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Silica-immobilized piperazine: A sustainable organocatalyst for aldol and Knoevenagel reactions

Saravanakumar Shanmuganathan[a], Lasse Greiner[a,b], Pablo Domínguez de María[a,*]

[a] Institute of Technical and Macromolecular Chemistry (ITMC), RWTH Aachen University, Worringerweg 1, 52074 Aachen, Germany
[b] DECHEMA e.V., Karl-Winnacker-Institut, Theodor-Heuss-Allee 25, 60486 Frankfurt am Main, Germany

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ABSTRACT

Silica-supported piperazine was found to be an efficient catalyst for aldol reactions of aromatic aldehydes and ketones with straightforward product isolation and catalyst reuse. Furthermore, the catalyst is active in Knoevenagel-type reactions to afford coumarin derivatives, using 2-methyltetrahydrofuran (2-MeTHF) as a novel bio-based solvent.

Proline-like organocatalysis represents a promising entry to afford important building blocks under mild reaction conditions,[1] bio-mimicking the performance of some aldolases (C–C bond formation).[2] The field has experienced an enormous development in last years with examples of highly selective amines designed as catalysts.[1] However, high organocatalyst loadings are often needed to afford efficient syntheses. To overcome this, catalysts have been immobilized on a range of supports.[3] In some cases these supports may also mimic the role that a protein scaffold (enzyme) induces over an organic cofactor (e.g., providing an adequate hydrophobic micro-environment).[3a]

Despite the number of secondary amines as organocatalysts, the use of piperazines (and analogues) has been scarce.[4] Interestingly, piperazine chemistry may provide straightforward possibilities for catalyst design, together with a simple immobilization procedure compared to other less-functionalized organocatalysts.[5] Herein, the assessment as an organocatalyst of a commercially available[6] silica-immobilized piperazine is reported (Fig. 1).

In a first set of experiments, aldol condensations with aromatic aldehydes (benzaldehyde and furfural) and excess of acetone were evaluated. Organocatalysis involving secondary amines may occur via enamine or iminium routes, affording either aldol **3** or Mannich-type condensation **4**, respectively. Low conversions have been reported for these reactions when free piperazine is used.[4d] Thus, for comparison with a non-immobilized amine, the same reaction was conducted with pyrrolidine as soluble catalyst (Table 1).[7]

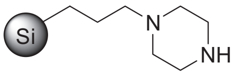

Figure 1. Silica-immobilized piperazine assessed as immobilized organocatalyst (see technical details in Section 1).[6]

Silica-immobilized piperazine is an efficient organocatalyst for the C–C bond formation between aromatic aldehydes and acetone at room temperature, leading to full conversion within 16 h. Notably, the addition of carboxylic acids as co-catalysts was not needed to afford high efficiencies, in contrast to previous works with analogous amines.[4a,7] Interestingly, variations in the product distribution between aldol **3** and Mannich-type product **4** were observed. With immobilized piperazine, benzaldehyde afforded some proportion of Mannich-type product **4**, whereas furfural led to a complete selective process in favour of the aldol product **3**.[8] That suggests differences between catalytic routes depending on the substrate. Mannich-type routes have been mostly observed for secondary amines as organocatalysts,[7] consistent with the results obtained with pyrrolidine (Table 1). Therefore, silica-support is not a mere inert structure in the reaction, but it is apparently influencing the catalytic role of piperazine. Notably, furfural-based aldol- and Mannich-products are presently being considered as promising candidates to further produce liquid alkanes as biofuels.[9] Obviously, an immobilized organocatalytic-based approach

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[*] Corresponding author. Tel.: +49 241 8020468; fax: +49 241 8022177.
E-mail address: dominguez@itmc.rwth-aachen.de (P. Domínguez de María).

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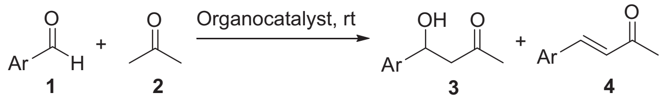
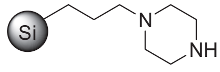
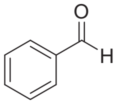
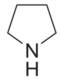
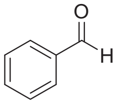
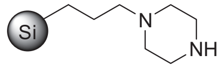
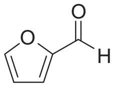
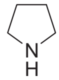
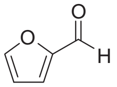
Table 1

Cross condensation of aromatic aldehydes with acetone catalyzed by silica-immobilized piperazine. Aldehyde: 1 mmol; acetone: 10 mmol. Total volume: 3 mL. Catalyst loading: immobilized piperazine: 100 mg (0.1 mmol); pyrrolidine: 10 mol %. 16 h, room temperature. Conversions and yields based on ^{1}H NMR assessment. Aliphatic aldehydes afforded lower conversions (10–15% in 16 h), together with some self-condensation products (data not shown)



Organocatalyst	Aldehyde	Conversion (%)	Aldol 3 (%)	Mannich-type 4 (%)
		100	70	30
		100	24	76
		100	100	0
		100	79	21

leading to these syntheses under those conditions and at room temperature might be a promising entry for the bio-based society.

Subsequently, catalyst recovery and reuse was evaluated taking the condensation of benzaldehyde with acetone as a model reaction, and showing that the immobilized catalyst could be efficiently re-used. Likewise, the ratio between the aldol product **3** and the Mannich-type one **4** remained unaltered within the error margin (Fig. 2).

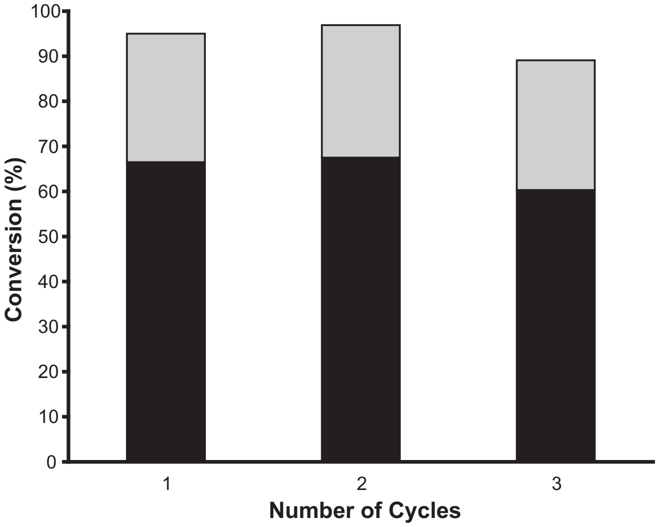
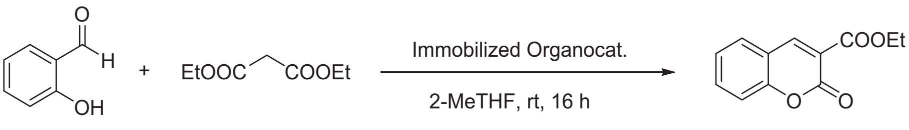


Figure 2. Catalyst recovery and recycling. Black: yield of aldol **3**; grey: yield of Mannich-type product **4**. Aldehyde: 1 mmol; acetone: 10 mmol. Total volume: 3 mL. Catalyst loading: 100 mg (0.1 mmol). 16 h, room temperature. Conversions and yields based on ^{1}H NMR assessment.

The catalytic scope of the silica-immobilized piperazine was also assessed for the Knoevenagel condensation between salicylaldehyde **5** and diethyl malonate **6**. The base-mediated reaction of *o*-hydroxyaromatic aldehydes with malonic esters leads to coumarins.[10] Consistently, silica-immobilized piperazine afforded coumarin **7** in high conversions (99%) and moderate yields under non-optimized work-up (Scheme 1).

For this reaction, 2-methyltetrahydrofuran (2-MeTHF) was used as a solvent. 2-MeTHF can be derived from bio-based resources,[11] and presents promising properties (boiling point of 80 °C, almost non-miscible with water), being considered a sustainable solvent. Until now, 2-MeTHF has been scarcely used in several metal-catalyzed procedures[12] as well as in biocatalysis.[13] Assessing its use in further organocatalyzed-reactions may represent an interesting approach for more sustainable organic processes. Likewise, for the Knoevenagel-type reaction herein reported, 2-MeTHF may provide proper conditions that could avoid by-product formation often reported in the literature for piperazine-based organocatalysts.[4f]

In summary, the use of a commercially available silica-immobilized piperazine as an organocatalyst has been assessed, and proof-of-principle results are herein reported. Efficient condensations between aromatic aldehydes and ketones have been conducted at room temperature, providing different aldol—Mannich-type bias depending on the substrate. Immobilized



5 6 7

Conversion 99% (Yield 55%)

Scheme 1. Knoevenagel-type condensation of salicylaldehyde **5** with diethyl malonate **6** to afford coumarin-type adduct **7**. Reagents and conditions: 1 equiv aldehyde, 1 equiv malonate. Catalyst loading: 100 mg (0.1 mmol). 2-MeTHF as solvent (3 mL), 16 h, room temperature. Conversion and yield based on ^{1}H NMR assessment.

organocatalysts may be recovered and reused for several cycles. Furthermore, Knoevenagel-type reactions have also been studied in 2-MeTHF as a promising, bio-based, sustainable solvent for organocatalysis.

1. Experimental

1.1. Materials

Immobilized piperazine was kindly donated by *dichrom* GmbH (formerly *SeQuant* GmbH)—*Silicycle*® Inc., Lot# 21354. Technical details: Catalyst loading: 1.01 mmol g^{-1}; surface coverage (μmol m^{-2}) based on molecular loading: >1.91; particle size: 40–63 μm; pore diameter (Å, BJH): 60; specific surface area (m^2 g^{-1}, BET): 470–530; specific pore volume (mL g^{-1}, BJH): 0.70–0.85. Other reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification.

1.2. Aldol reaction

The reaction was typically performed by mixing benzaldehyde (105 mg, 1 mmol), acetone (580 mg, 10 mmol) and silica-piperazine catalyst (100 mg, 1.01 mmol g^{-1}) in screw cap vial, and stirring the mixture for 16 h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated in vacuum to afford the crude product. The conversion was determined from NMR. For recycling the catalyst, the solid filtrate was washed with acetone (5 × 2 mL), and dried, being ready for a new catalytic reaction.

1.3. Knoevenagel reaction

In screw cap vial charged with salicylaldehyde (61 mg, 0.5 mmol), diethylmalonate (80 mg, 0.5 mmol) and 2-methyltetrahydrofuran (4 mL), silica-piperazine (100 mg, 1.01 mmol g^{-1}) was aggregated. The reaction was stirred for 16 h at room temperature and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). After removal of solvents, the crude product was purified by silica chromatography (petroleum ether/ethylacetate 80:20) to afford the pure yellow solid as product (61 mg, 55%).

Mixture of compounds **3** and **4**: ^{1}H NMR (400 MHz, CDCl$_3$): 7.8–7.1 (m, 10H), 6.7 (d, *J* = 12 Hz, 0.3 H of ^{1}H) 5.1 (d, *J* = 7.0, 3.0 Hz, 0.7 H of ^{1}H), 2.7–2.9 (m, 1.4H of ^{1}H), 2.3 (s, 2.1H of ^{1}H), 2.1 (s, 0.9H of ^{1}H); ^{13}C NMR (100 MHz, CDCl$_3$): 209.1, 198.5, 143.5, 142.6, 133–125, 68.8, 52.0, 30.9, 27.5.

Compound **3** (from furfural): ^{1}H NMR (400 MHz, CDCl$_3$): 7.3 (m, 1H), 6.3 (m, 1H), 6.2 (d, *J* = 3 Hz, 1H), 5.1–5.1 (m, 1H), 2.8–3.0 (m, 2H), 2.2 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 212.1, 155.0, 142.2, 110.3, 106.3, 64.0, 48.1, 31.0.

Compound **7**: ^{1}H NMR (400 MHz, CDCl$_3$): 8.5 (s, 1H), 7.5–7.6 (m, 2H), 7.2–7.3 (m, 2H), 4.4 (q, *J* = 7.0, 2H), 1.4 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): 163.0, 155.3, 148.5, 136.7, 134.3, 129.4, 125.7, 124.8, 117.7, 116.8, 62.0, 14.2.

Note added in proof

During the peer-review assessment of this article, the use of 2-MeTHF as solvent for organocatalysis has also been addressed by another group, showing also promising properties as bio-based solvent for these reactions (see: Yang, H.; Mahapatra, S.; Cheong, P.H.Y.; Carter, R.G. *J. Org. Chem.* **2010**, doi:10.1021/jo1015008.

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