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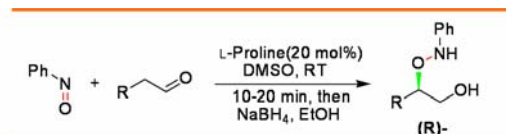
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Organic Synthesis, Asymmetric Catalysis and Medicinal & Bioorganic Chemistry

We are interested in the development of new synthetic methodologies in organic synthesis and asymmetric catalysis as well as their uses in the synthesis of biologically active compounds. Learning from Nature is always inspiring. Our studies started from developing new approaches to mimic the natural Class-I aldolases that use an amine functionality in its active site and a covalent catalysis involving imine and enamine intermediates. If we could create the ability to efficiently exploit imine and enamine intermediates, we might have a way of finding or making useful chiral catalysts for many asymmetric reactions. Towards this end a new approach combining "the transition state theory" and "the reactive immunization" was used to generate antibodies with the features of Class-I aldolases and the aldolase antibodies obtained can match the catalytic efficiency of the natural enzyme. These aldolase antibodies not only catalyzed a broad range of aldol reactions with excellent enantioselectivities, but also catalyzed their reverse reactions, namely retro-aldol reactions, which allowed to realize the asymmetric kinetic resolution of aldols. So using the same antibodies, pairs of aldol enantiomers were made.

Antibody catalysis provided significant conceptual model which promoted our interest to find organocatalysts of similar reactions. New asymmetric routes with organocatalysis were then developed, that can be ideally performed under ambient conditions in benign media using small organic molecules as catalysts. With the development of organocatalytic asymmetric reactions, a new asymmetric aminoxylation was discovered. Unmodified aldehydes were reacted with nitrosobenzene in the presence of chiral proline catalyst affording α -aminoxy aldehydes with excellent enantioselectivities (94 - >99% ee). Since the amino group on aminoxy functional group can be easily removed to give free hydroxy, the reaction provided with a direct methodology to the synthesis of α -hydroxy aldehydes, a basic element in carbohydrates and sugars.



Enantioselective α -Aminoxylation of Aldehydes (up to $\geq 99\%$ ee)

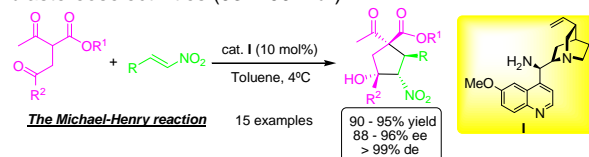
The asymmetric construction of a quaternary carbon atom represents one of the most challenging and demanding topics in the synthesis of natural products and chiral drugs. The development of efficient methods to access complex molecules with multiple stereogenic centers also continues to be a substantial challenge in both academic research and industrial applications. The aminoxylation directed domino reactions have been developed, from which pure aldehyde

products could be isolated in good to excellent yields with excellent stereocontrol.^{4,5}

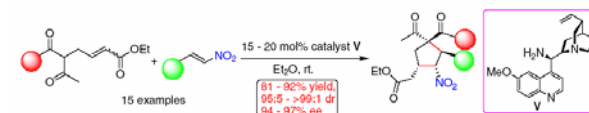


17 examples, up to 90% yield, $\geq 99\%$ e.e., $>99:1$ d.r.

We have developed a novel organocatalytic tandem Michael-Henry reaction. The reaction was efficiently catalyzed by readily available 9-amino-9-deoxyepiquinine (**V**) to give synthetically useful, highly functionalized chiral cyclohexanes with four stereogenic centers containing two quaternary stereocenters in good to excellent yields (85-94%), excellent enantioselectivities (97% to $>99\%$ ee) and high diastereoselectivities (93:7-99:1 dr).^{1,6}



We have also extended the above tandem process to a novel enantioselective and diastereoselective organocatalytic domino double Michael reaction that provides expedited access toward highly functionalized cyclopentane derivatives. Simple operational procedures, excellent enantioselectivity (90-97% ee), diastereoselectivities (95:5 to $>99:1$ dr), and immense potential of synthetic versatility of the products render this new methodology highly appealing for asymmetric synthesis.^{7,8,2,4}



Recent Publications

1. B. Tan, X. Zhang, P. J. Chua, G. Zhong, *Chem. Commun.* **2009**, 4585-4588. (cover article)
2. L. Yang, B. Tan, F. Wang, G. Zhong, *J. Org. Chem.* **74** (2009), 1744-1746.
3. B. Tan, Z. Shi, P. J. Chua, Y. Li, G. Zhong, *Angew. Chem. Int. Ed.* **48** (2009), 758-761.
4. M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem. Int. Ed.* **47** (2008), 10187-10191.
5. D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang, G. Zhong, *Org. Lett.* **10** (2008), 4585-4588.
6. B. Tan, P. J. Chua, Y. H. Li, G. Zhong, *Org. Lett.* **10** (2008), 2437-2440.
7. B. Tan, P. J. Chua, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **10** (2008), 3489-3492.
8. B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **10** (2008), 3425-3428.