



Chiral Brønsted Acid Catalyzed Highly Stereoselective Mannich-type reaction of Azlactone with Aldimines

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INTRODUCTION

The asymmetric Mannich reaction is one of the most powerful carbon-carbon bond reactions in organic synthesis. The resulting β -amino carbonyls products are key intermediates in the preparation of biologically chiral amines such as α,β -diamino acids.¹ The organocatalytic version of this reaction presents a series of advantages, such as high yields and enantioselectivities, free-metal catalysts and environment-friendly conditions.^{2,3} In this work we report the Mannich-type reaction between azlactone and aldimines, employing a chiral phosphoric acid as organocatalyst.

RESULTS AND DISCUSSION

Our studies raised from the Mannich-type reaction between the Alanine-derivative azlactone and the benzaldehyde-derivative aldimine, employing as organocatalyst a BINOL-derivative chiral phosphoric acid (S-TRIP). THF as solvent gave the corresponding product in excellent enantioselectivities, however low dr and yield. Switching to an apolar solvent, the product was obtained in reasonable yield and perfect selectivities (Table 1, entry 3).

Table 1. Optimization of the reaction conditions for the stereoselective Mannich-type reaction.

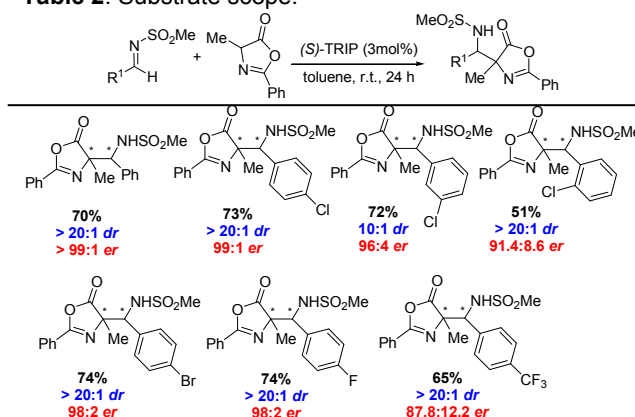
Ent.	Solvent	d.r. ^a (anti/syn)	e.e. ^b (%)	Yield ^c (%)
1	THF	1:1	98/98	40
2	CH ₂ Cl ₂	1:1	ND	Traces
3	PhMe	>20:1	>99	70
4 ^d	PhMe	-	-	-

^a From ¹H NMR of crude reaction mixture; ^b Measured from chiral HPLC; ^c Yield after flash chromatography; ^d No catalyst, 48 h.

It's important to mention that the Mannich reaction product has two stereogenic centers, one being quaternary.

Building on these initial results, we decided to investigate the Mannich-type reaction between different aldimines with the Alanine-derivative azlactone (Table 2). Different substituents on the aromatic ring were well tolerated, for example, the *p*-Cl group gave the corresponding product with high diastereoselectivity (> 20:1 dr) and high er (99:1).

Table 2. Substrate scope.



CONCLUSION

In this work we presented the use of chiral Brønsted acid for a highly stereoselective Mannich-type reaction between azlactone and aldimines. As a result, a new asymmetric σ C-C bond was created and the Mannich adducts were obtained with good yields and high stereoselectivities (up to >20:1 dr and > 99% ee). Studies involving X-ray diffraction are underway in our laboratory to elucidate the absolute and relative stereochemistry.

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