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Synthesis of New Chiral Aliphatic Amino Diselenides and Their Application as Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

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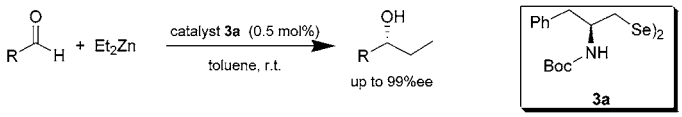
ABSTRACT



A set of chiral aliphatic amino diselenides have been synthesized from readily available starting materials in a straightforward synthetic route via the ring-opening reaction of the parent aziridines. These ligands have been tested as catalysts for the enantioselective addition of diethylzinc to aldehydes. The influence of the alkyl group substituents on the stereoselectivity has been studied, and in the best case, an enantiomeric excess up to 99% could be obtained by using only 0.5 mol % of the chiral diselenide 3a.

Nucleophilic addition of organometallic reagents to carbonyl compounds is a very important operation in organic synthesis, and the asymmetric version of this reaction is particularly useful. Several highly enantioselective additions to prochiral aldehydes leading to optically active alcohols have been reported,[1] and among the various organometallic compounds, diorganozincs serve as excellent alkyl nucleophiles.

After the discovery by Oguni and Omi that various additives catalyze the addition of dialkylzinc reagents to aldehydes,[2] there has been a rapid growth of research aimed at this reaction.[3] Much of these efforts have been directed toward the design of new chiral ligands, specially β-amino alcohols.

On the other hand, chiral selenium-based methods have developed rapidly over the past few years and are now a very important tool in organic synthesis.[4] Among the many classes of organoselenium compounds, the chiral diselenides have received special attention due to their higher stability and easier handling when compared with the parent selenols. They can be used in the stereoselective ring opening of epoxides,[5] anti-stereoselectivity, and Markovnikoff regioselectivity in the electrophilic selenenylation of alkenes.[6] Most importantly chiral diselenides have been employed as useful ligands and catalysts in various asymmetric transformations such as diethylzinc addition to aldehydes,[7] asym-

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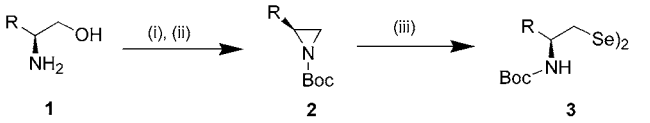
metrichydrosilylation,[8] and 1,4 addition of Grignard reagents to enones.[9] To the best of our knowledge, an interesting feature of the ligands used in such transformations is that all of them have a selenium atom attached to an aromatic ring.

To extend our studies in the organochalcogen mediated stereoselective transformations,[9,10] we sought to obtain a new class of Se, N-ligands in a straightforward synthetic route, using inexpensive and easily available starting materials, and to test them as chiral ligands in the enantioselective addition of diethylzinc to aldehydes. The present paper reports the development of a new class of chiral amino diselenides **3** and **4** with the selenium atom attached to an alkyl group.

Scheme 1. Synthesis of Amino Diselenides **3**[a]



1 **2** **3**

3a R = Bn 76%
3b R = *i*-Pr 73%
3c R = *i*-Bu 71%
3d R = *s*-Bu 72%

[a] Reagents and conditions: (i) Boc_2O, CH_3CN, rt, 3 h; (ii) KOH, TsCl, THF, reflux, 4 h; (iii) Li_2Se_2, THF, rt, 12 h.

The chiral amino diselenides **3** were easily prepared from the corresponding, commercially available α-amino alcohols **1**, which were further quantitatively converted into the Boc-protected derivatives by reaction with di-*tert*-butyl dicarbonate in acetonitrile. The chiral aziridines **2** were obtained in good yields by treatment of N-Boc amino alcohols with *p*-toluenesulfonyl chloride and potassium hydroxide in boiling THF. Finally, the selenium atom was efficiently introduced by regioselective nucleophilic ring opening by attack of Li_2Se_2[11] at the less hindered carbon[12] of the aziridines **2**, furnishing the aliphatic chiral amino diselenides **3a**−**d**[13] without any loss of enantiomeric purity, as determined by chiral HPLC.

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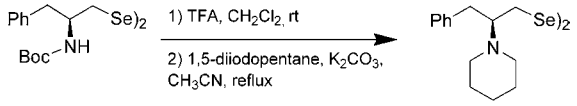
To examine the possibility of steric and electronic refinement in the structure of ligands **3** at the amine moiety, the replacement of the Boc group by another bulky alkyl group was realized. Deprotection of the chiral diselenide **3a** with TFA proceeded smoothly at room temperature to give the free amino diselenide. Subsequent treatment of this compound with di-iodopentane in the presence of potassium carbonate in boiling acetonitrile furnished the respective piperidine diselenide **4** in 35% yield for the 2 steps.

Scheme 2. Synthesis of Piperidine Diselenide **4**



3a **4**

With this sterically and electronically varied set of enantiopure aminodiselenides in hand, we have examined their efficiency as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde.

Aiming to evaluate the catalytic potential of the amino diselenides synthesized, ligand **3a** was chosen as a model compound to determine the optimum conditions for the reaction. Our studies had started varying the loading of the catalyst and the results are depicted in Table 1.

Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde Varying the Loading of the Catalyst **3a**

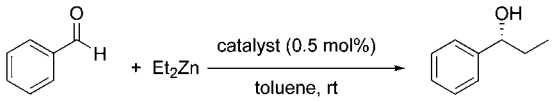
entry	loading of **3a** (mol %)	% yield[a]	% ee[b]
1	10	93	96 (*R*)
2	5	93	95 (*R*)
3	2.5	92	95 (*R*)
4	1	92	95 (*R*)
5	0.5	91	95 (*R*)

[a] Determined by GC analysis. [b] Determined by chiral GC analysis with use of a Hydrodex *β*-3P column; the absolute configuration was determined by comparing the sign of the optical rotation.

It could be observed that the level of enantioselection in the reaction is not affected by changing the amount of **3a**. Even when 0.5 mol % was used, the enantiomeric excess of 1-phenyl-1-propanol was 95%. The yield has slighty decreased with lowering the loading of the catalyst. The conversion to the desired alcohol is still high with the lowest amount used of the chiral amino diselenide, showing that a highly effective catalytic cycle is formed.

With these results, the efficiency of the other ligands prepared as chiral catalysts in the addition of diethylzinc to benzaldehyde was also examined. The results obtained in this reaction in the presence of ligands **3** and **4** are shown in Table 2. The reactions were performed under standard

Table 2. Screening of Ligands **3a**−**d** and **4** in the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde



entry	catalyst	% yield[a]	% ee[b]
1	**3a**	91	95 (*R*)
2	**3b**	71	91 (*R*)
3	**3c**	80	92 (*R*)
4	**3d**	72	91 (*R*)
5	**4**	82	90 (*R*)
6[c]	**3a**	51	91 (*R*)

[a] Determined by GC analysis. [b] Determined by chiral GC analysis with use of a Hydrodex β-3P column; the absolute configuration was determined by comparing the sign of optical rotation. [c] Reaction performed at 0 ° C.

conditions: 0.5 mol % of ligand **3** or **4**, benzaldehyde (1 mmol), diethylzinc (2.5 mmol) in toluene, at room temperature. The reaction was also performed at 0 °C but a dramatic decrease in the yield was observed (Table 2, entry 6).

All the reactions led to the predominant formation of the alcohol (*R*)-1-phenyl-1-propanol with different levels of enantiocontrol. We can verify the effect of the R substituents derived from amino alcohols in Table 2 (entries 1−4). The catalyst **3a** (R = Bn) showed better enantioselection than the other alkyl groups (**3b**−**d**). Interestingly, when the reaction was carried out at lower temperature (Table 2, entry 6), a significant decrease in the yield was observed. Probably, the complexes are formed slower at this temperature, decreasing the efficiency of the complexation. The effect of the amine group substituents was also studied, using the modificated catalyst **4**. This ligand showed good performance, but the results obtained with **3a** are still higher in terms of conversion and enantiomeric excess, as well as the simplicity of the catalyst.

To extend the scope of the optimal ligand **3a** as a chiral catalyst in the addition of diethylzinc to aldehydes, several aromatic and aliphatic aldehydes were screened. In all cases, the reactions were performed in toluene at room temperature and, as for the addition to benzaldehyde, the corresponding (*R*) configuration alcohol was always obtained as the major isomer, all with similar enantiomeric excesses (Table 3). For the aromatic aldehydes, high levels of enantioselection were observed. Additions to the less reactive aliphatic aldehydes gave distinct results (Table 3, entries 4 and 5). Reaction with hexanal results in an excellent ee of >99%. A four-carbon extension decreases the ee dramatically to 45%.

Table 3. Enantioselective Addition of Diethylzinc to Aromatic and Aliphatic Aldehydes Employing Chiral Diselenide **3a**

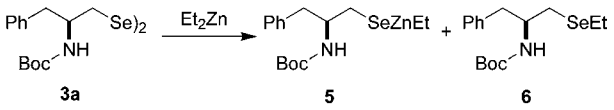
entry	aldehyde	% yield[a]	% ee
1[b]	*o*-methoxybenzaldehyde	93	95 (*R*)
2[b]	*p*-methoxybenzaldehyde	93	>99 (*R*)
3[c]	2-pyridinecarboxaldehyde	85	91 (*R*)
4[c]	decanal	56	45 (*R*)
5[c]	hexanal	63	>99 (*R*)

[a] Conversion was determined by GC analysis. [b] Determined by chiral GC analysis with use of a Hydrodex β-3P column; the absolute configuration was determined by comparing the sign of optical rotation. [c] Determined by chiral HPLC analysis with use of a Daicel Chiralcel OD column.

The stereochemistry of the products is in accordance with the mechanistic rationalization described in the work of Noyori.[3a,14]

To elucidate the mechanistic aspects and to identify the catalytically active species, we treated the diselenide **3a** with an excess of diethylzinc in toluene, at room temperature (Scheme 3).

Scheme 3



3a **5** **6**

We assumed that the diselenide linkage is cleaved by nucleophilic attack of diethylzinc, resulting in the selenolate **5** and the selenoether **6**, according to the results reported by Kellogg[15] and Wirth.[7b] We believe that the active catalyst of the reaction is the selenolate **5**, since in an additional experiment, the selenoether **6** did not catalyze the alkylation reaction of benzaldehyde.

In summary, a new series of chiral, aliphatic, amino-containing diselenides was synthesized in a straightforward synthetic route, starting from an inexpensive and easily available chiral pool. The crucial step was the regioselective ring opening of the chiral aziridines by a selenium nucleophile, leading to the aliphatic diselenides in good yields.

(13) **General Procedure for the Ring-Opening Reaction of Aziridines 2a with Li_2Se_2. Synthesis of Aminodiselenide 3a.** Lithium diselenide was generated by reaction of gray elemental selenium (0.0947 g, 1.2 mmol) with lithium triethylborohydride (1.2 mL, 1.2 mmol) in dry THF (5 mL). The suspension was allowed to stir for at least 20 min,[11] and a THF (10 mL) solution of aziridine **2a** (0.233 g, 1.0 mmol) was added dropwise within 20 min. The resulting solution was stirred for 12 h at room temperature, quenched with a saturated NH_4Cl solution (20 mL), and extracted with CH_2Cl_2, the combined organic fractions were collected, dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo yielding a yellow solid that was purified by flash chromatography (hexane/ethyl acetate 90:10). Drying in vacuo afforded 0.235 g (0.375 mmol, 75%) of the amino diselenide **3a**: The enantiomeric purity was determined by HPLC analysis (column, Chiralcel-OD; eluent, hexane/2-propanol 98:02; flow rate, 1 mL/min; *R* isomer, t_R = 16.3 min, *S* isomer, t_R = 17.2 min) and found to be >99.9%: mp 96 − 98 °C; $[\alpha]^{20}_D$ −8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24−7.11 (m, 5H), 4.89−4.87 (m, 1H), 4.09−4.05 (m, 1H), 3.11−2.99 (m, 2H), 2.83−2.80 (m, 2H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.06, 137.46, 129.22, 128.95, 126.35, 79.14, 51.99, 39.75, 34.77, 28.25. ^{77}Se NMR ($CDCl_3$) δ 314.421. HRMS-ESI *m*/*z* calcd for $C_{28}H_{40}N_2O_4Se_2 + Na^+$ 651.1209980, found 651.1210725.

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Besides, these compounds have been evaluated in the enantioselective addition of diethylzinc to aldehydes. The chiral secondary alcohols could be obtained in high yields and enantiomeric excesses by using a very small amount of catalyst. Further studies are in progress in our laboratories concerning new metal-catalyzed asymmetric reactions and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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