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Diastereo and enantioselective reactions synthesis of heterocyclic building blocks of biological importance

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In biologically active compounds, stereochemistry is of great importance. For example in the case of thalidomide, prescribed for the treatment of morning sickness in pregnant women, the (R)- and (S)-enantiomers have not the same bioactivity. One is safe and the other one is teratogenic. Thus, it is of importance to develop methods that are highly stereoselective to produce diastereomers and enantiomers. In this context, we have explored the construction of heterocycles such as substituted piperidines, α -C- and β -C-glycosides, using reactions catalyzed by transition metals or thermal reactions. Enantioselective ring expansion of prolinols were tuned up to produce a diversity of C3-substituted piperidines. Excellent enantioselectivity were obtained when prolinols were activated by trifluoroacetic anhydride (TFAA), (diethylamino)sulfur trifluoride (DAST). We have demonstrated that an aziridium intermediate was involved in the enantioselective ring expansion of substituted prolinols leading to optically active substituted piperidines. As α -C- and β -C-glycosides have interesting biological activities, the development of efficient and stereoselective methods to access α -C- and β -C-glycosides are of importance. For our part, we were able to synthesize α -C-glycosides from hydroxy-allylic alcohols when treated with a Lewis acid and we were able to synthesize β -C-glycosides from bromo-C-glycosides when these latter were treated with Grignard reagents in the presence of transition metal catalysts. On the other hand, we were able to access functionalized heterocycles containing oxygen with excellent diastereoselectivity from substituted cyclopropenes when treated with transition metals. The obtained compounds can be useful synthons that can be used to synthesize bioactive products. The scope and limitations of the developed methods, to access heterocycles containing nitrogen and oxygen, will be presented and the obtained stereoselectivities will be rationalized.

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Stereoselective control in the Michael addition of thiols to nitroolefins

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Nitroalkyl thioacetates and nitro thioethers are important organic intermediates and have been widely applied in synthesis of amino thiols and thioethers and aminoalkanesulfonic acids, such as taurine derivatives. The sulfur-Michael additions of thioacetic acid and thiols to nitroolefins are ones of crucial methods to prepare Nitroalkyl thioacetates and nitro thioethers. Although impressive advances have been made in organocatalyzed asymmetric sulfur-Michael additions of nitroalkenes with thiols and thioacetic acid, the diastereoselective control in the sulfur-Michael addition is still unclear issue. Our recent studies reveal that the diastereoselectivity in the triethylamine-catalyzed sulfur-Michael addition of nitroalkenes and thiols is kinetic control at the beginning and thermodynamic control at the end for less bulky reactants. Thus, kinetic and thermodynamic-controlled adducts can be obtained as major products by controlling the reaction time in those cases. The diastereoselective control in the sulfur-Michael addition of nitroalkenes and lithium thiolates followed by protonation was investigated as well. Lithium thiolates first added to nitroalkenes to afford cyclic lithium-chelated nitronates. The subsequent kinetic protonation of nitronates was proved to be the stereochemical determinant through the chelate-controlled six-membered half-chair transition state bearing two approximately 1,2-diaxial substituents due to stereoelectronic effect control. The stereoelectronic effect in the cyclic chelated transition state was probed and verified by tuning the steric bulkiness of the corresponding substituents. The current investigation provided not only comprehensive insights into the diastereoselective control in the sulfa-Michael addition of nitroalkenes and thiolates, but also an important role of the stereoelectronic effect in certain organic reactions involving cyclic chelate transition states.

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