ORGANOCATALYTIC STEREOSELECTIVE ONE-POT SYNTHESIS OF HIGHLY FUNCTIONALIZED CYCLOHEXANONES

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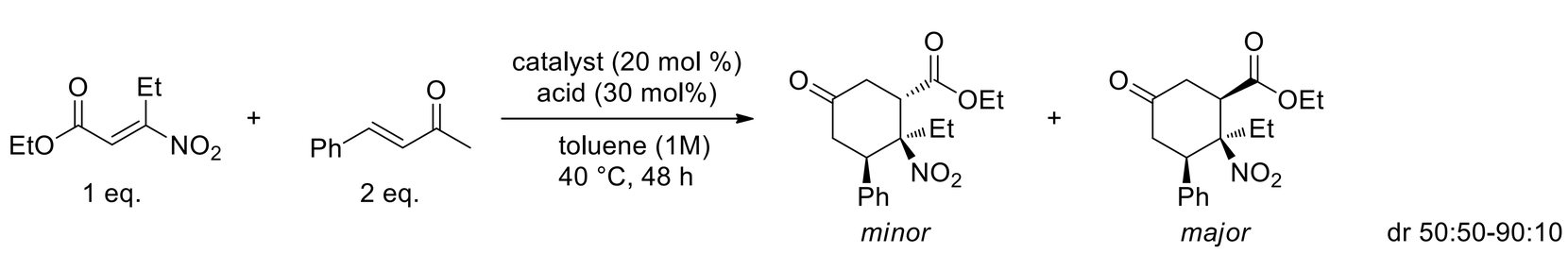
Organocascade catalysis is a synthetic strategy that efficiently meets economical and environmental issues, employing small chiral organic molecules to obtain complex products, in a stereochemically highly enriched form, in a one-step reaction.[1] Herein, it is reported the use of chiral primary amines to promote the one-pot formation of highly functionalized cyclohexanone derivatives endowed with three stereogenic centers, starting from nitroacrylates and α,β-unsatured ketones.

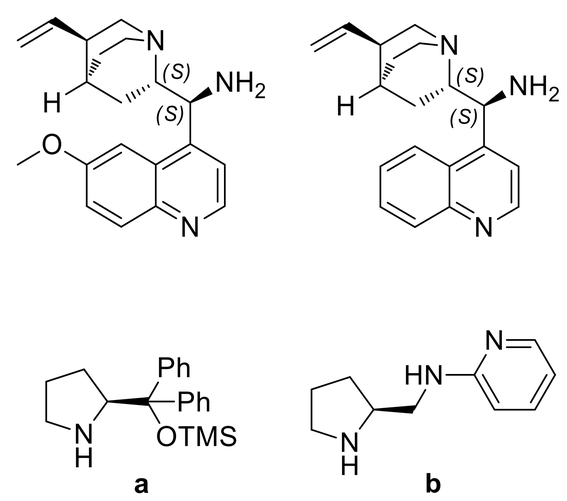


The relative configuration has been determined through NMR experiments.

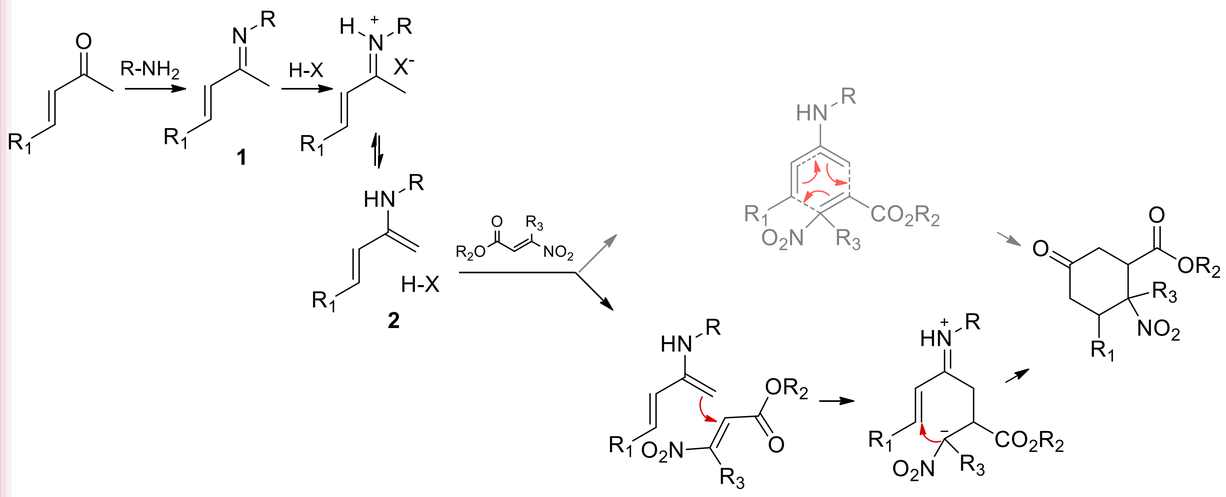
Using 9-amino-epicinchona alkaloids as catalysts, the reaction proceeds in a completely regioselective way and products are obtained with high yield and enantiomeric excess.
In particular, the reported catalytic system leads to the synthesis of cyclohexanone derivatives typically in **80% yield** and up to **96% ee** for both diasteroisomers. The presence of the methoxy group on position 6 of the quinolinic ring does not affect the stereoselectivity of the process.
Pseudo-enantiomers of these amines show opposite sense of enantioselection.

Despite secondary amines have already been used to promote formal Diels-Alder reactions between nitrostyrene derivatives and α,β-unsatured ketones,[2] catalysts **a**[3] and **b** were not able to catalyze this type of transformation.

catalysts



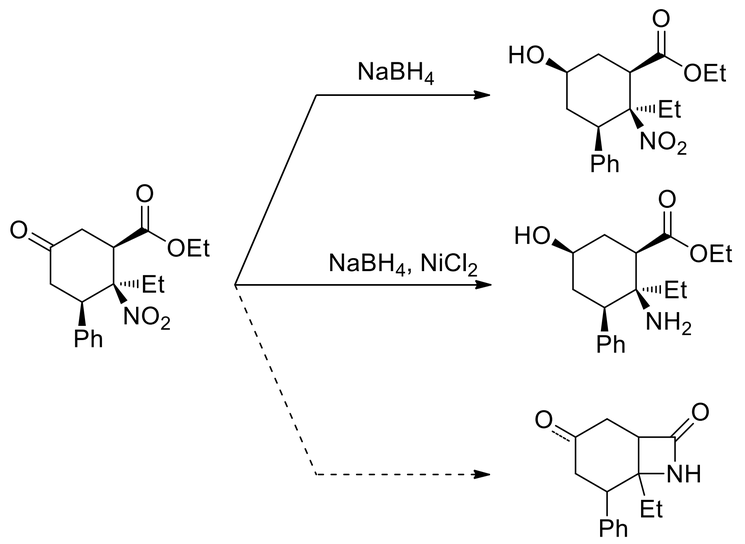
Proposed reaction mechanism



Catalyst condensation with the α,β-unsaturated ketone generates the imine intermediate **1**. In the presence of the acidic co-catalyst **1** is protonated to give an iminium ion characterized by an increased acidity of the α-protons. The conjugated base drives the tautomerization toward the cross-conjugated dienamine **2**, the activated nucleophile attacking the nitroacrylate.[4]
As the relative *trans* configuration of the nitro and the ester group is maintained only in one of the two diastereoisomers obtained, it seems more reasonable to assume that the reaction proceeds through a step-wise rather than a concerted mechanism.

Product derivatisation

To underline the importance of creating structures endowed with different functional groups, the obtained cyclohexanones have been further transformed. In particular, reduction of the carbonyl and of the nitro moieties gave access to cyclohexanols and to hydroxy-substitued β-amino esters, valuable products as high functionalized synthetic building blocks for pharmaceutical applications.[5]



References: [1] K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 –7186; [2]R.Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka C. F. Barbas, *Tetrahedron Lett.,* **2002***, 43,* 3817; G. N. Stowe, K. D. Janda, *Tetrahedron Lett.,* **2011***, 52,* 2085–2087; [3] For a review about the use diarylprolinol-silyl-ether: *Acc. Chem. Res.*, **2012**, *45*, 248-264; [4]P. Melchiorre*, Angew. Chem. Int. Ed.* **2012**, *51*, 9748 – 9770, L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7196 –7199; [5]F. Fulop, *Chem. Rev.,* **2001,** *101,* 2181-2204.