

Tandem Organocatalytic Functionalization and Fisher Indole Synthesis: A Greener Approach for the Synthesis of Indoles

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INTRODUCTION

The indole core is featured in a number of natural products as well as medicinally relevant compounds¹. Recently, the concepts of organocatalytic sequential reaction has inspired several research groups to design novel stereoselective strategies for assembling target structure and most importantly, reproducing the rich structural diversity found in natural products. Herein, we describe the application of a new class of organocatalysts in the enantioselective synthesis of indole alkaloids under the principles of green chemistry (Figure 1).

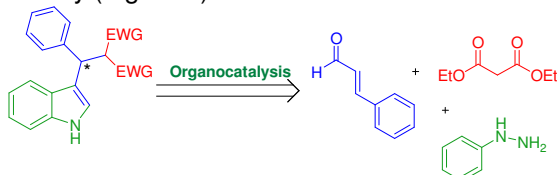
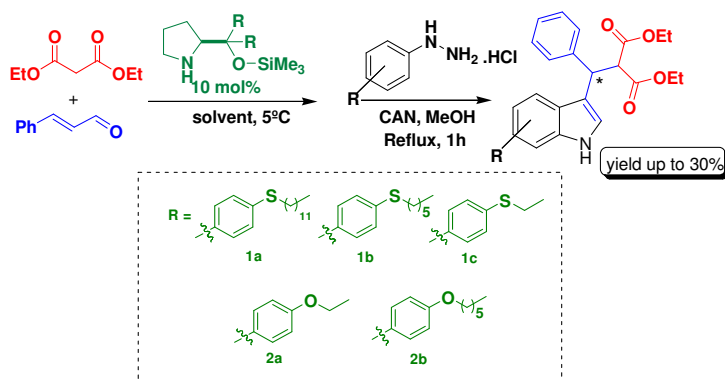


Figure 1- Retrosynthetic analysis.

RESULTS AND DISCUSSION

The organocatalytic enantioselective addition of malonates to aromatic α,β -unsaturated aldehydes² was initially developed by reaction of cinnamaldehyde with diethyl malonate in different solvents at 5 °C (Scheme 1).



Scheme 1

The screening of the reaction conditions in Table 1 shows that the reaction is very solvent dependent. The reaction proceed very well, especially in the conditions of entries 3 and 6, given the desired product with enantiomeric excesses and yields above

90% in a short reaction time (34 hours) by using Brine as solvent.

Table 1. Solvent and catalyst screening for the addition of diethyl malonate to cinnamaldehyde

Entry	Catalyst ^[a]	Solvent	Yield [%] ^[b]	Ee [%] ^[c]	Time [h]
1	1a	EtOH	93	96	61
2	1a	H ₂ O ^[f]	71	94	61
3	1a	NaCl _{sat.} ^[f]	98	94	34
4	1b	EtOH	56	96	61
5	1b	H ₂ O ^[f]	93	96	111
6	1b	NaCl _{sat.} ^[f]	93	95	34
7	1c	EtOH	43	93	61
8	2a	EtOH	30	29	97
9	2b	EtOH	100	94	84
10	1b ^[d]	NaCl _{sat.} ^[f]	57	96	39
11	1b ^[e]	NaCl _{sat.} ^[f]	49	94	39
12	1b	NaCl _{sat.}	53	93	48,5
13	1b	EtOH ^[f]	87	94	38

* [a] All reactions were performed on a 0.3 mmol scale with 10 mol% of catalyst. [b] Yield of the isolated product. [c] Determined by chiral HPLC after oxidation to the corresponding ethyl ester. [d] 5 mol % of catalyst. [e] reaction at rt. [f] reaction with 10 mol % of PhCO₂H.

After determined best reaction condition, the reaction was carried out using dibenzil malonate with trans-cinnamaldehyde furnished the product in 54% yield with 95% ee.

CONCLUSION

The new library of organocatalyst had been shown a great performance on the enantioselective conjugate addition under the principles of green chemistry. Furthermore, the asymmetric synthesis of chiral indoles are under evaluation.

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