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Efficient Organocatalyst Supported on a Simple Ionic Liquid as a Recoverable System for the Asymmetric Diels–Alder Reaction in the Presence of Water

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The synthesis, characterization, and evaluation of a new highly efficient organocatalyst, namely, (5*S*)-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 the 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 moderate to good yields and from good to excellent enantioselectivities. The conformation study confirms that in the transition state the *Re* face is shielded completely by the phenyl ring and an approach on the less hindered *Si* face is preferred. Particularly remarkable is the fact that the entire ionic liquid/HCl 0.01 м/catalyst system can be recovered and reused in up to six runs without an 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 nontraditional solvents to form highly recyclable systems is one of the most innovative fields of chemistry to access a wide variety of chiral compounds under eco-friendly conditions.[1] Asymmetric Diels–Alder reactions provide a 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 metal complexes. The immobilization of the organocatalyst in the polar ionic liquid (IL)/H_2O system facilitates the separation and reuse of the mixture, which promotes economic and environmental benefits.

Initially, MacMillan[3] studied iminium ion organocatalysis in Diels–Alder reactions through a typical mechanism based on LUMO-lowering activation. 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 study[4a] we demonstrated that the use of methylpyridinium ILs, such as methylpyridinium triflate ([mPy][OTf]), as a solvent in the 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 yields, and shorter reaction times were observed in comparison with reactions performed in classical organic solvents.

Herein, we report the new highly efficient organocatalyst (5*S*)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone (**3**) in combination with ILs. The new organocatalyst **3** bears an S atom that increases the solubility and enhances the interactions with the IL; in addition, intramolecular interactions caused by the S atom ensure the rigidity of the intermediate iminium ion and provide a high enantiofacial selectivity. Additional advantages are the ease of the synthetic procedure, good recovery of products, and recyclability of the whole IL/organocatalyst system.

Results and Discussion

Compound **3** was prepared in excellent chemical yield from benzylcysteine methyl ester hydrochloride (**1**) by adding methylamine in aqueous solution followed by treatment with ace-

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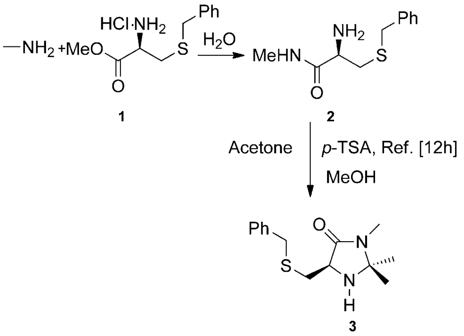
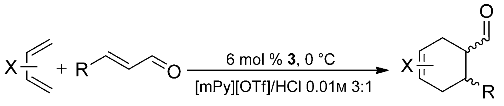


Scheme 1. Synthesis of **3**.

tone in methanol and *p*-toluenesulfonic acid (*p*-TSA; Scheme 1).

With this product in hand and with the experience of previous work, we developed a highly efficient IL/HCl 0.01 M/catalyst system to promote Diels–Alder reactions of a broad range of dienes and dienophiles under mild and recyclable conditions, which afforded the corresponding cycle in a high yield with good to high enantioselectivity (Scheme 2).



Scheme 2. General procedure for Diels–Alder reactions.

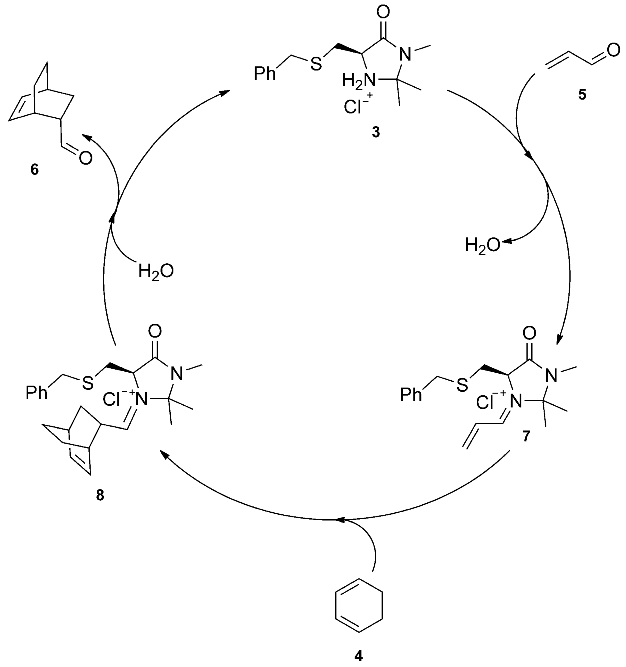
Initially, the catalytic ability of **3** in pyridinium-derived ILs and HCl 0.01 M was examined in a model Diels–Alder reaction between cyclohexadiene **4** and acrolein **5** (Table 1). The cycloaddition is performed conveniently at 0 °C using 6 mol% catalyst and is completed after 16 h with the formation of **6** with an excellent *endo*/*exo* ratio of 98:2% and an enantiomeric ratio (*er*) of 95:5%. The catalytic cycle is illustrated in Scheme 3.

In agreement with MacMillan's model, it is expected that the *E* isomer will be formed preferentially, which prevents interactions between the olefin and the methyl substituent in the geminal position. Under these circumstances, the benzyl group on the catalyst framework acts as a shield on the *Re* face of the dienophile and promotes the approach of the diene by the less hindered *Si* face.

Table 1. Screening of reaction time and catalyst loading.

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

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



Scheme 3. Catalytic cycle for the cycloaddition process.

To explore the scope of the reaction, we applied the optimized reaction conditions to various substrates. The Diels–Alder reaction that involves α,β-unsaturated aldehydes and various dienes proceeded efficiently in the system [mPy][OTf]/HCl 0.01 M/catalyst to lead to the cycloadduct in good yields with good to excellent enantioselectivities (Table 2).

With the success of the reactions described above, we studied the recyclability of the IL/HCl 0.01 M/catalyst polar phase used in the Diels–Alder reaction. The recovery and recycling of the entire catalytic system can be exemplified as shown below. After the reaction, the polar phase was extracted three times by adding Et_2O (5 mL per time) directly into the separatory funnel; the extracted crude was purified by routine silica gel column chromatography, and catalyst **3** remained dissolved in the IL/water mixture.

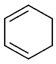
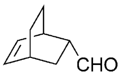
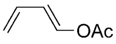
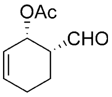
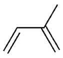
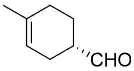
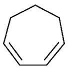
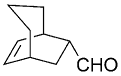
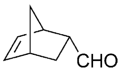
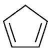
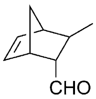
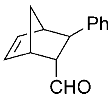
Therefore, IL-supported **3** can be reused directly in further reactions. As shown in the histogram, only a slight decrease in catalytic activity was observed if IL-supported **3** was recovered and reused in further reactions (Figure 1).

Theoretical calculations

The asymmetric induction observed in all cases that involve 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 the *E* and *Z* configurations of the iminium moiety were involved. Thus, a total of 54 conformers were considered of which 10 were eliminated because they led to a collision of atoms. The resulting 44 conformers were optimized fully at the CPCM=H_2O/M06-2X/6-31G(d) level.[6] A total of 42 energy minima that have different dihedral angles were obtained. In

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

Entry	Diene	R	Product (**6 a–g**)	Yield [%]	*endo/exo*	*endo er*
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

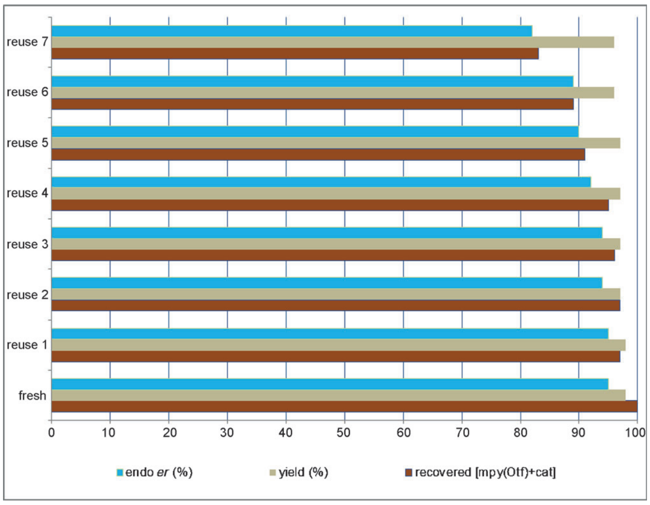


Figure 1. Histogram of recovery and reuse of the IL/HCl 0.01 м/catalyst system.

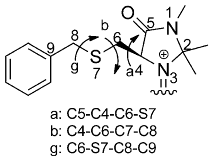


Figure 2. Dihedral angles of **7**.

general, *Z* isomers are less stable than the corresponding *E* conformers in agreement with previous results reported by Houk et al.[6] that demonstrated a high steric hindrance between the two methyl groups at C2 of the imidazolidinone ring and the substituent attached to N1. The seven energy minima below a difference of 2.0 kcal mol^{-1} with respect to the global minimum that accounts for 91.6% of all the conformations are listed in Table 3.[7] As a result of the large number of conformations studied, calculations that involve higher levels of theory were not performed for all of them. Full optimizations at the CPCM = H_2O/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 the 2ξ and 3ξ levels, and the observed dihedral angles are almost identical in all cases. Calculations at the highest level provided four conformations within a difference of 1.0 kcal mol^{-1} (Figure 3). Of these conformations, three ((*E*)-c06, (*E*)-c07, and (*E*)-c02), which include 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 the rotation of dihedral angles β and γ, which corresponds to different orientations of the S–benzyl group. C–H···S interactions have been reported experimentally[8] and studied theoretically.[9]

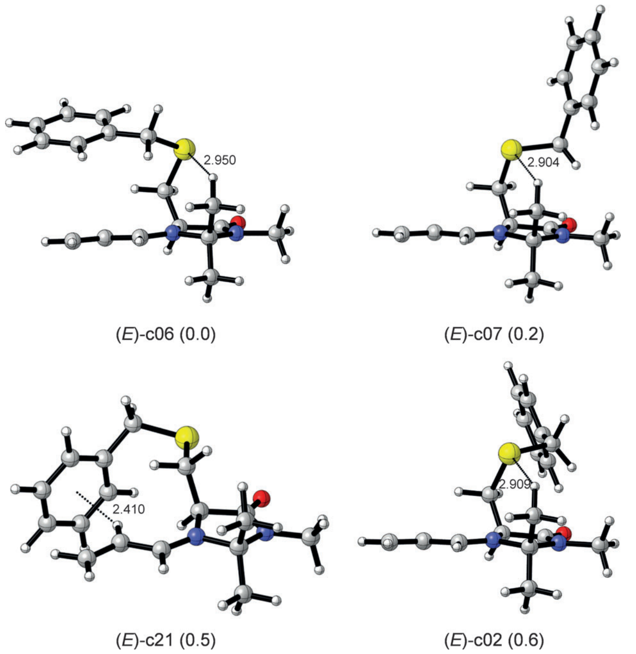
In particular, theoretical calculations at the MP2/6-311+G(d,p) level[10] found an optimum S–HC(sp^3) distance of 3.095 Å. Notably, the global minimum of iminium ion **7** ((*E*)-c06) places the phenyl ring directly above the double bond to shield the *Re* face of the dienophile and promote approach of the diene by the less hindered *Si* face.

Therefore, the S atom plays a major role in the high enantioselectivity observed experimentally by fixing a partial conformation (through the above-mentioned C–H···S interaction)

Table 3. Dihedral angles [°] and relative energies [kcal mol^{-1}] of the more stable conformers of iminium intermediate **7**.

	ΔG (2ξ level)[a]				ΔG (3ξ level)[b]			
Conformer	α	β	γ	$\Delta\Delta G$	α	β	γ	$\Delta\Delta G$
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 = H_2O/M06-2X/6-31G(d). [b] CPCM = H_2O/M06-2X/6-311+G(d,p).



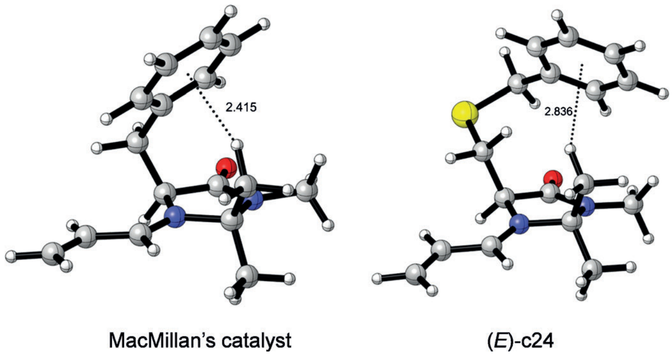
(*E*)-c06 (0.0) (*E*)-c07 (0.2)

(*E*)-c21 (0.5) (*E*)-c02 (0.6)

Figure 3. Most stable conformers for **7**. (Structures optimized at the CPCM = H_2O/M06-2X/6-311+G(d,p) level; relative energies given in kcal mol^{-1}).

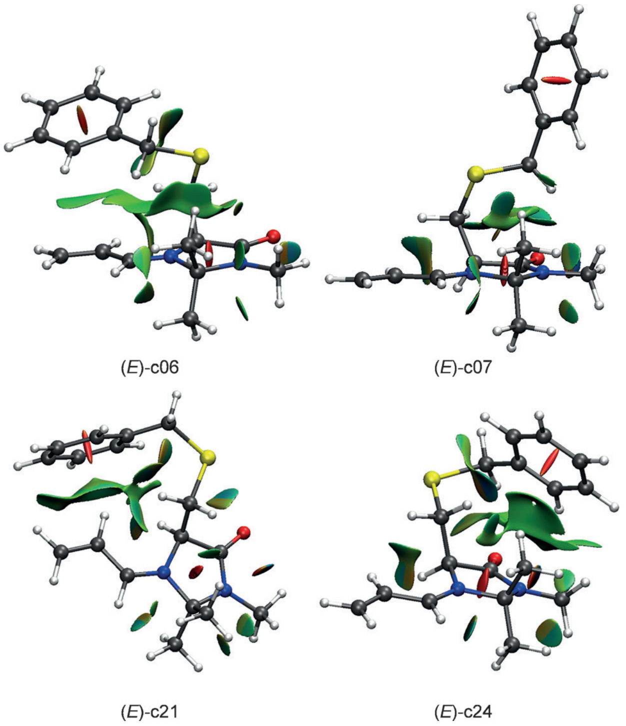
that facilitates the orientation of the phenyl ring to hinder one of the diasterofaces of the iminium intermediate **7** completely.

Conformer (*E*)-c21 presents a C–H⋯π interaction between the phenyl ring and a vinylic proton (Figure 3). This sort of stabilizing interaction has 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 the iminium ion of **3** (2.84 Å). The NCI (non-covalent interaction) analyses performed for conformers (*E*)-c06, (*E*)-c07, (*E*)-c21, and (*E*)-c24, which show three different types of interactions, are illustrated in Figure 5.



MacMillan's catalyst (*E*)-c24

Figure 4. C–H⋯π interactions for optimized structures (CPCM = H_2O/M06-2X/6-311+G(d,p)) of the most stable conformer of the iminium ion of MacMillan's catalyst and conformer (*E*)-c24 of the iminium ion of catalyst **3**.



(*E*)-c06 (*E*)-c07

(*E*)-c21 (*E*)-c24

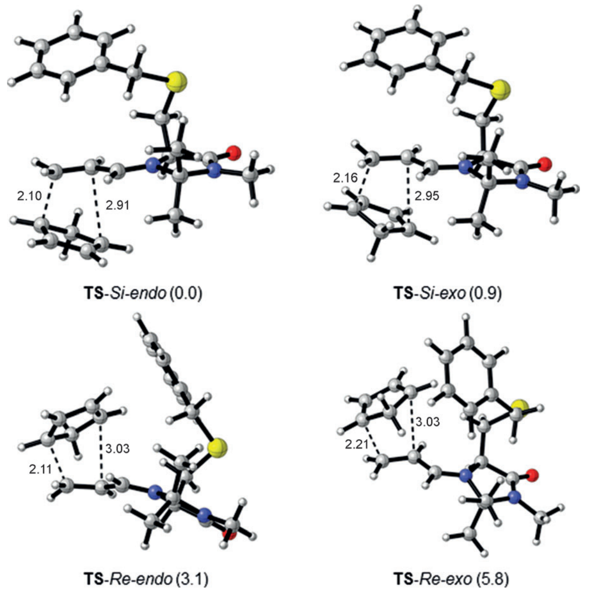
Figure 5. NCI analysis showing NCI isosurfaces for conformers (*E*)-c06, (*E*)-c07, (*E*)-c21, and (*E*)-c24. Color-coded according to $(\lambda_2)\rho$, the eigenvalue of the density Hessian, to indicate attraction (green–blue) or repulsion (red). The cutoff ($\rho = 0.2$ a.u.) was chosen to isolate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

To evidence the stabilizing interactions, the M06-2X/6-311+G(d,p) wave functions were used for further NCI analysis, a semiquantitative visualization index based on the electron density and its derivatives that enables the identification of noncovalent interactions.[11] Visualization of favorable and unfavorable interactions was performed with NCI Plot Program[12] and VMD software.[13]

Both (*E*)-c06 and (*E*)-c07 conformers show a reduced density gradient (RDG) green surface that confirms the C–H⋯S noncovalent stabilizing interactions. In addition, the global minimum (*E*)-c06 shows a green surface that corresponds to a stabilizing interaction between the phenyl ring and the double bond. This interaction, difficult to identify by a 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 that corresponds to a C–H⋯π interaction in which a green conical form with a vertex that points 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 atom for conformer (*E*)-c21 and the methyl group at C2 for conformer (*E*)-c24.

We used the most stable conformation of the catalyst (*E*)-c06 to locate the preferred transition structures for *endo* and *exo* approaches of cyclopentadiene by both *Re* and *Si* faces. The geometrical features and relative energies [kcal mol^{-1}] of the four transition structures are illustrated in Figure 6.



TS-*Si-endo* (0.0) **TS**-*Si-exo* (0.9) **TS**-*Re-endo* (3.1) **TS**-*Re-exo* (5.8)

Figure 6. Transition structures for the reaction between (*E*)-c06 and cyclopentadiene. (Structures optimized at the CPCM = H2O/M06-2X/6-311+G(d,p) level; relative energies given in kcal mol^{-1}).

The energy difference between TS-*Si-endo* and TS-*Si-exo* is 0.84 kcal mol^{-1}, which justifies the formation of *endo/exo* mixtures in the case of the reaction with cyclopentadiene. A difference of more than 3 kcal mol^{-1} between the *Re* and *Si* approaches in the case of *endo* adducts (more than 5.0 kcal mol^{-1} for *exo* adducts) justifies the excellent enantioselectivity observed. The bond-formation lengths are in agreement with a highly asynchronous reaction as expected for a reaction performed in a highly polar medium.

Conclusions

We have described and characterized a new chiral organocatalyst as an efficient, economical, and practical method for enantioselective Diels–Alder reactions by using a reaction medium composed of an ionic liquid (IL), HCl 0.01 M, and organocatalyst, which leads to the desired products in good yields with good to excellent enantioselectivities. Theoretical calculations confirmed the presence of C–H⋯π interactions similar to those found for MacMillan's catalyst. However, important C–H⋯S stabilizing interactions are also evidenced by both DFT calculations and NCI analysis, which justifies the high stability of conformer (*E*)-c06. In this conformer the phenyl ring is placed over the unsaturated system to render the *Si* face as the less hindered one for the attack of the dienophile. The calculated relative energies between transition structures are in good agreement with both the formation of mixtures of *endo*/*exo* adducts in some cases and the excellent enantioselectivity observed experimentally. Notably, the complete polar system can be recovered readily and recycled for further transformations at least six times with the retention of its catalysis and enantioselectivity. In addition, only 6 mol % of catalyst and a slight excess of donor aldehyde (1.5 equiv.) are required, and no organic solvent is necessary except during the final purification step. These remarkable advantages make this approach effective and practical in the synthesis of fine chemicals.

Experimental Section

General methods

Commercial starting materials were used without further purification. Solvents were distilled before use. ^{1}H 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 ppm and coupling constants in Hz. The diastereoisomeric ratio has been determined by a GC–MS instrument (Shimadzu QP2010) equipped with a Quadrex 007–5 MS column, 30 m, coated with a 0.25 mm film, helium as a carrier gas, injector temperature of 270 °C, and oven temperature program: 50 °C hold 3 min, ramp 14 °C min^{-1} to 280 °C and held for 1 min. The enantiomeric ratio has been evaluated by using a Focus GC–FID Thermo Scientific instrument (FID = flame ionization detector) 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, and oven temperature program: 50 °C, ramp 2 °C min^{-1} to 200 °C and hold for 1 min. ESI-HRMS spectra were recorded by using a Thermo Scientific Q Exactive (Thermo Fisher, Milan, Italy) mass spectrometer using ESI with positive polarities at 70 000 resolving power (defined as full width at half maximum (FWHM) *m/z* 200), IT (injection time) = 30 ms, and AGC (automatic gain control) target = 1 000 000, for selected-ion monitoring (SIM) by infusion at flow of 10 μL min^{-1}. Source conditions were: spray voltage 3.5 kV, sheath gas: 15 arbitrary units, auxiliary gas: 0 arbitrary units, sweep gas: 0 arbitrary units. Heater temperature: 30 °C, cap temperature: 320 °C. S-Lens RF level: 50. The instrument was calibrated using the recommended Thermo Scientific Calibration solution at the beginning of the analysis. Detection of the target compound was based on the theoretical exact mass. Data were evaluated by using Xcalibur 2.2.SP1 (Thermo Fisher Scientific, Bremen, Germany): the mass accuracy, calculated directly from Xcalibur, is defined with the formula Δ [ppm] = [(theoretical mass − measured mass)/theoretical mass] × 1 000 000. Stock solution at a concentration of 1 mg mL^{-1} were prepared in UHPLC–MS-grade methanol. Before analysis, the solution was diluted 1:1000 v/v in a vial to obtain a concentration of 1 μg mL^{-1}

Synthesis of methylpyridinium triflate ([mPy][OTf])

The IL [mPy][OTf] was prepared by halide-free direct synthesis by placing dry pyridine (0.29 mol) in a two-necked flask to which methyltrifluoromethanesulfonate (0.30 mol) was added dropwise. The mixture was reacted at 80 °C for 12 h. The crude product was washed with dichloromethane and dried under vacuum to yield 68.04 g (96 %) of pure IL. The synthesis of [mPy][OTf] was confirmed by comparison of the spectra with literature reports.[14]

Synthesis of catalyst 3

To an aqueous solution of $MeNH_2$ (2 M, 60 mL) was added (*S*)-benzyl-L-cysteine methyl ester hydrochloride (10 g, 40 mmol), and the solution was stirred at RT for 10 h. The crude solution was treated with a saturated aqueous solution of $NaHCO_3$ (50 mL), and the free amine was extracted with $CHCl_3$ (40 mL × 3), dried (Na_2SO_4), filtered, and concentrated. To this residue was added

MeOH (100 mL), acetone (16.6 mL, 220 mmol), and *p*-TSA (93.2 mg, 0.48 mmol). The solution was heated to reflux for 12 h, cooled to RT, and then concentrated in vacuo. The residue was washed with hexane (30 mL × 3), and yielded 8.36 g (80 % overall) of (5*S*)-2,2,3-trimethyl-5-thiobenzylmethyl-4-imidazolidinone (**3**) as a yellow oil. ^{1}H NMR (300 MHz, [D]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(H,H) = 4.2, ^2J(H,H) = 14.1 Hz; HCH$_2$S), 2.9 (dd, 1H, ^3J(H,H) = 5.9, ^2J(H,H) = 14.1 Hz; HCH$_2$S), 3.6 (dd, 1H, ^3J(H,H) = 4.2, ^3J(H,H) = 5.9 Hz; 5-H), 3.7 (d, 1H, ^2J(H,H) = 13.4 Hz; HCH$_2$Bn), 3.8 (d, 1H, ^2J(H,H) = 13.4 Hz, HCH$_2$Bn), 7.2–7.4 ppm (m, 5H, Ar); ^{13}C NMR (75 MHz, [D]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 ppm; HRMS (ESI): *m*/*z*: calcd for [C$_{14}$H$_{20}$ON$_2$S+H]$^+$: 265.1369; found 265.1368.

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

In a representative procedure catalyst **3** (0.036 mmol, 6 mol %) was dissolved in a mixture of [mPy][OTf]/HCl 0.01 M 3:1 v/v. The dienophile (0.6 mmol) and the diene (0.4 mmol) were added sequentially. After the appropriate time, the reaction mixture was extracted with ether (2 mL × 3). The ether layer was dried by Na$_2$SO$_4$, filtered, evaporated under reduced pressure, and purified by flash chromatography. ^{1}H and ^{13}C NMR data were consistent with values reported previously.[3, 15]

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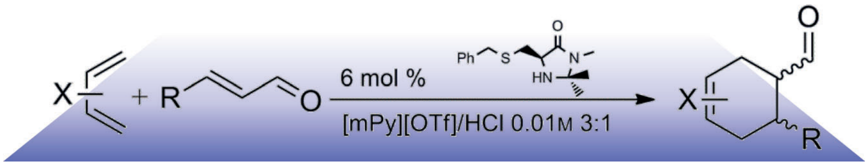

Confirming the conformation: The synthesis, characterization, and evaluation of a new highly efficient imidazolidinone organocatalyst is achieved. The catalyst is investigated in enantioselective Diels–Alder reactions, and a conformation study confirms the approach on the less hindered *Si* face. [mPy][OTf] = Methylpyridinium triflate.

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Efficient Organocatalyst Supported on a Simple Ionic Liquid as a Recoverable System for the Asymmetric Diels–Alder Reaction in the Presence of Water