A combined DFT and experimental study of the oxa-Michael reaction in THP synthesis: interpretation of the selectivity-determining factors

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Abstract: Our research group has been maintaining a longstanding interest in the synthesis of tetrahydropyran-containing natural products. The base catalyzed intramolecular oxa-Michael cyclisation proved to be a widely applicable method for the stereoselective construction of the tetrahydropyran moiety with various substitution patterns. Despite the more than fifty precedents of this transformation in the literature, there has been no clear elucidation of the origin of stereocontrol. Hence, the purpose of the present study is to provide a reasonable explanation for the observed selectivity based on the results of our intensive experimental and computational investigations. We first investigated the role of the cation. There was no change in the selectivity when a suitable crown-ether was used to sequestrate the cation. In sharp contrast to the popular hypothesis that the stereoselectivity is due to the chelation control, we showed that the presence of the cation does not play a role in the stereochemical control. On the basis of our theoretical findings, we suspect that stereoselectivity is governed by a gauche interaction in an early-transition state of the cyclisation reaction. After having tested further substrates, our theory proved to be applicable to explain the observed stereoselectivity in a number of disubstituted tetrahydropyrans synthesis.

Keywords: Tetrahydropyran; oxa-Michael cyclisation; DFT; Kinetic control