



# Synthesis of non-racemic nitrogen-containing diselenides as efficient precursor catalysts in the diethylzinc addition to benzaldehyde

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Received 23 February 1999; accepted 10 March 1999

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## Abstract

Short synthetic procedures for the preparation of new chiral, non-racemic nitrogen-containing diselenides are described. Only 1 mol% of these diselenides can very efficiently catalyze the diethylzinc addition to benzaldehydes affording the secondary alcohols in high enantiomeric purities (up to 97% *ee*). © 1999 Elsevier Science Ltd. All rights reserved.

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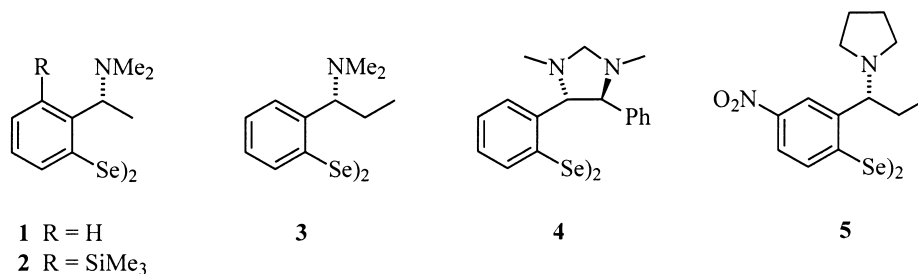
The enantioselective addition of dialkylzinc reagents to aldehydes can be catalyzed by a large variety of chiral compounds affording optically active secondary alcohols.<sup>1</sup> Detailed mechanistic studies have also been performed.<sup>2</sup> Diols, diamines and amino alcohols were found to be highly efficient catalysts for this reaction. Recently, it has been shown that both sulfur-<sup>3</sup> and selenium-containing<sup>4</sup> amines are also able to catalyze diethylzinc addition reactions.

We observed a positive nonlinear relationship (asymmetric amplification) between the enantiomeric excesses of the catalyst generated from nitrogen-containing diselenides and the product.<sup>4c</sup> This phenomenon<sup>5</sup> was subsequently also observed in the corresponding sulfur-containing compounds.<sup>3e</sup> By NMR studies we demonstrated that the catalyst derived from **1** is aggregated and acts as a bidentate ligand.<sup>4c</sup>

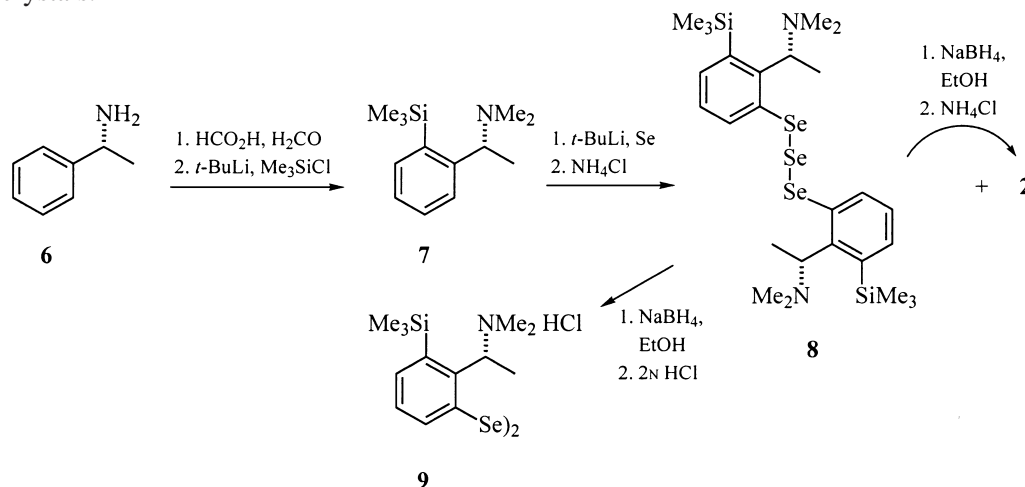
In this paper we report on efficient and simple routes for the synthesis of new chiral non-racemic nitrogen-containing diselenides as precatalysts for diethylzinc addition to benzaldehyde.

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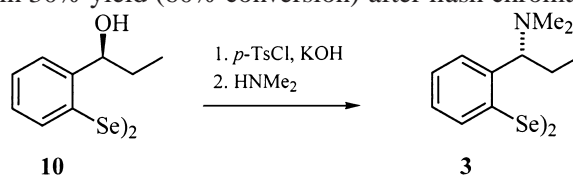
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Having investigated diselenides of type **1** in detail, we prepared compound **2** with a second *ortho*-substituent. Chiral diselenide **2**<sup>6</sup> was prepared in a few steps from commercially available 1-phenylethylamine **6**. After alkylation, the first *ortho*-deprotonation was achieved by treatment with *t*-BuLi.<sup>7</sup> By addition of trimethylsilyl chloride, **7** was obtained in quantitative yield. Compound **7** was then converted into a mixture of triselenide **8** and diselenide **2** by treatment with *t*-BuLi and elemental selenium. Reduction of this mixture with NaBH<sub>4</sub> in ethanol was followed by reoxidation in an ammonium chloride solution to convert **8** into **2**. Diselenide **2** was obtained in 67% overall yield. When the reoxidation was performed in 2 N HCl, the corresponding salt **9** was obtained in 55% yield as pale yellow crystals.

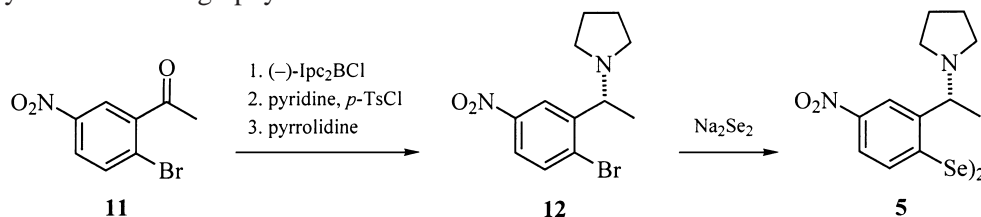


To study the influence of the side chain, the nitrogen-containing diselenide **3**<sup>8</sup> was prepared starting from hydroxy diselenide **10** using a one-pot procedure. Diselenide **10** was transformed in situ to the corresponding tosylate by treatment with *p*-TsCl and KOH at  $-15^{\circ}\text{C}$ . After addition of dimethylamine, diselenide **3** was obtained in 30% yield (60% conversion) after flash chromatography.



Diselenide **4** is readily accessible starting from (1*S*,2*S*)-1,2-diphenylethylenediamine through a two-step procedure as reported recently.<sup>9</sup> The electronically modified diselenide **5**<sup>10</sup> was synthesized starting from 2-bromo-5-nitroacetophenone **11**.<sup>11</sup> This compound was enantioselectively reduced with (–)-diisopinocampheylchloroborane [(–)-Ipc<sub>2</sub>BCl]. The resulting chiral alcohol was tosylated and substituted

by pyrrolidine to give compound **12**. The following reaction with  $\text{Na}_2\text{Se}_2$  led to diselenide **5** which was purified by flash chromatography.



Diselenides **1–5** and **9** have been investigated as procatalysts in the enantioselective addition of diethylzinc to benzaldehyde. The reaction was carried out in toluene at  $-15^\circ\text{C}$  using 1.25 equiv. diethylzinc, 1 equiv. freshly distilled benzaldehyde and 1 mol% of the diselenide. The reaction mixture was stirred at  $-15^\circ\text{C}$  overnight and then quenched with 2 N HCl. The secondary alcohol was purified by flash chromatography and the enantiomeric purities and absolute configurations are reported in Table 1. Because we have previously shown that a variety of aldehydes can be used successfully in this reaction,<sup>4b,c</sup> we are discussing herein only the results obtained with benzaldehyde.

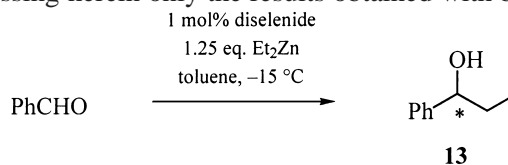
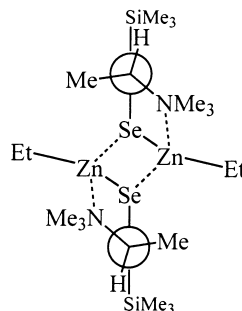


Table 1  
Diethylzinc addition to benzaldehyde using 1 mol% diselenide as procatalyst

Entry	Diselenide	<b>13</b> Yield	<b>13</b> ee%	<b>13</b> Configuration
1	( <i>R,R</i> )- <b>1</b>	87%	92%	S
2	( <i>R,R</i> )- <b>3</b>	95%	91%	S
3	( <i>R,R</i> )- <b>5</b>	78%	41%	S
4	( <i>S,S,S,S</i> )- <b>4</b>	89%	97%	S
5	( <i>R,R</i> )- <b>2</b>	98%	96%	S
6	( <i>S,S</i> )- <b>2</b>	95%	96%	R
7	( <i>R,R</i> )- <b>9</b>	20%	10%	S

We have already reported that diselenide **1**, using the conditions described above, is an efficient catalyst producing alcohol **13** in 92% enantiomeric excess (entry 1).<sup>4c</sup> A similar level of selectivity is observed for diselenide **3** (entry 2) with an aminopropyl instead of an aminoethyl side chain. After electronic modification of the aromatic ring by a nitro group in position 4 (diselenide **5**) the enantiomeric excess as well as the chemical yield decreases (entry 3). Diselenide **4** containing an additional stereogenic center in the five-membered ring is more efficient in generating product **13** with 97% ee (entry 4).

Particularly interesting is the comparison between the enantiomeric excesses obtained with diselenide **2** (entries 5+6) and the data reported for **1** (entry 1). Diselenide **2** bears a second *ortho*-substituent with respect to the chiral moiety. The higher selectivity observed with diselenide **2** (96% ee) might indicate that the presence of the second *ortho*-substituent is pushing the nitrogen moiety of the chiral side chain towards the selenium atom in facilitating the coordination to zinc as shown below. This selectivity, however, was completely lost when hydrochloride **9** was employed as a procatalyst in the addition reaction (entry 7).



In conclusion, we have prepared new chiral nitrogen-containing diselenides by using simple procedures. The selectivities in diethylzinc addition to benzaldehyde, catalyzed by these diselenides as procatalysts, were investigated with respect to the steric and electronic features of these compounds. The results should give useful information for the design of new catalysts for these kinds of reactions.

## Acknowledgements

This work was supported by the Schweizer Nationalfonds and by the Treubel-Fonds (fellowship for T.W.). We thank Professors B. Giese and M. Tiecco for their generous support. This research was performed under MURST National Project ‘Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni’ (C.S.).

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- Selected spectroscopic data of diselenide **2**:  $^1\text{H}$  NMR:  $\delta$  7.93 (dd, 1H,  $J=1.1$ , 7.9 Hz), 7.28 (dd, 1H,  $J=1.1$ , 7.3 Hz), 7.03 (dd, 1H,  $J=7.3$ , 7.9 Hz), 3.66 (q, 1H,  $J=6.7$  Hz), 2.30 (s, 6H), 1.53 (d, 3H,  $J=1.5$  Hz), 0.35 (s, 9H).  $^{13}\text{C}$  NMR:  $\delta$  151.3, 138.3, 134.0, 133.4, 132.3, 127.8, 67.2, 43.6, 19.8, 2.4.  $^{77}\text{Se}$  NMR:  $\delta$  463.5 (broad 250 Hz). FAB-MS  $m/z$  (rel. int.) 601 (11), 300 (100), 254 (3), 149 (4), 73 (77), 44 (9).
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- Selected spectroscopic data of diselenide **3**:  $^1\text{H}$  NMR:  $\delta$  7.81 (dd, 1H,  $J=7.4$ , 1.3 Hz), 7.2–7.0 (m, 3H), 3.48 (t, 1H,  $J=7.5$  Hz), 2.29 (s, 6H), 1.91 (quint, 2H,  $J=7.5$  Hz), 0.84 (t, 3H,  $J=7.5$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  141.8, 133.5, 131.6, 127.7, 127.6, 125.7, 71.0, 42.1, 22.5, 11.4.  $^{77}\text{Se}$  NMR:  $\delta$  444.5. FAB-MS  $m/z$  (rel. int.) 485 (15), 242 (100), 197 (12), 86 (20), 69 (11), 57 (21), 44 (30).
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10. Selected spectroscopic data of diselenide **5**:  $^1\text{H}$  NMR:  $\delta$  8.07 (t, 1H,  $J=1.5$  Hz), 7.88 (d, 2H,  $J=1.5$  Hz), 3.85 (q, 1H,  $J=6.8$  Hz), 2.64 (m, 4H), 1.86 (m, 4H), 1.52 (d, 3H,  $J=6.8$  Hz).  $^{13}\text{C}$  NMR:  $\delta$  146.6, 146.1, 141.3, 131.6, 122.1, 121.2, 63.0, 50.5 (2C), 23.8 (2C), 17.5.  $^{77}\text{Se}$  NMR:  $\delta$  483.0. FAB-MS  $m/z$  (rel. int.) 599 (8), 299 (100), 283 (12), 138 (20), 98 (41), 70 (92), 55 (35).
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