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Intermolecular hydroamination and hydroarylation reactions of alkenes in ionic liquids

Alexandre A. M. Lapis,[a] Brenno A. DaSilveira Neto,[a] Jackson D. Scholten,[a]
Fabiane M. Nachtigall,[b] Marcos N. Eberlin[b] and Jairton Dupont[a,*]

[a]*Laboratory of Molecular Catalysis, IQ, UFRGS, Porto Alegre-RS, 91501970, Brazil*
[b]*Thomson Mass Spectroscopy Laboratory, IQ, UNICAMP, Campinas-SP, 13083970, Brazil*

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Abstract—Intermolecular hydroamination or hydroarylation reactions of norbornene and cyclohexadiene performed with catalytic amounts of Brönsted or Lewis acid in ionic liquids were found to provide higher selectivity and yields than those performed in classical organic solvents. The ionic liquid increases the acidity of the media and stabilizes ionic intermediates through the formation of supramolecular aggregates.

Catalytic hydroamination and hydroarylation reactions are important synthetic methodologies for forming nitrogen-containing compounds such as amines, imines and enamines. Both protocols may afford these classes of compounds in a single step from readily available unsaturated hydrocarbons.[1] Various catalysts derived from alkali, early and late transition metals as well as lanthanides have been developed for addition of N–H bonds to unsaturated compounds,[2] but a more general and selective process is still to be found. Additionally, the cost of these transition metal catalysts, ligands or additives is also a major drawback of these protocols.[3] The use of acid-catalyzed reactions could represent a less expensive alternative for synthesis using these nitrogen-containing products. Indeed, it has been recently reported[4] that the hydroamination/hydroarylation reaction of alkenes with anilines proceeds smoothly in the presence of Brönsted acids. The catalytic activity of these systems is strongly influenced by the counteranion coordination ability, that is, the efficiency of the reaction increases as the coordination ability of the counteranion decreases. The proposed reaction pathway involves proton transfer from the anilinium salt ($[PhNH_3]^+$) to the C=C bond—thus generating a carbocation—followed by nucleophilic addition of neutral aniline species that yields ionic adducts. These adducts eliminate H^+ in a process assisted by free aniline to give the N- and/or C-arylated product. It is reasonable to assume that counteranion coordination ability not only influences the Brönsted acidity of the medium but also the stabilization/destabilization of the ionic species involved in the process. Therefore, the catalytic activity and selectivity of this acid catalysis may be modulated by controlling the solvation process of the medium. In this respect, ionic liquids (ILs)[5] and especially those based on the imidazolium cation are known to have great ability to stabilize ionic intermediates and transition states through different types of ions pairs.[6] These properties have been recently exploited in some reactions that involve ionic species such as Mannich-type reactions, the Mukaiyama aldol reaction, Baylis–Hillman reactions and tetrahydropyranylation.[7] ILs are also very effective media for 'classic' acid catalysis[8] and the acidity of acids normally increases when dissolved in ILs. Furthermore, ILs are less solvating than water.[9]

Herein, we describe our preliminary results concerning the performance of acid catalysis (both Lewis and Brönsted acids) in the hydroamination/hydroarylation reactions in imidazolium-based IL media as well as the investigation by electrospray ionization mass spectrometry (ESI-MS) of the possible ionic species involved in the process. The reaction conditions were optimized for the reaction of norbornene in the presence of aniline with different Brönsted and Lewis acids (5 mol %) in $BMI{\cdot}NTf_2$ (Scheme 1 and Table 1).

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* Corresponding author. Tel.: +555133166321; fax: +555133167304; e-mail: dupont@iq.ufrgs.br

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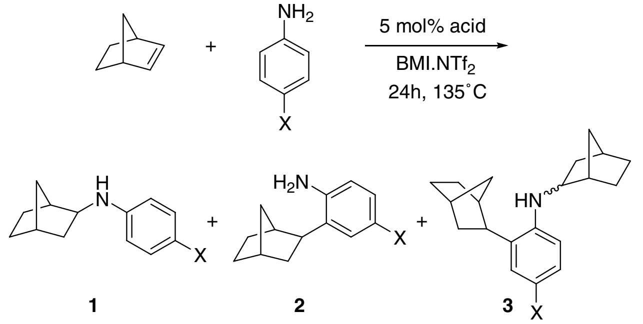


Scheme 1.

Table 1. Hydroamination/hydroarylation of norbornene by aniline (X = H) with different acids as catalyst in BMI·NTf$_2$[a]

Entry	Acid (5 mol %)	Yield (%)[b]	**1**:**2**:**3**[c]
1	CF_3SO_3H	70	1.9:1:Trace
2	CF_3SO_3H in PhH[4]	13	1:1.4:0
3	CH_3SO_3H	48	1.8:1:0
4	CF_3CO_2H	28	1:1:Trace
5	*p*-TolSO$_3$H	22	1.5:1:0
6	PhB(OH)$_2$	38	1.6:1:0
7	HBF_4	80	1.5:1:0
8	BF_3·OEt$_2$	83	1.4:1:Trace

[a] Reaction conditions: norbornene (1.08 mmol), aniline (2.16 mmol), acid (0.05 mmol) and BMI·NTf$_2$ (0.2 mL); 135 °C; 24 h.

[b] Combined yield of isolated products.

[c] Products ratios were determined by GC.

This IL fluid has been chosen since it possesses one of the least coordinating anions of the imidazolium IL family and has been successfully used in acid catalysis.[8a] The best yields were obtained using BF$_3$·OEt$_2$ (Table 1, entry 8) and HBF$_4$ (Table 1, entry 7) acids. The Brönsted acid catalyzed reactions also afforded good yields considering that hydroamination and/or hydroarylations are difficult to perform using protic acid catalysis.[1] It is also quite fitting that both yield and selectivity are higher for the reaction performed using CF$_3$SO$_3$H in BMI·NTf$_2$ than that performed in benzene[4] under the same reaction conditions (Table 1, entry 2).

A small selectivity towards hydroamination products in the IL was obtained in almost all cases, except for trifluoroacetic acid for which no selectivity was observed (Table 1, entry 4). In these cases, nucleophilic attack may occur preferentially through the aniline nitrogen atom, following reaction pathway 1 (Scheme 2). Therefore, the hydroarylation products were formed by the following pathway 2, which the aromatic ring acts as a nucleophile as proposed by Bergman.[4]

As already mentioned, the acid counteranion has an important effect on the reaction efficiency and it is assumed that the acids would rapidly react with aniline to form an anilinium salt ([PhNH$_3$]$^+$) (see proposed reaction path in Scheme 2).[4] Therefore, a low coordination ability of the counteranion facilitates alkene protonation, which may imply that the IL could be acting in this reaction step by decreasing the ionic interactions between the cation and anion, thus facilitating the protonation step.

To determine the influence of the ILs anion in the hydroamination and hydroarylation reactions, other ILs were tested with BF$_3$·OEt$_2$ and HBF$_4$ acids (Table 2). As expected, the acidity of the anilinium salt decreased with increasing IL anion coordination ability ($OTf^- > PF_6^- > BF_4^- > InCl_4^- > NTf_2^-$)[7d,10] and thereby the reaction yield decreased. The BMI·InCl$_4$ has an intrinsic acid pattern[7d] and could be used directly to afford products **2** and **3** with reasonable selectivity for

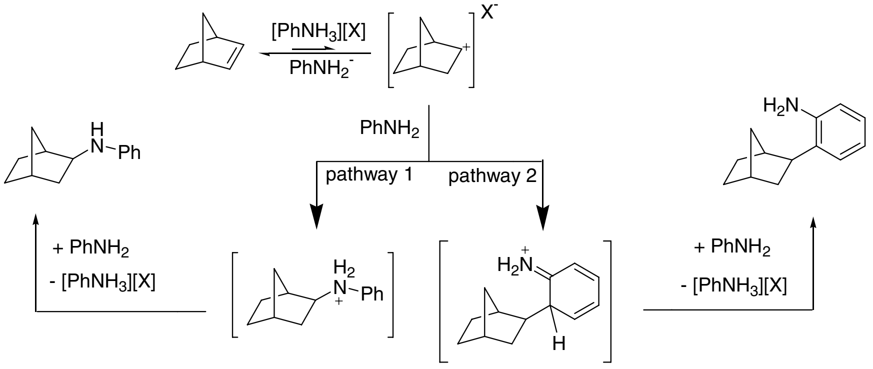
Table 2. Hydroamination/hydroarylation of norbornene in different ILs[a]

Entry	ILs	Acid (5 mol %)	Yield (%)[b]	**1**:**2**:**3**[c]
1	BMI·NTf$_2$	HBF_4	80	1.5:1:0
2	BMI·NTf$_2$	BF_3·OEt$_2$	83	1.4:1:Trace
3	BMI·InCl$_4$		37	2.6:1:Trace
4	BMI·InCl$_4$	$InCl_3$	57	3.3:1.6:1
5	BMI·BF$_4$	HBF_4	12	2:1:0
6	BMI·BF$_4$	BF_3·OEt$_2$	40	1.4:1:Trace
7	BMI·PF$_6$	HBF_4	7	2.3:1:0
8	BMI·PF$_6$	BF_3·OEt$_2$	35	2:1:0
9	BMI·OTf	HBF_4	9	1.3:1:0
10	BMI·OTf	BF_3·OEt$_2$	28	1.3:1:0

[a] Reaction conditions: norbornene (1.08 mmol), aniline (2.16 mmol), acid (0.05 mmol) and IL (0.2 mL); 135 °C; 24 h.

[b] Combined yield of isolated products.

[c] Products ratios were determined by GC.



Scheme 2.

the hydroamination products. An additional amount of $InCl_3$ led to a slight increase in selectivity and yield (Table 2, entry 4).

The reaction time was optimized for the reaction of norbornene with aniline in the presence of $BF_3{\cdot}OEt_2$ in $BMI{\cdot}NTf_2$, at 135 °C (Graphic S1 in the Supplementary material). A maximum conversion of 96% was achieved after 6 h. The effect of temperature on the addition of aniline to norbornene was also investigated using $BF_3{\cdot}OEt_2$ in $BMI{\cdot}NTf_2$. When the reaction was performed at 135 °C, the yield was 83% and preferential hydroamination selectivity was observed (1.4:1 of products **1**:**2**, Table 1, entry 8) together with small amounts of the hydroamination and hydroarylation product **3**. The use of lower reaction temperatures of 100 °C or 70 °C decreases the products yields (30% and 16%, respectively) and the selectivity drastically changes. At 100 °C, no preference for hydroamination or hydroarylation products was observed (product ratio of 1:1 for **1**:**2**). However, at 70 °C, the products ratio reversed (1:1.4 of **1**:**2**), when compared with the first run at 135 °C.

Therefore, the hydroamination reaction is favored at higher temperatures, whereas the hydroarylation is favored at lower temperatures.

The electronic effect on substituted anilines was also evaluated in the hydroamination/hydroarylation reaction using the optimized reaction conditions for aniline. The chemoselectivity of the transformation depends on the electron density of the aniline nitrogen atom (Table 3). Electron-donating substituents on the aniline moiety favored the hydroarylation products in a stereospecific way (*ortho*-position) while decreasing the yield (Table 3, entries 2 and 3). Electron-withdrawing substituents increased the overall reaction yield and only the hydroamination product was obtained (Table 3, entry 4).

Table 3. Effect of aniline substitution on hydroamination and hydroarylation product ratios[a]

Entry	X	Yield (%)[b]	**1**:**2**:**3**[c]
1	H	83	1.4:1:Trace
2	Me	74	1:2:0
3	OMe	50	1:1.6:0
4	NO_2	94	Only **3**

[a] Reaction conditions: norbornene (2.16 mmol), substituted aniline (4.32 mmol), acid (0.11 mmol) and $BMI{\cdot}NTf_2$ (0.4 mL); 135 °C; 24 h.

[b] Combined yield of isolated products.

[c] Products ratios were determined by GC.

Table 4. Acid catalysis hydroarylation between 1,3-cyclohexadiene and substituted anilines in a $BMI{\cdot}NTf_2$[a]

Entry	X	Yield (%)[b]	**4**:**5**[c]
1	H	56	Only **4**
2	Me	46	1:Trace
3	OMe	40	13:1
4	NO_2	11	only **4**

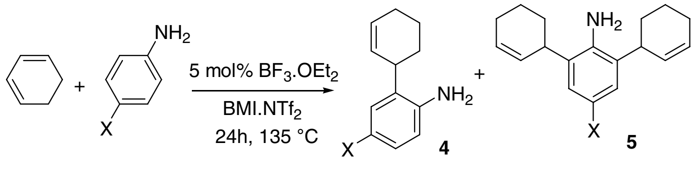
[a] Reaction conditions: 1,3-cyclohexadiene (2.16 mmol), aniline (4.32 mmol), acid (0.11 mmol) and $BMI{\cdot}NTf_2$ (0.4 mL); 135 °C; 24 h.

[b] Combined yield of isolated products.

[c] Products ratios were determined by GC.

Cyclohexadiene undergoes similar addition reactions (Scheme 3) yielding almost exclusively the hydroarylation product **4** (Table 4). No hydroamination product was observed. The di-addition products **5** were only observed for anilines with electron-donating substituents (Table 4, entries 2 and 3).

To investigate the possible intervention of supramolecular ionic species, the evolution of a mixture of aniline, norbornene, CF_3SO_3H or HBF_4 in 0.1 mL of IL was monitored by both ESI(+)/MS and ESI(−)/MS.[5] Using ESI(−)/MS, no ionic species directly related to the proposed reaction path could be detected. However, in the positive ion mode (ESI(+)/MS), species involving supramolecular interactions of the IL with other reaction mixture components were indeed detected. All putatively assigned ions were then characterized by ESI-MS/MS experiments. The ion of *m*/*z* 187 (detected in the mixture of equal molar proportion of norbornene, aniline, $BMI{\cdot}NTf_2$ and CF_3SO_3H—Fig. 1) was characterized as the protonated dimer of aniline; it looses a neutral molecule of 93 Da (neutral aniline). The supramolecular ionic species of *m*/*z* 711 was characterized (Fig. 1) as $[(PhNH_3)_3(CF_3SO_3)(NTf_2)]^+$; it loses $[(PhNH_3)CF_3SO_3]$ preferentially, which indicates that the relative strength of coordination of the anion is $CF_3SO_3 > NTf_2$. In this experiment, the supramolecular species that associate with the imidazolium cation were also observed such as the ions of *m*/*z* 382 and 513 corresponding to $[(BMI)(PhNH_3)(CF_3SO_3)]^+$ and $[(BMI)(PhNH_3)NTf_2]^+$. Using HBF_4 instead of CF_3SO_3H, protonated aniline is also detected as cationic dimers associated with acid counteranions, that is, $[(PhNH_3)_2(BF_4)]^+$ of *m*/*z* 275 and IL counteranion, that is, $[(PhNH_3)_2(NTf_2)]^+$of *m*/*z* 468. The ions of *m*/*z* 320 and *m*/*z* 513 correspond to the supramolecular species H-bonded to the BMI cation and structurally characterized by ESI-MS/MS as $[(BMI)(PhNH_3)(BF_4)]^+$ and $[(BMI)(PhNH_3)(NTf_2)]^+$ (Figure S1 in the Supplementary material). ESI-MS/MS of the ion of *m*/*z* 649 ($[(PhNH_3)_3(BF_4)(NTf_2)]^+$) reveals the intrinsic relative strength of coordination of



Scheme 3.

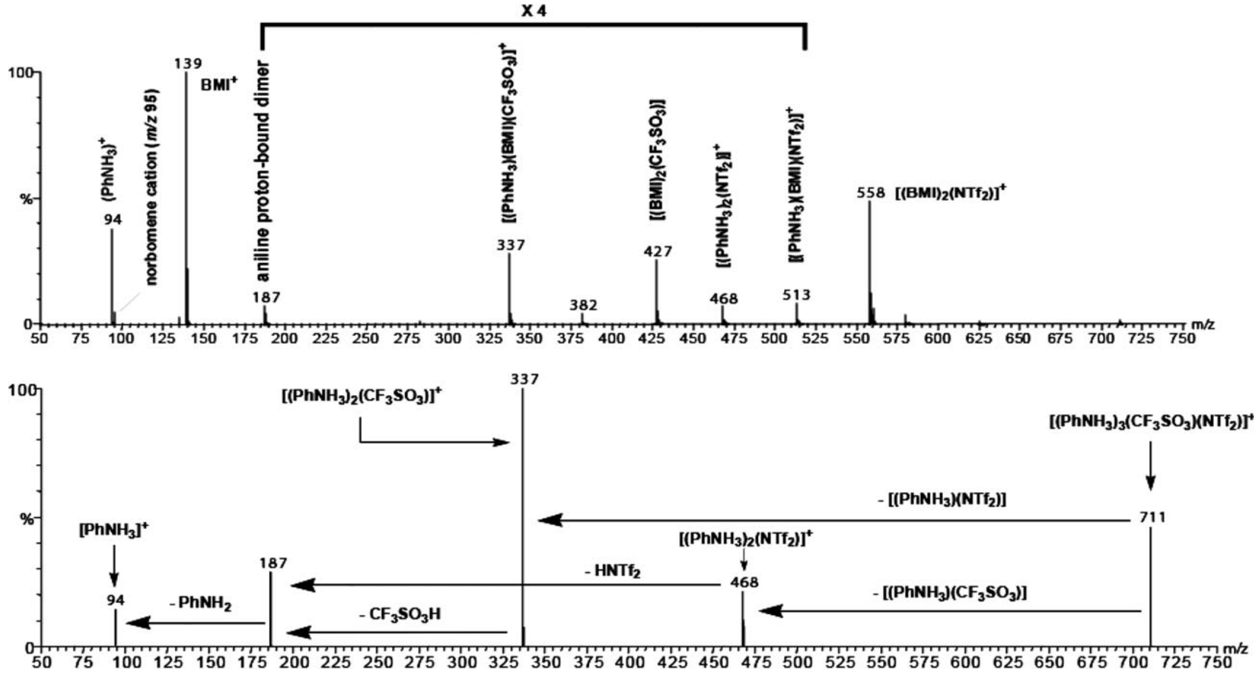


Figure 1. ESI(+)MS of a reaction mixture containing aniline, norbornene, CF_3SO_3H in 0.1 mL of BMI·NTf_2 (top). ESI(+)MSMS of the ion of *m/z* 711 assigned as $[(PhNH_3)_3(CF_3SO_3)(NTf_2)]^+$ (bottom).

the anion with protonated aniline. The preferential loss of neutral $(PhNH_3)(BF_4)$ indicates that the relative strength of coordination of the anion is $BF_4 > NTf_2$. The detection and characterization of supramolecular BMI species clearly indicates that the imidazolium ILs stabilize the charged intermediates in the proposed reaction paths (Scheme 2).

In summary, as compared to those performed in classical organic media the yield and selectivity of hydroamination and hydroarylation reactions of alkenes promoted by acid catalysis are improved when performed in IL media, especially in BMI·NTf_2. The IL not only increases the acidity of the media, especially of the anilinium salt, but it also stabilizes the key intermediate ionic species via the formation of supramolecular aggregates. The hydroamination/hydroarylation promoted by acids in ILs is an attractive alternative to the more expensive metal catalyzed reaction. Moreover, this transformation is air and moisture tolerant while providing satisfactory yields and the possibility of directing selectivity for N–H or Ar–H products by changing the reaction conditions and aniline substitution patterns.

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Supplementary data

Experimental procedures, ESI spectra and spectroscopic data for new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.073.

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