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An in-depth look at the effect of Lewis acid catalysts on Diels–Alder cycloadditions in ionic liquids

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Abstract—The present work explores in detail the Diels–Alder reaction between cyclopentadiene and a series of dienophiles, performed in an innovative medium such as an ionic liquid. The potential activation of different Lewis acid catalysts and their load effect when used in combination with this solvent have been explored, in order to settle the improvement on rates and selectivities. © 2005 Elsevier Ltd. All rights reserved.

1. Introduction

Cycloadditions and, especially the Diels–Alder reaction, represent the favourite protocol to synthesise six-membered carbo- or heterocycles, which are otherwise ubiquitous in natural products. It is not by chance that the Diels–Alder reaction has emerged as the most versatile tool in organic synthesis and its robustness proved with a large and heterogeneous variety of solvents, catalysts, and reaction conditions, which often lead to significant accelerations and selectivity changes.¹

For more than a decade, cycloaddition reactions have been a dominant research topic in our laboratories,² although our interest has increasingly moved forward and upward to the research of cleaner methodologies. Thus, both Diels–Alder and Michael reactions have been studied under microwave activation,^{3,4} often catalysed by clays and other non-pollutant minerals under solventless conditions.^{3–5} Likewise, we have now turned our attention to room-temperature ionic liquids (RTILs), which have experienced an impressive development in a record time.⁶

In recent years, RTILs have emerged as exciting reaction media for a wide variety of organic processes.⁶

There is a certain controversy on the non-innocent nature of ionic liquids, particularly those containing $AlCl_4$ and PF_6 anions.⁷ Thus, it has been reported that, under certain

conditions, hydrolysis of the PF₆ anion produces hydrogen fluoride.⁸ Moreover, under basic conditions some RTILs may likely form carbenes and, in high-energy conditions such as those provided by thermal or sonochemical activation, haloalkanes can also be generated.⁹ Despite the above considerations, and when compared with most organic solvents, RTILs are certainly greener.^{6h,10,11} This is due to some key properties: (a) their negligible vapour pressure, and (b) the usual potentiality of recovering and recycling.

Although some ionic liquids (ILs) have already been utilised in cycloaddition chemistry,¹² most studies simply suggest that they constitute a suitable medium in terms of reaction rates and practical work-up. Herein, we describe the effect of a series of Lewis acids on Diels–Alder reactions performed in a typical alkyl imidazolium ionic liquid. In a subsequent paper, we also report on the synergic effect of that ionic liquid with mineral supports and, especially, when activated by microwave irradiation.

2. Results and discussion

For this study, 1-hexyl-3-methylimidazolium tetrafluoroborate, [HMI][BF₄], was chosen as a representative ionic liquid. The various reasons for this choice are: (a) it has no Lewis acid character, hence it would not interfere with the catalyst study, (b) it is moisture stable, thus simplifying its handling, (c) it allows simple and quantitative extraction of the products with diethyl ether, and, (d) it is accessible in terms of both ease and cost of preparation. Moreover, it is

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Scheme 1.

synthesised in a simple two-step procedure; the first step being the alkylation of an amine to obtain the halide salt, and the second an anion metathesis.

In previous works, it has been established that not only Lewis acidic ionic liquids,¹³ but also non-Lewis acidic RTILs exert a catalytic effect on Diels-Alder reactions.¹² Even a catalytic amount of an ionic liquid is capable of inducing activation.^{12b} In the light of the results reported, we studied the Diels-Alder reaction between cyclopentadiene (CPD) and several dienophiles encompassing the use of [HMI][BF₄] with the addition of Lewis acid catalysts (Scheme 1).

Table 1. Reaction of CPD and dienophiles in [HMI][BF4] at rt^a

At a first stage of this research, several dienophiles were reacted with cyclopentadiene (CPD) in the ionic liquid, with no catalyst added. The results obtained are summarised in Table 1.

The two ketones tested (exp. 1 and 2) gave moderate results, while among the aldehydes, acrolein reacted similarly (exp. 3), but methacrolein and crotonaldehyde did not react at all (exp. 4 and 5 respectively). Acrylonitrile and methyl acrylate underwent low transformations in one hour (exp. 6 and 7). For N-phenylmaleimide, maleic anhydride and 2-methyl-1,4-benzoquinone (exp. 8, 9 and 11), the results were excellent, for such reactions were completed in 5 min

Exp. ^b	Dienophile	t (min)	Yield (%) ^c	endo:exo ^d	Exp. ^b	Dienophile	t (min)	Yield (%) ^c	endo:exo ^d
1	o I	60	52	85:15	7	OMe	60	16 ^e	79:21
2		60	54	88:12	8	O N—Ph O	5	94	100:0
3	ощ н	120	59	77:23	9		5	90	100:0
4	о Н	120	0	_	10		30	80	97:3 ^f
5	O H	120	0	_	11		5	88	100:0
6	CN	60	17 ^e	66:34	12		30	81	100:0

^a 2.2 mmol of CPD +2.0 mmol of dienophile in 2 mL [HMI][BF₄].

^b Experiment number. All different experiments in this paper are given one number, regardless the Table in which they appear, for the ease of comparison. Results correspond to, at least, duplicate runs.

^c Isolated yield.

^d Determined by ¹H NMR (400 MHz).

^e Not isolated, estimated by ¹H NMR (400 MHz).

Table 2. Reaction of CPD and MVK with catalyst (0.5 mol%) in [HMI][BF4] at rt^a

Exp.	Catalyst (0.5 mol%)	5	min	60 min		
		Conversion (%) ^b	endo:exo ^b	Conversion (%) ^b	endo:exo ^b	
13	Li(OTf)	15	82:18	64	86:14	
14	$Li(NTf_2)$	15	82:18	66	86:14	
15	ZnI ₂	24	89:11	73	91:9	
16	AlCl ₃	24	88:12	68	84:16	
17	BF ₃	15	94:6	68	88:12	
18	HOTf	67	90:10	>99	93:7	
19	HNTf ₂	84	93:7	>99	94:6	
20	$Ce(OTf)_4 \cdot 5H_2O^{14}$	>99	94:6	с	с	
21	Y(OTf) ₃	95	93:7	>99 ^d	95:5	
22	$Sc(OTf)_3$	95	93:7	>99 ^d	95:5	
23	$Sc(NTf_2)_3$	95	94:6	>99 ^d	95:5	
1	None	e	e	52	85:15	

 a 2.2 mmol of CPD+2.0 mmol of MVK+0.5 mol% of catalyst in 2 mL [HMI][BF4].

^b Determined by ¹H NMR (400 MHz) on, at least, two runs.

^c Not measured, reaction was completed in 5 min.

^d Results after 15 min.

^e Not measured.

yielding only the *endo* isomer. Interestingly, methylbenzoquinone reacted with 100% selectivity; this is thought to be provoked by the steric hindrance caused on one side by the methyl group. 1,4-Benzoquinone produced the *endo*monoadduct in high yield (exp. 10). 1,4-Naphthoquinone (exp. 12) gave also very good results, with a reaction time of thirty minutes and with the *endo* isomer as the sole product. For 1,2-naphthoquinone (not shown in the table), the reaction medium showed decomposition and was not further analysed.

It is well known that Diels–Alder reactions can be accelerated by Lewis acids.¹ For this reason, and at this point, we decided to study the combined influence of both an ionic liquid and a Lewis acid on these cycloadditions. The reaction between cyclopentadiene and methyl vinyl ketone (MVK) was chosen as a model due, on one hand, to the moderate yield and selectivity shown in the reaction with the ionic liquid, so any potential improvement could easily be observed (Table 1, exp. 1). On the other hand, for comparative purposes, as Lewis acid-catalysed reactions are widely referenced in the literature. This reaction was tested

with several Lewis acid catalysts, loaded initially in a 0.5 mol% ratio, in [HMI][BF₄] (Table 2).

The reactions proceeded smoothly at room temperature and were monitored until completion or 60 min, whichever first, by ¹H NMR. All the tested catalysts accelerated the reaction, remarkably with no loss of stereoselection. The ability of Lewis acids to increase both the reaction rate and the selectivity of the cycloaddition is known.¹⁵ It can be seen that the cerium trifluoromethanesulphonate-catalysed reaction was quantitative in 5 min (exp. 20). endo:exo Selectivity was very good for this experiment as well (94:6, endo:exo). Also with the scandium or yttrium salts tested, reactions came to completion in a short time (15 min) with high stereoselection (exp. 21-23). Cerium, scandium and yttrium triflates (or trifluoromethanesulphonates) are strong Lewis acids known to be quite effective catalysts in the cycloadditions of cyclopentadiene with acyclic aldehydes, ketones, quinones and cycloalkenones.^{1,16} These compounds are expected to act as strong Lewis acids because of their hard character and the electron-withdrawing triflate group.

Table 3. Reaction of CPD and MVK with catalyst (0.2 mol%) in [HMI][BF4] at rt^a

Exp.	Catalyst (0.2 mol%)		60 min	180 min		
		Conversion (%) ^b	endo:exo ^b	Conversion (%) ^b	endo:exo ^b	
24	Li(OTf)	60 (64)	84:16	93	86:14	
25	$Li(NTf_2)$	58 (66)	87:13	85	86:14	
26	ZnI ₂	68 (73)	86:14	93	87:13	
27	AlCl ₃	67 (68)	88:12	89	90:10	
28	BF ₃	68 (68)	84:16	84	84:16	
29	HOTf	61 (>99)	82:18	87	85:15	
30	HNTf ₂	72 (>99)	86:14	87	88:12	
31	$Ce(OTf)_4 \cdot 5H_2O^{14}$	$> 99 (>99^{\circ})$	94:6	d	d	
32	Y(OTf) ₃	$90 (>99^{e})$	93:7	f	f	
33	$Sc(OTf)_3$	$96 (>99^{e})$	92:8	f	f	
34	$Sc(NTf_2)_3$	$95 (>99^{e})$	93:7	f	f	
1	None	52	85:15	78	83:17	

^a 2.2 mmol of CPD +2.0 mmol of MVK +0.2 mol% of catalyst in 2 mL [HMI][BF₄].

^b Determined by ¹H NMR (400 MHz) on, at least, two runs; results with 0.5 mol% shown into brackets for comparison.

^c Result after 5 min.

^d Not measured, reaction was completed in 5 min.

^e Results after 15 min.

^f Not measured, reaction was completed in 15 min.

Entry	Catalyst	Load (mol%)	t (min)	Isolated yield %	endo:exo ^a	
a	Ce(OTf) ₄ ·5H ₂ O	0.5	5	98	94:6	
b	$Ce(OTf)_4 \cdot 5H_2O$	0.2	60	97	94:6	
с	Y(OTf) ₃	0.5	15	96	95:5	
d	Y(OTf) ₃	0.2	60	85	93:7	
e	$Sc(OTf)_3$	0.5	15	98	95:5	
f	$Sc(OTf)_3$	0.2	60	92	92:8	
g	$Sc(NTf_2)_3$	0.5	15	98	95:5	
ĥ	$Sc(NTf_2)_3$	0.2	60	90	93:7	

Table 4. Isolated yields after work up of reactions of CPD and MVK

^a Determined by ¹H NMR on the isolated product.

On the other hand, it took one hour for complete transformation when either triflic or triflamic acids were used, resulting also in a good *endo:exo* ratio, (exp. 18 and 19). The rest of the Lewis acids tested (exp. 13–17), showed catalytic activity, yet not as good as the ones previously described. Enhancement of *endo:exo* ratio was achieved in some cases, compared with exp. 1. It is known that traditional Lewis acids are sensitive to water, and therefore they turn inactive when used in lower quantity than the residual water content of the reaction medium. This could account for the poor catalytic activity shown in some experiments.

At this stage, we turned our attention to the catalyst load. Although a catalyst loading of 0.5 mol% is quite low, and typical Sc(OTf)₃ loadings range from 5 to 15 mol%, we checked the activity of a 0.2 mol% load (Table 3). Eventually, this set of experiments would also allow us to distinguish among some of the catalysts that showed similar results in the previous experiments. Results obtained with 0.5 mol% load after 60 min have been included into brackets for comparative purposes.

At first glance, it is clear that the presence of the catalyst in either load does affect the reaction rates (compare with the run without catalyst, experiment 1). Although both loads accelerate the processes, this acceleration is higher with the 0.5 mol% load. For the rest of the catalysts studied the *endo:exo* ratio values are within the same experimental range.

Again, cerium triflate was the most active catalyst (exp. 31), with a reaction time of 60 min along with a good *endo:exo* ratio of 94:6. Scandium-based catalysts were next in line, with conversions over 95% in one hour, accompanied by *endo:exo* selectivities around 93:7 (exp. 33 and 34); yttrium

triflate was a bit less active a catalyst, with 90% conversion and 93:7 *endo:exo* outcome in one hour (exp. 32).

It can be noted that little difference was found when comparing the two loads tested of lithium, zinc, aluminium and boron catalysts, which reinforce the idea of a possible partial deactivation due to residual water content in the ionic liquid. However since they showed some catalytic activation, compared with exp. 1, this fact suggests that some remain of the catalyst is still active in the medium.

Isolation of cycloadducts was accomplished for the best results for the two sets of reactions. Work-up consisted of the extraction of the products from the reaction media with diethyl ether and further purification by flash chromatography. This protocol afforded pure cycloadducts in excellent yields, as shown in Table 4. Isolation of the final products, following this simple procedure, proved to be quantitative for both stereoisomers.

At this point, the activity of the best reaction media found was tested against a choice of dienophiles, to broaden the scope of the protocol. As for the reaction media, two of them were selected: scandium triflate or cerium triflate, loaded in 0.5 mol% in the ionic liquid. The chosen dienophiles were representatives of three families of compounds. Hence, acrolein, acrylonitrile, and methyl acrylate were tested. Furthermore, we decided to use the two aldehydes that did not react at all in the ionic liquid; that is, methacrolein and crotonaldehyde (experiments 4 and 5, shown in Table 1). Reactions of N-phenylmaleimide, maleic anhydride and 2-methyl-1,4-benzoquinone were not tested with catalysts, since they gave excellent results with the ionic liquid only as solvent. Table 5 summarises the experiments undertook (methyl vinyl ketone run showed as reference). These reactions were also monitored by ¹H NMR until completion or 60 min, and then processed.

Table 5. Reaction of CPD and dienophile with catalyst (0.5 mol%) in [HMI][BF4] at rt^a

Dienophile	Exp. ^b	Ce(OTf) ₄ ·5H ₂ O		Exp. ^b	Sc(OTf) ₃			
		Time	Yield ^c	endo:exo ^d		Time	Yield ^c	endo:exo ^d
Methyl vinyl ketone	20	5 min	98	94:6	22	15 min	98	95:5
Acrolein	35	5 min	96	82:18	40	15 min	95	85:15
Acrylonitrile	36	24 h	40	63:37	41	24 h	50	67:33
Methyl acrylate	37	24 h	52	84:16	42	24 h	56	84:16
Methacrolein	38	5 min	98	87:13	43	30 min	97	87:13
Crotonaldehyde	39	30 min	60	79:21	44	30 min	72	79:21

^a 2.2 mmol of CPD+2.0 mmol of dienophile+0.5 mol% of catalyst in 2 mL [HMI][BF₄].

^b Experiment number.

^c Isolated yield (%).

^d endo:exo Ratio determined by ¹H NMR (400 MHz) on the isolated product.

Table 6. Best results reported for the reaction of CPD and MVK in different conditions

Entry	Conditions	Time	Temperature	Yield (%)	endo:exo	Reference
a	Sc(OTf) ₃ 10 mol%/CH ₂ Cl ₂	12 h	0 °C	96	89:11	16c,d
b	InCl ₃ (20 mol%)/H ₂ O	4 h	rt	84	87:13	17
c	CH ₃ ReO ₃ (1%)/CHCl ₃	1 h	rt	95	>99:1	18
d	Sc(OSO ₂ C ₄ F ₉) ₃ (5 mol%) /MS5 Å/CH ₂ Cl ₂	3 h	- 20 °C	100 ^a	98:2	19

^a Determined by GC analysis.

The most outstanding results in these experiments are those of methacrolein and crotonaldehyde; these substrates, which gave no reaction in the absence of catalyst (Table 1), are dramatically activated by either catalytic system tested. Scandium or cerium triflates gave excellent results for methyl vinyl ketone and acrolein as well. It should be noted that even acrylonitrile and methyl acrylate are catalysed under these conditions.

For the sake of comparison, Table 6 shows some of the best results published for the reaction of CPD and MVK in conditions similar to those tested in this research.

Finally, the recyclability of the medium was examined. In processes with no Lewis acid catalyst added, the ionic liquid [HMI][BF₄] was recovered and reused up to six times without loss of activity nor selectivity, after extraction with diethyl ether and drying under vacuum.

The catalytic systems using Ce(OTf)₄·5H₂O or Sc(OTf)₃ were also recycled and reused, extracting the products with petroleum ether. No drop of activity was observed until five runs for reactions with cerium triflate (72% transformation and 90:10 *endo/exo* selectivity after 5 min reaction in the fifth cycle), and ten runs for reactions with scandium triflate (89% transformation and 93:7 *endo/exo* selectivity after 15 min reaction in the tenth cycle), this meaning that catalyst remained within the IL after simple work-up.

3. Conclusions

In summary, several catalysts have been successfully used in the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone in an ionic liquid. We have shown that, among several Lewis-acid catalysts, those based on Ce^{IV} , Sc^{III} or Y^{III} salts are extraordinarily active when used in [HMI] [BF₄] in Diels–Alder reactions. In fact, cerium triflate performs better than any other catalyst tested, although scandium triflate is usually considered the most active in the literature.

The scope of this procedure has been extended to a wide variety of dienophiles. The combination of 1-hexyl-3methylimidazolium tetrafluoroborate with cerium triflate, as well as with scandium triflate, gave excellent results not only in terms of reaction rates, but also in enhanced stereoselection. This protocol competes favourably with others reported previously.

It is possible to recycle IL medium up to six runs without any loss of activity. Catalytic systems consisting on $Sc(OTf)_3$ plus [HMI][BF₄] and $Ce(OTf)_4 \cdot 5H_2O$ plus [HMI][BF₄] can also be recycled and reutilised after extraction of the products for at least five times without loss of activity and *endolexo* selectivity.

Further investigation on the application of this novel methodology along with non-conventional activation technologies is currently under way in our lab. A series of preliminary results obtained with other techniques are to be presented in a future paper.

4. Experimental

4.1. General

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures. All chemicals were used as purchased from Aldrich or Acros except cyclopentadiene that was cracked from dicyclopentadiene (Aldrich) and then freshly distilled before use. Melting points were determined on Gallenkamp and/or Electrothermal apparatus. Analytical TLC were performed on precoated Merck 60 GF₂₅₄ silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. Flash chromatography²⁰ was performed on Merck 60 silica gel (230-400 mesh). IR spectra were recorded in the range 4000–600 cm^{-1} on an FT-IR MIDAC spectrophotometer. Solid samples were recorded on KBr (Merck) pellets and liquid samples as a film between NaCl plates (Spectra-Tech).¹H and ¹³C NMR spectra were recorded on a Bruker AM400 instrument at 400 and 100 MHz, respectively in CDCl₃. TMS was used as the internal standard ($\delta = 0.00$ ppm). Ionic chromatographic analysis were recorded on an Ion Chromatograph DIONEX, DX-120 with suppressor column ASRS-ULTRA (4 mm), equipped with an AS-HC anion analytical column (4 mm) and an AG-9-HC guard column (4 mm) and performed by CTAEX Laboratories, Badajoz (Spain) following a previously described procedure.²¹

4.1.1. Preparation of 1-hexyl-3-methylimidazolium chloride [HMI][Cl]: the Menschutkin reaction.²² The amine, 1-methylimidazol, (1 equiv) is mixed with 1-chlorohexane (1.2 equiv) and the homogeneous phase is heated to 80 °C under stirring for 2 days. After completion, the excess of haloalkane is decanted and the halide salt obtained is washed thoroughly with dry diethyl ether. The solvent is decanted and the liquid salt then dried under vacuum. The product is a yellowish liquid of a yield of ca. 80%. IR (liquid film) ν_{max} 3139, 2931, 2859, 1634, 1571, 1465, 1168 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 10.85 (s, 1H, H-2), 7.49 (s, 1H, H-4), 7.35 (s, 1H, H-5), 4.32 (t, 2H,

 $J=8.0 \text{ Hz}, \text{ N-CH}_2\text{)}, 4.14 \text{ (s, 3H, N-CH}_3\text{)}, 1.91 \text{ (m, 2H, CH}_2\text{)}, 1.31 \text{ (m, 6H, CH}_2\text{)}, 0.88 \text{ (m, 3H, CH}_3\text{)}. {}^{13}\text{C} \text{ NMR} \text{ (CDCI}_3\text{, 100 MHz) } \delta \text{ 137.11 (C2), 123.43 (C4), 121.61 (C5), 49.52 (C1'), 36.06 (N-CH}_3\text{)}, 30.60 (C2'), 29.78 (C3'), 25.38 (C4'), 21.86 (C5'), 13.46 (C6').$

4.1.2. Preparation of 1-hexvl-3-methylimidazolium tetrafluoroborate [HMI][BF₄]: the Finkelstein reaction.²² A solution of the [HMI][Cl] (1 equiv), NaBF₄ (1 equiv) and water (14 equiv) is stirred at room temperature for 48 h. The product is extracted into CH₂Cl₂ and the organic phase is then washed with successive small portions of deionised water, until no chloride ions are detected by testing with AgNO₃. The collected organic layer is dried over MgSO₄, filtered and CH₂Cl₂ is then removed on a rotary evaporator. The ionic liquid is dried by heating under vacuum for 48 h. The product is obtained in 79% yield. The water content in the ionic liquid was determined using a Karl-Fischer titrator (Aquapal(R) III, CSC Scientific Co. Inc.) and showed a value of 1000 ppm for the melt used.²³ Purity was examined using ion chromatography to check for residual chloride ion impurities.²¹ The residual chloride concentration was 217 ppm. IR (liquid film) ν_{max} 3161, 3121, 2958, 2933, 2862, 1573, 1467, 1170, 1059 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 8.74 (s, 1H, H-2), 7.42 (s, 1H, H-4), 7.38 (s, 1H, H-5), 4.17 (t, 2H, J=7.6 Hz, N-CH₂), 3.94 (s, 3H, N–CH₃), 1.86 (m, 2H, CH₂), 1.32 (m, 6H, CH₂), 0.86 (m, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz) δ 135.84 (C2), 123.62 (C4), 122.13 (C5), 49.80 (C1'), 35.93 (N-CH₃), 30.81 (C2'), 29.78 (C3'), 25.56 (C4'), 22.14 (C5'), 13.70 (C6[']).

4.2. Typical procedure for cycloaddition reactions

A typical experimental procedure. In a flat-bottomed vial of 25 mL capacity, 2.2 mmol of freshly distilled cyclopentadiene and 2.0 mmol of dienophile were added to a mixture of 2 mL of [HMI][BF₄] and, if applicable, 0.2 or 0.5 mol% catalyst. The reaction is stirred for a given reaction time. All processes were monitored by ¹H NMR and/or TLC. After reported reaction time, the crude was extracted with diethyl ether (5×4 mL). The ethereal solution was reduced to half volume in a rotavapor and then filtered through a 3 cm-silica gel bed, to avoid contamination of the ionic liquid. The final adducts were isolated by evaporation of the crude mixture and, if necessary, purified by chromatography or crystallization.

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