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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.

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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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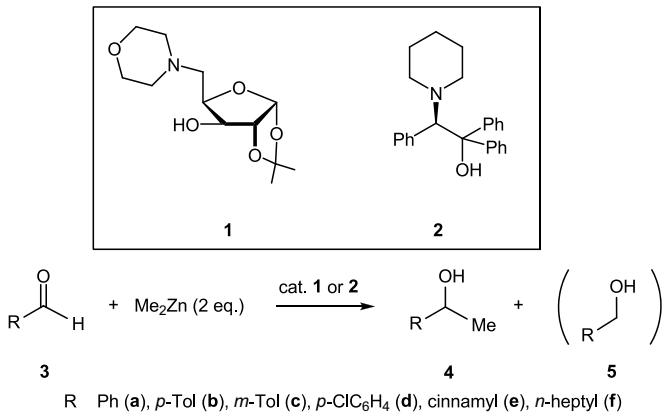

Scheme 1.

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**.

somewhat lower yield (94%) of the classic heating compared to the microwave heating (Table 1, entry 7) could be explained with the higher efficiency and the "bulk heating" ability of the microwaves [23]. It is very important to note that reducing the catalyst loading of **2** to 5% still produced **4a** in 95% yield and 80% ee in 1 h (Table 1, entry 9), while the corresponding room temperature reactions always required 10 mol% of catalyst in order to achieve the maximum product yield of **4a**. At the same time the reduction of the catalyst loading from 10 to 5 mol% never caused a drop of enantioselectivity in our reactions. Obviously, the gain in shortening the time to get a high yield of the reaction is to be weighed against the reduction in selectivity, but still high ee's are obtained an the procedure can be synthetically interesting in particular cases.

In view of the high efficiency achieved with **2** for Me_2Zn addition we decided to study the microwave heated reaction with other aldehydes (**3b**–**f**). In order to better illustrate the microwave acceleration effect we report the reaction results achieved in 1 h at room temperature with 10% ligand, compared with the results obtained in 1 h at 75 °C with only 5% ligand. It should be noted that, in all the cases with the ligand **2** reported in the literature at room temperature, to obtain reaction yields comparable to the values reported here under microwave heating in 1 h, 24 h or higher reaction times are required.

The room temperature reaction of 4-methylbenzaldehyde (**3b**) (Table 1, entry 10) resulted in 36% yield and 90% ee in 1 h with 10 mol% of **2**. Under microwave heating at 75 °C the desired product was obtained in 82% yield and 81% ee (Table 1, entry 11) but with only 5 mol% of the catalyst. With 3-methylbenzaldehyde (**3c**) we obtained similar results: The conventional reaction gives after 1 h **4c** in only 45% yield and 90% ee (Table 1, entry 12) while the microwave version with 5 mol% of **2** for the same time results in 89% product yield and 80% ee (Table 1, entry 13).

The same trend has been demonstrated with the next two aldehydes, 4-chlorobenzaldehyde (**3d**) (Table 1, entry 14 vs. entry 15) and cinnamaldehyde (**3e**) (Table 1, entry 16 vs. entry 17). Generally, in all these cases the enantioselectivity decreases no more than 10% while reaction rate increases dramatically.

The microwave acceleration of the addition of Me_2Zn catalysed by **2** was examined also with an aliphatic substrate. 1-Heptanal **3f** was chosen as a representative of linear chain aldehydes. The standard room temperature reaction gave the product **4f** in 62% yield and 65% ee (Table 1, entry 18), while somewhat more satisfactory conversion of 85% yield and 65% ee took 36 h at room temperature [22]. Remarkably our microwave-accelerated reaction afforded **4f** in 93% yield without any loss of enantioselectivity (65%) (Table 1, entry 19) compared to the reference reaction. In this case the microwave conditions are by all means better than the room temperature conditions. This result may be of importance for further optimization of organozinc addition reactions to aliphatic aldehydes.

3. Conclusions

In summary, we have performed microwave-assisted additions of Me_2Zn to various aldehydes catalyzed by aminoalcohols and have shown that the reactions can be carried out with considerable retention of stereoselectivity in the process, provided that the temperatures are moderate. Obviously this saving of time should be particularly interesting for the slow reagent (Me_2Zn) or for slow ligands (such as **1**). In these cases the use of microwave for performing the enantioselective addition of Me_2Zn to aldehydes is to be considered as a serious alternative. Moreover, it was possible to reduce the ligand loading from 10 mol% to 5 mol% while preserving a high reaction rate and a good enantioselectivity. Remarkably, the enantioselectivity of the reaction with aliphatic aldehydes as heptanal **3f** remains intact compared with the room temperature version.

Additionally, it is worth noting that microwave-heated reactions can be very useful, even in cases when the enantioselectivity achieved was nor satisfactory, for rapid screening to find out reaction conditions for slow reactions. In effect our results suggest that, once the results of the microwave screening are available, moderate (5–10%) but not extraordinary improvement in enantioselectivity should be expected in general for reactions carried out in slower, non-irradiated conditions.

4. Experimental

All reactions were carried out under dry Ar. Hexanes and toluene were dried over sodium and distilled prior to use. Dimethylzinc (2 M in toluene) were purchased from Aldrich. Analytical gas chromatography was performed on a Hewlett Packard 5890 Series II machine equipped with a CHIRASIL-DEX CB (25 m × 0.25 mm × 0.25 mm) capillary column. Microwave-promoted experiments were carried out with a CEM Discover 300W single mode microwave instrument, with simultaneous cooling with compressed air. The reaction mixtures were prepared under dry Ar in 10 ml special glass reaction tubes with self-sealing septa that control the pressure with a pressure sensor on top of the vial. The temperature was monitored through a non-contact infrared sensor centrally located beneath the cavity floor. Magnetic stirring was provided to ensure complete mixing of the reaction mixture. The power applied was 300 W with a ramp time of 1 min.

4.1. General procedure for Me_2Zn addition reaction at room temperature (Table 1)

In a dry 50 ml Schlenk flask with a Young's tap and Teflon stirring bar was introduced the corresponding amount of **1** or **2** and dissolved in 1 ml of toluene. At room temperature, 1 ml of a 2 M toluene solution of Me_2Zn was added. After stirring for 30 min at room temperature, 1 mmol of the corresponding aldehyde **3** was added and the reaction mixture. After 1 h stirring at room temperature the mixture was carefully hydrolyzed with saturated NH_4Cl solution, extracted with Et_2O, filtered trough a short pad of silica and analyzed with GC.

4.2. General procedure for Me_2Zn addition reactions under microwave heating (Table 1)

The corresponding amount of 1 or 2 was dissolved in 1 ml of toluene. At room temperature, 1 ml of a 2 M toluene solution of Me_2Zn was added. After stirring for 30 min at room temperature, 1 mmol of the corresponding aldehyde 3 was added and the reaction vessel was sealed and irradiated at the corresponding temperature and for the time indicated in Table 1. After cooling down the mixture was carefully hydrolyzed with saturated NH_4Cl solution, extracted with Et_2O, filtered trough a short pad of silica and analyzed with GC.

In the case of **4f**, the crude dry reaction mixture was redissolved in Et_3N and then 100 ml of acetyl chloride were added carefully. The mixture was then extracted with diethyl ether, dried, filtered, and analyzed by GC.

4.3. Chiral gas chromatography

For **4d**: isotherm at 120 °C. For all other: 15 min at 100 °C, then at 120 °C with a ramp of 10 °C/min.

Retention times:

3a: t_r = 5.5 min; (*R*)-**4a**: t_r = 18.6 min, (*S*)-**4a**: t_r = 19.8 min; **5a**: t_r = 18.2 min.
3b: t_r = 9.9 min; (+)-**4b**: t_r = 22.6 min, (−)-**4b**: t_r = 24.1 min; **5b**: t_r = 21.6 min.
3c: t_r = 9.4 min; (+)-**4c**: t_r = 24.5 min, (−)-**4c**: t_r = 25.4 min; **5c**: t_r = 23.9 min.
3d: t_r = 7.1 min; (+)-**4d**: t_r = 30.5 min, (−)-**4d**: t_r = 34.8 min; **5d**: t_r = 27.6 min.
3e: t_r = 27.2 min; (+)-**4e**: t_r = 39.5 min, (−)-**4e**: t_r = 40.0 min; **5e**: t_r = 40.5 min.
3f: t_r = 3.6 min; **4f**: t_r = 8.0; acetylated (*S*)-**4f**: t_r = 8.4 min; acetylated (*R*)-**4f**: t_r = 10.4 min; **5f**: t_r = 7.6 min.

The absolute configuration of the products was determined by comparison of the sign of the optical rotation with the literature data [24,25].

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