New Efficient Organocatalyst Supported on Simple Ionic Liquid as Recoverable System for Asymmetric Diels-Alder Reaction in Presence of Water


Abstract: The synthesis, characterization and evaluation of a new highly efficient organocatalyst, namely (5S)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone hydrochloride has been achieved. The catalyst possesses important structural features that should increase the catalytic efficiency and solubility in polar media. The application of ionic liquid-supported imidazolidinone catalyst in enantioselective Diels–Alder reactions was investigated. The Diels–Alder reactions of several dienes and dienophiles proceeded efficiently in the presence of the catalyst to provide the desired products in a range from moderate to good yields and from good to excellent enantioselectivities. The conformational study confirms that in the transition state the Re face is completely shielded by phenyl ring preferring approach on less hindered Si face. Particularly remarkable is the fact that the entire system IL/HCl 0.01 M/Catalyst can be recovered and reused for up to six runs without appreciable loss of catalytic activity.

Introduction

Asymmetric organocatalysis is an attractive branch of chemistry and, in particular, the development of new chiral catalysts integrated with non-traditional solvents to form highly recyclable systems is one of the most innovative fields of chemistry to access a wide variety of chiral cyclic compounds and the elaboration of several efficient and reliable enantioselective catalytic methods is realized using metal-free organocatalysts.[2] In this regard, we have developed a new chiral organocatalyst and an efficient recyclable system that promotes Diels–Alder reactions, without the use of metallic complexes. The immobilization of the organocatalyst in the polar system IL/H2O facilitates the separation and reuse of the mixture, promoting economic and environmental benefits.

MacMillan[3] and co-workers initially studied the iminium ion organocatalysis in Diels–Alder reactions through a typical mechanism based on LUMO-lowering activation. The MacMillan’s imidazolidinone catalyst is highly efficient in terms of yield and selectivity; however it still has some drawbacks such as high catalyst loading and no possibility of recycling. In this context, several attempts have been made to recycle the catalyst in recent years.[4] In a previous work[4a] we demonstrated that the use of a methylpyridinium ionic liquid, such as [mPy][OTf], as a solvent in Diels–Alder reactions of α,β-unsaturated aldehydes with both cyclic and acyclic dienes lead to the corresponding endo-cycloadducts with excellent diastereoselectivities and enantioselectivities. Higher selectivity, better yield and shorter reaction times were observed in comparison with reactions performed in classical organic solvents. Herein, we report the new highly efficient organocatalyst 3 in combination with ionic liquids. The novel organocatalyst 3 bears a sulfur atom which increases the solubility and enhances the interactions with the ionic liquid; in addition intramolecular interactions due to the sulfur atom ensure the rigidity of the intermediate iminium ion providing a high enantiofacial selectivity. Additional advantages are the easiness of the synthetic procedure, good recovery of products and recyclability of the whole system ionic liquid/organocatalyst.

Results and Discussion

Compound 3 was prepared in excellent chemical yield, starting from benzylcysteine methyl ester hydrochloride 1 by adding methyamine in aqueous solution followed by treatment with acetone in methanol and p-toluensulfonic acid (Scheme 1).
With this product in our hands and with the experience of previous work we developed a highly efficient system IL/HCl 0.01 M/Catalyst to promote Diels –Alder reactions of a broad range of dienes and dienophiles under mild and recyclable condition, affording the corresponding cycle in high yield with good to high enantioselectivity (Scheme 2).

Initially the catalytic ability of (5S)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone 3 in pyridinium derived ionic liquids and HCl 0.01 M was examined in a model Diels–Alder reaction between cyclohexadiene 4 and acrolein 5. The pertinent results are collected in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>t(h)</th>
<th>Catalyst mol(%)</th>
<th>Yield[a] (%)</th>
<th>Endo/exo[b] (%)</th>
<th>Endo ee[b] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3</td>
<td>70</td>
<td>98:2</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>6</td>
<td>75</td>
<td>98:2</td>
<td>95:5</td>
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<tr>
<td>3</td>
<td>10</td>
<td>10</td>
<td>80</td>
<td>98:2</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>6</td>
<td>98</td>
<td>98:2</td>
<td>95:5</td>
</tr>
</tbody>
</table>

In agreement with MacMillan’s model, it is expected that in our case the E-isomer is also preferentially formed, thus preventing interactions between the olefin and the methyl substituent in the geminal position.

To explore the scope of the reaction we applied the optimized reaction conditions to various substrates. As summarized in Table 2, the Diels–Alder reaction involving α,β-unsaturated aldehydes and various dienes proceeded efficiently in the system [mPy][OTf]/HCl 0.01M/Catalyst leading to the cycloadduct in good yields with good to excellent enantioselectivities.
With the success of the reactions above described, we studied the recyclability of the polar phase IL/HCl 0.01 M/Catalyst used in the Diels–Alder reaction.

The recovery and recycling of entire catalytic system can be exemplified as shown below. After the reaction, the polar phase was extracted three times by directly adding Et₂O (5 mL per time) into the separator funnel; the extracted crude was purified by routine silica gel column chromatography, while imidazolidinone catalyst 3 remained still solubilized in the ionic liquid-water mixture.

Therefore, the ionic liquid-supported imidazolidinone catalyst 3 can be directly reused in further reactions. As shown in histogram only a slight decrease in catalytic activity was observed when ionic liquid-supported imidazolidinone catalyst 3 was recovered and reused in further reactions (Figure 1).

### Table 2. [mPy][OTf] mediated imidazolidinone catalyst 3 catalyzed, Diels-Alder reaction of various dienes and dienophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>R</th>
<th>Product (6a-6g)</th>
<th>Yield (%)</th>
<th>endo:exo(%)</th>
<th>er (%)</th>
<th>endo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>H</td>
<td></td>
<td>98</td>
<td>98:2</td>
<td>95:5</td>
<td></td>
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<tr>
<td>2</td>
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<td>H</td>
<td></td>
<td>93</td>
<td>94:6</td>
<td>97:3</td>
<td></td>
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<tr>
<td>3</td>
<td></td>
<td>H</td>
<td></td>
<td>97</td>
<td>97:3</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>H</td>
<td></td>
<td>90</td>
<td>95:5</td>
<td>99:1</td>
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<tr>
<td>5</td>
<td></td>
<td>H</td>
<td></td>
<td>95</td>
<td>86:14</td>
<td>94:6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Me</td>
<td></td>
<td>85</td>
<td>75:25</td>
<td>95:5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Ph</td>
<td></td>
<td>90</td>
<td>82:18</td>
<td>83:17</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Histogram of recovery and reuse of the system IL/HCl 0.01 M/Catalyst
Theoretical Calculations

The asymmetric induction observed in all cases involving the catalyst 3 is consistent with the conformation of the iminium ion 7. The conformational preferences of the iminium intermediate were studied in detail. We considered the three dihedral angles α, β and γ illustrated in Figure 2.[5]

For each dihedral angle, three staggered conformations were studied and both (E) and (Z) conformations of the iminium moiety were involved. Thus, a total of 54 conformers were considered from which 10 were eliminated because they lead to collision of atoms. The resulting 44 conformers were full optimized at CPCM=H2O/M06-2X/6-31G(d) level.[6] A total of 42 energy minima having different values of dihedral angles were obtained. In general (Z)-isomers are less stable than the corresponding (E)-conformers in agreement with previous results reported by Houk and col. that demonstrated a high steric hindrance between the two methyl groups at C2 of the imidazolidinone ring and the substituent attached to N1. Table 3 lists the seven energy minima below 2.0 kcal/mol of difference with respect to the global minimum that accounts for 91.6% of all the conformations.[7] Due to the large number of conformations studied, calculations involving higher levels of theory were not carried out for all of them. Full optimizations at CPCM=H2O/M06-2X/6-311+G (d,p) level of theory were performed for the above mentioned seven energy minima. The relative energy values are also listed in Table 3.

No substantial changes were observed between calculations at 2ξ and 3ξ levels, the observed dihedral angles being almost identical in all cases. Calculations at the highest level provided four conformations, illustrated in Figure 3, within 1.0 kcal/mol of difference. From these conformations three of them ((E)-c06, (E)-c07 and (E)-c02), including the global minimum (E)-c06, present a stabilizing C-H···S interaction between one of the methyl groups at position C2 of the imidazolidinone ring, and the methylthio group at position C5. The S-H distance was in the range of 2.91-2.95 Å. The differences between these conformers correspond to rotation of dihedral angles β and γ, corresponding to different orientations of the S-benzyl group. The C-H···S interactions have been experimentally reported[8] and theoretically studied.[9]

In particular, theoretical calculations at MP2/6-311++G(d,p) level[10] found an optimum S-HC(sp3) distance of 3.095 Å. Noteworthy, the global minimum of iminium ion 7 ((E)-c06) place the phenyl ring directly above of the double bond shielding the Re face of the dienophile and promoting approach of the diene by the less hindered Si Face. Therefore, the sulfur atom plays a major role on the high enantioselectivity control observed experimentally, fixing a partial conformation (through the above-mentioned C-H···S interaction) that facilitates the orientation of the phenyl ring to completely hinder one of the diastereofaces of the iminium intermediate 7.

Conformer (E)-c21 presents a C-H···π interaction between the phenyl ring and a vinylic proton as also illustrated in Figure 3. This sort of stabilizing interactions have also been reported in the case of MacMillan’s catalyst for which the global minimum exhibits a stabilizing C-H···π interaction between the methyl group at C2 and the phenyl ring of the benzyl group at C5.[1,6a] The same interaction has also been found for one of the more stable conformers of iminium ion 7 (E-c24). These interactions are illustrated in Figure 4 for both the iminium ion of MacMillan’s catalyst (2.42 Å) and conformer (E)-c24 of iminium ion of catalyst 3 (2.84 Å). The NCI analyses carried out for conformers (E)-c06, (E)-c07, (E)-c21 and (E)-c24 showing three different types of interactions are illustrated in Figure 5.

| Table 3. Dihedral angles (º) and relative energies (kcal/mol) of the more stable conformers of iminium intermediate 7. |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|
| conformer       | ΔG (2ξ level)[a] | ΔG (3ξ level)[b] |
|                 | α   | β   | γ   | α   | β   | γ   | ΔΔG |
| E-c06           | -55.8 | -97.1 | -53.5 | 1.6  | -54.7 | -97.6 | -55.4 | 0.0 |
| E-c07           | -66.8 | 79.0 | 164.0 | 1.3  | -67.0 | 78.0 | 163.9 | 0.2 |
| E-c21           | 71.5  | 119.5 | -56.3 | 0.4  | 71.6  | 115.9 | -56.6 | 0.5 |
| E-c02           | -58.3 | 93.8 | 60.7 | 0.0  | -67.3 | 89.4 | 63.1  | 0.6 |
| E-c24           | 64.4  | -84.2 | -32.9 | 1.5  | 65.5  | -85.0 | -33.4 | 1.4 |
| E-c26           | 64.8  | 49.5 | 47.3 | 1.6  | 65.8  | 50.1 | 47.7  | 1.7 |
| E-c04           | -59.5 | -93.8 | -169.6 | 1.7  | -59.5 | -93.6 | -168.9 | 1.6 |

[a] CPCM=H2O/M06-2X/6-31G(d). [b]CPCM=H2O/M06-2X/6-311+G(d,p).
In order to evidence the stabilizing interactions the M06-2X/6-311+G(d,p) wave functions were used for further NCI analysis, a semi-quantitative visualization index based on the electron density and its derivatives that enables identification of non-covalent interactions.\[11\] Visualization of favorable and unfavorable interactions was carried out with NCI Plot Program\[12\] and VMD software.\[13\] Both (E)-c06 and (E)-c07 conformers show a reduced density gradient (RDG) green surface confirming the C-H···S non-covalent stabilizing interactions. In addition, the global minimum (E)-c06 show a green surface corresponding to a stabilizing interaction between the phenyl ring and the double bond. This interaction, difficult to be identified by mere visual inspection of the model, can be identified as a π–π interaction and it stabilizes the (E)-c06 conformer.

Conformers (E)-c21 and (E)-c24 show a typical RDG surface corresponding to a C-H···π interaction in which a green conical form with the vertex pointing to the center of the aromatic ring can be appreciated. As stated above the C-H···π interaction takes place between the aromatic ring and the vinylic hydrogen for conformer (E)-c21 and the methyl group at C2 for conformer (E)-c24.

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**Figure 3.** More stable conformers for iminium intermediate 7. (Structures optimized at level CPCM=H2O/M06-2X/6-311+G(d,p); relative energies given in kcal/mol).

**Figure 4.** C-H···π interactions for optimized structures (CPCM=H2O/M06-2X/6-311+G(d,p)) of the most stable conformer of iminium ion of MacMillan’s catalyst and conformer (E)-c24 of iminium ion of catalyst 3.

**Figure 5.** NCI analysis showing NCI isosurfaces for conformers (E)-c06, (E)-c07, (E)-c21 and (E)-c24. Colour coded according to $(\lambda_2)$, the eigenvalue of the density Hessian, to indicate attraction (green-blue) or repulsion (red). The cutoff ($\rho=0.2$ a.u.) has been chosen to isolate purely non-covalent interactions.
Conclusions

In summary, we have described and characterized a new chiral organocatalyst than an efficient, economical, and practical method for enantioselective Diels–Alder reactions by using a reaction medium composed of ionic liquid, HCl 0.01M and organocatalyst leading to the desired products in good yields with good to excellent enantioselectivities. Noteworthy, the complete polar system can be readily recovered and recycled for further transformations at least six times while still retaining its high characteristics of catalysis and enantioselectivity. In addition, only 6 mol% of catalyst and a slight excess of donor aldehydes (1.5 equiv.) are required, no organic solvent is necessary except during the final purification step. These remarkable advantages make this approach an effective and practical use in the synthesis of fine chemicals.

Experimental Section

General Methods

Commercial starting materials were used without further purification. Solvents were distilled before use. ¹H and ¹³C NMR spectra were recorded at 300 and 75MHz respectively in CDCl₃ using tetramethylsilane (TMS) as internal standard (Bruker ACP 300 MHz). Chemical shifts are given in parts per million and coupling constants in Hertz. The diastereoisomeric ratio has been determined by a GC/MS instrument Shimadzu QP2010 equipped with a Quadrex 007-5MS column, 30 m, coated with a 0.25 mm film, helium as a carrier gas, instrument Shimadzu QP2010 equipped with a Quadrex 007-5MS, 30 m, coated with a 0.25 mm film, helium as a carrier gas, injector temperature 270 °C, oven temperature program: 50 °C hold 3 min, ramp 2 °C/min to 280 °C and held for 1 min. The enantiomeric ratio has been valued by computer time at clusters Terminus and Memento. D.R. -L. gratefully acknowledges the Institute of Biocomputation and Physics of Complex Systems (BIFI) at the University of Zaragoza (Spain) and the University of Calabria for financial support.

Synthesis of Methylpyridinium Triflate [mPy][OTf]

The synthesis of methylpyridinium triflate [mPy][OTf] was obtained by comparison of the corresponding spectra with literature reports.[14]

Synthesis of catalyst 3

To a solution of aqueous MeNH₂ (2 M, 60 mL) was added (S)-Benzyll-L-cysteine methyl ester hydrochloride (10 g, 40 mmol) and the resulting solution was stirred at room temperature for 10 hours. The crude solution was treated with saturated aqueous solution of NaHCO₃ (50 mL) and the free amine was extracted with CHCl₃ (40 mLx3), dried (Na₂SO₄), filtered and concentrated. To this residue was added MeOH (100mL), acetoic acid (16.6 mL, 220 mmols) and p-TSA (93.2 mg, 0.48 mmols). The resulting solution was heated to reflux for 12 h, cooled to room temperature, and then concentrated in vacuo. The residue washed with hexane (30 mLx3) gives 8.36 g (80 % of overall yield) of (5S)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone 3. Yellow oil.

¹H NMR (300 MHz, [D]CHCl₃, 25 °C, TMS): δ = -1.3 (s, 3H; CH₃), 1.4 (s, 3H; CH₃), 2.2 (bs, 1H; N-H), 2.8 (s, 3H = C-NH₂), 2.8 (dd, 1H; H-β), 3.9 (d, 1H; JH,H = 14.1 Hz; H-α), 4.2 (dd, 1H; JH,H = 4.2 Hz; 3J H,H = 5.9 Hz; 5-H), 3.6 (d, 1H; JH,H = 4.2 Hz; JH,H = 5.9 Hz; 5-H), 3.2 (d, 1H; JH,H = 13.4 Hz; H-CH₃), 3.8 (d, 1H; JH,H = 13.4 Hz, H-CH₃), 7.2-7.4 (m, 5H, Ar). ¹³C NMR (75 MHz, [D]CHCl₃, 25 °C, TMS): δ = 25.2, 25.3, 27.0, 33.1, 36.8, 57.8, 75.6, 127.0, 128.5, 128.9, 138.2, 172.4.

Electrospray with positive polarities at 70,000 resolving power (defined as FWHM m/z 200), IT = 30 ms and AGC Target = 1,000,000, for SIM conditions were: Spray voltage 3.5 kV, Sheath gas: 15 arbitrary units. Heater conditions were: Spray voltage 3.5 kV, Sheath gas: 15 arbitrary units. Source conditions were: Spray voltage 3.5 kV, Sheath gas: 15 arbitrary units. Source conditions were: Spray voltage 3.5 kV, Sheath gas: 15 arbitrary units. The resulting solution was heated to reflux for 12 h, cooled to room temperature, and then concentrated in vacuo. The residue washed with hexane (30 mLx3) gives 8.36 g (80 % of overall yield) of (5S)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone 3. Yellow oil.

ESI-HRMS calc. for [C₁₄H₂₀ON₂S +H]⁺ 265.1369, found 265.1369.

Acknowledgements

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**Keywords:** Organic catalysis; Enantioselectivity; Diels–Alder reaction; Conformation analysis; Recycle.


5. A similar but simpler conformational analysis for the MacMillan’s catalyst has been carried out by Houk and col. See: R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* 2004, 346, 1175-1185. In that case the analysis involved six different conformations since only one dihedral angle needed to be considered in addition to (E) and (Z) configurations of the iminium moiety.

6. a) This level of theory and solvent model was also used by Gordillo and Houk in a previous study of the organocatalytic Diels-Alder reaction promoted by MacMillan’s catalyst. See: R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* 2006, 128, 3543-3553. b) Since the reaction is carried out in a polar medium constituted by a mixture of an aqueous acid solution and ionic liquid we chose water as a solvent to modelize a high dielectric constant by using CPCM model, which has shown its validity for such a solvent (see ref. 1). Modelization of a ionic liquid as a solvent is not well implemented yet and it should require high computational costs by considering a supermolecule with sever units of ionic liquid. For a recent study on approaching solvation models for ionic liquids see: V. S. Bemales, A. V. Marenich, R. Contreras, C. J. Crämer, D. G. Trautler, *J. Phys. Chem. B* 2012, 116, 9122-9129.

7. For the complete list of conformers, their relative energies and abundance according to Boltzmann distribution see Supporting Information.


The synthesis, characterization and evaluation of a new highly efficient imidazolidinone organocatalyst has been achieved and investigated in enantioselective Diels-Alder reactions. The conformational study confirms the approach on less hindered Si face.