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Enantioselective Alkylation of Aldehydes Catalyzed by New Chiral Diselenides

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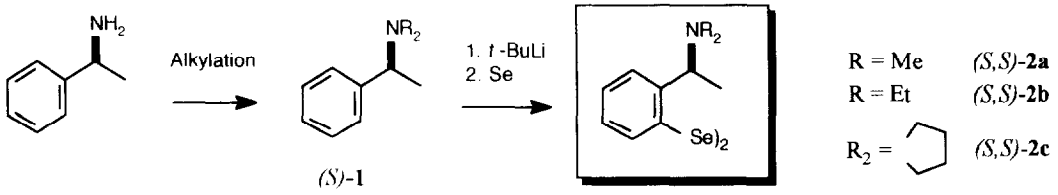
Abstract: New chiral diselenides were synthesized from readily available chiral amines. Their application in the catalytic addition of diethylzinc to aldehydes provided the secondary alcohols in up to 98 % *ee*.

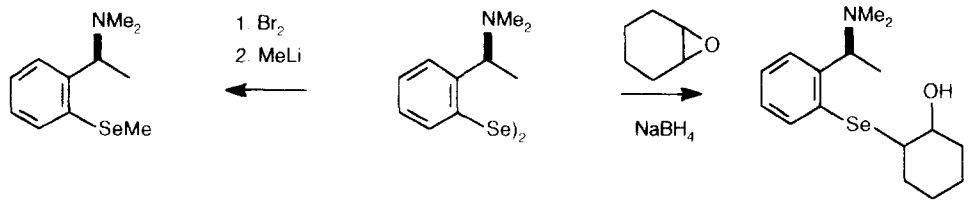
Catalytic asymmetric induction in reactions forming carbon-carbon bonds has developed rapidly during the last decade. For the enantioselective addition of diethylzinc to aldehydes a variety of chiral catalysts have been developed.[1] Among them, β-aminoalcohols and diamines with C_2-symmetry have been recognized to be highly efficient catalysts. With the access to polyfunctional diorganozinc reagents it is now even possible to prepare functionalized optically active secondary alcohols.[2]

This paper describes the synthesis of new chiral selenium containing compounds and their application as enantioselective catalysts in the alkylation of aldehydes.



(S)-**1**

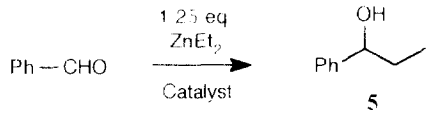
The chiral diselenides **2a**, **2b** and **2c** were prepared in two steps from 1-phenylethylamine. Because both enantiomers of 1-phenylethylamine are commercially available, the chiral diselenides **2** with *(R,R)* and *(S,S)* configuration were synthesized. **1a** (R = Me) is obtained by Clarke-Eschweiler methylation[4], **1b** and **1c** by alkylation with iodoethane and 1,4-dibromobutane, respectively. The subsequent diselenide formation was achieved after ortho deprotonation with *t*-BuLi[5], treatment with elemental selenium and oxidative work-up.[3] To gain some understanding of the behavior of selenium based catalysts, some derivatives of **2a** were prepared. Cleavage of the Se-Se bond with bromine and methylation yields compound *(S)*-**3**. After nucleophilic opening of cyclohexene oxide *(S,RS,RS)*-**4** is obtained. Compounds **3** and **4** are able to catalyze the addition of diethylzinc to benzaldehyde (Table 1, entry 1 and 2), but alcohol **5** is obtained in low yields with only 27 and 64 % *ee*, respectively. **3** can coordinate to zinc via nitrogen and selenium which enhances the reactivity of the



(S)-**3** *(S,S)*-**2a** *(S,RS,RS)*-**4**

diethylzinc.[6] The additional hydroxy group in **4** does not seem to have an influence upon the enantioselectivity of the addition reaction, although recently reported chiral selenium based catalysts with hydroxy groups show different behavior.[7] Even the amine *(S)*-**1a** is able to catalyze the addition reaction, but the lack of a second coordination site results in a racemic product (entry 3).

The diselenides **2** having two alkylamino moieties are much more efficient catalysts for the diethylzinc addition to aldehydes. Only 1 mol % is necessary to obtain good yields and enantioselectivities up to 98% *ee* whereas in most of the reactions reported so far 5 mol % of a catalyst is needed.[1b] Even with only 0.2 mol % of *(R,R)*-**2a**, 1-phenylpropan-1-ol **5** is obtained with still 85 % *ee* in 64 % yield (entry 4-6).

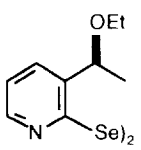


5

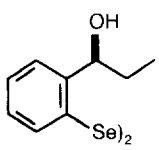
Table 1. Asymmetric Addition of Diethylzinc to Benzaldehyde Using Chiral Ligands[a]

Entry	Catalyst	mol %	Reaction time [h]	Yield [%]	*ee* [%][b] (Config.)
1	*(S)*-**3**	2.5	13	14	64 *(R)*
2	*(S,RS,RS)*-**4**	1	14	23	27 *(R)*
3	*(S)*-**1**	2.5	13	8	0
4	*(R,R)*-**2a**	5	14	79	92 *(S)*
5	*(R,R)*-**2a**	1	20.5	70	91 *(S)*
6	*(R,R)*-**2a**	0.2	85	64	85 *(S)*
7[c]	*(S,S)*-**2a**	1	12.5	82	93 *(R)*
8	*(R,R)*-**2b**	1	13	57	91 *(S)*
9	*(R,R)*-**2c**	1	22	91	96 *(S)*
10[d]	*(R,R)*-**2c**	1	15	91	98 *(S)*
11	*(S,S)*-**6**	5	13.5	32	8 *(R)*
12	*(S,S)*-**7**	5	13.5	10	15 *(S)*
13	*(R,R)*-**8**	5	13.5	1	8 *(R)*
14	*(S,S)*-**9**	1	12.5	71	92 *(R)*

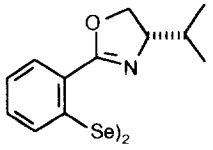
a) Reactions were carried out in toluene at room temperature. b) The *ee* values were determined by GC (Chrompack, β-CD-permethylated, 25m). c) Reaction was carried out in hexane at room temperature. d) Reaction was carried out in toluene at 0 °C.



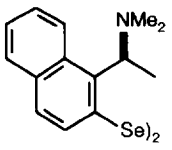
(S,S)-**6**



(S,S)-7



(R,R)-**8**



(S,S)-**9**

Variation of the alkyl group R shows that the pyrrolidine moiety in **2c** gave the best results (entry 8, 9). If the reaction temperature is lowered to 0 °C, 98 % *ee* is obtained by using 1 mol % of **2c** (entry 10). Other solvents like hexane (entry 7) can be used as well, with more polar solvents like acetonitrile or tetrahydrofuran the reaction proceeds very slowly and with low enantioselectivity. Although other chiral diselenides bearing different oxygen and nitrogen functionalities e.g. **6**, 7[8], and **8** are poor catalysts (entries 11-13), the diselenide **9** is as efficient as **2a** in catalyzing the addition of diethylzinc to benzaldehyde (entry 14).

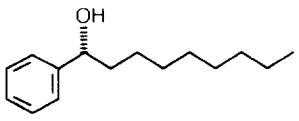
With the new chiral diselenides **2** it is also possible to catalyze the ethyl transfer to other aromatic and aliphatic aldehydes as shown in table 2.

Table 2. Addition of Diethylzinc to Various Aldehydes in the Presence of 1 mol % *(S,S)*-**2a**.

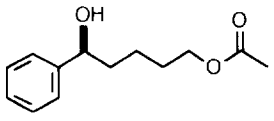
Entry	Aldehyde	Yield [%]	*ee* [%] (Config.)	Ref.
1	1-Naphthaldehyde	62	82 *(R)*	9
2	2-Bromobenzaldehyde	67	72 *(R)*	8
3[a]	4-Methoxybenzaldehyde	77	93 *(R)*	10
4	*(E)*-Cinnamylaldehyde	61	45 *(R)*	11
5	Pentanal	91	76 *(R)* [b]	12

a) 5 mol % *(S,S)*-**2a** was used. b) Determined by ^{19}F NMR analysis of the corresponding MTPA ester.

The use of other dialkylzinc compounds required a larger amount of catalyst. Dioctylzinc was added to benzaldehyde in the presence of 10 mol % *(S,S)*-**2a** to give *(R)*-**10**[13] with 53 % *ee* in 11% yield. Addition of di[4-(acetyloxy)butyl]zinc to benzaldehyde catalyzed by 5 mol % *(R,R)*-**2c** produced the alcohol *(S)*-**11**[2c] in 13 % yield with 48 % *ee*



(R)-**10**



(S)-**11**

New chiral diselenides and their use as readily accessible catalysts in dialkylzinc additions to aldehydes have been presented. Further studies towards the preparation of new chiral diselenides and their application in stoichiometric as well as in catalytic reactions are in progress.

Acknowledgments:

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3. General procedure for the synthesis of the diselenides **2a-c** and **9**:
   The dialkylated amine (10 mmol) was dissolved in 15 ml pentane and treated slowly with *t*-butyllithium (1.7M in pentane, 6.5 ml, 11 mmol) at room temperature. After stirring for 3 h the white precipitate was dissolved with 5 ml anhydrous THF and grey selenium (1.18 g, 15 mmol) was added slowly. After stirring for an additional 3 h at room temperature 1N HCl (100 ml) was added. The resulting mixture was extracted three times with *tert*-butylmethyl ether and again three times after neutralization of the aqueous phase with 1N NaOH. The combined organic phases were dried with $MgSO_4$. After addition of KOH (100 mg), the solvent was removed under vacuum and the residue purified by column chromatography on silica gel (pentane *tert*-butylmethyl ether 1:1) yielding the diselenides as yellow oils.
   Selected spectroscopic data of *(S,S)*-**2a**
   ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 1.35 (d, *J*=6.5 Hz, 6H), 2.26 (s, 12H), 3.77 (q, *J*=6.5 Hz, 2H), 7.05 - 7.25 (m, 6H), 7.84 (dd, *J*=7.5 Hz, *J*=1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] 14.1, 41.0, 63.6, 125.9, 126.2, 127.6, 131.4, 133.3, 144.1
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