

# A Case Study of Thiourea-Assisted Iminium Formation by Hydroxyl Anion Binding: Kinetic, Spectroscopic and Computational Evidences.

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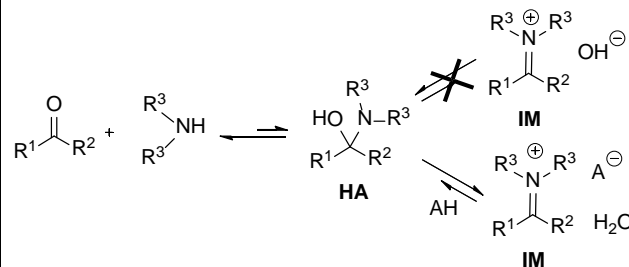


Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

**Abstract.** The experimental and computational study of the mechanism of the iminium-organocatalyzed formation of *N*-hydroxypyrrolidines from nitrones, as a case study, revealed a hitherto unknown mode of action for the Schreiner's thiourea used as co-catalyst. The experimental data suggest that thiourea promotes the formation of the iminium ion through hydroxyl anion recognition forming a stable ion pair. Such an ion pair facilitates enolization of the nitron through a H-bond network thus promoting the reaction with iminium ion. The computational model supports the mechanism and the catalytic cycle. This mechanistic rationale is supported by the lack of reactivity of preformed iminium ion with the nitron in the absence of thiourea-hydroxyl complex and the observed reactivity when a complex thiourea-tetrabutylammonium hydroxide is added.

**Keywords:** Thioureas; Iminium catalysis; Nitrones; Hydroxide binding; Squaramides

catalysis generally involves a secondary amine and an acid co-catalyst, the iminium ion forming an ion pair with the counteranion of the acid. By using strong acids such as trifluoroacetic acid or perchloric acid, iminium ions have been isolated and characterized.<sup>[5]</sup> In this respect, the non-nucleophilic character of the counterion is crucial.<sup>[6]</sup>



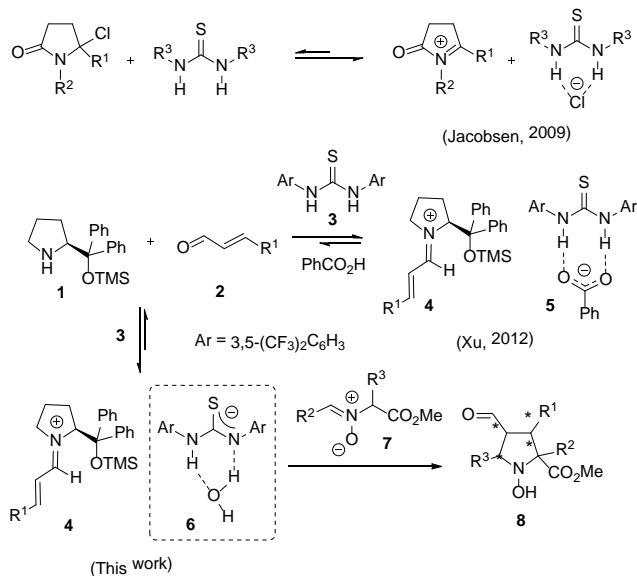
**Scheme 1.** Formation of iminium ions assisted by a Brønsted acid.

Iminium catalysis has emerged over the past twenty years as one of the most powerful methods in organocatalysis.<sup>[1]</sup> When a carbonyl compound is placed in the presence of a secondary amine, an equilibrium with the hemiaminal **HA** is established. **HA** can lead to the corresponding iminium ion **IM** but this process is not spontaneous (Scheme 1).<sup>[2]</sup>

In particular cases, a reagent can assist -by means of H-bond interactions- the elimination of the hydroxyl group and subsequent iminium formation, as in the case of an oxa-Michael reaction recently reported from our laboratories.<sup>[3]</sup> Depending on substrates and reaction, the formation of the iminium ion might not be strictly required,<sup>[4]</sup> although it is a rare circumstance. In any case, the commonest situation is that a Brønsted acid (AH) helps to form **IM** by protonation of the hydroxyl group of the hemiaminal. In fact, iminium

The reversibility of the process illustrated in Scheme 1 is often a drawback for many organocatalytic reactions requiring long reaction times due to the limited availability of the iminium ion. In order to increase the concentration of iminium ion **IM**, the use of thioureas capable of sequestering the counteranion (typically a benzoate) has been reported by Xu and co-workers.<sup>[7]</sup> Indeed, thioureas are known as reagents for anion recognition.<sup>[8]</sup> Organocatalytic activity of thioureas,<sup>[9]</sup> including their role in bifunctional catalysts,<sup>[10]</sup> is closely related with their role in molecular recognition processes.<sup>[11]</sup> Jacobsen and co-workers reported that recognition of chloride by an amidothiourea was crucial for generating the required iminium ion in an asymmetric Pictet-Spengler-type reaction (Scheme

2).<sup>[12]</sup> In general, thioureas act as co-catalysts either facilitating the catalytic action of the chiral catalyst or activating one of the reagents,<sup>[13]</sup> typically electrophiles such as carbonyl compounds, imines and nitroalkenes, among others, against nucleophiles.<sup>[14]</sup>



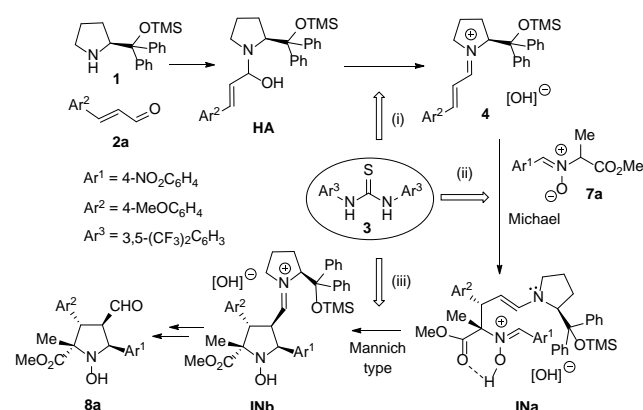
**Scheme 2.** Recognition of anions by thiourea.

In this work, we report experimental and computational evidences of hydroxyl anion recognition by Schreiner's thiourea **3** promoting the formation of iminium salt **4** from amine **1** and aldehyde **2** without any additional acid co-catalyst (Scheme 2). The formation of counterion **6** agrees with previous investigations reporting anion-induced partial deprotonation of (thio)ureas.<sup>[15]</sup> and with the only reported recognition of hydroxyl anion by a thiourea.<sup>[16]</sup> We chose as a case study our recently reported reaction of **2** with nitrones **7**, catalyzed by **1** leading to *N*-hydroxypyrrolidines **8** (Scheme 2).<sup>[17]</sup> The crucial role of ionic pair **4·6** for the reaction and the full mechanism, including the catalytic cycle, have also been studied experimental- and computationally. The effect of hydrogen bonds, and the factors that influenced the stereochemistry were explored to get useful information on organocatalytic reactions of nitron ylides and the potential role of thiourea in iminium catalysis.

Both in our preliminary communication<sup>[17]</sup> and a previous similar study with isatin-derived nitrones,<sup>[18]</sup> triethylamine was used to deprotonate the nitron **7** and generate the nitron ylide assuming a mechanism involving the anion derived from **7**. Under this hypothesis the role of thiourea **3** was limited to activate the carbonyl group in the first step and/or the nitron moiety in the second one.<sup>[19]</sup> However, a more in-depth analysis of the reaction conditions showed that the reaction with nitrones **7** does not require the presence of any base. On the other hand, the presence of thiourea **3** in catalytic amounts was essential for the progress of the reaction, which does not work in the

absence of **3**. The results in the absence of triethylamine were similar in yield and identical in dr and ee to those obtained in the presence of triethylamine (see SI).<sup>[17]</sup>

To investigate in detail the mechanism of the reaction we carried out some kinetic analysis of the reaction (see SI). We used as representative substrates nitron **7a** and aldehyde **2a** (Scheme 3) and determined that the reaction is first-order in both **7a** and **2a**. The kinetic measurements also confirmed the reaction to be first-order in **1** and **3**. The observed linear effects between ee and catalyst loading confirmed that the active catalyst is a monomeric species.

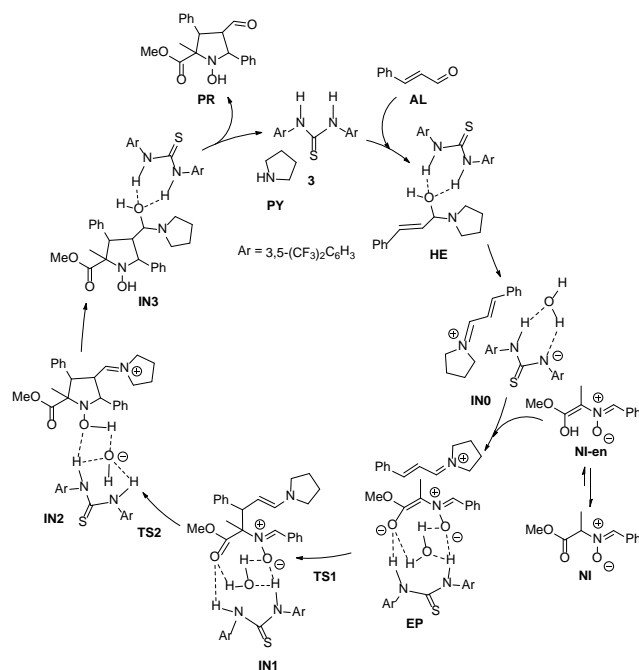


**Scheme 3.** Reaction between **2a** and **7a** in the presence of **1** and possible steps in which thiourea **3** might be involved. (i) formation of the iminium ion; (ii) enolization of nitron and (iii) activation of nitron in Mannich step.

The first-order dependence on both aldehyde and nitron observed experimentally indicates that both reactants are not associated in the resting state, suggesting a typical mechanism via formation of an iminium ion. Once the iminium ion is formed, the reaction can take place in a concerted way or in two steps through a tandem Michael-Mannich reaction as we previously reported for electron-poor alkenes.<sup>[20]</sup> In principle, thiourea activation can occur at different non-exclusive levels, i.e.: (i) by promoting the formation of the iminium ion; (ii) by facilitating enolization of the nitron required for both mechanisms, considering that the reaction does not need the presence of a base, and (iii) by activating the nitron towards the electrophilic addition. The stepwise mechanism, involving an initial nucleophilic attack to the iminium ion followed by a second nucleophilic attack of the intermediate enamine to the nitron moiety, should be much more sensitive to electronic effects at the substituents. To evaluate such effects, we measured the rates of the reaction for several substituted nitrones and aldehydes. Hammett plots revealed a clear dependence of the electronic effects of the substituents indicating that the most favorable situation corresponds to nitrones with electron-withdrawing groups and aldehydes with electron-donating groups (ee SI). These data provide



the iminium ion and one of the aromatic rings of thiourea **3** (see SI).



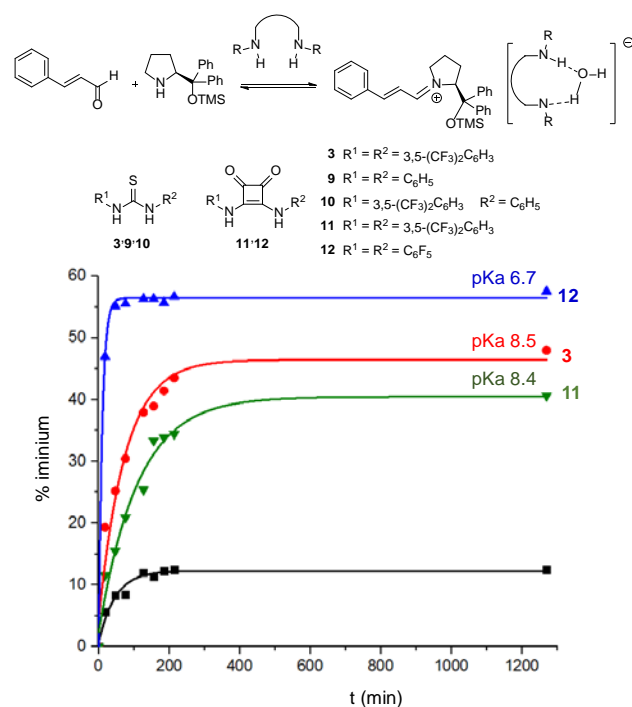
**Scheme 4.** Catalytic cycle for the reaction between **AL** and **NI** in the presence of **PY** and **3**.

Incorporation of nitron **NI** results in the formation of encounter pair **EP** in which the counteranion of the iminium salt stabilizes the enol tautomer of the nitron. After the first transition state, **TS1**, located at 3.1 kcal/mol and identified as the rate-limiting step, the enamine intermediate **IN1** is formed. This intermediate is ready for the next step through a second transition state, **TS2**, located at 1.8 kcal/mol. In this transition structure thiourea facilitates a H-bond network responsible for activating the nitron moiety towards the intramolecular nucleophilic attack. This step yields **IN2** formed by a new iminium ion (detected by ESI-MS) having complex **6** as counteranion which interacts with the hydroxyamino functionality through H-bonds. Intermediate **IN2** evolves to hemiaminal **IN3**, a transformation thermodynamically favored by 4.4 kcal/mol (for the preferred diastereomer). Releasing of product **PR** regenerates catalyst **PY** and co-catalyst **3**. The driving force of the catalytic cycle is determined by the regeneration of **HE** from **IN3** with concomitant release of the final product. This final catalyst-turnover step involves a favored energy of  $\Delta G = -22.8$  kcal/mol (for a complete energy profile see SI). Two approaches of the iminium ion to the activated enolized nitron are possible in **EP**, leading to two diastereomers. The corresponding transition structures **TS1a** and **TS1b** differ in 2.4 kcal/mol in favor of that leading to (2*S*\*,3*S*\*,4*R*\*,5*S*\*)-isomer, in excellent agreement with the experiments. The almost complete enantioselectivity is due to the essentially exclusive attack by the less hindered face of the

iminium formed from catalyst **1** as reported elsewhere.<sup>[25]</sup>

The calculated catalytic cycle is in good agreement with the experimental observations, including ESI-MS monitoring that allowed identifying iminium ions from **IN0** and **IN2**. Calculations also support the three keypoints of the reaction in which thiourea acts on the reaction, i.e: promoting formation of iminium ion, nitron enol and activating nitron functionality in the second step.

In addition to **3** we also studied the formation of iminium **4** mediated by thioureas **9** and **10**, and squaramides **11** and **12**. The observed rates for **3** and **10-12** (no reaction was observed with **9**) are illustrated in Figure 2. Although the formation of iminium ion was not complete, the best result (ca. 56%) was found for the most acidic squaramide **12**. Indeed, the iminium formation showed to be dependent on the  $\text{pK}_a$  (we determined  $\text{pK}_a$  for **12**, see SI), the higher acidity, the higher rate of iminium formation. The amount of iminium at the equilibrium was found to be linearly dependent on the relative stability between the iminium and the precursor hemiaminal.<sup>[26]</sup>



**Figure 2.** Reaction rates for the formation of iminium ion **4** from catalyst **1** and cinnamaldehyde **2a** in the presence of thioureas **3**, **9** and **10**, and squaramides **11** and **12**.

The reaction between **2a** and **7a** catalyzed by **1** in the presence of squaramides **11** and **12** led to essentially identical results in yield and enantioselectivity without observable effects in the rate of the reaction. This result agrees with calculations, which showed **TS1** (and not the formation of the iminium ion) as the rate-limiting step. Accordingly,

the observed rates of iminium ion formation for thiourea **3** and squaramides **11** and **12** are enough for feeding the catalytic cycle.

In summary, we have demonstrated that thioureas and squaramides can promote the formation of iminium ions without the presence of a Brønsted acid. The case study has demonstrated that hydroxide anion recognition is the main driving force helped by  $\pi,\pi$ -interactions between aromatic rings of co-catalyst and iminium, which thermodynamically favors the formation of the ionic pair **IN0** (formed by iminium ion **4** and complex  $[3\cdot\text{OH}]^-$ ) from the precursor hemiaminal (**HE**) in equilibrium with the reagents. Because of the absence of those hydrophobic interactions in the final iminium ion (**IN2**), the formation of hemiaminal (**IN3**) is thermodynamically favoured closing the catalytic cycle. The formed anion  $[3\cdot\text{OH}]^-$  has an additional effect facilitating enolization of the nitron and promoting the attack to the iminium ion **4**; this step is the rate-limiting step (**TS1**).

Consequently, it is possible to predict that the use of thioureas or squaramides might promote cascade reactions starting and ending with iminium ions, which should be formed and hydrolyzed, respectively. The formation of anion  $[3\cdot\text{OH}]^-$ , which can be considered a weak base with capability of promoting H-bond networks, could also exert additional effects on the substrates. In this respect, it should of great interest to consider reagents requiring enolization or any kind of H-bond activation.

It is expected that these findings, in particular generation of iminium ions in a neutral or weakly basic medium, will allow evaluating the significance of iminium formation in a variety of organocatalytic reactions. Moreover, the observation of the same behaviour with squaramides expands considerably the number of organocatalytic processes susceptible to be modulated.

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- [22] The same lack of reactivity was observed with the trifluoroacetate evidencing that it is not a matter of counteranion
- [23] Treatment of **7a** with Et<sub>3</sub>N and with a solution of a 1:1 mixture of thiourea **3** and Bu<sub>4</sub>NOH in the presence of deuterium oxide showed the same proton-deuterium exchange demonstrating that both situations render **7a** nucleophilic, and evidencing that additional favorable circumstances should be present when the ion pair 3·6 is present.
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- [25] Catalyst **1** is known to operate according to a steric model, particularly when it catalyzes Michael-type reactions. Consequently, only the attack through the less hindered *Re* face of the iminium needs to be considered. For details see SI.
- [26] The iminium ion is, actually, in equilibrium with the substrates (aldehyde and catalyst) and the intermediate hemiaminal so, it is necessary to consider the thermodynamic (and not the kinetic) of the process. Admittedly, it is necessary to establish equilibrium conditions providing enough concentration of iminium to feed the reaction.

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