

Development and application possibilities of new, hydrogen bond donor organocatalysts

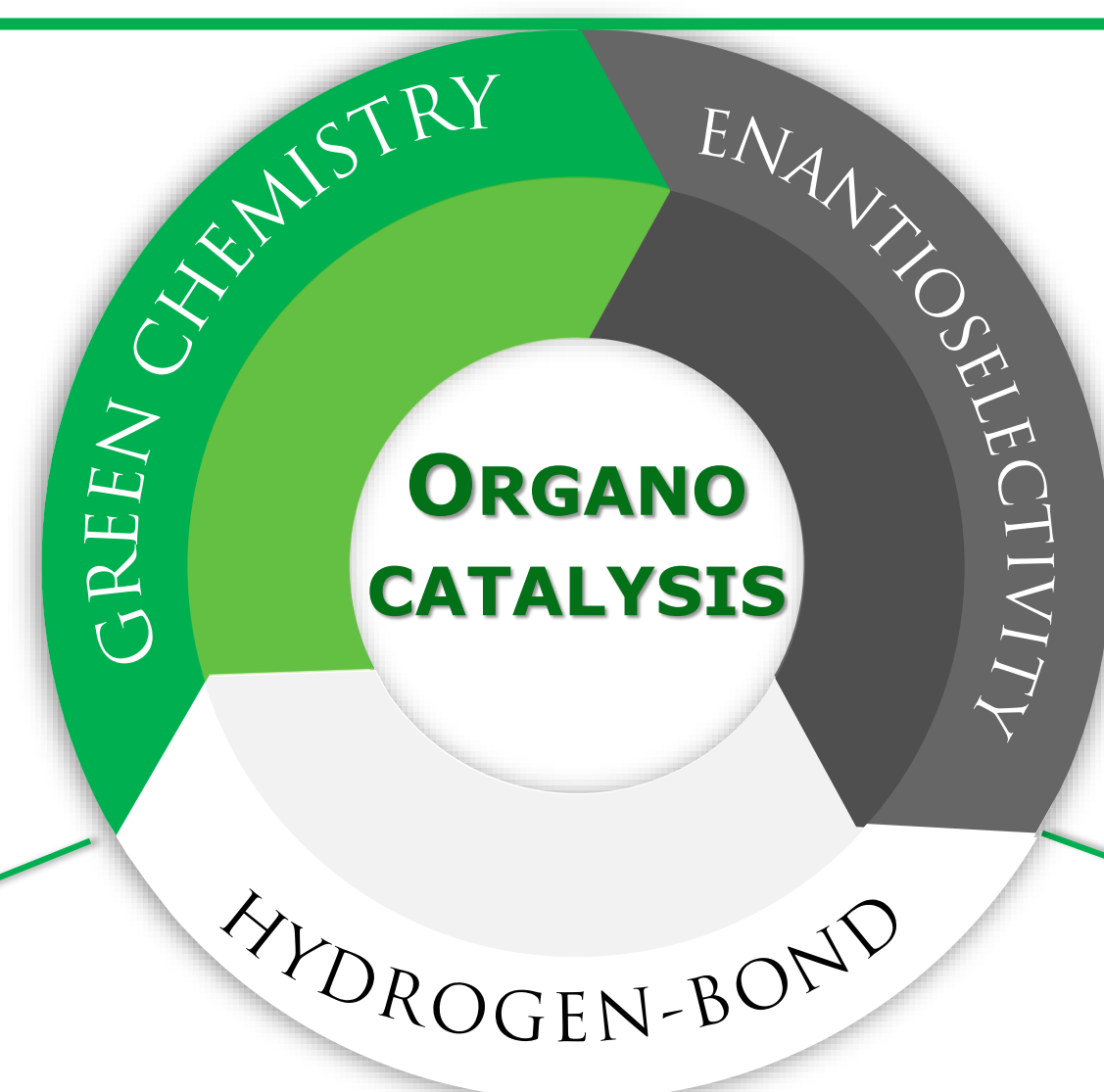
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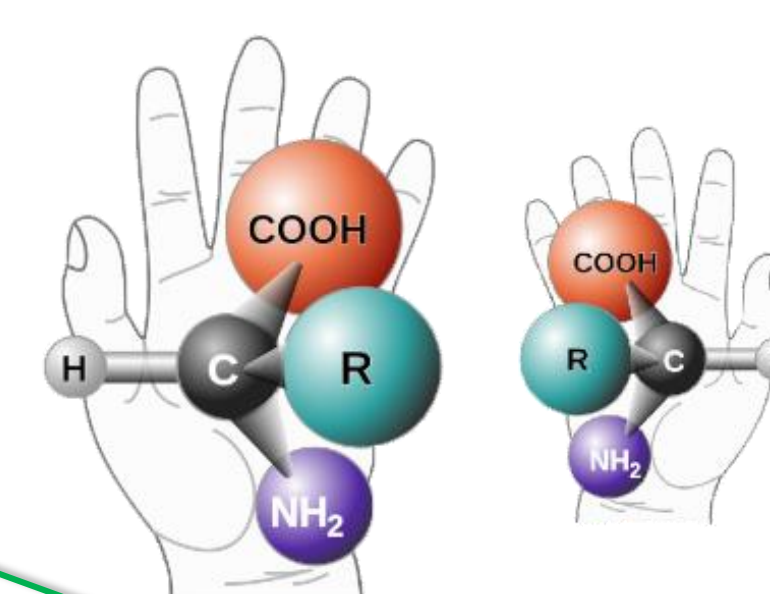
INTRODUCTION

In the past decade using dual H-bond donors as organocatalysts' unit has become of great interest. Their activities are directly related to their hydrogen bond donation capability which is correlated with the acidity of the NH groups. The first, dual hydrogen bond donor unit was the widely known urea. During the evolution of hydrogen bond donors many other strained ring structures were discovered, which have even higher acidity of NH groups. [1]

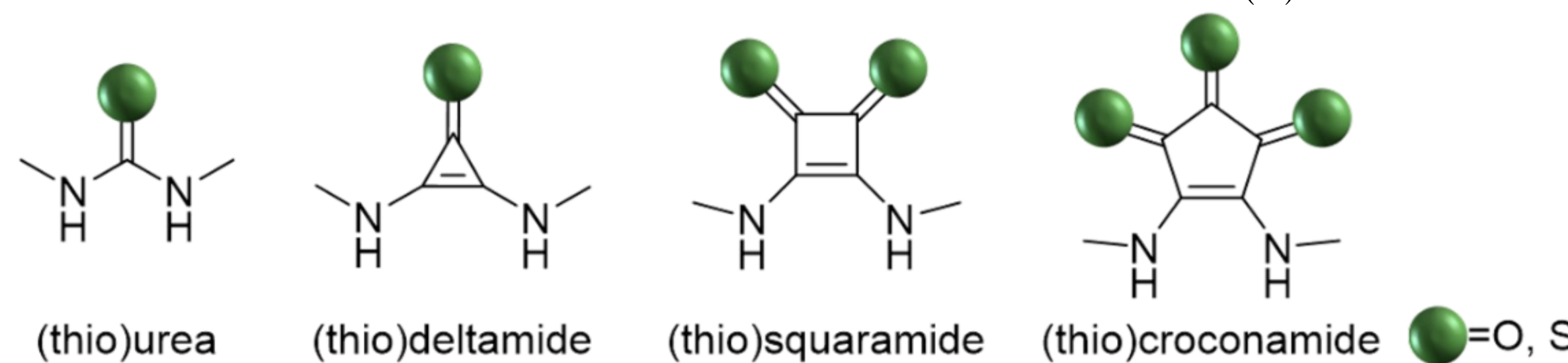
ORGANOCATALYSTS ARE SMALL ORGANIC MOLECULES CONSISTING ONLY OF CARBON, HYDROGEN, SULFUR AND OTHER NONMETAL ELEMENTS



ENANTIOSELECTIVE SYNTHESIS IS A KEY PROCESS IN PHARMACEUTICAL INDUSTRY, AS THE DIFFERENT ENANTIOMERS OR DIASTEREOMERS OF A MOLECULE OFTEN HAVE DIFFERENT BIOLOGICAL ACTIVITY

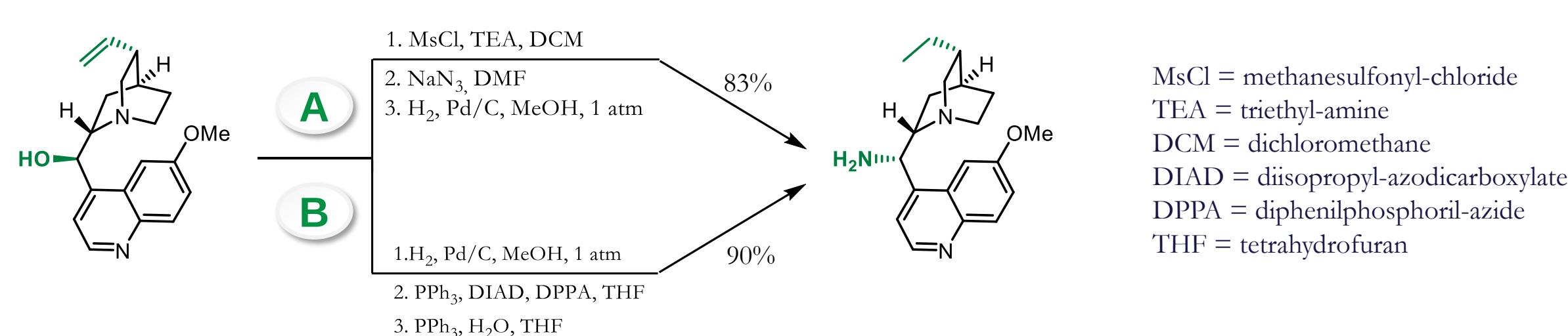


HYDROGEN-BOND DONOR CATALYSIS IS USING NON-COVALENT INTERACTIONS TO ACTIVATE CHEMICAL REACTIONS, AND TO INFLUENCE THE STEREOCHEMISTRY OF THE PRODUCT(S)



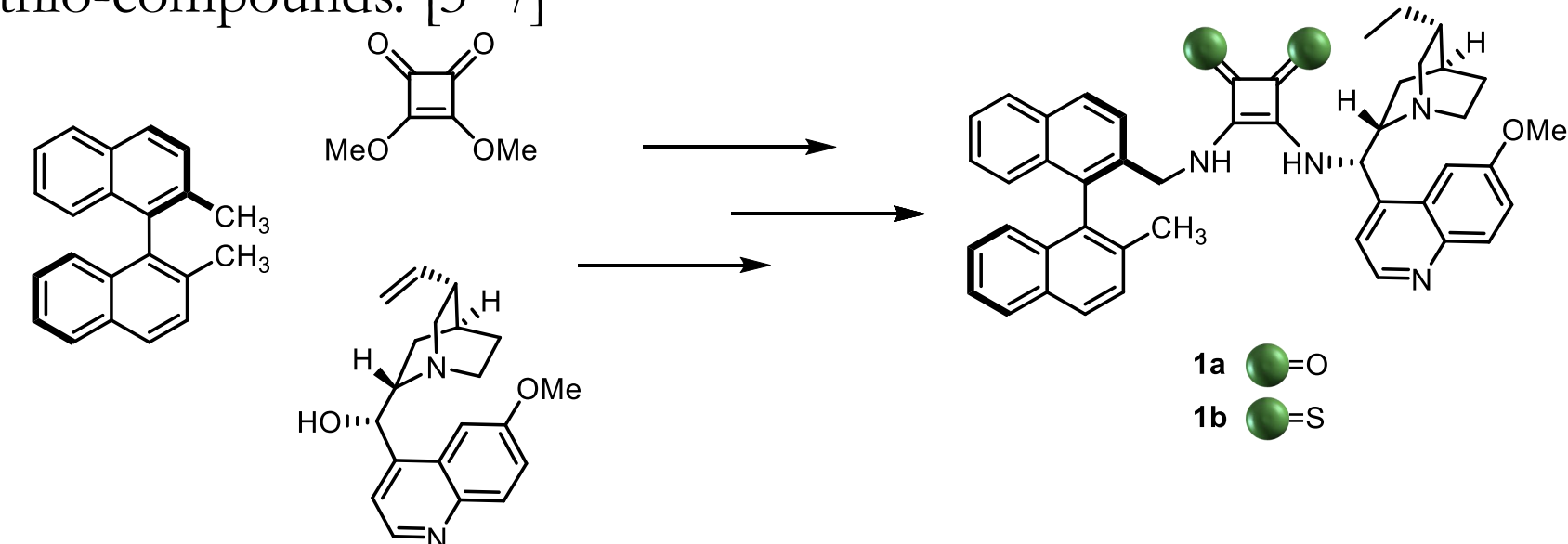
(THIO)SQUARAMIDES

During my research I aimed to synthesize new, chiral (thio)squaramide, and (thio)deltamide hydrogen-bond donor organocatalysts. In these organocatalysts the chiral induction is provided by a well-known, natural, chiral scaffold: the cinchona alkaloid. I used cinchona-amine to build this cinchona skeleton into the catalyst. This cinchona unit was prepared in two reaction pathways: the first one (A) contains a stereoselective nucleophilic substitution with sodium azide, meanwhile the second route (B) is a one-pot reaction in which the appropriate cinchona-amine derivative was gained using *Bose-Mitsunobu*, and *Staudinger* reactions. [2] (Scheme 1.)



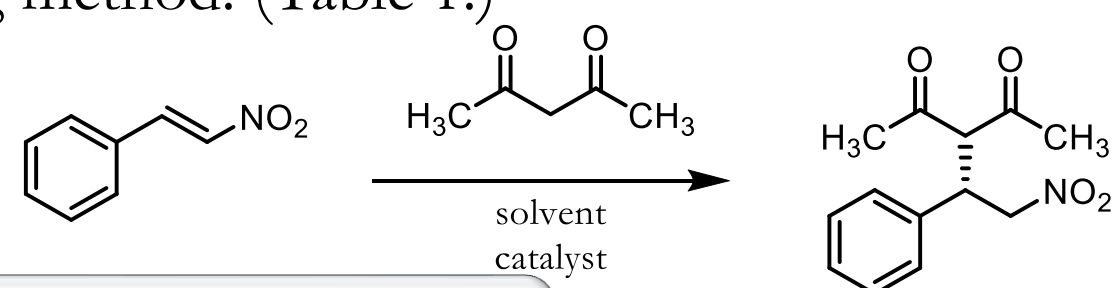
Scheme 1. Synthesis of cinchona-amine from chiral quinine

The new binaphthyl-cinchona-squaramides were synthesized using commercially available (*R*)-dimethyl-binaphthalene, dimethyl squarate and the beforementioned cinchona-amine. (Scheme 2.) The development of the thio analogue organocatalyst was attempted in many ways, but the thiosquaramide was only gained when the former binaphthyl-cinchona-squaramide **1a** was thionated with P_4S_{10} ·pyridine complex. It must be noted that thiosquaramide-derivatives decompose on silica gel hence it is obligated to use neutral aluminium oxide for the purification of these thio-compounds. [3–7]



Scheme 2. Synthesis of binaphthyl-cinchona-(thio)squaramides

The catalytic activity of the prepared organocatalysts **1a**, **1b** was studied in enantioselective *Michael* addition which is widely used as a C–C coupling method. (Table 1.)



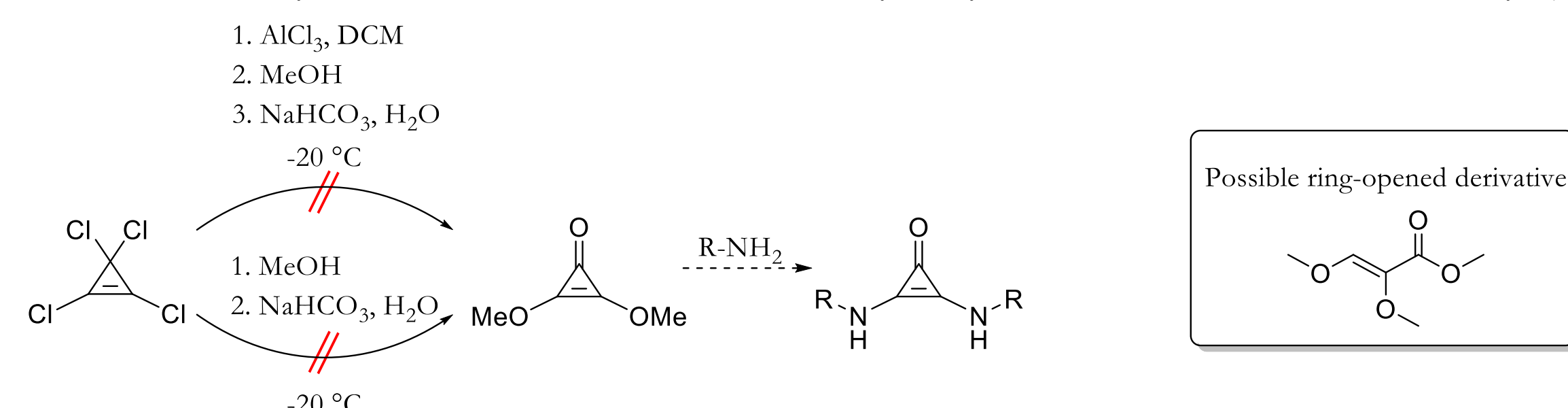
1a  =O		5 mol% cat. 48 hours	1b  =S	
YIELDS [%]	ee [%]	SOLVENT	YIELDS [%]	ee [%]
56	95	DCM	44	80
80	96	toluene	85	96
83	98	EtOAc	76	98
70	97	MTBE	63	98
52	61	MeOH	51	67
42	93	H ₂ O	71	98
59	98	-	52	100

1a 		EtOAc 24 hours	1b 	
YIELDS [%]	ee [%]	CATALYST LOAD [mol%]	YIELDS [%]	ee [%]
85	98	5	81	98
93	98	1	92	97
93	96	0,5	90	97
90	93	0,2	91	98
88	88	0,1	88	77

Table 1. Application of organocatalysts (**1a**, **1b**) in asymmetric *Michael* addition of β -nitrostyrene and acetylacetone (ee = enantiomeric excess)

(THIO)DELTAMIDE

To prepare the new (thio)deltamide organocatalysts I first attempted to synthesize deltic acid methyl ester from the commercially available tetrachlorocyclopropene (TCCP). For this purpose two different reaction routes were used, both performed at low temperature ($-20\text{ }^{\circ}\text{C}$) due to the high reactivity of TCCP. In the first route TCCP was reacted with methanol using $AlCl_3$ as a *Lewis* acid catalyst in dichloromethane, and then hydrolysed with aqueous $NaHCO_3$ solution. In the second pathway I avoided the non-eco-friendly $AlCl_3$ catalyst and added directly the TCCP into methanol, and hydrolysed in the aforementioned way. (Scheme 3.)

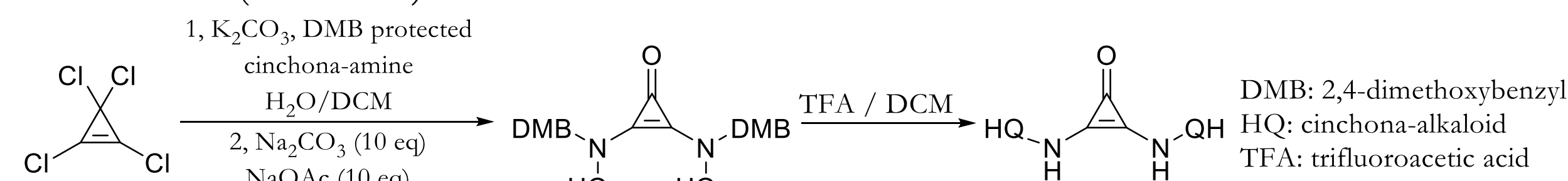


Scheme 3. Preparation of deltic acid methyl ester, and the possible structure of by-product

In both ways the similar side-product was gained, but unfortunately I could not isolated the required product. Possibly, this side-product was one of the ring-opened derivative of cyclopropene [8], consequently I would like to use less reactive reagents to prevent the ring opening of cyclopropene in the future.

FUTURE PLANS

According to literature [9] only secondary amines can react with TCCP without ring opening therefore I would like to produce the 2,4-dimethoxybenzyl (DMB) protected cinchona-amine derivative. This DMB protected amine can form an ionic intermediate with TCCP which can be converted to the proper protected deltamide with excess of base. After this, DMB protection group can be removed with the application of trifluoroacetic acid. (Scheme 4.)



Scheme 4. An alternative synthetic route for disubstituted deltamide

After successful synthesis of deltamides I would like to examine, and compare their catalytic activity with squaramide analogues in enantioselective *Michael* addition.

ACKNOWLEDGEMENT



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