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Effect of Lewis acids on the Diels–Alder reaction in ionic liquids with different activation modes

Ana Vidiš[a], Ernst Küsters[b], Gottfried Sedelmeier[b] and Paul J. Dyson[a]*

The Diels–Alder reaction has been examined in room temperature ionic liquids with high molar concentrations of Lewis acids under various conditions. A molar ratio of 10% catalyst gave a large increase in the selectivity and the yield of the reaction. The effect of catalysts on reaction rates was also examined under 100 MPa of pressure which leads to modest improvements in reaction rates. Ultrasound and microwave dielectric heating were also shown to improve the rate and, to a minor extent, selectivity of the examined reactions. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: ionic liquids; Diels–Alder reaction; Lewis acid catalysts; high pressure; infrared spectroscopy; ultrasound; microwave dielectric heating

INTRODUCTION

The Diels–Alder reaction is one of the most important carbon–carbon bond forming reactions used to prepare cyclic structures.[1] It usually affords a mixture of isomers and the selectivity, and reaction rate, are highly solvent dependent. Ionic liquids represent an interesting class of solvent in which to conduct Diels–Alder reactions, since they are polar and have low vapour pressure, potentially leading to high selectivities with the possible added advantage of facile product separation. A number of Diels–Alder reactions have been conducted in ionic liquids,[2–9] and from these studies it would appear that the selectivity of Diels–Alder reactions is dependent on the hydrogen bond donor capacity of the ionic liquids that can stabilize the transition state. Moreover, bulky cations lead to lower selectivities and strong electrostatic associations between the ionic liquid ions results in a lower interaction between the ionic liquid and the transition state. It would appear that the design of ionic liquids with cations that contain specific groups to facilitate alignment of the substrate to improve selectivities may not lead to vastly improved systems. A far simpler and more effective approach might be to incorporate Lewis acid anions as a component of the ionic liquid, which has been shown in some instances to lead to large improvements in selectivity.[5] The ability of Lewis acids to increase *both* the reaction rate *and* the selectivity of cycloadditions contrasts with other catalysed reactions, in which an increase in the reaction rate is accompanied by a decrease in selectivity, according to the reactivity–selectivity principal.[10,11]

The cycloaddition of cyclopentadiene to methyl acrylate in chloroaluminate ionic liquids takes place with very high rates and selectivities, although the ionic liquids cannot be reused.[4] Chloroaluminate ionic liquids have also been shown to promote selectivities towards different products depending on the molar fraction of aluminium(III) chloride employed.[5] It has also been reported that the addition of Lewis acids such as $Sc(CF_3SO_3)_3$, to an ionic liquid, can dramatically increase the selectivity and the rate of Diels–Alder reactions.[12] Choline dizincpentachloride type ionic liquids also show promise, but their high viscosities, typically greater than 1000 cP, necessitate the use of either a cosolvent or mechanical stirring.[6] Recyclable organotungsten Lewis acids have been used to assist the Diels–Alder reaction in ionic liquids and moderate selectivities and good yields were obtained.[13] A series of Lewis acids (0.5 mol%) have been used in combination with ionic liquids to investigate the reaction of cyclopentadiene and methyl vinyl ketone and good selectivities and yields were observed.[14] Overall, however, in the majority of cases the combined influence of ionic liquids and Lewis acids offer modest improvements in selectivities and yields on the Diels–Alder reaction.

High pressure can influence the Diels–Alder reaction by accelerating the reaction, modifying regioselectivity and diastereoselectivity, and by causing changes to the chemical equilibrium.[1] The pressure effect on cycloaddition reactions has been widely explored in organic solvents,[15,16] aqueous solutions[17] and fluorous media.[18] The pressure effect in the cycloaddition of 2,6-dimethylbenzoquinone to isoprene and hexachlorocyclopentadiene in ionic liquids was shown to have the same effect as that observed in organic solvents.[19] The influence of ionic liquids on the Diels–Alder reaction under pressure was studied in other reactions and again ionic liquids were shown to have a similar influence on selectivities and rates to ethanol, although improvements in the rates and the

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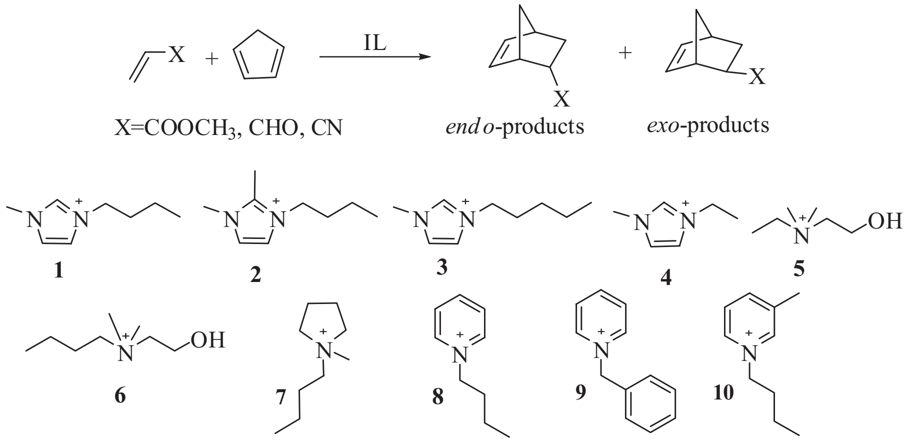
* Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne, (EPFL), CH–1015 Lausanne, Switzerland.
E-mail: paul.dyson@epfl.ch

a A. Vidiš, P. J. Dyson
Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne, (EPFL), CH–1015 Lausanne, Switzerland

b E. Küsters, G. Sedelmeier
Novartis Pharma AG, WSJ-145.6.54, CH-4002 Basel, Switzerland



Scheme 1. Diels–Alder cycloadditions studied and ionic liquid cation structures employed; in all cases as the $[Tf_2N]^-$ salts

selectivities were observed when the reaction was conducted under pressure in ionic liquids containing the Lewis acid catalyst ZnI_2 (0.5 mol%).[20]

Since Lewis acids are highly soluble in ionic liquids,[21] we decided to investigate the influence of high concentrations of Lewis acids in $[Tf_2N]$-based ionic liquids on the Diels–Alder reaction, also exploring the influence of high pressure, ultrasound and dielectric heating.

RESULTS AND DISCUSSION

The reaction of cyclopentadiene with three different dienophiles (Scheme 1) was investigated in $[bmim][Tf_2N]$ **1** using different molar ratios (0.2–20%) of the Lewis acid catalysts ZnI_2, $AlCl_3$, $InCl_3$ or $Sc(OTf)_3$.

Reactions were performed at 25°C for either 2 or 4 h, 2 h for acrolein (the more reactive dienophile) and 4 h for the less activated methyl acrylate and acrylonitrile dienophiles. All the reactants were added at 0°C to suppress polymerization of the substrates that can occur at room temperature. The results from these studies are listed in Table 1 and further details are provided in the Experimental Section.

High molar ratios of the catalyst result in increased selectivity of the reaction. The optimal amount of the catalyst is 10% molar ratio; exceeding 15% molar ratio of the catalyst results in a reduction of the yield due to polymerization of the starting materials, although the selectivity is improved. At 20% molar ratio of catalyst the yield and *endo:exo* ratio decreases and the extraction of the products becomes difficult. It is worth noting that $Sc(OTf)_3$ and ZnI_2 do not completely dissolve in **1**$[Tf_2N]$ at high loadings, ca. >15% ratio. The activity of the catalysts follow the trend: $ZnI_2 < AlCl_3 < InCl_3 < Sc(OTf)_3$. Higher selectivites are observed in the ionic liquids compared to EtOH and water under comparable conditions. Due to the lower reactivity of acrylonitrile, as expected, the improvement in the selectivity was only modest. Therefore, for further experiments only the more active dienophiles methyl acrylate and acrolein were used such that spectroscopic data could be acquired within reasonable time frames.

Neat chloroaluminate and chloroindate ionic liquids were also studied (i.e. in the absence of Tf_2N^-). As mentioned in the Introduction the former have been evaluated previously,[5] and chloroindate ionic liquids have recently been shown to offer certain advantages over chloroaluminates in Friedel–Craft acylation reactions.[22] Accordingly, chloroindate(III) ionic liquids $[X(InCl_3) = 0.55$ and $0.67]$ were prepared by mixing the appropriate amounts of the organic chloride salt with anhydrous indium(III) chloride at 80°C. The amount of chloroindate(III) melt used was calculated so that the molar excess of $InCl_3$ compared to [bmim]Cl was 5 or 10 mol% with the respect to the dienophile, hereafter denoted as $\xi = 5$ or 10. The ensuing results (see Table 2) confirm that $InCl_3$-based ionic liquids represent a good alternative to $AlCl_3$ systems, since superior yields and selectivities were observed. The advantage of chloroindate ionic liquids over chloroaluminate ionic liquids is probably related to its hydrolytic stability and reduced oxophylicity, as noted previously.[22]

The effect of pressure on the Diels–Alder reaction between cyclopentadiene and methyl acrylate in the presence of the Lewis acid catalysts (10 mol%) was also investigated (Table 3). Only methyl acrylate was chosen for high pressure studies as this substrate reacts at an ideal rate for *in situ* spectroscopic analysis. Reactions were followed by high pressure IR spectroscopy and the reaction profiles were evaluated using Eqn (1) by solving the relevant second-order rate law differential analytically.[23] Only an overall rate could be calculated from the spectroscopic data in order to establish the influence of the Lewis acid catalyst on the reaction rate under pressure.

$$-\frac{\mathrm{d}[A]}{\mathrm{d}t} = [A]_t\,[B]_t\,k \qquad (1)$$

$[A]_t$: dienophile concentration; $[B]_t$: cyclopentadiene concentration; k: rate constant for the product mixture

Under 100 MPa pressure reaction rates were enhanced only modestly in ionic liquids containing 10% mol ratio of Lewis acid catalyst, with the largest pressure induced acceleration obtained in the presence of $InCl_3$. Again, compared to ethanol, superior selectivities were observed in ionic liquids, although they are either the same or only marginally improved compared to reactions conducted at ambient pressure.

Although the use of ultrasound on the Diels–Alder reaction conducted in organic solvents has only a limited influence,[24,25] ultrasonic activation of cycloaddition reactions has been investigated in one ionic liquid and an improvement in the yield and selectivity was observed.[26] The reaction between cyclopentadiene and acrolein was therefore conducted in ionic

Table 1. Effect of Lewis acid catalysts on the selectivities and yields for the cycloaddition of cyclopentadiene to dienophiles in **1**[Tf_2N], ethanol and water at 25°C

		Solvent	1[Tf_2N]-ZnI_2		1[Tf_2N]-$AlCl_3$		1[Tf_2N]-$InCl_3$		1[Tf_2N]-$Sc(OTf)_3$		EtOH-$InCl_3$		H_2OInCl_3	
Substrate	Time (h)	Molar ratio (%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)
Acrolein	8	0	4.4	80	4.4	80	4.4	80	4.4	80	5.5	85	3.3	83
Acrolein	2	0.2	4.9	92	5.0	90	5.1	91	5.2	90	—	—	—	—
Acrolein	2	0.5	5.1	94	5.2	92	5.4	92	5.6	95	—	—	—	—
Acrolein	2	1	5.6	91	5.7	93	5.8	94	6.2	94	—	—	—	—
Acrolein	2	2	6.3	93	7.3	91	8.1	96	9.3	95	—	—	—	—
Acrolein	2	5	7.7	94	9.0	93	12.2	95	15.1	94	—	—	—	—
Acrolein	2	10	9.9	95	13.2	96	16.0	97	18.8	96	8.8	96	8.5	95
Acrolein	2	15	12.5	73	13.8	71	17.4	72	19.1	70	—	—	—	—
Acrolein	2	20	8.6	50	10.2	52	12.3	51	13.5	54	12.9	80	9.9 (10.1)[a]	81
Methyl acrylate	24	0	4.2	97	4.2	97	4.2	97	4.2	97	5.8	96	3.5	96
Methyl acrylate	4	0.2	4.8	95	4.9	93	5.0	92	5.2	96	—	—	—	—
Methyl acrylate	4	0.5	5.0	92	5.1	95	5.2	94	5.4	95	—	—	—	—
Methyl acrylate	4	1	5.4	94	5.5	93	5.6	93	5.9	94	—	—	—	—
Methyl acrylate	4	2	5.9	95	6.8	96	7.6	94	8.7	95	—	—	—	—
Methyl acrylate	4	5	7.1	93	8.2	95	11.4	96	14.3	95	—	—	—	—
Methyl acrylate	4	10	9.1	98	12.5	97	15.2	98	18.1	95	8.2	93	7.8	94
Methyl acrylate	4	15	12.4	80	14.5	83	17.2	81	19.7	80	—	—	—	—
Methyl acrylate	4	20	10.1	71	12.3	70	13.3	72	14.3	74	11.6	82	9.5 (9.0)[a]	80
Acrylonitrile	24	0	1.5	97	1.5	96	1.5	97	1.5	98	—	—	—	—
Acrylonitrile	4	0.2	1.6	90	1.6	91	1.6	92	1.7	93	—	—	—	—
Acrylonitrile	4	0.5	1.7	93	1.7	92	1.7	94	1.8	95	—	—	—	—
Acrylonitrile	4	1	1.8	92	1.8	94	1.8	93	1.9	95	—	—	—	—
Acrylonitrile	4	2	1.8	93	1.9	93	1.9	94	2.0	94	—	—	—	—
Acrylonitrile	4	5	2.0	95	2.0	94	2.0	95	2.1	96	—	—	—	—
Acrylonitrile	4	10	2.1	98	2.1	97	2.2	96	2.3	98	2.2	97	2.1	96
Acrylonitrile	4	15	2.2	91	2.2	93	2.3	92	2.4	91	2.3	90	2.2	93
Acrylonitrile	4	20	2.3	84	2.2	83	2.0	83	2.1	85	—	—	—	—

Table 2. Effects of $InCl_3$- and $AlCl_3$-based ionic liquids on the cycloaddition of cyclopentadiene and two dienophiles: MCl_3-[bmim]Cl [$X(MCl_3) = 0.55$ or 0.65] ionic liquid, $\xi = 10$ of MCl_3 (in parenthesis $\xi = 5$ of MCl_3), (M = In or Al). Reaction time, 4 h for methyl acrylate and 2 h for acrolein, 25°C

	Methyl acrylate		Acrolein	
(%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)
$InCl_3$ 55	9.0 (8.8)	98	8.7 (8.5)	95
$InCl_3$ 65	9.7 (9.1)	97	9.0 (8.7)	94
$AlCl_3$ 55	7.7	97	7.3	94
$AlCl_3$ 65	10.1	40	9.7	35

Table 3. Rate constants and rate constant ratios for the reaction of cyclopentadiene with methyl acrylate in [bmim][Tf_2N] containing 10% molar ratio Lewis acid catalyst at 0.1 and 100 MPa. Temperature = 5°C, time = 4 h[a]

Solvent	**1**[Tf_2N][b]	EtOH-$InCl_3$	**1**[Tf_2N]-ZnI_2	**1**[Tf_2N]-$AlCl_3$	**1**[Tf_2N]-Sc(Otf)$_3$	**1**[Tf_2N]-$InCl_3$
p (MPa)	$k^a \times 10^4$	$k^a \times 10^4$	$k^a \times 10^4$	$k^a \times 10^4$	$k^a \times 10^4$	$k^a \times 10^4$
0.1	0.169	2.9	3.0	3.1	4.9	5.5
100	0.413	7.1	7.8	8.4	13.7	16.0
$k_{100/0.1}$	2.4	2.4	2.6	2.7	2.8	2.9
endo:exo 0.1/100 MPa	4.2:4.5	8.2:8.4	9.1:9.2	12.5:12.7	18.1:18.2	15.2:15.3

[a] In (M^{-1} sec^{-1}) and the standard deviation is at the 95% confident level.
[b] Without Lewis acid catalyst.

liquids in the presence of ultrasound, with [Tf_2N]-based systems because the anion is not decomposed by sonication.[26] Sonication promotes the formation, growth and implosive collapse of bubbles in a liquid; the rapid collapse of such bubbles results in the formation of hot spots which can influence the reaction. Ultrasound results in a slight enhancement in the selectivity of the reaction and a significant increase in yield (Table 4). The reaction was stopped after 4 h and the yields for the silent reactions are typically 75–85%, while the reactions employing ultrasound exceed 90%. The observed selectivities follow the same trends as those obtained under normal (silent) conditions, which implies that although the ionic liquids are unlikely to enter the cavity (because of their low vapour pressure) they still influence the selectivity of the reaction.

It was possible to obtain near quantitative yields under sonicated conditions using high concentrations of Lewis acid

Table 4. Influence of ionic liquids and Lewis acid catalysts (10 mol%) on the yields and *endo:exo* selectivities in the sonicated cycloaddition of cyclopentadiene with acrolein or methyl acrylate in [Tf_2N]$^-$-based ionic liquids. Reactions were monitored at 25°C and stopped after 8 h for methyl acrylate and 4 h for acrolein

Entry	Cation	Dienophile	Ratio (yield %) silent	Ratio (yield %)
1[a]	—	Acrolein	3.4 (78)	3.5 (91)
2	1	Acrolein	4.4 (80)	5.1 (93)
3	2	Acrolein	4.8 (79)	5.4 (90)
4	3	Acrolein	4.4 (83)	5.0 (94)
5	4	Acrolein	4.6 (82)	5.3 (94)
6	5	Acrolein	5.9 (83)	6.6 (93)
7	6	Acrolein	5.5 (84)	6.2 (91)
8	7	Acrolein	5.1 (80)	5.7 (92)
9	8	Acrolein	4.4 (81)	5.0 (92)
10	9	Acrolein	4.3 (79)	4.9 (91)
11	10	Acrolein	4.2 (77)	4.8 (90)
12	1-**ZnI_2**	Acrolein	9.9 (92)	11.2 (99)
13	1-**$AlCl_3$**	Acrolein	13.2 (93)	14.7 (96)

(Continues)

Table 4. (Continued)

Entry	Cation	Dienophile	Ratio (yield %) silent	Ratio (yield %)
14	1-**$InCl_3$**	Acrolein	16.0 (93)	17.1 (99)
15	1-**$Sc(OTf)_3$**	Acrolein	18.8 (90)	19.2 (97)
16[a]	—	Methyl acrylate	3.2 (82)	3.4 (93)
17	1	Methyl acrylate	4.2 (84)	4.6 (95)
18	2	Methyl acrylate	4.4 (83)	4.8 (94)
19	3	Methyl acrylate	4.1 (82)	4.5 (96)
20	4	Methyl acrylate	4.3 (80)	4.7 (97)
21	5	Methyl acrylate	5.5 (83)	6.0 (95)
22	6	Methyl acrylate	5.1 (85)	5.6 (97)
23	7	Methyl acrylate	4.8 (84)	5.2 (96)
24	8	Methyl acrylate	4.1 (84)	4.5 (97)
25	9	Methyl acrylate	4.0 (82)	4.5 (95)
26	10	Methyl acrylate	3.9 (83)	4.4 (97)
27	1-**ZnI_2**	Methyl acrylate	9.1 (94)	10.8 (99)
28	1-**$AlCl_3$**	Methyl acrylate	12.5 (94)	13.8 (96)
29	1-**$InCl_3$**	Methyl acrylate	15.2 (91)	16.8 (97)
30	1-**$Sc(OTf)_3$**	Methyl acrylate	18.1 (90)	20.9 (98)

[a] Neat reaction without solvent.

catalysts (10 mol%) in **1**[Tf_2N]. Improvements in the selectivities were observed in all the Lewis acid catalysed reactions, with an *endo:exo* ratio >20 being achieved (Table 4, entry 30).

Numerous reactions conducted in ionic liquids or in molecular solvents containing ionic liquids under microwave heating have been reported.[27] However, as far as we are aware, Diels–Alder reactions have not been examined in detail,[13,28,29] with the exception of a study focussed on the ionic liquid *N*-hexyl-*N*′-methylimidazolium tetrafluoroborate. Essentially, it was found that under equivalent conditions yields were significantly improved in the absence of any change to the selectivity.[30] The reaction between cyclopentadiene and acrolein was conducted in different ionic liquids with microwave dielectric heating using acrolein as the substrate. The reaction was carried out for 10 min at a fixed temperature of 60°C and for comparison the reactions were monitored under the ambient conditions and at 60°C using conventional heating (Table 5).

From Table 5, it is evident that despite the excellent reaction rates, lower selectivities are observed under microwave irradiation, compared to reactions conducted at room temperature, as observed previously.[30] It has been reported that the reaction course in ionic liquids under microwave irradiation is driven by the effect of efficient microwave dielectric heating of materials and not by the overall temperature of the medium during the process,[30] which is in good agreement with our observations. The reactions were accelerated considerably and the selectivities were improved slightly when compared to reactions using conventional heating methods.

Table 5. Effect of microwave irradiation on the yield and selectivity in the Diels–Alder reaction between cyclopentadiene and acrolein

	Microwave 60°C	Irradiation (10 min)	Conventional 60°C	Heating (25 min)[a]	Ambient RT	Conditions(4 h)
Ionic liquid	*endo:exo*	Yield(%)	*endo:exo*	Yield (%)	*endo:exo*	Yield (%)
1[Tf_2N]	3.7	99	3.4	95	4.4	80
2[Tf_2N]	4	94	3.5	94	4.8	79
3[Tf_2N]	3.6	97	3.8	98	4.3	83
4[Tf_2N]	3.8	96	3.4	93	4.6	82
5[Tf_2N]	5.4	99	4.9	97	5.9	83
6[Tf_2N]	5	98	4.5	92	5.5	84
7[Tf_2N]	4.4	90	4.0	96	5.1	80
8[Tf_2N]	3.7	93	3.2	92	4.4	81
9[Tf_2N]	3.6	97	3.1	98	4.3	79
10[Tf_2N]	3.5	95	3.1	97	4.2	77

[a] Reaction time established by monitoring the reaction *in situ* using ^{1}H NMR spectroscopy.

CONCLUSIONS

Herein, the influence of physical activation modes (high pressure, ultrasound and microwave heating) individually or in combination with chemical activation modes (Lewis acid catalysts), on the Diels–Alder reaction in ionic liquids have been investigated. It has previously been reported that the strength of ion pairing between the ionic liquid cation and anion is important in controlling Diels–Alder reactions.[8] That is, the weaker the ion pairing interaction the stronger the interaction between the ionic liquid anion and substrate, leading to increased selectivities. Our correlations fit very well with data reported by Chiappe and coworkers who demonstrated by ESI-MS the relative ion pairing strengths of a series of ionic liquid cations and anions, and notably that $[Tf_2N]^-$ interacts relatively weakly with ionic liquid cations.[31] Weak anion–cation interactions allow the substrate to interact more intimately with the ionic liquid cation in agreement with the work of Welton and coworkers.[9]

From this study, we were able to show that the relatively high concentrations of Lewis acid catalysts can improve the selectivity and the yield of Diels–Alder reactions conducted in the ionic liquids. High concentrations of $InCl_3$ gave good results, presumably due to its high solubility and stability in the ionic liquid, in agreement with a previous study on alkylation reactions.[22] These results demonstrate that the interaction of the substrate(s) with the Lewis acid catalyst dissolved in ionic liquid is the dominant factor.

High pressure accelerates the catalysed reaction, although only minor improvements in the selectivity were observed. Microwave irradiation accelerates the reaction considerably, although the selectivities are lower then those obtained at room temperature, but still significantly higher than in reactions using conventional heating. These results imply that microwave dielectric heating in ionic liquids does not only include the 'thermal effect' but also 'nonthermal microwave effects'. Ultrasound irradiation leads to an increase in the reaction yields and the selectivities. In the best case, reactions in ionic liquids containing Lewis acids under sonication give selectivities of up to 21:1 under optimized conditions.

EXPERIMENTAL SECTION

Methyl acrylate, acrolein and acrylonitrile were distilled prior to use and cyclopentadiene was obtained by cracking dicyclopentadiene, distilled under reduced pressure, and stored at −70°C. The ionic liquids **1**$[Tf_2N]$,[32,33] **2**$[Tf_2N]$,[33] **3**$[Tf_2N]$,[7] **4**$[Tf_2N]$,[32] **5**$[Tf_2N]$,[7] **6**$[Tf_2N]$,[7] **7**$[Tf_2N]$,[34] **8**$[Tf_2N]$,[35] **9**$[Tf_2N]$,[36] **10**$[Tf_2N]$,[7] (Scheme 1) were prepared according to the literature procedures, analysed by ^1H and ^{13}C NMR spectroscopy, washed four times with water to minimize residual chloride (<0.1%) and dried under high vacuum for 24 h ($H_2O < 0.1\%$) Lewis acids were purchased from Alfa Aesar and stored in glovebox.

Diels–Alder reactions

In a typical reaction, cyclopentadiene (0.16 mL, 1.9 mmol) and dienophile (1.6 mmol) were added to the ionic liquid or organic solvent (2 mL) at 0°C. For catalysed reactions, the ionic liquid was doped with the appropriate Lewis acid catalyst in a glovebox and stirred at 80°C for 2 h until dissolved (>10% mol ratio of ZnI_2, and $Sc(Otf)_3$ did not dissolve completely). Reactions were carried out at 25°C. Alternatively the reactions were carried out in a high pressure IR cell with sapphire windows at 5°C for 2 h with spectra recorded at 2 min intervals.[37] FT-IR spectroscopic data were analysed using TimeBase version 2.0 (Perkin-Elmer). Numerical analyses were carried out with Scientist 2.0 (Micromath).

After reaction, the products were analysed by ^{13}C NMR spectroscopy and GC. NMR spectra were recorded on Bruker DRX 400 MHz spectrometer. GC analyses were carried out on a Varian Chrompack CP-3380 equipped with capillary (25 m × 0.25 mm, using He as carrier gas). Sonicated reactions were performed as described for silent reactions except vials were sonicated in an ultrasonic bath operating at 40 kHz. Reactions were carried at 25°C and were monitored periodically by ^1H and ^{13}C NMR spectroscopy. Microwave reactions were performed as described for the silent reactions in a microwave reactor under the fixed temperature of 60°C and power of 300 W for 10 min. All the samples were closed in special vials equipped with a stirrer and analysed immediately after reaction by ^1H NMR spectroscopy.

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