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Ionic liquids as a recyclable reaction medium for the Baylis–Hillman reaction

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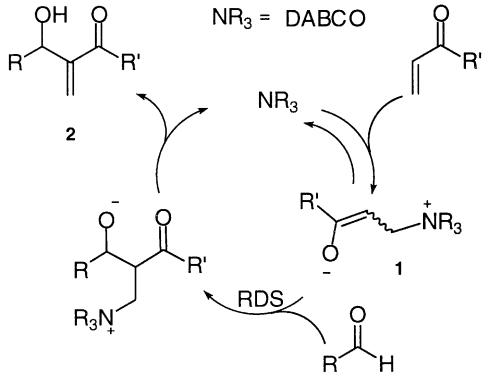
Abstract—The Baylis–Hillman reaction using 1,4-diazabicyclo[2.2.2]octane (DABCO) has been shown to be 33.6 times faster in the recyclable ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) than in acetonitrile. Low yields (14–20%) of adducts are obtained from aliphatic aldehydes and moderate to high yields (39–72%) from aromatic aldehydes. Recycling and reuse of the reaction medium was demonstrated.

1. Introduction

Room temperature ionic liquids, especially those based upon the 1-*n*-alkyl-3-methylimidazolium cation, have attracted growing interest in the last few years.[1] They offer an alternative and ecologically sound medium compared to conventional organic liquids as they are non-volatile, recyclable, non-explosive, thermally robust and can exhibit an electrochemical window of up to 3.0 V. They are excellent solvents for carbonyl compounds, alkyl halides, alcohols and amines and, depending on the anion, they can be immiscible with water and some organic solvents, such as alkanes and dialkyl ethers.[1] Studies on regioselective alkylation of naphthol and on Diels–Alder reactions in ionic liquids have suggested reactivity patterns similar to those observed, respectively, in DMF and in alcoholic solvents.[2] On the other hand, when the ionic solvent was used as a stationary phase for gas chromatography, it appeared to have a dual nature; behaving as a non-polar stationary phase for non-polar analytes but polar for analytes with proton-donor (e.g. phenol, carboxylic acids) or proton-acceptor groups (e.g. amines).[3] These media have also been applied to non-catalytic[1,2a,2c,4] and catalytic reactions[1,2a,5] as well as to selective extraction.[6]

The Baylis–Hillman reaction is a totally atom-efficient reaction, since all the atoms from the reagents are incorporated in the product, thus being an inherently 'green' transformation.[7] It also allows the synthesis of highly functionalized and useful intermediaries in a single step.[7,8] In the proposed mechanism (Scheme 1) the rate determing step corresponds to the reaction between the aldehyde and the enolate **1**.[9a] Further studies also suggested that, at least in the case of using 1,4-diazabicyclo[2.2.2]-octane (DABCO) as a catalyst, the overall condensation is reversible.[9b] Although this reaction has the potential to be synthetically useful, it suffers from a series of drawbacks; the major one being its very slow rate even in the absence of solvent and with high concentrations of catalyst (usually DABCO).[7] A series of efforts have been made to improve the reaction rate: these include high pressure,[10a] microwave[10b] or ultra-sounds,[10c] and it has also been reported,[10d] though unconfirmed by other researchers,[10e] that low temperatures increase the rate of this reaction. The use of catalysts other than DABCO, such as DBU,[10f] $TiCl_4$,[10g] $Ti(OiPr)_4$,[10h] Me_2S,[10h] phosphines,[7,10i] and calcogenide[10j] compounds, or additives (co-catalysts) including $LiClO_4$,[10k] Lewis acids and hydrogen-bond donors such as alcohols[10e] has also been reported to markedly increase the reaction rate. Some examples of chiral catalysts have also been reported.[7c,10l,10m]

Although the Baylis–Hillman reaction is often conducted in



Scheme 1.

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the absence of a solvent, this may not be feasible under certain circumstances, for instance when the reactants are not liquid. In these cases an increase in the reaction rate has been observed both in water and fluorinated solvents. Due to charge separation in the intermediate steps, polar solvents such as THF or acetonitrile favour the reaction.[7,10e] The expectation that the polar nature of the ionic liquid could also promote this transformation, prompted us to study the use of the 1-*n*-butyl-3-methylimidazolium [bmim] cation based ionic liquid medium in the Baylis–Hillman reaction.

2. Results and discussion

In order to compare the reaction rates in ionic liquids with conventional solvents, the condensation between benzaldehyde, and methyl acrylate was carried out in acetonitrile, [bmim][BF_4] and in [bmim][PF_6]. The results are shown in Table 1 and Fig. 1. Using 100 mol% and 20 mol% DABCO in [bmim][PF_6] the reaction was, respectively, 33.6 and 11.1 times faster than in acetonitrile (with 100 mol% DABCO, Table 1, Entries 3 and 4) which has been reported as the optimal conventional solvent.[10e] The ionic liquid [bmim][BF_4] gave also a reaction 14.1 times faster than in acetonitrile (Table 1, Entry 2). In the case of the ionic solvent [bmim][PF_6], the fastest reaction occured at room temperature, with both higher (50°C) or lower temperatures (3°C and −50°C) decreasing the reaction rate (Table 1, Entries 4 to 7). This temperature dependence has also been reported in acetonitrile.[10e] The reason for the reactivity increase in ionic solvents in relation to the conventional organic solvent acetonitrile could be attributed to a shift in the equilibrium, due to stronger stabilization of the zwitterionic intermediate **1**. Similar argument has recently been presented to explain the increase of the reaction rate in the presence of DBU.[10f]

Table 1. Relative rates observed for methyl acrylate/benzaldehyde/DABCO reaction in ionic solvents under various conditions[a]

Entry	Solvent	T /°C	Additive[b]	Relative rate[c]
1	CH_3CN	rt	no	1.0
2	[bmim][BF_4]	rt	no	14.1
3	[bmim][PF_6]	rt	no	11.1[d]
4	[bmim][PF_6]	rt	no	33.6
5	[bmim][PF_6]	50	no	21.0
6	[bmim][PF_6]	3	no	6.3
7	[bmim][PF_6]	−50	no	1.8
8	[bmim][PF_6]	rt	$Me_2O{\cdot}BF_3$	13.1
9	[bmim][PF_6]	rt	$Et_2O{\cdot}BF_3$	13.8
10	[bmim][PF_6]	rt	*t*-BuMeO·BF_3	12.1
11	[bmim][PF_6]	rt	$SnCl_4$	21.4
12	[bmim][PF_6]	rt	$LiClO_4$[e]	52.8
13	[bmim][PF_6]	rt	$Zn(OTf)_2$	18.8
14	[bmim][PF_6]	rt	$Cu(OTf)_2$	14.4
15	[bmim][PF_6]	rt	$Sc(OTf)_3$	16.1
16	[bmim][PF_6]	rt	$La(OTf)_3$	21.8
17	[bmim][PF_6]	rt	$Yb(OTf)_3$	19.5

[a] All reactions were carried out on a 1.0 mmol scale, in 100 μl solvent using a ratio of 1.1:1:1 methyl acrylate/benzaldehyde/DABCO.
[b] 10 mol% of additive were used.
[c] Relative rates were measured by comparison against initial rate constants (t≤300 min).
[d] 20 mol% DABCO were used.
[e] 15 mol% of $LiClO_4$ were used.

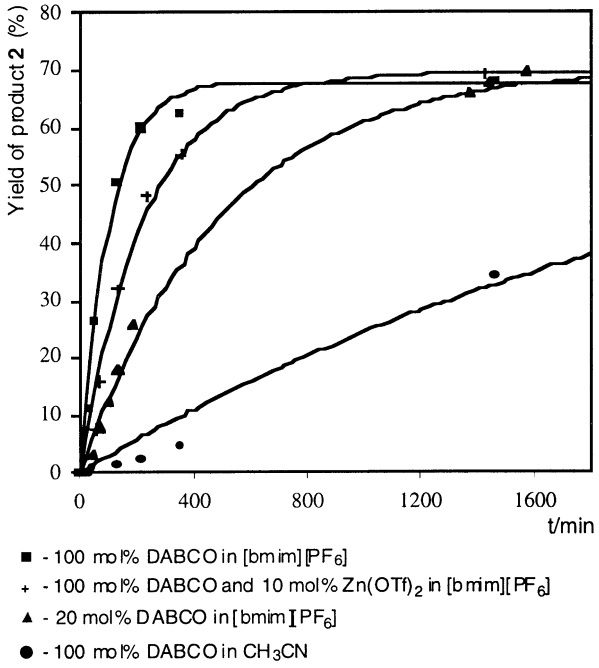


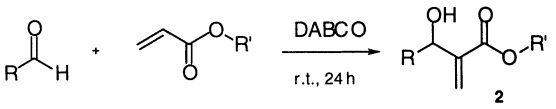
Figure 1. Effect of the ionic liquid [bmim][PF_6] on reaction rates. Reactions were performed on a 1 mmol scale, in 100 μl solvent using a ratio of 1.1:1 methyl acrylate/benzaldehyde at room temperature.

Seeking for further improvement on the reaction rate using DABCO (100 mol%) in [bmim][PF_6], several Lewis acids in 10 mol% to 15 mol% were tested as presented in Fig. 1 and Table 1 (Entries 8 to 17). An increase of the reaction rate by 1.6 times was observed only in the case of $LiClO_4$. Other Lewis acids lead to a general decrease (in the range of 0.4–0.6) which appears to be independent of the hardness and affinity of the Lewis acids. This inhibition may result from a decrease in the amount of DABCO in solution due to the interference of the Lewis acid with the base DABCO.

Not only the reaction rates, but also the isolated yields obtained after 24 h in [bmim][PF_6] in the presence of some selected Lewis acids, were lower than in the absence of additive (Table 2, Entries 5 to 9). Despite promoting an increase of the reaction rate by 1.6 times, $LiClO_4$ was the only one that produced a lower yield (46%) after 24 h (Table 2, Entry 9) which can be due to the reversible nature of the reaction[9b] promoted by the system DABCO/$LiClO_4$.

In order to test the generality of ionic liquids as media for the Baylis–Hillman reaction, several aldehydes were allowed to react with acrylates in [bmim][PF_6], as shown in Table 2. Aliphatic aldehydes gave poor yields (14–20%, Entries 11 to 13), while moderate to high yields were obtained with aromatic aldehydes (39–72%, Entries 5, 10 and 16–19), which is in line with what is usually observed for this reaction.[7] In the case of benzaldehyde, the isolated yield of **2** in [bmim][PF_6] was close to that of the reaction performed in the absence of solvent and considerably higher than in acetonitrile (Table 2, Entries 1, 2 and 5). Using 3,4,5-trimethoxybenzaldehyde, the yield of **2** (61%) in [bmim][PF_6], in the presence of 50 mol% of DABCO for 48 h, is considerably higher than the one reported (5%) in the absence of solvent and in the presence of a large excess of methyl acrylate[11] (Table 2, Entries 20 and 21).

Table 2. Preparative Bayllis-Hillman reactions in ionic media



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Entry	Aldehyde	R′	Solvent	Yield (%)
1	PhCHO	Me	CH_3CN	35
2	PhCHO	Me	Neat	68
3	PhCHO	Me	Neat	69[a]
4	PhCHO	Me	[bmim][BF_4]	57
5	PhCHO	Me	[bmim][PF_6]	65
6	PhCHO	Me	[bmim][PF_6]	57[b]
7	PhCHO	Me	[bmim][PF_6]	61[c]
8	PhCHO	Me	[bmim][PF_6]	33[d]
9	PhCHO	Me	[bmim][PF_6]	46[e]
10	PhCHO	*t*-Bu	[bmim][PF_6]	42
11	$CH_3(CH_2)_2CHO$	Me	[bmim][PF_6]	20
12	$(CH_3)_2CHCHO$	Me	[bmim][PF_6]	14
13	*c*-$C_6H_{11}CHO$	Me	[bmim][PF_6]	20
14	4-ClC_6H_4CHO	Me	[bmim][PF_6]	72
15	4-$MeOC_6H_4CHO$	Me	[bmim][PF_6]	39
16	4-MeC_6H_4CHO	Me	[bmim][PF_6]	61
17	PhCH=CHCHO	Me	[bmim][PF_6]	43
18	2-furaldehyde	Me	[bmim][PF_6]	68
19	3,4,5-$(MeO)_3C_6H_2CHO$	Me	[bmim][PF_6]	72
20	3,4,5-$(MeO)_3C_6H_2CHO$	Me	[bmim][PF_6]	61[f]
21	3,4,5-$(MeO)_3C_6H_2CHO$	Me	[bmim][PF_6]	40[g]

All reactions were carried out on a 5.0 mmol scale, in 500 μl solvent using a ratio of 1.1:1:1 acrylate /aldehyde/DABCO at room temperature for 24 h, except for entries 14–21 which were performed on 1.0 mmol scale, in 100 μl solvent.

[a] Using 11 mol% of DABCO for 3 days.
[b] Using 50 mol% of $Cu(OTf)_2$.
[c] Using 50 mol% of $Zn(OTf)_2$.
[d] Using 50 mol% of $Sc(OTf)_3$.
[e] Using 50 mol% of $LiClO_4$.
[f] Using 50 mol% of DABCO for 48 h.
[g] Using 50 mol% of DABCO for 24 h.

To evaluate the possibility of recycling the ionic liquid used for the reaction, *p*-chlorobenzaldehyde, methyl acrylate and DABCO in [bmim][PF_6] were allowed to react in the ionic solvent for 24 h and then the products were extracted with ethyl ether. A second amount of aldehyde, acrylate and DABCO was added and the process was repeated up to 4 times, as shown in Table 3. The increase in the isolated yields after the first cycle can be attributed to an accumulation in the amount of DABCO, uncompleted extracted with diethyl ether.

In summary, a considerable increase in the reaction rate of the Baylis–Hillman reaction was observed in ionic liquid [bmim][PF_6] when compared to acetonitrile, the reported optimal conventional solvent. In this reaction no significant improvements in reaction yield were observed by further addition of Lewis acids. Nevertheless, the reaction in ionic liquids was shown to perform well with aromatic aldehydes as substrates. The ionic liquid medium [bmim][PF_6] can be recycled after the reaction and reused without reduction of reaction yields.

Table 3. Reuse of the ionic liquid [bmim][PF_6]

Cycle	Yield (%)	Cycle	Yield (%)
1	53	3	59
2	69	4	76

All cycles were carried out on a 2 mmole scale, in 200 μl [bmim][PF_6] using a ratio of 1.1:1:1 methyl acrylate/*p*-chlorobenzaldehyde/DABCO at room temperature for 24 h.

3. Experimental section

3.1. General remarks

All glassware was oven dried and cooled in a desiccator (P_2O_5 desiccant) prior to use. Commercially supplied reagents were used as supplied, except for benzaldehyde, cinnamaldehyde, furfuraldehyde and methyl acrylate, which were distilled and stored under an argon atmosphere and protected from light. Acetonitrile was distilled over calcium hydride powder under argon. 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) were prepared following reported procedures.[6b,12]

^1H and ^{13}C NMR spectra were recorded on a Brüker AMX 400 spectrometer. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethyl silane taken as the reference. Infrared spectra (IR) were recorded on a PerkinElmer FTIR 683 or a Buck Scientific M-500 spectrometers as thinly dispersed films (from dichloromethane).

Gas liquid chromatography (GLC) was carried out on a United Technologies Packard 437A gas chromatograph using N_2 as carrier gas and carbowax 20M over chromosorb 101 as stationary phase. Flash chromatography column was carried out using MN Kieselgel 60M gel (40–63 μm, Art. 815381). All eluents were distilled prior to use. Preparative and analytical thin layer chromatography (TLC) was carried out using MN Kieselgel G/UV_{254} (Art. 816320) glass backed plates and MN Alugram® SIL G/ UV_{254} (Art. 818133), respectively. The plates were visualized using ultraviolet light (254 nm).

3.2. General procedure for the Baylis–Hillman reaction followed by GLC (Table 1 and Fig. 1)

Methyl acrylate (100 μl, 1,1 mmol) was added to a stirred mixture of benzaldehyde (100 μl, 1.0 mmol), 1,4-diazabicyclo[2,2,2]octane (DABCO) (112 mg, 1.0 mmol) and additive (Lewis acid, 0.1 mmol) in classic solvent or ionic liquid, at 0–50°C under argon atmosphere, and the mixture was further stirred for at least 24 h at the same temperature. The course of the reaction was followed by GLC, by taking 5 μl samples from the reaction media at determined time intervals, and diluting with dichloromethane (1 ml) followed by injection in the gas chromatograph (carrier gas flow: 25 ml/min, oven T=190°C). The convertion of the reaction for each sample was determined by comparing the peak areas for the Baylis–Hillman product **2** (t_R=4.7 min) and for unreacted benzaldehyde (t_R=1.2 min) using a detector response factor of 1.1 relative to mol benzaldehyde/mol product **2**.

3.3. General procedure for preparative Baylis–Hillman reaction (Table 2)

Alkyl acrylate (5.5 mmol for Entries 1–13 and 1.1 mmol for Entries 14–21) was added to a stirred solution of aldehyde (5 mmol for Entries 1–13 and 1 mmol for Entries 14–21), 1,4-diazabicyclo[2,2,2]octane (DABCO) (560 mg, 5 mmol for Entries 1–13 and 112 mg, 1 mmol for Entries 14–21) and Lewis acid (0.5 mmol, only for Entries 6–9) in 500 μl (Entries 1, 4–13) or 100 μl of solvent (usually [bmim][PF_6]), at room temperature. The resulting mixture was further stirred for 24 h at room temperature under argon atmosphere. The reaction medium was diluted with dichloromethane (10 times the volume of solvent used for the reaction) and the resulting solution was purified on a TLC plate or flash chromatography column (silica gel).

3.3.1. Methyl 3-hydroxy-3-phenyl-2-methylenepropanoate (Table 2, Entry 5). Benzaldehyde (500 μl) and methyl acrylate (500 μl) were used in a 5 mmol scale. Purification by flash chromatography using *n*-hexane/ethyl acetate 9:1 afforded the title compound as a colourless oil (615 mg, 65%). Spectral data were identical to those previously reported.[10m]

3.3.2. t-Butyl 3-hydroxy-3-phenyl-2-methylenepropanoate (Table 2, Entry 10). Benzaldehyde (500 μl) and *t*-butyl acrylate (726 μl) were used in 5 mmol scale. Purification by flash chromatography using *n*-hexane/ethyl acetate 19:1 afforded the title compound as a colourless oil (492 mg, 42%). Spectral data were identical to those previously reported.[9b]

3.3.3. Methyl 3-hydroxy-2-methylenehexanoate (Table 2, Entry 11). Butyraldehyde (451 μl) and methyl acrylate (500 μl) were used in 5 mmol scale. Purification by flash chromatography using *n*-hexane/ethyl acetate 9:1 afforded the title compound as a colourless oil (182 mg, 20%). Spectral data were identical to those previously reported.[13]

3.3.4. Methyl 3-hydroxy-4-methyl-2-methylenepentanoate (Table 2, Entry 12). Isobutyraldehyde (456 μl) and methyl acrylate (500 μl) were used in 5 mmol scale. Purification by flash chromatography using *n*-hexane/ethyl acetate 9:1 afforded the title compound as a colourless oil (121 mg, 14%). Spectral data were identical to those previously reported.[10m]

3.3.5. Methyl 3-cyclohexyl-3-hydroxy-2-methylenepropanoate (Table 2, Entry 13). Cyclohexanecarboxaldehyde (606 μl) and methyl acrylate (500 μl) were used in 5 mmol scale. Purification by flash chromatography using *n*-hexane/ethyl acetate 9:1 afforded the title compound as a colourless oil (198 mg, 20%). Spectral data were identical to those previously reported.[10c,10m]

3.3.6. Methyl 3-(*p*-chlorophenyl)-3-hydroxy-2-methylenepropanoate (Table 2, Entry 14). *p*-Chlorobenzaldehyde (141 mg) and methyl acrylate (100 μl) were used in 1 mmol scale. Purification by TLC using *n*-hexane/ethyl acetate 9:1 afforded the title compound as a colourless oil (163mg, 72%); IR (neat): 3448, 2952, 1716, 1630, 1596, 1489, 1438, 1407, 1284, 1195, 1150, 1090, 1042, 1014, 961 cm^{-1}. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ 51.9, 72.6, 126.4, 128.0, 128.6, 139.8, 141.7, 166.7. Other spectral data were identical to those previously reported.[14]

3.3.7. Methyl 3-hydroxy-3-(*p*-methoxyphenyl)-2-methylenepropanoate (Table 2, Entry 15). *p*-Methoxybenzaldehyde (122 μl) and methyl acrylate (100 μl) were used in 1 mmol scale. Purification by TLC using *n*-hexane/ethyl acetate 3:1 afforded the title compound as a colourless oil (87 mg, 39%); IR (neat): 3470, 3000, 2952, 2836, 1720, 1610, 1511, 1439, 1394, 1250, 1174, 1148, 1033, 958 cm^{-1}. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ 51.8, 55.1, 72.5, 113.8, 125.5, 128.0, 133.6, 142.3, 159.3, 166.9. Other spectral data were identical to those previously reported.[15]

3.3.8. Methyl 3-hydroxy-3-(*p*-methylphenyl)-2-methylenepropanoate (Table 2, Entry 16). *p*-Methylbenzaldehyde (118 μl) and methyl acrylate (100 μl) were used in 1 mmol scale. Purification by TLC using *n*-hexane/ethyl acetate 3:1 afforded the title compound as a colourless oil (119 mg, 61%); IR (neat): 3447, 3024, 2951, 2922, 1722, 1629, 1512, 1438, 1397, 1275, 1195, 1149, 1040, 957 cm^{-1}. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ 20.9, 51.8, 73.0, 125.9, 126.6, 129.2, 137.6, 138.5, 142.2, 166.9. Other spectral data were identical to those previously reported.[14]

3.3.9. Methyl 3-hydroxy-5-phenyl-2-methylene-4-pentenoate (Table 2, Entry 17). Cinnamaldehyde (126 μl) and methyl acrylate (100 μl) were used in 1 mmol scale. Purification by TLC using *n*-hexane/ethyl acetate 3:1 afforded the title compound as a colourless oil (94 mg, 43%); Spectral data were identical to those previously reported.[10m,15,16]

3.3.10. Methyl 3-(2-furyl)-3-hydroxy-2-methylenepropanoate (Table 2, Entry 18). Furaldehyde (83 μl) and methyl acrylate (100 μl) were used in 1 mmol scale. Purification by TLC using *n*-hexane/ethyl acetate 17:3 afforded the title compound as a colourless oil (124 mg, 68%); IR (neat): 3440, 3120, 2953, 1721, 1633, 1500, 1439, 1385, 1284, 1197, 1152, 1040, 1012, 955 cm^{-1}. Other spectral data were identical to those previously reported.[15]

3.3.11. Methyl 3-hydroxy-3-(3,4,5-trimethoxyphenyl)-2-methylenepropanoate (Table 2, Entry 19). 3,4,5-Trimethoxybenzaldehyde (196 mg) and methyl acrylate (100 μl) were used in 1 mmol scale. Purification by TLC using *n*-hexane/ethyl acetate 3:2 afforded the title compound as a colourless oil[10b] (203 mg, 72%); IR (neat): 3487, 2998, 2942, 2838, 1720, 1629, 1593, 1504, 1461, 1421, 1327, 1233, 1192, 1126, 1056, 1005 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ 3.57 (s, 3H, CO_2CH3), 3.74 (s, 3H, $ArOCH_3$), 3.76 (s, 6H, $Ar(OCH_3)_2$), 5.43 (s, 1H, HOC*H*), 5.81 (s, 1H, =C*H*), 6.25 (s, 1H, =C*H*), 6.52 (s, 2H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ 51.8, 55.9, 60.6, 73.0, 103.6, 126.0, 137.0, 137.4, 142.0, 153.2, 167.0.

3.4. Recycling assays

Methyl acrylate (200 μl, 2.2 mmol) was added to a stirred solution of *p*-chlorobenzaldehyde (281 mg, 2 mmol) and DABCO (224 mg, 2 mmol) in 200 μl of [bmim][PF_6], at

room temperature. The resulting mixture was further stirred for 24 h at room temperature. The reaction medium was extracted with diethyl ether (2×4 ml) for 2×1 h and the volume of the combined ethereal extracts was reduced to about 3 ml under reduced pressure. The resulting solution was applied on a TLC plate (silica gel) and eluted with n-hexane/ethyl acetate 9:1. A new portion of reactants and DABCO was added to the recycled [bmim][PF_6], and the cycle was repeated.

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