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OrganoCatalysed CannaBinoid Target-oriented synthesis of pyrazoline

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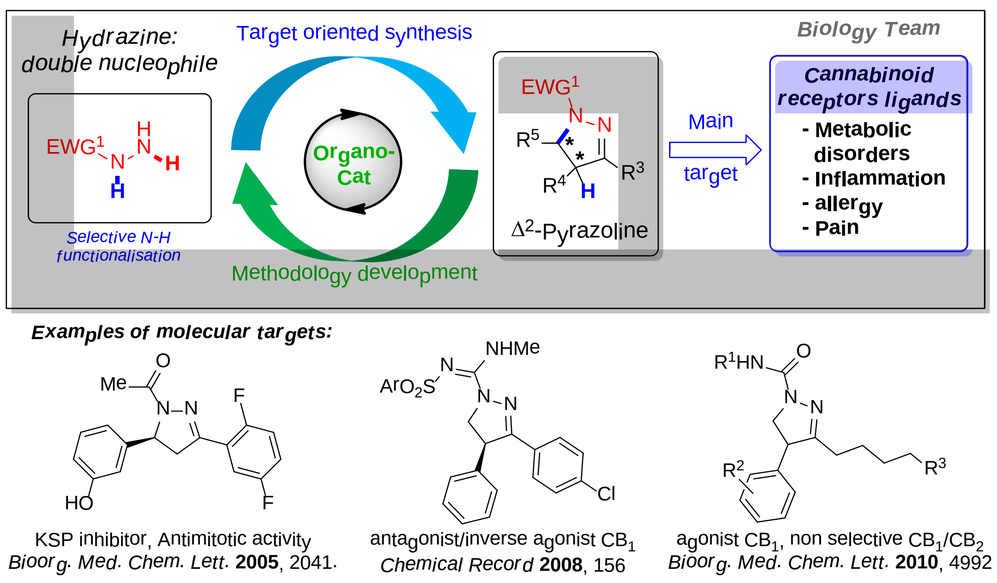
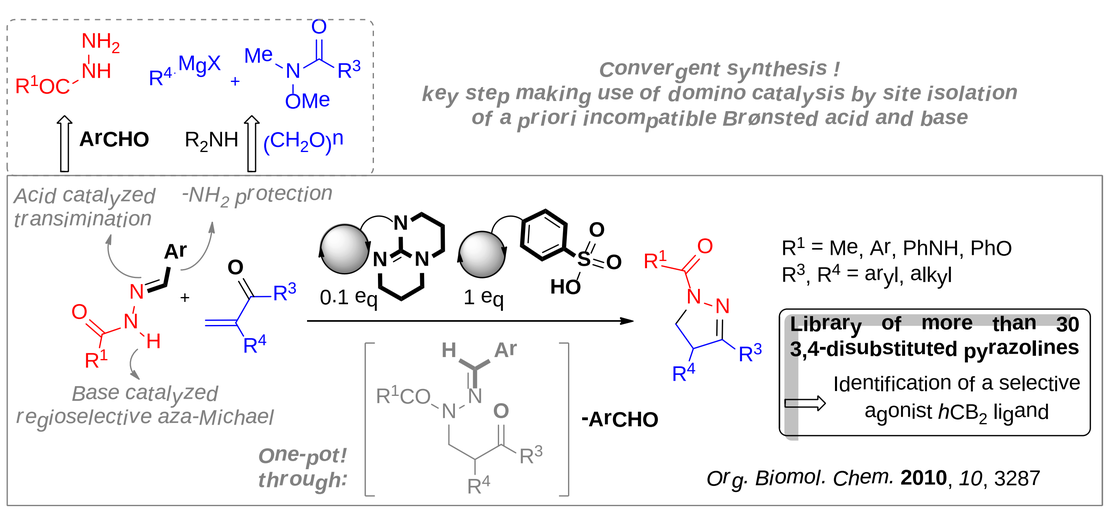
R. Millet, C. Furman and P. Chavatte, Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille Nord de France.

Context



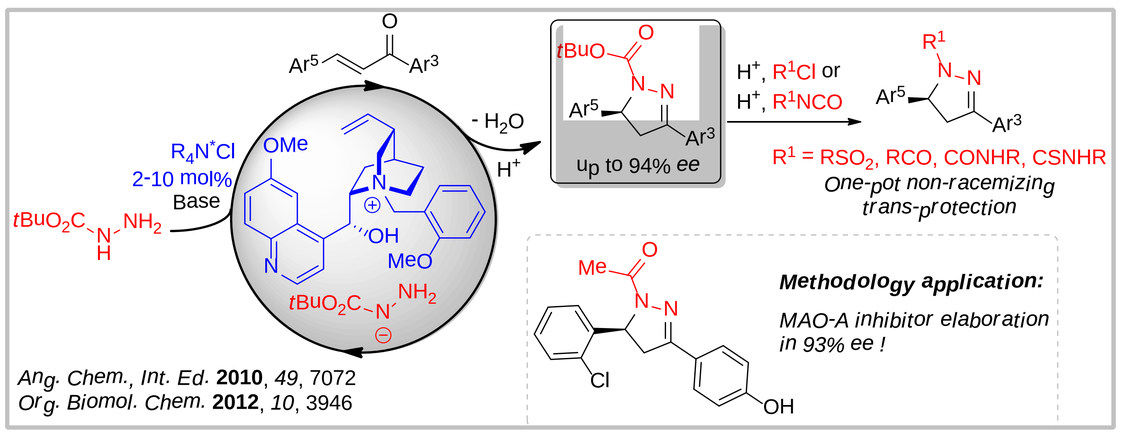
The increased demand from pharmaceutical industry for chiral heterocylic compounds, accessible by environmentally benign and economically reliable asymmetric and/or catalytic methodologies, have placed the use of organocatalysts as major tools for research and development. The cornerstone of the project aimed to achieve organocatalytic biotarget-oriented syntheses of libraries of *N*-EWG chiral pyrazoline derivatives by means of hydrazines as building blocks, through ion-paired organocatalysis. Especially, we leaned upon our organocatalysed methodologies to construct Cannabinoid CB_2 receptor ligands, based on pyrazoline scaffolds or congeners thereof, owing to the promising potential of these GPCR receptors to regulate pain and inflammation through immune system.

Site isolation concept in action: 3,4-disubstituted pyrazolines



(*Vincent Gembus, Postdoc*) Toward the elaboration of biologically important 3,4-substituted pyrazolines, an organocatalyzed aza-Michael/transimination domino sequence between hydrazones as 'masked hydrazines' and enones was achieved by a mixture of heterogeneous resin-bound acid/base reagents, allowing the simultaneous one-pot use of otherwise destructive reactive functionalities using the site isolation concept. The non-soluble reagents are easily removed by filtration facilitating the synthesis of heterocycles libraries. In collaboration with our pharmaceutical partners and following a convergent synthetic approach, a small series of molecules were identified with a significant *h*CB_2/*h*CB_1 selectivity in favor of *h*CB_2 receptors along with an agonist behavior. This CB_2 selectivity is unique within the pyrazoline CB ligands although the affinity remains to be improved with further structure-activity relationship investigations.

Phase Transfer Catalysis in action: 3,5-diaryl pyrazolines



(*Olivier Mahé, PhD*) Under catalytic phase transfer conditions the formation of an original chiral ion pair between quininium cation and hydrazine anion led to an enantioselective aza-Michael cyclocondensation domino reaction to furnish enantioenriched pyrazolines. A convenient one-pot protocol allowed the introduction of various functional groups (R^1) on the nitrogen atom through a facile *N*-Boc transprotection process. A straightforward access to an enantioenriched Mono-Amine Oxidase MAO-A inhibitor was achieved thereby.

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