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Synthesis of new chiral imidazolidine disulfides derived from L-cystine and their application in the enantioselective addition of diethylzinc to aldehydes

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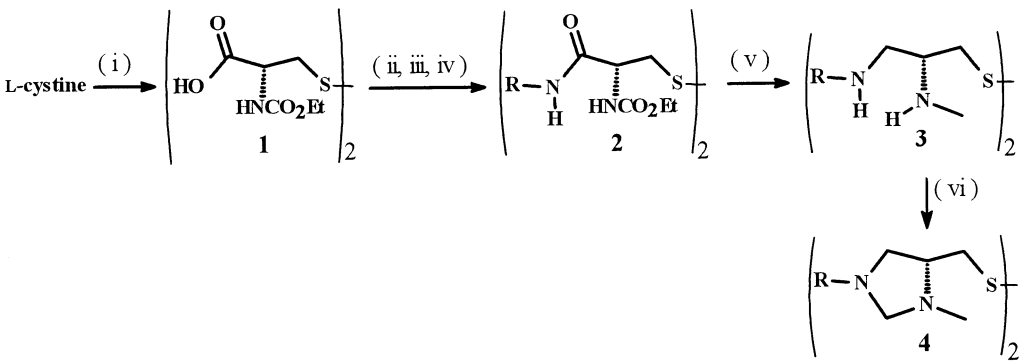
Abstract—Several chiral imidazolidine disulfides **4a–d** derived from L-cystine have been synthesized. These ligands have been applied as chiral catalysts in the asymmetric addition of diethylzinc to aldehydes. The best results were obtained by employing 5 mol% of imidazolidine disulfide **4a**, and chiral secondary alcohols were obtained in up to 91% e.e.

One of the most challenging subjects in organic synthesis during this decade is the development of new and efficient chiral ligands for catalytic asymmetric synthesis.[1] Numerous reports have shown that reagents like β-amino thiols and β-amino disulfides are efficient for asymmetric induction.[1b] Among them, we can find some derived from ephedrine,[2] norephedrine,[3] L-proline,[4] (*S*)-phenylglycine,[5] (*R*)-cysteine,[6] (*S*)-valine,[7] (1*R*,2*S*)-(−)-1,2-diphenyl-2-amino-1-ethanol[8] and others.[9] They have been used as highly effective catalysts for the diethylzinc addition to aldehydes. The interest in the development of cost-effective catalysts that exhibit high reactivity and enantioselectivity together with the availability of a wide variety of diorganozinc reagents[10] have attracted much attention by research groups in this field. As part of our continuing interest in sulfur-containing catalysts,[6] we report herein the studies of the synthesis of new chiral imidazolidine disulfides **4** derived from L-cystine and their use as chiral ligands in the addition of $ZnEt_2$ to aldehydes.

The chiral imidazolidine disulfides **4a–d** were prepared from commercially available L-cystine as follows: initially we protected the amino group of L-cystine with $ClCO_2Et$ in 1 M aq. NaOH (98% yield). The protected L-cystine was treated with the appropriated amines



Scheme 1. Synthesis of chiral imidazolidine disulfides **4a–d**. *Reagents*: (i) 1 M aq. NaOH, ethyl chloroformate; (ii) *N*-methylmorpholine, $CHCl_3$; (iii) ethyl chloroformate; (iv) RNH_2 (**a**: R = (*R*)-methylbenzyl; **b**: R = (*S*)-methylbenzyl; **c**: R = phenethyl; **d**: R = *n*-butyl); (v) $LiAlH_4$, reflux in THF; (vi) $(CH_2O)_n$, reflux in benzene.

Keywords: chiral ligands; disulfides; imidazolidine; enantioselective addition; L-cystine.

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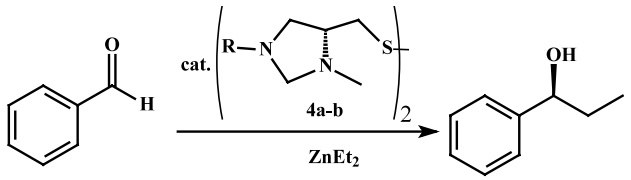
using the mixed anhydride coupling method[11] to give the amides **2** in 75–85% yields. The amines disulfides **3** were obtained by treatment of **2** with $LiAlH_4$ in THF followed by stirring with aqueous basic and aerial oxidation (45–54%). These compounds were treated with paraformaldehyde to give the desired imidazolidine disulfides **4a–d** in 45–55% yields (Scheme 1).

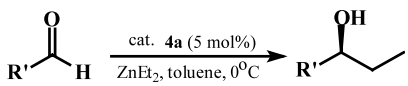
Table 1. Enantioselective addition of $ZnEt_2$ to benzaldehyde promoted by chiral ligands **4a–b**[a]



Entry	Ligand (mol%)	Yield[b] (%)	E.e. (%)[c] (config.)[d]
1	**4a** (30.0)	99	91 (*S*)
2	**4a** (15.0)	99	91 (*S*)
3	**4a** (10.0)	99	91 (*S*)
4	**4a** (5.0)	99	91 (*S*)
5	**4a** (5.0)[e]	99	84 (*S*)
6	**4a** (5.0)[f]	82	77 (*S*)
7	**4b** (5.0)	99	86 (*S*)
8	**4c** (5.0)	99	68 (*S*)
9	**4d** (5.0)	92	66 (*S*)

[a] The reactions were carried out in toluene at 0°C for 48 h; benzaldehyde/$ZnEt_2$ = 1.0/2.0 (mmol).
[b] Based on isolated product.
[c] Determined by GC analysis using a chiral column (2,6-Me-3-Pe)-β-cyclodextrin (20% in Polysiloxan OV-1701).
[d] Configurations were assigned by comparison with the sign of optical rotation of known compound.[12]
[e] The reaction was carried out in toluene at rt for 24 h.
[f] Tetrahydrofuran as reaction solvent.

Table 2. The enantioselective addition of $ZnEt_2$ to aldehydes promoted by ligand **4a**[a]



Entry	R′	Yield[b] (%)	E.e. (%)[c] (config.)[d]
1	Ph	99	91 (*S*)
2	*p*-ClPh	92	89 (*S*)
3	*o*-ClPh	93	89 (*S*)
4	*o*-BrPh	94	90 (*S*)
5	*p*-MeOPh	60	70 (*S*)
6	*o*-MeOPh	62	76 (*S*)
7	*p*-MePh	94	84 (*S*)
8	*n*-Nonyl	52	66 (*S*)[e]
9	*n*-Pentyl	59	76 (*S*)[e]

[a] The reactions were carried out in toluene at 0°C for 48 h; aldehyde/$ZnEt_2$ = 1.0/2.0 (mmol).
[b] Based on isolated product.
[c] Determined by GC analysis using a chiral column (2,6-Me-3-Pe)-β-cyclodextrin (20% in Polysiloxan OV-1701).
[d] Configurations were assigned by comparison with the sign of optical rotation of known compounds.[12]
[e] Determined by GC analysis of its *N*-tosyl-prolyl-ester derivatives.

In order to examine the effectiveness of these ligands (**4a–d**), we first evaluated their behavior in the enantioselective addition of diethylzinc to benzaldehyde (Table 1). The active catalyst is most likely to be the corresponding ethylzinc thiolate, obtained from disulfide cleavage by diethylzinc as described by Kellogg.[2a] However, this likely process was not rigorously proven for our catalysts, but offers the future prospect of cutting the amount of catalyst required in half, if the thiol-form is applied.

We investigated the effects of a variety of reaction conditions including solvent, temperature, ligand and the amount of ligand (Table 1, entries 1–10). We found that the use of 5 mol% imidazolidine disulfide **4a**, as the ligand in toluene at 0°C gave the best result (99% yield, 91% e.e., entry 4). When catalysts **4b–d** were used (66–86% e.e., Table 1, entries 7–9), the results showed lower enantiomeric excess than **4a**. These results suggest that the substituent at the nitrogen atom plays an important role in the enantioselection of the addition reaction.

Next, we decided to apply the addition of diethylzinc to various aldehydes under standard conditions and the results are summarized in Table 2. As can be seen from the results, *p*-methoxybenzaldehyde and *o*-methoxybenzaldehyde gave low e.e.s of 70 and 76%, respectively (entries 5 and 6). This fact can be explained by the presence of an electron-donating group on the benzene ring, due to an electronic effect.[13] When we tested other aldehydes such as *o*-bromobenzaldehyde, *o*-chlorobenzaldehyde and *p*-chlorobenzaldehyde (entries 2–4) a good enantioselectivity comparable to that of benzaldehyde was observed (entry 1). For aliphatic aldehydes the enantioselectivity of the reaction was moderate (66 and 76% e.e., entries 8 and 9). In this reaction, all the product alcohols were obtained with (*S*)-configuration.

In summary, we have successfully synthesized a new class of chiral disulfides (imidazolidine disulfides)[14] and evaluated their catalytic efficiency in the enantioselective addition of diethylzinc to aldehydes. Further studies of these ligands in other catalytic asymmetric reactions are in progress.

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14. Compound **4a**: $[\alpha]_D^{25}=+162$ (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.36–7.21 (m, 10H), 3.77 (d, $J=5.56$ Hz, 2H), 3.35 (quart, $J=6.52$ Hz, 2H), 3.09 (d, $J=6.76$ Hz, 2H), 3.10–2.88 (m, 6H), 2.77–2.66 (m, 2H), 2.52 (dd, $J=9.28$, 6.40 Hz, 2H), 2.40 (s, 6H), 1.36 (d, $J=6.40$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.60, 128.42, 127.11, 126.95, 77.46, 64.51, 64.02, 57.03, 42.73, 40.51, 23.13; IR (film; cm^{-1}) 3024, 2967, 2870, 2790, 1699, 1491, 1453, 1369, 1245, 1122, 1090, 967, 868, 763, 701; LRMS (rel. int.) *m*/*z* 470 (1), 412 (1), 235 (2), 203 (2), 134 (7), 118 (3), 102 (100), 87 (3), 77 (12), 70 (17), 56 (7). Compound **4b**: $[\alpha]_D^{25}=+84$ (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.36–7.20 (m, 10H), 3.60 (d, 2H, $J=5.40$ Hz), 3.30 (q, $J=6.40$ Hz, 2H), 3.11 (d, $J=5.40$ Hz, 2H), 2.97–2.65 (m, 10H), 2.38 (s, 6H), 1.33 (d, $J=6.52$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 144.51; 128.43, 127.23, 126.95, 77.54, 64.37, 63.78, 56.81, 42.99, 40.51, 22.94; IR (film; cm^{-1}) 3026, 2973, 2880, 2785, 2778, 1677, 1604, 1492, 1452, 1371, 1316, 1245, 1127, 1100, 971, 869, 764, 701; LRMS (rel. int.) *m*/*z* 470 (1), 235 (3), 203 (3), 134 (10), 118 (5), 102 (100), 87 (3), 77 (15), 70 (25), 56 (10). Compound **4c**: $[\alpha]_D^{25}=+89$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.30–7.15 (m, 10H), 3.78 (d, $J=5.60$ Hz, 2H), 3.24 (d, $J=5.56$ Hz, 2H), 3.09 (dd, $J=9.34$, 7.32 Hz, 2H), 3.03–2.90 (m, 4H), 2.85–2.69 (m, 12H), 2.44 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 139.76, 128.59, 128.37, 126.14, 78.73, 64.39, 58.23, 56.55, 43.06, 40.63, 35.35; IR (film; cm^{-1}) 3025, 2965, 2870, 2789, 1690, 1490, 1456, 1372, 1245, 1120, 1090, 971, 861, 761, 703; LRMS (rel. int.) *m*/*z* 470 (1), 235 (3), 203 (2), 134 (34), 102 (100), 87 (5), 77 (14), 70 (30), 56 (14). Compound **4d**: $[\alpha]_D^{25}=+145$ (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 3.64 (d, $J=5.56$ Hz, 2H), 3.11 (d, $J=5.52$ Hz, 2H), 2.94 (dd, $J=9.20$, 7.36 Hz, 2H), 2.90 (dd, $J=12.64$, 4.36 Hz, 2H), 2.67 (dd, $J=12.78$, 7.84 Hz, 2H), 2.54 (dd, $J=9.34$, 6.20 Hz, 2H), 2.49 (m, 4H), 2.36 (s, 6H), 1.39 (quint, $J=7.60$ Hz, 4H), 1.27 (sext, $J=7.68$ Hz, 4H), 0.84 (t, $J=7.28$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 78.89, 64.39, 58.33, 54.65, 43.26, 40.70, 30.81, 20.52, 13.91.; IR (film; cm^{-1}) 2927, 2860, 2792, 1456, 1368, 1243, 1127, 1038, 904; LRMS (rel. int.) *m*/*z* 373 (1), 220 (3), 187 (57), 163 (8), 158 (16), 141 (100), 116 (9), 102 (9), 70 (36), 56 (27).