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Theoretical investigation of classic Passerini reaction mechanisms

Virginia C. Rufino[1*], Juliana A. dos Santos[2], Pedro P. de Castro[3], Giovanni W. Amarante[2], Hélio F. Dos Santos[1]

[1] Universidade Federal de Juiz de Fora, Núcleo de Estudos em Química Computacional (NEQC)/Departamento de Química/instituto de Ciências Exatas, Juiz de Fora, Minas Gerais, Brasil, 36036-900.
[2] Universidade Federal de Juiz de Fora, Grupo de Pesquisas em Metodologias Sintéticas (GPMS)/Departamento de Química/instituto de Ciências Exatas, Juiz de Fora, Minas Gerais, Brasil, 36036-900.
[3]Universidade Federal de Juiz de Fora, Departamento de Farmácia, Campus Governador Valadares, Governador Valadares, Minas Gerais, Brasil, 35010-180.

***e-mail:** virginiacamila12@gmail.com

The Passerini three-component is one of the most important multicomponent reactions.[1] Over the years, some chiral catalysts have been proposed. Despite some very good results for specific substrates, it is still necessary to search for catalytic protocols that require lower catalyst concentrations and that can be conducted at room temperature.[2] Among some challenges developing this type of protocol is the competition for the uncatalyzed and catalyzed pathways by one of the reagents themselves, the carboxylic acid, making it necessary to have a mechanistic understanding of them.[2,3] This work, therefore, aims to theoretically elucidate the reaction mechanisms between benzaldehyde, 4-chlorobenzoic acid and, tert-butyl isocyanide, in the absence of a chiral catalyst in pentane solvent, using DFT methods and SMD solvation model. According to our results, the uncatalyzed mechanism (Figure 1(a)) leads initially to the formation of an imidate intermediate (MSasc). It stops in this step, due to kinetic unviability for the reaction to continue. The catalyzed mechanism (Figure 1(b)), on the other hand, has the first step as rate-determining, and the presence of a second molecule of carboxylic acid catalyzing the proton transfer, allows the following steps to be liable to occur at room temperature. By understanding these mechanisms, we hope to obtain a sufficient basis for the elucidation of the reaction mechanism catalyzed by a chiral catalyst.

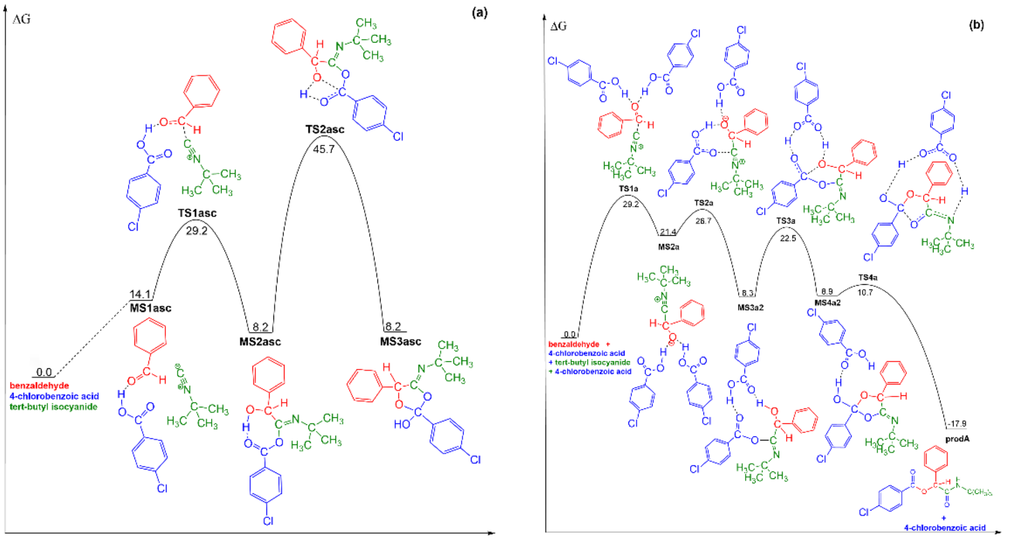

Figure 1. Free energy profile for: **(a)** Uncatalyzed Passerini reaction mechanism; **(b)** Catalyzed Passerine reaction mechanism.

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