

Sequential organocatalytic β -hydroxy and Mukayama addition: A perspective for the synthesis of Orlistat

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INTRODUCTION

Orlistat is a reduced form of the natural product lipstatin, which is an antiobesity agent marked under the tradename of Xenical approved by the FDA as the first over-the-counter weight-loss medication.

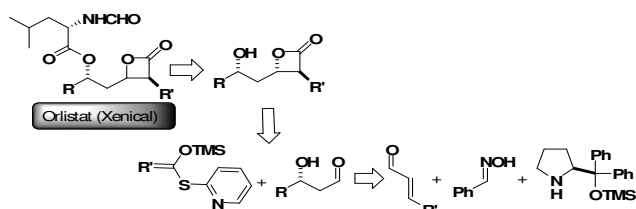
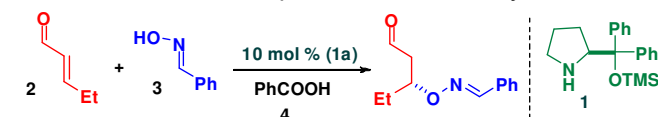


Figure 1: Retrosynthetic analysis

RESULTS AND DISCUSSION

Firstly, the addition was mediated by 10 mol% of catalyst and the reaction condition (temperature and solvent) were optimized. The results are summarized in Table 1.

Table 1: Optimization of the reaction of conjugate addition of oxime to α - β -unsaturated aldehyde.



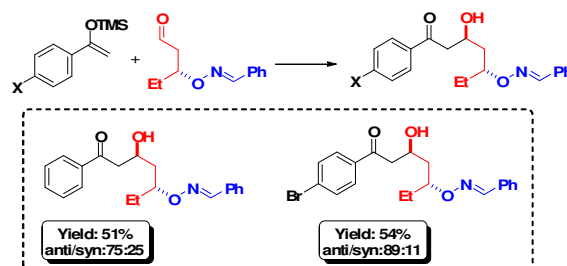
Entry ^a	Solvent	T (°C)	Yield(%)	ee(%) ^b
1	Tol.	0	51	40
2	MeCN	0	49	56
3	THF	0	56	90
4	THF	25	53	34
5	THF	-10	58	96
6	THF	-20	54	91

^a Performed with **1** (0,05 mmol) **2** (0,5mmol), **3** (1,5 mmol), **4** (0,05mmol) in 0,25 mL of solvent. ^bDetermined by chiral stationary phase HPLC.

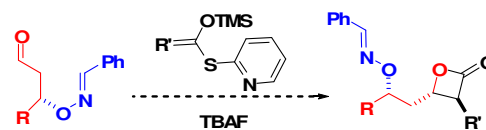
When the reaction was performed in THF as solvent, the β -hydroxy carbonyl compound could be obtained

with 90% ee and 56% yield (Entry 3). Decreasing the reaction temperature to -10 °C and -20 °C (entries 5 and 6) furnished desired product in 96% and 91% ee respectively. The Mukayama aldol reaction with silyl enol ether were carried out using 50 mol % of TBAF, figure 2.

Figure 2: Screening of different silyl enol ether



Further analysis of the crude mixture showed a diastereoisomeric ratio of 75:25 and 89:11. Further optimization are under evaluation to improve the diastereoselectivity as well as the application or mercapto pyridinil enol ether for the synthesis of β -lactone ring.



CONCLUSION

In conclusion, the have optimized the application of organocatalysts **1** as a perfect mediator in the enantioselective addition of oxime α - β -unsaturated aldehyde. The nature of the solvent is very important once the one-pot sequential Mukayama additions are under evaluation.

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