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# Microwave-accelerated enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines catalysed by β-aminoalcohols with the prolinol skeleton

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ABSTRACT

The addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines in the presence of a catalytic amount of a β-aminoalcohol with the prolinol framework under microwave irradiation gives the expected addition products in good yields and with an ee of up to 92%. The reaction times (20–30 min) are much shorter than the ones observed in the same reactions performed at room temperature without microwave irradiation. In most cases, in the microwave-promoted reactions yields improve and enantiomeric excesses are very close to the ones achieved in the reactions stirred at room temperature. High enantioselectivities are obtained in the addition of dialkylzincs to both aromatic and aliphatic imines.



## 1. Introduction

The addition of organometallic reagents to imines is a valuable method for the synthesis of primary and secondary amines,[1,2] which are important compounds extensively used as resolving agents,[3] starting materials for the preparation of biologically active substances[4] and as chiral auxiliaries in asymmetric synthesis.[5] However, this methodology presents some problems due to the low electrophilic character of the C=N bond. This low electrophilicity of the imine can be overcome by introducing an electron-withdrawing group attached to the nitrogen atom. Amongst the activated imines, *N*-phosphinoylimines have found a variety of synthetic applications, including asymmetric processes.[2,6] Concerning carbon nucleophiles, dialkylzinc reagents are very attractive, since organozinc reagents[7] bearing several functional groups can be easily prepared,[8] which can lead to polyfunctionalised organic compounds after reaction with electrophiles. However, the reaction of *N*-phosphinoylimines with dialkylzincs is very slow, unless some additives are used, such as β-aminoalcohols.[9] In connection with this, we have recently reported the use of easily accesible and inexpensive chiral aminoalcohols with the prolinol skeleton as catalysts for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines.[10] The use of 0.5 equiv of the catalyst led to the expected addition products in a reaction time of only 4 h at room temperature in good yields and with an ee of up to 94%, which is the highest value reported so far using 0.5 equiv of an aminoalcohol as a promoter.

On the other hand, microwave irradiation has proven to be a very efficient technique to accelerate different kinds of reactions.[11] Microwave-heated reactions have been shown to be complete in much shorter reaction times than the ones needed under conventional heating. In a very recent report, microwave heating has been successfully applied to the acceleration of the enantioselective addition of diethylzinc to aromatic aldehydes catalysed by chiral aminonaphthols.[12] This article made us think about the application of microwaves to the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines in the presence of our prolinol derived ligands, since we had demonstrated that those reactions can be heated up without detriment of the enantioselectivity.[10] Thus, we herein report our results on this matter. To the best of our knowledge, this is the first time that microwave irradiation has been applied to this type of addition reaction.

## 2. Results and discussion

We chose the commercially available and inexpensive *N*-benzyl-L-prolinol **1b** (Fig. 1) as a catalyst for the addition of diethylzinc to *N*-(diphenylphosphinoyl)benzaldimine **2a** (Scheme 1). A careful study of this model reaction was performed with the aim of trying to find the optimum reaction conditions. In our first attempt, the reaction catalysed by 0.5 equiv of the ligand **1b** was heated in a microwave reactor (50 °C, 70 W, 0.8 bar) and, to our delight, the expected addition product was obtained in 87% yield and 90% ee (Table 1, entry 1), which was almost equal to the ee that we attained when the same reaction was carried out by stirring at room temperature without microwave irradiation.[10] In order to see if there was any special effect of the microwave irradiation,[11] the

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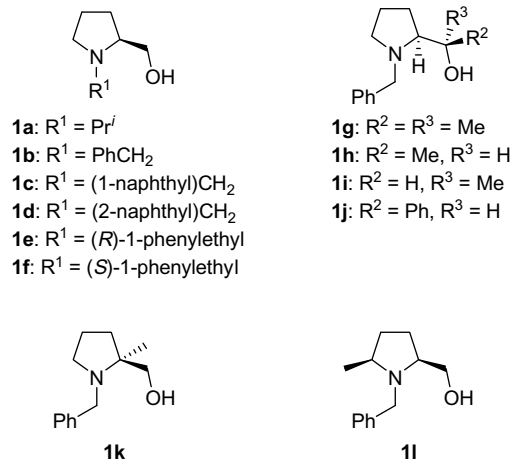
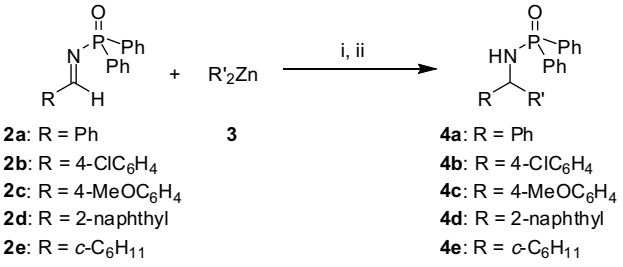



**Figure 1.**




**Scheme 1.** Reagents and conditions: (i) ligand **1** (0.5 equiv), toluene, MW, 50 °C; (ii) $NH_4Cl$ (aq).

reaction was repeated by heating it up in an oil bath at 50 °C. After 20 min, 40% of unreacted starting imine remained (Table 1, entry 2, footnote g). The reaction required 60 min to reach completion and both yield and ee were very similar to the ones obtained in the first experiment. This results show that the difference between the microwave and the conventional heatings is mainly the rate to reach the final temperature of 50 °C, which is higher in the former case. Thus, it seems that there is no special effect of the microwave irradiation in this reaction.

When 0.25 equiv of the ligand **1b** was used as catalyst, the addition product **4aa** was obtained in 70% yield and 80% ee (Table 1, entry 3). The ee is the same as that we had obtained in the reaction with the same amount of the ligand at 50 °C under conventional heating, the time being reduced from 3 h to 30 min.[10] The effect of the concentration of the reaction mixture was investigated and it was found that both the yield and the ee decreased when the concentration was increased (compare entries 1, 4 and 5 in Table 1). A more diluted reaction mixture did not cause almost any detriment to the ee, but the yield was dramatically reduced (compare entries 1 and 6 in Table 1). The ideal temperature turned out to be 50 °C. The reaction irradiated to reach a temperature of 70 °C (120 W, 1.1 bar) gave a lower yield and ee with a reaction time of 10 min (Table 1, entry 7). When the temperature control of the microwave reactor was set up to 40 °C (70 W, 0.3 bar), the ee was the same as for the reaction at 50 °C, but the yield decreased considerably (Table 1, entry 8). Finally, we tried to reduce the amount of diethylzinc using 1 equiv of the catalyst in order to maintain a fast reaction; the yield and the ee were slightly lower (Table 1, entry 9) than in the first experiment. According to all of these results, we chose as the optimum reaction conditions the ones corresponding to entry 1.

**Table 1**
Microwave-promoted enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine **2a** in the presence of aminoalcohol **1b** (optimisation of the reaction conditions[a])

| Entry | Equiv of **1b** | Toluene[b] (mL) | *T* (°C) | Time (min) | Product **4aa** | | |
|---|---|---|---|---|---|---|---|
| | | | | | Yield[c] (%) | ee[d] (%) | Configuration[e] |
| 1 | 0.5 | 1.3 | 50 | 20 | 87[f] | 90 | (*R*) |
| 2 | 0.5 | 1.3 | 50[g] | 60 | 89 | 86 | (*R*) |
| 3 | 0.25 | 1.3 | 50 | 30 | 70 | 80 | (*R*) |
| 4 | 0.5 | 0.5 | 50 | 20 | 52 | 86 | (*R*) |
| 5 | 0.5 | — | 50 | 10 | 56 | 84 | (*R*) |
| 6[h] | 0.5 | 1.3 | 50 | 30 | 40 | 88 | (*R*) |
| 7 | 0.5 | 1.3 | 70 | 10 | 61 | 82 | (*R*) |
| 8 | 0.5 | 1.3 | 40 | 40 | 50 | 90 | (*R*) |
| 9[i] | 1 | 1.3 | 50 | 20 | 82 | 86 | (*R*) |

[a] All reactions were performed by microwave irradiation of a mixture of imine **2a** (0.25 mmol), ligand **1b** and diethylzinc (0.75 mmol) in anhydrous toluene under argon during the time indicated.
[b] Volume of anhydrous toluene in which imine **2a** and ligand **1b** were dissolved prior to the addition of the solution of $Et_2Zn$.
[c] Yield estimated by $^1H$ NMR using diphenylformamide as an internal standard.
[d] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column.
[e] The absolute configuration of the major enantiomer was determined by the comparison of the sign of the specific rotation of the free primary amine with the one reported in the literature.
[f] Isolated yield after column chromatography (silica gel, hexane/acetone) based on starting imine **2a**. The isolated compound was ⩾95% pure (GC and/or 300 MHz $^1H$ NMR).
[g] The reaction was heated in an oil bath without microwave irradiation. After 20 min, 40% of the unreacted starting imine was still present.
[h] The reaction was performed with 0.13 mmol of imine **2a** and 0.38 mmol of $Et_2Zn$.
[i] 0.50 mmol of $Et_2Zn$ was used.

The versatility of our procedure concerning the dialkylzinc reagent and the starting imine was then studied. All of the imines **2** were prepared from the corresponding aldehydes according to literature procedures.[13] Table 2 collects the results of the addition of several dialkylzinc reagents to imine **2a** and the addition of diethylzinc to imines **2b–e** (Scheme 1). In all cases, 0.5 equiv of ligand **1b** was used as a catalyst. For the sake of comparison, the isolated yields and ees that we had obtained in our previous articles[10] for the same reactions stirred at room temperature without microwave irradiation are also reported in brackets in columns 6 and 7 of Table 2. As it can be seen, in most cases, the yields of the microwave-promoted reactions were higher than the ones corresponding to the reactions stirred at room temperature (Table 2, entries 1–6 and 8). Concerning the enantioselectivities, a very slight decrease (⩽4%) was observed when the reactions were irradiated by microwaves (Table 2, entries 1 and 3–8), the ees in all cases being in the range of 86–92%. The case of the addition of dimethylzinc to imine **2a** is remarkable (Table 2, entry 2): although it has been reported that dimethylzinc is much less reactive than diethylzinc,[9c,d,10] the reaction time in this case was only 30 min using 9 equiv of dimethylzinc and both yield and ee improved in comparison with the reaction at room temperature. All imines derived from aromatic aldehydes gave very good ees irrespective of the electronic nature of the substituents on the aromatic ring (Table 2, entries 5–7). The ee of the addition product to the aliphatic imine **2e**, derived from cyclohexanecarbaldehyde, was of the same level as the ones obtained with the aromatic imines (88%, Table 2, entry 8).

We also attempted to use the activated ketimine **5** (Fig. 2) as a substrate, but the reaction of this imine with dimethylzinc (9 equiv) in the presence of aminoalcohol **1b** (0.5 equiv) did not work, the unaltered starting material being recovered after 30 min of irradiation by microwaves.

Having established that microwave irradiation is an efficient technique to promote the addition of dialkylzinc reagents to several *N*-(diphenylphosphinoyl)imines in the presence of

**Table 2**
Microwave-promoted enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines **2** in the presence of *N*-benzyl-L-prolinol **1b** (preparation of compounds **4**[a])

| Entry | Imine | R′ | Time (min) | Product | | | |
|---|---|---|---|---|---|---|---|
| | | | | No. | Yield[b] (%) | ee[c] (%) | Configuration[d] |
| 1 | **2a** | Et | 20 | **4aa** | 87 (79) | 90 (92) | (*R*) |
| 2[e] | **2a** | Me | 30 | **4ab** | 67 (51)[f] | 92 (90)[f] | (*R*) |
| 3 | **2a** | $Pr^i$ | 20 | **4ac** | 97 (80) | 87 (90) | (*R*) |
| 4 | **2a** | $Bu^n$ | 20 | **4ad** | 80 (64)[g] | 88 (90)[g] | (*R*) |
| 5 | **2b** | Et | 20 | **4b** | 82 (80) | 86 (90) | (*R*) |
| 6 | **2c** | Et | 20 | **4c** | 77 (71)[h] | 88 (92)[h] | (*R*) |
| 7 | **2d** | Et | 20 | **4d** | 85 (86) | 88 (90) | (*R*) |
| 8 | **2e** | Et | 20 | **4e** | 52 (36) | 88 (90) | (*R*) |

[a] All reactions were performed by microwave irradiation of a mixture of imine **2** (0.25 mmol), ligand **1b** (0.13 mmol) and diethylzinc (0.75 mmol) in anhydrous toluene (1.3 mL) under argon, at 50 °C, during the time indicated.

[b] Isolated yield after column chromatography (silica gel, hexane/acetone) based on the starting imine **2**. All isolated compounds **4** were ⩾95% pure (GC and/or 300 MHz $^1$H NMR). In brackets, the isolated yield of the product **4** obtained when the same reaction was stirred for 4 h at room temperature without microwave irradiation is shown.

[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column or a Chiralpak AD column. In brackets, enantiomeric excess of the product **4** obtained when the same reaction was stirred for 4 h at room temperature without microwave irradiation.

[d] The absolute configuration of the major enantiomer was determined by comparison of the sign of the specific rotation of the free primary amine with the one reported in the literature. The absolute configuration of the major enantiomer was the same in both the microwave-promoted reactions and the reactions stirred at room temperature without microwave irradiation.

[e] 9 equiv of $Me_2Zn$ was used in this reaction.

[f] Yield and ee in brackets correspond to the reaction stirred at room temperature for 72 h without microwave irradiation, using 9 equiv of $Me_2Zn$.

[g] Yield and ee in brackets correspond to the reaction stirred at room temperature for 24 h without microwave irradiation.

[h] Yield and ee in brackets correspond to the reaction stirred at room temperature for 12 h without microwave irradiation.

**Table 3**
Microwave-promoted enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)benzaldimine **2a** in the presence of aminoalcohols **1**[a]

| Entry | Ligand | Time (min) | Product **4aa** | | |
|---|---|---|---|---|---|
| | | | Yield[b] (%) | ee[c] (%) | Configuration[d] |
| 1 | **1a** | 20 | 80 (80) | 82 (84) | (*R*) |
| 2 | **1b** | 20 | 87 (79) | 90 (92) | (*R*) |
| 3 | **1c** | 20 | 72 (70) | 78 (80) | (*R*) |
| 4 | **1d** | 20 | 82 (85) | 66 (90) | (*R*) |
| 5 | **1e** | 30 | 54 (66)[e] | 40 (60)[e] | (*R*) |
| 6 | **1f** | 20 | 85 (80) | 90 (94) | (*R*) |
| 7 | **1g** | 30 | 63 (45)[f] | 56 (60)[f] | (*R*) |
| 8 | **1h** | 20 | 84 (73) | 92 (94) | (*R*) |
| 9 | **1i** | 30 | 48 (35)[f] | 60 (66)[f] | (*R*) |
| 10 | **1j** | 20 | 88 (76)[g] | 92 (88)[g] | (*R*) |
| 11 | **1k** | 20 | 87 (86) | 86 (90) | (*R*) |
| 12 | **1l** | 30 | 87 (62)[e] | 48 (60)[e] | (*R*) |

[a] All reactions were performed by microwave irradiation of a mixture of imine **2a** (0.25 mmol), ligand **1** (0.13 mmol) and diethylzinc (0.75 mmol) in anhydrous toluene (1.3 mL) under argon, at 50 °C, during the time indicated.

[b] Isolated yield after column chromatography (silica gel, hexane/acetone) based on the starting imine **2a**. All isolated compounds were ⩾95% pure (GC and/or 300 MHz $^1$H NMR). In brackets, the isolated yield of the product **4aa** obtained when the same reaction was stirred for 4 h at room temperature without microwave irradiation is shown.

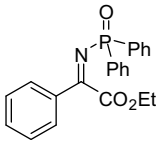
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column. In brackets, enantiomeric excess of the product **4aa** obtained when the same reaction was stirred for 4 h at room temperature without microwave irradiation.

[d] Absolute configuration of the major enantiomer determined by comparison of the sign of the specific rotation of the free primary amine with the one reported in the literature. The absolute configuration of the major enantiomer was the same in both the microwave-promoted reactions and the reactions stirred at room temperature without microwave irradiation.

[e] Yield and ee in brackets correspond to the reaction stirred at room temperature for 6 h without microwave irradiation.

[f] Yield and ee in brackets correspond to the reaction stirred at room temperature for 24 h without microwave irradiation.

[g] Yield and ee in brackets correspond to the reaction stirred at room temperature for 7 h without microwave irradiation.




**5**

**Figure 2.**

aminoalcohol **1b**, we decided to test all the other substituted prolinols **1a** and **1c–l** (Fig. 1) (shown to be active in our previous reports[10]) as catalysts (0.5 equiv) for the reaction between imine **2a** and diethylzinc (3 equiv). The results of these reactions are collected in Table 3. As shown above for Table 2, we have included in brackets in columns 4 and 5 of Table 3, the isolated yields and ees that we obtained previously[10] for the same reactions stirred at room temperature without microwave irradiation. As it was the case for the reactions catalysed by ligand **1b**, in most cases the yields improved when the reactions were performed under microwave irradiation (Table 3, entries 1–3 and 6–12). The ees were also slightly reduced under microwave heating in comparison with the experiments at room temperature (Table 3, entries 1–3 and 6–11), with the exception of ligands **1d**, **1e** and **1l** for which higher losses of ee were observed (Table 3, entries 4, 5 and 12).

The microwave-promoted reactions showed the same trend of variation of the enantioselectivity as a function of the substituents on the ligand as for the reactions at room temperature. The ee improved with the size of the nitrogen substituent (Table 3, entries 1 and 2). The presence of an aromatic ring in $R^1$ seems to be important, since *N*-benzylprolinol **1b** gave 90% ee (Table 3, entry 2). Substitution of the phenyl group by either a 1-naphthyl or a 2-naphthyl group reduced the enantioselectivity (Table 3, entries 3 and 4). These results are different to the ones previously obtained in the reactions stirred at room temperature: in this case, ligand **1d**, bearing a 2-naphthyl group, gave an ee very close to the one obtained with *N*-benzylprolinol **1b**.[10] Introduction of a methyl group on the α-carbon atom of the benzylic substituent at nitrogen also affected the enantioselectivity. The (*S*)-1-phenylethyl substituent of ligand **1f** did not cause any reduction in the enantioselectivity in comparison to ligand **1b** (Table 3, entry 6), whereas the (*R*)-1-phenylethyl substituent gave an ee of 40% (Table 3, entry 5), much lower than the one obtained with the unsubstituted benzyl group.

As was previously observed,[9c,d,10] the enantioselectivity decreased upon increasing the size of the $R^2$ substituent (compare entries 2 and 7 in Table 3). A comparison of entries 8 and 9 in Table 3 shows the importance of the absolute configuration of the stereogenic centre introduced in ligands **1h–j**: ligand **1h**, having an (*R*) configuration, gave product **4aa** in good yield and with 92% ee, whereas the ligand with an (*S*)-carbinol carbon **1i** afforded the addition product in low yield and only 60% ee. Ligand **1j**, with a phenyl group instead of methyl at the carbinol site, gave the same ee of 92% (Table 3, entry 10), which is the highest one that was achieved in all our microwave-promoted experiments. Concerning the effect of further steric bulkiness close to the nitrogen atom of the ligand, no additional benefits were achieved by the introduction of a methyl group at C2 of the pyrrolidine ring, since the ee (86%, Table 3, entry 11) was slightly lower than the one obtained with *N*-benzylprolinol **1b**. The introduction of a methyl group at

C5 of the pyrrolidine ring of the ligand was detrimental to the enantioselectivity, giving only 48% ee (Table 3, entry 12). The latter ee is rather lower than the one that was obtained for the same reaction at room temperature (60%).[10]

Since most of the results of these microwave-heated reactions show the same trends for the influence of the ligand substituents on the enantioselectivity as for the reactions stirred at room temperature without microwave irradiation, we assume that the same mechanism could be operative in both cases. The acceleration of the reactions observed could just be a result of the fast heating caused by microwaves. This fast heating could also accelerate the reaction between the dialkylzinc reagent and the imine without any participation of the ligand, which could explain the small loss of ee that was observed in most cases in comparison to the reactions at room temperature.

## 3. Conclusions

In conclusion, we have reported that microwave irradiation is a very efficient technique to accelerate the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines in the presence of several β-aminoalcohols with the prolinol skeleton. Very fast enantioselective addition reactions can be achieved using 0.5 equiv of the ligand. Reaction times are very short (20–30 min) and the expected addition products are obtained with improved yields and with ees very similar to the ones previously observed in the same reactions performed at room temperature without microwave irradiation. This procedure is especially useful for the addition of dimethylzinc, since both yield and ee improved in the microwave-promoted reaction and the reaction time was only 30 min.

## 4. Experimental

### 4.1. General

For general experimental information, see Ref. 14. Imines **2** were prepared according to literature procedures.[13] Commercially available compound **1b** {Aldrich, 99%, $[\alpha]_D^{20} = -72.2$ (neat)} was used as received. The rest of the ligands **1a** and **1c–l** were prepared as previously described by us.[10b] Optical rotations were measured on a Perkin–Elmer 341 polarimeter. HPLC analyses were performed at 25 °C on a JASCO apparatus, equipped with a PU-2089 Plus pump, a MD-2010 Plus detector and an AS-2059 Plus automatic injector. Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. The temperature of the reaction mixture was monitored using a calibrated infrared temperature control under the reaction vessel, and control of the pressure was performed with a pressure sensor connected to the septum of the vessel.

### 4.2. Addition of dialkylzinc reagents to imines 2 catalysed by ligands 1. Preparation of compounds 4. General procedure

The dialkylzinc reagent (0.75 mmol) was added to a stirred solution of imine **2** (0.25 mmol) and ligand **1** (0.13 mmol) in anhydrous toluene (1.3 mL) under argon at room temperature. The reaction vessel was placed into the microwave reactor and was heated to 50 °C (constant microwave irradiation at 70 W, 0.8 bar, with air stream cooling) for 20 or 30 min (see Tables 2 and 3). The reaction was then hydrolysed with an aqueous saturated solution of $NH_4Cl$ (2 mL). Water (2 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (5 mL), and then dried ($Na_2SO_4$). After filtration and evaporation of the solvents, the crude residue was purified by column chromatography (silica gel, hexane/acetone) to give products **4** in the yields and enantiomeric excesses indicated in Tables 2 and 3. Compounds **4** were characterised by comparison of their physical and spectroscopic data with the ones reported in the literature.[10b] These products were analysed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent and a flow rate of 0.5 mL/min or on a Chiralpak AD column using a 254 nm UV detector, 20% *i*-PrOH in hexane as eluent and a flow rate of 1.0 mL/min. The retention times were reported in our previous article.[10b] The absolute configuration of the major enantiomer of **4aa** was determined by hydrolysis of it[9c] and comparison of the sign of the specific rotation of the free amine obtained with the reported data.[9c] The absolute configuration of the major enantiomer of **4ab–ad** was tentatively assigned according to the order of elution of the two enantiomers in the HPLC analysis on the analogy of product **4aa**. For addition products **4b–d**, the absolute configuration of the major enantiomer was tentatively assigned according to the HPLC data described in the literature for similar compounds under the same conditions.[15] The retention times of the two enantiomers of compound **4e** have already been described.[15]

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