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Synthesis of natural fragrance jasminaldehyde using silica-immobilized piperazine as organocatalyst.

María Pérez-Sánchez, Pablo Domínguez de María*

Institut für Technische und Makromolekulare Chemie (ITMC),
RWTH Aachen University. Worringerweg 1. 52074 Aachen, Germany

Corresponding Author:

Dr. Pablo Domínguez de María.

Tel.: +49 241 8020468.

Fax: +49 241 8022177.

E-mail: dominguez@itmc.rwth-aachen.de

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Abstract

Jasminaldehyde (α-pentyl cynnamaldehyde) is a natural fragrance that can be produced *via* aldol-type C-C bond formation between heptanal and benzaldehyde. The use of bases like NaOH to form jasminaldehyde typically leads to significant waste and by-product formation. To provide sustainable options with diminished waste formation and high conversions and selectivities, herein a silica-immobilized piperazine is used as organocatalyst for the jasminaldehyde synthesis either in bio-based solvents (*e.g*. 2-methyltetrahydrofuran, 2-MeTHF), or in solvent-free (using neat substrates as reaction media). Under reported conditions, a production of ~ 7 g jasminaldehyde L^{-1} h^{-1} is observed, delivering *on-spec* conversions and selectivities (> 90 % each). Selectivity remains unaltered along catalyst recycling, whereas a loss of conversion is significantly observed after reusing the catalyst for several cycles.

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1.- Introduction.

Organocatalysis has flourished in the last years as a powerful tool to perform highly selective chemical transformations, with C-C bond forming reactions (*e.g.* aldol-type processes) representing a core step in this area.[1-3] Initially envisaged for asymmetric synthesis, the use of chiral organocatalysts from the natural pool (*e.g.* proline and derivatives) emerged combining efficiency and bio-based catalysis, with outstanding cases of efficient chiral transfer processes. Based on that knowledge, however, in recent years a number of applications of organocatalysis in the production of less valuable (*e.g.* non chiral) products has started to appear, with several examples using proline or DBU,[4] chitosan,[5] or other secondary amines such as piperidine,[6] to afford, for instance, biofuel-type precursors. Albeit these reactions can be conducted using more classic base-catalyzed concepts (*e.g.* using NaOH), the motivation of using organocatalysis for these non-chiral organic syntheses relies in the provision of more sustainable chemistry, as less waste formation is expected from organocatalytic processes, together with a more controllable catalysis to diminish the formation of by-products, often observed when base-catalyzed processes are conducted. Herein, another important present trend for organocatalysis is the introduction of heterogeneous catalysts to reduce the typically needed high organocatalyst loadings, to enable simplified process set-ups, and eventually to allow a straightforward catalyst recovery and further reuse. Immobilized organocatalysts can be found in Nature, as in the case of chitosan,[5] or can be designed for tailored applications, *e.g.* by using ionic liquids as additives and “tag” molecules.[7,8]

In another approach, the immobilization of organocatalyts in silica supports may represent a cost-effective and useful approach to put forth novel heterogeneous

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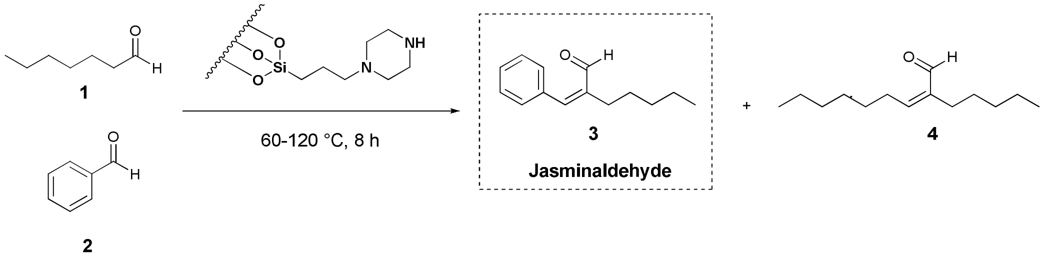
organocatalysis to deliver efficient options for non-asymmetric synthesis (*e.g.* in flow chemistry).[9-11] In this area, our research group has assessed silica-immobilized TEMPO for the selective oxidation of 5-Hydroxymethylfurfural (HMF),[12] as well as silica-immobilized piperazine for aldol- and Knoevenagel-like condensations – namely C-C bond formations – to afford either biofuel-type precursors based on furfural and acetone,[13] or novel phosphonate-containing acyclic nucleosides with potential antiviral activity, by using aldehyde-bearing nucleobases and different ketones.[14] Following these studies, herein the organocatalytic synthesis of jasminaldehyde **3** using silica-immobilized piperazine is reported (Scheme 1).



Scheme 1. Synthesis of jasminaldehyde **3** *via* immobilized organocatalysis.

Jasminaldehyde **3** (α-pentyl cynnamaldehyde) is a natural fragrance that can be synthetized by the selective crossed aldol condensation between heptanal **1** and benzaldehyde **2** under basic conditions (*e.g.* NaOH), typically adding stoichiometric amounts of base.[15] In addition to the envisaged environmental problems that such a synthesis may bring, reaction process lacks often the required selectivity, as self-condensation of heptanal to afford **4** (Scheme 1) may occur as well. To overcome these issues, apart from process design options (*e.g.* adding heptanal stepwise to minimize secondary reactions), the use of heterogeneous catalysts such as solid acids,

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zeolites or aluminosilicates have been put forth.[16-20] However, the application of organocatalysis for the synthesis of jasminaldehyde has been rather scarce, with some few examples focusing on chitosan in different derivatized forms.[21-23] Aiming at combining heterogeneous organocatalysis, sustainable chemistry and application-driven catalysis, herein the use of silica-immobilized piperazine for the jasminaldehyde synthesis is reported for the first time.

2.- Results & Discussion.

Focusing on the delivery of sustainable chemistry options, in a first set of experiments, jasminaldehyde synthesis was organocatalytically conducted using different solvents or directly in neat substrates (solvent-free), that is, in benzaldehyde and heptanal as reaction media. As solvents, 2-methyltetrahydrofuran (2-MeTHF) and *tert*-butanol were selected. The rationale behind these choices is that 2-MeTHF can be derived from biomass resources and shows promising biodegradability and valuable preliminary toxicological data, thus conferring it an increasing interest as sustainable organic solvent for future syntheses.[24] Likewise, *tert*-butanol is presently produced from petroleum-based isobutylene. However, recent fermentative routes to biosynthesize isobutylene from sugars by means of genetically modified microorganisms have been reported, and would certainly pave the way for the provision of *tert*-butanol as a future bio-based solvent as well, within the so-called biorefineries.[25] Envisaging such potential importance in the future, our research group has recently proposed the use of *tert*-butanol as solvents for the biocatalystic selective oxidation and / or esterifications of HMF and furfural.[12,26]

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Results of jasminaldehyde **3** synthesis using silica-immobilized piperazine in solvent-free, 2-MeTHF and *tert*-butanol as solvents are depicted in Figure 1.

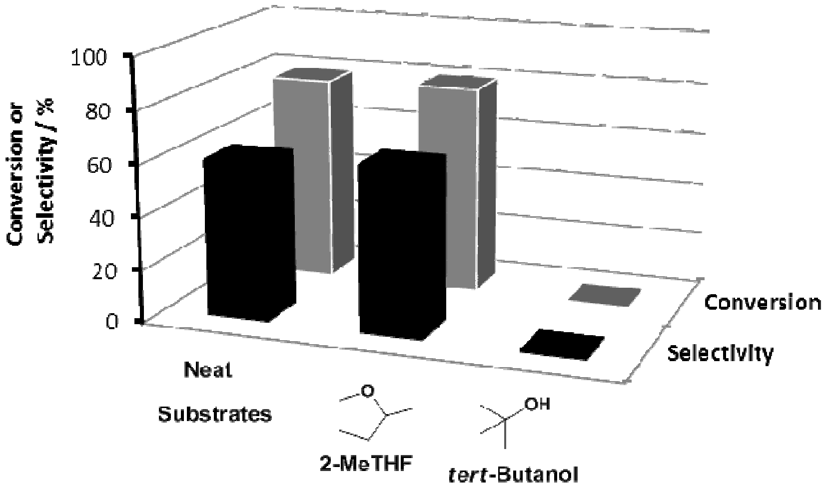

Figure 1. Synthesis of jasminaldehyde **3** using silica-immobilized piperazine as organocatalyst in different solvent conditions: Solvent-free, 2-MeTHF and *tert*-butanol. Conditions: Heptanal **1**, 0.42 mmol, benzaldehyde **2**, 2.1 mmol, completed with 1 mL solvent; 100 mg catalyst (1.1 mmol g^{-1}), 60 °C, 18 h magnetic stirring. Conversion and selectivity determined by ^{1}H-NMR. Blank experiments either using silica, non-immobilized piperazine, or catalyst-free did not show any conversion in the reaction conditions applied.

As observed (Figure 1), reactions conducted in solvent-free (only substrates were added) or in 2-MeTHF led to analogous results in terms of selectivity (~ 60 %) and conversion (~ 80 %) under these still non-optimized conditions, 60 °C, 18 h reaction time. Conversely, the introduction of more polar solvents like *tert*-butanol led to unsatisfactory results, affording very low to negligible formation of jasminaldehyde **3** under the applied reaction conditions. A plausible reason for that might be the *tert*-

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butyl-alkylation of the active secondary amine of the immobilized piperazine. On the other hand, the use of 2-MeTHF for catalytic reactions in general, and for organocatalytic reactions in particular, has been recently reported by several research groups under different catalytic systems, representing a promising entry for efficient sustainable chemistry.[5,13,14,24] Furthermore, the set-up of solvent-free reactions – performed in neat substrates – is very valuable from a practical viewpoint, as high substrate loadings can be combined with straightforward downstream processing and a diminished waste formation. Since the jasminaldehyde synthesis was successful under these *neat* conditions as well, the following studies focusing on processing optimization were conducted in such solvent-free system, as higher product loadings can be achieved.

Once the proof-of-principle with silica-immobilized piperazine was successfully shown, in a next set of experiments the emphasis was put on optimizing both the conversion and selectivity of the reaction. Especially, to reach *on-spec* values for jasminaldehyde, a selectivity of **3** over by-product **4** (Scheme 1) must be higher than 90 %,[16-23] and for obvious economic and technical reasons, a conversion higher than 90 % is mandatory as well. Whereas for classic base-catalyzed processes reaching these optimized figures is more challenging – due to the high reactivity of such reaction systems –, the use of heterogeneous catalysts should provide more controllable conditions. With these considerations in mind, the organocatalytic reaction was studied by varying temperature and benzaldehyde–heptanal relationship. Results regarding conversion and selectivity are depicted in Figure 2.

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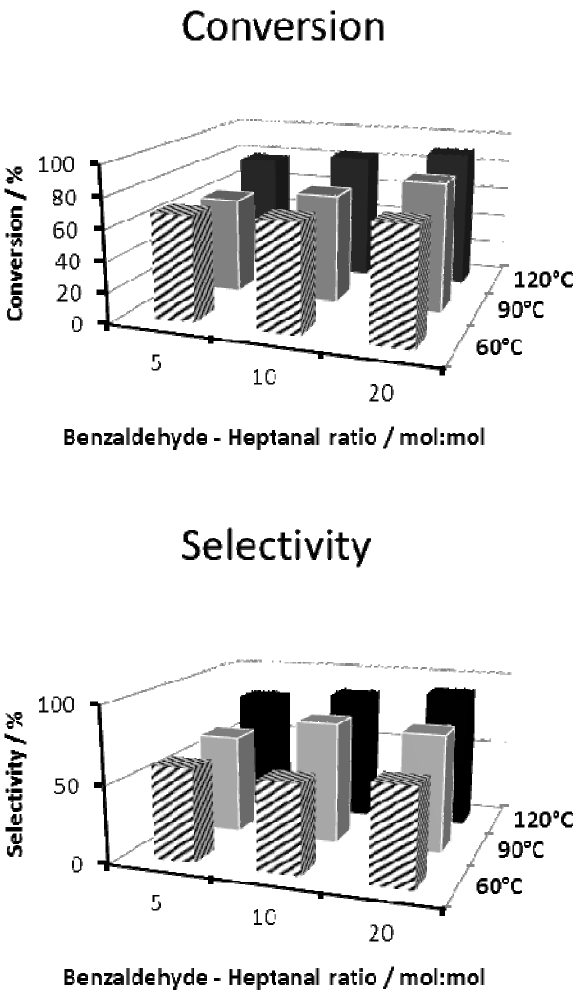

Figure 2. Optimizations in conversion (above) and selectivity (below) by changing temperature and benzaldehyde–heptanal ratio (mol:mol). Conditions: 0.42 mmol heptanal **1**, variable amounts of benzaldehyde **2** as surplus (2.1, 4.2, and 8.4 mmol), and different temperatures (60-120 °C); 100 mg organocatalyst (1.1 mmol g^{-1}), 24 h, 8 h reaction, magnetic stirring. Conversion and selectivity determined by ^{1}H-NMR.

Gratifyingly, the optimization reaction parameters like temperature and benzaldehyde–heptanal ratio led to largely improved results, both in conversion and

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selectivity, reaching in both cases ~ 90 % when conducted at 120 °C and at 20 benzaldehyde–heptanal ratios (Figure 2). Further improvements by setting a stepwise addition of heptanal to benzaldehyde may be envisaged as well for future improvements. Moreover, the setup of reactions in solvent-free conditions at 120 °C led to these outstanding values in 8 h reaction time, thus showing a more optimized process timing as well, with expected diminished waste formation, especially when the process is compared with more classic homogeneous base catalysts (*e.g.* aqueous NaOH).[13] The formation of benzoic acid upon oxidation of benzaldehyde was observed under this conditions (~ 5 % at 8 h compared to benzaldehyde), and could be suppressed by performing the reactions under argon atmosphere. To further assess the potential of the system the immobilized organocatalyst loading was subsequently evaluated (Figure 3).

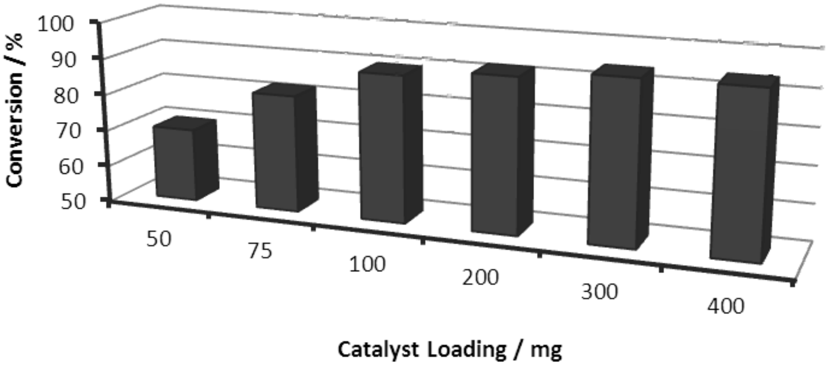

Figure 3. Influence of the catalyst loading in the jasminaldehyde synthesis under optimized conditions. Conditions: Heptanal **1** 0.42 mmol, benzaldehyde **2** 8.4 mmol, 120 °C, solvent-free conditions, magnetic stirring, 8 h reaction time. Variable catalyst loadings from 50-400 mg (1.1 mmol g^{-1}). Conversion determined by ^{1}H-NMR.

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As observed (Figure 3), catalyst loadings of 100 mg almost led to full conversion under the process timing reported (8 h). According to observed results, an optimal catalyst–limiting substrate ratio (heptanal) of ~ 0.027 mmol of active catalytic amino groups / mmol heptanal can be inferred for the jasminaldehyde synthesis. Under those conditions, ~ 7 g jasminaldehyde L^{-1} h^{-1} are produced under these solvent-free mild reaction conditions.

Finally, experiments aiming at assessing the catalyst recyclability were conducted, studying the activity (based on conversion always at the same reaction time) in jasminaldehyde **3**. To this end, two approaches were followed. In the first one the immobilized catalyst was washed with acetone and then with dichloromethane, dried, and studied again in catalytic cycles (the so-called "organic washing" in Figure 4). In the second approach, after such organic washing the catalyst was further washed with water (starting with pH 9 to pH 7) until the pH of the solution remained neutral. After drying the catalyst, it was assessed again in a new catalytic cycle. Results are depicted in Figure 4.

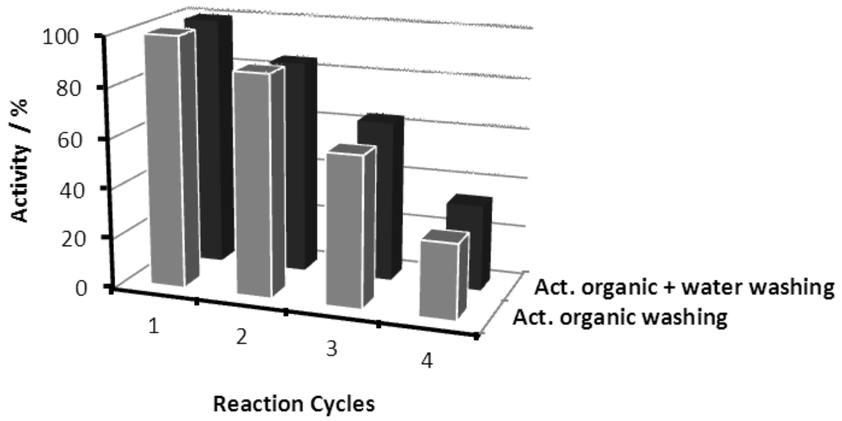

Figure 4. Assessment of the reusability of the organocatalyst under several cycles, based on activity (conversion). Conditions: Heptanal **1** 0.42 mmol,

benzaldehyde **2**, 8.4 mmol, 120 °C, solvent-free conditions, 8 h reaction time, 100 mg organocatalyst (1.1 mmol g^{-1}). Activity determined by ^{1}H-NMR.

In all cases the selectivity for jasminaldehyde remained always in excellent values (*on-spec*, ~ 90 %, data not shown) along 4 consecutive cycles, under the evaluated solvent-free reaction conditions. However, a lowering in the catalyst activity over cycles was clearly observed when conversion was assessed, and the trend turned out to be analogous in both washing systems. While the immobilized piperazine could be virtually reused for two cycles maintaining its activity, a significant loss of conversion was observed during the third and fourth rounds. Apart from some expected physical losses of the catalyst under the non-optimized conditions at lab scale, the formation of water during the reaction might break the siloxane bridge that keeps the catalyst linked to the surface,[27-29] as well as chemical losses of the catalyst.[28,30] Potential optimizations of the system might involve the use of azeotropic distillation along the catalytic cycles, to avoid the accumulation of water. Likewise, assessment of other chemical modifications derived from the interaction of substrates (or products) with the catalysts should be further studied for an in-depth clarification of the reasons for catalyst deactivation. Looking beyond, the combination of different organocatalysts has proven to be successful in enamine catalysis,[31] and may well fit in the design of future bi-functional catalysts for more sustainable and straightforward processes.

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3.- Experimental

Chemicals. All compounds were purchased by Sigma-Aldrich and were used without further purification. Silica-immobilized piperazine was a kind gift of *dichrom* GmbH (formerly *SeQuant* GmbH) – *Silicycle*® Inc (Lot# 51343). Details: Catalyst loading: 1.1 mmol g^{-1}; surface coverage based on molecular loading: > 1.91 μmol m^{-2}; particle size: 40-63 μm; pore diameter: 60 Å, BJH; specific surface area (BET): 470-530 m^2 g^{-1}; specific pore volume: 0.70-0.85 mL g^{-1}, BJH.

Organocatalytic reactions. 0.42 mmol of heptanal **1** were mixed with different amounts of benzaldehyde **2** (2.1-8.4 mmol). Reactions took place mostly in solvent-free conditions at 60-120 °C, with variable catalyst loadings (100-400 mg). Reaction times were set from 8-18 h. For the work-up, suspended catalyst was filtered and the reaction mixture analysed by 1H-NMR to assess conversion and selectivity. For recycling experiments, the filtered catalyst was washed either with acetone and dichloromethane (“washing with organic solvents”), or with acetone and dichloromethane followed by water washing at pH 9, and subsequently with neutral water at pH 7 until was neutral (“washing with oganic solvents + water”). After these treatments, the immobilized catalyst was dried under vacuum (120 °C) under constant weight, and added in a new reactor and fresh substrates were added.

^{1}H-NMR (300 MHz, $CDCl_3$): (**3**): 9.53 (s, 1H); 7.53-7.38 (m, 5H); 7.21 (s, 1H); 2.52 (t, 2H); 1-55-1.32 (m, 3H): 0.91 (t, 3H); (**4**) ^{1}H-NMR (300 MHz, $CDCl_3$): 9.75 (s, 1H); 6.40 (t, 1H); 2.41 (t, 2H); 2.20 (t, 2H); 1.37 (m, 2H); 1.25 (m, 12H); 0.76 (m, 6H). The conversion was measured comparing the substrate (**1**) and the product (**3**) and the selectivity by comparing products (**3**) and (**4**).

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4.- Conclusions.

In summary, the use of silica-immobilized piperazine as organocatalyst for the synthesis of jasminaldehyde **3** has been reported for the first time. Emphasis is given to the increasing interest in using heterogeneous organocatalysis for non-chiral applications, in which a straightforward set up (immobilized catalysts) combined with efficiency, high selectivity, and promising sustainable reaction conditions may be envisaged. For this specific case, under optimized conditions *on-spec* high conversions and selectivities (> 90%) can be achieved in solvent-free conditions (using neat substrates) enabling a production of jasminaldehyde of ~ 7 g L^{-1} h^{-1}. The immobilized catalyst proved to be reusable, keeping such outstanding high selectivity within all catalytic cycles, albeit a significant catalyst deactivation was observed along these reuses. More research with this and other immobilized organocatalysts is needed to further improve conditions for waste-free and efficient non-chiral aldol condensations like jasminaldehyde synthesis.

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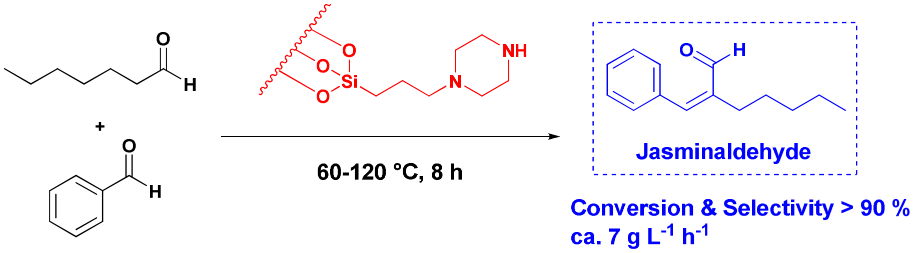

Heterogeneous organocatalysis may contribute to the sustainable production of low-to-medium added-value products under neat conditions.

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