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Proceeding Paper

Organocatalytic Cascade Reactions for the Synthesis and Diversification of Privileged Structures †

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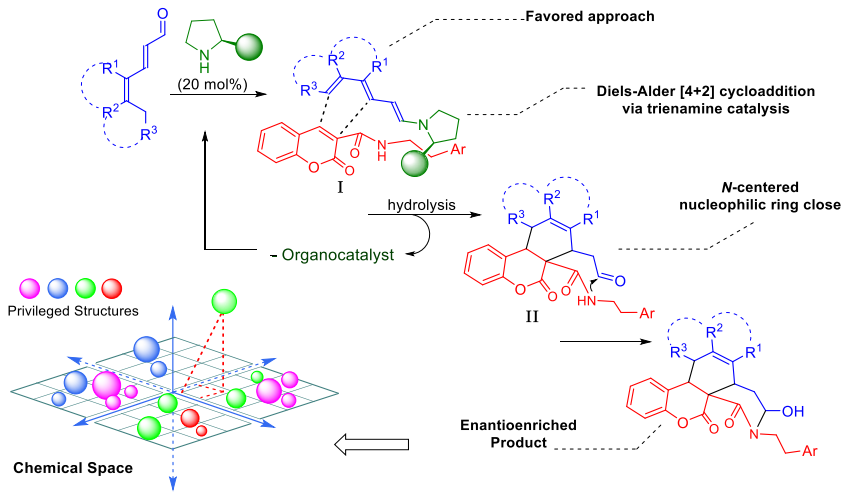
Abstract: Herein, we present the development of new organocatalytic cascade reactions for the synthesis and diversification of privileged structures, using trienamine activation as a key step. An important feature of this process is that once it has been completed, it is possible to generate new reactive species within the same molecule. In this sense, a series of consecutive reactions can be carried out incorporating dienophiles with an addition-nucleophilic functionality. As a result, complex and diverse compounds can be accessed through simple starting materials.

Keywords: asymmetric aminocatalysis; privileged structure; biological activity

1. Introduction

Diversity Oriented Synthesis and asymmetric aminocatalysis constitute two important tools to access new compounds of interest. The extraordinary development of these two areas has allowed chemists to populate new regions of chemical space. Therefore, new libraries of complex and diverse structures are available for the development of new drugs. In recent years, the term Aminocatalytic privileged-structure Diversity Oriented Synthesis (ApDOS) has been conceptualized, highlighting its potential towards the asymmetric synthesis and diversification of privileged structures, small base molecules of complex natural architectures that usually present important biological activities. Currently, our group is working with organocatalytic cascade reactions between 2,4-dienals and single and double dienophiles with a coumarin-based structure.



Scheme 1. Conceptualization of the cascade reactions via trienamine activation.

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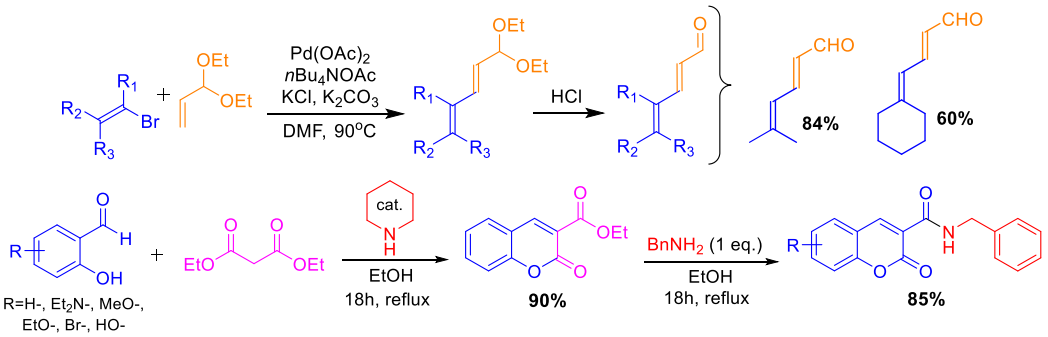
2. Methods

Starting materials and reagents used in the project are commercially available unless synthesis is described. Proton (^{1}H) NMR spectra were recorded on a Bruker 500 MHz spectrometer. Flash column chromatography was performed on silica gel as stationary phase using hexane/ethyl acetate as eluent.

3. Results and Discussion

Once the experimental conditions were optimized and the reaction products isolated, the study of stereoselectivity and absolute configuration of the cascade reaction were performed using HPLC (chiral column) and XRD. It should be noted that, under this methodology, it will be possible to obtain polycyclic structures with up to four stereogenic centers. The correct choice of aminocatalyst is very important to enable processes with a high degree of stereoselectivity.



Scheme 2. Synthesis of 2,4-dienals (Heck) and coumarin-based amides (Knoevenagel).

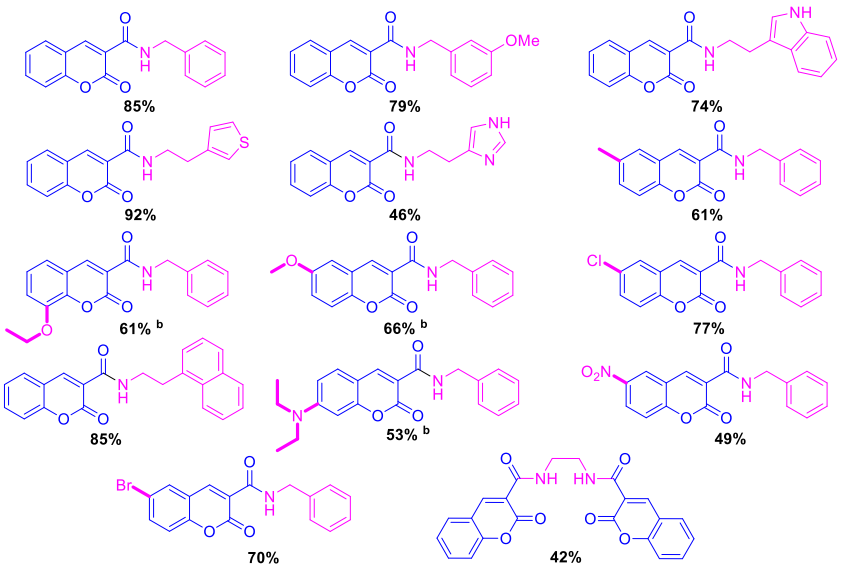
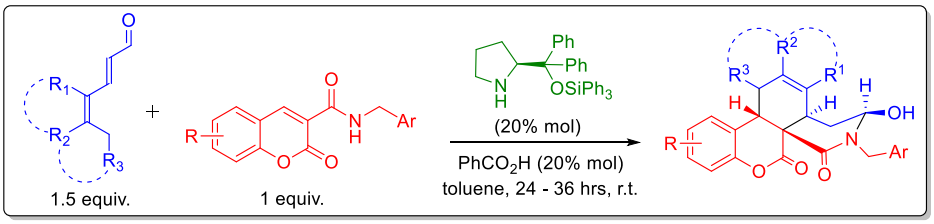
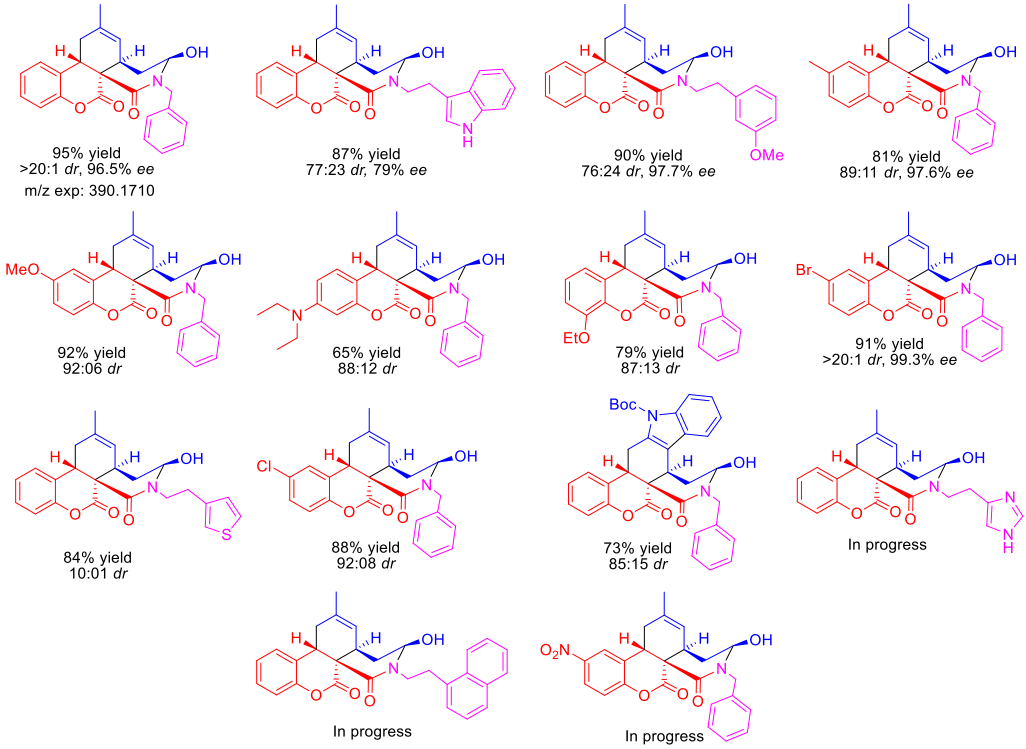


Figure 1. Synthetic scope of the coumarin-based amides.





Scheme 3. General reaction conditions and ApDOS scope.

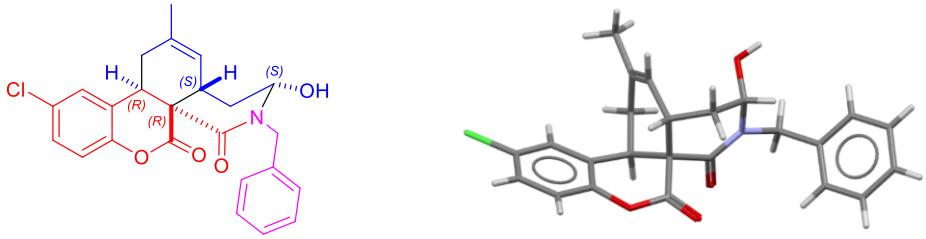


Figure 2. Relative configuration assignment and XRD structure.

4. Conclusions

In conclusion, has been possible the organocatalytic reactions between 2,4-dienales and dienophiles with a coumarin-based structure using trienamine activation as a key step. These aminocatalytic methodologies open new perspectives for the synthesis of privileged polycyclic structures with a complex diversity from simple starting materials.

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Conflicts of Interest:

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