

The Increased Reactivity of the Proline Carboxylate Derived Enamine

Category

Organo- and Biocatalysis

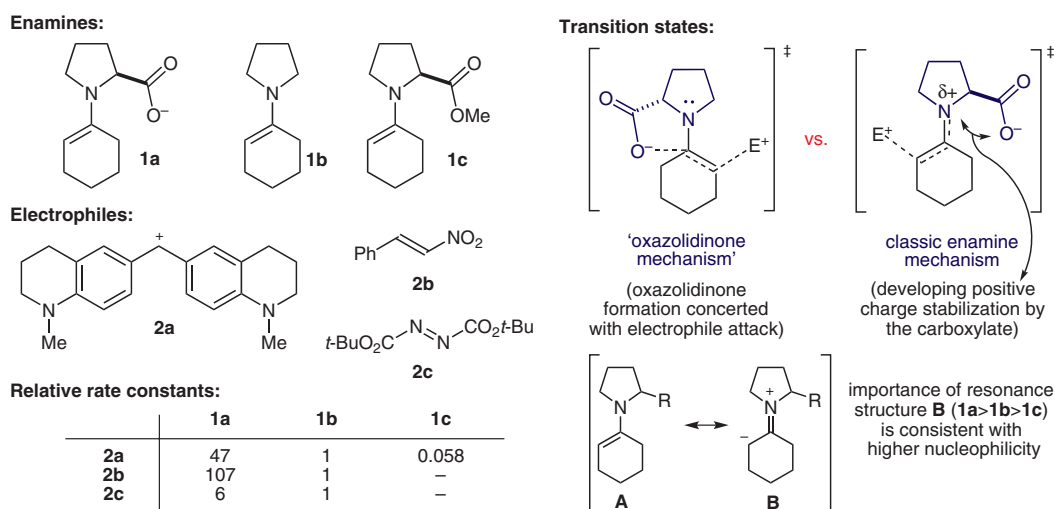
Key words

enamine catalysis

proline

oxazolidinones

SYNFACT
of the month



Significance: Mayr and co-workers have performed a kinetic analysis of the reaction of proline carboxylate enamine **1a**, pyrrolidine enamine **1b**, and proline ester enamine **1c** with electrophiles **2a–c**. The superior reactivity of the proline carboxylate **1a** compared to **1b–c** was interpreted as evidence for the operation of an alternative mechanistic pathway that includes anchimeric assistance of the carboxylate group in the addition to the electrophile. These data were suggested to support the formation of oxazolidinones in the stereogenic step of proline carboxylate catalyzed reactions (D. G. Blackmond et al. *J. Am. Chem. Soc.* **2010**, *132*, 7598), although catalytic reactions have not actually been studied.

Comment: Recently, Seebach, Eschenmoser, and co-workers suggested Hajos' 'oxazolidinone mechanism' (*J. Org. Chem.* **1974**, *39*, 1615) as an alternative to the commonly accepted List–Houk model in proline enamine catalysis (*Helv. Chim. Acta.* **2007**, *90*, 425). Blackmond, Armstrong, and co-workers discussed a variation of this mechanism (to account for the opposite stereochemical outcome) for proline carboxylate catalyzed reactions as an alternative to a simple steric argumentation (*J. Am. Chem. Soc.* **2010**, *132*, 7598). Proline and proline carboxylate catalyzed reactions seem to consistently give the opposite stereochemistry in agreement with the crucial role of the COOH proton in the Houk–List model. In the current paper, the kinetics of reactions of enamines **1** with electrophiles **2** were examined. The lower reactivity of **1c** was explained by the electron-withdrawing influence of the ester group and higher reactivity of **1a** by anchimeric assistance of the carboxylate group. Alternatively, the higher nucleophilicity of **1a** compared to **1b** could also be a consequence of the electrostatic stabilization by the carboxylate of the positive charge generated on the nitrogen in the transition state.