ACS Catalysis
Research Article
pubs.acs.org/acscatalysis

Ionic Liquid Effect over the Biginelli Reaction under Homogeneous and Heterogeneous Catalysis

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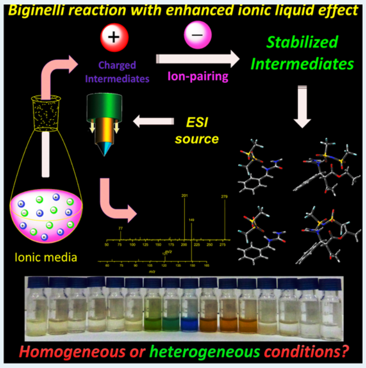
Ⓢ *Supporting Information*

ABSTRACT: Bronsted and Lewis acid catalysts with ionic tags under homogeneous and heterogeneous conditions have been tested to perform the Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (DHPMs). Metal-containing ionic liquids were evaluated as the catalysts with reasonable results (homogeneous systems). Heterogeneous catalysts (zeolite β and $H_3PW_{12}O_{40}$ supported on zeolite β) have been tested, as well, with good to excellent results. The use of a functionalized acid ionic liquid with a heteropolyacid in the anion moiety (homogeneous system) gave the best results using no excess of the three reagents. The preferred mechanistic pathway was investigated by electrospray ionization (tandem) mass spectrometry in both positive and negative ion modes with very elucidative results. The ionic liquid effect and its origin were also investigated using mass spectrometry and DFT calculations.



KEYWORDS: *Biginelli, ionic liquids, homogeneous and heterogeneous catalysis, mechanism and mass spectrometry*

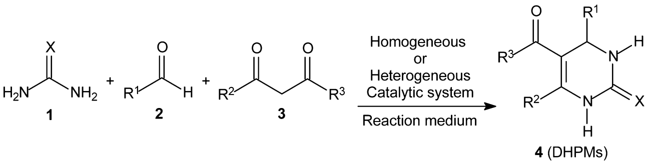
■ INTRODUCTION

Modern catalysis and related methodologies are centered on the development of more efficient catalysts, which must be used under both more sustainable and eco-friendly conditions; hence, envisaging all possible principles of the so-called green chemistry, with special attention to strategies to approach a renewable chemical industry.[1] In this sense, major concerns regarding waste minimization and sustainability, which are significant current issues in catalysis, are noted.[2]

On the basis of those considerations, many attempts are presently found to connect the advantages and beneficial features of catalytic chemistry carried out in ionic liquids (ILs)[3−7] with multicomponent reactions (MCRs).[8−10] Definitely, the description of such combination as "a perfect synergy for eco-compatible heterocyclic synthesis"[11] is far from overrated. ILs have been described as one possible pathway to environmental acceptability,[12] and nowadays, the use of ILs in the chemical industry is a reality under expansion.[13] The use of heterogeneous and homogeneous catalysts to perform MCRs (also in ILs) is a subject that has been very recently reviewed.[14] It is currently known that these two types of catalysis play important roles for many chemical transformations, and both have some advantages and disadvantages. Whether the catalytic system performing the MCR is heterogeneous or homogeneous, the chemistry and biology of MCRs play a prominent role[15] of paramount importance in never-ending biologically active compound syntheses and discovery.[16−18]

Among MCRs, the Biginelli reaction[19] (Scheme 1) is used to the direct synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives.[20] DHPMs such as enastron,[21] monastrol,[22] piperastrol,[23] and other derivatives[24] have already displayed interesting biological activities. Moreover, many DHPMs are being studied because of their activities as calcium channel modulators, mitotic Kinesin inhibitors, adrenergic receptor antagonists, antibacterials, antivirals, and others, as reviewed elsewhere.[25] Considering all

Scheme 1. The Biginelli Reaction[a]



[a]Note it is possible to use homogeneous or heterogeneous conditions to perform the reaction.

Received: April 17, 2013
Revised: May 10, 2013
Published: May 30, 2013

dx.doi.org/10.1021/cs400291t | *ACS Catal.* 2013, 3, 1420−1430

attractive features of DHPMs, methodologies to improve the Biginelli synthesis under more amenable and sustainable conditions naturally appeared,[26] and ILs became once more an attractive medium to perform the reaction.[27] Functionalized ILs, also known as task-specific ionic liquids (TSILs) have already been employed with success as catalysts for the Biginelli reaction.[28−30] Despite all improvements experienced toward better reaction conditions, this transformation still has many drawbacks associated with it. Problems such as low yields, long reaction times, cost, nonsustainable catalysts, and purification issues, among others, are still challenging the scientific community.[31−35] In addition, the main drawback is the fact that the Biginelli reaction usually requires a (large) excess of at least one of the three commonly used reagents (i.e., aldehyde, 1,3-dycarbonyl compound, or (thio)urea); hence, a major limitation toward a greener and sustainable process.

Recently, we have demonstrated the importance of BMI·PF_6 to direct the formation and stabilization of some reactive intermediates of the Biginelli reaction carried out in ILs.[36] Due to our interest in the development of more sustainable catalytic reaction conditions[37,38] and our interest in the chemistry of ILs,[39,40] we report herein new results under heterogeneous and homogeneous catalysis to promote the Biginelli reaction. The developed conditions were then applied in the synthesis of biologically active DHPMs (e.g., enastron, monastrol, piperastrol). Finally, we also investigated both the mechanism and the origin of the ionic liquid effect over this reaction on the basis of mass spectrometry analyses and DFT calculations.

■ RESULTS AND DISCUSSION

Initially, we investigated the combination of a Bronsted acid TSIL with metal-containing (Lewis acid) anions as the catalysts to promote the Biginelli reaction (Scheme 2) using benzaldehyde, ethyl acetoacetate, and urea as the model reaction (Scheme 2). We also envisaged the reaction using the proportion 1.00:1.00:1.00 between the reagents toward a more efficient and greener process. The reaction performed with no catalyst resulted in only traces of the product independent of the reaction media, including the commonly used ILs (Scheme 2).

The efficiency of anionic Lewis acids with imidazolium cations has already been demonstrated by us[41] and by others[42] for different reactions. The cooperative effect of this combination (protic and metal-containing ILs as catalysts) may be very promising for catalysis, as some have recently explored.[43,44] The sulfonic acid group was chosen because some have demonstrated it may have a beneficial effect for the Biginelli reaction with encouraging results.[45] The use of preformed or in situ-prepared catalysts gave similar results. Table 1 summarizes the screening for the Lewis acid metal for the anion and the best solvent/medium for the reaction.

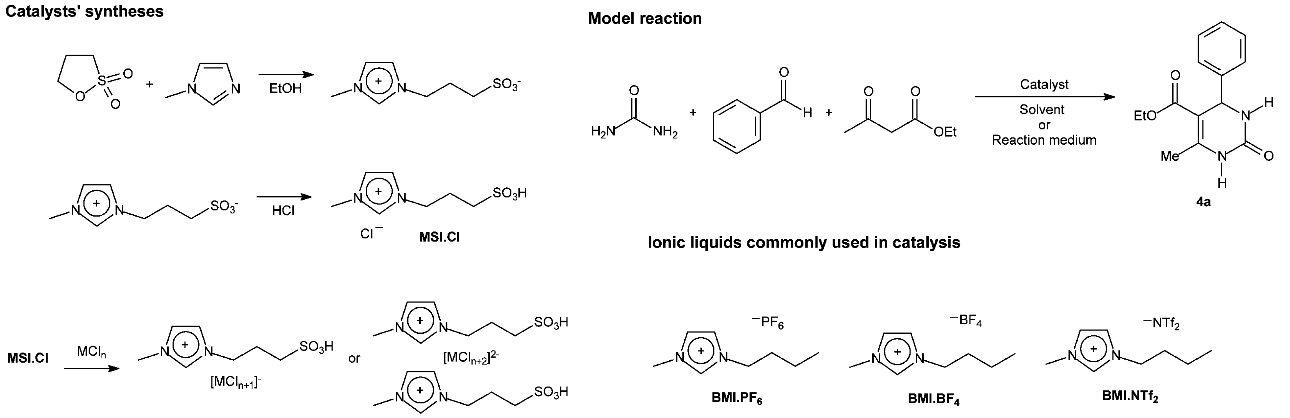
Table 1. Biginelli Reaction with Different Protic (MSI cation) Metal-Containing ILs as Catalysts[a]

entry	catalyst (10 mol %)	ionic liquid (or organic solvent) (1.0 mL)	yield (%) (1 h)	yield (%) (4h)
1	MSI·Fe_2Cl_7	H_2O	traces	
2	MSI·Fe_2Cl_7	MeOH	16	
3	MSI·Fe_2Cl_7	EtOH	26	
4	MSI·Fe_2Cl_7	MeCN	3	
5	MSI·Fe_2Cl_7	PhMe	4	
6	MSI·Fe_2Cl_7	CH_2Cl_2	traces	
7	MSI·Fe_2Cl_7	THF	4	
8	MSI·Fe_2Cl_7	BMI·NTf_2	29	
9	MSI·Fe_2Cl_7	BMI·PF_6	27	
10	MSI·Fe_2Cl_7	BMI·BF_4	40	73
11	MSI·$FeCl_4$	BMI·BF_4	37	70
12	$(MSI)_2$·$FeCl_4$	BMI·BF_4	26	60
13	$(MSI)_2$·$SnCl_5$	BMI·BF_4	29	44
14	$(MSI)_2$·$CuCl_4$	BMI·BF_4	40	47
15	MSI·$CuCl_2$	BMI·BF_4	27	43
16	$(MSI)_2$·$CoCl_4$	BMI·BF_4	32	52
17	$(MSI)_2$·$ZnCl_4$	BMI·BF_4	18	32
18	$(MSI)_2$·$ZrCl_5$	BMI·BF_4	32	50
19	$(MSI)_2$·$MnCl_4$	BMI·BF_4	22	54
20	MSI·$InCl_4$	BMI·BF_4	21	47

[a]Reactions were carried out with benzaldehyde (3.00 mmol), ethyl acetoacetate (3.00 mmol), and urea (3.00 mmol) at 90 °C. All reactions were conducted under homogenous catalytic conditions, and all yields refer to te isolated product (**4a**).

The reactions were initially analyzed using MSI·Fe_2Cl_7 over 60 min to evaluate the most active reaction media (Table 1, entries 1−10). It is worth highlighting that reactions performed in ILs, but in the absence of any catalyst, gave poor results (down to 35% at 90 °C). These results, indeed, are not surprising, since it is necessary to have a synergic effect using protic (acidic) ILs as the catalyst for the Biginelli reaction and under ultrasound irradiation to obtain good results, as already demonstrated.[46] After BMI·BF_4 proved to be the best media for

Scheme 2. Synthesis of the Bronsted Task-Specific Ionic Liquid (MSI cation) with Lewis Acid Anions Tested as the Catalysts for the Model Biginelli Reaction[a]



the Biginelli reaction, both other metal-containing catalysts and longer reaction times (4 h) were evaluated, as well (Table 1, entries 10–20). For all reactions, the product precipitates in the reaction media, allowing easy separation through filtration. The TSIL chloroferrate derivative (MSI·$FeCl_4$, Table 1, entry 11) showed good results but lower than the nonfunctionalized IL BMI·$FeCl_4$ (88–91%),[47] as previously reported. The same is true for the TSIL with the indate anion (MSI·$InCl_4$, Table 1, entry 20) when compared with the nonfunctionalized IL BMI·$InCl_4$ (95–98%).[48] These experiments show that the presence of a functionalization on the system indeed results in a destabilization of the catalytic system, thus lowering the obtained yields. It is worth highlighting, however, that those better yields (already reported) are described with reagent excess and optimized conditions. The use of MSI·Fe_2Cl_7 (Table 1, entry 10) proved to be a promising system, and reactions performed with different solvents (Table 1, entries 1–7) gave poor results when compared with BMI·BF_4 (Table 1, entry 10) as the ionic medium. BMI·NTf_2 (Table 1, entry 8) and BMI·PF_6 (Table 1, entry 9) also gave worse results compared with BMI·BF_4 (Table 1, entry 10), but much better yields than those in organic solvents. The system then had the temperature and catalyst concentration optimized (Figure 1) for the reaction.

The reaction profile (Figure S1 in the Supporting Information) showed that, under homogeneous catalytic conditions and using equimolar proportions of each reagent, the reaction requires 4 h to complete under optimized conditions. The effect of reagent excess was then tested under the same experimental conditions (Table 2).

It can be seen from Table 2 that an aldehyde excess has a direct beneficial effect over the reaction yields. Urea and ethyl acetoacetate excess have the opposite effect, indicating the preferred mechanism among the three accepted mechanisms (i.e., iminium, enamine and Knoevenagel mechanism, Supporting Information Scheme S1) is the iminium mechanism. These results are in full accordance with kinetic experiments recently reported, which indicate that an aldehyde excess favors the iminium mechanism.[49] The preferred mechanism pathway for the transformation under the developed conditions will be discussed in due course. It is clear from Table 2, however, that the iron-containing catalyst may be of great utility for the Biginelli synthesis, as will be shown herein.

It has been already reviewed that Bronsted acid (and Bronsted acid TSILs) may behave as superacids when supported (embedded) in ILs.[50,51] In this sense, we decided to support a strong known Bronsted acid ($H_3PW_{12}O_{40}$; HPW) to help in the promotion of the Biginelli reaction carried out in ILs. Drago and co-workers[52] reported the evaluation of several strong acids using pyridine as the basic probe. They observed that HPW was the strongest acid when compared with CF_3SO_3H, p-$CH_3C_6H_4SO_3H$, H_2SO_4, and others. Some doped Keggin heteropolyacids[53] and HPW[54] have already been tested as the catalyst for the Biginelli reaction in solvent-free versions (with good results). When tested under microwave irradiation[55] or supported in silica,[56] demonstrated yields ranged from reasonable to very good. The use of HPW in acetic acid as the solvent has also been described,[57] but it required long reaction times, and the use of pure acetic acid with reagent excess is not a sustainable condition. To the best of our knowledge, despite all promising results, experiments conducted in ILs to probe the effect on the reaction have not yet been described. Moreover, some drawbacks of such methodologies were the reagent excess and, in one of the cases, the requirement of a large catalyst load to obtain satisfactory results. Considering the expected superacid behavior in ILs, we supported the HPW in those three ILs and monitored the Biginelli reaction (Table 3).

Table 2. Effect of Reagent Concentrations Variation for the Model Reaction[a]

	reagent (mol %)			
entry	benzaldehyde	urea	ethyl acetoacetate	isolated yield (%) (**4a**)
1	3.00	3.00	3.00	65
2	3.00	3.00	4.50	65
3	3.00	4.50	3.00	57
4	4.50	3.00	3.00	82
5	3.00	3.00	9.00	74
6	3.00	9.00	3.00	60
7	9.00	3.00	3.00	85

[a] BMI·BF_4 (1.0 mL), 90 °C, 7 mol % (MSI·Fe_2Cl_7) for 4 h of reaction.

Table 3 shows that BMI·NTf_2 was the best IL for all cases, whereas for BMI·PF_6, the known anion degradation was noted,[58] making BMI·PF_6 not a good medium for the Biginelli reaction under the tested conditions. After 4 h and with 4 mol % of HPW in BMI·NTf_2, the desired Biginelli adduct **4a** was obtained almost quantitatively. It is worth highlighting that **4a** was synthesized with equimolar quantities of the reagents, thus representing a significant improvement on the reaction conditions.

Heterogeneous catalytic conditions by using zeolite beta as the acid catalyst have also been investigated in ILs. Zeolite β framework has a tridimensional channel system with micropores of 0.68 × 0.73 nm ([100] and [010] directions) and 0.56 × 0.56 nm ([001] direction) and that its disordered

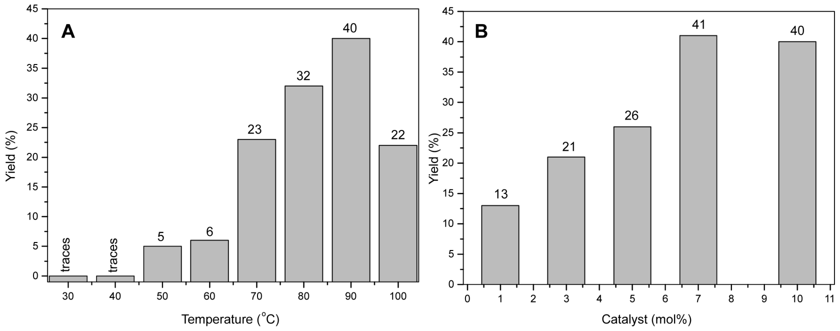


Figure 1. (A) Temperature and (B) catalyst concentration optimization using the model reaction (3.00 mmol of each reagent). The catalyst concentration was optimized at 90 °C (B), and the temperature was optimized with 10 mol % (A) of MSI·Fe_2Cl_7 in BMI·BF_4 (1.0 mL). Importantly, when the reaction was carried out with 7 mol % of the catalyst and at 90 °C, the desired product was obtained at 65% of yield (data not shown).

Table 3. Biginelli Reaction Promoted by HPW as the Catalyst in Ionic Liquids (1.0 mL)[a]

entry	catalyst (mol %)	ionic liquid (1.0 mL)	time (h)	yield (%) of **4a**
1	1	BMI·NTf$_2$	1	37
2	1	BMI·PF$_6$	1	30[b]
3	1	BMI·BF$_4$	1	30
4	1	BMI·NTf$_2$	2	41
5	1	BMI·PF$_6$	2	41[b]
6	1	BMI·BF$_4$	2	33
7	1	BMI·NTf$_2$	3	55
8	1	BMI·PF$_6$	3	42[b]
9	1	BMI·BF$_4$	3	37
10	1	BMI·NTf$_2$	4	69
11	1	BMI·PF$_6$	4	46[b]
12	1	BMI·BF$_4$	4	40
13	2	BMI·NTf$_2$	4	71
14	3	BMI·NTf$_2$	4	87
15	4	BMI·NTf$_2$	4	99
16	5	BMI·NTf$_2$	4	99

[a] Reactions were performed with 3.00 mmol of each reagent (model reaction) at 90 °C as homogeneous systems. [b] The system is dark, and product/reagent degradation was noted.

structure also shows as mesoporous, originating from the intergrowth of both polymorphs A and B.[59] Some of us have shown that the acidity of zeolite β is strongly dependent on its activation procedure.[60] The presence of strong Bronsted sites was observed only at lower calcination temperature (450 °C). These kinds of acid zeolites have been used for several catalyzed reactions, as reviewed elsewhere;[61−63] however, it is surprising that no study is found for the Biginelli reaction (or any multicomponent reaction) promoted by any zeolite when supported in ILs, despite the promising features of this combination. Some groups have described a catalytic system combining a TSIL (Bronsted acid ILs) supported in zeolitic structures as an ecoapproach for the synthesis of spiro compounds.[64] In this sense, some experiments have been carried out envisaging the achievement of an efficient catalytic system through the combination of the acid zeolite beta embedded in ILs. Moreover, the results could be used for comparing the efficiency of this heterogeneous system with homogeneous catalytic systems when applied to the Biginelli reaction carried out in ILs. Table 4 summarizes the obtained results of the heterogeneous catalytic system.

Reactions carried out in BMI·PF$_6$ and BMI·BF$_4$ could not be tagged as “green” because of anion and product degradation. The use of BMI·NTf$_2$, however, was shown to be promising. In the third reaction hour (Table 4, entry 7), compound **4a** was obtained in 65%. With 3 mol % of the catalyst, the reaction reaches almost quantitative yields in 3 h (Table 4, entry 14), thus showing great potential for use of the heterogeneous system in ILs. One drawback is that the product precipitates in the reaction media, thus making the product and catalyst (heterogeneous) separation a difficult task.

Because of the promising results obtained by the heterogeneous catalytic system, we decided to support the HPW (1%) in the zeolite beta and test the formed heterogeneous system. Some of us have recently described the citronellal cyclization using supported HPW on MCM-41[65] and some HPW derivatives as efficient catalysts in the esterification reaction of oleic acid with ethanol.[66] The obtained results for the Biginelli reaction are summarized in Table 5.

Table 4. Biginelli Reaction Promoted by Zeolite Beta as the Catalyst in Ionic Liquids (1.0 mL)[a]

entry	catalyst (mol %)	ionic liquid (1.0 mL)	time (h)	yield (%) of **4a**
1	1	BMI·NTf$_2$	1	23
2	1	BMI·PF$_6$	1	46[b]
3	1	BMI·BF$_4$	1	26
4	1	BMI·NTf$_2$	2	22
5	1	BMI·PF$_6$	2	19[b]
6	1	BMI·BF$_4$	2	12
7	1	BMI·NTf$_2$	3	65
8	1	BMI·PF$_6$	3	[b]
9	1	BMI·BF$_4$	3	11[b]
10	1	BMI·NTf$_2$	4	50[b]
11	1	BMI·PF$_6$	4	[b]
12	1	BM·BF$_4$	4	20[b]
13	2	BMI·NTf$_2$	3	90
14	3	BMI·NTf$_2$	3	99
15	4	BMI·NTf$_2$	3	99
16	5	BMI·NTf$_2$	3	99

[a] Reactions were performed with 3.00 mmol of each reagent (model reaction) at 90 °C as heterogeneous systems. [b] The system is dark, and product/reagent degradation was noted.

Table 5. Biginelli Reaction Promoted by Zeolite Beta Doped with HPW (1%) as the Catalyst in Ionic Liquids (1.0 mL)[a]

entry	catalyst (mol %)	ionic liquid (1.0 mL)	time (h)	yield (%) of **4a**
1	1	BMI·NTf$_2$	1	2
2	1	BMI·PF$_6$	1	6[b]
3	1	BMI·BF$_4$	1	4
4	1	BMI·NTf$_2$	2	20
5	1	BMI·PF$_6$	2	14[b]
6	1	BMI·BF$_4$	2	10
7	1	BMI·NTf$_2$	3	41
8	1	BMI·PF$_6$	3	[b]
9	1	BMI·BF$_4$	3	11[b]
10	1	BMI·NTf$_2$	4	59
11	1	BMI·PF$_6$	4	[b]
12	1	BMI·BF$_4$	4	[b]
13	2	BMI·NTf$_2$	3	62
14	3	BMI·NTf$_2$	3	85
15	4	BMI·NTf$_2$	3	75[b]
16	5	BMI·NTf$_2$	3	77[b]

[a] Reactions were performed with 3.00 mmol of each reagent (model reaction) at 90 °C as heterogeneous systems. [b] The system is dark and product/reagent degradation was noted.

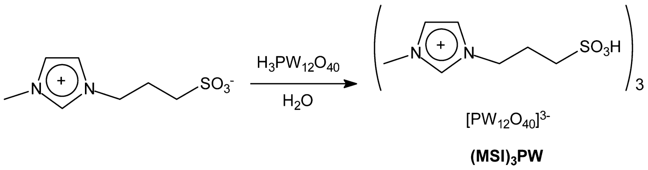
The strategy of doping the zeolite with HPW showed poor results. Indeed, a fast degradation of the product and the aldehyde was observed. Lower yields were observed when compared with those described in Table 4, even though **4a** could be obtained in 85% in 3 h with 3 mol % of the catalyst (Table 5, entry 14).

Overall, when comparing the catalytic systems (homogeneous and heterogeneous) described herein, the homogeneous systems showed some advantages, such as:

(i) No product/reagent degradation was noted;
(ii) The system is easy to handle, and the product separation is easier, since only one filtration is necessary (the product precipitates in the reaction media);
(iii) The metal-containing catalysts could be prepared in situ;
(iv) It is easier to visualize the reaction.

Despite the fact that the heterogeneous catalysis proceeds faster (3 h) than the homogeneous (4 h), the promising features of the homogeneous systems and the drawbacks for the heterogeneous systems (product and catalyst separation) prompted us to perform the synthesis of other MSI-derivative catalysts, as shown in Scheme 3, and to test them under homogeneous catalytic conditions.

Scheme 3. Synthesis of the Bronsted IL (MSI cation) with Lewis Anions Tested as the Catalysts for the Model Biginelli Reaction



The catalyst $(MSI)_3PW$ has already been described[67] and applied for esterification[68] and desulfurization of fuels.[69] Some heteropolyanions ($PW_{12}O_{40}{}^{3-}$) with other cations (rather than imidazolium) have also been used for Prins reactions,[70] esterification,[71] and desulfurization of fuels.[72] For the above-mentioned reasons, we envisaged this combination could be very useful for Biginelli synthesis (Table 6).

Table 6. Biginelli Reaction Promoted by $(MSI)_3PW$ as the Catalyst in Ionic Liquids (1.0 mL)[a]

entry	catalyst (mol %)	ionic liquid (1.0 mL)	time (h)	yield (%) of **4a**
1	1	BMI·NTf$_2$	1	6
2	1	BMI·PF$_6$	1	15[b]
3	1	BMI·BF$_4$	1	6[b]
4	1	BMI·NTf$_2$	2	16
5	1	BMI·PF$_6$	2	17[b]
6	1	BMI·BF$_4$	2	5[b]
7	1	BMI·NTf$_2$	3	60
8	1	BMI·PF$_6$	3	31[b]
9	1	BMI·BF$_4$	3	10[b]
10	1	BMI·NTf$_2$	4	65
11	1	BMI·PF$_6$	4	33[b]
12	1	BMI·BF$_4$	4	15[b]
13	2	BMI·NTf$_2$	4	71
14	3	BMI·NTf$_2$	4	77
15	4	BMI·NTf$_2$	4	87
16	5	BMI·NTf$_2$	4	99

[a] Reactions were performed with 3.00 mmol of each reagent (model reaction) at 90 °C as homogeneous systems. [b] The system is dark, and product/reagent degradation was noted.

Once more, BMI·NTf$_2$ was shown to be the best reaction media. The catalyst $(MSI)_3PW$ has the advantage of being completely ionic, thus rendering it possibly a more efficient support in the tested ILs and allowing the possibility of recycling. Indeed, five runs were conducted (Figure 2), and from the third run on, a slight loss of the catalytic activity was noted, indicating a slight catalyst leaching from the ionic media.

Once we had optimized all the catalytic reaction conditions with the different developed catalysts, we decided to extend the methodology to the synthesis of different DHPMs to compare five developed catalytic systems. The results are summarized in Table 7.

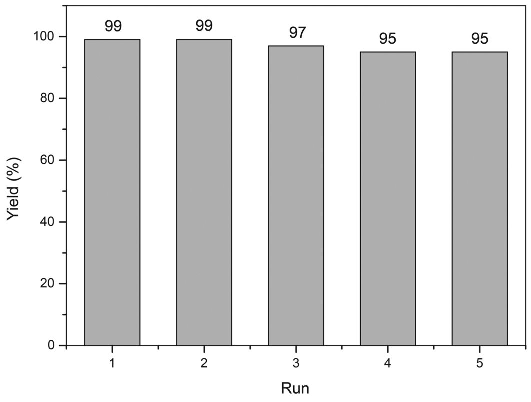


Figure 2. Catalyst's recycling (5 mol % of the catalyst ($(MSI)_3PW$), 4 h in BMI·NTf$_2$ (1 mL) at 90 °C; recharges using 3.00 mmol of each reagent).

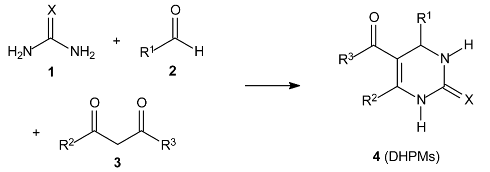
It is noted from Table 7 that all compounds could be obtained at least with very good yields (above 76%). The biologically active compounds Monastrol (**4e**, 98%) and its oxo-analogue (**4d**, 99%), Enastron (**4j**, 76%), Dimethylenastron (**4k**, 87%), and Piperastrol (**4n**, 85%) were obtained in excellent yields (see Table 7), thus showing that different methodologies could be used for a straightforward synthesis of a desired DHPM derivative.

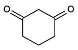
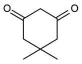
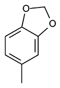
To investigate the mechanism with $(MSI)_3PW$ as the catalyst, high-resolution electrospray ionization quadrupole-time-of-flight mass spectrometry (ESI-QTOF-MS) analyses were performed. Very recently, we have determined the role of the reagents for the in situ formation of some reactive intermediates for a Lewis acid-catalyzed version of the Biginelli reaction.[36] The potential of MS to evaluate the Biginelli reaction has already been reported, and it proved to be efficient for studying all three accepted mechanisms[73] (see Supporting Information Scheme S1 for the mechanisms). The soft ionization from the ESI source allows continuous snapshots of the reaction with a gentle transfer from the solution to the gas phase,[74] thus allowing excellent online monitoring of several reactions with the possibility of detection and characterization of supramolecular species[75] (including transient intermediates of catalyzed reactions[76,77]). First, the best catalyst ($(MSI)_3PW$) was characterized in both positive (Supporting Information Figure S2) and negative (Figure 3) ion modes.

It is noted that the most intense set of signals (m/z 953–963) is attributed to PW^{3-} (PW = $PW_{12}O_{40}$), indicating an excellent dissociation of the acidic hydrogens and the relative stability of the triply charged anionic species. The doubly charged anionic species $[PW + H]^{2-}$ was also detected (m/z 1432–1448), thus in accordance with the good stability of the conjugate base. A low-intensity set of signals in the range of m/z 1635–1651 ($[PW + MSI + (MSI - H)]^{2-}$, where MSI − H is the zwitterionic MSI derivative, i.e., the dissociation of the acid hydrogen from the side group) could be attributed to the neutral zwitterionic species (MSI − H) associated with $[PW + MSI]^{2-}$ (m/z 1532–1548), which in turn was also detected (see Figure 3). No set of signals related to $[PW + 2H]^-$ was noted. To probe the ionic liquid effect and its influence on the catalyst behavior, a mixture of $(MSI)_3PW$ and BMI·NTf$_2$ was analyzed (Figure 4) and compared with the spectrum in the absence of any IL (Figure 3).

In the presence of BMI·NTf$_2$, the set of signals of m/z 1432–1448 ($[PW + H]^{2-}$) almost disappeared, thus showing that

Table 7. Dihydropyrimidinones (DHPMs) Synthesized Using the Developed Conditions with Different Catalysts at 90 °C Using 3.00 mmol of Each Reagent and 1.0 mL of the Ionic Liquid



DHPM	Product				Yields (%) for the tested catalysts				
(4a-o)	R^1	R^2	R^3	X	MSI.Fe_2Cl_7[a]	HPW[b]	Zeolite beta[c]	Zeolite beta (1% HPW)[d]	$(MSI)_3PW$[e]
4a	Ph	CH_3	CH_3CH_2O	O	87	99	99	85	99
4b	Ph	CH_3	CH_3	O	76	96	82	79	99
4c	Ph	CH_3	CH_3CH_2O	S	43	88	99	98	99
4d	3-OH-Ph	CH_3	CH_3CH_2O	O	99	37	66	60	75
4e	3-OH-Ph	CH_3	CH_3CH_2O	S	50	98	33	98	50
4f	3-NO_2-Ph	CH_3	CH_3CH_2O	O	41	81	69	63	98
4g	3-NO_2-Ph	CH_3	CH_3	O	57	93	54	63	98
4h	H	CH_3	CH_3CH_2O	O	56	82	86	76	94
4i	4-OH-3OCH_3-Ph	CH_3	CH_3CH_2O	O	59	43	46	80	99
4j	3-OH-Ph			S	76	59	59	59	60
4k	3-OH-Ph			S	21	87	21	53	60
4l	2-NO_2-Ph	CH_3	CH_3	O	65	98	70	70	86
4m	2-OH-Ph	CH_3	CH_3CH_2O	S	12	36	15	97	60
4n		CH_3	CH_3CH_2O	S	35	85	19	71	74
4o	3-OH-Ph	CH_3	CH_3	O	76	99	33	65	85

[a] 7 mol % of the catalyst, 4 h in BMI·BF_4, and 9.00 mmol of the aldehyde (homogeneous system). [b] 4 mol % of the catalyst, 4 h in BMI·NTf_2 (homogeneous system). [c] 3 mol % of the catalyst, 3 h in BMI·NTf_2 (heterogeneous system). [d] 3 mol % of the catalyst, 3 h in BMI·NTf_2 (heterogeneous system). [e] 5 mol % of the catalyst, 4 h in BMI·NTf_2 (homogeneous system).

in the presence of the IL, the dissociation of the acid is even more effective, hence, making the acidic character of the catalyst stronger. A set of signals of m/z 1501−1517 appeared and was attributed to $[PW + BMI]^{2-}$, where BMI is the imidazolium cation (1-*n*-butyl-3-methylimidazolium of 139 Da). The MS data clearly showed a more effective dissociation of the acidic moiety, thus, in accordance with the expected superacid behavior of Bronsted acids supported in ILs.

After the catalyst and catalyst + BMI·NTf_2 interactions and behavior characterizations, the model reaction was monitored online, and interesting signals could be detected and characterized by collision-induced dissociation (CID) showing some Biginelli reaction intermediates in high resolution ESI-QTOF product ion spectra (Figure 5).

It is noted that the iminium mechanism (Scheme 4, also see Supporting Information Scheme S1) is clearly favored under the tested conditions. The key intermediate of m/z 149 was isolated and characterized. The intermediate of m/z 279 could also be isolated and characterized by ESI(+)-MS/MS. An intermediate of m/z 237 from the Knoevenagel mechanism should also be noted; however, only the intermediate from the first step could be intercepted, indicating the addition takes place in a reversible manner and the preferred pathway is the iminium mechanism.

To gain insights into the mechanism and mainly into the ionic liquid effect in the stabilization of the charged intermediates, theoretical calculations were also performed and discussed. The theoretical investigations were centered on the key intermediates from the iminium mechanism (Scheme 4), that is, the iminium cation (ion of m/z 149, Figure 5A, **Int I**) and the ion from the addition to the iminium (ion of m/z 279, Figure 5B, **Int II**). We have also considered the association with the anion $[NTf_2]^-$ (bis(trifluoromethylsulfonyl)imide)) to those ions in both cis and trans conformations (Figure 6).

It is shown in Figure 6 that upon association with the anion (cis or trans conformations), intermediates **Int I** and **Int II** change their conformations in a similar manner. When **Int I** is close to the anion, the anion changes its conformation from cis to trans (Figure 6E), and this was not observed for intermediate **Int II**. This conformational change allows a better ion-pairing formation with steric interactions minimized. The thermodynamics involved in

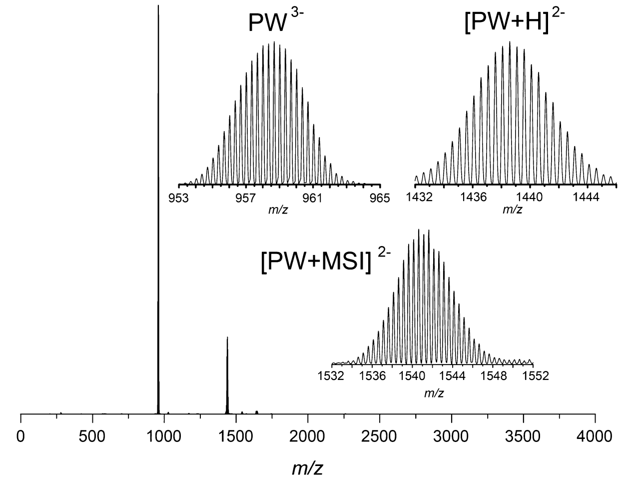


Figure 3. ESI(−)-QTOF mass spectrum of the catalyst $(MSI)_3PW$. MSI = functionalized cation (205 Da) and PW = $[PW_{12}O_{40}]^{3-}$.

the stabilization of intermediates through ion-pairing has been investigated, as well (Table 8).

Table 8. Thermodynamics Parameters Calculated at the M062X/6-311++g(2d,2p)//B3LYP/6-31+G(d,p) Level of Theory for the Ion-Pairing of Intermediates Int I and Int II upon Association with $[NTf_2]^-$

step/ parameter	ΔG (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS (cal mol^{-1} K^{-1})	binding energy (kcal mol^{-1})
Int I + NTf_2 (cis)	−84.05	−96.01	−40.13	−97.00
Int I + NTf_2 (trans)	−83.04	−94.34	−37.88	−95.37
Int II + NTf_2 (cis)	−76.80	−89.94	−44.09	−90.86
Int II + NTf_2 (trans)	−73.95	−86.1s1	−40.80	−87.07

No significant difference was noted for $[NTf_2]^-$ in either of its conformations, only a slight difference favoring the trans isomer. For all cases, the Gibbs free energy shows a highly favored process, in accordance with the stabilization of charged intermediates promoted by ILs through ion-paring and formation of aggregates (ionic liquid effect). A large binding energy is also noted for all cases, indicating a strong interaction between the charged intermediates and $[NTf_2]^-$. Theoretical calculated values are in accordance with the observed ionic liquid effect over the Biginelli reaction expressed by testing homogeneous and heterogeneous conditions. For all cases, ILs were better than organic solvents. It is necessary to bear in mind that in the ionic medium, additional associations (with both imidazolium cations and $[NTf_2]^-$ anions) will take place, therefore, with additional stabilizing effects over the system. In this sense, theoretical calculations were important and point firmly to the spontaneous formation of supramolecular aggregates with the charged intermediates.

In summary, we have demonstrated the efficiency of several catalytic conditions to perform the Biginelli reaction with a considerable ionic liquid effect. Heterogeneous and homogeneous conditions were tested, and homogeneous conditions were shown to be more appropriate for many cases, avoiding product/reagent degradation. Five biologically active compounds (Monastrol (**4e**) and its oxo-analogue (**4d**), Enastron (**4j**), Dimethylenastron (**4k**), and Piperastrol (**4n**)) were obtained in excellent yields under different conditions. ESI-MS analyses showed that under the best homogeneous conditions (using $(MSI)_3PW$ as the catalyst) the iminium mechanism is favored, and two key intermediates were detected and characterized via ESI-MS/MS. MS analyses also revealed the origin for the high stability of the conjugate base using the Bronsted acid catalyst $(MSI)_3PW$, allowing a better understanding of the superacid behavior of Bronsted acids when supported in ILs.[50,51] Finally, theoretical calculations helped us to understand the efficiency of the stabilization of the charged intermediates of the Biginelli reaction in ILs. The calculated values showed how spontaneous, efficient, and strong the associations of those positively charged intermediates with the anion ($[NTf_2]^-$) are. It also allowed us to understand the ionic liquid effect over the reaction through ion-pairing and aggregate formation. The application of the described catalysts under optimized conditions for other multicomponent reactions is underway and will be published in due course.

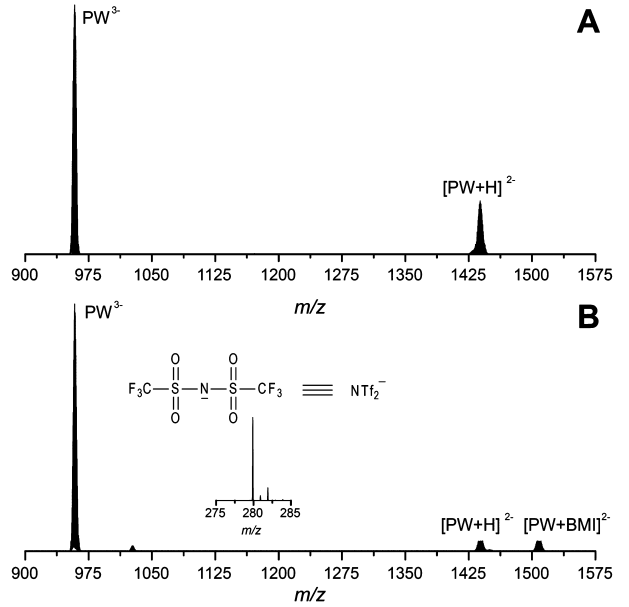


Figure 4. (A) ESI(−)-QTOF mass spectrum of the catalyst $(MSI)_3PW$. (B) ESI(−)-QTOF mass spectrum of the catalyst $(MSI)_3PW$ in the presence of BMI·NTf_2. Note the anion $[NTf_2]^-$ of *m*/*z* 280 (see the inset). BMI = 1-*n*-butyl-3-methylimidazolium cation (139 Da).

■ EXPERIMENTAL SECTION

General. Chemicals and solvents were purchased from commercial sources. Liquid reagents and solvents were distilled prior to use.

ESI-MS and ESI-MS/MS measurements were performed in the positive ion mode (*m*/*z* 50−2000 range) on a HDMS instrument. This instrument has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-flight (oa-TOF) geometry and was used in the TOF V+ mode. All samples were dissolved in methanol to form 50 μM solutions and were directly infused into the ESI source at a flow rate of 10 μL/min after 5 min at 90 °C. ESI source conditions were as follows: capillary voltage 3.0 kV, sample cone 20 V, extraction cone 3 V.

All electronic structure calculations performed in this work were performed within Kohn−Sham density functional theory (DFT) formalism.[78,79] The geometry optimizations were carried out using the B3LYP/6-31+G(d,p) level of calculation. At the

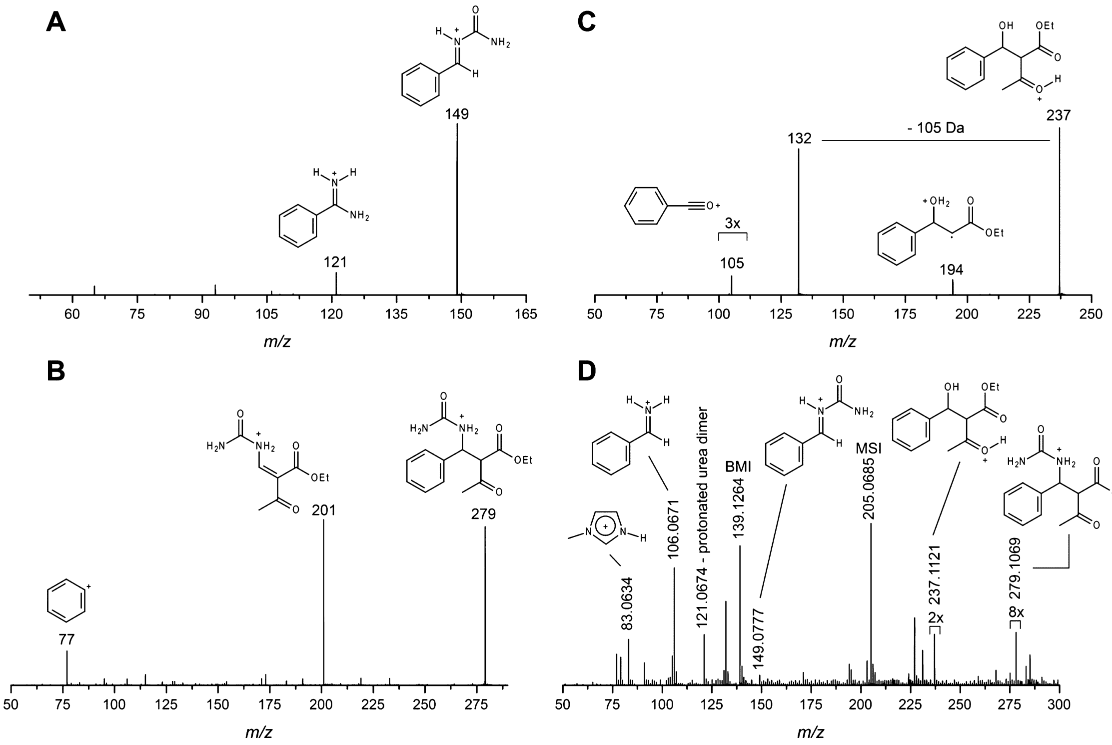
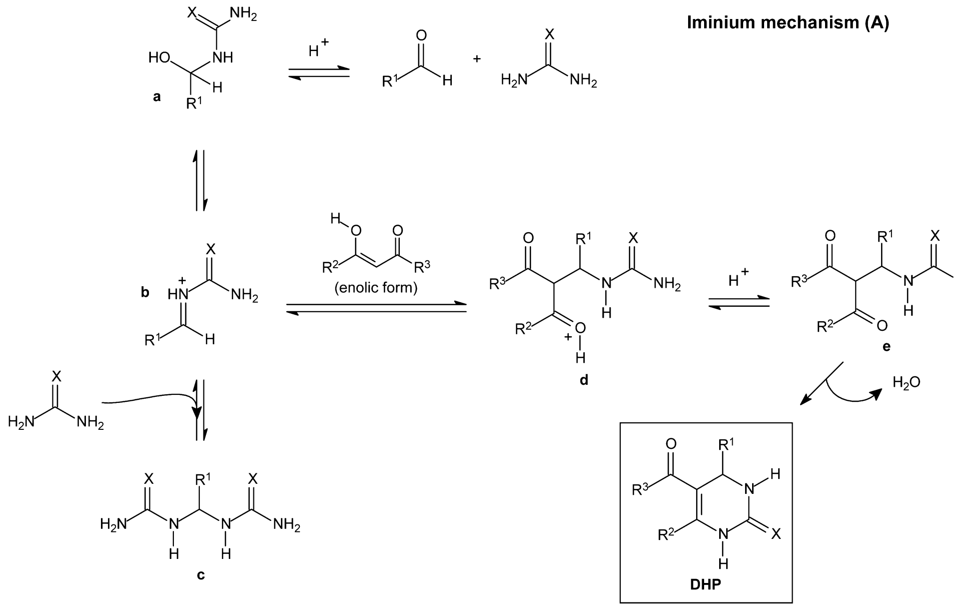


Figure 5. Model reaction catalyzed by $(MSI)_3PW$ in the presence of BMI·NTf_2. (A) ESI(+)-QTOF product ion spectrum of *m/z* 149. (B) ESI(+)-QTOF product ion spectrum of *m/z* 279. (C) ESI(+)-QTOF product ion spectrum of *m/z* 237. (D) ESI(+)-QTOF mass spectrum of the model reaction.

Scheme 4. The Proposed Iminium Mechanism for the Biginelli Reaction under Acidic Conditions



same level of theory, the fundamental vibrational frequency calculations were carried out to ensure the true minima, to compute zero-point vibrational energy (ZPVE), and to derive the thermochemical corrections for the heat of formation, Gibbs free energy, and the binding energy. The calculated frequencies were scaled by a factor of 0.9642, and the ZPVE and thermodynamic functions were calculated at 298.15 K and 1 atm. The optimized geometries were used for the single point calculation at the M06-2X/6-311++g(2d,2p) level of calculation. The M06-2X meta exchange-correlation functional is recommend for applications involving main-group thermochemistry, kinetics, noncovalent interactions, and electronic excitation energies to valence and Rydberg states.[80] To avoid a basis-set superposition error, the thermodynamics properties and binding energies were counter-poise-corrected using the standard approach by Boys and Bernardi.[81] All theoretical calculations were carried out using the Gaussian 09 program suite.[82]

NMR spectra were recorded on a 7.05 T instrument using a 5-mm internal diameter probe operating at 300 MHz for ^1H and at 75 MHz for ^{13}C. Chemical shifts were expressed in

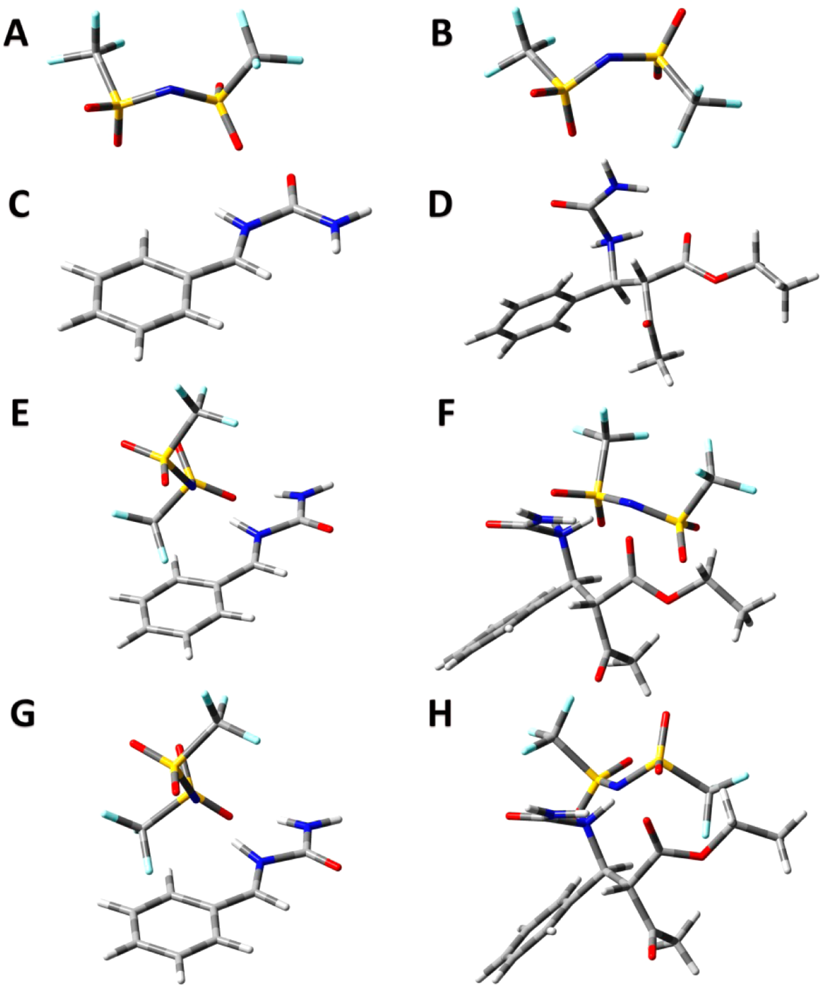


Figure 6. Optimized geometries at the B3LYP/6-31+G(d,p) level of theory. (A) Anion (NTf_2) cis. (B) Anion (NTf_2) trans. (C) **Int I** (iminium). (D) **Int II** (addition to the iminium). (E) **Int I** associated with the anion $[NTf_2]^-$. Note the anion changed to its trans conformation. (F) **Int II** associated with the anion $[NTf_2]^-$ (cis). (G) **Int I** associated with the anion $[NTf_2]^-$ (trans). (H) **Int II** associated with the anion $[NTf_2]^-$ (trans).

parts per million (ppm) and referenced by the signals of the residual hydrogen atoms of the deuterated solvent (DMSO-d_6), as indicated in the legends.

Zeolite β in the ammonium form was calcined at 450 °C for 1 h in a muffle furnace. The zeolite full characterization has been described elsewhere.[60] The 12-tungstophosphoric acid ($H_3PW_{12}O_{40}\cdot nH_2O$ or HPW) was obtained from commercial sources and dried at 200 °C for 1 h before its utilization. Zeolite β doped with HPW (1%) was prepared by the aqueous impregnation procedure. The zeolitic structure was stirred in a HPW solution at 80 °C until dryness, affording the doped zeolite quantitatively.

The known MSI cation[83] was synthesized as follow: To a solution of 1,3-propanesultone (20 mmol) dissolved in ethanol (100 mL) was added 1-methylimidazole (20 mmol), and the mixture was allowed to react at 100 °C for 24 h. The white zwitterionic solid formed was washed with ethyl acetate, filtered, and dried in vacuum. Afterward, a stoichiometric amount of acid (HCl) was added to an aqueous solution of the zwitterionic solid, and the mixture was heated at 50 °C for 18 h. The solution was concentrated under vacuum, and a white solid precipitated after the addition of toluene. The solid with MSI cation was washed with ethyl acetoacetate and dried in vacuum at 50 °C for 6 h. Alternatively, dry HCl can be bubbled in a suspension of the zwitterionic solid in CH_2Cl_2 for 24 h. All metal (anion)-containing catalysts (see Table 1) were obtained by mixing the metal chloride salt with MSI·Cl and heating (80 °C) under inert atmosphere for 1 h, affording the metal catalysts in quantitative yields. The known[72] $(MSI)_3PW$ was prepared by treating the zwitterionic solid (15 mmol) with HPW (5 mmol) in 30 mL of water:methanol (1:1) at 50 °C for 24 h. Afterward, the solvent was concentrated under vacuum, and the white solid precipitated was washed with ethyl ether and dried in vacuum, affording the desired product in quantitative yield.

General Procedure for the Biginelli Reaction with the Five Different Methods.

(a) A sealed Schlenk tube containing 1 mL of BMI·BF_4, 9.00 mmol of the aldehyde, 3.00 mmol of the 1,3-dicarbonyl compound, 3.00 mmol of urea (or thiourea), and MSI·Fe_2Cl_7 (7 mol %) was allowed to react at 90 °C for 4 h. Products were purified by chromatographic column eluted with mixtures of hexane/ethyl acetate, or if the product precipitated in the reaction medium, it was filtered and washed with cold ethanol.

(b) A sealed Schlenk tube containing 1 mL of BMI·NTf_2, 3.00 mmol of the aldehyde, 3.00 mmol of the 1,3-dicarbonyl compound, 3.00 mmol of urea (or thiourea), and HPW (4 mol %) was allowed to react at 90 °C for 4 h. Substrates were purified by a chromatographic column eluted with mixtures of hexane/ethyl acetate, or if the product precipitated in the reaction medium, it was filtered and washed with cold ethanol.

(c) A sealed Schlenk tube containing 1 mL of BMI·NTf$_2$, 3.00 mmol of the aldehyde, 3.00 mmol of the 1,3-dicarbonyl compound, 3.00 mmol of urea (or thiourea), and zeolite beta (3 mol %) was allowed to react at 90 °C for 3 h. Substrates were purified by a chromatographic column eluted with mixtures of hexane/ethyl acetate, or if the product precipitated in the reaction medium, it was filtered and washed with cold ethanol.

(d) A sealed Schlenk tube containing 1 mL of BMI·NTf$_2$, 3.00 mmol of the aldehyde, 3.00 mmol of the 1,3-dicarbonyl compound, 3.00 mmol of urea (or thiourea), and zeolite beta-1% HPW (3 mol %) was allowed to react at 90 °C for 3 h. Substrates were purified by a chromatographic column eluted with mixtures of hexane/ethyl acetate, or if the product precipitated in the reaction medium, it was filtered and washed with cold ethanol.

(e) A sealed Schlenk tube containing 1 mL of BMI·NTf$_2$, 3.00 mmol of the aldehyde, 3.00 mmol of the 1,3-dicarbonyl compound, 3.00 mmol of urea (or thiourea), and MSI$_3$PW (5 mol %) was allowed to react at 90 °C for 4 h. Substrates were purified by a chromatographic column eluted with mixtures of hexane/ethyl acetate, or if the product precipitated in the reaction medium, it was filtered and washed with cold ethanol.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for the synthesized compounds, cited Schemes and Figures, and Cartesian coordinates and energy and thermal corrections for all of the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

B.A.D.N. thanks INCT-Catalysis and all founding sources. This work has been supported in part by CAPES, CNPq, FINEP-MCT, FINATEC, FAPESP, FAPDF, DPP-UnB, and ANP-PETROBRAS.

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