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Chiral Ligands Derived from *Abrine*. 2. Oxazolidines as Promoters for Enantioselective Addition of Diethylzinc toward Aromatic Aldehydes

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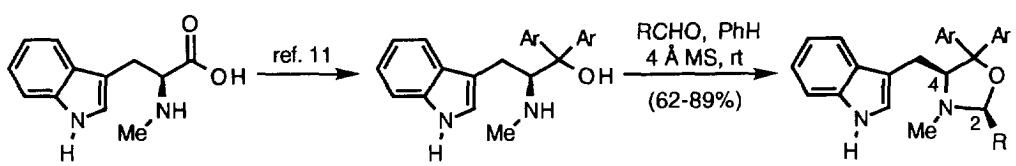
Abstract: A number of indole-containing chiral oxazolidines **2a-i** have been synthesized from *Abrine* readily available from the seeds of *Abrus precatorius*. Catalysis of these oxazolidines for the addition of diethylzinc toward benzaldehyde was examined. A significant role of the substituent(s) in the catalyst on the degree of asymmetric induction was noted. Moderate enantioselectivity up to 59.8% was recorded.

Addition of achiral organometallic reagents toward prochiral carbonyl compounds influenced by chiral ligands[1] has been playing an very important role in synthesis of chiral alcohols and contributes to the rapid development in catalytic enantioselective synthesis.[2] It has been known that addition of dialkylzinc toward aldehydes could be promoted by chiral β-amino alcohols to produce secondary alcohols in high enantiomeric excess.[1,3] A hydroxyl group is necessary for the chiral ligand to form a zinc alkoxide as the catalytic species.[4] Beside cyclic amines, other nitrogen-containing unsaturated heterocycles including pyridines,[5] pyrimidines,[6] quinolines,[7] pyrazoles,[8] imidazoles,[8] and oxazolines[9] can be efficient promoters for the addition of dialkylzinc if a hydroxyl group is incorporated into the substituent. However, to our best knowledge, only on one occasion, chiral oxazolidines[10] lacking a hydroxyl group showed catalysis for the addition of diethylzinc toward benzaldehyde to provide chiral 1-phenyl-1-propanol in 11-12% ee. We report here on the ethylation of benzaldehyde with diethylzinc promoted by the indole-containing oxazolidines **2a-i**.

Scheme 1



Abrine **1**: Ar = *p*-MePh **2a-i**

The chiral amino alcohol **1**[11] was synthesized from the alkaloid *Abrine* [(*S*)-*N*-methyltryptophan][12] isolated from the seeds of *Abrus precatorius* collected in Yunnan Province of China. Condensation of **1** with a

number of aldehydes gave the *cis* oxazolidines **2a-i** as a single isomer in good yield (Scheme 1).[13,14] The catalytic potency of **2a-i** was evaluated by the reaction of diethylzinc with benzaldehyde using 10% catalyst (Scheme 2). The results are summarized in Table 1. In general, the oxazolidines **2a-i** lacking a free hydroxyl group are less efficient promoters. Formation of considerable amount of benzyl alcohol was observed. The asymmetric induction by **2a-i** varied remarkably from 0% to *ca.* 60 % op. It was found that the R group at C_2 of oxazolidines **2a-i** has a determining role on the degree of enantioselectivity. Ligand **2a** possessing a phenyl group at C_2 exhibited no enantioselectivity at all (Table 1, entry 1). A zigzag line was obtained if op of **3**[15] was

Scheme 2

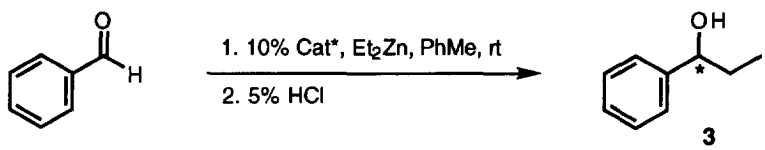


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Table 1. Enantioselective addition of Et_2Zn toward benzaldehyde in PhMe.

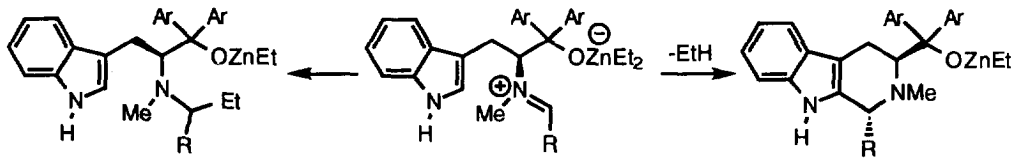
Entry	Cat*	Reation Time	Yield (%)[a]	$[\alpha]_D^{20}$ (c)[b]	op%[c]	Configuration[c]
1	**2a**: R = Ph	6 days	45.0	0	0	----
2	**2b**: R = Me	94 h	57.3	-17.71 (2.19)	38.8	*S*
3	**2c**: R = Et	100 h	51.0	-12.20 (2.10)	26.8	*S*
4	**2d**: R = *n*-Pr	89 h	57.8	-27.25 (3.74)	59.8	*S*
5	**2e**: R = *n*-Bu	100 h	47.2	-3.92 (3.19)	8.6	*S*
6	**2f**: R = $(CH_2)_2Ph$	96 h	52.1	-2.79 (3.41)	6.1	*S*
7	**2g**: R = *i*-Pr	96 h	56.3	+2.61 (3.11)	5.7	*R*
8	**2h**: R = CH_2-*i*-Pr	100 h	52.7	-15.10 (2.46)	33.1	*S*
9	**2i**: R = CH_2-*t*-Bu	100 h	50.6	-14.50 (2.47)	31.8	*S*

[a]Yield is based on the isolated product. Benzyl alcohol was formed in most of the reactions as the by-product. [b]Measured in $CHCl_3$. [c]The reported specific rotation $[\alpha]_D$ +45.6 ($CHCl_3$)[15] for *R* enantiomer was used for the calculation of op%.

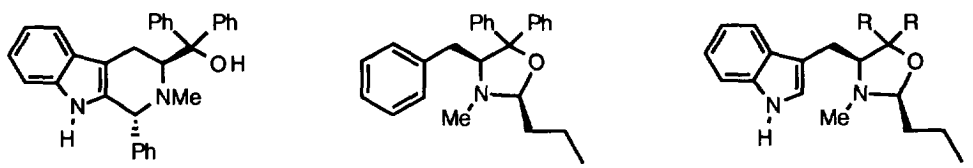
plotted against the number of carbon atoms of the R group in **2b-e** (Table 1, entries 2-5). Dependency of enantioselectivity on structure of the promoters can be best illustrated by entries 7 and 8. Insertion of one -CH_2- to **2g** altered the absolute stereochemistry of **3** from *R* to *S*. The *n*-propyl-substituted oxazolidine **2d** afforded the best enantioselectivity among the nine ligands listed in Table 1.

The interesting aspect of the indole-containing oxazolidine promoters is the mechanism of catalysis. The lack of a free hydroxyl group in **2a-i** puts a big question mark on their action. One might suggest that a ring-opening reaction takes place on mixing the oxazolidines with diethylzinc to form an iminium intermediate **4** which is ethylated to provide the zinc alkoxide **5**. Also, **4** can undergo a Pictet-Spengler reaction[16] to form the zinc alkoxide **6** possessing a 1,2,3,4-tetrahydro-β-carboline skeleton. To address this issue, **2b** was treated with diethylzinc in toluene at rt for 96 h. After acid-base workup and column chromatography, only **2b** was

obtained (72% recovery) without loss of optical rotation. Neither **5** nor **6** was detected from the reaction. Thus, we can propose that **5** and **6** are not involved in the catalytic cycle of the ethylation reaction. The 1,2,3,4-tetrahydro-β-carboline **7** was independently synthesized from *Abrine*.[17] Compound **7** catalyzed the addition of diethylzinc toward 4-chlorobenzaldehyde to give *R*-alcohol in 19% op (71% yield).



5 **4**: Ar = *p*-MePh **6**



7 **8**: *cis*:*trans* = 88:12 **9a**: R = Ph; **9b**: R = Et

Our next question is that does the indole skeleton play any role in catalysis? To answer this, the C_4 benzyl-substituted oxazolidine **8** was prepared[17] from (*L*)-phenylalanine as an inseparable mixture of *cis* and *trans* isomers. Treatment of benzaldehyde with diethylzinc in the presence of **8** (10%) in toluene at rt for 88 h gave *ca.* 20% of (*S*)-**3** with 30% recovery of benzaldehyde. The enantioselectivity induced by **8** was below 40%. The chemical yield of the ethylation reaction using **8** is significantly low than the indole analog **9a** (*vide infra*). These results support that the indole residue in oxazolidines **2a-i** participates in the catalysis.

The effect of substituents at C_5 of the oxazolidines on the catalysis is astonishing. Diphenyl-substituted **9a**[14] failed to induce high enantioselectivity (96 h, 59.4% chemical yield, 15.6% op) compared to di-*p*-tolyl analog **2d** (Table 1, entry 4). (*R*)-(+)-(4'-Chlorophenyl)-1-propanol was produced from the reaction of 4'-chlorobenzaldehyde catalyzed by **9b**[14] in 7.1% op (117 h, 87.3% chemical yield). The remarkable influence of *p*-tolyl substituent at C_5 on the enantioselectivity was not observed in the indole-containing tertiary amino alcohols reported by us previously.[11]

In summary, we have confirmed the catalysis of chiral oxazolidines in the enantioselective ethylation of benzaldehyde with diethylzinc. The indole-containing oxazolidines **2a-i** and **9a,b** were found to promote the ethylation much efficiently than other oxazolidines[10] such as **8** in terms of the chemical conversion and asymmetric induction. Substituents at C_2 and C_5 of the oxazolidines were revealed to dictate the degree of enantioselectivity. Enantiomeric excess up to 59.8% was obtained with oxazolidine **2d**. Possible catalytic species **7** which might be formed from reaction of oxazolidine with diethylzinc was investigated and different result from oxazolidine was obtained. Even though the exact mechanism of catalysis by the indole-containing chiral oxazolidines is not clear yet, the above described observations are of encouragement in searching for new chiral promoters for catalytic enantioselective synthesis.

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