ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

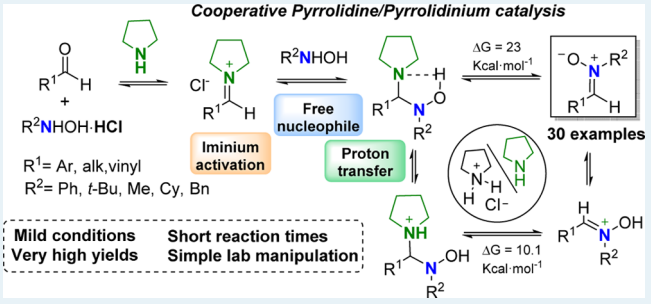
Dual Role of Pyrrolidine and Cooperative Pyrrolidine/Pyrrolidinium Effect in Nitrone Formation

Sara Morales, Fernando G. Guijarro, Inés Alonso, José Luis García Ruano,* and M. Belén Cid*

Department of Organic Chemistry, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Supporting Information

ABSTRACT: The formation of nitrones by direct condensation between equimolecular amounts of N-substituted hydroxylamine hydrochlorides and aromatic or aliphatic aldehydes is efficiently promoted by pyrrolidine in a matter of minutes under very mild conditions in almost quantitative yields after a simple filtration through a short pad of silica gel. According to theoretical, spectroscopic, and experimental studies, this success is due to the ability of pyrrolidine to liberate the hydrochloride of the hydroxylamine and catalyze the reaction via iminium activation ion. Moreover, a cooperative pyrrolidine/pyrrolidinium chloride effect facilitates several steps of the catalytic cycle through proton transfer without hampering the nucleophilicity of the hydroxylamine by protonation.



KEYWORDS: *nitrone preparation, iminium activation, cooperative catalysis, pyrrolidine/pyrrolidinium, DFT calculations*

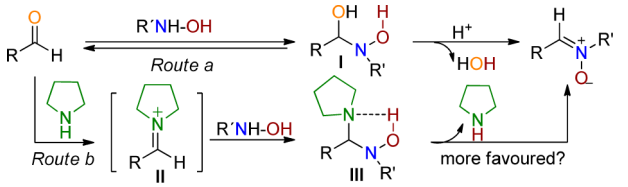
INTRODUCTION

Nitrones are very useful and versatile intermediates in organic synthesis,[1] especially in the field of 1,3-dipolar reactions.[2] Moreover, they have shown interesting free-radical-trapping properties that reduce damage in a variety of biological systems,[3] being therefore attractive as therapeutic agents.[4]

The two typical procedures[1b,5] to prepare nitrones involve oxidation reactions (of secondary hydroxylamines,[6] amines,[7] and even imines[8]) or condensation of aldehydes with N-monosubstituted hydroxylamines.[5,6a,9] The former methods require metal-catalytic systems, which usually present environmental problems,[10] as well as a careful control of the reaction conditions, which may cause selectivity problems in non-symmetric substrates. Due to the scarce stability of the free hydroxylamines, the condensation strategies generally start from the corresponding hydrochloride salts, and the conditions usually involve previous base-mediated liberation of the hydrochloride or the in situ formation of the corresponding hydroxylamine. Moreover, excess of reagents (aldehyde or hydroxylamine) and dehydrating agents are usually employed, thus imposing additional purification steps. Furthermore, relatively long reaction times (usually at high temperatures) or the use of techniques like MW[11] are commonly required. As the yields provided by all these procedures are usually high, the search for new methods must be focused on improving aspects like efficiency, wide scope, environmental features, and experimental simplicity.

According to the literature,[12] the condensation of aldehydes and hydroxylamines takes place in two steps (*route a*, Scheme 1): the attack of the R−NH−OH nucleophile to the carbonyl group to form the hemiaminal intermediate **I**, and the elimination of water from **I** to form the C═N bond. Assuming that nucleophilicity of the nitrogen at *N*-hydroxylamines is increased by the presence of OH group,[13] a fast first step is anticipated, which determines that, in the absence of acid catalysts, the limiting step is the second one, because of the poor ability of the $^-$OH as leaving group. Thus, the presence of an acid that protonates the $^-$OH group in some extension would catalyze its elimination as H_2O. However, these catalysts can protonate the hydroxylamine, decreasing the rate of the first step, which could become the limiting one. As a result of these opposite tendencies, it is usually assumed that the rate-determining step at neutral and weakly acidic pH is the elimination of the $^-$OH group, whereas at more acidic pH values, it is the formation of the hemiaminal **I**[12] (*route a*, Scheme 1). Consequently, the magnitude of the catalytic effect of the acids is rather moderate, and it is restricted to a narrow pH interval. In order to eliminate this situation, which is

Scheme 1. Influence of Pyrrolidine on the Two Steps Involved in the Formation of the C═N Bonds of Nitrones



Received: August 7, 2015
Revised: November 8, 2015

DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91

common in most of the C═N bond formation processes, it would be of great interest to find new catalytic systems able to simultaneously accelerate both steps.

Recently, we have developed an efficient aminocatalytic condensation of aldehydes with different *N*-nucleophiles for the synthesis of a variety of C═N−R′ compounds via iminium activation using pyrrolidine as catalyst.[14] This methodology provided high yields of different types of aldimines under mild conditions, in the absence of acids and metals. From these results, it could be expected that pyrrolidine would accelerate the first step in the synthesis of nitrones by forming an iminium ion **II** (much more reactive than the corresponding aldehyde[15]) easily transformed into the aminal **III** (first step at *route b*, Scheme 1). Moreover, its catalytic effect would be more remarkable if it had some role in making easier the second step in the absence of acids. We hypothesized that the higher basicity of the nitrogen at **III**, with respect to the oxygen at **I**, would facilitate the proton transfer under nonacidic conditions, determining that elimination of pyrrolidine from **III** would become easier than that of H_2O from **I**. In such a case, pyrrolidine could be an ideal catalyst facilitating both steps, being conceivable the synthesis of nitrones under very mild conditions.

In this paper, we describe the catalytic role of pyrrolidine in the synthesis of nitrones by direct condensation of aldehydes and N-substituted hydroxylamines. Additionally, we have found that this catalytic effect can be substantially increased by the presence of pyrrolidinium ion, generated from pyrrolidine when commercially available hydroxylamine hydrochlorides are used as starting materials. This new cooperative pyrrolidine/pyrrolinium system provides a very efficient and simple method for the synthesis of nitrones, which can be applied in several solvents and exhibits clear environmental and practical advantages with respect to any other one so far reported in the literature.

RESULTS AND DISCUSSION

We first performed theoretical calculations in order to support our assumption about the positive influence of the pyrrolidine on the second step of the mechanism indicated in Scheme 1 (*route b*). In this sense, we studied the elimination of water and pyrrolidine (from **I** and **III** respectively) by DFT calculations,[16] using as model reaction the formation of the *N*-methyl-substituted nitrone derived from benzaldehyde in MeOH as solvent (Figure 1).

According to the free energy profile, the activation barrier for the elimination of water from the corresponding hemiaminal **I** (*route a*, Scheme 1) was 7.4 kcal·mol^{-1} higher than the one required for the elimination of pyrrolidine from aminal **III** (*route b*, Scheme 1). Similar results were observed in CH_2Cl_2 (values in parentheses). The intramolecular proton transfer from the OH of *N*-methylhydroxylamine to the leaving group of **I** and **III** provided us reasonable free energy barriers in both cases. However, the participation of other molecules as proton relay cannot be ruled out.[17]

A detailed analysis of the structure of both transition states points out that the accelerating effect of pyrrolidine could be related to its basicity (Figure 2). **TSI** shows that the cleavage of the C−O(2) bond is highly developed (2.17 Å) when the proton transfer is yet clearly lower than 50% ($d_{H-O(1)} < d_{H-O(2)}$), suggesting that the $^-$OH (and not the OH_2) might be mainly acting as leaving group. This would explain the high value calculated for the activation barrier (30.4 kcal·mol^{-1}). By

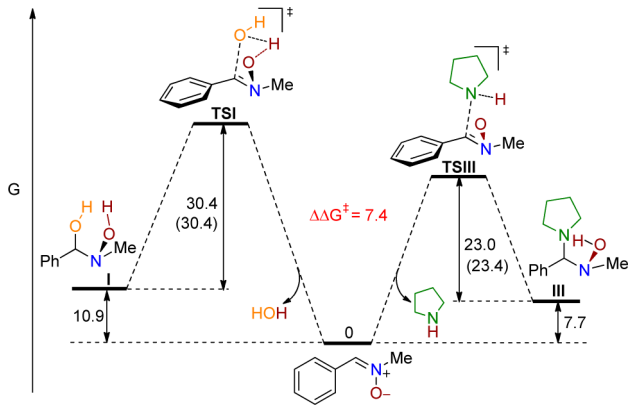


Figure 1. Reaction pathways and energies in kcal·mol^{-1} at 298 K comparing nitrone formation from hemiaminal **I** and aminal **III** in MeOH ($CPCM_{Solvent}$wB97xd/tzvp). Activation barriers in CH_2Cl_2 are indicated in parentheses.

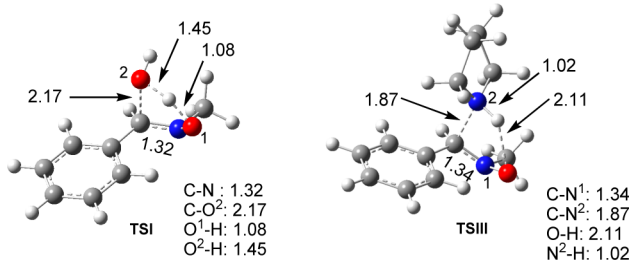
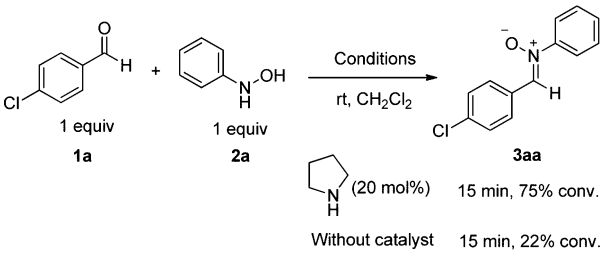


Figure 2. Optimized geometries of transition states **TSI** and **TSIII** (distances in Å).

contrast, the geometry of **TSIII** shows that the proton is almost completely transferred ($d_{H-O(1)} \gg d_{H-O(2)}$) when the cleavage degree of the C−N is moderated yet ($d_{C-N(2)}$ = 1.87 Å), thus indicating the leaving group might be now the protonated nitrogen. As pyrrolidine is a better leaving group than the $^-$OH, the activation barrier is clearly lower (23 kcal·mol^{-1}), and therefore, the reaction must be faster, presumably.

With this promising perspective and in order to check the validity of these predictions, we first studied the influence of pyrrolidine on the condensation of *p*-chlorobenzaldehyde **1a** (a nonvolatile aldehyde) with *N*-phenyl hydroxylamine **2a**, one of the few hydroxylamines that is commercially available in its free form (Scheme 2). The addition of pyrrolidine in catalytic

Scheme 2. Synthesis of the Nitrone 3aa



amount (0.2 equiv) determined the formation of the *N*-phenyl nitrone **3aa** in 75% of conversion after 15 min in CH_2Cl_2.[18] In the absence of pyrrolidine, the conversion was lower (22% after 15 min), which demonstrates the ability of pyrrolidine to catalyze this process.[19]

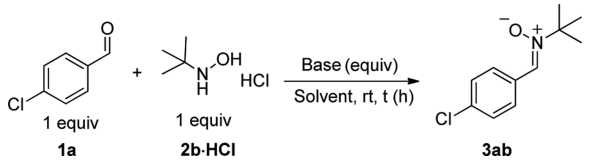
DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91

Despite the theoretical significance of this finding, the practical interest of the reactions using free hydroxylamines (like **2a**) as starting materials is rather moderated, because they are scarcely stable and therefore are usually generated in situ from their hydrochlorides, which are the commercially available forms of these compounds. Thus, it was necessary to look for the proper conditions to prepare nitrones from the hydroxylamine hydrochlorides.

We decided to evaluate the ability of pyrrolidine in the formation of nitrones starting from hydroxylamine hydrochlorides by using *N*-*t*-butylhydroxylamine hydrochloride **2b**·HCl. Several facts prompted us to focus on the formation of *N*-*t*-butylnitrones. The *t*-butyl group is the most challenging substituent due to its low reactivity in direct condensation.[20] At the same time, a wide variety of interesting therapeutic properties have been described for aromatic *N*-*t*-butylnitrones.[11c,21] Moreover, it is interesting from a synthetic point of view because the *t*-butyl group is potentially removable under acidic conditions.[22]

According to the relative pK_a values of pyrrolidine (11.2)[23] and *N*-methylhydroxylamine (5.96),[23] we would expect a fast and complete proton exchange between hydroxylamine hydrochlorides **2**·HCl and pyrrolidine.[24] Thus, we investigated the formation of *t*-butyl nitrone **3ab** starting from *N*-*t*-butylhydroxylamine hydrochloride **2b**·HCl with different amounts of pyrrolidine (Table 1).

Table 1. Optimization of the Reaction Conditions To Form *t*-Butyl Nitrone 3ab, Starting from 2b·HCl



entry[a]	base (equiv)	solvent	*t* (h)	conv. (%)[b]
1	--	MeOH	16	--[c]
2	--	CH_2Cl_2	16	--
3	--	H_2O	16	20
4	pyrrolidine (1)	MeOH	6.5	100
5	pyrrolidine (1)	CH_2Cl_2	3	100
6	pyrrolidine (1)	H_2O	6 (20)	41 (38)
7[d]	pyrrolidine (1)	H_2O/MeOH	6 (**16**)	78 (**100**)[e]
8	Et_3N (1)	MeOH	16 (80)	24 (83)
9	Et_3N (1)	CH_2Cl_2	16	0
10	Et_3N (1)	H_2O/MeOH	16	41
11	pyrrolidine (1.2)	MeOH	3.5	100
12	pyrrolidine (1.2)	CH_2Cl_2	0.33	100
13	pyrrolidine (1.2)	H_2O/MeOH	6	100
14	pyrrolidine (2.0)	CH_2Cl_2	0.4	93

[a]0.2 mmol scale. [b]Determined by ^{1}H NMR. [c]A complete conversion into hemiacetal was observed. [d]Conditions employed to scale up the reaction until 7.9 mmol (16 h, 92%). [e]The same conversion was observed after 16 h in EtOH, CH_3CN, and EtOAc.

The reaction of equimolecular amounts of **1a** and **2b**·HCl in dichloromethane at room temperature did not provide **3ab** after 16 h (entry 2), which was expected because of the absence of free hydroxylamine **2b**, the real nucleophile of this reaction. The change of solvent to MeOH (entry 1) produced the complete conversion of the aldehyde into the hemiacetal, but the signals of the nitrone **3ab** did not appear in the ^{1}H NMR spectrum. Nevertheless, the use of water as solvent allowed the formation of nitrone **3ab** in 20% conversion (entry 3). This fact could be due to the slight dissociation in water of the hydrochloride **2b**·HCl, able to provide a little amount of free hydroxylamine **2b**.

The addition of 1 equiv of pyrrolidine, required for the complete liberation of the hydroxylamine,[25] had a significant influence on the reactivity. The conversion into **3ab** was complete after 6.5 h in MeOH and 3 h in CH_2Cl_2 (entries 4 and 5). Looking for solvents with better environmental features, which would be interesting for large-scale transformations, we first studied reactions in water, but only a moderate conversion was observed after 6 h, which did not increase with time (entry 6).[16] Fortunately, the use of a 1:1 mixture H_2O/MeOH as solvent (entry 7) allowed the complete conversion after 16 h at room temperature, and the nitrone **3ab** could be isolated in almost quantitative yield (94%). Under these conditions, the reaction was slower (78% conversion after 6 h, entry 7) than in MeOH or CH_2Cl_2 (entries 4 and 5), but it presented some environmental advantages and it could be performed in a larger scale (6.4 mmol, 1 g) without any substantial decrease in the yield (92%). Interestingly, the reaction was also successful in other solvents, like EtOH, CH_3CN, and EtOAc, being the yields and reaction times similar to those observed in the 1:1 mixture H_2O/MeOH.[16]

We then compared the reaction of **1a** with **2b**·HCl in the presence of Et_3N, one of the bases used in the literature to liberate the free hydroxylamines from their hydrochlorides but unable to form iminium species. The conversion degrees observed in MeOH, CH_2Cl_2 and 1:1 mixture of H_2O/MeOH (entries 8−10) were, respectively, lower than those observed in entries 4, 5, and 7 using pyrrolidine, which put forward that pyrrolidine exerts some additional role to that of liberating the free hydroxylamine.[26]

The reaction of **1a** and **2b**·HCl in the presence of some excess of pyrrolidine (1.2 equiv) required significantly lower reaction times in the studied solvents, which respectively became 3.5 h in MeOH (entry 11), 20 min in CH_2Cl_2 (entry 12) and 6 h in the 1:1 mixture H_2O/MeOH (entry 13). The use of a larger excess of pyrrolidine (2 equiv) did not produce any additional improvement in the reaction times (in CH_2Cl_2, conversion was only 93% after 24 min, entry 14). We will analyze the optimum amount of pyrrolidine below (see also SI).

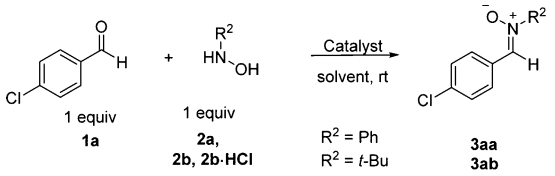
With the suitable conditions to prepare nitrones from hydroxylamine hydrochlorides using pyrrolidine, to both liberate the hydrochloride and accelerate the reaction, we were poised to evaluate the effect of the resulting pyrrolidinium chloride in the reaction rate. For that purpose, we carried out the experiments of Table 2, monitoring by ^{1}H NMR the nitrone formation at short times using **2a**, **2b**, and **2b**·**HCl** as nucleophiles under different conditions.

For the sake of clarity, entry 1 shows the result of Scheme 2 using **2a** in the presence of 0.2 equiv of pyrrolidine in CD_2Cl_2. Conditions of entry 2 tried to mimic the optimized conditions of entry 12 (Table 1) as if the reaction was performed with the corresponding hydrochloride using a mixture of 1 equiv of pyrrolidinium chloride (preformed) and 0.2 equiv of pyrrolidine as catalysts. Comparison of entries 1 and 2 suggests a cooperative effect of the pyrrolidine/pyrrolidinium combination, as conversion in entry 2 was higher than in entry 1 where only pyrrolidine was used.

This effect was corroborated when comparing the reaction times and conversions of entries 3−5 using the *t*-butyl

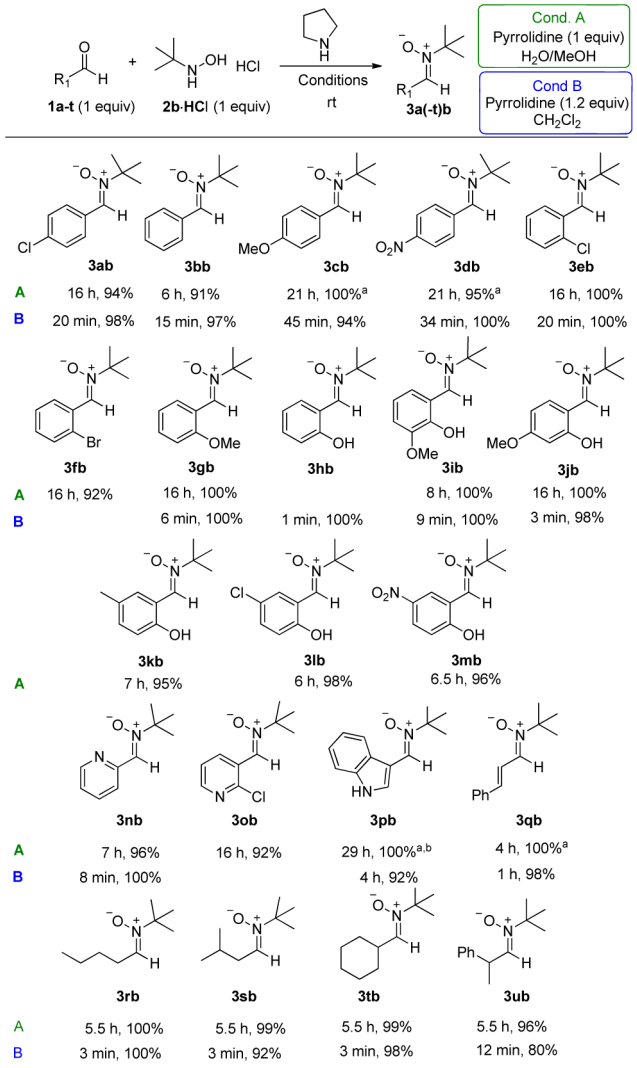
DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91

Table 2. Monitoring of Nitrone Formation at Short Times Using 2a, 2b, and 2b·HCl under Different Conditions



entry	Nu	solvent	catalyst (equiv)	time (min)	conv. to **3**
1	**2a**	CD_2Cl_2	pyrrolidine (0.2)	15	75 (**3aa**)
2	**2a**	CD_2Cl_2	pyrrolidine·HCl (1) + pyrrolidine (0.2)	15	100 (**3aa**)
3	**2b**	MeOH-d_4	pyrrolidine (0.2)	24	21 (**3ab**)
4	**2b**·HCl	MeOH-d_4	pyrrolidine (1)	11	68 (**3ab**)
5	**2b**·HCl	MeOH-d_4	pyrrolidine (1.2)	4	79 (**3ab**)

Table 3. Synthesis of *N*-*t*-Butylnitrones Derived from Aldehydes under Conditions A and B[†]



[†]Reactions carried out under conditions B were monitored by ^{1}H NMR until complete conversion. [a]MeOH was used as solvent. [b]1.1 equiv of pyrrolidine were used.

derivatives **2b** and **2b·HCl** in MeOH as solvent. We reasoned that under conditions of entries 1 and 3, the free pyrrolidine (0.2 equiv) could act as catalyst as proposed in Scheme 1. The presence of 1 equiv of pyrrolidinium chloride, formed after the hydrochloride liberation, could accelerate the process not only via iminium activation but also favoring some steps by protonation without affecting the concentration of the nucleophile **2b** (entry 4). Synergy of both activation pathways seems to be optimal when 1 equiv of pyrrolidinium chloride and 0.2 equiv of free pyrrolidine are present in the reaction media (entry 5).

Once we confirmed the cooperative pyrrolidine/pyrrolididinium effect, the conditions of entry 12 (1.2 equiv of pyrrolidine in CH_2Cl_2, identified as Conditions B) were selected as the optimal ones to study the scope of the reaction using *N*-*t*-butylhydroxylamine hydrochloride **2b**·HCl. Additionally, reactions under conditions of entry 7 (1 equiv of pyrrolidine in 1:1 mixture H_2O/MeOH, identified as Conditions A) were also evaluated in the scope because of the better environmental features of the solvent and less amount of pyrrolidine used.

Therefore, we studied the reactions of equimolecular amounts of aromatic and aliphatic aldehydes **1** with **2b**·HCl at room temperature under conditions A and B (Table 3). Reactions of aromatic aldehydes were efficient under both types of conditions,[27] regardless of the nature and position of the substituents at the ring, the yields obtained being excellent in all cases. It could be observed that reaction times to get complete conversions were longer under conditions A (hours) than under the B ones (minutes).

Substituted benzaldehydes (**1a**−**f**) show small differences depending on the substituent. Under both conditions, the reaction times required are slightly longer to prepare nitrones **3cb** and **3db**, derived both from benzaldehydes bearing substituents with strong electronic effects. Nitrones derived from salicylaldehyde are interesting due to their pharmacological properties.[21b] We have prepared some of these compounds in excellent yields (**3gb**−**3mb**). Moreover, very short reaction times were required under conditions B (**3gb**−**jb**), which suggests the presence of the *o*-OH or *o*-OMe groups seems to facilitate the formation of the C═N bond. Nitrones **3nb** and **3ob**, derived from 2- and 3-pyridyl carboxaldehydes, could also be obtained satisfactorily under both conditions, but the reaction time was lower in the first one under conditions A, exhibiting a similar reactivity than that of the *o*-hydroxy benzaldehydes.[28]

Surprisingly, the reaction with 2-indolylcarboxaldehyde to form nitrone **3pb** could not be performed under the standard conditions A, being necessary to use MeOH as solvent and 1.1 equiv of pyrrolidine to obtain a quantitative yield of this compound after 29 h of reaction (see SI for more details). Moreover, its isolation was not possible under the usual conditions (see later), as it is described in SI. Following the protocol corresponding to conditions B, **3pb** could be isolated

DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91

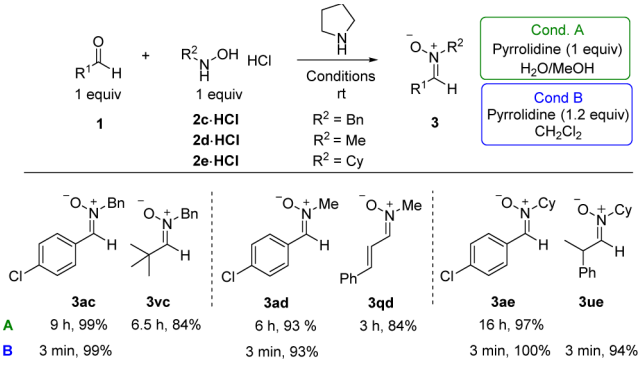
in 92% yield, but the reaction time was anomalously long (4 h). Similarly, the α,β-unsaturated aldehyde **1q** required 1 h to be completely transformed into the nitrone **3qb**. This complete regioselectivity can be attributed to the reversibility in the attack at C-3, observed for some heteronucleophiles,[29] and/or to the fact that the reaction of *N*-nucleophiles at C-1 is favored by the anomeric stabilization of the aminal species resulting in this attack.[15] In fact, it was possible to observe by ^{1}H NMR the reversible formation of the product resulting in the conjugate addition (attack of **2b** to C-3) to **1q** under conditions B, which was completely transformed into **3qb** in 1 h. This evolution could explain the longer times required in this reaction for aldehyde **1q** (hours instead of minutes). A similar explanation would be valid for **1p**.

Finally, nitrones **3rb**−**3ub**, derived from aliphatic aldehydes, could also be prepared under conditions A and B. Reactivity of these aldehydes was higher than that of the aromatic ones. Thus, reaction times are usually shorter (5.5 h under conditions A and few minutes under conditions B) for both linear and branched aliphatic aldehydes, with almost quantitative yields in all cases.

As an additional interest of all these reactions, which are performed at room temperature, starting from equimolecular amounts of the reagents, the resulting nitrones can be obtained as pure compounds by simple filtration through a short pad of silica gel, which retains both pyrrolidinium chloride and the small excess of pyrrolidine, being therefore applicable to conditions A and B. The instability of the nitrones **3rb**−**3ub**, derived from aliphatic aldehydes, imposed the filtration through Al_2O_3 (basic) instead of silica gel (acidic).

Encouraged by these results, we applied our approach to the preparation of nitrones using different N-substituted hydroxylamines **2c**−**e**·HCl with similar advantages to those mentioned before (Table 4). First, *N*-benzylnitrones, like **3ac** and **3vc**,

Table 4. Reactions of Aldehydes with *N*-Alkyl Hydroxylamine Hydrochlorides 2c−e·HCl

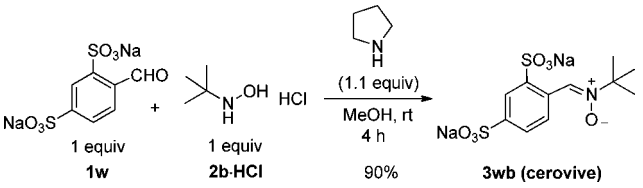


which are valuable intermediates because of the easy elimination of the benzyl group, were prepared with aromatic (**1a**) and aliphatic (**1v**) aldehydes and *N*-benzyl hydroxylamine hydrochloride (**2c**·HCl) in excellent yields. A similar behavior was observed in reactions with *N*-methyl hydroxylamine (**2d**·HCl) and *N*-cyclohexyl hydroxylamine (**2e**·HCl). The synthesis of **3ad** in larger scale (6 and 1 g of **2d**·HCl were, respectively, used under conditions A and B) was satisfactorily performed without any reduction of the yield (see SI). However, the reaction of the cinamaldehyde **1q** with **2d**·HCl under conditions B was not satisfactory, due to the formation of complex reaction crudes.

In all cases the reaction times under both conditions were shorter than those required using *N*-*t*-butyl hydroxylamine, due to the negative influence of the steric size around the nitrogen on the reaction rate. Filtration through a short pad of silica gel or basic Al_2O_3 provided pure nitrones, being unnecessary any additional purification step.

We have applied the strategy to the synthesis of cerovive[30] (Scheme 3), a nitrone which demonstrated anticancer activity

Scheme 3. Synthesis of 3wb (Cerovive)



and reached phase III clinical trials as the first neuroprotective agent (NXY-059).[31] Methods so far reported to prepare this drug are experimentally complex and require excess (1.4−4 equiv) of *N*-*t*-butylhydroxylamine (or *N*-*t*-butylhydroxylammonium acetate), high temperature, and long reaction times to give yields ranging between 65% and 82%. Starting from equimolecular amounts of the reagents in their commercially available form, dissolved in methanol, the addition of 1.1 equiv of pyrolidine allowed the synthesis of cerovive in 90% yield after 4 h at room temperature. Conditions B could not be applied to the synthesis of cerovive due to the low solubility of the starting salt **1w** in CH_2Cl_2.

All our trials to obtain nitrones derived from ketones under conditions indicated for aldehydes were unsuccessful. A similar result, observed in the synthesis of imines catalyzed by pyrrolidine,[14] was attributed to the high steric interactions associated with the tetrasubstituted C═N bond of the resulting iminium ion.

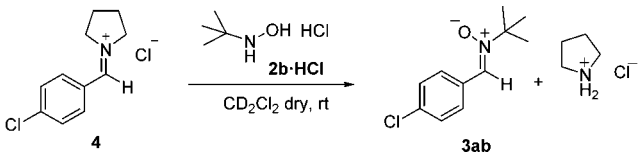
At this point, it is interesting to compare the reaction conditions we have used in the synthesis of the nitrones collected in Tables 3 and 4 with those of the best methods reported to prepare the same compounds (see SI). Most of them provide excellent yields but require an excess of some of the reagents, high temperatures, and the use of extraction, chromatographic columns and/or recrystallization techniques to isolate and purify the resulting nitrones. Moreover, long reaction times are usually required, and special techniques, like MW or ball milling, are frequently used to shorten them. Our method not only satisfies the main requirements of the green chemistry (no hazardous materials and minimal experimental manipulation and waste) but also competes with those previously described in yields, mild conditions, reaction times, easiness of purification, and experimental simplicity. It is also remarkable the dispersion of conditions used in the literature to prepare the concerned nitrones, which contrast with the almost identical ones used in our procedure. To our knowledge, the synthesis of the nitrones **3kb**, **3ib**, **3rb**, **3eb**, **3gb**, and **3ae** had never been reported in the literature.

To gain some insight into the reaction mechanism and demonstrate the hypothesis proposed in *route b* (Scheme 1), we accomplished several experiments. As mentioned above the comparison of results in nitrone formation between pyrrolidine and Et_3N (Table 1, entries 4, 5, and 7 with 8−10) pointed out that the role of pyrrolidine must not be limited to the liberation of the corresponding hydrochloride. In order to demonstrate

DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91

our hypothesis of iminium ion activation, we preformed the iminium chloride ion **4** (using the procedure reported in the SI) and followed by ^{1}H NMR its evolution in the presence of **2b**·HCl in CD_2Cl_2 at rt. We could confirm the instantaneous formation of nitrone **3ab** and the liberation of pyrrolidinium chloride (Scheme 4).

Scheme 4. Reaction of 4 with 2b·HCl



In Figure 3, we have depicted the mechanistic proposal to explain the cooperative pyrrolidine/pyrrolidinium effect,

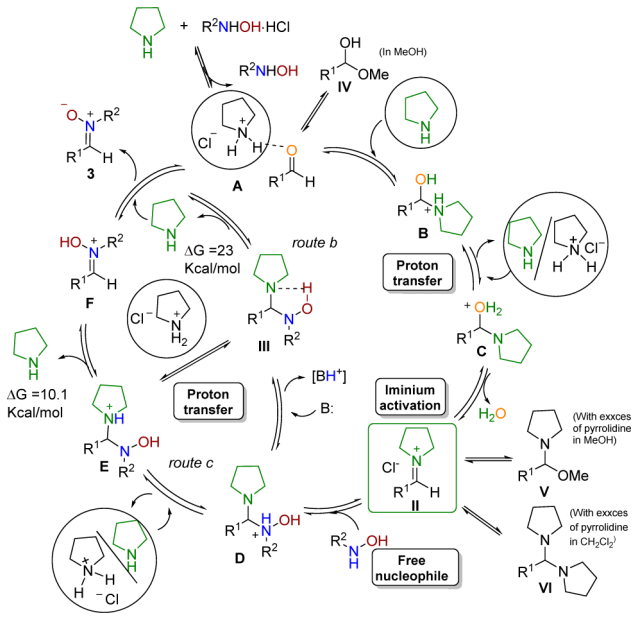


Figure 3. Mechanistic proposal.

demonstrated in the results of Table 2, which allows the synthesis of nitrones under the mildest and general conditions ever reported (see SI). We have highlighted the three key points that define the efficiency of the method: (a) iminium activation of the aldehyde, favored by the free pyrrolidine, (b) the cooperative effect of the pyrrolidine/pyrrolidinium system in the proton-transfer of some steps, and (c) the preservation of the free N-substituted hydroxylamine nucleophile under the reaction conditions.

The treatment of the starting N-substituted hydroxylamine hydrochloride (R^2NHOH·HCl) (1 equiv) with pyrrolidine should lead to 1 equiv of pyrrolidinium chloride,[23] the free N-substituted hydroxylamine and a variable amount of free pyrrolidine according to the amount of pyrrolidine added (0.2 equiv under ideal conditions B).

We propose that pyrrolidinium ion could favor the iminium formation activating the aldehyde through protonation (**A**) toward the attack of the free pyrrolidine[32] giving **B** and favoring the proton transfer to produce **C** and therefore allowing the loss of H_2O (instead of $^-$OH) facilitating the elimination step. The evolution of iminium **II**, a much better electrophile than the corresponding carbonyl compound, into the nitrone **3** involves the attack of the free hydroxylamine to form **D**, which could evolve through two different routes. In the first one (*route b*), it would be transformed into **III** with a base, which could evolve into the nitrone as it was indicated in Scheme 1 and Figure 1. In the second one, the presence of the pyrrolidinium chloride could afford species **E** (*route c*, in Figure 3), which should eliminate pyrrolidine more easily because the nitrogen is protonated. This was confirmed by theoretical calculations[16] of the $\Delta G^{\ddagger}$ for the transformation of **E** into **F**, which resulted much lower (10.1 kcal·mol^{-1}) than that calculated for the elimination of pyrrolidine from **III** (23 kcal·mol^{-1}, Figure 1).[33] Deprotonation of **F** with pyrrolidine affords the nitrone and closes the catalytic cycle liberating the pyrrolidinium ion.

Figure 3 also includes hemiacetal **IV**, hemiaminal **V**, and aminal **VI**, which have been identified by monitoring by ^{1}H NMR the evolution of several reactions between **1a** and **2b**·HCl.[16] The species **V** and **VI** were detected when an excess of pyrrolidine was used in MeOH-d_4 and CD_2Cl_2, respectively. Their presence reinforces the formation of the iminium ion as intermediate, whose concentration must be higher with the higher concentration of free pyrrolidine, but slows down the complete conversion toward nitrone formation. These facts would explain that the optimal amount of pyrrolidine is 1.2 equiv and led us to represent species **V** and **VI** out of the catalytic cycle. The longer reaction times observed in MeOH could be partially due to the formation of hemiacetal **IV**, which must also be out of the catalytic cycle (Figure 3).

Another issue to consider is that it is admitted that the counterion of the iminium ion determine its stability,[34] and therefore, we can not rule out an effect of the chloride ion in the iminium stability. This effect is not possible when the reaction is directly carried out with the free hydroxylamine derivative. Moreover, according to our experiments, the pyrrolidinium ion could also decrease the amount of the species **IV**–**VI** pushing them into the catalytic cycle.[16] Additionally, we cannot discard a role as simple acid (as in *route a*, Scheme 1) competing to some extent with the mechanism shown in Figure 3 when a low concentration of free pyrrolidine is present in the reaction media (conditions A).

CONCLUSIONS

We have developed the most efficient, simple, robust and reliable protocol so far reported to form nitrones from the condensation between equimolecular amounts of aldehydes and N-substituted hydroxylamine hydrochlorides (see SI for comparison with other methods). The traditional problem of acid/base catalysis, that hampers the simultaneous nucleophile and electrophile activation, has been overcome by using pyrrolidine, which is able to favor the two steps represented in Scheme 1. Pyrrolidine allows the complete liberation of the hydroxylamine hydrochloride, increase the electrophilicity of the carbonyl group through the formation of the iminium ion and favors nitrone formation because it is a better leaving group than the $^-$OH. Moreover, the simultaneous formation of the pyrrolidinium chloride provides to the reaction media with a cooperative system able to accelerate some of the steps by proton transfer without hampering the nucleophilicity of the N-substituted hydroxylamine by protonation. This cooperative pyrrolidine/pyrrolidinium approach proved to be general for a wide range of both condensation partners in an inexpensive, facile, fast, sustainable, metal-free, and scalable way. The usefulness of this procedure in the preparation of other

DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84–91

important compounds containing C=N bonds is currently being investigated in our lab.[13]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01726.

Additional optimization studies, the comparison of conditions previously reported for the prepared compounds, the ^{1}H NMR experiments, spectroscopy data of each compound, and computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: belen.cid@uam.es.

*E-mail: joseluis.garcia.ruano@uam.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Spanish Government (CTQ-2012-35957) for financial support. S.M. thanks the Spanish Ministry of Economy and Competitiveness for a predoctoral fellowship (FPI). We also thank the Centro de Computación Científica (UAM) for generous allocation of computer time and Dr. Pablo Mauleón and Dr. José Luis Aceña for useful discussions.

■ REFERENCES

(1) (a) Tufariello, J. *Acc. Chem. Res.* **1979**, *12*, 396−403. (b) Grigor'ev, I. A. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Feurer, H., Ed.; John Wiley & Sons: Hoboken, NJ, 2008; pp 129−434. (c) Yang, J. *Synlett* **2012**, *23*, 2293−2297 and references cited therein.

(2) (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909. (b) Raymond, C. F. J. In *Synthetic Applications of 1,3-Dipolar Cycloadditions. Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: Hoboken, NJ, 2003; Vol. *59*, pp 1−81.

(3) (a) Carney, J. M.; Floyd, R. A. *J. Mol. Neurosci.* **1991**, *3*, 47−57. (b) Thomas, C. E.; Ohlweiler, D. F.; Carr, A. A.; Nieduzak, T. R.; Hay, D. A.; Adams, G.; Vaz, R.; Bernotas, R. C. *J. Biol. Chem.* **1996**, *271*, 3097−4104.

(4) (a) Floyd, R. A.; Hensley, K.; Forster, M.; Kelleher-Andersson, J. A.; Wood, P. L. *Mech. Ageing Dev.* **2002**, *123*, 1021−1031. (b) Floyd, R. A. *Aging Cell* **2006**, *5*, 51−57. (c) Floyd, R. A.; Kopke, R. D.; Choi, C. H.; Foster, S. B.; Doblas, S.; Towner, R. A. *Free Radical Biol. Med.* **2008**, *45*, 1361−1374.

(5) (a) Merino, P.; Padwa, A. *Science of Synthesis*; Thieme: Stuttgart, 2004; Vol. *27*, pp 511−580. (b) Merino, P. *Science of Synthesis*; Thieme: Stuttgart, Update 2010; Vol. *4*, pp 325−403.

(6) (a) Breuer, E. I. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; pp 459−564. (b) Saladino, R.; Neri, V.; Cardona, F.; Goti, A. *Adv. Synth. Catal.* **2004**, *346*, 639−647. (c) Matassini, C.; Parmeggiani, C.; Cardona, F.; Goti, A. *Org. Lett.* **2015**, *17*, 4082−4085.

(7) Zonta, C.; Cazzola, E.; Mba, M.; Licini, G. *Adv. Synth. Catal.* **2008**, *350*, 2503−2506.

(8) (a) Christensen, D.; Jørgensen, K. A. *J. Org. Chem.* **1989**, *54*, 126−131. (b) Hanquet, G.; Lusinchi, X. *Tetrahedron* **1994**, *50*, 12185−12200. (c) Soldaini, G.; Cardona, F.; Goti, A. *Org. Lett.* **2007**, *9*, 473−476.

(9) A recent umpolung approach toward *N*-aryl nitrones starts from 1,2-dicarbonyl compounds and nitroso electrophiles, see: Chavannavar, A. P.; Oliver, A. G.; Ashfeld, B. L. *Chem. Commun.* **2014**, *50*, 10853−10856.

(10) For a metal-free protocol for oxidation of secondary amines to nitrones see: Gella, C.; Ferrer, E.; Alibes, R.; Busque, F.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6365−6367 and references cited therein. See also ref 6c.

(11) (a) Andrade, M. M.; Barros, M. T.; Pinto, R. C. *Tetrahedron* **2008**, *64*, 10521−10530. (b) Valizadeh, H. *Heteroat. Chem.* **2010**, *21*, 78−83. (c) Samadi, A.; Soriano, E.; Revuelta, J.; Valderas, C.; Chioua, M.; Garrido, I.; Bartolomé, B.; Tomassolli, I.; Ismaili, L.; González-Lafuente, L.; Villarroya, M.; García, A. G.; Oset-Gasque, M. J.; Marco-Contelles, J. *Bioorg. Med. Chem.* **2011**, *19*, 951−960.

(12) Reimann, J. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1966**, *88*, 3973−3982.

(13) Nigst, T. A.; Antipova, A.; Mayr, H. *J. Org. Chem.* **2012**, *77*, 8142−8155.

(14) Morales, S.; Guijarro, F. G.; García Ruano, J. L.; Cid, M. B. *J. Am. Chem. Soc.* **2014**, *136*, 1082−1089.

(15) Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579−6587.

(16) See SI for more details.

(17) Intramolecular proton transfer through a five-membered transition states have also been proposed in the literature to be involved in nitrone formation, see Zhao, J.; Sun, C.; Sun, N.; Meng, L.; Chen, D. *Int. J. Quantum Chem.* **2013**, *113*, 2457−2463. However, the participation of other molecules as a proton relay could also be possible. This approach had been proposed in related processes such us enamine formation, see: Patil, M. P.; Sunoj, R. B. *J. Org. Chem.* **2007**, *72*, 8202−8215. In our case, when a molecule of methanol was included in transition states, despite unfavorable entropic factors, both free energy barriers as well as the difference between them decreased (see SI for more details).

(18) This reaction is slower in methanol (it needs 48 h to be completed) affording **3aa** in 71% along with azoxybenzene as side product. It is described that azoxybenzene can be formed in basic media; see: Bigelow, H. E. *Chem. Rev.* **1931**, *9*, 117−167. In fact, the use of proline instead of pyrrolidine as catalyst avoided the formation of the azoxybenzene and provided an almost quantitative yield of **3aa** in 16 h. Nevertheless, the formation of the azoxybenzene was not observed using catalytic pyrrolidine in dichloromethane as solvent.

(19) Under pyrrolidine catalysis, the complete conversion of **3aa** was obtained in 3 h in 94% yield, whereas it required 7.5 h in the absence of catalyst.

(20) Dias, A. G.; Santos, C. E. V.; Cyrino, F. Z. G. A.; Bouskela, E.; Costa, P. R. R. *Bioorg. Med. Chem.* **2009**, *17*, 3995−3998.

(21) (a) Rosselin, M.; Choteau, F.; Zéamari, K.; Nash, K. M.; Das, A.; Lauricella, R.; Lojou, E.; Tuccio, B.; Villamena, F. A.; Durand, G. *J. Org. Chem.* **2014**, *79*, 6615−6626. (b) Waterbury, L. D.; Carney, J. M.; Wilcox, A. L. PCT Int. Appl. 2000003977, 2000.

(22) Murarka, S.; Studer, A. *Org. Lett.* **2011**, *13*, 2746−2749.

(23) Hall, H. K., Jr *J. Am. Chem. Soc.* **1957**, *79*, 5441−5444.

(24) We could confirm by ^{1}H NMR the effective liberation of **2b**·HCl and the formation of pyrrolidinium chloride when 1 equiv of pyrrolidine was used in DMSO-d_6 (see SI).

(25) We demonstrated that substoichiometric amounts of pyrrolidine allowed the formation of nitrone, probing the catalytic effect of pyrrolidine (63% conversion with 0.5 equiv after 3 days). Nevertheless, at least 1 equiv of pyrrolidine is mandatory to completely liberate hydroxylamine hydrochloride. Other reaction conditions were investigated, including the use of other bases to liberate the hydrochloride along with pyrrolidine, but the results were less significant than those indicated in Table 1 (see SI).

(26) The magnitude of the catalytic effect of the pyrrolidine with respect to Et_3N in MeOH is lower than that in CH_2Cl_2, but quite significant yet, as it was established following the evolution of the reactions by NMR using both reagents in MeOH-*d*4 (see SI).

(27) In some cases, only one of the conditions has been used, because the generality of the method has been demonstrated in comparable compounds.

(28) The higher reactivity of the *orto*-hydroxybenzaldehydes and the 2-pyridylcarboxaldehyde was detected by Kool in the formation of

DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91

hydrazones at neutral pH, see: Kool, E. T.; Park, D.-H.; Crisalli, P. *J. Am. Chem. Soc.* **2013**, *135*, 17663−17666. According to this author, the protonated pyridinic nitrogen and the *ortho*-hydroxy group make easier the formation of the C═N bond because theyintramolecularly transfer their proton to the OH at the hemiaminal intermediate, thus favoring its elimination as H_2O.

(29) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983−1987.

(30) (a) Villamena, F. A.; Das, A.; Nash, K. M. *Future Med. Chem.* **2012**, *4*, 1171−1207. (b) Floyd, R. A.; Chandru, H. K.; He, T.; Towner, R. *Anti-Cancer Agents Med. Chem.* **2011**, *11*, 373−379.

(31) Blixt, J.; Kruk, H.; Mcginley, J.; Pouhov, S.; Vajdaal, J. PCT Int. Appl. 2001051460, 2001.

(32) It is consistent with the clearly higher value of nucleophilicity parameter of the pyrrolidine (N = 18.64 in MeCN): Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, *2009*, 6379−6385 with respect to *N*-methylhydroxylamine (N = 14.10 in MeCN): see ref 13.

(33) It is important to note that the purpose of the theoretical study is not to explain the extremely complex multistep process indicated in Figure 3 but to support our hypothesis concerning the possible accelerating effect of the pyrrolidine and pyrrolidinium in the elimination step. Moreover, the calculated values do not take into account the presence of other molecules such as water, methanol, or even pyrrolidine or the nucleophile *N*-alkylhydroxylamine, which may also have an important role in different steps of the process (see also ref 17).

(34) (a) Mayr, H.; Ofial, A. R.; Würthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, *119*, 12727−12733. (b) Lakhdar, S.; Mayr, H. *Chem. Commun.* **2011**, *47*, 1866−1868.

DOI: 10.1021/acscatal.5b01726
ACS Catal. 2016, 6, 84−91