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N-Benzyl-L-prolinol: an efficient catalyst for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines

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This paper is dedicated to Professors Juan Forniés and José Gimeno on occasion of their 60th anniversary†

Abstract—Commercially available *N*-benzyl-L-prolinol has shown to be a very efficient catalyst for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines. The use of 0.5 equiv of this β-aminoalcohol as a catalyst leads to the expected addition products in good yields and with ees up to 92% in a reaction time of only 4 h at room temperature. This ee is almost equal to the highest value reported so far using 0.5 equiv of an aminoalcohol as promoter, although the reaction time is much shorter in our case. The amount of the catalyst can be reduced to 0.25 equiv with a slight decrease in the ee. An interesting effect of the addition rate and temperature on the enantioselectivity has been observed.

1. Introduction

Optically active amines are important compounds extensively used as resolving agents,[1] starting materials for the preparation of biologically active substances[2] and chiral auxiliaries in asymmetric synthesis.[3] In recent years, there has been a great interest in the development of methodologies for their asymmetric preparation. The addition of organometallic reagents to imines is a valuable method for the synthesis of primary and secondary amines.[4,5] However, it presents some problems due to the low electrophilic character of the C=N bond and to the tendency of enolizable imines to undergo α-deprotonation instead of addition. The electrophilicity of the imine can be enhanced by introducing an electron-withdrawing group attached to the nitrogen atom, such as the phosphinoyl group. *N*-Phosphinoylimines[6] are very attractive since the phosphinoyl group can easily be removed from the addition products under mild reaction conditions, leading to the free amines.[7] *N*-Phosphinoylimines have found a variety of synthetic applications, including asymmetric processes.[5] Among the carbon nucleophiles, dialkylzinc reagents are very useful since organozinc reagents[8] bearing several functional groups can be easily prepared,[9] and can lead to polyfunctionalised organic compounds. However, the reaction of *N*-phosphinoylimines with dialkylzincs is very slow, leading to low yields of addition products with very long reaction times. Improved reaction rates and much higher yields have been observed by using some additives such as β-aminoalcohols,[7,10] iminoalcohols,[10j] hydroxyoxazolines[11] and copper,[12] zirconium[13] or nickel[14] complexes. Concerning chiral β-aminoalcohols, there is a trend to believe that a rigid backbone in the ligand is generally required to obtain a high enantioselectivity.[7,10c,e–g] However, the synthesis of structurally rigid aminoalcohols often involves a multistep process, which makes the procedure inconvenient and expensive. The development of easily accessible and inexpensive chiral ligands is thus very interesting. Herein, we report our preliminary results on the use of the simple and commercially available aminoalcohol *N*-benzyl-L-prolinol as an efficient catalyst for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines.

2. Results and discussion

We decided to test *N*-benzyl-L-prolinol **1** (Fig. 1) as a promoter of the addition of dialkylzincs to *N*-(diphenylphosphinoyl)imines for three reasons: (a) the prolinol

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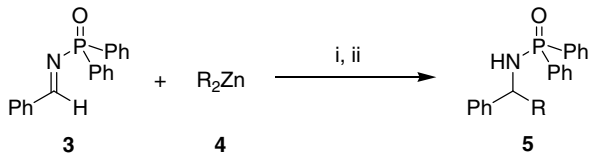
substructure can be found in the ligands with 2-azanorbornylmethanol framework **2** (Fig. 1) that have been successfully applied as catalysts for the same reaction;[10c,e,g] (b) ligands with a prolinol skeleton have given good enantioselectivities in several asymmetric processes;[15] and (c) ligand **1** is commercially available and inexpensive and can be easily prepared in two steps from the readily accessible natural aminoacid L-proline.

1 **2**

Figure 1.

In the first experiment, diethylzinc (3 equiv) was added dropwise to a solution of benzaldimine **3** (Scheme 1) and ligand **1** (1 equiv) in toluene at 0 °C during ca. 10 min. The reaction was stirred allowing the temperature to rise to room temperature and, after 24 h, a disappointing 74% ee was obtained (Table 1, entry 1), which was lower than the one reported for the analogous ligand with 2-azanorbornylmethanol skeleton **2** ($R^1 = PhCH_2$, $R^2 = H$; 91% ee).[10c,16] However, when diethylzinc was slowly added over 3 h using a syringe pump, the ee increased to 86% (Table 1, entry 2). Gratifyingly, we decided to screen the reaction conditions further. Since yields were only moderate in both cases, we repeated the reaction using 9 equiv of diethylzinc instead of 3 and the yield improved to 84% with almost the same enantioselectivity as before, with the time needed for completion of the reaction being much shorter (8 h; Table 1, entry 3).

Next, we studied the effect of temperature. When the addition of diethylzinc (9 equiv in 3 h) to imine **3** in the presence of ligand **1** (1 equiv) was stirred for 24 h at 0 °C, the reaction did not go to completion and the ee decreased to 58% (Table 1, entry 4). However, when the addition of diethylzinc was performed at room temperature, the expected addition product was obtained in only 4 h with 89% yield and 92% ee, which was slightly higher than the one reported for the rigid ligand **2** ($R^1 = PhCH_2$, $R^2 = H$; 91% ee).[10c] Since the reaction was quite fast under these conditions, we thought about reducing the amount of diethylzinc. Setting up the reaction with 3 equiv of it and maintaining the addition rate, the same ee of 92% was obtained in 4 h, although the yield decreased to 60% (Table 1, entry 6). Since we had observed before that the addition rate was very important for the enantioselectivity, we repeated the last experiment with addition times of 10 min and 2 h. In the first case, the reaction was completed in 4 h and the addition product was isolated in 79% yield and 92% ee (Table 1, entry 7). Lenghtening the addition time to 2 h caused a decrease in both yield and ee (Table 1, entry 8). When the reaction under the conditions of entry 7 was set up at 50 °C (oil bath temperature) instead of room temperature, it was finished in only 1 h, affording the expected product in 96% yield and 90% ee (Table 1, entry 9). We were pleased by this result, since, to the best of our knowledge, this is the fastest addition reaction of diethylzinc to imine **3** that has ever been reported using an aminoalcohol as promoter.



3 **4** **5**

Scheme 1. Reagents and conditions: (i) ligand **1** (1–0.25 equiv), toluene, T; (ii) NH_4Cl (aq).

The possibility of using a substoichiometric amount of the ligand was then investigated. We were pleased to see that we obtained the same result using either 0.5 or 1 equiv of ligand **1** (compare entries 7 and 10 in Table 1). The ee of 92% is almost equal to the highest ee reported so far using this amount of an aminoalcohol (93%)[10j] and our reaction was much faster (4 h instead of 48 h). With 0.25 equiv of the ligand, the reaction time increased to 20 h and the ee decreased to 80%. However, when the reaction temperature was 50 °C instead of 25 °C, the same results were achieved and the reaction was finished in only 3 h (compare entries 11 and 12 in Table 1). It is worth noting that, to the best of our knowledge, this is the fastest reaction of this type reported so far using 0.25 equiv of an aminoalcohol as catalyst with the ee obtained close to the highest ee reported in the literature for that amount of the ligand (85%).[10c]

The versatility of our procedure concerning the dialkylzinc reagent was also studied. Dimethyl-, diisopropyl- and dibutylzinc were used as nucleophiles for the addition to imine **3** under the reaction conditions of entry 10 in Table 1. As previously reported,[7,10c] dimethylzinc turned out to be much less reactive than diethylzinc. The use of 9 equiv was necessary in order to obtain a moderate yield of the addition product in 3 days at room temperature, but 90% ee was obtained (Table 1, entry 13). Setting up the reaction at 50 °C led to an improved yield (74%) in only 1 day with a very slight decrease in the ee (Table 1, entry 14). Diisopropylzinc was as efficient as diethylzinc, giving good yield and enantioselectivity in a reaction time of only 4 h (Table 1, entry 15). The reaction with dibutylzinc also required a longer time to reach completion, affording the addition product in 64% yield and 90% ee (Table 1, entry 16). The same reaction at 50 °C improved both the reaction rate and yield with almost the same enantioselectivity (Table 1, entry 17).

As described above, by proper choice of the reaction conditions, *N*-benzyl-L-prolinol was shown to be a catalyst for the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)benzaldimine even more effective than the analogous bicyclic ligand **2**. It is worth noting that the enantiomer of ligand **1** is also commercially available, which provides the opportunity of preparing both enantiomers of the final amine products. Further efforts to improve the enantioselectivity by introducing different substituents on the ligand, to extend the substrate scope and to elucidate the mechanism of the reaction are currently underway in our laboratories.

Table 1. Enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imine **3** in the presence of aminoalcohol **1**: preparation of compounds **5**

Entry	R_2Zn		Equiv of **1**	*T* (°C)	Add. time (h)[a]	Time (h)	Product			
	R	Equiv					No.	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	Et	3	1	0 to 25	0.2	24	**5a**	52	74	(*R*)
2	Et	3	1	0 to 25	3	24	**5a**	48	86	(*R*)
3	Et	9	1	0 to 25	3	8	**5a**	84	84	(*R*)
4	Et	9	1	0	3	24	**5a**	45	58	(*R*)
5	Et	9	1	25	3	4	**5a**	89	92	(*R*)
6	Et	3	1	25	1	4	**5a**	60	92	(*R*)
7	Et	3	1	25	0.2	4	**5a**	79	92	(*R*)
8	Et	3	1	25	2	4	**5a**	48	76	(*R*)
9	Et	3	1	50	0.2	1	**5a**	96	90	(*R*)
10	Et	3	0.5	25	0.2	4	**5a**	79	92	(*R*)
11	Et	3	0.25	25	0.2	20	**5a**	76	80	(*R*)
12	Et	3	0.25	50	0.2	3	**5a**	75	80	(*R*)
13	Me	9	0.5	25	0.2	72	**5b**	51	90	(*R*)
14	Me	9	0.5	50	0.2	24	**5b**	74	88	(*R*)
15	Pr^i	3	0.5	25	0.2	4	**5c**	80	90	(*R*)
16	Bu^n	3	0.5	25	0.2	24	**5d**	64	90	(*R*)
17	Bu^n	3	0.5	50	0.2	4	**5d**	86	88	(*R*)

[a] Period of time during which the dropwise addition of the dialkylzinc reagent to the solution of **1** and **3** was performed.
[b] Isolated yield after column chromatography (silica gel, pentane/acetone) based on starting imine **3**. All isolated compounds **5** were $\geqslant$ 95% pure (GC and/or 300 MHz ^{1}H NMR).
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column.
[d] Absolute configuration of the major enantiomer determined by comparison of the specific rotation of the free primary amine with the one reported in the literature.

3. Conclusions

In conclusion, we have reported that *N*-benzyl-L-prolinol is an efficient catalyst for the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imine **3** in short reaction times and with good ee. Fast enantioselective addition reactions can be achieved using 0.5 equiv of the ligand. Our results show the importance of carefully screening the reaction conditions to get high levels of enantioselectivity in this reaction. Another important conclusion is that a rigid structure in the ligand is not always a requisite to obtain high enantioselectivities. An interesting effect of the addition rate and temperature on the enantioselectivity has been observed. Moreover, it is possible to improve both the reaction rates and yields by setting up the experiments at 50 °C with only a very slight decrease in the enantioselectivity.

4. Experimental

Typical experimental procedure: diethylzinc (1.5 mmol, 1.4 mL of a 1.1 M solution in toluene) was added dropwise over ca. 10 min to a stirred solution of imine **3** (153 mg, 0.5 mmol) and ligand **1** (48 mg, 0.25 mmol) in anhydrous toluene (3 mL) under argon at room temperature. After stirring for 4 h, the reaction was hydrolysed with an aqueous saturated solution of NH_4Cl (5 mL). Water (5 mL) was added and the mixture then extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (5 mL), and then dried over Na_2SO_4. After filtration and evaporation of the solvents, the crude residue was purified by column chromatography (silica gel, pentane/acetone), to give product **5a** in 79% yield as a white solid. This product was 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. The retention times were 13.7 (*R*) and 18.0 (*S*). The absolute configuration of the major enantiomer was determined by hydrolysis of product **5a**[7] and comparison of the specific rotation of the free amine obtained with the reported data.[7]

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16. Note that the absolute configuration of the major enantiomer in Ref. 10c is (*S*), opposite to the one obtained in our case, due to the fact that the prolinol substructure found in ligand **2** ($R^1 = PhCH_2$, $R^2 = H$) is enantiomeric with respect to our ligand **1**.