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Facts, Presumptions, and Myths on the Solvent-Free and Catalyst-Free Biginelli Reaction. What is Catalysis for?

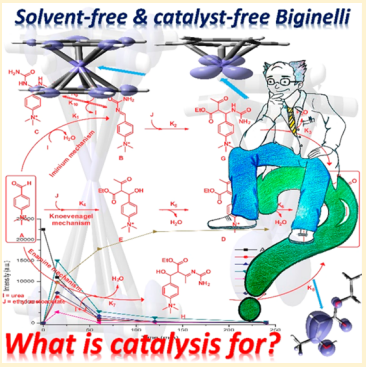
Haline G. O. Alvim,[†] Tatiani B. Lima,[‡] Aline L. de Oliveira,[†] Heibbe C. B. de Oliveira,[†] Fabricio M. Silva,[†] Fabio C. Gozzo,[‡] Roberto Y. Souza,[†] Wender A. da Silva,[†] and Brenno A. D. Neto*[,†]

[†]Laboratory of Medicinal and Technological Chemistry, University of Brasília, Chemistry Institute (IQ-UnB), Campus Universitário Darcy Ribeiro, P.O.Box 4478, Brasília, Distrito Federal CEP 70904-970, Brazil

[‡]Institute of Chemistry, University of Campinas (Unicamp), Campinas, São Paulo 13083-970, Brazil

Supporting Information

ABSTRACT: The current manuscript describes the role and importance of catalysis and solvent effects for the Biginelli multicomponent reaction. The overwhelming number of new catalysts and conditions recently published for the Biginelli synthesis, including in some manuscripts entitled "catalyst-free" and/or "solvent-free" have incentivized controversies and hot debates regarding the importance of developing new catalysts and reaction conditions to perform this very important multicomponent reaction. These so-called "catalyst-free" reports have generated much confusion in the field, requiring urgent elucidations. In this manuscript, we exemplify, demystify, and discuss the crucial role of catalysis, solvent effects, mechanisms, kinetics, facts, presumptions, and myths associated with the Biginelli reaction aiming to avoid current and future confusion and to stimulate new approaches.



INTRODUCTION

Especially in the last 2 decades, the chemistry and biology of 3,4-dihydropyrimidin-2(1*H*)-ones (or -thiones), also referred to as DHPMs, have experienced a return to prominence. This fact is clearly evidenced by the large number of important reviews directly dealing with developments and improvements of the reaction conditions for DHPM synthesis, new catalysts, solvent effects, and biological/medicinal effects.[1−18]

Because of their already known biological activities as calcium channel modulators, mitotic kinesin inhibitors, adrenergic receptor antagonists, antibacterials, antivirals, and others (see the cited reviews), DHPM derivatives (examples in Figure 1) have attracted much attention and interest of many research groups, mainly considering the possibility of diversity generation and direct access to new libraries of bioactive compounds, which may be even active also as racemic compounds.[19−24]

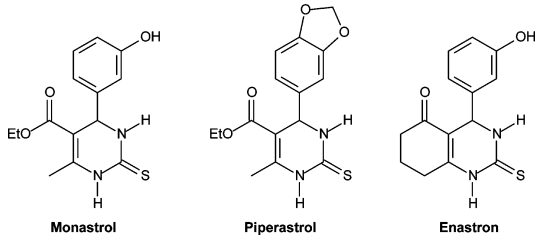
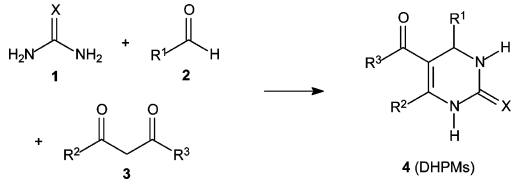


Figure 1. Some examples of known biologically active dihydropyrimidinones (DHPMs).

In this context, the Biginelli multicomponent reaction (Scheme 1), announced by Pietro Biginelli in 1891 in a series of four preliminary descriptions,[25−28] is the most direct and elegant methodology currently applied for the synthesis of DHPMs. Indeed, what is nowadays known as his eponymous reaction was born as a controversial reaction, since the original proposed structure for the Biginelli adduct was wrongly assigned and had to be later revisited.[29] Curiously, many authors wrongly describe that the Biginelli reaction was discovered in 1893, while actually in this year Biginelli published the full account of his reaction.[30,31] The history of this reaction and of the man behind the reaction has been nicely reviewed elsewhere.[29]

Scheme 1. The General Biginelli Reaction Used in the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones (or -thiones), also Known as DHPMs



Somehow, controversies surrounding the Biginelli reaction are still hotly debated. For instance, there is no consensus about the

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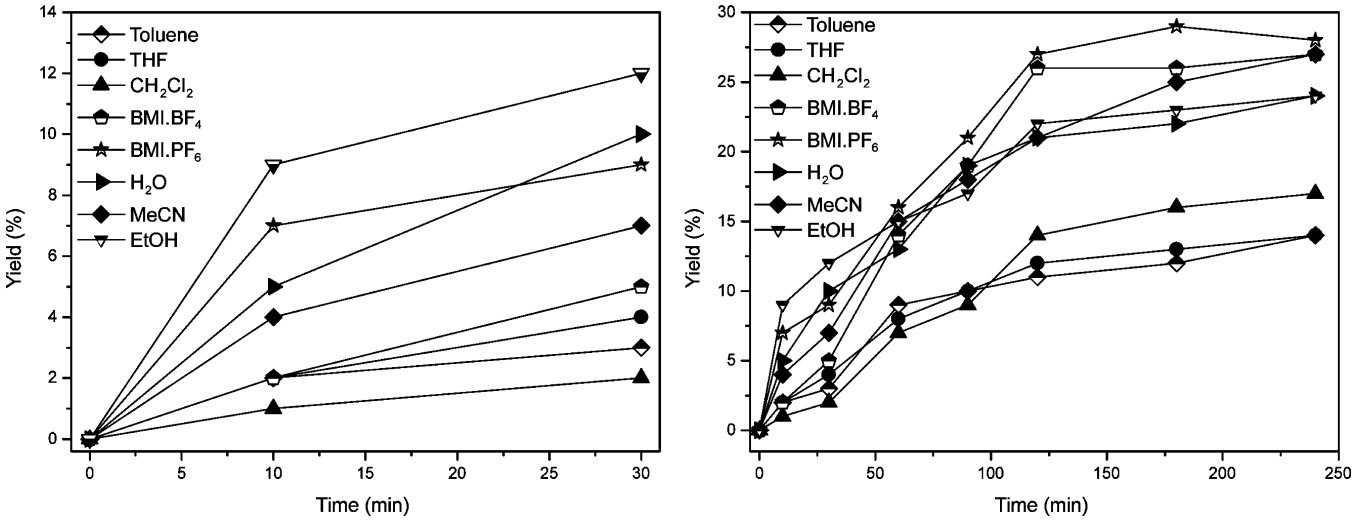

Figure 2. Reaction profiles (model reaction) in different solvents in a real catalyst-free version of the Biginelli reaction at 100 °C: (left) initial time and (right) the full profile. All points refer to isolated yields.

actual mechanism for this transformation, and at least three propositions are well accepted and discussed (i.e., iminium, enamine, or Knoevenagel mechanisms).[32−36] Independently of the used methodology or the preferred reaction mechanism, to the best of our knowledge, the importance of DHPMs have never been questioned or doubted.

As one could expect, mostly motivated by their biological importance, several new approaches to perform the Biginelli reaction can be found in the literature. However, harsh reaction conditions, reagent excess, high temperatures, toxic solvents, expensive catalysts, purification issues, low yields, low selectivities, and long reaction times are drawbacks commonly observed for DHPM syntheses using this three-component reaction. The development of improved reaction conditions and new catalysts therefore became the natural solution to overcome all these shortcomings associated with the Biginelli reaction (as highlighted in the cited reviews). Despite the increasing number of new catalysts and conditions for DHPMs syntheses, some contentious publications have described the supposedly "catalyst-free" version of the Biginelli reaction, as will be discussed and analyzed in due course. It is a fact that the Biginelli reaction can be carried out in catalyst-free versions, but with severe limitations, and this topic will be deeply evaluated herein.

Another controversial issue related to the Biginelli reaction is the solvent effect. Despite being considered to be an effective reaction due to its multicomponent character (one-pot reaction), many of the developed conditions require the use of toxic and expensive solvents, therefore contrasting with the green and promising features of the Biginelli reaction. In this sense, alternative solvents or media such as ionic liquids (ILs),[5] PEG,[37] and water[38] have been successfully tested. Moreover, aiming at greener, more sustainable, and ecofriendly conditions, many solvent-free versions of this reaction have also been reported.[14] As cited before, PEG has also been used with success,[39] but the unique properties of PEG as an alternative phase-transfer catalyst[40] and its effect on catalytic efficiency (catalyst-philic) are well documented.[41]

At this point, one could reasonably question why it is necessary to develop new catalysts or the use of any solvent (or other medium) considering that the reaction works under solvent-free and catalyst-free versions. Despite appearing to be a tough question to answer, the truth is relatively simple: it is necessary to surpass all of the aforementioned drawbacks associated with this reaction. It is also important to bear in mind that there are many reagents and substrates less reactive and more sensitive than the generally tested model Biginelli reaction, that is, a mixture of benzaldehyde, urea, and ethyl acetoacetate affording one of the simplest DHPM. Moreover, as is general knowledge, there are dozens of catalyzed reactions that work with no catalyst but, under noncatalyzed conditions, important features such as low temperatures, fast reactions, higher yields, higher selectivities, more amenable reaction conditions, higher TON and TOF, and other important features are usually severely limited. For instance, under catalyzed conditions, the synthesis of DHPMs may occur in only 10−15 min of reaction,[42] but reagent excesses were unfortunately still required. In a different example, the catalyzed reaction is described to proceed with yields ranging from poor to excellent at 25 °C,[43] but long reaction times were needed to achieve such yields. Alternative methodologies such as microwave irradiation[44] and ultrasound[45] have also been reported with yields ranging from reasonable to good. The application of some catalysts for the Biginelli reaction under microwave[46] or ultrasound[47] conditions has been already described, and improved yields could be achieved when compared with those catalyst-free versions. More recently, the reaction under a grinding process has also been described, but the presence of an iron-based catalyst was needed.[48]

Due to our interest in the Biginelli reaction,[49−51] in the current manuscript, we intend to evaluate the so-called "catalyst-free" conditions and solvent effects and compare some new results and mechanistics insights with those previously reported. We also intend this manuscript to be critical and elucidative regarding facts, presumptions, and myths surrounding the Biginelli reaction, aiming to avoid current and future confusion, strife, and doubts about the importance of catalysis for the development and improvements of this very important multicomponent reaction (MCR).

RESULTS AND DISCUSSION

We initially tested the reactions in actual catalyst-free versions upon mixing benzaldehyde (2.00 mmol), urea (3.00 mmol), and ethyl acetoacetate (2.00 mmol) at 100 °C (known as the model

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reaction) in several solvents (1 mL) to evaluate the solvents effects. Reaction profile monitoring is shown in Figure 2.

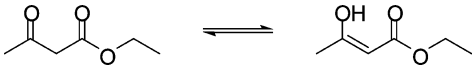
It is important to note that the tested ionic liquids (ILs) did play a role for the Biginelli reaction and the best yields were obtained with those ionic fluids (28% for BMI·PF_6 and 27% for BMI·BF_4). The positive IL effect over MCRs has already been reviewed,[5] and the origin for this effect has been recently suggested.[50,51] However, it is necessary to remember that trace impurities such as acids (or metal traces)[52−54] have a direct and significant effect over many reactions conducted in these ionic media. In this sense, it is necessary to guarantee the purity (quality) of the IL to avoid misinterpretations and false results. For some, the combination of a MCR and ILs can be designated as "a perfect synergy for eco-compatible heterocyclic synthesis".[5] Acetonitrile, water, and ethanol, which are three commonly used solvents in the Biginelli synthesis, gave comparable results with those observed for the tested ILs.

It is also noted that most of these time courses for product formation are sigmoidal, which is characteristic of an autocatalyzed reaction. The Biginelli MCR is not autocatalyzed, but the time courses have a similar behavior because of solubility effects, which are directly associated with the nature of the chosen solvent. The Biginelli adduct usually precipitates in the reaction medium (thus leaving the reactive phase), therefore displacing the equilibrium toward product formation. All three components used in the reaction are usually soluble in most of the commonly used solvents, whereas the product is usually insoluble. That is why a similar effect as in autocatalyzed reactions can be observed, and this effect is reflected by the sigmoidal curves for most of the experiments. Bearing in mind the possibility of recycling a catalytic system, solubility effects may be crucial, and in this sense the role of a solvent is of paramount importance. This possibility for solvent-free versions is severely impaired.

The importance of the solvent associated with a catalyst for the Biginelli reaction and its crucial effect for the 1,3-dicarbonyl reagent has been very recently elucidated by Clark and co-workers.[55] The authors evaluated in their landmark article different solvents, but in the presence of 10 mol % of hydrochloric acid as the catalyst, and concluded that the solvent affects the keto−enol tautomerization equilibrium. Indeed, the formation of the enol (or enolate) and its stabilization (through solvent interactions) are crucial for the reaction success, as recently demonstrated by us[51] and others.[55] Some have used metals to promote the formation of 1,3-dicarbonyl complexes to improve the nucleophilicity of the carbon at C2 in the 1,3-dicarbonyl reagent.[56] Supposedly, upon displacing the equilibrium toward the enol form, a positive kinetic effect would be observed. Unfortunately, this presumption has been only assumed rather than asserted with convincing tests. It was shown[55] that, indeed, the metal−enolate complex (which results from the application of a Lewis acidic catalyst) may actually hinder the reaction; and for these cases (once again), the solvent choice is crucial in returning considerable reactivity to the dicarbonyl reagent, which is not a possibility in the solvent-free versions of the reaction.

There is no doubt that the presence of a catalyst (Bronsted or Lewis) will affect the keto−enol tautomerization equilibrium. However, in order to verify the pure solvent effect over the keto−enol equilibrium constant (K_T), we have conducted NMR experiments to determine the proportion of each of the species in the equilibrium for the different solvents (see the NMR spectra in Figures S1−S7 in the Supporting Information). The results are summarized in Table 1. Only for comparison purposes, the solventless (and catalyst-free) entry is also shown (see Table 1),

Table 1. Solvent Effect over the Keto−Enol Tautomerization Equilibrium



solvent	keto (%)	enol (%)	K_T (enol/keto)	ln(K_T)	ln(**4**/urea)	yield of isolated **4** (%)[a]
solventless	57	43	0.76	−0.27	−0.99	54
toluene	64	36	0.57	−0.56	−2.30	14
ethanol	39	61	1.54	0.43	−1.67	24
CH_2Cl_2	29	71	2.50	0.92	−2.04	17
water	38	63	1.67	0.51	−1.66	24
BMI·PF_6	43	57	1.33	0.29	−1.56	28
BMI·BF_4	50	50	1.00	0.00	−1.51	27

[a]Reaction for 4 h at 100 °C (model reaction).

but our interest at the moment is the solvent effect. Moreover, in lieu of an actual equilibrium among all possible intermediates (for the three most likely mechanism propositions) for the Biginelli reaction, a relationship of the Biginelli adduct (**4**) and the urea concentration (**4**/urea) was used for this metric (Figure 3), hence avoiding the need for a discussion of the mechanism at the present moment. The mechanism of the catalyst-free reaction will be evaluated and discussed in due course.

As can be depicted from Table 1, the supposition that favoring the enol formation favors the Biginelli adduct formation is not as direct as supposed. In this sense, the assumptions and conclusions previously described[55] that the reaction is thermodynamically and not kinetically ruled seem to be correct. It is important to highlight that the current experiments were conducted in catalyst-free versions whereas those previously reported[55] had at least 10 mol % of a catalyst (Bronsted or Lewis acids). Furthermore, results in Table 1 indicate that assuming a fast keto−enol equilibrium and knowing that the solvent is responsible for this equilibrium, thermodynamics would be therefore responsible for the observed yields and not the kinetic control. These results already point firmly to the importance of catalysis to improve the reaction yields and discard any possibility of the so-called "catalyst-free" Biginelli reaction. The values for K_T directly reflected the observed solvent effects, but solvent effects did not interfere in the final yields after their maxima are reached (see Figure 2). Solvent effects, however, had a direct influence over the initial period of the reaction (Figure 2, left), and this may be the origin for the assumption that keto−enol equilibrium is crucial and that kinetic controls rule the Biginelli adduct formation. DFT calculations and the Fukui functions (f^-) showed that, indeed, the enol tautomer is considerably more reactive than its keto counterpart as the nucleophilic species and therefore in accordance with the need for the enol formation to further the reaction (Figure 3, right). If a fast keto−enol equilibrium is assumed, the formed enol (even if present at low proportions) would react and immediately be restored to advance the Biginelli reaction. In this sense, once more, the solvent seems to have a crucial role for the reaction and for the Biginelli adduct formation upon favoring (facilitating) the enol restoration. Yet again, these positive solvent effects would not be possible in solvent-free versions of this MCR.

After evaluation of the solvent effects (under catalyst-free conditions), we decided to evaluate the so-called "catalyst-free"

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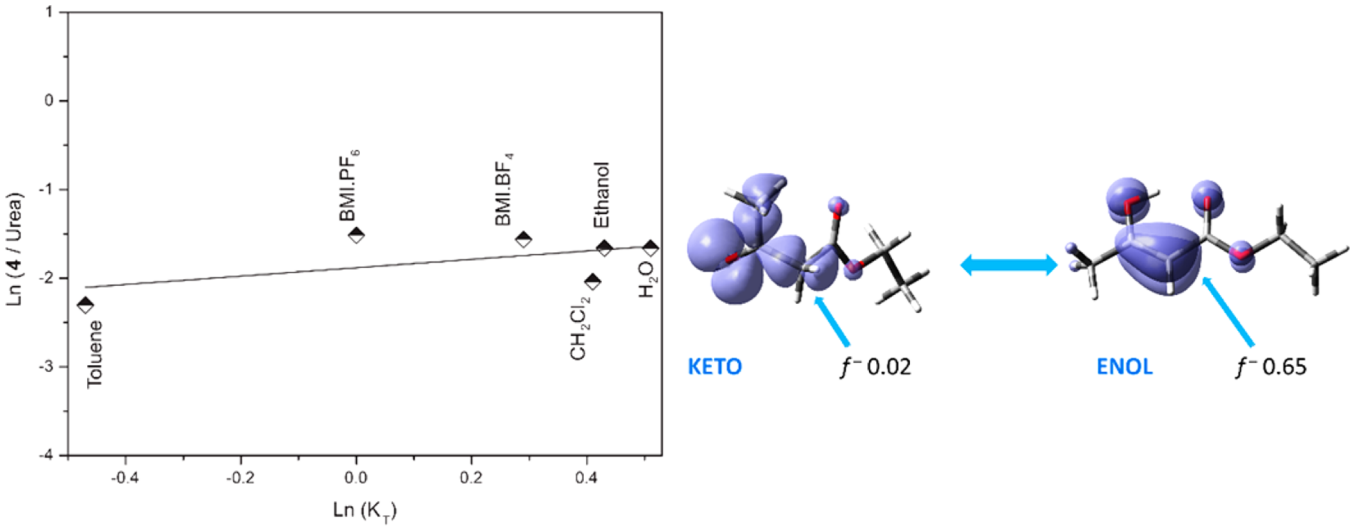

Figure 3. (left) The influence of the solvent on the $\ln(K_T)$ for the catalyst-free Biginelli reaction and (right) optimized geometries and calculated Fukui functions (f^-) for the indicated atoms and isosurfaces for both tautomers using the CAM-B3LYP/6-311+G(2df,p)/LANL2DZ level of theory.

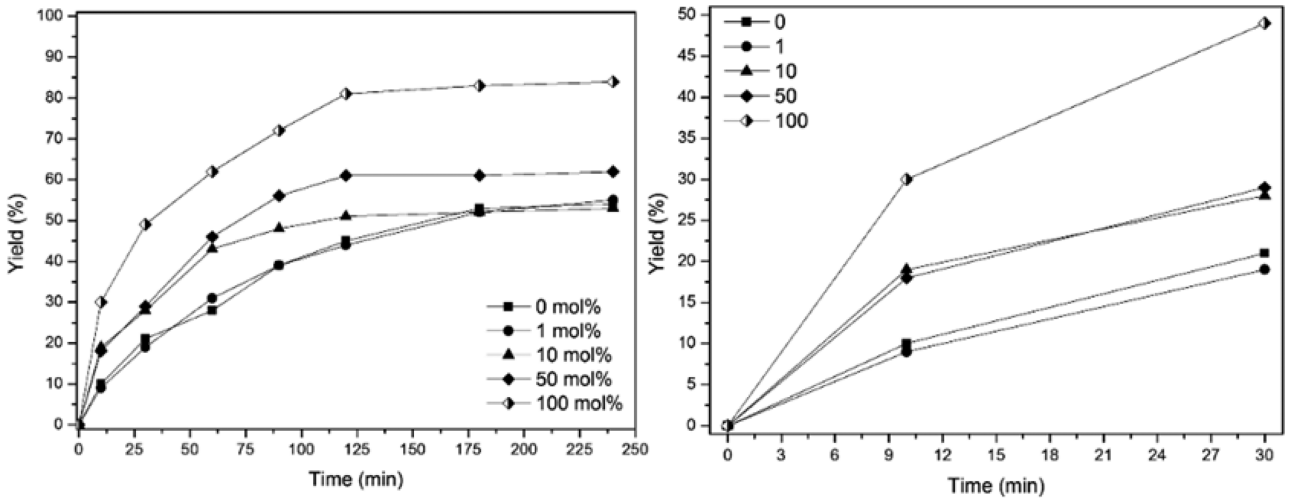

Figure 4. Reaction profiles (for the model reaction) with different ferrocene amounts (0−100 mol %) in solvent-free versions of the Biginelli reaction at 100 °C. (left) The full reaction profile and (right) the initial minutes of the reactions, which clearly indicate the catalytic effect of ferrocene. Note that an actual solvent-free and catalyst-free reaction was accomplished and the maximum yield was 54%. All points refer to isolated yields.

Biginelli reaction. A recent publication has described the synthesis of ferrocene-containing DHPMs to test these derivatives in their abilities as radical scavengers.[57] In the title of this article, one could read "*Solvent-Free and Catalyst-Free Biginelli Reaction*". Despite the excellent report regarding the radical scavenger ability for those iron-containing DHPM derivatives, the chosen title may induce the reader to have some confusion regarding the importance of catalysts to promote the Biginelli reaction. In this case, the reactions were conducted at 100 °C (a typical temperature for the Biginelli reaction), and the yields for the iron-containing derivatives ranged from 25% to 50% in 4 h of reaction. It is important to note two significant features of ferrocene: (i) $Fe^{II}(C_5H_5)_2$ can be easily oxidized to $[Fe^{III}(C_5H_5)_2]^+$ (ferrocenium cation); (ii) if $Fe^{II}(C_5H_5)_2$ can decompose affording $[Fe^{II}(C_5H_5)]^+$, evidently, catalysis may take place easily as a consequence of a vacant coordination site in the metal center of the $[Fe^{II}(C_5H_5)]^+$ derivative. Moreover, the beneficial effect of iron compounds (catalysts) for the Biginelli reaction are well documented,[58−60] despite no ferrocene derivative having been described as a catalyst for this MCR.

In order to evaluate the ferrocene effect as the catalyst for the Biginelli reaction, we conducted several reactions at 100 °C for 4 h using different amounts of the iron derivative and a control reaction, that is, a real catalyst-free version. The model reactions (in solvent-free versions) were therefore carried out, and the results are better visualized in Figure 4.

The observed rate constant (k_{obs}) for the global reactions could be easily calculated according to eq 1,

$$Y = Y_0(1 - e^{-(k_{obs}t)}) \quad (1)$$

where Y is the yield (%), t is the time (min), and k_{obs} (min^{-1}) is the global kinetic rate constant (first order). The following k_{obs} were obtained for the different ferrocene amounts: 0.013 (0 mol %), 0.014 (1 mol %), 0.029 (10 mol %), 0.024 (50 mol %), and 0.030 (100 mol %), respectively. These values leave no doubt of the catalytic effect that ferrocene is exercising over the Biginelli reaction. The reaction with equimolar amounts of the iron compound has a yield approximately 6-fold higher than that without the catalyst in the first 10 min of reaction (Figure 4, right). It may also be noted that reactions with 1 mol % have

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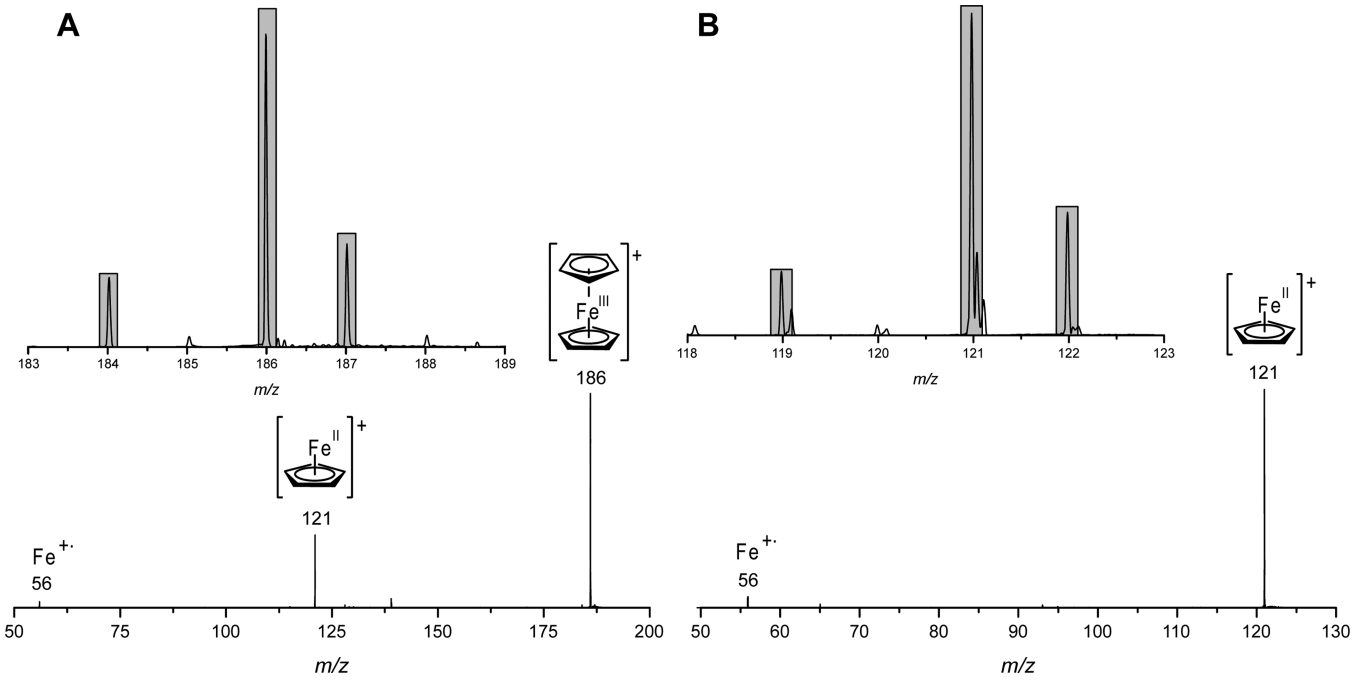

Figure 5. (A) ESI(+)-MS/MS of the ion of m/z 186. (B) ESI(+)-MS/MS of the ion of m/z 121. The insets show the expanded regions and the isotope pattern matching from the ESI(+)-MS spectra (calculated patterns shown in gray bars).

almost no effect and that starting from 10 mol %, the catalytic effect is more pronounced. It is also noted that the highest yield obtained with 100 mol % of ferrocene was 84%, that is, a 30% increase compared with the reaction without any metal (the catalyst-free and solvent-free conditions), pointing again to the positive influence of ferrocene over both the kinetics (time required to form the Biginelli adduct **4**) and the final yields (isolated Biginelli adduct).

To gain insights on the role of ferrocene for the Biginelli reaction and how it is influencing the Biginelli reaction, electrospray (tandem) mass spectrometry (ESI-MS(/MS) experiments were conducted. ESI-MS(/MS) is known to be a powerful tool capable of connecting solution and gas phase chemistries[61] through continuous snapshots of the changing ionic composition of reaction solutions,[62−65] therefore facilitating the detection of key intermediates, including transient species.[66]

Initially, ESI-MS of a 100 μM methanolic solution of ferrocene was directly injected. Both ESI-MS and ESI-MS/MS could be acquired (Figure 5).

During the ESI process, the metal center (i.e., Fe^{II}) might be oxidized to Fe^{III}.[67] The high abundance of the signal of m/z 186 suppressed almost all other signals. To avoid iron oxidation and to be sure of the cyclopentadienyl anion decomposition, the experiment was once more repeated using an atmospheric pressure chemical ionization (APCI) source instead of ESI. APCI is known to generate ions by gas-phase proton transfer reactions, thus eliminating the possibility of metal reduction by redox reactions.[68]

APCI-MS and APCI-MS/MS experiments returned very elucidative results. The probe was heated varying the temperature from 100 to 600 °C. At 100 °C, the ion of m/z 121 could be detected, therefore showing that at the reaction temperature the cation $[Fe(C_5H_5)]^+$ (m/z 121) forms as a consequence of ligand decomposition; hence a stronger Lewis acid is available (and formed in situ) being capable of catalyzing the Biginelli reaction.

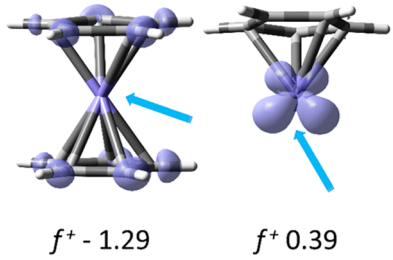

Figure 6. Optimized geometries and calculated Fukui functions (f^+) for the indicated iron atoms (see the arrows) and their isosurfaces using the CAM-B3LYP/6-311+G(2df,p)/LANL2DZ level of theory.

Once again, theoretical calculations (DFT) were used to shed light on the ferrocene effect over the Biginelli reaction (Figure 6). The calculations showed Fukui function values for the metal center of f^+ 0.39 (decomposed ferrocene, $[Fe^{II}(C_5H_5)]^+$), whereas before decomposition the calculated f^+ is considerable lower (f^+ −1.29, virtually silent to the reaction as a Lewis acid).

As concluded from Figure 6, before one of the cyclopentadienyl ligands leaves, no aldehyde is allowed to coordinate to the metal center. However, after releasing one of the ligands, the calculated Fukui function indicated that the metal center is considerably more prone to aldehyde coordination, with electrophilic character enhancement for the carbon of the C═O bond of the aldehyde. These results point firmly to the catalytic effect of ferrocene-based derivatives and are in accordance with the experimental data presented herein.

Another very controversial and polemic article described the use of NaCl as catalyst for the Biginelli reaction.[69] The reaction was conducted in DMF using an external temperature of 220−230 °C in the presence of 10 mol % of NaCl during 40−180 min. The yield obtained for product **4** (model reaction) was only 56%. It is even more curious to note that two authors of the NaCl article had already published[70] (two years before) a manuscript describing an actual catalyst-free Biginelli reaction conducted in

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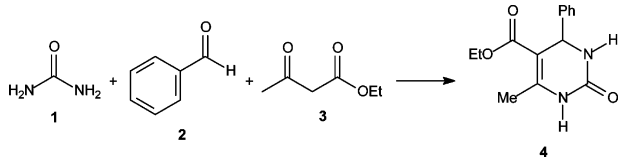
Table 2. Real Catalyst-Free Biginelli Reactions under Several Conditions Reported Previously



entry	**1**:**2**:**3** (mmol)	temp (°C)	solvent	time	yield (%)	ref
1	23.1:15.4:15.4	65	THF	8–18 h	20–50	73
2	1.50:1.00:1.00	90	EtOH	5–7 h	0	74
3	4.50:3.00:4.50	reflux	EtOH	8 h	<12	75
4	7.50:5.00:5.50	reflux	EtOH	8 h	6	76
5	1.00:1.00:1.00	reflux	EtOH	6 h	0	77
6	5.20:4.00:4.00	reflux	EtOH	7 h	13	78
7	3.00:2.00:2.00	reflux	EtOH	24 h	26	79
8	7.50:5.00:5.00	reflux	EtOH	210 min	0	80
9	1.50:1.00:1.00	40	EtOH	2 h	0	81
10	1.50:1.00:1.00	reflux	EtOH	6 h	traces	82
11	2.00:2.00:2.00	25	MeCN	4–12 h	0	43
12	1.00:1.00:1.00	reflux	MeCN	1 h	0	83
13	1.20:1.00:1.20	reflux	MeCN	3–4 h	0	84
15	300:200:200	reflux	MeCN	48 h	traces	85
16	not available	rt	MeOH	48 h	0	86
17	0.50:1.00:1.00[a]	115	octane	1 h	traces	87
18	10.0:5.00:5:00	80	water	8–12 h	20–30	88
19[b]	5.00:5.00:7.50	75	AcOH or EtOH or *p*-cymene	16 h	25, 6, 14[c]	55
20[d]	11.0:10.0:10.0	30	MeCN or EtOH or THF or CH_2Cl_2	40–90 min	0	89
21	3.00:3.00:3.00	90	BMI·BF_4 or BMI·PF_6	1 h	<35	49
22	7.50:5.00:5.00	140	ethylene glycol	5 h	traces	90
23	1.50:1.00:1.00	rt	solvent-free or BMI.BF_4	10 min	0	42
24	1.20:1.00:1.00	70	DMF	8 h	13	91
25	15.0:10.0:10.0	80	solvent-free	6 h	traces	92
26	1.50:1.00:1.00	25	solvent-free	3 h	0	59
27[e]	1.50:1.00:1.00	not available	solvent-free	30 min	10	93
28	15.0:10.0:10.0	45 and higher	solvent-free	45 min	0	94
29	5.00:5.00:5.00	50	solvent-free	25 min	0	95
30	2.50:2.00:2.00	100	solvent-free	9 h	traces	96
31	37.5:25.0:25.0	100	solvent-free	30 min	0	97
32	12.0:10.0:10.0	90	solvent-free	2 h	43	98
33	3.00:2.00:2.00	80	solvent-free	8 h	0	99
34	4.50:3.00:4.50	100	solvent-free	1 h	29	100
35[b]	1.20:1.00:1.00	80	solvent-free	9 h	59	101
36	1.00:1.00:1.00	60	solvent-free	3 h	0	102
37	3.00:2.00:2.00	120	solvent-free	3 h	20	103

[a]4-MePhCHO instead of PhCHO. [b]Methyl acetoacetate instead of ethyl acetoacetate. [c]Respective yields for AcOH, EtOH, and *p*-cymene. [d]Sonication (ultrasound). [e]Microwave irradiation.

refluxing DMF for 90 min, and the Biginelli adduct **4** was obtained in 51%. The 5% difference is absolutely insignificant; therefore the NaCl in the reaction medium is no more than an unnecessary (and inert/silent) component. Moreover, after the reaction, the NaCl had to be separated from the product. In this sense, one can fairly ask why NaCl has been described as a catalyst for this MCR. Unfortunately, we have no plausible explanation for this question why NaCl received the status of "catalyst". As we have shown (Table 1 and Figure 4), the catalyst-free version of the reaction affords the Biginelli adduct in 54% and the use of NaCl is at least senseless or redundant.

A description of a catalyst-free Biginelli reaction version conducted at 100–105 °C for 1 h was described in 2002.[71] The authors claimed to obtain compound **4** (model reaction) in 81% after purification by means of recrystallization from hot ethanol. This result was later directly questioned by others.[72] As we have described (Table 1 and Figure 4), in our hands, this result could not be reproduced at all. Table 2 describes several real catalyst-free results already reported, and it seems that no one was able to reproduce this controversial yield for the model reaction (even under several different conditions). Note that most of the references cited in Table 2 are more recent than that reported in 2002.

In a general way, as is shown in Table 2, the yields are really poor for the catalyst-free versions of the Biginelli reaction, and most of these reports have been recently published. These reports seem to indicate how important the presence of a catalyst is for the Biginelli reaction, and indeed, most of them discuss this issue. Moreover, as noted, no one could reproduce that yield

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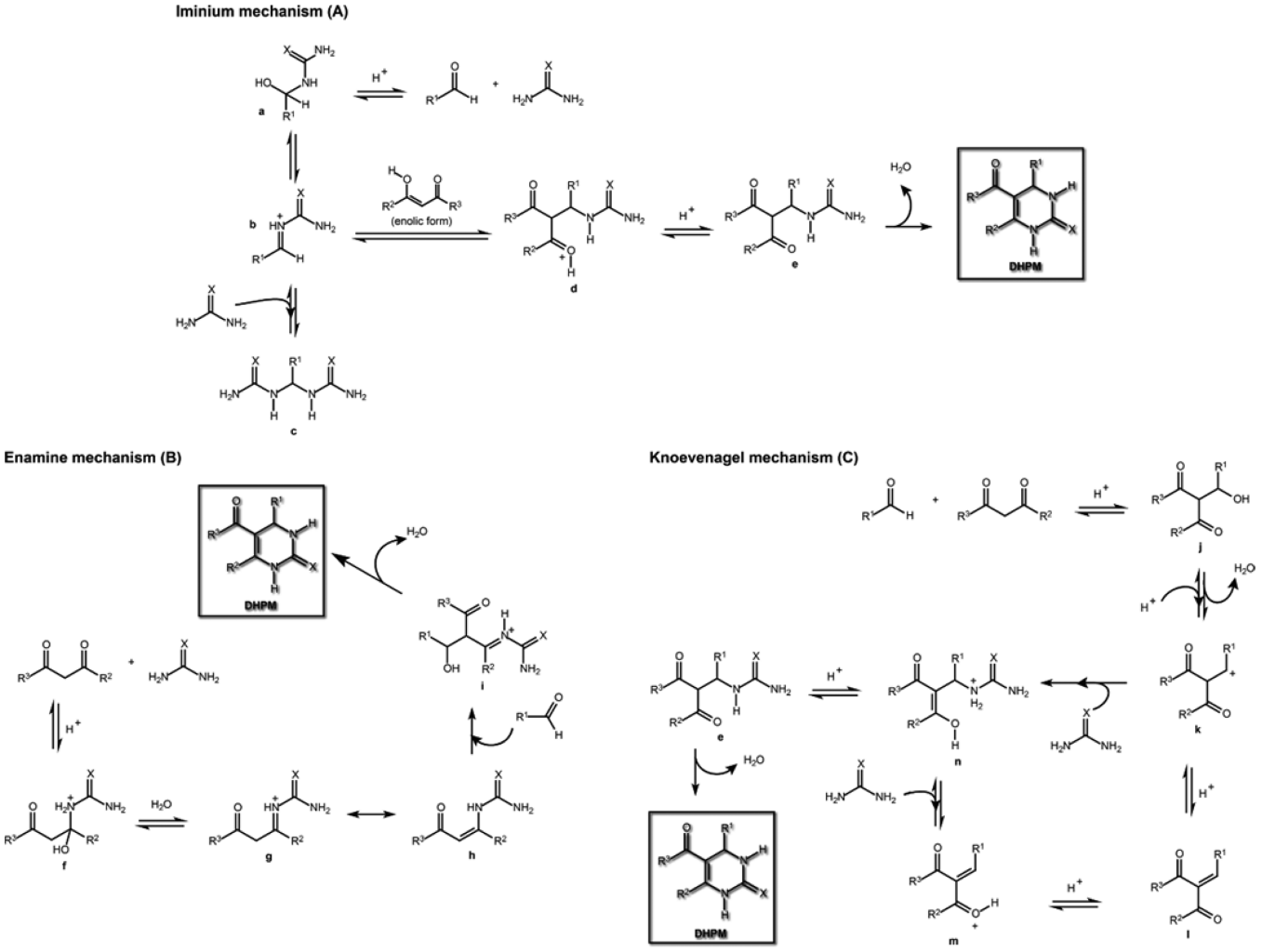
Scheme 2. Three Proposed and Discussed Mechanisms for the Biginelli Reaction: Iminium (A), Enamine (B), and Knoevenagel (C) Mechanisms[a]



[a]Note that several charged and polar intermediates are invoked (**a**–**n**) and that the charge is the result of a direct protonation of those intermediates. Moreover, without protonation, these intermediates would be neutral and therefore invisible to MS analysis.

reported in 2002 using several different conditions nor with similar conditions (see Table 2).

Finally, we decided to investigate the real catalyst-free Biginelli reaction mechanism. Today, three major mechanistic pathways are accepted and discussed, that is, iminium, enamine, and Knoevenagel mechanisms[33−36] (Scheme 2).

ESI-MS has already proven to be an outstanding and unsurpassed tool to investigate the Biginelli reaction mechanism.[32] Considering that MS is blind to neutral components, the only restriction is that the intermediates had to be protonated (Bronsted acid catalysts) to be detected or to be found associated with a metal catalysts for a residual charge.[51] As expected, the protonation or complexation may result in significant alterations on the intrinsic reactivity of the system,[104] thereby making the mechanistic analysis of the catalyst-free version of the Biginelli reaction more challenging, and moreover, under protonation or complexation conditions, the system may not reflect the actual catalyst-free reaction.

To overcome this major shortcoming of the MS technique, the elegant strategy of charge tags has been developed and successfully applied for mechanistic investigations.[105−108] Hence, we decided to use a known charge-tagged aldehyde derivative to investigate the real catalyst-free Biginelli mechanism and follow the naturally charged intermediates using quantitative ESI-MS experiments. Fortunately, we were able to detect and characterize several intermediates (Figure 7) and follow their relative abundances for a period of 4 h. A mixture of equimolar quantities of the charge-tagged aldehyde (**A** in Figure 7), ethyl acetoacetate, and urea were heated at 100 °C. After 15 min, the crude mixture melts completely allowing it to be injected and monitored online (Figure 7). The first ESI-MS could be acquired only after 15 min (homogeneous mixture), and then, other ESI-MS were obtained after 1, 2, and 4 h of reaction at 100 °C (see Figures S10−12 in the Supporting Information).

Based on the MS data (Figure 7 and Figures S10−12), it was possible to follow the reaction profile (Figure 8) and to propose a kinetic model for the real catalyst-free transformation, as seen in Scheme 3.

The MS data allowed the proposal of a simplified kinetic model (Scheme 3). Up to now, no other technique has been applied describing the simultaneous online monitoring and detection (and characterization) of all of these intermediates quantitatively. Moreover, despite it being a simplified model, it is still a complex model (10 constants to be considered), and it is by

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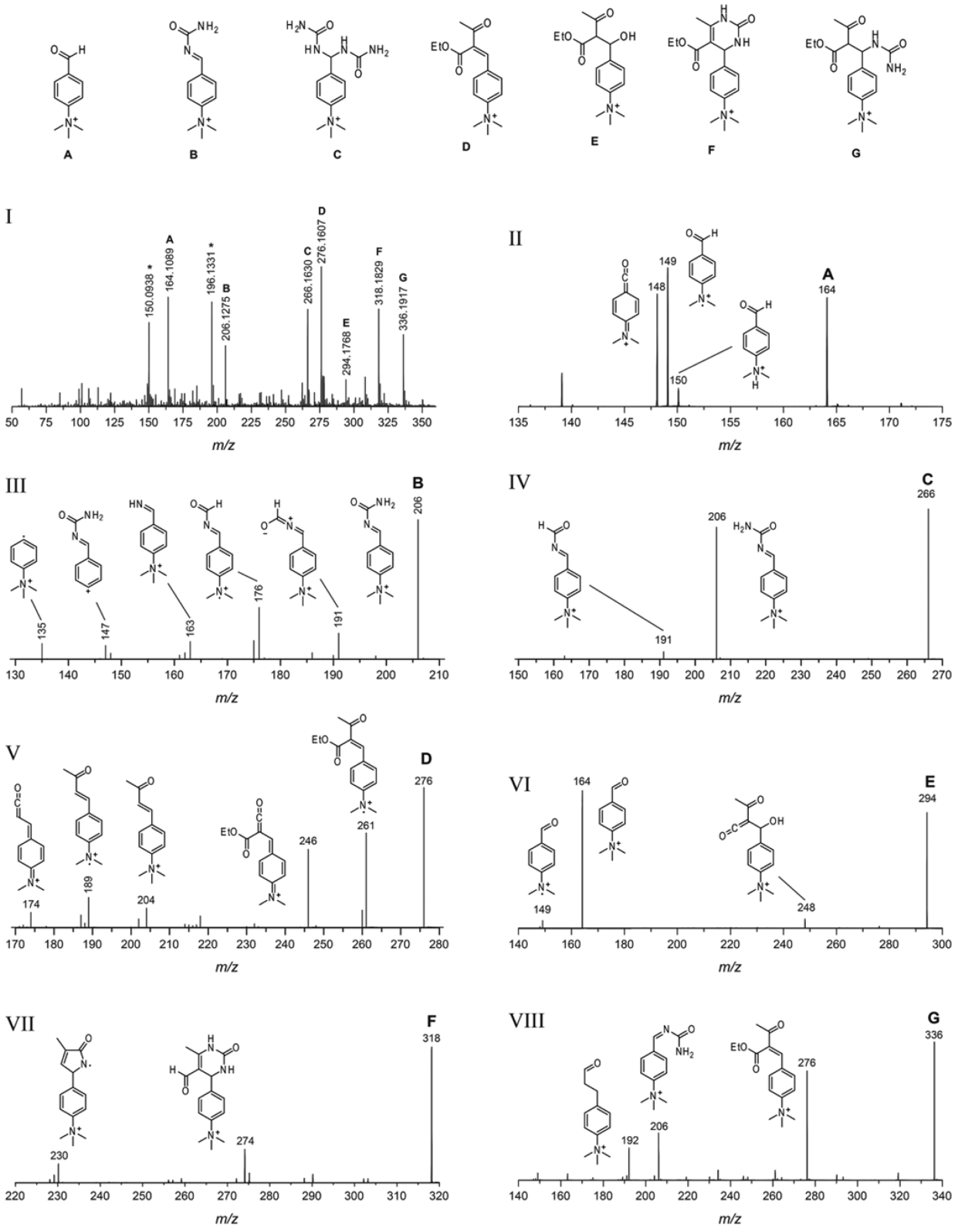

Figure 7. Catalyst-free Biginelli reaction conducted at 100 °C and the charge-tagged intermediates. (I) High resolution ESI(+)-MS of the Biginelli reaction using the charge-tagged aldehyde derivative after 15 min of reaction. (II) ESI(+)-MS/MS of the charge-tagged aldehyde **A**. (III) ESI(+)-MS/MS of the charge-tagged intermediate **B**. (IV) ESI(+)-MS/MS of the charge-tagged intermediate **C**. (V) ESI(+)-MS/MS of the charge-tagged intermediate **D**. (VI) ESI(+)-MS/MS of the charge-tagged intermediate **E**. (VII) ESI(+)-MS/MS of the charge-tagged intermediate **F**. (VIII) ESI(+)-MS/MS of the charge-tagged intermediate **G**.

far the most complete kinetic model ever proposed for a Biginelli MCR. Intermediate **H** has not been detected, indicating its very transient nature, but even so, **H** has been considered in the kinetic model and for the calculations. The unsuccessful

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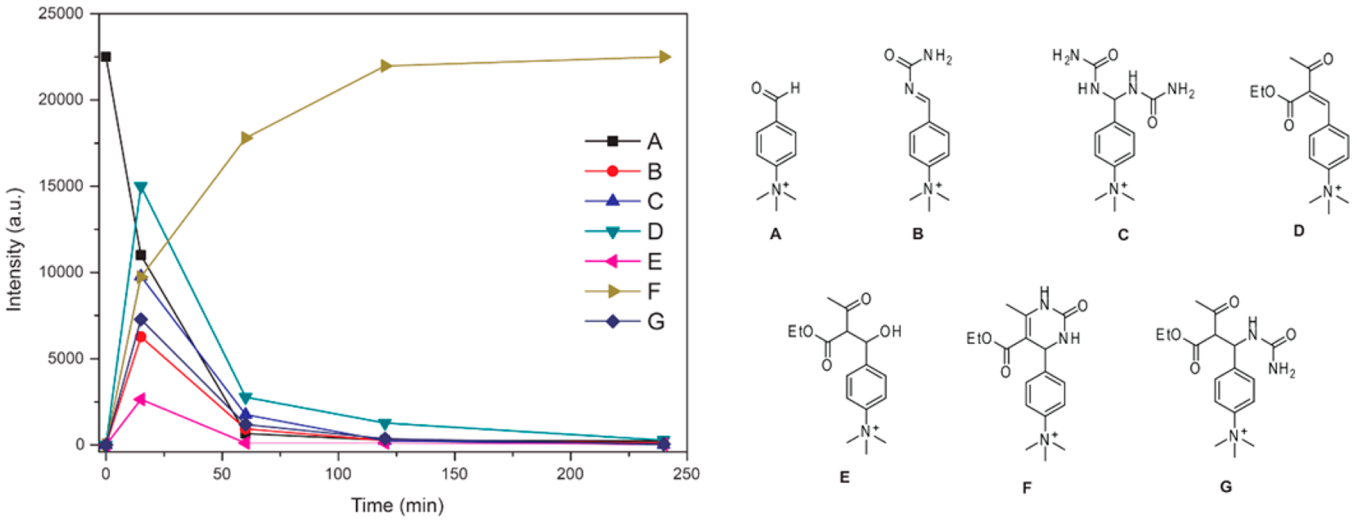
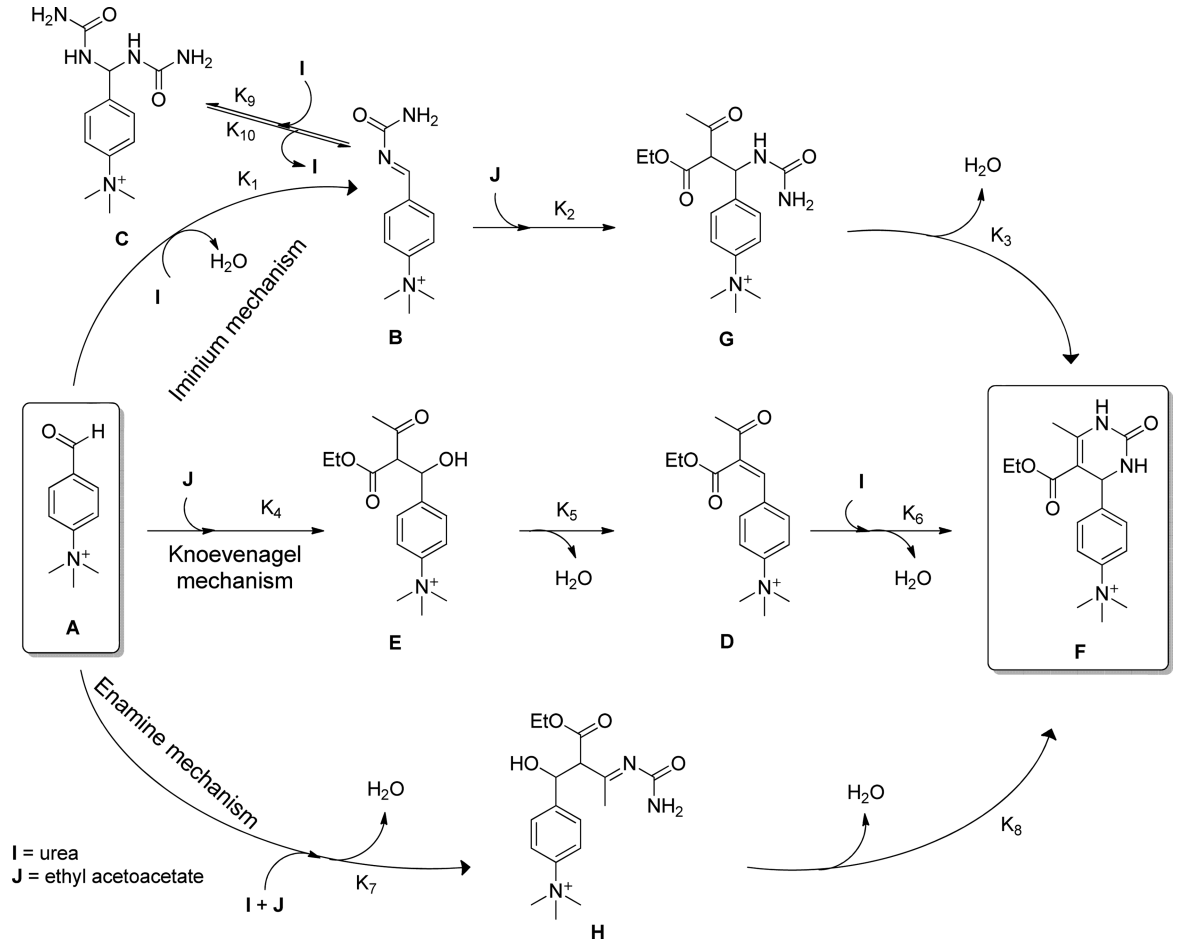


Figure 8. ESI(+)-MS intensity data over time for all key intermediates containing the charge tag derivative. The initial plot for the charge-tagged aldehyde (**A**) is an assumption whereas all other points were obtained from ESI(+)-MS experiments.

Scheme 3. Competing Mechanism for the Catalyst-Free Biginelli Reaction Based on the Iminium, Knoevenagel, and Enamine, Respectively[a]



[a]Note that intermediate **H** has not been detected.

detection of its signal does not necessarily means it is not formed, but it may be a case where the intermediate (**H**) is formed and instantaneously consumed. Urea has been named **I** and ethyl acetoacetate named **J** (the two unlabeled reagents). The data from MS analyses have been normalized for the description of the kinetic model.

Initially, the global kinetics, that is, the consumption of **A** and formation of **F** were evaluated according to eqs 2 and 3:

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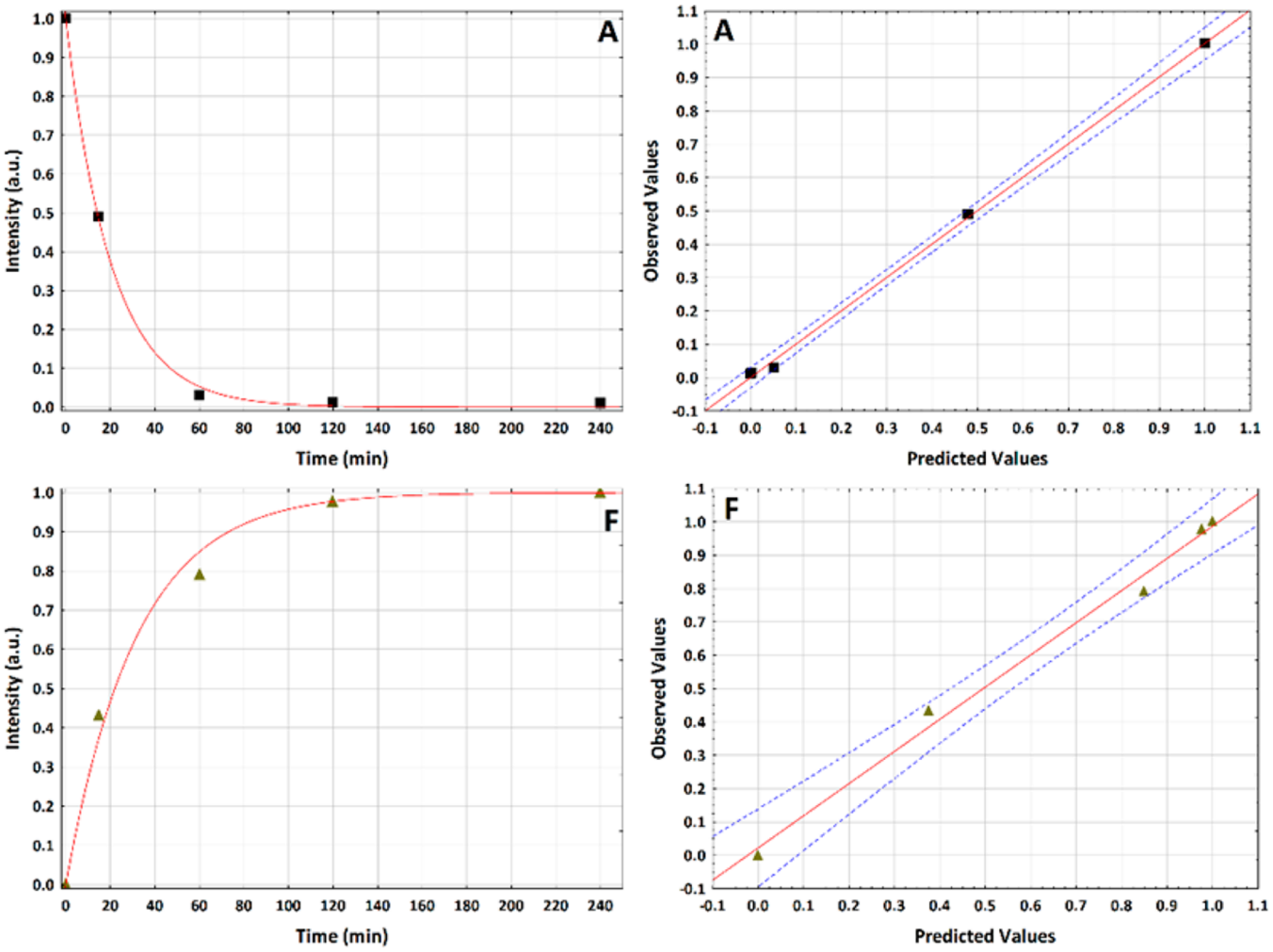

Figure 9. Global kinetics associated with **A** consumption (top) and **F** formation (bottom). The dashed lines indicate the regression bands constructed with a confidence level of 95%.

$$A = \exp(-k_A t) \tag{2}$$

$$F = 1 - \exp(-k_F t) \tag{3}$$

where k_A is the kinetic constant associated with the consumption of the starting charge-tagged aldehyde (**A**), whereas k_F is the kinetic constant associated with formation of the final product (**F**). The results are better visualized in Figure 9.

The global kinetic model approach proved to be simple and capable of an excellent description (behavior and prediction) of the concentration profiles based on the charge tag strategy used in the MS experiments to monitor the consumption of the charged reagent (aldehyde) and the formation of the Biginelli adduct (k_A = 0.0491 ± 0.0016 min^{-1} and k_F = 0.0315 ± 0.0030 min^{-1}). The complete kinetic model based on Scheme 3, however, has the limitation that several intermediates (as seen in Scheme 2) could not be detected due to the absence of a charge tag in their structures. Despite this severe limitation, a reasonable approximation could be depicted based on the normalized data from the MS experiments, as shown in Scheme 3. Equations 4−13 describe the equations for the kinetic model considering only the charge-tagged intermediates detected and characterized by the quantitative ESI-MS. Figure 10 shows the visualization of the model. The solutions for eqs 4−13 were performed using the DASSL numerical method.[109,110]

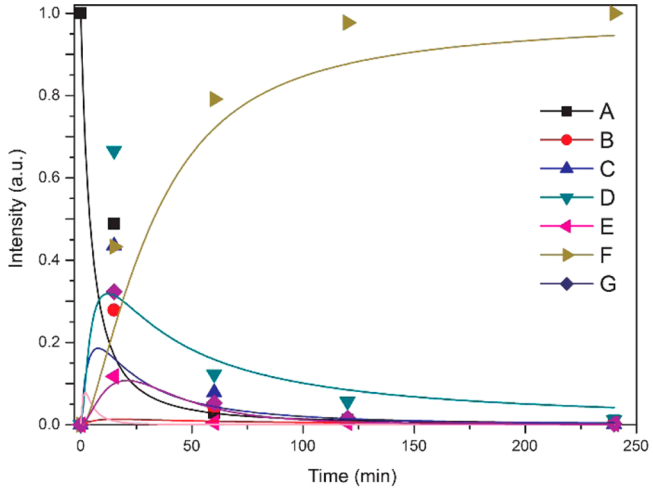

Figure 10. Kinetic plots obtained from the numerical solutions from eqs 4−13. The lines represent the plots based in the kinetic model, and the points are from the normalized experimental data from the MS experiments.

$$\frac{dA}{dt} = -k_1 AI - k_4 AJ - k_7 AIJ \tag{4}$$

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$$\frac{dB}{dt} = k_1AI - k_2BJ - k_9BI + k_{10}C \quad (5)$$

$$\frac{dC}{dt} = k_9BI - k_{10}C \quad (6)$$

$$\frac{dD}{dt} = k_5E - k_6DI \quad (7)$$

$$\frac{dE}{dt} = k_4AJ - k_5E \quad (8)$$

$$\frac{dF}{dt} = k_3G + k_6DI + k_8H \quad (9)$$

$$\frac{dG}{dt} = k_2BJ - k_3G \quad (10)$$

$$\frac{dH}{dt} = k_7BI - k_{10}C \quad (11)$$

$$\frac{dI}{dt} = -k_1AI - k_6DI - k_7AIJ - k_9BI + k_{10}C \quad (12)$$

$$\frac{dJ}{dt} = -k_2BJ - k_4AJ - k_7AIJ \quad (13)$$

The set of differential equations derived from the kinetic mechanism was solved numerically with the numerical integrator DASSL.[109,110] The values of kinetic constants in the eqs 4 to 13 were estimated with the help of a standard maximum likelihood estimation procedure,[111,112] as shown in Table 3.

Table 3. Estimated Kinetic Model Constants[a]

kinetic constant (min^{-1})	estimate	standard deviation
k_1	9.71×10^{-2}	3.45×10^{-2}
k_2	1.69	1.62
k_3	7.84×10^{-2}	4.99×10^{-2}
k_4	1.25×10^{-1}	2.59×10^{-2}
k_5	1.11	2.07
k_6	1.14×10^{-1}	2.62×10^{-2}
k_7	~0	
k_8	~0	

[a]Depicted in Scheme 3.

Overall, the kinetic model clearly indicates the competition of the possible reaction pathways and highlights the importance of a catalyst, especially considering that the catalyst not only reduces reaction times and improves yields but also is responsible for the reaction pathway selection, thereby favoring one of the possible mechanisms. This issue is also fundamental for the consideration of improved reaction condition optimizations and higher selectivities and for the predictions and the design of new catalysts. The values of the standard deviations express the limitations of the methodology, because many intermediates could not be monitored online.

Finally, the data from MS experiments also indicated a fast equilibrium between **B** and **C** (Figure 11), thereby pointing to the fact that urea excess does not have a beneficial effect when the iminium mechanism is favored in a determined reaction condition. Despite an excess of urea favoring the iminium formation, this also favors the second addition, and as previously reported,[49,50] the reaction yields have a clear tendency to be lowered.

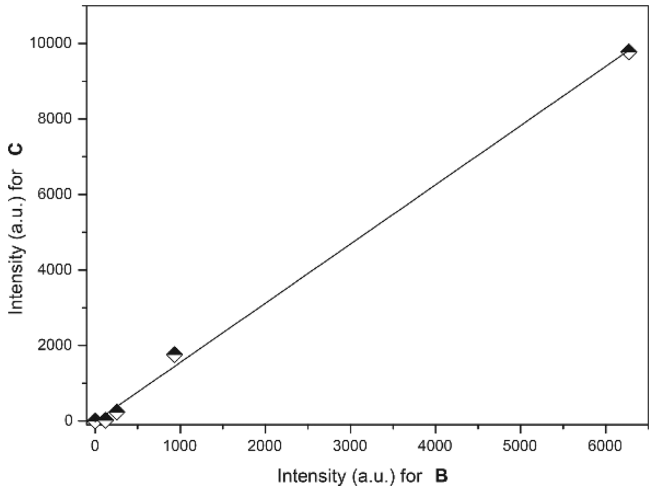

Figure 11. Kinetic correlation between intermediates **B** and **C** indicating a fast equilibrium.

The kinetic constants obtained for the equilibrium (86.4 and 2.60 min^{-1}, k_9 and k_{10}, respectively) are considerably larger than the other constants, indicating therefore the fast equilibrium and that, under catalyst-free conditions, a second urea addition to the iminium intermediate (iminium mechanism) is much more likely than the ethyl acetoacetate addition, which would be expected to lead to the Biginelli adduct formation. Once again, the importance of a catalyst to favor the Biginelli reaction desirable pathway is indicated by the kinetic constants. Moreover, the constant affording **C** (k_9) is considerably larger than its counterpart (k_{10}), showing therefore the negative effect of urea excess in the reaction in which the iminium mechanism is taking place.

In summary, we have demonstrated facts, presumptions, and myths about the solvent-free and/or catalyst-free Biginelli reaction. The literature has documented an increasing number of publications regarding this important MCR. Many real achievements have been observed for the Biginelli reaction; however, several publications are, indeed, no more than simple descriptions of new systems, which bring no actual improvements. Indeed, the knowledge generated from the increasing number of works with no more than the description of a new reaction condition is usually deficient, or even misleading. Imprecision and a fundamental lack of understanding are problems commonly observed in publications regarding the Biginelli reaction. The increasing number of papers, however, has not led to a proportional increase in the knowledge about the Biginelli reaction. There is no reasonable doubt of the importance of catalysis for the Biginelli reaction, and the role of the catalyst is not only to facilitate the formation of the final product but also to select a preferred reaction pathway among other important features highlighted in this manuscript. The solvent effect, in many cases, is crucial to favoring the enol tautomer (from the 1,3-dicarbonyl compound) and to speed up the reaction. A solvent-free system represents a desirable condition, but it is not essentially, since it often is used in the isolation or purification of the Biginelli product. In this sense, we would like to suggest some issues to be observed aiming at real improvements for the Biginelli reaction:

(i) Reactions above 100 °C should be avoided. Many substrates are sensitive to temperature effects, and above this temperature side reactions, decompositions, and lack

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of selectivity are highly favored. Room temperature conditions to perform the reaction are necessary for the progress of the reaction, and only a few successful examples have been described (see the cited reviews).

(ii) Solvent-free conditions are welcome but not essential. In cases in which a solvent is required, the preferred conditions use water, PEG, ethanol, and ionic liquids. Other alternative solvents (media) not listed, but with a green appeal, are also welcome.

(iii) Aiming at a proper recycling of the catalytic system, the solvent effect plays a very unique role since the Biginelli adducts are usually insoluble in most of the solvents used in the reaction. The solvent usually facilitates catalytic system recycling, which is considerably harder to perform with no solvent.

(iv) Reactions conditions that require one of the reagents to be used in excess mean that no actual improvement has been attained. Some conditions have been described with two (of three) reagents in excess (see the cited reviews). However, at the current stage of development of the Biginelli reaction, such conditions represent no improvement at all. Indeed, equimolar use of the reagents has not been described in many examples reported so far. When a significant gain in terms of yields, selectivity, and time is achieved, the use of one reagent in excess may be justified. If one of the reagents needs to be used in large excess, the condition has no actual improvement, and equimolar conditions (for the three reagents) are still highly desirable.

(v) Catalyst amounts above 10 mol % should not be used at all, except for asymmetric versions of the Biginelli reaction, since this field is only beginning to be developed[113] and the first asymmetric version was published only in 2005.[114] Otherwise, it makes no sense anymore to describe new systems requiring catalysts loads above 10 mol %. Indeed, the conditions should be adjusted to use no more than 5 mol %, despite the fact that, for some exceptions, it is still acceptable to use 10 mol %. However, to use such a large catalyst amount (10 mol %), other conditions must clearly be favored, for example, lower temperatures, no reagent excess, etc.

(vi) Catalytic systems that require long reaction times (above 6−8 h) do not bring significant contributions, except for asymmetric versions of the Biginelli reaction that today usually require several days (typically a week).

(vii) Catalytic systems with yields below 80% for the model reaction under optimized conditions do not represent any improvement.

(viii) Catalyst recycle and reuse is often difficult, and this issue has much room for improvements. To label a catalytic system as "recyclable" for the Biginelli reaction, at least five runs must be conducted without significant decrease in yields.

(ix) As noted for the catalyst-free mechanism, the importance of a catalyst is not only to improve yields and shorten reaction times but also to improve selectivity of the reaction pathway. Reports without any supportive mechanistic suggestions are only descriptive and bring no actual improvement to the knowledge already available for the Biginelli reaction.

(x) It is not appropriate to label a new Biginelli reaction condition as "green" when it does not fulfill the above criteria I−VIII or when nongreen procedures are required during product isolation or recycling of the catalytic system.

(xi) The use of "catalyst-free" in manuscript titles is, in a general way, no more than a buzzword and only brings confusion to the Biginelli reaction.

Finally, we suggest authors to bear those issues in mind prior to the writing and publishing of a new catalytic system for the Biginelli reaction. Otherwise, no real improvements nor advances of the reaction will be described. Hopefully, this manuscript contributes to avoiding current and future confusion, strife, and misinterpretation regarding the Biginelli reaction and the fundamental role of catalysis for this very important MCR.

EXPERIMENTAL SECTION

General. Reagents were purified (distilled or crystallized) previous to their use. Solvents were used as HPLC grades of purity.

MS Analyses. ESI-MS(/MS) and APCI-MS(/MS) measurements were performed in the positive ion mode (m/z 50−2000 range) on a Synapt HDMS (Waters Co.) 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 ferrocene samples were dissolved in methanol to form 100 μM solutions and were directly infused into the ESI source at a flow rate of 20 μL/min. The charge-tagged aldehyde (0.12 mmol), urea (0.12 mmol), and ethyl acetoacetate (0.12 mmol) were mixed and melted at 100 °C prior to the analysis. After the mixture melts, 2 μL of the crude mixture was diluted to 1.00 mL (MeOH) and immediately injected. ESI source conditions were as follows: capillary voltage 3.0 kV; sample cone 20 V; extraction cone 3 V.

Theoretical Calculations. The theoretical treatment of the systems included in this work was performed using the density functional theory (DFT) approach of the Gaussian 09 series of programs.[115] The CAM-B3LYP DFT functional was used in this study.[116] CAM-B3LYP combines the features of hybrid functionals such as B3LYP[117] with the long-range corrected functionals of Hirao and co-workers.[118] Geometry optimization was conducted with the 631LAN basis set (i.e., Lanl2dz for Fe and 6-31G(2df,p) for the other elements). Harmonic frequency calculations were performed to verify whether we have located a genuine minimum. The optimized geometries were used for the single point calculation at CAM-B3LYP/6-311++G(2df,p)/LANL2DZ level of calculation. The Fukui functions[119] were employed to determine the reactivity sites in the molecule. This function, denoted as $f(\vec{r})$, is defined as the derivative of the electron density, $\rho(\vec{r})$, with respect to the total number of electrons of the system, N, under a constant external potential, $v(\vec{r})$:

$$f(\vec{r}) = \left[\frac{\partial \rho(\vec{r})}{\partial N}\right]_{v(\vec{r})} \tag{14}$$

Due to the discontinuity of the first derivative in eq 14 with respect to the number of electrons, N, the following three functions can be defined in a finite difference approximation:

$$f^{+}(\vec{r}) = \rho(\vec{r})_{N+1} - \rho(\vec{r})_{N} \tag{15a}$$

$$f^{-}(\vec{r}) = \rho(\vec{r})_{N} - \rho(\vec{r})_{N-1} \tag{15b}$$

$$f^{0}(\vec{r}) = \frac{1}{2}[\rho(\vec{r})_{N+1} - \rho(\vec{r})_{N-1}] \tag{15c}$$

where $\rho(\vec{r})_{N+1}$, $\rho(\vec{r})_{N}$ and $\rho(\vec{r})_{N-1}$ are the electronic densities of the system with $N + 1$, N, and $N - 1$ electrons, respectively, all with the ground state geometry of the N electron system. Equations 15a, 15b, and 15c are evaluated for nucleophilic, electrophilic, and free radical attacks, respectively. The finite difference formulation is frequently used in combination with the condensed Fukui function. The condensed Fukui functions can also be employed to determine the reactivity of each atom in the molecule. The corresponding condensed functions are given by

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$$f_k^+ = q_k(N+1) - q_k(N) \quad \text{(for nucleophilic attack)} \tag{16a}$$

$$f_k^- = q_k(N) - q_k(N-1) \quad \text{(for electrophilic attack)} \tag{16b}$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)]/2 \quad \text{(for radical attack)} \tag{16c}$$

where $q_k(N+1)$, $q_k(N)$, and $q_k(N-1)$ are the partial charges at atom k on the anion, neutral, and cations species, respectively. We calculated the partial charges of each atom using CHELPG (charges from electrostatic potentials using a grid based) method.[120]

NMR Analyses. NMR spectra were recorded on a 7.05 T instrument using a 5 mm internal diameter probe operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Chemical shifts were expressed in 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. Investigative experiments for the keto−enol equilibrium determination (200 μL of ethyl acetoacetate and 800 μL of the solvent) were performed at 20 °C in an NMR tube containing a sealed capillary tube charged with D_2O/TMSP-d_4, which was used for field homogeneity adjustment and scale reference (0.0 ppm).

General Procedure for the Model Biginelli Reactions. A Schlenk tube containing 1 mL of the solvent (or no solvent), 2.00 mmol of benzaldehyde, 2.00 mmol of the 1,3-dicarbonyl compound (ethyl acetoacetate), and 3.00 mmol of urea was allowed to react at 100 °C for 4 h (or the indicated time). As indicated in the text, a catalyst may be included in the reaction, but most of those are real catalyst-free versions (see the main text). After the indicated time, the precipitated substrates were purified by washing them with cold water. Crystallizations may be required to reach the maximum yields. *Important: we performed many reactions using urea in excess because most of the manuscripts already published described the Biginelli synthesis using an excess of this reagent. Therefore, we used urea excess for comparative purposes. However, we have already demonstrated that, despite urea excess favoring the iminium formation* (Scheme 2A*), it also favors a second urea addition to the iminium cation and, for those conditions in which the iminium mechanism is favored, aldehyde excess is highly preferred.*[50] *Excess of the 1,3-dicarbonyl may also favor the reaction yields,*[121] *and the only reagent that should not be used in excess is urea.*[49,50] *Unfortunately, the use of urea excess is another myth surrounding the Biginelli reaction and has been widely used without scientific criteria.*

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ ppm 9.22 (s, 1H), 7.76 (s, 1H), 7.29−7.18 (m, 5H), 5.14 (s,1H), 3.97 (q, 2H, J = 6.8 Hz), 2.24 (s, 3H), 1.07 (t, 3H, J = 6.8 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm 165.8, 152.6, 148.8, 145.3, 128.8, 127.7, 126.7, 99.7, 59.6, 54.4, 18.2, 14.5. FT-IR (KBr, cm^{-1}) 3252, 3109, 2972, 1728, 1689, 1645, 1468, 1230, 1097, 778. Mp 212−213 °C (literature[100] 203−204).

General Procedure for the Catalyst-Free Biginelli Reaction with the Charge-Tagged Aldehyde. A mixture of 0.12 mmol of each reagent (charge-tagged aldehyde, ethyl acetoacetate, and urea) was heated at 100 °C. After 15 min, the mixture melted completely and could be injected and analyzed by MS.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR, MS spectra, Cartesian coordinates, energies, and Fukui functions for all calculated structures. These materials are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: brenno.ipi@gmail.com. Phone: (+) 55 61 31073867. Fax: (+) 55 61 31073901

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated to Prof. Roberto Fernando de Souza (in memoriam) for all his contributions to the development of ionic liquid chemistry and catalysis in Brazil.

■ REFERENCES

(1) Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083−3135.
(2) Climent, M. J.; Corma, A.; Iborra, S. *RSC Adv.* **2012**, *2*, 16−58.
(3) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439−4486.
(4) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Chem.—Eur. J.* **2013**, *19*, 2218−2231.
(5) Isambert, N.; Duque, M. D. S.; Plaquevent, J. C.; Genisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347−1357.
(6) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969−4009.
(7) Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948−4962.
(8) Panda, S. S.; Khanna, P.; Khanna, L. *Curr. Org. Chem.* **2012**, *16*, 507−520.
(9) Gupta, A. K.; Singh, N.; Singh, K. N. *Curr. Org. Chem.* **2013**, *17*, 474−490.
(10) Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371−382.
(11) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957−4980.
(12) Gu, Y. L. *Green Chem.* **2012**, *14*, 2091−2128.
(13) Slobbe, P.; Ruijter, E.; Orru, R. V. A. *Med. Chem. Commun.* **2012**, *3*, 1189−1218.
(14) Singh, M. S.; Chowdhury, S. *RSC Adv.* **2012**, *2*, 4547−4592.
(15) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17−57.
(16) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043−1052.
(17) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879−888.
(18) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937−6963.
(19) Lacotte, P.; Buisson, D. A.; Ambroise, Y. *Eur. J. Med. Chem.* **2013**, *62*, 722−727.
(20) Crespo, A.; El Maatougui, A.; Biagini, P.; Azuaje, J.; Coelho, A.; Brea, J.; Loza, M. I.; Cadavid, M. I.; García-Mera, X.; Gutiérrez-de-Terán, H.; Sotelo, E. *ACS Med. Chem. Lett.* **2013**, *4*, 1031−1036.
(21) Canto, R. F. S.; Bernardi, A.; Battastini, A. M. O.; Russowsky, D.; Eifler-Lima, V. L. *J. Braz. Chem. Soc.* **2011**, *22*, 1379−1388.
(22) Kaan, H. Y. K.; Ulaganathan, V.; Rath, O.; Prokopcova, H.; Dallinger, D.; Kappe, C. O.; Kozielski, F. *J. Med. Chem.* **2010**, *53*, 5676−5683.
(23) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R. A.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119−129.
(24) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; Oreilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254−3263.
(25) Biginelli, P. *Gazz. Chim. Ital.* **1891**, *21*, 337−340.
(26) Biginelli, P. *Gazz. Chim. Ital.* **1891**, *21*, 455−461.
(27) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1317−1319.
(28) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962−2967.
(29) Tron, G. C.; Minassi, A.; Appendino, G. *Eur. J. Org. Chem.* **2011**, 5541−5550.
(30) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360−416.
(31) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 447.

(32) De Souza, R.; da Penha, E. T.; Milagre, H. M. S.; Garden, S. J.; Esteves, P. M.; Eberlin, M. N.; Antunes, O. A. C. *Chem.—Eur. J.* **2009**, *15*, 9799−9804.
(33) Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 8741−8749.
(34) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201−7204.
(35) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3784−3791.
(36) Cepanec, I.; Litvic, M.; Filipan-Litvic, M.; Grungold, I. *Tetrahedron* **2007**, *63*, 11822−11827.
(37) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195−218.
(38) Gawande, M. B.; Bonifacio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, *42*, 5522−5551.
(39) Jain, S. L.; Singhal, S.; Sain, B. *Green Chem.* **2007**, *9*, 740−741.
(40) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64−82.
(41) Tundo, P.; Perosa, A. *Chem. Soc. Rev.* **2007**, *36*, 532−550.
(42) Dewan, M.; Kumar, A.; Saxena, A.; De, A.; Mozumdar, S. *PLoS One* **2012**, *7*, No. e43078.
(43) Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305−3308.
(44) Khunt, R. C.; Akbari, J. D.; Manvar, A. T.; Tala, S. D.; Dhaduk, M. F.; Joshi, H. S.; Shah, A. *Arkivoc* **2008**, 277−U278.
(45) Dadhania, A. N.; Patel, V. K.; Raval, D. K. *J. Braz. Chem. Soc.* **2011**, *22*, 511−516.
(46) Dallinger, D.; Kappe, C. O. *Nat. Protoc.* **2007**, *2*, 317−321.
(47) Liu, C. J.; Wang, J. D. *Molecules* **2010**, *15*, 2087−2095.
(48) Safari, J.; Gandomi-Ravandi, S. *RSC Adv.* **2014**, *4*, 11486−11492.
(49) Alvim, H. G. O.; de Lima, T. B.; de Oliveira, H. C. B.; Gozzo, F. C.; de Macedo, J. L.; Abdelnur, P. V.; Silva, W. A.; Neto, B. A. D. *ACS Catal.* **2013**, *3*, 1420−1430.
(50) Ramos, L. M.; Guido, B. C.; Nobrega, C. C.; Corrêa, J. R.; Silva, R. G.; de Oliveira, H. C. B.; Gomes, A. F.; Gozzo, F. C.; Neto, B. A. D. *Chem.—Eur. J.* **2013**, *19*, 4156−4168.
(51) Ramos, L. M.; Tobio, A.; dos Santos, M. R.; de Oliveira, H. C. B.; Gomes, A. F.; Gozzo, F. C.; de Oliveira, A. L.; Neto, B. A. D. *J. Org. Chem.* **2012**, *77*, 10184−10193.
(52) Hallett, J. P.; Welton, T. *Chem. Rev.* **2011**, *111*, 3508−3576.
(53) Dupont, J.; Scholten, J. D. *Chem. Soc. Rev.* **2010**, *39*, 1780−1804.
(54) Siedlecka, E. M.; Czerwicka, M.; Stolte, S.; Stepnowski, P. *Curr. Org. Chem.* **2011**, *15*, 1974−1991.
(55) Clark, J. H.; Macquarrie, D. J.; Sherwood, J. *Chem.—Eur. J.* **2013**, *19*, 5174−5182.
(56) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587−590.
(57) Wang, R.; Liu, Z. Q. *J. Org. Chem.* **2012**, *77*, 3952−3958.
(58) Lu, J.; Ma, H. R. *Synlett* **2000**, 63−64.
(59) Adibi, H.; Samimi, H. A.; Beygzadch, M. *Catal. Commun.* **2007**, *8*, 2119−2124.
(60) Martinez, S.; Meseguer, M.; Casas, L.; Rodriguez, E.; Molins, E.; Moreno-Manas, M.; Roig, A.; Sebastian, R. M.; Vallribera, A. *Tetrahedron* **2003**, *59*, 1553−1556.
(61) Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 5261−5263.
(62) Eberlin, M. N. *Eur. J. Mass Spectrom.* **2007**, *13*, 19−28.
(63) Cooks, R. G.; Chen, H.; Eberlin, M. N.; Zheng, X.; Tao, W. A. *Chem. Rev.* **2006**, *106*, 188−211.
(64) Ifa, D. R.; Wu, C. P.; Ouyang, Z.; Cooks, R. G. *Analyst* **2010**, *135*, 669−681.
(65) Santos, L. S. *J. Braz. Chem. Soc.* **2011**, *22*, 1827−1840.
(66) Santos, L. S. *Eur. J. Org. Chem.* **2008**, 235−253.
(67) Vanberkel, G. J.; McLuckey, S. A.; Glish, G. L. *Anal. Chem.* **1992**, *64*, 1586−1593.
(68) Bruins, A. P. *Mass Spectrom. Rev.* **1991**, *10*, 53−77.
(69) Kolosov, M. A.; Orlov, V. D.; Beloborodov, D. A.; Dotsenko, V. V. *Mol. Divers.* **2009**, *13*, 5−25.
(70) Kolosov, M. A.; Orlov, V. D.; Vashchenko, V. V.; Shishkina, S. V.; Shishkinb, O. V. *Collect. Czech. Chem. Commun.* **2007**, *72*, 1219−1228.
(71) Ranu, B. C.; Hajra, A.; Dey, S. S. *Org. Process Res. Dev.* **2002**, *6*, 817−818.
(72) Arfan, A.; Paquin, L.; Bazureau, J. P. *Russ. J. Org. Chem.* **2007**, *43*, 1058−1064.
(73) Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454−3457.
(74) Mondal, J.; Sen, T.; Bhaumik, A. *Dalton Trans.* **2012**, *41*, 6173−6181.
(75) da Silva, D. L.; Fernandes, S. A.; Sabino, A. A.; de Fatima, A. *Tetrahedron Lett.* **2011**, *52*, 6328−6330.
(76) Shi, X.-L.; Yang, H.; Tao, M.; Zhang, W. *RSC Adv.* **2013**, *3*, 3939−3945.
(77) Li, P.; Regati, S.; Butcher, R. J.; Arman, H. D.; Chen, Z. X.; Xiang, S. C.; Chen, B. L.; Zhao, C. G. *Tetrahedron Lett.* **2011**, *52*, 6220−6222.
(78) Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801−4807.
(79) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889−2891.
(80) Kang, L. Q.; Jin, D. Y.; Cai, Y. Q. *Synth. Commun.* **2013**, *43*, 1896−1901.
(81) Safari, J.; Zarnegar, Z. *RSC Adv.* **2013**, *3*, 17962−17967.
(82) Safaei Ghomi, J.; Teymuri, R.; Ziarati, A. *Monatsh. Chem.* **2013**, *144*, 1865−1870.
(83) Kalita, H. R.; Phukan, P. *Catal. Commun.* **2007**, *8*, 179−182.
(84) Shobha, D.; Chari, M. A.; Mano, A.; Selvan, S. T.; Mukkanti, K.; Vinu, A. *Tetrahedron* **2009**, *65*, 10608−10611.
(85) Litvic, M.; Vecenaj, I.; Ladisic, Z. M.; Lovric, M.; Vinkovic, V.; Filipan-Litvic, M. *Tetrahedron* **2010**, *66*, 3463−3471.
(86) Bao, S. S.; Ma, L. F.; Wang, Y.; Fang, L.; Zhu, C. J.; Li, Y. Z.; Zheng, L. M. *Chem.—Eur. J.* **2007**, *13*, 2333−2343.
(87) Murata, H.; Ishitani, H.; Iwamoto, M. *Org. Biomol. Chem.* **2010**, *8*, 1202−1211.
(88) Yadav, J. S.; Reddy, B. V. S.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Eur. J. Org. Chem.* **2004**, 552−557.
(89) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147−150.
(90) Wang, A. Q.; Liu, X.; Su, Z. X.; Jing, H. W. *Catal. Sci. Technol.* **2014**, *4*, 71−80.
(91) Rostamnia, S.; Morsali, A. *RSC Adv.* **2014**, *4*, 10514−10518.
(92) Nazari, S.; Saadat, S.; Fard, P. K.; Gorjizadeh, M.; Nezhad, E. R.; Afshari, M. *Monatsh. Chem.* **2013**, *144*, 1877−1882.
(93) Safari, J.; Gandomi-Ravandi, S. *J. Mol. Catal. A: Chem.* **2013**, *373*, 72−77.
(94) Chen, W. Y.; Qin, S. D.; Jin, J. R. *Catal. Commun.* **2007**, *8*, 123−126.
(95) Joseph, J. K.; Jain, S. L.; Singhal, S.; Sain, B. *Ind. Eng. Chem. Res.* **2011**, *50*, 11463−11466.
(96) Tayebee, R.; Amini, M. M.; Ghadamgahi, M.; Armaghan, M. *J. Mol. Catal. A: Chem.* **2013**, *366*, 266−274.
(97) Peng, J. J.; Deng, Y. Q. *Tetrahedron Lett.* **2001**, *42*, 5917−5919.
(98) Chen, X. F.; Peng, Y. Q. *Catal. Lett.* **2008**, *122*, 310−313.
(99) Sehout, I.; Boulcina, R.; Boumoud, B.; Berree, F.; Carboni, B.; Debache, A. *Lett. Org. Chem.* **2013**, *10*, 463−467.
(100) Liberto, N. A.; De Paiva Silva, S.; De Fátima, Â.; Fernandes, S. A. *Tetrahedron* **2013**, *69*, 8245−8249.
(101) Karimi, B.; Mobaraki, A.; Mirzaei, H. M.; Zareyee, D.; Vali, H. *ChemCatChem* **2014**, *6*, 212−219.
(102) Pramanik, M.; Bhaumik, A. *ACS Appl. Mater. Interfaces* **2014**, *6*, 933−941.
(103) Safari, J.; Zarnegar, Z. *New J. Chem.* **2014**, *38*, 358−365.
(104) Vikse, K. L.; Kwok, S.; McDonald, R.; Oliver, A. G.; McIndoe, J. S. *J. Organomet. Chem.* **2012**, *716*, 252−257.
(105) Hinderling, C.; Adlhart, C.; Chen, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2685−2689.
(106) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204−8214.
(107) Li, R. M.; Smith, R. L.; Kenttamaa, H. I. *J. Am. Chem. Soc.* **1996**, *118*, 5056−5061.

(108) Chisholm, D. M.; McIndoe, J. S. *Dalton Trans.* **2008**, 3933−3945.
(109) Ascher, U. M.; Petzold, L. R. *Computer Methods for Ordinary Differential Equations and Differential-Algebraic Equations*; SIAM: Society for Industrial and Applied Mathematics: Philadelphia, 1998.
(110) Petzold, L. R. Sandia National Laboratory, Report no. SAND82-8637, 1982.
(111) Bard, Y. *Nonlinear Parameter Estimation*; Academic Press: London, 1974.
(112) Schwaab, M.; Silva, F. M.; Queipo, C. A.; Barreto, A. G., Jr.; Nele, M.; Pinto, J. C. *Chem. Eng. Sci.* **2006**, *61*, 5791−5806.
(113) Heravi, M. M.; Asadi, S.; Lashkariani, B. M. *Mol. Divers.* **2013**, *17*, 389−407.
(114) Huang, Y. J.; Yang, F. Y.; Zhu, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 16386−16387.
(115) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.
(116) Yanai, T.; Tew, D. P.; Handy, N. C. *Chem. Phys. Lett.* **2004**, *393*, 51−57.
(117) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(118) Tawada, Y.; Tsuneda, T.; Yanagisawa, S.; Yanai, T.; Hirao, K. *J. Chem. Phys.* **2004**, *120*, 8425−8433.
(119) Parr, R. G.; Yang, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 4049−4050.
(120) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361−373.
(121) Xie, Z.-B.; Wang, N.; Wu, W.-X.; Le, Z.-G.; Yu, X.-Q. *J. Biotechnol.* **2014**, *170*, 1−5.