L-Isoleucine in a Choline Chloride/Ethylene Glycol Deep Eutectic Solvent: a Reusable Reaction Kit for the Asymmetric Cross-Aldol Carboligation

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ABSTRACT: L-Isoleucine is able to catalyze the cross-aldol reaction between cyclohexanone and aromatic aldehydes in a deep eutectic solvent consisting in choline chloride and ethylene glycol, rendering products with high diastereo- and enantioselectivity. This protocol is straightforward and green: the organocatalyst and the reaction medium can be recycled up to five times, allowing the preparation of different substrates with a single load of solvent and catalyst.

The independent discoveries of List, Lerner and Barbas,1 and MacMillan,2 in 2000, put forward how small organic molecules are able to catalyze organic transformations with optimum levels of selectivity. Since then, the interest of the scientific community in the so-called field of asymmetric organocatalysis has increased rapidly, newly catalysts and organocatalyzed reactions being discovered at a breathtaking pace.

Research dealing with organocatalysis is particularly attractive for the industry, as it is considered a green technology. The concept of Green Chemistry refers to actions aimed to improve the efficiency in the use of natural resources, comprising the design and implementation of new chemical processes and transformations operating in a more efficient, safer, and more environmentally friendly way. In order to evaluate the “greenness” of a certain process, Green Chemistry has been formulated according to twelve universal principles.3 Organocatalytic transformations satisfy several of them: high atomic efficiency, low generation of residues, and use of reagents in catalytic amounts, among others. However, as a drawback, most of these practices imply the use of organic solvents.

With the intention of developing yet more sustainable processes, deep-eutectic solvents (DESs) have been recently introduced as environmentally benign reaction media, capable of pushing aside hazardous volatile organic solvents. First reported in 2001 by Abbot and co-workers,5 DESs typically consist in a combination of an electron neutral hydrogen-bond donor unit (HBD) and an ammonium-, or phosphonium-based, salt. The HBD partner is able to establish a complex network of strong hydrogen-bonding interactions with the anion (commonly a halide anion) of the salt. Such interactions organize DESs according to a layered sandwich-like structure,5 which is ultimately responsible of the unique physicochemical properties of this kind of fluids, mainly: (a) low glass transition temperature at a specific molar ratio of salt to HBD,6 affording DESs with melting points lower than either of their individual components; (b) low vapor pressure, therefore avoiding vapor emissions to the atmosphere; (c) an easily tunable nature; (d) compatibility with water. Furthermore, both the ammonium salt (commonly choline chloride) and the HBD units (mainly ethylene glycol, glycerol, urea, lactic acid) required to form the DESs are costless, and readily-available, biodegradable and non-cytotoxic.7

Considering the advantages listed above, DESs are starting to encounter extensive applications in metal-catalyzed organic transformations,8 as well as in enzymatic processes.9 In contrast, to the best of our knowledge, only few examples have been recently reported dealing with organocatalytic transformations operating in a DES-based reaction media.10 Following our interest in environmentally-friendly organocatalysis,11 herein we report an exhaustive study on the asymmetric cross-aldol reaction catalyzed by a natural primary amino acid, L-isoleucine, carried out in a benign deep-eutectic solvent consisting of choline chloride and ethylene glycol.

The aldol reaction is one of the most renowned transformations in organic synthesis, privileged as a carboligation process for assembling the backbone of complex organic molecules.12 This C–C bond forming reaction is receiving particular attention since the advent of organocatalysis,13 being nowadays considered as an standard playground for testing the chemical behavior of novel chiral organocatalysts and their methodologies. In this sense, in order to study the feasibility of DESs as reaction media in organocatalyzed processes, we adopted the reaction of Scheme 1 as a case of study.

Scheme 1. Case of study for the asymmetric cross-aldol reaction in [ChCl/2 EG].4

A Deep Eutectic Solvent consisting of a 1:2 molar mixture of choline chloride (ChCl) and ethylene glycol (EG) was chosen as reaction medium, considering that this specific compo-
sition of DES had not been previously explored in other works dealing with organocatalysis.\textsuperscript{10} ChCl and EG are both rather inexpensive and they are meant to present very low toxicity. Looking for developing a green methodology amenable of being adopted by a broad audience readily accessible off-the-bench proteinogenic amino acids were thought as potential chiral catalysts (Supporting Information (SI), Table S1). The effectiveness of the organocatalysts was evaluated in terms of conversion, diastereoselectivity and enantiomeric excess of product 2a. Interestingly, L-isoleucine provided the best results, with an ee peaking at 96%, favoring the (2S,3R)-enantiomer of adduct 2a. It is worth noting that the isoleucine-catalyzed cross-aldol reaction between cyclic ketones and aromatic aldehydes has received little attention in classical methodologies that employ organic solvents.\textsuperscript{14} In this protocol, L-proline fails in providing competitive selectivities (SI, Table S1, entry 1), in agreement with the work of Guillena and Ramón and their study of this catalyst in ChCl-based DESs.\textsuperscript{15c} [Please insert Table 1 here]

To our delight, picking out L-isoleucine as the organocatalyst of choice for the cross-aldol reaction in ChCl/EG, an exhaustive screening of reaction parameters (catalyst loading, concentration, reaction temperature, and reaction time; see SI, Tables S2-S8) revealed an ideal setup: when a solution of 4-nitrobenzaldehyde 1a (1.0 equiv), L-isoleucine (20 mol %) cyclohexanone (10.0 equiv) and distilled water\textsuperscript{15} (10.0 equiv), in ChCl/EG (1:2, c = 0.25 M), was vigorously stirred for 90 h\textsuperscript{16} at 20 °C (controlled by a thermostatic bath), the corresponding aldol adduct 2a was rendered in full conversion, with good anti-diastereoselectivity (90:10 anti/syn) and excellent enantioselectivity (98% ee, for (2S,3R)-anti-2a) (Table 1, entry 1). The reaction is carried out in a closed-cap test tube, under air, with no special care against moisture. In spite of its substantial polarity, the aldol adduct 2a could be fully extracted from the eutectic solvent with portions of ethyl acetate (EtOAc), being purified afterwards by flash chromatography. Interestingly, when the reaction between cyclohexanone and aldehyde 1a was run under analogous conditions, but using pure EG as the solvent, the corresponding aldol product 2a was produced in very low conversion, featuring modest diastereo- and enantioselectivity (Table 1, entry 2), hence manifesting the positive cooperative effect of the DES and the chiral catalyst. Another blank experiment confirmed that the DES itself, without isoleucine, does not suffice to catalyze the reaction (Table 1, entry 3).

With ideal conditions in hand, to establish the scope of our aldol protocol a selection of aldehydes 2b-k bearing diverse functional groups and substitution patterns were reacted with cyclohexanone. All the reactions shown in Table 1 proceeded smoothly:aldols 2b-i, decorated with nitro, nitrile, amide, or halide substituents were isolated in good yield, and with high diastereo- and enantioselectivity (Table 1, entries 4-11). 4-Carboxymethyl benzaldehyde 1j, was conveniently converted into the corresponding β-hydroxyketone 2j with no hydrolysis or transesterification of the ester function (Table 1, entry 12). Interestingly, aldol 2k, derived from pyridine 2-carboxaldehyde, a challenging substrate in the aldol reaction, was isolated in fair yield (Table 1, entry 13). Moreover, isobutyraldehyde also proved to be an acceptable substrate for the cross-aldol reaction with 4-nitrobenzaldehyde 1a, giving rise to the aldol adduct 3a in good yield, although with modest enantioselectivity (Table 1, entry 14). In either case, such an ee value for 3a is comparable to the one previously reported in the literature for the same product, prepared by a cross-aldol methodology that employs 50 mol % of L-isoleucine in DMSO.\textsuperscript{17}

At this stage, the recyclability of the DES containing L-isoleucine was assessed. To this end, a reaction between cyclohexanone and 4-nitrobenzaldehyde, 1a, was set up as in Table 1, entry 1. With the completion of the reaction (full conversion), the crude mixture was treated with several portions of EtOAc (3 x 1 mL), being decanted each time. The organic phases were collected together and evaporated under reduced pressure to afford product 2a quantitatively. L-isoleucine, presumably as its zwitterionic form, remained solubilized in the ChCl/EG DES, and was not transferred into the organic solvent. The DES medium was further subjected to vacuum to remove rests of EtOAc, cyclohexanone or water, before it was reused in subsequent reactions. By these means, the DES could be reused up to 5 times, upon addition of fresh reagents (aldehyde 1a, ketone, and water), without jeopardizing the conversion or the enantioselectivity of β-hydroxy ketone 2a, but with a slight decrease of its diastereoselectivity from the fifth catalytic cycle, probably due to some co-extraction of L-isoleucine and the concomitant decrease of catalyst loading (Table 2). After the fifth run L-isoleucine displays a catalytic turn over number (TON) of over 24 units, which is a convenient figure for an organocatalyzed transformation.

Table 2. Recyclability of DES and L-isoleucine in the asymmetric cross-aldol reaction between cyclohexanone and 4-nitrobenzaldehyde 1a.\textsuperscript{a}

<table>
<thead>
<tr>
<th>cycle</th>
<th>conv (%)\textsuperscript{b}</th>
<th>dr (anti/syn)\textsuperscript{c}</th>
<th>ee (%)\textsuperscript{d}</th>
<th>TON\textsuperscript{e}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99</td>
<td>90:10</td>
<td>98</td>
<td>4.9</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
<td>90:10</td>
<td>98</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
<td>99</td>
<td>89:11</td>
<td>98</td>
<td>14.7</td>
</tr>
<tr>
<td>4</td>
<td>99</td>
<td>88:12</td>
<td>97</td>
<td>19.6</td>
</tr>
<tr>
<td>5</td>
<td>98</td>
<td>82:18</td>
<td>97</td>
<td>24.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: aldehyde 1a (0.2 mmol), cyclohexanone (2.0 mmol), distilled water (2.0 mmol) and L-isoleucine (0.04 mmol) were added to [ChCl/2 EG] (0.8 mL), at 20 °C. The reaction mixture was stirred for 90 h. Recycling was performed as stated in the main text. \textsuperscript{b} Conversion of aldehyde 1a to anti- and syn-2a, as determined by \textsuperscript{1}H NMR spectroscopy of crude reaction mixtures. Resonances of 2a were integrated and quantified against CHBr\textsubscript{3} (9 \textmu L, 0.103 mmol) used as analytical internal standard. \textsuperscript{c} Diastereomeric ratio (dr) determined by \textsuperscript{1}H NMR spectroscopy from crude reaction mixtures. \textsuperscript{d} Enantiomeric excess of major diastereoisomer (anti), as determined by chiral HPLC on crude reaction mixtures. \textsuperscript{e} Accumulative turn over number (TON) values (TON = mol product/mol catalyst).
Table 1. Scope of the cross-aldol reaction catalyzed by L-isoleucine in [ChCl/2 EG].

\[
\begin{align*}
\text{entry} & \quad \text{Ar-} & \quad 2 & \quad \text{yield (%)}^a & \quad \text{dr} \ (\text{anti/syn})^e & \quad \text{ee} \ (%)^d \\
1 & \text{1a, 4-NO}_2\text{-C}_6\text{H}_4 & \text{2a} & 82 \ (99) & 90:10 & 98 \\
2 & \text{1a, 4-NO}_2\text{-C}_6\text{H}_4 & \text{2a} & (34) & 84:16 & 90 \\
3 & \text{1a, 4-NO}_2\text{-C}_6\text{H}_4 & \text{2a} & 0 & - & - \\
4 & \text{1b, 3-NO}_2\text{-C}_6\text{H}_4 & \text{2b} & 75 & 93:7 & 97 \\
5 & \text{1c, 2-NO}_2\text{-C}_6\text{H}_4 & \text{2c} & 80 \ (99) & 90:10 & 99 \\
6 & \text{1d, 2,4-NO}_2\text{-C}_6\text{H}_4 & \text{2d} & 68 & 93:7 & 96 \\
7 & \text{1e, 4-CN-C}_6\text{H}_4 & \text{2e} & 81 & 93:7 & 98 \\
8 & \text{1f, 2-CN-C}_6\text{H}_4 & \text{2f} & 70 & 95:5 & 98 \\
9 & \text{1g} & \text{2g} & 82 & 88:12 & 97 \\
10 & \text{1h, 4-Cl-C}_6\text{H}_4 & \text{2h} & 71 & 87:13 & 97 \\
11 & \text{1i, 4-Br-C}_6\text{H}_4 & \text{2i} & 66 & 93:7 & 98 \\
12 & \text{1j, 4-CO}_2\text{-C}_6\text{H}_4 & \text{2j} & 71 & 93:7 & 98 \\
13 & \text{1k, 2-pyridyl} & \text{2k} & 63 & 83:17 & 84 \\
14^b & \text{1a, 4-NO}_2\text{-C}_6\text{H}_4 & \text{3a} & 72 & -- & 66 \\
\end{align*}
\]

\(^a\) General reaction conditions: aldehyde (0.2 mmol), cyclohexanone (2.0 mmol), distilled water (2.0 mmol) and L-isoleucine (0.04 mmol) were added to the [ChCl/2 EG] DES (0.8 mL), at 20 °C. The reaction mixtures were stirred for 90 h, and the reaction products were extracted with EtOAc. \(^b\) Isolated yield of analytically pure products. In entries 1, 2 and 4 reaction conversion is given in brackets. \(^c\) Diastereomeric ratio (dr) determined by \(^1\)H NMR spectroscopy from crude reaction mixtures. \(^d\) Enantiomeric excess of major diastereoisomer (anti), as determined by chiral HPLC on analytically pure products. \(^e\) Control reaction carried out under analogous experimental conditions using pure EG as reaction medium. \(^f\) Blank experiment with no participation of isoleucine. \(^g\) Water was not added. \(^h\) Isobutyraldehyde (2-methylpropanal) was used instead of cyclohexanone, affording product 3a.

Challenging our system further, we next decided to carry out recycling experiments in which the aldehyde used as substrate would be changed after each catalytic run. Thus, after setting up a reaction between cyclohexanone and 4-nitrobenzaldehyde 1a (Table 3, cycle 1), the DES and L-isoleucine were recovered as stated in the previous paragraph. The so recycled material was then treated with cyclohexanone (2 mmol) and 2-nitrobenzaldehyde 1c (0.2 mmol), being the mixture vigorously stirred for 90 h, to render adduct 2c in quantitative conversion and excellent diastereoad and enantioselectivity (Table 3, cycle 2), with no traces of any product 2a coming from the previous run. It is worth noting that product 2c obtained by this way shows the same selectivity values as those reported in Table 1, entry 5, when it is prepared using fresh organocatalyst and DES. Finally, after recycling DES plus catalyst from the second cycle, a third reaction could be run within the same medium employing 4-nitrobenzaldehyde 1a (Table 3, cycle 3). Gratifyingly, the desired \(\beta\)-hydroxy ketone 2a was produced with comparable selectivities as those of Table 2, entry 3, and Table 1, entry 1, which refer to the same product. The aldol adduct 2c was not detected as a contaminant.

Table 3. Recyclability of DES and L-isoleucine in the asymmetric cross-aldol reaction between cyclohexanone and 4-nitrobenzaldehyde 1a, or 2-nitrobenzaldehyde 1c.

\[
\begin{align*}
\text{cycle} & \quad \text{ArCHO} & \quad 2 & \quad \text{conv} \ (%)^b & \quad \text{dr} \ (\text{anti/syn})^e & \quad \text{ee} \ (%)^d \\
1 & \text{1a} & \text{2a} & 99 & 90:10 & 98 \\
2 & \text{1c} & \text{2c} & 99 & 90:10 & 99 \\
3 & \text{1a} & \text{2a} & 99 & 88:12 & 98 \\
\end{align*}
\]

\(^a\) Reaction conditions: aldehyde (0.2 mmol), cyclohexanone (2.0 mmol), distilled water (2.0 mmol) and L-isoleucine (0.04 mmol) were added to [ChCl/2 EG] (0.8 mL), at 20 °C. The reaction mixture was stirred for 90 h. Recycling was performed as stated in the main text. \(^b\) Conversion of aldehydes 1a or 1c to anti/syn-2a or anti/syn-2c, as determined by \(^1\)H NMR spectroscopy of crude reaction mixtures. Resonances of aldol adducts were integrated and quantified against CHBr\(_3\) (9 µL, 0.103 mmol) used as analytical internal standard. \(^c\) Diastereomeric
ratio (dr) determined by $^1$H NMR spectroscopy from crude reaction mixtures. Enantiomeric excess of major diastereoisomer (anti), as determined by chiral HPLC on crude reaction mixtures. No water was used.

To the light of the experiments presented in Table 3, the reaction system DES-isoleucine keeps no memory when it is recycled and reused in further transformations. Therefore, the combination of l-isoleucine + [ChCl/2 EG] can be foreseen as a reaction kit for the asymmetric cross-aldol reaction between cyclohexanone and aromatic aldehydes, being reusable a minimum of three times with different substrates. Furthermore, the simplicity of the experimental setup, and the low cost of naturally-occurring l-isoleucine and DES, makes this methodology amenable of being adopted by any non-specialized group interested in getting access to compounds of the like of 2a–k.

To conclude, we have developed and implemented a novel l-isoleucine-based organocatalytic system for the cross-aldol reaction between cyclohexanone and aromatic aldehydes that operates in a ChCl/EG DES. This protocol is green and straightforward. The reaction products can be isolated in a ChCl/EG DES. This protocol is green and environmentally-friendly recyclable systems able to catalyze multiple organic transformations is currently underway in our laboratory, and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

General procedures, spectroscopic data, copies of $^1$H and $^13$C NMR spectra, and chromatographic data for compounds 2a–k, 3a.

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REFERENCES

15. The addition of some water was found to increase significantly the enantiomeric excess of the aldol products, in agreement with literature: Jimeno, C. *Org. Biomol. Chem.* **2016**, *14*, 6147–6164.
16. Reaction time was set to 90 h to guarantee full conversion of aldehyde 1a into product 2a. Conversion rises up under long reaction times at the expense of diastereoselectivity of aldol products 2 (Supporting Information, Table S8).