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Effect of microwave heating in the asymmetric addition of dimethylzinc to aldehydes

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ABSTRACT

Microwave-heated enantioselective additions of dimethylzinc to various aldehydes are reported. Dramatically reduced reaction times and lower catalyst loadings (5%), compared with conventionally used conditions, can be achieved, with excellent yields and just small loss of enantioselectivity (up to 83% enantioselectivity is achieved). In the reaction with aliphatic aldehydes the same enantioselectivity has been achieved for microwave-heated and conventional room temperature conditions.

1. Introduction

The asymmetric addition of dialkylzinc compounds to aldehydes is today one of the most powerful methodologies to access to optically active secondary alcohols, which are important structural fragments of many natural products and drug compounds [1–3]. Since the initial report of Oguni and Omi in 1983 on the reaction of diethylzinc with benzaldehyde, with 49% enantioselectivity [4], and the synthetic breakthrough of Noyori and coworkers raising the enantioselectivity to 95% (using (−)-3-exo-dimethylaminoisoborneol as ligand) [5], the research on asymmetric organozinc additions to carbonyl compounds has continued receiving attention [6]. In spite of that, there are only very few examples reporting highly enantioselective asymmetric additions of dialkylzincs to aldehydes proceeding rapidly (20–30 min) [7,8]. Most of the published cases require longer reaction times, ranging from several hours to several days [1,9–11]. There are two main approaches to catalyze the reactions of benzaldehyde with diethylzinc and dimethylzinc:1,6 by chiral aminoalcohols, and by chiral diols in combination with Ti(O-*i*Pr)$_4$. The second approach seems to be less efficient, according to the higher catalyst loadings. Particularly slow and difficult are the reactions with the less reactive dimethylzinc. Therefore, methods to accelerate these reactions should be very welcome, provided that a sensible compromise between reaction rate, yield and enantioselectivity can be reached.

Microwave irradiation has become recently a possibility for improving reaction yields and shortening the reaction times [12,13]. Possibly due to the concern that higher reaction temperatures typically lead to reduced enantioselectivities, there are comparatively few reports in the literature involving microwave-heated asymmetric reactions [14–17]. Amongst them, we have reported recently the successful application of microwave heating to asymmetric Pd-catalyzed Suzuki and Negishi reactions [18].

In the lack of precedents of application of microwave irradiation to the enantioselective asymmetric additions of dialkylzincs to aldehydes, we decided to study the reaction system with the sluggish Me_2Zn at higher temperatures induced by a microwave reactor, and compare them with reference reactions with conventional methods, in order to check whether the reactions could be accelerated at a reasonable enantioselectivity cost. Due to the very much lower reactivity of Me_2Zn compared to its higher homologues the development of efficient methodologies for addition of a methyl group to a carbonyl group in short times still remains a challenge.

2. Results and discussion

The synthetic procedure chosen to study representative reactions under microwave heating was the chiral aminoalcohol-catalyzed version (Scheme 1), which is usually more efficient. As chiral catalysts we selected the easily available aminoalcohols **1** and **2**. Both have been reported to give excellent enantioselectivities although in different reaction times. The α-D-xylose derived γ-aminoalcohol 2-*O*-isopropylidene-5-deoxy-5-morpholino-α-D-xylofuranose (**1**) was synthesized according to the literature

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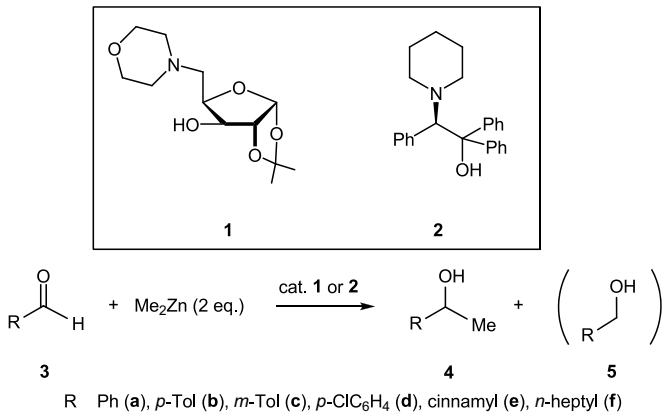

Scheme 1.

procedure [19]. It has been shown to be a very efficient catalyst for the reaction of diethyl- and diisopropylzinc with benzaldehyde (reaction times in the range 10–16 h) [20,21]. The commercially available β-aminoalcohol 2-piperidino-1,1,2-triphenylethanol (**2**) also provides excellent enantioselectivity in the reactions of benzaldehyde with diethyl- and dimethylzinc [8,22].

In order to compare the performance under microwave heated reactions with the original conventional low temperature reactions reported by Cho and Kim, and Pericàs and coworkers, respectively, reactions were carried out setting the other reaction conditions (concentration, solvent amounts and catalyst loadings) exactly according to the original reports [8,20–22]. Moreover, we reproduced some reported reactions in order to make sure that our experimental handling matched the reported work, and also to obtain reference values for unreported reagent concentrations used in our M_w experiments. The active intermediate (presumably a complex of Me_2Zn with **1** or **2**) was formed *in situ* by mixing the corresponding amount of Me_2Zn and **1** or **2**, and stirring for 30 min at room temperature. Then, the aldehyde was added and the reaction was irradiated for the time specified in Table 1, which summarizes the results of the microwave-heated reactions of benzaldehyde with dimethylzinc catalyzed by **1** or **2**, along with some conventional reactions for comparison. Hexane, toluene, or mixtures of both, are known to give the best results in conventional conditions. Thus, the reactions were carried out in toluene with 0.5 mmol/ml concentration of PhCHO, or in a hexane/toluene mixture with 0.2 mmol/ml of PhCHO, using a twofold excess of Me_2Zn, at 75 °C. In all the reactions the formation of reduction byproduct **5** was insignificant.

For the slow ligand **1**, the conventional reaction with benzaldehyde **3a** at room temperature catalyzed by **1** (10 mol%) gives, after 1 week, the product **4a** in 98% yield and 87% ee (Table 1, entry 1). Using ligand **1** in 10 mol% and 20 min irradiation time resulted in a considerable drop in yield (55%) but with a reasonable enantiomeric excess (83%) (Table 1, entry 2). Increasing the reaction time to 1 h improved the yield to 75% without loss of enantioselectivity (Table 1, entry 3). The 2 h reaction resulted in further improved yield of 88%, still with 82% ee (Table 1, entry 4). Finally, for 5 h irradiation time nearly quantitative yield of **5** was reached with 82% enantiomeric excess (Table 1, entry 5). Thus, although there is a reduction of ee from 87% to 82%, the reaction time is dramatically shortened in a ratio 33:1, which may be a reasonable trade-off for particularly difficult reagents.

For the catalysis with ligand **2** at low temperature, the results by Pericàs and coworkers producing **4a** in 87% yield and 94% ee in 24 h, in hexanes/toluene at 0 °C, are almost unbeatable [8,22]. Aimed at testing the microwave-heating methodology we carried out conventional room temperature reactions in 1 h, to compare them with the microwave results in the same time at moderate temperature (75 °C) (Table 1, entries 6–19). In some preliminary tests with benzaldehyde (**3a**), we noted that the use of only toluene as solvent improved the yields compared to the use of hexanes/toluene, so the reactions were made in toluene.

The conventional room temperature reaction of benzaldehyde (**3a**) (Table 1, entry 6) gave only 39% yield and 90% ee in 1 h in toluene. Under 75 °C microwave heating the reaction delivered the product in 98% yield and 82% ee (Table 1, entry 7). The conventional oil bath heated reaction at 75 °C for 1 h produced **4a** with 94% yield and 82% ee (Table 1, entry 8). This result clearly indicates that the acceleration observed is a matter of the higher temperature and not of any special non-thermal microwave effect. The

Table 1
Enantioselective addition of Me_2Zn to aldehydes[a]

Entry	Aldehyde **3**[b]	Ligand (mol%)	Time	Temperature (°C)	Product yield **4**[c] (%)	Reduction product **5** (%)	Ee (%)[d]
1	**3a**	**1** (10)	7 days	r.t.	98 (**4a**)	1	87 (*R*)
2	**3a**	**1** (10)	20 min	75	55 (**4a**)	1	83 (*R*)
3	**3a**	**1** (10)	1 h	75	75 (**4a**)		83 (*R*)
4	**3a**	**1** (10)	2 h	75	88 (**4a**)	1	82 (*R*)
5	**3a**	**1** (10)	5 h	75	97 (**4a**)	1	82 (*R*)
6	**3a**	**2** (10)	1 h	r.t.	39 (**4a**)		90 (*S*)
7	**3a**	**2** (10)	1 h	75	98 (**4a**)	⩽1	81 (*S*)
8	**3a**	**2** (10)	1 h	75 (oil bath)	94 (**4a**)	⩽1	82 (*S*)
9	**3a**	**2** (5)	1 h	75	95 (**4a**)	Traces	80 (*S*)
10	**3b**	**2** (10)	1 h	r.t.	36 (**4b**)	0.7	90 (*S*)
11	**3b**	**2** (5)	1 h	75	82 (**4b**)	1.3	81 (*S*)
12	**3c**	**2** (10)	1 h	r.t.	45 (**4c**)	0.5	90 (*S*)
13	**3c**	**2** (5)	1 h	75	89 (**4c**)	1.6	80 (*S*)
14	**3d**	**2** (10)	1 h	r.t.	55 (**4d**)		89 (*S*)
15	**3d**	**2** (5)	1 h	75	82 (**4d**)		80 (*S*)
16	**3e**	**2** (10)	1 h	r.t.	55 (**4e**)		75 (*S*)
17	**3e**	**2** (5)	1 h	75	96 (**4e**)		66 (*S*)
18	**3f**	**2** (10)	1 h	r.t.	62 (**4f**)	1	65 (*S*)
19	**3f**	**2** (5)	1 h	75	93 (**4f**)	1.5	65 (*S*)

[a] Ratio aldehyde: Me_2Zn = 1:2. Reactions carried out in toluene.
[b] Concentrations: 1 mmol aldehyde in 2 ml of solvent.
[c] Determined by GC analysis.
[d] Determined by GC analysis of the product or of its acetate for **4f**.