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Polarity-Directed One-Pot Asymmetric Cascade Reactions Mediated by Two Catalysts in an Aqueous Buffer

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Cascade Reactions Directed by Polarity

Category

Organo- and Biocatalysis

Key words

cascade reaction

condensation

conjugate addition

biphasic system

SYNFACT
of the month

$\text{R}^1, \text{R}^2 = \text{Alk}$ with polarity $\text{R}^1 > \text{R}^2$

Polarity-selective mode of action:

Significance: A polarity-directed organocatalytic cascade reaction of two different aldehydes with nitromethane in biphasic systems is reported. Since the involved aliphatic aldehydes exhibit similar reactivities, the predominantly formed cross-products of the reaction can be explained by slight differences in polarity. Most likely the proline (**1**)-catalyzed condensation of the more polar aldehyde with nitromethane succeeds first in the aqueous phase, thus releasing a nitroalkene intermediate. This species enriches in the organic phase consisting of the neat aldehydes, where it undergoes conjugate addition preferred with the less polar aldehyde, accelerated by secondary amine catalyst **2**, respectively.

Comment: In modern organic synthesis reactions are mostly driven by reactivity profiles of substrates. The present example illustrates that even completely different properties, in this case polarity, can be used to achieve differentiation in chemoselective reactions efficiently. The desired cross-products were obtained in high selectivities, proving the active principle of the cascade process. Since the Fréchet group has already shown that proline-containing macromolecular assemblies exhibit highly interesting properties in aldol reactions (Y. Chi et al. *J. Am. Chem. Soc.* **2008**, 130, 17287), the present examples underline the possibilities of this small organic catalyst and its derivatives.

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