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Chiral Ligands Derived from *Abrine*. 1. Synthesis of *sec*- and *tert*- β-Amino Alcohols and Catalysis for Enantioselective Addition of Diethylzinc toward Aromatic Aldehydes

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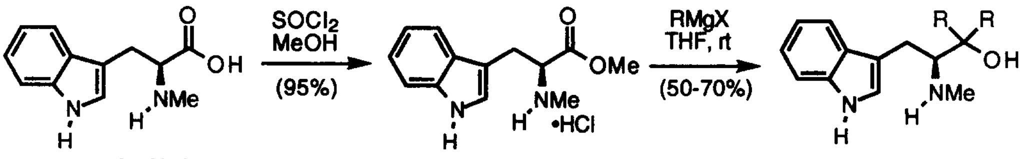
Abstract: A number of indole-containing chiral β-amino alcohols **3a-d** and **9a-e** have been synthesized from the alkaloid, *Abrine* (**1**) readily available from seeds of *Abrus precatorius* collected in Yunnan Province of China. Catalysis of the synthesized chiral ligands for the addition of diethylzinc toward benzaldehyde was examined. A significant role of the substituent(s) in the catalyst on the degree of asymmetric induction was uncovered. Enantiomeric excess of the product up to 94.2% was recorded.

Catalytic enantioselective reactions have received much attention in recent years and significant progress has been made in the carbon-carbon bond forming reactions using chiral ligand-modified metal complexes.[1] Enantioselective addition of achiral organometallic reagents toward carbonyl compounds in the presence of chiral ligands[2] plays an increasingly important role in the synthesis of chiral secondary alcohols which are found in the structures of many natural products and synthetic pharmaceuticals. Particularly, high enantioselectivity (>95% ee) has been achieved in the addition of dialkylzinc toward aromatic aldehydes catalyzed by chiral β-amino alcohols[2,3a] since the early work reported in 1984.[3b] Exploration of new chiral ligands for catalysis of the addition of dialkylzincs toward aldehydes is a very active research direction in modern organic synthesis.[4] In this communication, we report on the synthesis of indole-containing chiral β-amino alcohols derived from the alkaloid, *Abrine* (1)[5] and the catalytic efficiency on the addition of diethylzinc toward aromatic aldehydes.

Scheme 1

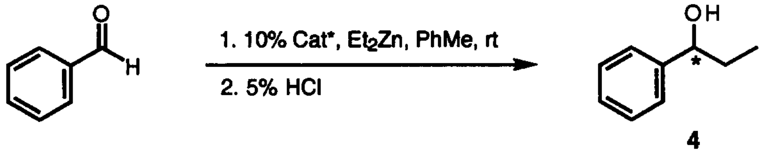


1: *Abrine* **2** **3a**: R = Et; **3b**: R = Ph;
3c: R = *p*-MePh; **3d**: R = *o*-MePh

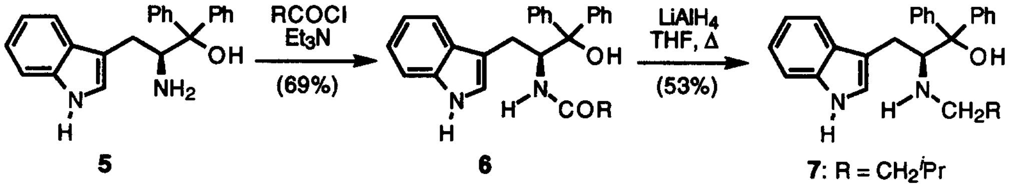
Amino acids and their derivatives have been used as chiral ligands in many catalytic enantioselective reactions.[1] Chiral secondary and tertiary β-amino alcohols derived from proline,[6] phenylalanine,[7] and tyrosine[7] have been reported to catalyze the addition of diethylzinc toward aldehydes in high enantiomeric excess (ee).

During the course of our joint research program of developing new chiral ligands, we focused on the natural products readily available from the plants which are rich in Yunnan Province of China. The alkaloid, *Abrine* [(*S*)-*N*-methyltryptophan, **1**]^5 isolated from the seeds of *Abrus precatorius* was selected for its availability and unique structural features of the indole ring^8 and the *N*-methyl group. The later sub-structure in **1** is ideal for synthesizing tertiary β-amino alcohols bearing three different alkyl groups on the nitrogen atom. Scheme 1 shows the synthesis of the alcohols **3a-d**^{9} which possess a secondary amino group. The ethylation of benzaldehyde with diethylzinc in the presence of 10% catalysts **3a-d**, respectively, was used as the prototype reaction for evaluating the enantioselectivity (Scheme 2, Table 1, entries 1-4). It was found that the *gem*-diethyl alcohol **3a** gave very low asymmetric induction of the reaction which provided the product (*R*)-**4**^{10} in only 7.1% optical purity (op) (Table 1, entry 1). The other *gem*-diaryl alcohols **3b-d** exhibited better catalytic ability (*ca.* 30% op); but the (*S*)-**4** was formed (Table 1, entries 2-4). We suspected that the low enantioselectivity of these catalysts **3a-d** may be due to the small methyl group attached on the nitrogen atom. Then, the catalyst **7**^{9} possessing $CH_2CH_2{}^iPr$ was synthesized from (*S*)-tryptophan (Scheme 3). An increase in the catalytic efficiency of **7** was obtained compared with **3b** (Table 1, entries 2 and 5). However, the degree of asymmetric induction was significant lower than a similar catalyst bearing a benzyl group^7 instead of the 3-indolemethyl group in **7**. This result indicated that the indole residue may function differently in the transition state of the reaction.

Scheme 2



Scheme 3



Scheme 4 described the synthesis of the tertiary amino alcohols **9a-e** from **3a,c**. Several interesting aspects of these catalysts for the ethylation of benzaldehyde (Scheme 2) were observed: (a) a reverse in the stereochemistry of the product **4** was obtained for catalysts **9b-d** compared with **3c** (Table 1, entries 7-9); (b) with the increase of the bulkiness of R^2 in **9b-d** in the order of $CH_2Ph < CH_2{}^iPr < CH_2{}^tBu$, the op was improved dramatically from 13.1%, 29.2%, and to 59.8%; (c) adding one more CH_2 to R^2 in **9a** reversed the stereochemistry of the product from *S* to *R* (Table 1, entries 6 and 7); and (d) incorporation of a $CH_2CH_2{}^tBu$ side chain into **3a** enhanced the op from 7.1% sharply to 94.2% (Table 1, entries 1 and 10). The best catalyst **9e** with the *gem*-diethyl alcohol structure is seldom^{11} seen to give such higher ee for the reaction of diethylzinc.

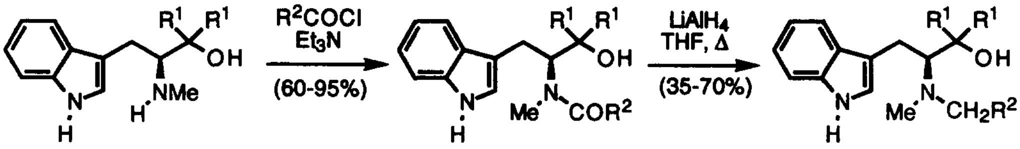
With the catalyst **9e** in hand, we explored the enantioselective ethylation of other aldehydes under the same reaction conditions. Table 2 showed the results of ethylation of *para*-substituted benzaldehydes, 2-naphthaldehyde, and cyclohexanecarboxaldehyde under the catalysis of **9e**. In general, aromatic aldehydes provided the best results in both chemical yield (90-99%) and enantioselectivity (91-100% op) (Table 2, entries

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

Entry	Cat*	Reation Time	**4**, Yield (%)[a]	$[\alpha]_D^{20}$ (c)[b]	op%[c]	Configuration[c]
1	**3a**	48 h	58.9	+3.3 (2.31)	7.1	*R*
2	**3b**	90 h	67.6	-13.5 (2.74)	29.5	*S*
3	**3c**	48 h	64.0	-13.8 (2.71)	30.1	*S*
4	**3d**	88 h	64.2	-14.4 (3.34)	31.6	*S*
5	**7**	61 h	54.2	-21.0 (3.05)	46.1	*S*
6	**9a**	52 h	50.0	-18.1 (1.27)	39.7	*S*
7	**9b**	96 h	50.5	+6.0 (2.94)	13.1	*R*
8	**9c**	69 h	50.7	+13.3 (2.21)	29.2	*R*
9	**9d**	92 h	47.5	+27.3 (2.12)	59.8	*R*
10	**9e**	96 h	70.1	+42.9 (3.58)	94.2	*R*

[a] Yield is based on the isolated product. Benzyl alcohol was formed in most of of the reactions as the by-product. [b] Measured in $CHCl_3$. [c] The reported optical rotation, $[\alpha]_D$ +45.6 ($CHCl_3$)[10] for *R* enantiomer was used for the calculation of op%.

Scheme 4



3a: R^1 = Et
3c: R^1 = *p*-MePh

8a-d

9a: R^1 = *p*-MePh, R^2 = Ph;
9b: R^1 = *p*-MePh, R^2 = CH_2Ph;
9c: R^1 = *p*-MePh, R^2 = $CH_2{}^iPr$;
9d: R^1 = *p*-MePh, R^2 = $CH_2{}^tBu$;
9e: R^1 = Et, R^2 = $CH_2{}^tBu$

Table 2. Enantioselective addition of Et_2Zn toward aldehydes catalyzed by **9e** in PhMe.

Entry	Substrate	Reation Time	Yield (%)[a]	$[\alpha]_D^{20}$ (c)	op%[d]	Configuration[d]
1	*p*-Anisaldehyde	96 h	89.6	+35.4 (4.84)[b]	92.0	*R*[12a]
2	4-Chlorobenzaldehyde	96 h	98.9	+26.4 (5.27)[b]	93.7	*R*[12b]
3	4-Tolualdehyde	96 h	90.3	+39.3 (3.65)[b]	91.0	*R*[12a]
4	2-Naphthaldehyde	96 h	99.1	+27.5 (3.80)[b]	100	*R*[12b]
5	Cyclohexane-carboxaldehyde	40 h	65.1	+5.3 (3.23)[c]	65.1	*R*[12c]

[a] Yield is based on the isolated product. [b] Measured in PhH. [c] Measured in $CHCl_3$. [d] Calculated based on the reported optical rotation values; see ref. 12 for details.

1-4). For saturated aldehyde (Table 2, entry 5), the enantioselectivity of the reaction was moderate (65% op). We believe that the principal structural features of the transition state[2] should be applied to the catalyst **9e**.

As described above, a number of indole-containing chiral β-amino alcohols **3a-d**, **7**, and **9a-e** have been synthesized and evaluated for the catalytic efficiency in enantioselective addition of diethylzinc with aldehydes. Effect of the substituent(s) was extensively examined which led to the discovery of an excellent catalyst **9e**. The structural information of **9e** may spark innovative ideas in designing novel chiral ligands for enantioselective synthesis.[13]

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