

Electrogenerated N-Heterocyclic Carbene in Ionic Liquid: An Insight into the Mechanism of the Oxidative Esterification of Aromatic Aldehydes

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Abstract: An N-heterocyclic carbene (NHC), generated by cathodic reduction of BMImBF₄, mediates the oxidative esterification of aromatic aldehydes with organic bromides in the corresponding ionic liquid as solvent. The product recovery by simple extractive work-up with diethyl ether allowed the ionic liquid to be recycled up to 9 times for subsequent electrolyses, with no significant loss in the product

yield. The isolation of an intermediate, whose structure was confirmed by synthesis and transformation into the ester, provided the key for a mechanistic insight into the reaction.

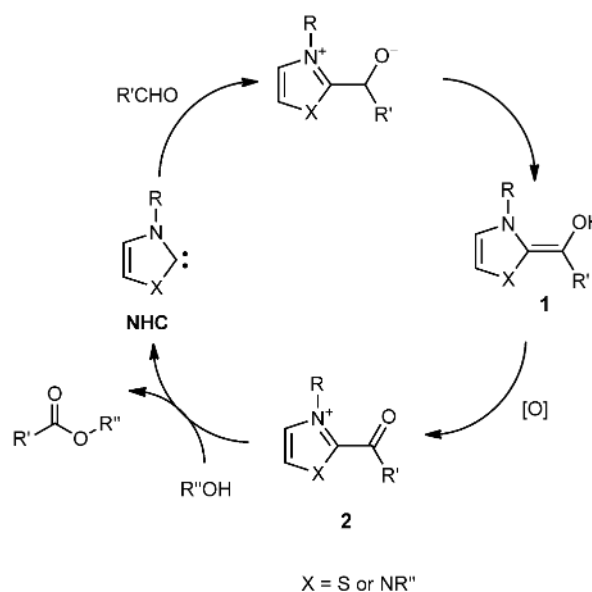
Keywords: aromatic esters; electrochemistry; ionic liquids; N-heterocyclic carbenes; oxidative esterification

Introduction

The manipulation of the aldehyde group is an attractive approach to the synthesis of esters. Unlike conventional routes, the *oxidative esterification* of aldehydes does not involve the direct activation of a carboxylic acid,^[1] usually achieved with harsh reaction conditions or expensive coupling reagents.^[2] N-heterocyclic carbenes (NHCs) induce the reaction of aldehydes featuring a reducible group with alcohols to yield the corresponding esters without additional oxidants.^[3] Thus, in the presence of NHCs, enals and α -substituted aldehydes form the Breslow intermediate, **1**,^[4] which undergoes an internal redox reaction leading to the electrophilic acyl azolium **2**. Instead, the conversion of aromatic aldehydes under analogous conditions requires the presence of exogenous oxidants and metal co-catalysts to form the acylating agent (Scheme 1).^[5]

It was in 2010 that Deng and co-workers first observed the formation of benzoates as by-products in the NHC-promoted synthesis of ketones, starting from aromatic aldehydes and aryl halides.^[6] Subsequent investigations pointed out how this unexpected side reaction turns into the major synthetic pathway

in the presence of air or pure oxygen and suggested that NHCs catalyze the formation of aromatic esters



Scheme 1. Mechanism of NHC-catalyzed oxidative esterification of aldehydes.

under mild and metal-free conditions, affording the products in excellent yields.^[7]

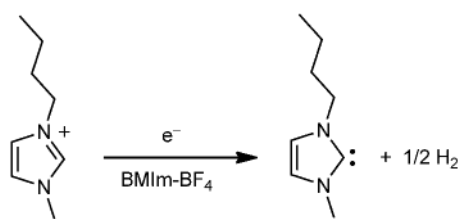
NHCs^[8] are generated by deprotonation or cathodic reduction of the corresponding azolium ions and promote various reactions, acting either as bases or as nucleophiles.^[9] Some of their precursors belong to the family of room temperature ionic liquids (ILs), which lately have gained much attention as potential alternatives to the classic volatile organic solvents in a greener approach to chemical synthesis,^[10] even though the high costs and the toxicity for aquatic organisms have prevented to date their wide use in large-scale processes.^[11]

Our group has recently focused on the electrochemical behaviour of 1-butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄), demonstrating that the corresponding carbene mediates some of the reactions promoted by NHCs in classic organic solvents.^[12]

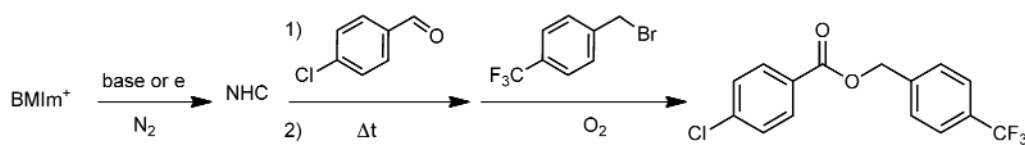
In such media, the synthesis of benzoates is achieved by reaction of aromatic aldehydes and organic bromides in the presence of oxidants and a stoichiometric amount of the azolium salt, precursor of the NHC. The active species is formed *in situ* by using an overstoichiometric amount of a base, suggesting that a deprotonation process may be involved during the conversion of the aldehydic group into the carboxylic acid derivative.

Results and Discussion

The direct cathodic reduction of the cation BMIm⁺ yields the related carbene 1-butyl-3-methylimidazol-2-ylidene (Scheme 2), which would act at the same time as catalyst and as base in the above-mentioned reaction, avoiding the use of additional bases.



Scheme 2. Formation of 1-butyl-3-methyl imidazol-2-ylidene by the cathodic reduction of BMIm⁺ cation.



Scheme 3. Addition sequence of the reagents for the oxidative esterification of aromatic aldehydes in the ionic liquid BMImBF₄ (see Experimental Section).

Moreover the use of BMImBF₄ as solvent in electrochemistry has undeniable advantages: (i) it is a good current conductor and does not require the use of supporting electrolytes; (ii) it is immiscible with diethyl ether, allowing an easy recovery of the products and the recycling of the IL as solvent for subsequent electrolyses.

Accordingly, BMImBF₄ was subjected to electrolysis under galvanostatic conditions at a temperature of 60 °C.^[13] Subsequently, the carbene solution in the IL was treated with *para*-chlorobenzaldehyde and *para*-(trifluoromethyl)benzyl bromide, taken as substrates for the optimization of the reaction conditions, in the presence of pure oxygen. The addition sequence of the reagents revealed to be crucial (*vide infra*) and we obtained the best results with the conditions reported in Scheme 3.

The reaction, using 1 F/mol, affords the ester in a very poor yield, while better results are achieved increasing the current over 2 Faradays per mole of aldehyde, suggesting a non-catalytic behaviour of the NHC. Any further increase over 3 equiv. of carbene generated did not correspond to a significant enhancement in the product yield (Table 1, entries 1–3).

A comparison with chemical bases shows the efficiency of the method. Indeed, when the carbene is generated by deprotonation with a base, the product is formed in very low yield regardless of the oxidant employed (Table 1, entries 4–11). Better, yet discouraging, results were obtained with a large excess of MnO₂ and combining DBU and Cs₂CO₃ (Table 1, entry 12),^[14] rendering the deprotonation of BMImBF₄ poorly competitive and markedly less eco-sustainable than its cathodic reduction.^[15]

IL Recycling

Using the reagents and conditions reported in Table 1, entry 3, the recycling of the solvent was performed (results summarized in Figure 1). Taking advantage from the negligible vapour pressure of BMImBF₄, and of the ILs in general, the solvent was dried under vacuum, after the extractive work-up, and subjected to a new cathodic reduction. The whole procedure was repeated up to 9 times with excellent results. Surprisingly, while the average yield stood in the range 60–70%, an abnormally high yield was ob-

Table 1. Oxidative esterification of aromatic aldehydes: screening of different bases and oxidants.^[a]

Entry	Deprotonating agent [equiv. ^[b]]	Oxidant [equiv. ^[b]]	Ester [%] ^[c]
1	e ⁻ (1 F/mol) ^[d]	O ₂	14
2	e ⁻ (2 F/mol) ^[d]	O ₂	64
3	e ⁻ (3 F/mol) ^[d]	O ₂	72
4	DBU (0.5)	air	4
5	DBU (1.0)	air	7
6	DBU (1.5)	air	13
7	DBU (0.5)	O ₂	4
8	DBU (1.0)	O ₂	12
9	DBU (1.0)	MnO ₂ (1.0)	8
10	Cs ₂ CO ₃ (1.5)	air	12 ^[e]
11	AcONa (1.0)	O ₂	ND ^[f]
12	DBU (1.0) + Cs ₂ CO ₃ (1.5)	MnO ₂ (5.0)	45

^[a] BMImBF₄ (2 mL), 60 °C, 0.5 mmol of *para*-chlorobenzaldehyde followed by the addition of oxidant and of 1.0 mmol of *para*-(trifluoromethyl)benzyl bromide.

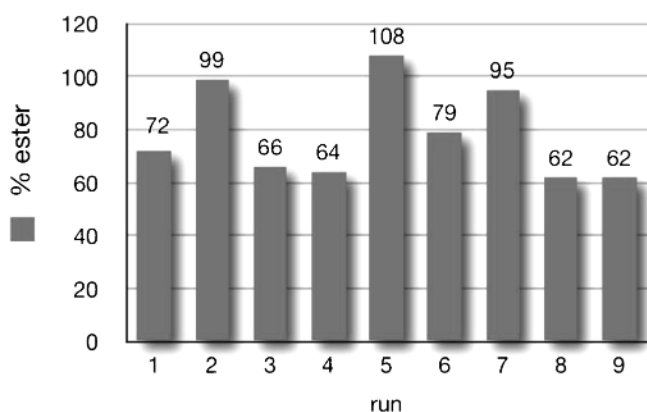
^[b] With respect to the starting aldehyde.

^[c] Isolated yields, with respect to the starting aldehyde.

^[d] Divided cell, galvanostatic conditions. $I = 20 \text{ mA} \cdot \text{cm}^{-2}$.

^[e] Di-*para*-(trifluoromethyl)benzyl carbonate was recovered.

^[f] *para*-(Trifluoromethyl)benzyl acetate formed.


Figure 1. Recycling of the solvent BMImBF₄.

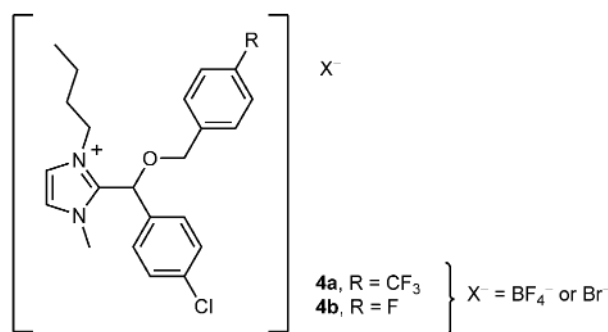
tained in a few cases, with a maximum of 108% in run #5.

These observations could be explained by assuming that a charged intermediate, previously postulated (but not isolated),^[6] gathers into the ionic liquid, being converted into the product in the subsequent run.

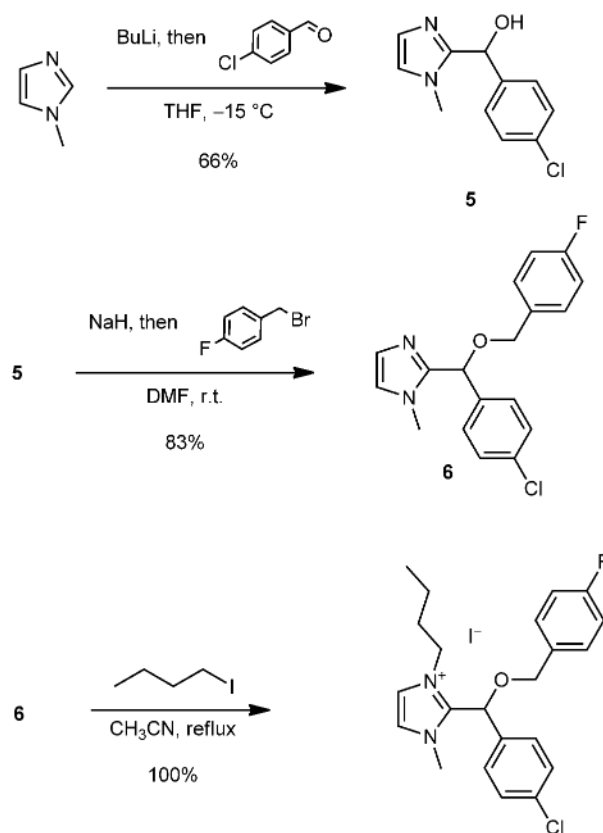
Reaction Mechanism

To shed light on this point, the IL was chromatographed after the synthesis of esters **3a** and **3b** and

the species **4** were isolated and characterized by NMR spectroscopy.



The structure was further confirmed by the synthesis of **4b** (X⁻ = I⁻), according to a slight modification of Miyashita's method (Scheme 4).^[16] To confirm that the isolated species are actual intermediates in the reaction, **4a** was treated with cesium carbonate and oxygen in CDCl₃ at 50 °C.^[17] Proton NMR spectra, recorded at regular time intervals, showed the disappearance of the singlet at $\delta = 4.18$ and the occurrence of the singlet at $\delta = 5.41$ (Figure 2).^[18]


Scheme 4. Synthesis of intermediate **4b**.

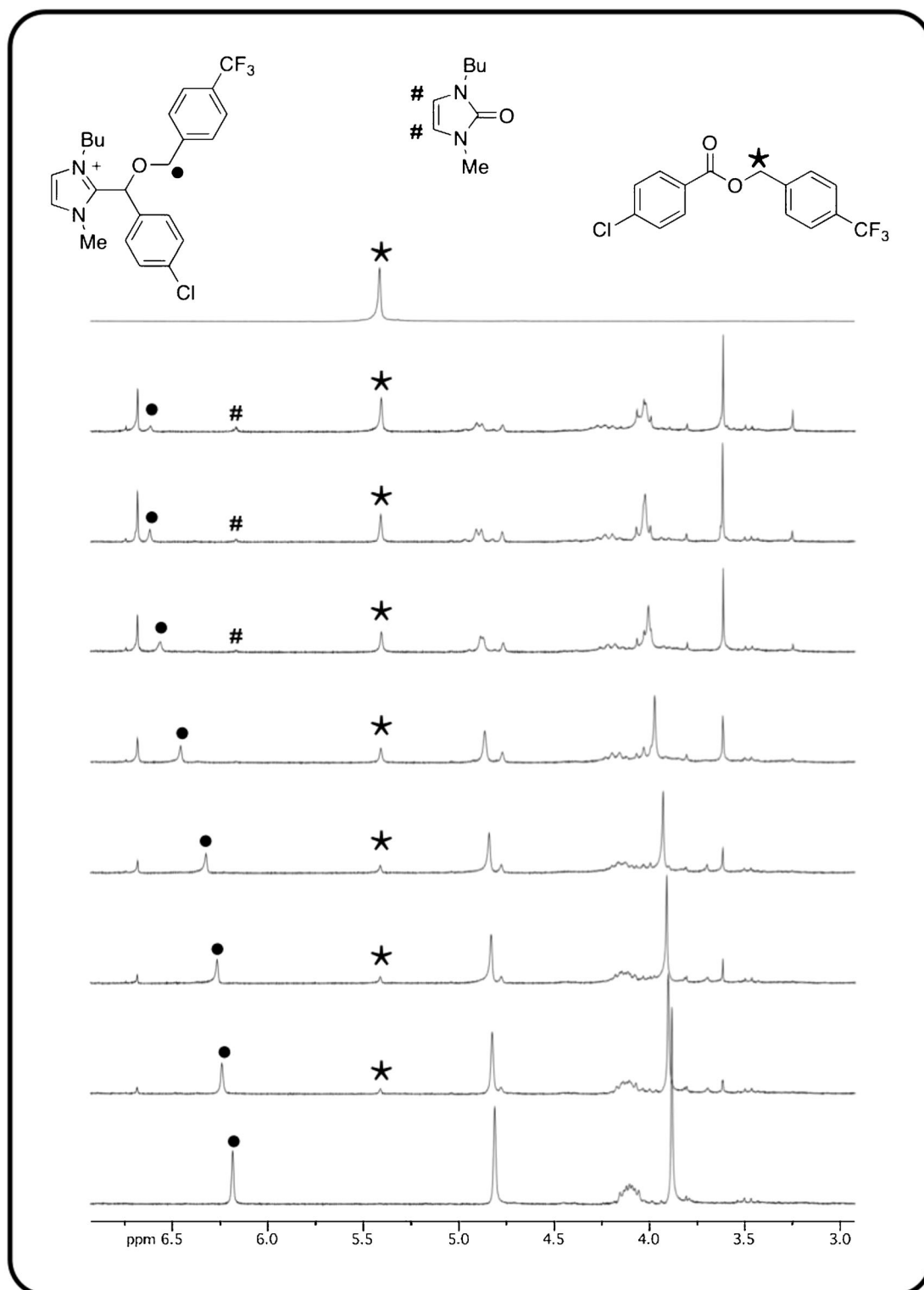
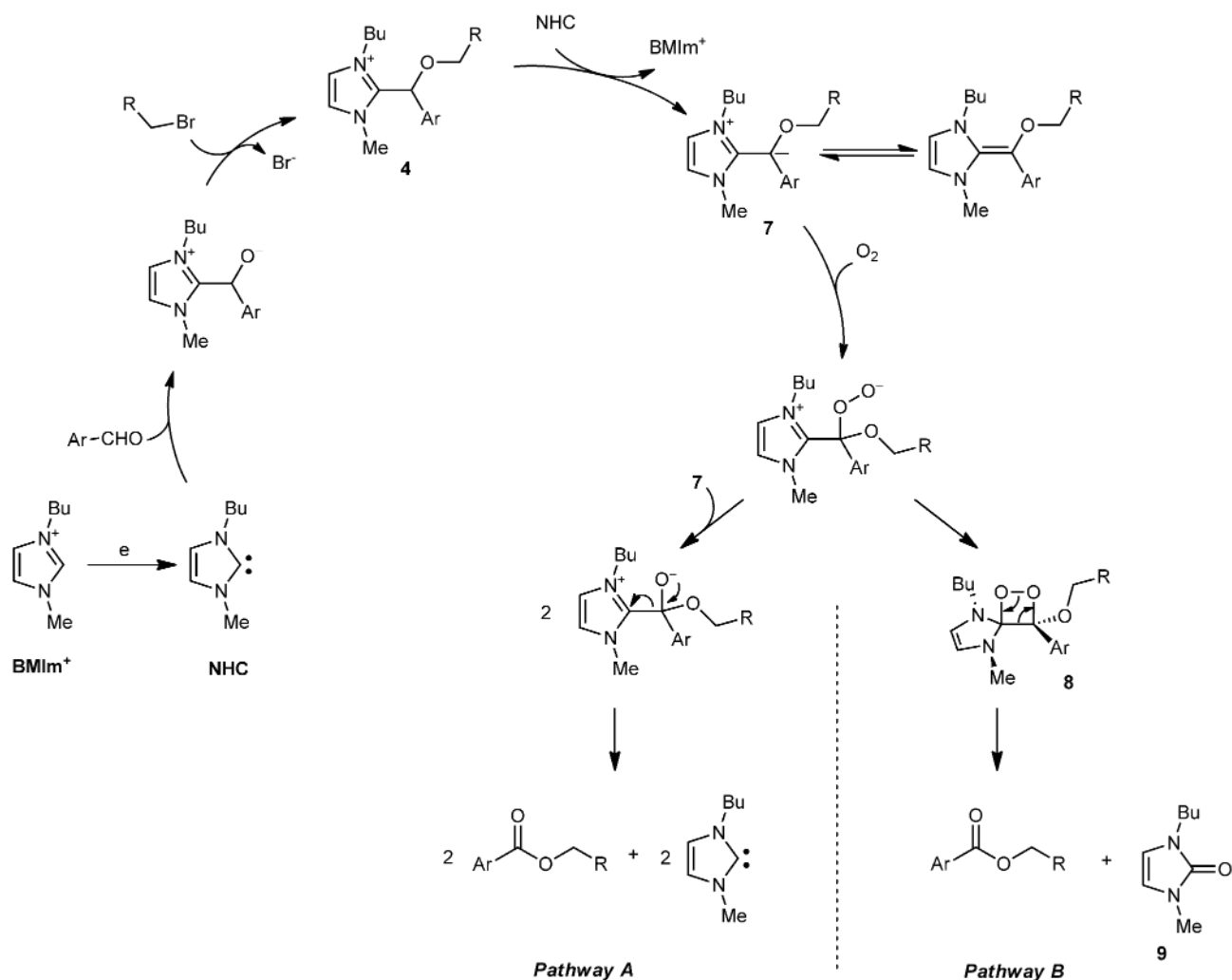


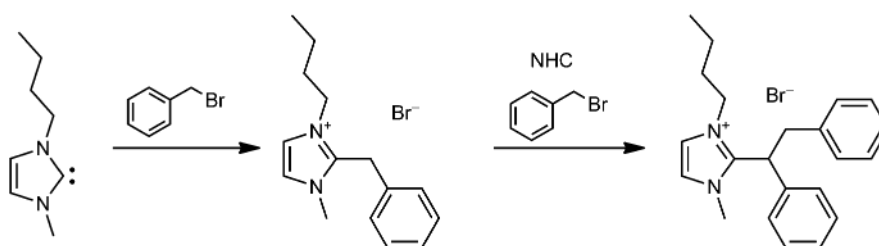
Figure 2. Conversion of the isolated intermediate **4a** into ester **3a** in CDCl_3 in the presence of an excess of Cs_2CO_3 and oxygen. *Top:* ¹H NMR spectrum of pure **3a**; *bottom:* ¹H NMR spectrum of isolated **4a**.

On these premises, we formulated two hypotheses for the mechanism operating in the reaction, relying on the involvement of **4** (Scheme 5).

The mechanism **B** involves the simultaneous formation of the ester and the imidazol-2-one **9** from the degradation of the endoperoxide species **8**. According to the ¹H NMR observation that **9** is present in traces



Scheme 5. Proposed pathways for the mechanism of the NHC-mediated oxidative esterification in BMIm BF₄.



Scheme 6. Alkylation of 1-butyl-3-methyl imidazol-2-ylidene with benzyl bromide.

at a later stage of the reaction (Figure 2), the occurrence of this pathway could be confidently ruled out.

The pathway **A**, instead, does not involve the direct formation of imidazolone species, which appear as by-product due to the oxidation of the carbene released at the end of the reaction.

Moreover, the mechanism **A** would clarify the crucial importance of the addition sequence of the reagents. In fact, to minimize the alkylation of the car-

bene (Scheme 6),^[19] this must quantitatively react with the aldehyde before the treatment with the bromide. This would also account for the requirement of over 2 equivalents of carbene per mole of aldehyde, one equivalent being used to form the adduct and the other as a stoichiometric base.^[20]

Few authors reported that the oxidative esterification of enals and aromatic aldehydes in organic solvents and in the presence of oxygen may proceed *via*

carboxylate species, which react with the bromides to afford the esters.^[21] When performing the reaction with electrogenerated NHC in BMImBF₄, in the absence of alkylating agents, no trace of carboxylic acid was recovered after acidic work-up, excluding the occurrence of such a mechanism in the case under examination.

Reaction Scope

To test the general applicability of the electrochemically generated NHC to the synthesis of aromatic esters in ionic liquids, we used the optimal conditions found for the reaction (Table 1, entry 3). The results are summarized in Table 2.

Table 2. Synthesis of differently substituted esters: reaction scope.^[a]

Reaction scheme showing the synthesis of esters **3a-w** from aromatic aldehydes (Ar-CHO) and alkyl bromides (R-Br) using electrogenerated NHC in BMIm-BF₄ under O₂.

Entry	Ester	Yield [%] ^[b]	Entry	Ester	Yield [%] ^[b]
1	3a 	72	13	3m 	70
2	3b 	75	14	3n 	33
3	3c 	62	15	3o 	58
4	3d 	62	16	3p 	43
5	3e 	63	17	3q 	50
6	3f 	65	18	3r 	64
7	3g 	60	19	3s 	71
8	3h 	54	20	3t 	58
9	3i 	68	21	3u 	67
10	3j 	84	22	3v 	43
11	3k 	59	23	3w 	35
12	3l 	39			

^[a] Reaction conditions: as reported in Table 1, entry 3.

^[b] Isolated yields, with respect to the starting aldehyde.

Benzyl and alkyl bromides react smoothly (Table 2, entries 1–4) and highly functionalized esters were obtained using substituted 1-bromoacetophenone derivatives bearing either electron-donating or electron-withdrawing groups on the aromatic ring (Table 2, entries 5–8).

Aromatic and heteroaromatic aldehydes are well tolerated, but the substituent position should be considered carefully as the steric hindrance in *ortho*-substituted benzaldehydes causes a dramatic decrease in the reactivity (Table 2, entry 14). Remarkably both dibromides and phthalic aldehydes react to give the corresponding diesters, opening intriguing perspectives towards the synthesis of aromatic polyesters.

Conclusions

We have reported here that aromatic esters can be synthesized in BMImBF_4 , starting from the corresponding aldehydes and organic bromides. The NHC, electrogenerated from the corresponding ionic liquid, plays the double role of catalyst and base in the reaction and avoids the use of external bases required when performing the reaction in organic solvents. A higher degree of atom economy, compared to analogous procedures reported, is hence achieved, along with undeniable advantages in the isolation and purification of the products. To the best of our knowledge, this is the first report of oxidative esterification of aromatic aldehydes with organic bromides mediated by NHC in ionic liquids.

In the paper we demonstrated that the ionic liquid, used also as reaction medium, can be recycled and effectively reused in subsequent electrolyses. The abnormally high yields observed in these cases can be ascribed to the accumulation of an ionic intermediate, isolated and characterized for the first time, which can be converted to the product in subsequent reactions.

Moving from the structural elucidation of the above-mentioned intermediate, a hypothesis on the mechanism of the oxidative esterification of aldehydes in ionic liquid is provided. Even though the occurrence of other pathways cannot be ruled out, such a mechanism is coherent with all the experimental observations and provides hints on the non-conventional behaviour of chemical species in IL with respect to classic organic solvents.

Experimental Section

Materials and Methods

Electrolyses under galvanostatic control were carried out with an Amel 552 potentiostat equipped with an Amel 721

integrator in a two-compartment home-made glass cell, whose design was already described,^[22] at 60°C, under a nitrogen atmosphere. Anolyte (ca. 0.5 mL BMImBF_4) and catholyte (ca. 2.0 mL BMImBF_4) were separated through a glass frit (porosity 4). The electrode apparent surface area was 1.0 cm² for the cathodic Pt spiral (99.9%) and 0.8 cm² for the anodic Pt spiral (99.9%). The current density was 20 mA·cm⁻². ¹H and ¹³C NMR spectra were recorded using a Bruker AC 200 spectrometer with CDCl_3 as internal standard. All ionic liquids and reagents were used as received.

General Procedure

After the consumption of 145 C, the current was switched off and the aldehyde (0.5 mmol) was added to the catholyte under stirring. After 10 min, the solution was saturated with oxygen and treated with the bromide (1.0 mmol). The mixture was kept at 60°C under oxygen bubbling for 1 h, and then at room temperature for 12 h without gas. The catholyte was extracted with diethyl ether and the solvent was removed under reduced pressure. The residue was analyzed by ¹H NMR and purified by flash chromatography, affording the corresponding ester in pure form. All known esters gave spectral data in accordance with those reported in the literature. When difunctional aldehydes were used, 0.25 mmol were added to 1.0 mmol of the bromide, while when dibromides were used, 0.25 mmol were added to 0.5 mmol of aldehyde.

Recycle of Catholyte

After extraction of the cathodic BMImBF_4 and isolation of **3a**, the catholyte was kept under vacuum at 60°C for 1 h and then reused in a new electrolysis (the catholyte was added with a further aliquot of IL, when necessary, while fresh IL was used as anolyte in each run). The same ionic liquid was recycled nine times, obtaining **3a** in 72, 99, 66, 64, 108, 79, 95, 62, and 62% yields, respectively.

Isolation of 1-Butyl-2-((4-chlorophenyl){[4-(trifluoromethyl)benzyl]oxy}methyl)-3-methyl-1H-imidazol-3-ium (**4a**) X[□] (X = Br or BF₄)

Following the general procedure, 4-chlorobenzaldehyde and 4-(trifluoromethyl)benzyl bromide were reacted. After ethereal extraction of the catholyte and elimination of residual diethyl ether under vacuum, the cathodic ionic liquid was subjected to flash column chromatography (silica gel, ethyl acetate) to give pure **4a**X[□] (X = Br or BF₄).

Transformation of **4a**X[□] into **3a**

4aX[□] was dissolved in CDCl_3 in an NMR tube, followed by the addition of an excess of Cs_2CO_3 . Molecular oxygen was bubbled into the tube, which was subsequently sealed. ¹H NMR spectra were recorded at regular time intervals (heating to 50°C in each interval) until reaction completion (about 7 days).

1-Butyl-2-((4-chlorophenyl)[(4-fluorobenzyl)oxy]-methyl)-3-methyl-1H-imidazol-3-ium (4b) Iodide

4b iodide was synthesized following a three-step literature procedure.^[23] To a stirred solution of BuLi (5 mmol) in THF (5 mL) at \square 15 °C, a solution of 1-methylimidazole (5 mmol) in THF (5 mL) was added dropwise. After 1 h, 4-chlorobenzaldehyde (5 mmol) in THF (5 mL) was slowly added and the mixture stirred for 1 h. The reaction was allowed to warm to room temperature and the solvent was removed under reduced pressure. Ice was added to the flask and the crude reaction was allowed to stand overnight. The separated solid was collected and washed with water and *n*-hexane to afford **5** (yield: 66%), which was directly used in the subsequent step.

To a DMF solution (5 mL) of **5** (3 mmol), NaH (1.5 equiv.) was slowly added. 4-Fluorobenzyl bromide (3 mmol) was added and the mixture stirred at room temperature for 2 h. The crude reaction mixture was poured into ice-water and extracted with diethyl ether. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (silica gel, *n*-hexane:ethyl acetate 8:2), affording **6**; yield: 83%.

To a solution of **6** (2 mmol) in acetonitrile (5 mL), butyl iodide (3 equiv.) was added and the mixture was refluxed for 2 h. The solvent was evaporated under reduced pressure and the solid washed with diethyl ether yielding the quaternary salt **4b** iodide in pure form; yield: 100%.

Transformation of 4b Iodide into Ester 3b

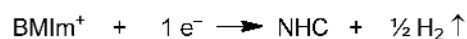
4a iodide was dissolved in CDCl₃ in an NMR tube, followed by the addition of an excess of DBU. Molecular oxygen was bubbled into the tube, which was subsequently sealed. ¹H NMR spectra were recorded at regular time intervals (heating to 50 °C in each interval) for 7 days (a further aliquot of DBU was added after 3 days).

Acknowledgements

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When using chemical bases, an acid-base equilibrium is established instead.

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- [18] The conversion of the intermediate to ester, at least in deuterated chloroform, is extremely slow and the consumption of **4a** and **4b** required more than one week to reach completeness, even with a large excess of Cs₂CO₃ or DBU (see the Supporting Information).
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