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Chiral tridentate versus bidentate pyridines as catalysts in the enantioselective alkylation of benzaldehyde with diethylzinc

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Abstract—Comparison of the enantioselectivity obtained with either bidentate or tridentate chiral pyridine derivatives demonstrated that both can be very efficient catalysts for the enantioselective addition of diethylzinc to benzaldehyde. This comparison also provided insights for the design of efficient new catalysts based on pyridine.

Chiral secondary alcohols are key intermediates in the preparation of many biologically active compounds, especially drugs. Enantioselective synthesis of such alcohols has thus become a major field of investigations in recent years. Among the possible strategies, the reaction of aldehydes with organometallic species modified using chiral ligands is one of the more attractive.[1] In this area, dialkylzinc addition catalyzed by amino alcohols has been extensively studied and remains an active research area.[2–4]

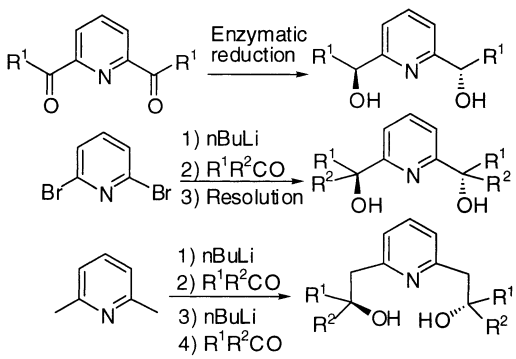
β-Amino alcohols have been the major class of chiral ligands investigated.[3,4] Two adjacent coordinating sites seem to facilitate the formation of the active zinc catalyst and induce enantioselectivity during the addition through a well organized bimetallic zinc species.[2,5,6] Ligands having three sites of coordination have been far less studied,[3b] although they should confer rigidity to the reactive zinc catalyst and may thus enhance the enantioselectivity of the addition reaction.

In this communication, we have compared for the first time the enantioselectivity obtained with chiral pyridine derivatives of similar structures but acting either as bidentate or tridentate ligands. We demonstrated here that chiral tridentate pyridines are indeed very efficient catalysts for the addition of diethylzinc to benzaldehyde, but no more so than the analogous chiral bidentate pyridines. We also highlight the requirements for an efficient catalyst based on pyridine.

Bidendate ligands based on a pyridine nucleus have already been investigated, although far less than amino alcohols.[3] Chiral tridentate pyridine derivatives have not been studied extensively and, to our knowledge, no comparison between these two types of ligand has been reported.[3b]

C_2-Symmetric chiral tridentate pyridines can easily be obtained either by enzymatic[7] or hydride[8] reductions of prochiral diketones or by standard alkylation followed by resolution[9] (Scheme 1). The results obtained with such pyridines as catalytic ligands for the addition of diethylzinc to benzaldehyde are collected in Table 1.

1,6-Bis(1-hydroxyalkyl)pyridines **1a–c** proved to be effective catalysts for the addition of diethylzinc to



Scheme 1.

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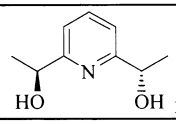
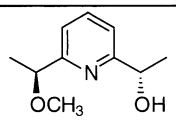
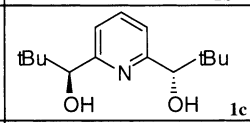
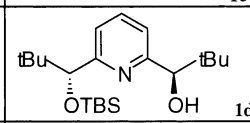
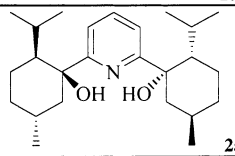
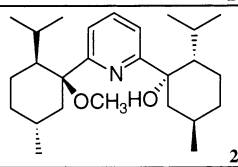
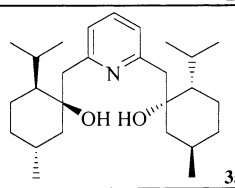
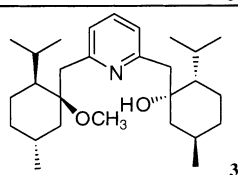
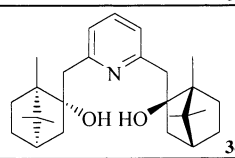
Table 1. Diethylzinc addition to benzaldehyde catalyzed by tridentate chiral ligands. Hex = hexane; Tol = toluene[13]

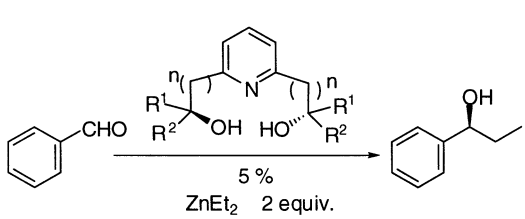
	Ligands	Solv.	Yield (%)	E.e. (%)	Conf
1	 **1a**	Hex	84	4	*S*
2	 **1b**	Hex	83	47	*S*
3	 **1c**	Hex	77	65	*S*
4[10]	 **1d**	Hex	79	67	*R*
5 6 7	 **2a**	Tol Hex PhH	81 " "	42 55 39	*S* " "
8	 **2b**	Hex	81	35	*S*
9 10 11	 **3a**	Tol Hex PhH	76 " "	95 93 "	*S* " "
12	 **3b**	Hex	84	95	*S*
13	 **3c**	Hex	78	75	*R*

benzaldehyde. However, the enantioselectivity was dramatically influenced by the bulk of the substituents about the hydroxyl group. The lowest member of this family of pyridine derivatives **1a**[7] induced very low enantioselectivity with a slight but consistent preference for the (*S*)-enantiomer (Table 1, entry 1). The bulkiest member **1c**[8] gave much higher selectivity but this was still too low to be of use for total synthesis applications (entry 3). Although the ligand **1c** has already been studied,[10] such an effect was unreported. Surprisingly enough, protection of one of the hydroxyl groups of **1a** as a methoxy ether led to a substantial increase in enantioselectivity (entry 2 versus 1). This result is surprisingly inconsistent with those described by Hoshino et al. with the *tert*-butyl analogs **1c** and **1d** (entry 4 versus 3),[10] where little difference in performance is seen between the unprotected ligand **1c** and the monoprotected **1d**.

These results suggest that increasing the bulk at the vicinity of the hydroxyl group or directly at the hydroxyl group leads to better facial differentiation in the transition state (Scheme 2). The literature indicates that moving from secondary alcohols to tertiary alcohols is sometimes detrimental to the performance of bidentate pyridinyls as ligands.[11,12] However, this effect has never been studied for tridentate pyridinyl ligands. Tertiary alcohol **2a** was thus prepared[9a] and applied in the ethylation reaction. Ligand **2a** did not induce higher enantioselectivity but led to lower e.e. irrespective of the solvent used (entries 5–7). These results are in agreement with those described by Chelucci et al. for the analogous bidentate derivatives.[11] The corresponding monoprotected derivative **2b** also induced lower enantioselectivity (entry 8 versus 6).

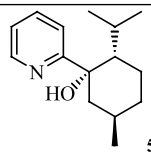
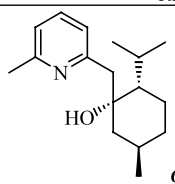
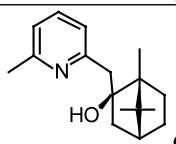
Molecular modeling studies and the above results support the theory that too rigid structures might be deleterious to discrimination of the two enantiotopic faces of benzaldehyde within the transition state complex. Therefore, compounds **3a**–**c**, having arms of one methylene group longer between the coordinating nitrogen and oxygen atoms were prepared.[9b] They indeed led to better enantioselectivity (entries 9–13) than their more rigid counterparts (entries 9–11 versus 5–7). A slight dependence upon the solvent nature was observed with the pyridyl menthyl derivative **3a** (entries 9–10). With the corresponding camphyl derivative **3c**, the enantioselectivity was lower than with **3a** (entry 12 versus 10). Contrary to its analog **2b**, the monoprotected derivative **3b** afforded the same enantioselectivity as the unprotected **3a** but its efficiency as a catalyst was improved (entry 12 versus 10).

For comparison, we prepared ligands **6a** and **6b** (Table 2)[9b] which are bidentate analogues of our best tridentate ligands **3a** and **3c**. These compounds thus have a longer arm between the coordinating atoms compared to Chelucci's ligand **5a**.[11] The result obtained with ligand **5a** for the same reaction was far from useful (Table 2, entry 1). However, comparison of this result with that for ligand **2a** (Table 2, entry 1 versus Table 1, entry 6) suggests that the second arm in ligand **2a** is beneficial to the selectivity. Surprisingly, the bidentate compounds **6a** and **6b** exhibited almost the same catalytic properties as their tridentate counterparts **3a** and



Scheme 2.

Table 2. Addition of diethylzinc to benzaldehyde catalyzed by bidentate chiral ligands. Hex = hexane[13]

	Ligands	Solv.	Yield (%)	E.e. (%)	Conf
1[11]	 **5a**	Hex/ Et_2O	93	21	*S*
2	 **6a**	Hex	85	95	*S*
3	 **6b**	Hex	81	77	*R*

3c. The enantioselectivies are identical for the menthyl derivatives **3a** and **6a** (Table 2, entry 2 versus Table 1, entry 10) and in the same range for the campheyl derivatives **3c** and **6b** (Table 2, entry 3 versus Table 1, entry 13). The bidentate ligands **6a** and **6b** gave better yields of addition products than the analogous tridentate ligands **3a** and **3c** (Table 2, entries 2 and 3 versus Table 1, entries 10 and 13).

Our results, combined with related published works, suggest that only one half of the C_2-symmetric ligand is part of the actual complex. The second arm seems to only play a screening role helping in the differentiation of the two enantiotopic faces of the aldehyde within the catalytic complex. Further works to clarify that role are now underway in our group.

In conclusion, we have demonstrated that a chain of appropriate length between the coordinating atoms is an essential requirement for a highly enantioselective catalyst based on pyridine. However, the beneficial role of a tridentate catalyst compared to a bidentate ligand is not as important as expected.

Acknowledgements

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13. **Typical procedure**: To a solution of catalyst (5% mmol) in toluene (2 mL) and hexane (2 mL) at 0°C was added a solution (1.0 M, 2 mL, 2.0 mmol) of diethylzinc in hexane. After stirring for 20 min at 0°C then 20 min at room temperature, freshly distilled benzaldehyde (1 mmol) was added. The reaction mixture was stirred at room temperature for 15 h and treated with aqueous H_2SO_4 (10% 10 mL). The layers were separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane and ethyl acetate (9:1) as eluent to give the corresponding alcohol. The enantiomeric excess of the product was determined by GC (chiral DEX G-TA, 20 m×0.25 mm, isothermal 90°C, $T_1 = 13.58$, $T_2 = 14.08$) and the configurations were determined by comparison of the specific rotation with the known compound.