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

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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 compounds in eco-friendly condition.^[1] The asymmetric Diels-Alder reactions provide simple and direct access to a variety of important 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.

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Results and Discussion

Compound **3** was prepared in excellent chemical yield, starting from benzylcysteine methyl ester hydrochloride **1** by adding methylamine in aqueous solution followed by treatment with acetone in methanol and *p*-toluenesulfonic acid (Scheme 1).

Entry	t(h)	Catalyst mol(%)	Yield ^[a] (%)	Endo/exo ^[b] (%)	Endo _{er} ^[b] (%)
1	10	3	70	98:2	92:8
2	10	6	75	98:2	95:5
3	10	10	80	98:2	95:5
4	16	6	98	98:2	95:5

Scheme 1. Synthesis of (5*S*)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone **3**.

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).

Scheme 2. General procedure for Diels–Alder reactions.

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

Table 1. Screening at different time and percent of catalyst.

[a] Isolated yield. [b] Determined by GC analysis.

The cycloaddition is conveniently carried out at 0 °C, using a 6 mol % catalyst and is completed after 16 h with the formation of

6 with an excellent *endo:exo* ratio of 98:2 percent and an enantiomeric ratio of 95:5 percent. The catalytic cycle is illustrated in Scheme 3.

Scheme 3. Catalytic cycle of the cycloaddition process.

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.

Under these circumstances, the benzyl group on the catalyst framework acts like a shield on *Re* face of the dienophile and promotes approach of the diene by the less hindered *Si* face.

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.

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

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

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).

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]

Figure 2. Dihedral angles of iminium intermediate **7**.

For each dihedral angle, three staggered conformations were studied and both (*E*) and (*Z*) configurations 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.

Table 3. Dihedral angles (°) and relative energies (kcal/mol) of the more stable conformers of iminium intermediate **7**.

conformer	ΔG (2 ξ level) ^[a]				ΔG (3 ξ level) ^[b]			
	α	β	γ	$\Delta\Delta G$	α	β	γ	$\Delta\Delta G$
<i>E</i> -c06	-55.8	-97.1	-53.5	1.6	-54.7	-97.6	-55.4	0.0
<i>E</i> -c07	-66.8	79.0	164.0	1.3	-67.0	78.0	163.9	0.2
<i>E</i> -c21	71.5	119.5	-56.3	0.4	71.6	115.9	-56.6	0.5
<i>E</i> -c02	-58.3	93.8	60.7	0.0	-67.3	89.4	63.1	0.6
<i>E</i> -c24	64.4	-84.2	-32.9	1.5	65.5	-85.0	-33.4	1.4
<i>E</i> -c26	64.8	49.5	47.3	1.6	65.8	50.1	47.7	1.7
<i>E</i> -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).

No substantial changes were observed between calculations at 2 ξ and 3 ξ 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.

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.

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).

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.

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 $(\lambda_2)\rho$, 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 ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively in CDCl_3 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, injector temperature 270 °C, oven temperature program: 50 °C hold 3 min, ramp 14 °C/min to 280 °C and held for 1 min. The enantiomeric ratio has been valued by Focus GC-FID Thermo Scientific instrument equipped with a chiral column Megadex DET Beta, 30 m, coated with a 0.25 mm film, helium as a carrier gas, injector temperature 250 °C, oven temperature program: 50 °C, ramp 2 °C/min to 200 °C and hold for 1 min. ESI-HRMS spectrum was recorded by a Thermo Scientific Q Exactive (Thermo Fisher, Milan, Italy) mass spectrometer using 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 (select ion monitoring) by infusion at flow of 10 $\mu\text{L}/\text{min}$. Source conditions were: Spray voltage 3.5 kV, Sheath gas: 15 arbitrary units, Auxillary Gas: 0 arbitrary units, Sweep gas: 0 arbitrary units. Heater temperature: 30°C, Cap Temp: 320°C. S-Lens RF level: 50. The instrument was calibrated using the recommended Thermo Scientific Calibration solution prior to the beginning of the analysis. Detection of the targeted compound was based on theoretical exact mass. Data were evaluated by Xcalibur 2.2.SP1 (Thermo Fisher Scientific, Bremen, Germany): the mass accuracy, direct calculated from Xcalibur is defined with the formula Δ (ppm) = [(theoretical mass - measured mass)/theoretical mass] $\times$ 1,000,000. Stock solution at a concentration of 1 mg/mL were prepared in UHPLC-MS grade methanol. Prior to analysis, the solution was diluted 1:1000 (v/v) in a vial to obtain a concentration of 1 $\mu\text{g}/\text{mL}$.

Synthesis of Methylpyridinium Triflate [mPy][OTf].

The ionic liquid [mPy][OTf] was prepared in total halide free direct synthesis by placing 0.29 mols of dry pyridine in a two-necked flask to which 0.30 mols of methyltrifluoromethanesulfonate dropwise were added. The mixture was reacted at 80 °C for 12 hours. The crude product was washed with dichloromethane and dried under vacuum,

providing 68.04 gr (yield 96%) of pure ionic liquid. The characterization of [mPy][OTf] was obtained by comparison of the corresponding spectra with literature reports.^[14]

Synthesis of catalyst 3

To a solution of aqueous MeNH_2 (2 M, 60 mL) was added (S)-Benzyl-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 NaHCO_3 (50 mL) and the free amine was extracted with CHCl_3 (40 mL $\times$ 3), dried (Na_2SO_4), filtered and concentrated. To this residue was added MeOH (100 mL), acetone (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 mL $\times$ 3) 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, $[\text{D}]\text{CHCl}_3$, 25 °C, TMS): δ = 1.3 (s, 3H; CH_3), 1.4 (s, 3H; CH_3), 2.2 (bs, 1H; N-H), 2.8 (s, 3H; N- CH_3), 2.8 (dd, 1H; $^3J(\text{H,H})$ = 4.2 Hz, $^2J(\text{H,H})$ = 14.1 Hz; $\text{H}_{\text{CH}_2\text{S}}$), 2.9 (dd, 1H, $^3J(\text{H,H})$ = 5.9 Hz, $^2J(\text{H,H})$ = 14.1 Hz; $\text{H}_{\text{CH}_2\text{S}}$), 3.6 (dd, 1H, $^3J(\text{H,H})$ = 4.2 Hz, $^3J(\text{H,H})$ = 5.9 Hz; 5-H), 3.7 (d, 1H, $^2J(\text{H,H})$ = 13.4 Hz; $\text{H}_{\text{CH}_2\text{Bn}}$), 3.8 (d, 1H, $^2J(\text{H,H})$ = 13.4 Hz, $\text{H}_{\text{CH}_2\text{Bn}}$), 7.2-7.4 (m, 5H, Ar). ^{13}C NMR (75 MHz, $[\text{D}]\text{CHCl}_3$, 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. ESI-HRMS calc. for $[\text{C}_{14}\text{H}_{20}\text{ON}_2\text{S} + \text{H}]^+$ 265.1369, found 265.1368.

General procedure for Diels-Alder reactions (6a-6g)

In a representative procedure catalyst **3** (0.036 mmols, 6 mol %) was dissolved in a mixture of [mPy][OTf]/HCl 0.01 M v:v 3:1. The dienophile (0.6 mmols) and the diene (0.4 mmols) were added sequentially. After the appropriate time the reaction mixture was extracted with ether (2 mL $\times$ 3). The ethereal layer was dried by Na_2SO_4 , filtered, evaporated under reduced pressure and purified by flash chromatography. ^1H NMR and ^{13}C NMR data were consistent with previously reported values.^[3,15]

Acknowledgements

This work was supported by the Ministerio de Ciencia e Innovación (MICINN) and FEDER Program (Madrid, Spain, project CTQ2013-44367-C2-1-P) and the Gobierno de Aragón (Zaragoza, Spain. Bioorganic Chemistry Group. E-10). We acknowledge the Institute of Biocomputation and Physics of Complex Systems (BIFI) at the University of Zaragoza (Spain) for computer time at clusters Terminus and Memento. D.R.-L. Thanks the Spanish Ministry of Education (MEC) for a pre-doctoral grant (FPU program). Molecular graphics have been performed with CYLview 1.0 software (C. Y. Legault, University of Sherbrooke, Canada). Thanks the Italian Ministry of University and Scientific Research (MIUR) for a doctoral grant and the University of Calabria for financial support.

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

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FULL PAPER

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.

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