



Nitroacrylates Reactivity In Stereoselective Organocatalyzed Cascade Reactions

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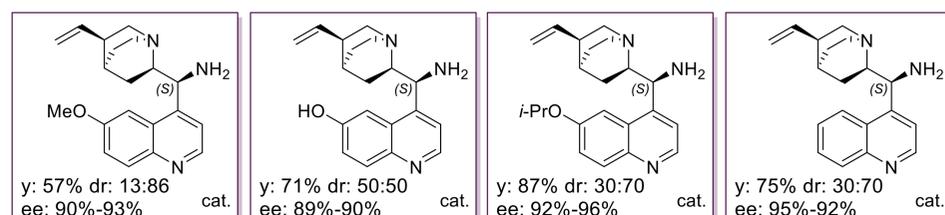
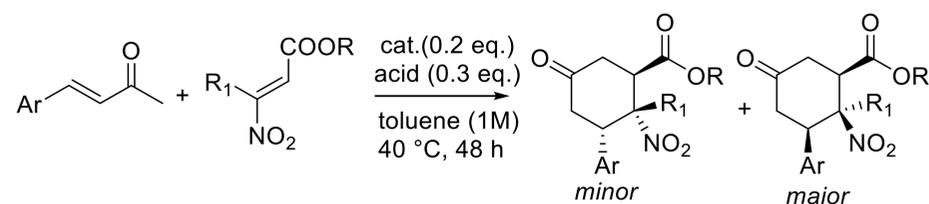
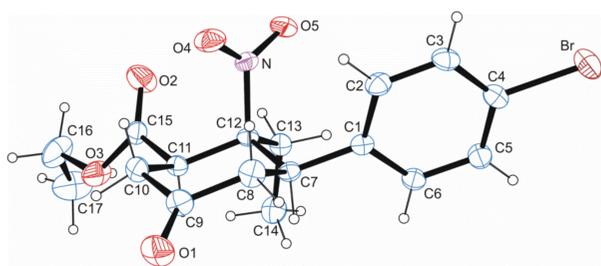
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Due to the simultaneous presence of two different functional groups, nitroacrylates give direct access to highly versatile compounds and have interesting applications as electrophiles¹ in anti-Michael additions² as well as dienophiles in Diels-Alder reactions.³

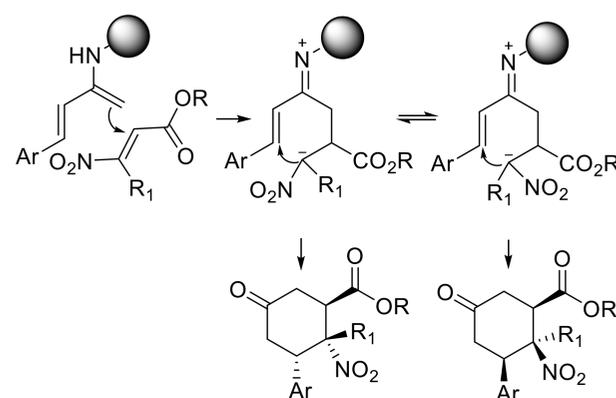
In a recent work by our group they have been employed as starting materials for the organocatalyzed stereoselective one-pot synthesis of cyclohexanones derivatives, **direct precursors of β -amino acids** and advanced intermediates for the synthesis of natural products.⁴

The reaction is catalyzed by primary amines derived from Cinchona alkaloids⁵ in the presence of an acidic co-catalyst and proceeds with **complete regioselectivity** and **high stereocontrol**, leading to the formation of two out of the eight possible diastereoisomers.

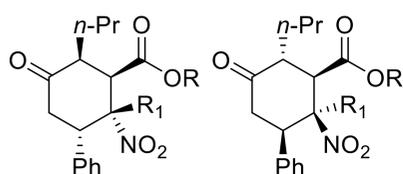
NMR experiments and anomalous X-ray scattering allowed to determine a *cis* configuration of the nitro and the ester functions in the major isomer. The proximity of these two groups in the crystal structure suggests stabilizing electrostatic interactions take place.



The relative configuration of the major isomer suggests a step wise mechanism passing through an anionic intermediate stable enough to equilibrate.



A solvent screening was performed, showing that also protic media were well tolerated, and an investigation on temperature and time effect revealed that after 2 hours at 40 °C maximum conversion is reached. Replacing conventional heating with **microwave irradiation** reaction time was reduced to **30 minutes** without affecting stereocontrol - **93% ee** for the major diastereoisomer.



Differently β -substituted nitroacrylates and butenones proved to be suitable substrates, but it was just thanks to the application of **microwave technology** that C1 substituted enones could be employed. These compounds, otherwise unreactive in this transformation, afforded cyclic ketones endowed with **four contiguous stereocenters** with **high enantioselectivity**, although in low yield and poor diastereomeric ratio.

Time, solvent and temperature effect were studied finding that best results are obtained in in toluene at 60 °C after 2 hours: 30% y, 45:55 dr and **98% ee** for the *trans* isomer. Heating to higher temperatures and using polar solvents did not have any positive effect on yields, but in almost all cases **ees exceeded 90%**.

The combination of different substitution patterns on both reaction partners is still under active investigation.

¹For a recent study on nucleophiles addition to nitroacrylates see: Massolo, E.; Benaglia, M.; Palmieri, A; Celentano, G. *Asian J. Org. Chem.* **2014**, *3*, 416-420. ²Jensen, K. L.; Dickmeiss, G.; Donslund, B. S.; Poulsen, P. H.; Jorgensen, K. A. *Org. Lett.*, **2011**, *13*, *14*, 3678-3681. ³For a Review on nitroacrylates reactivity see: Ballini, R.; Gabrielli, S.; Palmieri, A. *Curr. Org. Chem.* **2010**, *14*, 65-83. ⁴Massolo, E.; Benaglia, M., Annunziata, R; Palmieri, A; Celentano, G; Forni, A. *Adv. Syn. Catal.* **2014**, *356*, 493-500. ⁵For a review on Cinchona derived primary amines in organocatalysis see: Melchiorre, P. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9748-9770.