Substituted *N*-salicylidene β-aminoalcohols: preparation and use as chiral ligands in enantioselective sulfoxidation and conjugate addition

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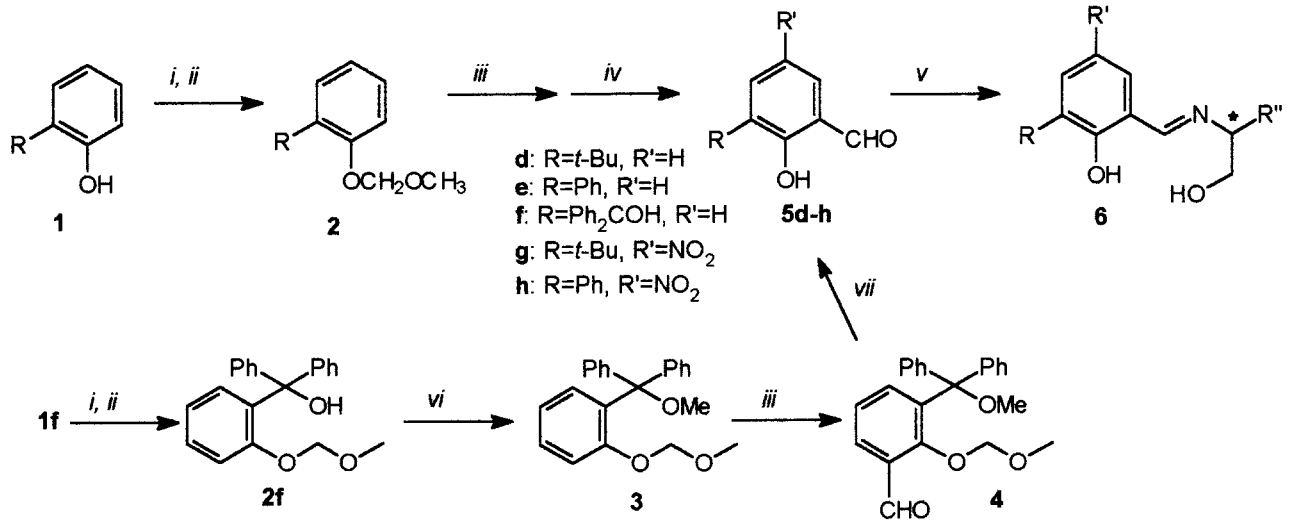
A high yielding synthesis of optically active 3,5-disubstituted salicylidene β-amino alcohols (**6**) is described. The catalytic use of D or L-*N*-(3-phenyl-5-nitrosalicylidene)valinol in enantioselective sulfoxidation (H_2O_2 / $VO(acac)_2$) gives up to 95% e.e. Asymmetric conjugate addition of thiophenol to 2-cyclohexen-1-one catalysed by Ti(OPr-*i*)$_4$ and **6** leads to maximum 31% e.e. in the product.

Keywords: enantioselection, Schiff bases, sulfoxidation, catalysis, Michael addition

The Schiff bases derived from substituted salicylaldehydes and optically active β-amino alcohols attract considerable attention as chiral ligands in transition metal catalysed reactions.[2–4] However, in many cases the details of their synthesis and/or properties have not been disclosed. We describe here an optimised method for the preparation of new chiral ligands and the results of their catalytic use in the enantioselective sulfoxidation and conjugate addition of thiophenol to enone.

The 3,5-disubstituted salicylaldehydes **5a–c** required were obtained from the parent phenols and paraformaldehyde,[5] and purified using column chromatography or recrystallisation. However, these methods of separation failed in the absence of substituent in the 5 position (R′ = H). For the preparation of pure aldehydes **5d–f** we applied the aromatic ring *ortho*-lithiation and subsequent reaction with DMF.[7] The sterically hindered hydroxyphenol **1f** was protected at both hydroxy groups and then formylated. The aldehydes (**5d, e**) were also nitrated according to the described method.[8]

For the preparation of chiral Schiff bases we modified the procedure of Oguni and coworkers.[9] The substituted salicylaldehyde and chiral β-amino alcohol in abs. ethanol were refluxed, then water evolved was removed as the azeotropic mixture with toluene added (Scheme 1).



5	R	R′
a	*t*-Bu	*t*-Bu
b	*t*-Bu	Me
c	*t*-Bu	OMe
d	*t*-Bu	H
e	Ph	H
f	$Ph_2C(OH)$	H
g	*t*-Bu	NO_2
h	Ph	NO_2

6	R	R′	R″
a	*t*-Bu	*t*-Bu	*i*-Pr
b	*t*-Bu	*t*-Bu	*t*-Bu
c	*t*-Bu	*t*-Bu	Ph
d	*t*-Bu	Me	*i*-Pr
e	*t*-Bu	OMe	*i*-Pr
f	*t*-Bu	OMe	*t*-Bu
g	*t*-Bu	NO_2	*i*-Pr
h	*t*-Bu	NO_2	*t*-Bu

6	R	R′	R″
i	*t*-Bu	NO_2	Ph
j	Ph	NO_2	*i*-Pr
k	Ph	NO_2	*t*-Bu
l	Ph	NO_2	Ph
m	Ph	H	*i*-Pr
n	$Ph_2C(OH)$	H	*i*-Pr
o	$Ph_2C(OH)$	H	*t*-Bu

Scheme 1 *Regeants and conditions: i*, KOH/toluene-DMF; *ii*, CH_3OCH_2Cl/toluene; *iii*, 1. BuLi/TMEDA/Et_2O, 2. DMF; *iv* HNO_3/AcOH, r.t.; *vi*; chiral β-amino alcohol/EtOH-toluene; *vi*, 1. NaH/DMF, 2. MeI/DMF; *vii*, 6M HCl/MeOH

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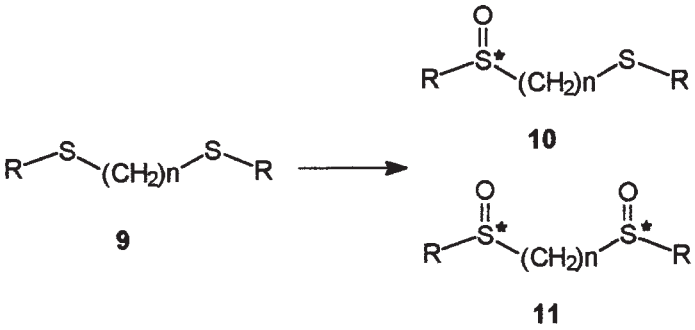

Scheme 2 Regeants and conditions: 2.3 eq. H_2O_2, CH_2Cl_2/H_2O, 2 mol% $VO(acac)_2$, 3 mol% **6j**, 0°C, 20–48h

Bis-sulfide **9**	R	*n*	Mono-oxide **10**		Bis-oxide **11**		
			Yield/%	E.e.[a]/%	Yield/%	D.e.[a]/%	E.e.[a]/%
a	t-Bu	0	41, 90b	17, 80b	–	–	–
b	Ph	1	32	72	38	50	84
c	Ph	2	35	57	41	60	95
d	Ph	3	–	–	92	>80	25

[a]Stereoselectivities were determined by ^1H NMR: d.es – directly, e.es – using $Eu(hfc)_3$ in CCl_4 solutions.
[b]Using **6b** instead of **6j**; for **6b** 94% conv. and 82% e.e. have been reported.[12]

With the series of chiral Schiff bases **6a–o** in hand, we have run model sulfoxidations with 30% hydrogen peroxide catalysed by their vanadyl complexes. This screening corroborates our finding[4] that **6j** is at least as good chiral inducer as the previously reported **6b**, **h**.[3] Moreover, **6j**, unlike **6b**, **h** is easily available in both enantiomeric forms. The catalytic oxidation gave the same configuration at the oxidised sulfur atom as it was in the catalyst, *i.e*. (+)-(*R*)-sulfoxide resulted from the reaction with (+)-**6** and (-)-(*S*)-isomer was formed with (-)-**6**. Thus, **6j** offers an easy way to both enantiomeric forms of sulfoxides. We also investigated the catalytic oxidation of bis-sulfenyl derivatives **9** to the respective chiral mono-*S*-oxides (**10**) and C_2 symmetric bis-sulfoxides (**11**) (Scheme 2). This simple catalytic reaction provides a synthesis of the valuable chiral building blocks **10b** and **11b.**[11]

We also tested the obtained chiral Schiff bases **6** in the titanium isopropoxide catalysed addition of thiophenol to 2-cyclohexene-1-one. The reaction was carried out with the pre-formed titanium complex, in toluene at 0°C and in the presence of (–)-**6,** the (–)-product was formed. Enantiomeric excesses obtained were low to moderate (up to 31%), however, better selectivity was observed for the ligands bearing electrodonating group in the salicylidene moiety. Interestingly, again the valinol derivative **6a** performed better than the more bulky compound of *tert*-leucinol **6b**.

Simple protocols for the preparation of 3,5-disubstituted *N*-salicylidene β-amino alcohols **6** were elaborated. The effectivenesses of **6j** as a chiral ligand in the catalytic sulfoxidation was confirmed and used for the synthesis of valuable chiral building blocks **10b** and **11b**, **c.**

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