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Effect of Microwaves in the Chiral Switching Asymmetric Michael Reaction†

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† This paper is dedicated to Prof H.C. Brown, a pioneer in Physical Organic Chemistry and Asymmetric Synthesis on the occasion of his 90th birthday

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Abstract: Highly enantioselective Michael reactions of malonates with cyclic enones are achieved in remarkably less time under microwave irradiation using newly developed heterobimetallic catalysts.

Keywords: Michael reaction, Al - complex, chiral switch, microwave irradiation

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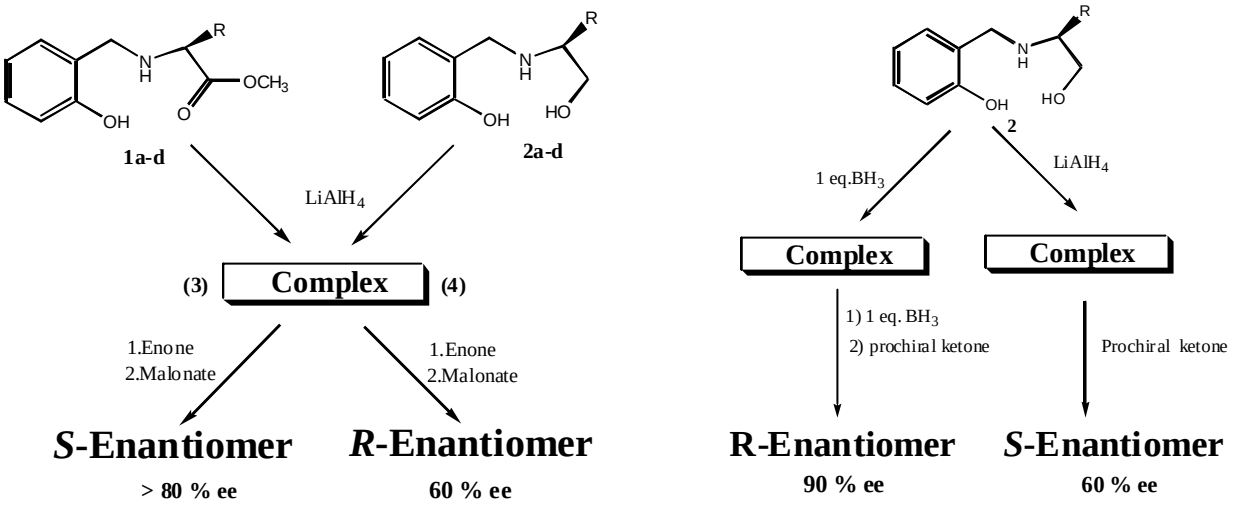
Introduction

Earlier, we have synthesized from readily available salicylaldehyde and L-valine the novel chiral catalysts **1** and **2a-d**, which displayed an interesting phenomenon of enantiomer switching in asymmetric reductions of prochiral ketones [1] and asymmetric Michael reactions [2] (Scheme 1). Catalytic asymmetric Michael reactions using chiral amines [3], alkaloids [4], polymer bound alkaloids [5], chiral crown ethers and bases [6], optically active Co (II) complexes [7], natural proteins [8] and amino alcohols [2] as catalysts have been extensively studied. A breakthrough in catalytic asymmetric Michael addition reactions was achieved with the introduction of heterobimetallic catalysts. In a series of reports Shibasaki and coworkers [9] elaborated the utility of such heterobimetallic catalysts of

BINOL –La (Al)-alkali metals in bringing about highly enantioselective Michael addition reactions, however, the Michael reaction usually requires prolonged reaction times.

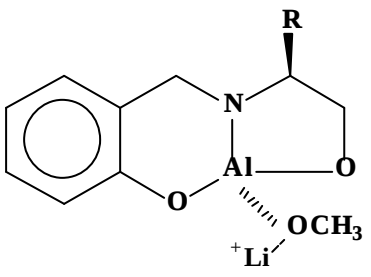
It is well known that ultrasound or microwaves [10] can accelerate the reaction rates in normal reactions. We were interested in exploring such techniques in the Michael addition reaction and their effect on enantioselectivity. Accordingly we modified a domestic microwave oven to allow the reactions to be carried out in a flask attached to a reflux condenser using a wide variety of solvents as the fire hazard is significantly reduced compared to an open vessel system.

Scheme 1

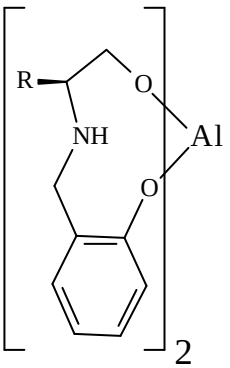


1a R = isopropyl, **1b** R= iso butyl, **1c** R= sec butyl, **1d** R = benzyl

When the asymmetric Michael reaction of cyclohexenone and diethyl malonate was carried out with the aluminium complex (**3**), the reaction was complete in 4 hours yielding the S-isomer in more than 80% *ee*, whereas the aluminium complex (**4**) gave the R – isomer in 60 % ee [2].



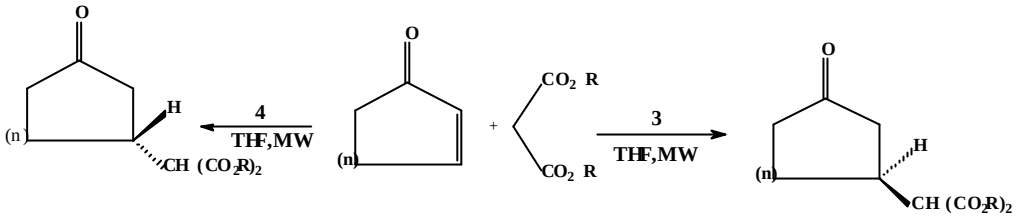
(3)



(4)

Interestingly the microwave assisted asymmetric Michael reaction using the aluminium complexes **3** and **4** was remarkably accelerated without altering the chiral switching nature (Scheme 2). Thus, cyclic enones when treated with various dialkyl malonates under microwave irradiation produced the adducts in less than 5 minutes. The results are presented in Table 1

Scheme 2



R - isomer **S - isomer**

Table 1. Asymmetric Michael additions of cyclic enones with malonates under microwave irradiation.

Catalyst	Enone	Malonate (R)	Time		Yield (%)		*ee* (%)[b]		$[\alpha_D^0]$ (c=5 in $CHCl_3$)
			RT (h)	MW (Min)	RT	MW	RT	MW	
3	n = 1	Ethyl	4	2	80	85	73	78	-25.8
3	n = 1	Isopropyl	6	3	74	75	-	-	-2.9 [c]
3	n = 1	Benzyl	5	2	85	88	82	80	-26.9
3	n = 2	Ethyl	4	2	82	82	80	78	-2.72
3	n = 2	Isopropyl	5	3	70	70	43	40	-2.1[d]
3	n = 2	Benzyl	4	2	86	85	84	80	-0.95
4	n =2	Ethyl	4	2	79	80	60	60	+2.14
4	n=2	Isopropyl	6	3	75	70	37	40	+2.05
4	n =2	Benzyl	5	2	80	85	55	50	+0.59

MWI was carried out in pulses of 1minute duration with 30 sec intervals; (b) *ee* was determined based on the optical rotation values available in the literature [9]; (c) Literature $[\alpha]_D$ was not available; (d) See [3a]

The results indicate that using microwaves comparable enantioselectivity could be achieved in a shorter period of time (2 min) in excellent yields. Also, chiral switching which occurred under room temperature conditions was reproduced under microwave conditions.

The study was extended to include acyclic α,β-unsaturated ketones and aldehydes (Scheme 3). The reaction times and yields are given in Table 2. Although the reaction was complete in a shorter period, resulting in 90 % yield of the Michael adduct, the expected enantioselectivity could not be achieved. This may be attributed to the loss of rigidity in the acyclic system, since the same reaction when carried out under normal conditions also resulted in a racemic product.

Scheme 3

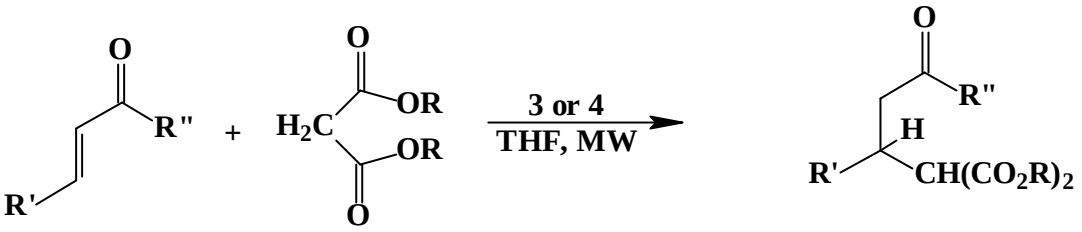


Table 2, Michael additions of acyclic α,β-unsaturated enone with dialkyl malonates under microwave irradiation.

Enone	Malonate (R)	Time		Yield (%)	
		RT (h)	MW (Min)	RT	MW
R'=R"=Ph	Ethyl	6	8	70	72
R'=R"=Ph	Isopropyl	7	7	65	68
R'=R"=Ph	Benzyl	5	10	75	70
R'=Ph, R"=H	Ethyl	4	5	75	70
R'=Ph, R"=H	Benzyl	3	7	72	72
R'=CH_3, R"=H	Ethyl	7	4	80	75
R'=CH_3, R"=H	Benzyl	7	6	75	72

In order to prove the versatility of the catalyst and the application of microwaves, thiols were also used as Michael donors, which is a useful methodology for C-S bond formation (Scheme 4). The Michael adducts are obtained in very good yield within remarkably reduced reaction times (1 minute). Results are presented in Table 3.

Scheme 4

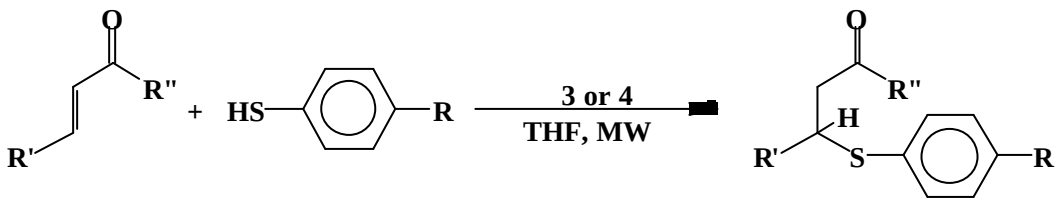


Table 3. Michael additions of thiols with acyclic and cyclic α,β-unsaturated enones

S.No	Enone	Thiol (R)	Time (Min)		Yield (%)	
			RT	MW	RT	MW
1	R'=R"=Ph	H	2	1	90	88
2	R'=R"=Ph	CH_3	2	2	88	90
3	R'=R"=Ph	CH_3COSH	30 sec	30 sec	95	95
4	Cyclohexenone	CH_3	1	1	92	90
5	"	H	2	1	90	92

The fact that the products obtained in the microwave assisted Michael reactions exhibit no change in the *ee* when compared with the same reaction carried out under normal conditions, indicates the "i***soentropic"*** nature of these reactions.

Conclusions

The newly developed heterobimetallic catalysts along with the microwave technology provide better methodology for asymmetric Michael reaction for a variety of substrates in lesser reaction time.

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Experimental

General

The solvents and chemicals used in this work were obtained commercially and were purified using conventional methods. All reactions were carried out in a modified domestic Microwave oven (IFB model 750W). The NMR spectra were recorded on BRUKER 200 MHz instrument. Optical rotations were recorded using an Autopol polarimeter using $CHCl_3$ as solvent at 23°C using the sodium D-line monochromator (2580 A°)

Procedure for the modification of the domestic microwave oven

The commercial domestic microwave oven used in our laboratory was provided with a facility for inserting a reflux condenser and magnetic stirrer (Table 4).

Table 4 . Modifications effected in the domestic microwave oven

Domestic Microwave oven	Modified Microwave oven
1. Rotating plate 2. Leak proof top cover 3. Microwave source (both from the side and top)	1. Removed and magnetic stirrer is fitted 2. Provision made for inserting a reflux condenser (B19 size) 3. Microwave source from one side only.

General experimental procedure for Michael addition reaction using Al – Complex **3**

In an oven dried side arm flask closed with a septum and containing $LiAlH_4$ (0.038 g, 1 mmol) in dry THF (2 mL) was added **3** (0.237 g, 1 mmol) in dry THF (3 mL) at room temperature. The resulting mixture was stirred for one hour. To the stirred solution 2-cyclohexenone (0.490g, 5 mmol) and diethyl malonate, (0.800 g, 5 mmol) were added and the mixture was irradiated in a microwave oven for the stipulated period of time. The reaction was quenched with dil. HCl and extracted with ethyl acetate (3x10 mL). The organic layer was washed with water, followed by saturated. $NaHCO_3$ solution. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent were removed under reduced pressure to yield the product. (1.1 g. 90 % yield, $[\alpha_D{}^o]$=-2.3 ^{o} 78 % *ee*). All the products were identified and characterized by their ^1H and ^{13}C-NMR spectral data and found identical with the literature reported values [11].

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Sample Availability: 100 mg of compounds **1a** and **2a** are available from MDPI