interfere with reactions, for example, by diffusing into a bead and interacting with catalytic centres. Initially we considered

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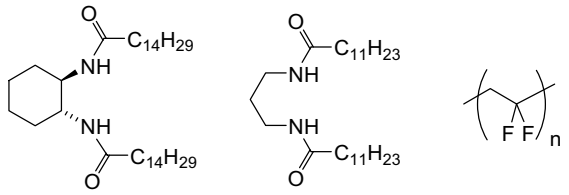
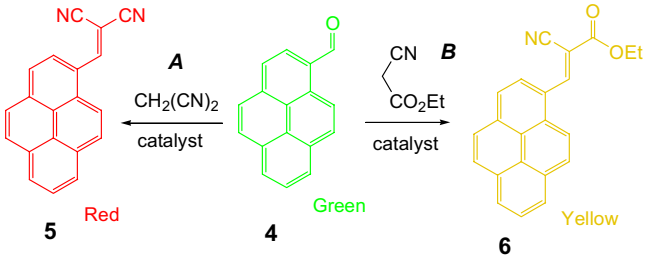
small-molecule gelling agents, on which there is extensive literature,[4] but the above criteria proved difficult to match. For example, gelator **1**[5] possesses useful properties but must be prepared from expensive 1*R*,2*R*-*trans*-cyclohexanediamine while diamide **2** forms gels, which are too soft.[6] Moreover, although these compounds are prepared in one step, their purification can be troublesome.



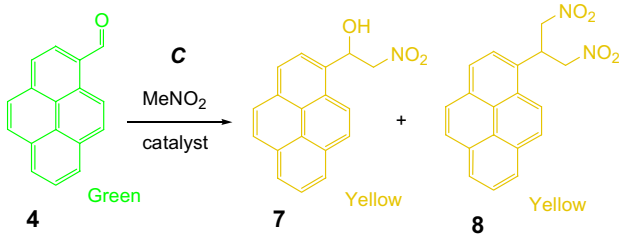
1 **2** **3**

We therefore turned to an alternative approach, the use of nonpolar polymers.[7] A literature search suggested two possibilities, poly(vinyl chloride) (PVC) and polyvinylidene fluoride (PVdF, **3**). PVC forms gels with a range of solvents, but these materials acquire sticky surfaces which interfered with bead picking and seemed to block substrate transfer. PVdF, however, proved more accommodating. It is reported to dissolve in ketone or ester solvents at high temperatures and set to gels on cooling.[8] In our hands, it also succeeded with a number of other solvents. At the level of 10% w/v, it formed thermoreversible gels with acetone, dioxane, acetonitrile, nitromethane and THF.[9] The gels were physically resilient without being sticky, and seemed good candidates for the screening system. To test their suitability, we employed three reactions chosen (a) for their chromogenicity and (b) for their susceptibility to catalysis by commercially-available resins. 1-Pyrenecarboxaldehyde **4** is coloured light green. Knoevenagel condensations with malononitrile (reaction A) and ethyl cyanoacetate (reaction B) give products **5** (red) and **6** (yellow). Both reactions could be catalysed by polymer-bound piperazine (Scheme 1), proceeding smoothly in the absence of PVdF with toluene as solvent. The Henry reaction of **4** with nitromethane (reaction C) could be catalysed by a polymer-bound guanidine base, giving **7** with **8** as a side product (Scheme 2). Both **7** and **8** are yellow.

For tests on gelated reaction mixtures, model 'catalyst libraries' were prepared by mixing the piperazine or guanidine beads with inactive controls (acetylated



Scheme 1. Catalyst = piperazinomethyl polystyrene (Nova biochem).



Scheme 2. Catalyst = 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine, polymer-bound (Aldrich).

aminomethyl polystyrene) in the ratio 1:10. Typically, the aldehyde **4** (100 mg) and PVdF (1 g) were added to acetonitrile (9 mL) and heated to 100 °C for ca. 30 min in a pressure tube with stirring. The liquid was decanted into a flat-bottomed vessel,[10] and ethyl cyanoacetate (1 mL), malononitrile (0.2 mL) or nitromethane (1 mL) was added with stirring. When the gel had set, the appropriate model library was spread on the surface and observed under a microscope. The results are illustrated in Figures 1–3. For all three reactions a clear distinction could be observed between catalytic beads and the inactive controls. In the case of reactions A and B, the active beads clearly took on the colour of the products **5** and **6**, respectively. In the case of reaction C, the active beads turned brown, possibly suggesting further reaction/decomposition. In no case could we see transfer of colour between active and inactive beads, even though they were in close contact. Beads could be removed from the gel without difficulty. These findings demonstrate that the gel can deliver substrates (and presumably solvent) to the beads, and that it provides the right physical environment for the screening experiment. Material transfer between beads is clearly slow, as found in our earlier work.[3]

Straightforward visual screening is of course limited by the need for chromogenic or fluorogenic substrates. An elegant alternative is the use of thermal imaging, as pioneered by Taylor and Morken.[2a,11] In its original

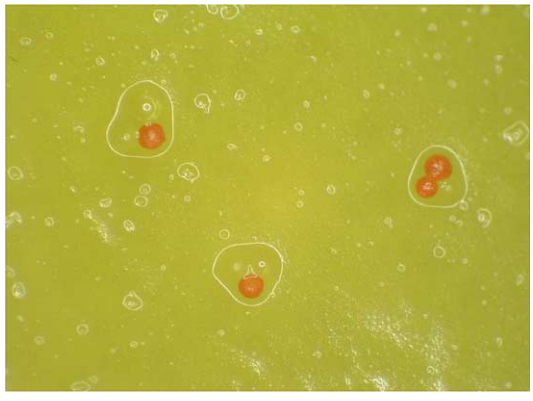


Figure 1. PVdF/MeCN gel containing **4** and malononitrile (reaction A), overlaid with model 'catalyst library' composed of resin-bound piperazine and inactive controls (1:10). Micrograph taken 2 h after application of beads. Four active beads (red) are clearly visible. Five inactive controls are also present. The beads appear in groups of 3 on the gel surface.

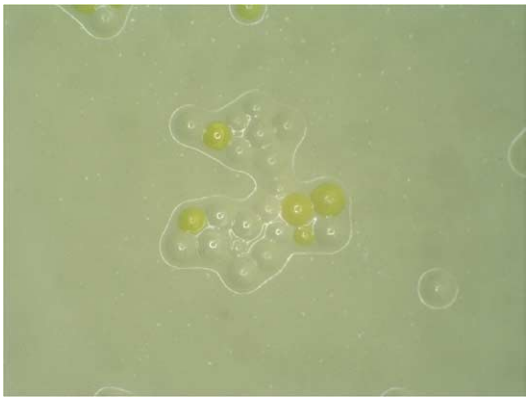


Figure 2. PVdF/MeCN gel containing **4** and ethyl cyanoacetate (reaction B), overlaid with beads as for Figure 1. Micrograph taken 24 h after application of beads.

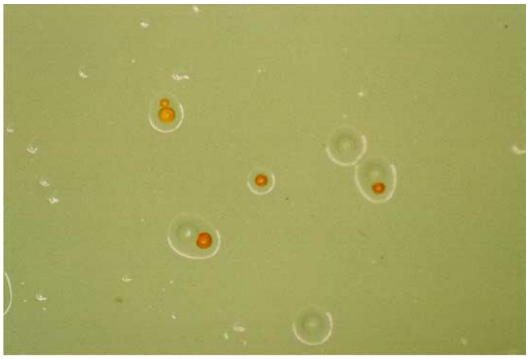


Figure 3. PVdF/MeCN gel containing **4** and nitromethane (reaction C), overlaid with model 'catalyst library' composed of resin-bound 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine and inactive controls (1:10). Micrograph taken 2 h after application of beads.

version, the method involved flotation of a library on a chlorinated (i.e., relatively dense) solvent containing reagent and substrate. Catalytic beads were raised in temperature by the heat of reaction, and were detected by an IR camera. We could see several advantages to performing this experiment on PVdF gels. Firstly, the beads would be immobilised and easily selected. Secondly, there would be no need for an especially dense solvent. Thirdly, heat conduction away from the beads may be reduced, leading to greater sensitivity. As a preliminary trial, we added triethylamine (16 μL) and benzyl alcohol (10 μL) to molten PVdF/MeCN gel (100 μL). The mixture was spread on glass and allowed to set. Acetic anhydride (10 μL) was applied to the surface, and appeared to be absorbed by the gel in ~3 min. Polymer-bound DMAP[12] was spread on the surface, which was then imaged with an IR camera.[13] Initially the beads could not be detected, but after ca. 30 s they appeared against the background (Fig. 4). The imaging data implied temperature rises of up to 0.7 °C, due to the exothermic DMAP-catalysed acetylation of the alcohol. Control experiments with inactive beads showed no detectable temperature variations.

In conclusion, we have found that PVdF forms gels with a range of polar aprotic solvents and that these gels may

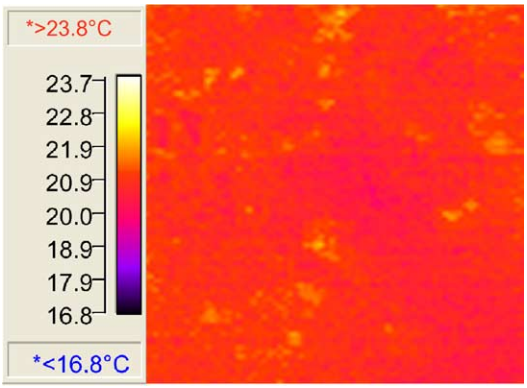


Figure 4. Thermographic image of polymer-bound DMAP beads on PVdF/MeCN gel containing $PhCH_2OH$, Et_3N and Ac_2O. The beads appear yellow, indicating temperatures of up to 0.7 °C above background.

be used in visual screening of resin beads for catalytic activity. Preliminary results suggest that the gels may also facilitate screening by IR thermography. In future work we hope to apply this methodology to the discovery of novel molecular catalysts through combinatorial chemistry.

Acknowledgements

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References and notes

1. Ding, K. L.; Du, H. F.; Yuan, Y.; Long, J. *Chem. Eur. J.* **2004**, *10*, 2872; Berkessel, A. *Curr. Opin. Chem. Biol.* **2003**, *7*, 409; de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799; Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071; Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335; Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885.
2. (a) Taylor, S. J.; Morken, J. P. *Science* **1998**, *280*, 267; (b) Berkessel, A.; Herault, D. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 102; (c) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306; (d) Harris, R. F.; Nation, A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 11270; (e) De Muynck, H.; Madder, A.; Farcy, N.; De Clercq, P. J.; Pérez-Payán, M. N.; Öhberg, L. M.; Davis, A. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 145; (f) Krattiger, P.; McCarthy, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1722; (g) Clouet, A.; Darbre, T.; Reymond, J.-L. *Angew. Chem., Int. Ed.* **2004**, *43*, 4612.
3. Müller, M.; Mathers, T. W.; Davis, A. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3813.
4. Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133; van Esch, J. H.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263.
5. Hanabusa, K.; Yamada, M.; Kimura, M.; Shirai, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1949.
6. Tomioka, K.; Sumiyoshi, T.; Narui, S.; Nagaoka, Y.; Iida, A.; Miwa, Y.; Taga, T.; Nakano, M.; Handa, T. *J. Am. Chem. Soc.* **2001**, *123*, 11817.
7. Guenet, J. M. *Thermoreversible Gelation of Polymers and Biopolymers*; Academic: New York, 1992; Osada, Y.;

Gong, J. P.; Tanaka, Y. *J. Macromol. Sci.—Polym. Rev.* **2004**, *C44*, 87.
8. Cho, J. W.; Song, H. Y.; Kim, S. Y. *Polymer* **1993**, *34*, 1024; Tazaki, M.; Wada, R.; Okabe, M.; Homma, T. *J. Appl. Polym. Sci.* **1997**, *65*, 1517; Kim, B. S.; Baek, S. T.; Song, K. W.; Park, I. H.; Lee, J. O.; Nemoto, N. *J. Macromol. Sci.—Phys.* **2004**, *B43*, 741.
9. Typical procedure: PVF pellets (Aldrich, m.w. 530,000, cat. no. 34,707-8; 500 mg) were placed in a pressure tube with MeCN (5 mL) and heated at 100 °C for 30 min with stirring. The resulting homogeneous solution was cooled to room temperature and formed a clear gel within ~5 min. The gel could be melted and reset as desired.
10. These experiments employed shallow beakers, ~5 cm in diameter, with tight fitting lids to prevent evaporation of solvent.
11. Thermal imaging has also been applied to reaction arrays. For examples, see: Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2647; Holzwarth, A.; Schmidt, P. W.; Maier, W. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2644; Reetz, M. T.; Becker, M. H.; Liebl, M.; Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1236; Berkessel, A.; Ashkenazi, E.; Andreae, M. R. M. *Appl. Catal. A: General* **2003**, *254*, 27.
12. 4-(*N*-Benzyl-*N*-methylamino)-pyridine, polymer bound; Aldrich cat. no. 35,988-2.
13. IR-thermography was performed using a ThermaCAM SC 1000 camera (Inframetrics) with ThermaGram 95® (Vers. 1.60.07) and DynaMite 97® (Vers. 1.01) software from Thermoteknix Systems Ltd., Cambridge, UK. No emissivity correction was applied. Detectable wavelength range of the camera is 3.4–5.4 μm.