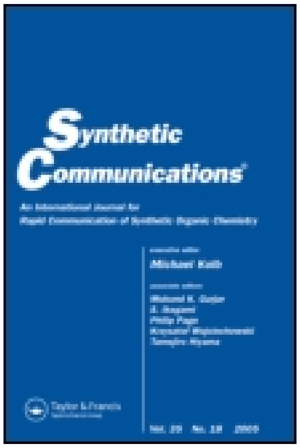

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

MICROWAVE ASSISTED ENANTIOSELECTIVE MICHAEL ADDITION REACTION USING BINOL-Al-Li CATALYST

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To cite this article: S. Narasimhan & S. Velmathi (2002): MICROWAVE ASSISTED ENANTIOSELECTIVE MICHAEL ADDITION REACTION USING BINOL-Al-Li CATALYST, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:24, 3791-3795

To link to this article: http://dx.doi.org/10.1081/SCC-120015397

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SYNTHETIC COMMUNICATIONS
Vol. 32, No. 24, pp. 3791–3795, 2002

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ABSTRACT

Enantioselective (*S*)-BINOL–Al–Li catalyzed Michael reaction of malonates and thiols with cyclic enones are achieved with high enantioselectivity in a remarkably lesser reaction time using microwaves.

Key Words: Microwave irradiation; Michael reaction; Enantioselectivity; Heterobimetallic catalyst

INTRODUCTION

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated carbonyl compounds are among the most widely used methods for C–C bond formation in organic syntheses.[1] Recently Shibasaki[2] and his co-workers introduced a new class of aluminium based BINOL complexes as effective catalysts for Michael addition reactions of malonate esters

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DOI: 10.1081/SCC-120015397
0039-7911 (Print); 1532-2432 (Online)

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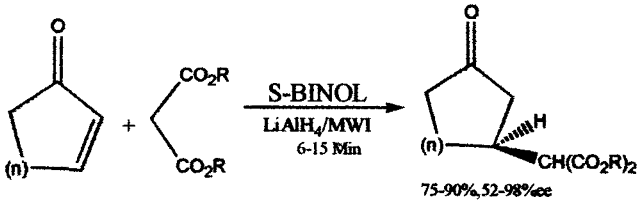
to cyclic enones. But the reactions require long reaction times for completion (72 h).

In recent years, microwave mediated organic reactions[3] have gained importance providing the advantages of short reaction times, reduced amount of solvent and eco-friendly nature of the process. This, coupled with the significance of Michael reaction in asymmetric C–C bond formation, prompted us to study enantioselective Michael addition reaction under microwave irradiation.

RESULTS AND DISCUSSION

We describe here the use of microwave technology in asymmetric Michael addition of malonates to cyclic α,β-unsaturated ketones in the presence of S-BINOL–Al–Li catalyst[4] (Sch. 1).

We adopted a similar procedure reported by Shibasaki[4] for preparing the heterobimetallic catalyst (which contains two different metal ions, Al and Li for coordinating with the reactants after each catalytic cycle). Typically a mixture of cyclohexenone and diethylmalonate was irradiated with microwaves in a domestic microwave oven (IFB model 750 W). After cooling to room temperature, the product was isolated (See Experimental). The experiment was performed with a number of different substrates and the results are presented in the table. Interestingly the reaction was complete within a short period of time (2–15 min) retaining high enantioselectivity (>98%). Although many reports are available on the catalytic asymmetric Michael addition using malonate derivatives, the same using thiols as substrates has not been explored in detail. The only catalyst that has shown reasonably good enantioselectivity in the asymmetric C–S bond formation was made from Lanthanum–sodium–BINOL (LSB).[5] However, the reaction required longer reaction times (from 20 min to 43 h). Hence we explored



MWI = Microwave irradiation

Scheme 1.

Table 1. Asymmetric Michael Adducts of Malonates and Thiols with Cyclic Enones Using S-BINOL-Al-Li Under MWI

		Time		Yield (%)		ee[c] (%)		
Enone	Malonate (R)	Ctrl[a] (h)	MWI[b] (min)	Ctrl	MWI	Ctrl	MWI	$[\alpha]_D^0$ ($c = 5$ in $CHCl_3$)[d]
$n = 1$	Ethyl	72	6	84	82	91	88	−29.75 (+24.2, $c = 1.89$ in $CHCl_3$ 82% ee for the R-isomer
$n = 1$	Isopropyl	–	12	–	80	–	–	−3.1 (–)[e]
$n = 1$	Benzyl	72	10	93	90	91	90	−3.0 (+28.35, $c = 1.89$, $CHCl_3$ 82% ee for the R-isomer)
$n = 2$	Ethyl	72	8	87	90	95	98	−3.50 (+2.9, $c = 2.56$, $CHCl_3$ 81% ee for the R-isomer)
$n = 2$	Isopropyl	46[f]	15	72	75	49	52	−2.78 (+2.3, $c = 1.0$, $CHCl_3$, 49% ee for the R-isomer)
$n = 2$	Benzyl	72	10	88	90	99	90	−1.1 (+1.10, $c = 2.21$, $CHCl_3$, 88% ee for the R-isomer)
	Thiols							
$n = 2$	R=H	30	2	82	88	29	31	−22.5 (−16.4, $c = 1.0$, benzene, 22.5% ee for the S-isomer)
$n = 2$	R=CH_3	25	2	83	85	30	28	−19.6 (+70.00, $c = 2.0$, benzene, 100% ee for the S-isomer)

[a] Ctrl = Control reaction at room temperature stirring.

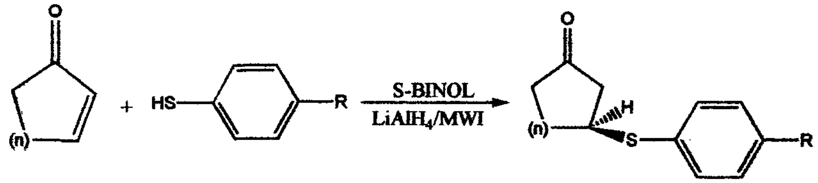
[b] MWI was carried out in pulse of 1 min duration with 30 sec interval.

[c] ee was determined based on the optical rotation values available in the literature see Ref. [4].

[d] Values in the parentheses indicate the reported $[\alpha]_D$ values. See Ref. [4].

[e] Literature $[\alpha]_D$ was not available.

[f] See Ref. [6].



Scheme 2.

the reaction using BINOL–Al–Li under microwave conditions. It was gratifying to note that the addition was complete in a remarkably less time (2 min) with moderate enantioseletivity (31%). The results are presented in Table 1 (Sch. 2).

In conclusion, the BINOL–Al–Li catalyst can be effectively used to promote the asymmetric Michael addition of malonates and thiols under microwave activation in short reaction times and with high enantioselectivity.

EXPERIMENTAL

Reactions were conducted under nitrogen atmosphere in an oven-dried flask closed with a septum. BINOL–Al–Li catalyst was prepared from *S*-BINOL and $LiAlH_4$ by the literature procedure.[4] To 0.5 mmol of BINOL–Al–Li catalyst generated in situ, 5 mmol of 2-cyclohexenone (490 mg, 5 mmol) and diethyl malonate (800 mg, 5 mmol) were added. The reaction mixture was kept under microwave irradiation for the stipulated period of time (See Table 1). The progress of the reaction was monitored by tlc. When all of the malonate had reacted, the reaction mixture was quenched with 1N HCl and extracted with ethyl acetate. The organic layer was washed successively with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a syrupy mass, which on flash column chromatography (using 230–400 mesh type silica gel, Hexane : ethyl acetate (98 : 2) as eluant) gave the product as a colorless oil (1.1 g, 90% yield, $[\alpha]_D^0 = -3.5°$ ee = 98%).

ACKNOWLEDGMENT

The authors thank Prof. T. R. Govindachari for his encouragement and S.V thanks CSIR for financial assistance.

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Received in the USA December 9, 2001

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