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Synergistic Catalysis: Enantioselective Cyclopropanation of alkylidene benzoxazoles by Pd(II) and Secondary Amine Catalysis. Scope, Limitations and Mechanistic Insight

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Abstract. The reaction of alkyl-benzoxazoles with enals has been reported using a synergistic approach. It consists on the activation of enals with a secondary amine catalyst and the activation of benzoxazoles with a metal Lewis acid. This approach has also been applied to the synthesis of cyclopropanes with excellent results. We demonstrated the applicability of this reaction in a cascade reaction (cyclopropanation + ring opening) that circumvents some of the limitations of the simple Michael addition between alkyl-benzoxazoles and enals. Finally, mechanistic studies have been reported to explain the stereoselectivity of the cyclopropanation reaction that renders an unusual *cis* conformation.

Introduction

In the last decades, organic chemists have been devoting their efforts to the development of new enantioselective methodologies that could mimic Mother Nature for the synthesis of highly complex molecules with a determined 3D shape. Three pillars have been used to afford this objective: Biocatalysis, Organometallic Catalysis and Organocatalysis. All three with their strengths and limitations, are based on the reduction of the energy gap of the reaction, by lowering the energy of the LUMO or increasing the energy of the HOMO. However, if we analyse how Nature makes chemical transformations, very often a combination of effects is present, reducing the energy gap by activating both the LUMO and the HOMO. These approaches can be implemented by the use of bifunctional catalysts, presenting however some disadvantages like the requirement to modify the catalyst each time to improve the outcome of the reaction. Another approach to reduce the time and the cost is the simultaneous use of two different catalysts where each one activates the LUMO or the HOMO separately. In this way the optimization of the reaction is easier due to the possibility to modify each catalyst separately. In organic chemistry this is called synergistic catalysis and remained almost unexplored for a long time (Figure 1).[1]

At the beginning of this decade the pioneering works of Cordova, List and many other scientists have shown the viability of this approach for example the silylation of enals, the allylic alkylation of aldehydes or the Overman rearrangement (Scheme 1).[2]

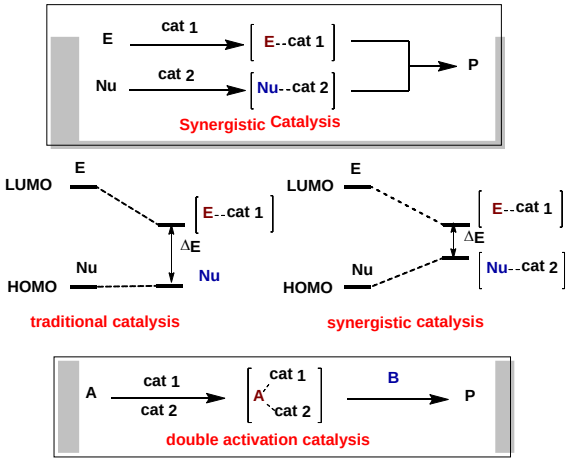
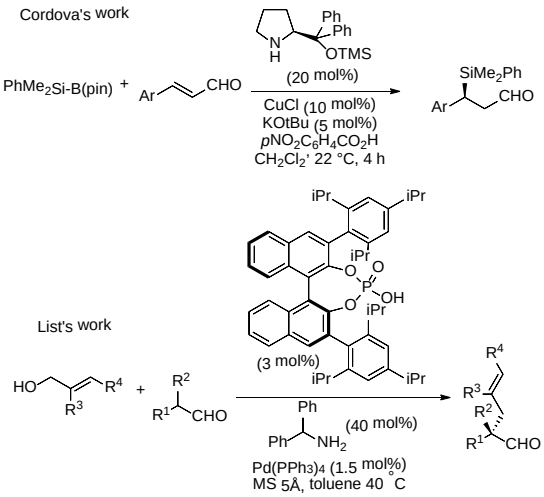


Figure 1. Synergistic catalysis



Scheme 1. Previous works in synergistic catalysis

Intrigued by the possibilities offered by this new approach, we started a research program on synergistic catalysis. One of the

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limitation of the use of organometallic compounds is the need for expensive and often reaction-tailored ligands. On the opposite hand, secondary amine catalysis presents also some limitations like the use of highly reactive starting materials. In order to overcome these limitations, we thought that the combination of the rich reactivity of transition metals with the cheap and easy stereoprediction of the secondary amine catalysis would allow the development of new enantioselective methodologies that will complement and improve the previous organometallic or organocatalytic ones.

Regarding alkyl azaarenes, our research group has been interested in the development of stereoselective synthesis of alkyl-azaarenes. The activation of alkyl-azaarenes has been accomplished by the use of a metal Lewis acids that coordinates to the nitrogen atom of the heterocycle increasing the acidity of the adjacent alkyl chain (Figure 2).

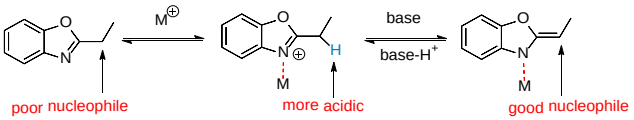
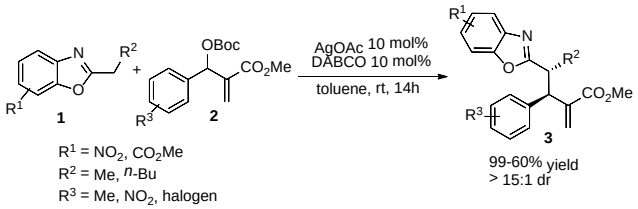


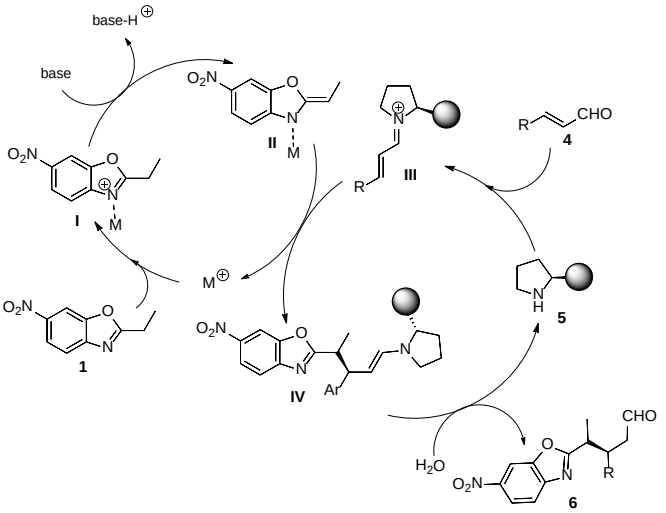
Figure 2. Activation of alkyl-benzoxazoles with a metal Lewis acid

One of the pioneering work, reported by Lam, consisted in the activation of azaarenes by Pd(II) complexes using bisoxazoline ligands, reacting with a range of highly activated electrophiles.[3] Inspired by these excellent works, we decided to explore the possibility to employ the activation of azaarenes by metal Lewis acids in combination with an organocatalyst, in a synergistic fashion. Despite some concerns regarding the autoquench of both catalysts, in 2014 we showed the viability of this approach developing the addition of alkyl-benzoxazoles **1** to MBH carbonates **2** in a highly diastereoselective fashion (Scheme 2).[4]



Scheme 2. Alkyl-benzoxazoles addition to MBH carbonates

Encouraged by these results, we envisioned the development of an enantioselective reaction based on the metal Lewis activation of alkyl-benzoxazoles and the organocatalytic activation of enals by a secondary amine catalyst. First, we focused our attention on the development of a Michael addition of alkyl-benzoxazoles to α,β-unsaturated aldehydes.[5] As can be seen in Scheme 3, the two catalytic cycles: metal Lewis acid activation of benzoxazoles (increasing the HOMO energy) and the secondary amine activation of enals (decreasing the LUMO energy) work in concert to generate a new C-C bond.[6] Moreover, the stereoselectivity of the reaction is efficiently controlled by the organocatalyst, without the requirement of expensive metal ligand.



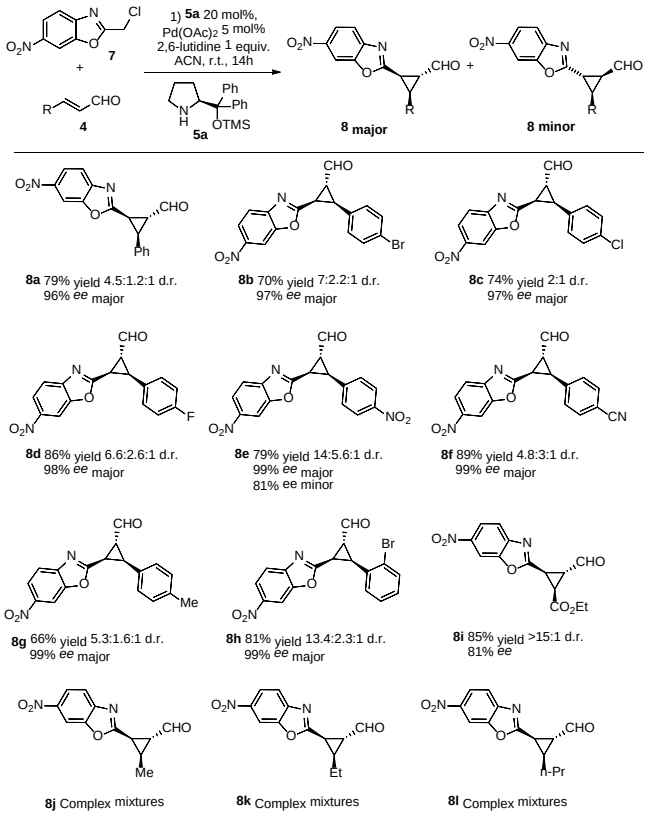
Scheme 3. Proposed mechanism of the Michael addition of alkyl-benzoxazoles to enals

Based on this concept, in 2016 we reported the first synergistic organocascade reaction for the synthesis of cyclopropanes[7] derived from benzoxazoles. The reaction led to the desired cyclopropanes with an unusual *cis* configuration between the benzoxazole and the phenyl ring with good yields and very good stereoselectivities. In the present paper we present the study of the reaction, the mechanism and the identification of the transition state. Moreover, we coupled the cyclopropanation reaction with a cyclopropane ring opening, catalyzed by NHC carbenes, that allows for the synthesis of enantioenriched benzoxazole derivatives that has not been possible with previous methodologies.

Results and Discussion

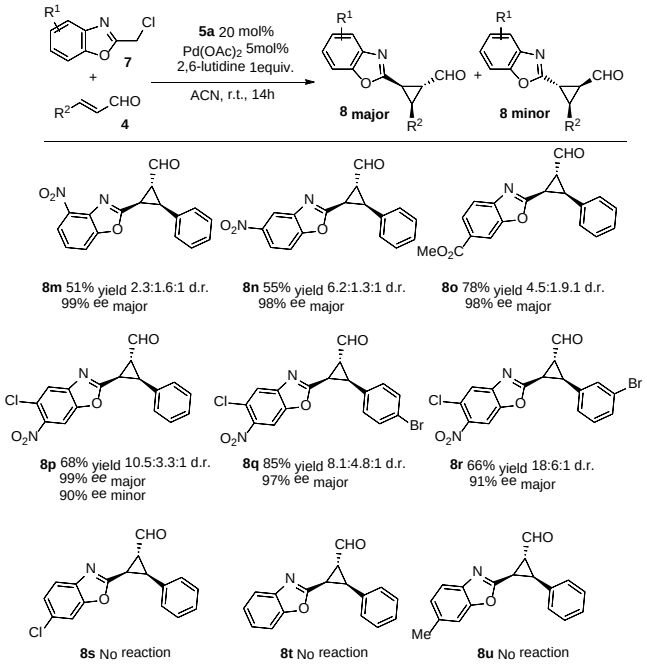
We tested the reaction between 2-(chloromethyl)-6-nitrobenzo[*d*]oxazole **7** and cinnamaldehyde **4**. After a screening of the reaction conditions, we found that 10 mol% of $Pd(OAc)_2$ and 20 mol% of the Jørgensen-Hayashi catalyst **5b** was the best catalytic system, giving the product **8a** in 79% yield, moderated dr and 96% ee. In contrast to the previously reported Michael addition, the final compounds were obtained in excellent yields, good to moderate diastereoselectivities and excellent enantioselectivities regarding the major diastereomer. In Scheme 4 is reported the scope of the reaction with different enals. Employing aromatic enals substituted with halogens in the *para* position, the products **8b-d** were obtained in good yields and dr (70-86% yield, 3:1 dr, up to 98% ee). When electron-withdrawing (4-NO_2 and 4-CN) or electron-donating (4-Me) substituents were present, the products **8e-g** were obtained in good yields (66 – 89%), good dr and 99% ee. When the Br is in the *ortho* position **8h**, even if the aldehyde is sterically hindered, the reaction worked with good yields, ee and dr. Then, we tested the aldehyde derived from the glioxylate, obtaining the final product **8i** in good yield and excellent diastereoselectivity but lower enantioselectivity. A

clear limitation of the present methodology is that aliphatic aldehydes gave only complex mixtures in the crude (**8j-l**).



Scheme 4. Scope of the cyclopropanation with different α, β unsaturated aldehydes

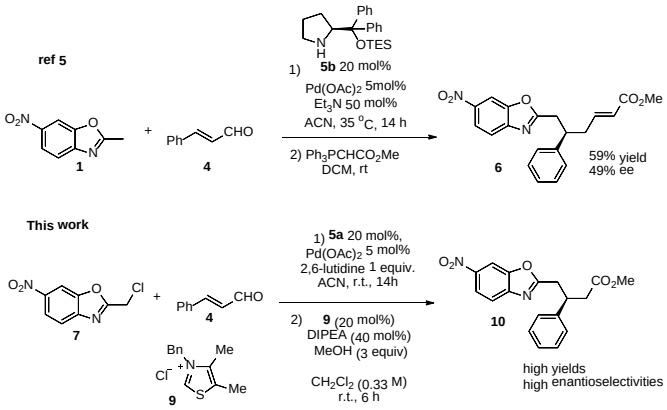
Next, we studied the scope of the benzoxazole moiety, as presented in Scheme 5.



Scheme 5. Scope of the cyclopropanation with different alkyl-benzoxazoles

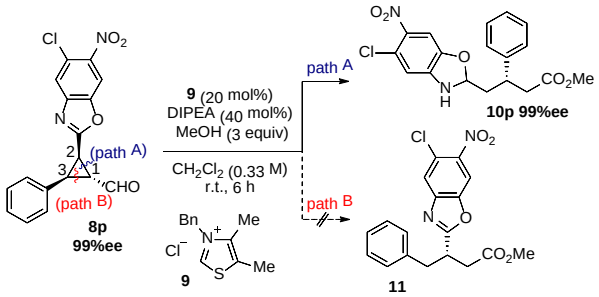
Benzoxazoles with the NO_2 group in different position of the aromatic ring were tested and lower yields but good dr and excellent ee were observed (**8m** and **8n**). When an ester group is present in position 6 of the benzoxazole, the final product **8o** was obtained in excellent yield and ee and good dr. With the 5-Cl,6-NO_2 substituted benzoxazole, the products **8p-r** were obtained in good yields and dr and 91-99% ee. As in the simple Michael addition, the limitation is that an electron-withdrawing group on the benzoxazole ring is needed to have reactivity. In fact, the reaction with the unsubstituted benzoxazole or substituted with non electron-withdrawing groups failed to give the product (**8r-u)**.

Encouraged by these results, we envisioned that the easier synthesis of the cyclopropanes could be used to obtain, in a one-pot fashion, lineal alkyl benzoxazoles that are difficult to obtain via a Michael addition. We envisioned that the ring-opening of cyclopropanes *via N*-heterocyclic carbene (NHC) catalysis will formally lead to highly enantioselective and diastereoselective addition of methyl benzoxazoles to enals (Scheme 6).



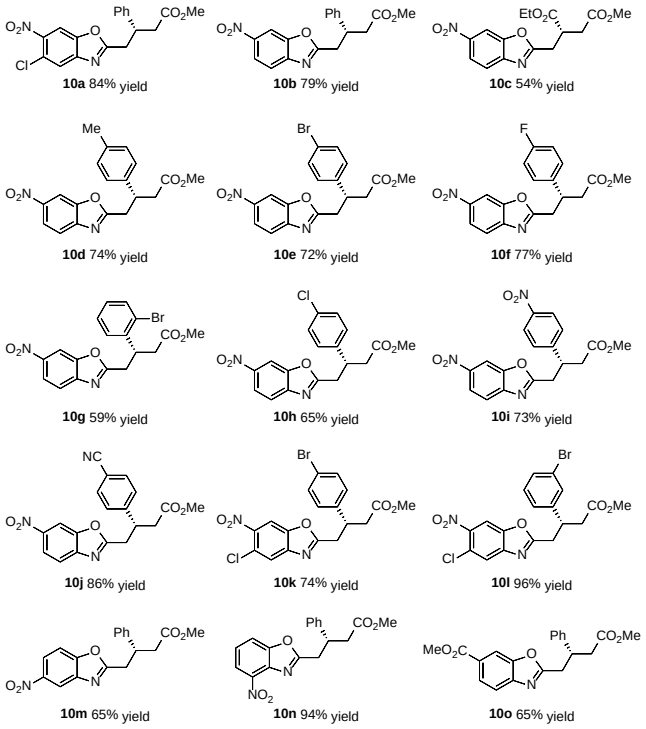
Scheme 6. Comparison between the two approaches

The regioselectivity associated with the ring-opening of cyclopropane derivatives is dependent on the nature of the functional groups present on the cyclopropanes. Exceptional regioselectivity is assured when strong electron- withdrawing groups (i.e., nitro, ketones, esters, and amides) and electron-donating groups are located in vicinal position. On the basis of the strong electron-withdrawing property of the benzoxazole moiety, we predicted a completely regioselective opening of the cyclopropanes.[8] To explain the origin of the regioselectivity of this reaction we propose the mechanism outlined in Scheme 7. At first, the nucleophilic addition of the NHC **9** to the aldehyde **8a** leads to the enaminol, the so-called Breslow intermediate. Then, two competitive pathways for the ring-opening are possible and the regioselectivity is determined by the substituents present on the two aromatic rings. The C2 position bearing the EWG nitrobenzoxazole is more electron-deficient and stabilizes better the carbanion resulting from the ring-opening, leading regioselectively to compound **10**. Importantly, the reaction led to the final compound with total retention of the enantioselectivity.



Scheme 7. Ring opening of cyclopropanes

The ring opening was performed with NHC carbene **9** as catalyst (20 mol%), DIPEA as the base and MeOH. In all the examples, a total regioselectivity was obtained without loss of the enantioselectivity during the process. Remarkably, even when electron-withdrawing groups were present on the phenyl moiety, the ring opening was totally regioselective. In Scheme 8 are presented the results obtained from the ring-opening of the major diastereomer of the cyclopropanes **8** to give products **10a-o** in 54-96% yield with total stereoretention.



Scheme 8. Scope of the ring opening reaction

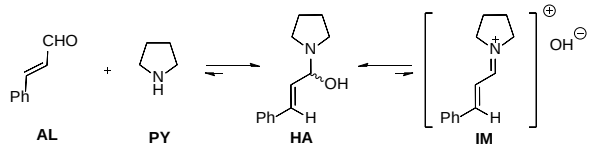
We also performed the reaction in a one-pot procedure, obtaining similar results compared to the 2 step procedure. This proves that the present approach is an excellent alternative to the use of methyl-benzoxazoles in a Michael reaction.

Mechanistic studies

With the aim of getting a good mechanistic understanding on the synergy exerted by the combination of palladium acetate with organocatalysts, we decided to carry out a detailed computational study, mainly directed to understand the pathway operating in the synergistic process and the origin of the diastereoselectivity. Considering the presence of at least two catalytic species and multiple reactive positions able to interact with those catalysts, we firstly carried out some studies related to non-linear effects. They showed a perfect linearity between the enantiomeric excess of the reaction and the enantiomeric excess of the catalysts indicating that only one molecule of involved catalysts participates in the rate-determining step of the overall catalytic cycle (See Supporting Information).

We next moved to study the different mechanistic possibilities with the help of computational methods. Computational studies were carried out with benzoxazole **OX** and cinnamaldehyde **AL**; trimethylamine was considered as the base and catalysts were modelled as palladium(II) acetate **PdAc** and pyrrolidine **PY**. Catalyst **I** is known to operate according to a steric model,[9] particularly when it catalyzes Michael-type reactions.[10] Consequently, only the attack through the less hindered *Re* face of the iminium needs to be considered in agreement with previous calculations for other reactions.[9] For unravelling the mechanism of the reaction and determining the diastereoselectivity of the reaction is not necessary to include chirality in the pyrrolidine. Just to illustrate the correct enantiomer that it is predicted, we have chosen for our study the attack by the *Re* face of the iminium derived from pyrrolidine.

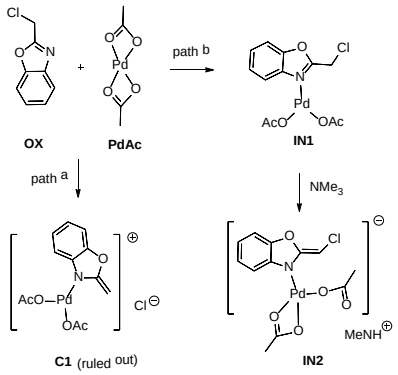
We need to consider two different catalytic cycles, i.e. one operating at the organocatalytic level with pyrrolidine **PY** and another one centered at **PdAc**. Catalyst **PY** and aldehyde **AL** are expected to form the corresponding iminium salt **IM** (in equilibrium with the corresponding hemiaminal **HA**), furnishing an electron-poor double bond ready to react (Scheme 9). For our calculations we considered the exclusive participation of the (*E,E*)-s-*trans* iminium species in agreement with previous reports.[11] Isomeric (*Z,E*)-iminium salts were also initially evaluated but they turned out to be more energetic, as expected.



Scheme 9. Activation of enal *via* iminium catalysis

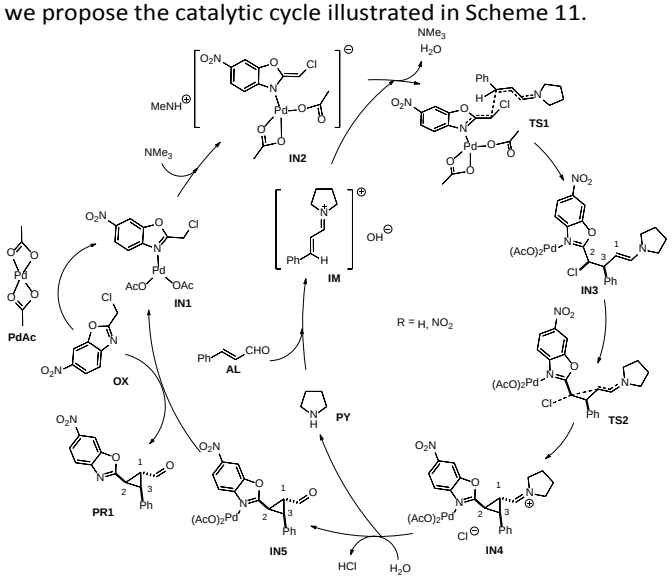
For the palladium catalyst **PdAc**, in principle, we might consider two different approaches for the interaction with benzoxazole **OX**. A direct interaction with the allylic system formed by the C=N bond of the benzoxazole would provide complex **C1** which could react with the double bond of **IM** through a sort of Pd-catalyzed coupling reaction (Scheme 10). Actually, the geometry of **C1** is that depicted in Scheme 10 in which Pd only coordinated to nitrogen atom. A close inspection of this approach pointed to the reactivity of **C1** without direct implication of Pd atom, clearly indicating that the process cannot be considered a typical Pd-catalyzed coupling reaction. We completed the full study for this approach and high

activation barriers were found suggesting that a different approach should be considered so, definitively the reaction between **C1** and **IM** was ruled out (see ESI for details).[12]



Scheme 10. Initial hypotheses for mode of action for Pd-catalyst

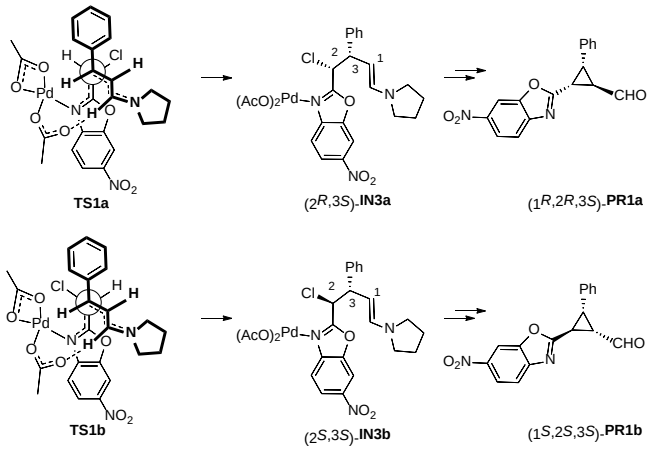
Palladium(II) acetate may also act just as a Lewis acid by coordinating the benzoxazole nitrogen, giving rise to complex **IN1**. This complex facilitates abstraction of a proton by the trialkylamine present in the reaction medium furnishing aza-enolate **IN2** in agreement with similar situations already reported.[13] The reaction between **IN2** and iminium **IM** is a typical Michael addition in which the latter is the electrophile and the former the nucleophile. According to this hypothesis, we propose the catalytic cycle illustrated in Scheme 11.



Scheme 11. Catalytic cycle

Once **IM** and **IN2** are formed they react through **TS1** to give intermediate **IN3** in which stereogenic carbons C2 and C3 have already been formed. The resulting enamine reacts intramolecularly through a typical SN2 process to furnish iminium **IN4** via **TS2**. Next steps concern the regeneration of catalytic species; thus, the hydrolysis of **IN4** regenerates catalyst **PY** and furnishes the product coordinated with palladium(II) acetate **IN5**. Ligand exchange with reactant **OX** restarts the cycle by regenerating **IN1** and releases the product of the reaction **PR1**.

As mentioned above, we fixed the attack to iminium **IM** by the *Re* face to be coherent with the less hindered face of the real catalyst **I**. Accordingly, configuration at C3 is *S*, and two diastereomers (2*R*,3*S*)-**IN3a** and (2*S*,3*S*)-**IN3b** can be obtained *via* diastereomeric transition structures **TS1a** and **TS1b** (see below). The observed diastereoselectivity is a consequence of the different orientations that the chlorine atom can adopt in **IN3** (Scheme 12). The origin of the diastereoselectivity could also arises from isomeric (*Z,E*)-iminium salts; however, as it has been stated above, they were initially evaluated and they turned out more energetic. The next step is an intramolecular SN2 reaction with a conditioned stereochemical course leading to an inversion at C2. The *trans*-enamine moiety in **IN3** approaches C2 in a stereospecific way that is from the *Si* face for (2*R*,3*S*)-**IN3a** and from the *Re* face for (2*S*,3*S*)-**IN3b**. Consequently, generation of the new stereogenic center at C1 can only furnish diastereomers (1*R*,2*R*,3*S*)-**IN4a** and (1*S*,2*S*,3*S*)-**IN4b**.[14] These intermediates ultimately provide (1*R*,2*R*,3*S*)-**PR1a** and (1*S*,2*S*,3*S*)-**PR1b** in full agreement with the experimental findings.



Scheme 12. Origin of diastereoselectivity

Figure 3 illustrates the energy profile for the catalytic cycle given in Scheme 12.

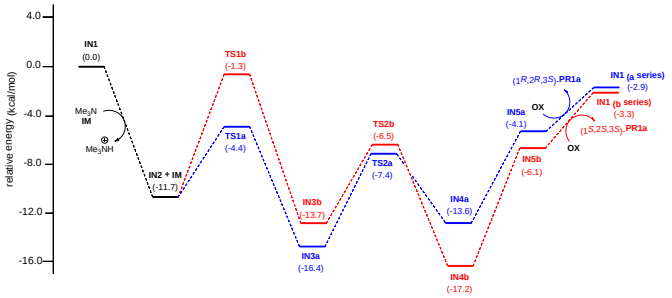


Figure 3. Energy profile for the catalytic cycle corresponding to the formation of (1R,2R,3S)-PR1/**8a** (blue trace) and (1S,2S,3S)-PR1 (red trace). Relative energies are given in kcal/mol.

The rate-limiting step corresponds to the formation of **IN3a,b** *via* **TS1a,b** so, the difference in activation barriers for the two diastereomeric pathways accounts for the diastereoselectivity of the reaction. In this respect, a clear preference (ca. 2.8 kcal/mol) for **TS1a** leading to (1*R*,2*R*,3*S*)-**IN3a** was found. Thus,

calculations predict the obtention of (1*R*,2*R*,3*S*)-**PR1a** preferentially, as indeed takes place experimentally.

The profile outlined in Scheme 11 shows the whole catalytic cycle for both diastereomers. The regeneration of **IN1** from **IN5** with the release of the product can be considered the driving force of the catalytic cycle. For both (1*R*,2*R*,3*S*)-**PR1a** and (1*S*,2*S*,3*S*)-**PR1b** the energy balance is favourable (ΔG = -12.9 and -11.14 kcal/mol, respectively) towards the formation of IN1 that restarts the cycle.

The optimized geometries for **TS1a** and **TS1b** are given in Figure 4. Both transition structures present an interaction between one of the acetates and iminium hydrogen atom, the stronger one being that of **TS1a** (1.97 Å *vs* 2.16 Å for **TS1b**). The red arrow indicates the position of the bulky group in the original enantiomerically pure catalyst that is irrelevant for the diastereoselectivity. The lower energy of TS1a is due to the absence of unfavorable interactions between the chlorine atom and one of the acetates, which are present in **TS1b**.

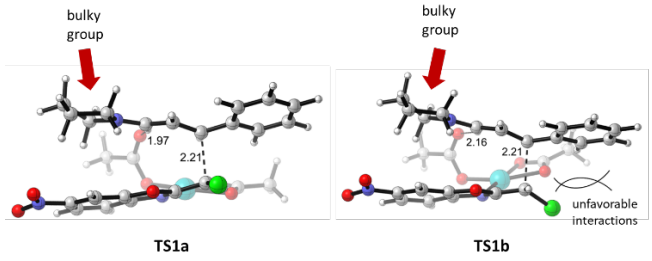


Figure 4. Optimized geometries (B3LYP-D3BJ/Def2SVP) for **TS2a** and **TS2b** leading to (2R,3S)-**IN3a** and (2S,3S)-**IN3b**, respectively.

Conclusions

In conclusion, we reported the reaction of alkyl-benzoxazoles with enals using a synergistic approach based on the activation of enals with a secondary amine catalyst and the activation of benzoxazoles by a metal Lewis acid. This approach has been applied in a Michael addition with moderate enantioselectivities and also to the synthesis of cyclopropanes with good yields and excellent ee. We demonstrated the applicability of this reaction in a cascade cyclopropanation and ring opening, circumventing the limitations of the enantioselectivities of the simple Michael addition. Finally, mechanistic studies have been reported to explain the stereoselectivity of the cyclopropanation reaction that renders an unusual *cis* conformation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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