A Purely Synthetic, Diversity Amenable Version of Norephedrine Thiols for the Highly Enantioselective Diethylzinc Addition to Aldehydes

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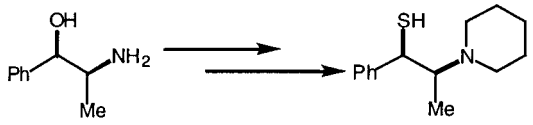
Received 19 April 2001

Abstract: A new β-aminothiol arising from purely synthetic yet enantiopure aminoalcohols has been prepared and successfully used in the addition of diethylzinc to aromatic aldehydes, yielding secondary alcohols in ee's up to 99%.

Key words: aminothiols, diethylzinc additions, enantioselective, catalytic, aziridinium salt

Chiral ligands for asymmetric catalysis[1,2] have been generally prepared from a limited chiral pool of readily available natural products.[3] This fact does not allow in many cases significant optimization of the catalytic properties because of the difficulties associated to the synthetic manipulation of the starting natural product. To circumvent this common problem, we have introduced several families of modular aminoalcohols[4,5] which can be readily prepared through the stereospecific and regioselective ring opening of enantiopure epoxides of synthetic origin.[6]

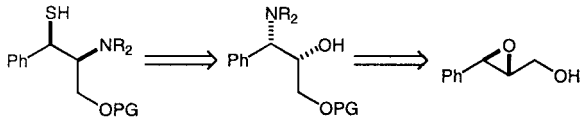
At this point, we realized that several aminothiols[7] and aminothioacetates[8] had been synthesized starting from (–)-norephedrine **1** (Scheme 1) and successfully used as catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes, yielding chiral secondary alcohols of high enantiomeric purity. Several sulfur-containing amino acid derivatives have also been used as ligands in the same reaction,[9] in the asymmetric reduction of prochiral ketones,[9a,b,10] and in other processes.[11]



1 **2**

Scheme 1

In line with previous experience in our group, which has led to the development of highly efficient β-aminoalcohol ligands[4] from enantiopure epoxyalcohols, we thought that modular aminothiols could easily be prepared in the same manner. Thus, we planned to synthesize norephedrine thiol analogues **3** starting from (2*R*,3*R*)- or (2*S*,3*S*)-2-alkoxy-3-dialkylamino-3-phenyl-2-propanols **4**, which, in turn, are prepared from epoxycinnamyl alcohol **5** (Scheme 2) through regioselective and stereospecific epoxide opening with secondary amines and subsequent selective protection of the primary hydroxyl group.[4a,b]



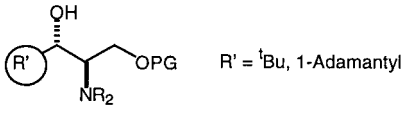
3 **4** **5**

Scheme 2

All the individual reactions used in this synthesis are known, so that the regio- and stereochemical outcome could be predicted as indicated in Scheme 2. An important advantage of this planning is that both enantiomers of **3** are equally accessible by simply changing the tartrate enantiomer used as the catalytic ligand in the Sharpless epoxidation leading to **5**. Furthermore, these β-aminothiols **3** have another modulable group besides the amino function; the protecting group of the primary alcohol is an important source of diversity since its variation can give rise to structures of very different bulkiness. We had previously observed that this factor exerts a deep influence on the catalytic properties of the ligand[4a,12] in aminoalcohols **4**.

We report herein the successful application of these ideas to the synthesis of the first members of a new family of aminothiols and S-acetyl derivatives thereof, and the preliminary results obtained in the addition of diethylzinc to aldehydes using these compounds as chiral ligands.

Two different aminoalcohols **4** were used as starting materials, the NR_2 substituent being specified as a piperidino (**4a**) or a dibutylamino (**4b**) group. The protecting group for the primary alcohol was initially chosen as a trityl, since it has been observed in the related family of aminoalcohols **4**[4a,b] and in the recently developed regioisomeric family **6**[12] that the very bulky trityl protecting group provides superior results in catalytic applications.



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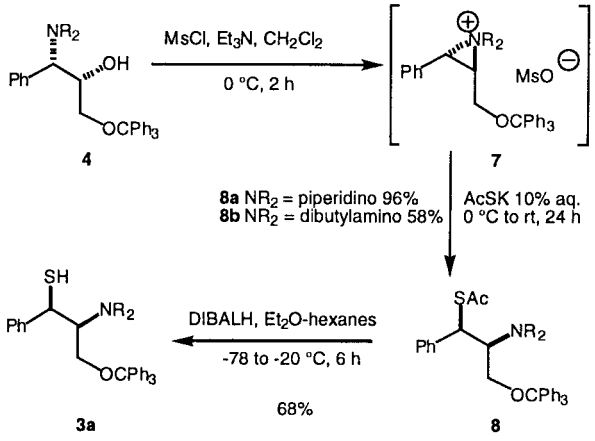
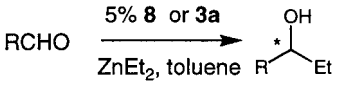


Scheme 3

Under these restrictions, the preparation of our target molecules was achieved through the sequence of reactions indicated in Scheme 3. Mesylation of the alcohol at 0 ºC in the presence of two equivalents of triethylamine led to formation of an intermediate aziridinium salt **7**[13] that was not isolated but treated in situ with a 10% aqueous solution of potassium thioacetate for 24 hours. After extractive work-up, aminothioacetate **8a** was isolated in excellent yield, in chemically pure form without further purification. In the case of **8b**, however, it was necessary to purify the S-acetyl derivative by column chromatography, and therefore yield was somewhat lower (58%). The regiochemistry was determined by MS-EI, and ions only compatible with fragmentation of the drawn structures were clearly observed. This is in accordance with the fact that the benzylic carbon atom in the aziridinium intermediate is the most reactive towards nucleophilic attack. Aminothioacetate **8a** was then reduced to the free thiol **3a**[14] with a commercial 1 M DIBALH solution in hexanes in good yield.

Due to the important steric effects exerted by the trityl group and, therefore, to the big difference with respect to the norephedrine derived aminothiol **2**, we had some concern on the catalytic activity of ligands **3a** and **8a,b**. Gratifyingly enough, the results of the initial trials in additions of diethylzinc to benzaldehyde[15] (Scheme 4) with β-aminothioacetates were excellent (Table 1, entries 1 and 2); addition took place with very high conversion and selectivity when **8a** was used, and enantioselectivities of 96% were achieved. The reaction was carried out in anhydrous toluene at 0 ºC for five hours, using a 5 mol% of **8a** (or whatever any other ligand used) and 2 equivalents of 1 M diethylzinc solution in hexanes, besides the corresponding aldehyde (1 equiv). Conversions were lower when the dibutylamino-containing ligand **8b** was used, but ee was still high (95% ee).

Most interestingly, β-aminothiol **3a** turned out to be an even better ligand, and the addition product to benzaldehyde was found to be of 99% ee (entry 3). Other aromatic aldehydes (entries 4-6) also showed excellent reactivity towards the diethylzinc addition (99% conversion and selectivity were observed), and led to the corresponding alcohols in 98-99% ee. When an aliphatic aldehyde, as n-heptanal, was tested, the resulting alcohol was only of 66% ee (entry 8), although total conversion and selectivity were achieved. This is not surprising when results previously obtained with other aminothiols are taken into account.[7] Finally, an α,β-unsaturated aldehyde was tested (entry 7), and the corresponding allylic alcohol was found to be of 99% ee.



Scheme 4

In conclusion, we have developed the first members of a new family of modular, synthetic analogues of norephedrine aminothiol ligands. Compound **3a** shows excellent catalytic activity and enantioselectivity in the addition reaction of diethylzinc to aromatic aldehydes, yielding secondary alcohols in 98-99% ee.

Table 1 Diethylzinc Additions to Aldehydes using 5% of **8a-b** or **3a**.

Entry	Ligand	Aldehyde	Conv.[%][a]	Select.[%][a]	ee [%][a, b]
1	(1*S*,2*R*)-**8b**	PhCHO	62	98	95 (*S*)
2	(1*S*,2*R*)-**8a**	PhCHO	99	98	96 (*S*)
3	(1*R*,2*S*)-**3a**	PhCHO	98	>99	99 (*R*)
4	(1*R*,2*S*)-**3a**	*p*-$CH_3C_6H_4CHO$	>99	>99	99 (*R*)
5	(1*R*,2*S*)-**3a**	*m*-$CH_3C_6H_4CHO$	>99	>99	99 (*R*)
6	(1*R*,2*S*)-**3a**	1-Naphtaldehyde	99	99	98 (*R*)
7	(1*R*,2*S*)-**3a**	(*E*)-$PhCHC(CH_3)CHO$	99[c]	99[c]	99 (*R*)[c]
8	(1*R*,2*S*)-**3a**	n-Heptanal	>99[c]	99[c]	66 (*R*)[c]

[a] Calculated by GC (β-DEX™ 120). [b] Absolute configuration assigned according to the elution order in the chiral capillary column. [c] The acetate derivative was analyzed.

The influence on catalytic activity of the steric effects created by the primary hydroxyl-protecting group in **3** is currently being investigated in our laboratories, and full data on the structural effects of aminothiols on their catalytic behavior will be reported soon.

Acknowledgement

This research was supported by MEC (grant PB98-1246) and DURSI (grant 2000SGR00019). CJ thanks Generalitat de Catalunya for a pre-doctoral fellowship.

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(14) A solution of **4** (0.817 g, 1.71 mmol) in CH_2Cl_2 (3 mL) under N_2 at 0 °C was treated with Et_3N (0.788 mL, 5.64 mmol) and MsCl (0.219 mL, 2.82 mmol). After 2 hours, 10% aq AcSK (5 mL, 6.57 mmol) was added, the mixture was allowed to warm up to r.t., and stirring was continued for 24 h. Water and CH_2Cl_2 (10 mL each) were added, the organic phase was separated, and the aqueous one extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated to afford pure **8a** (0.880 g, 96% yield) as an amorphous solid. Next, to a solution of **8a** (0.400 g, 0.750 mmol) in anhydrous Et_2O (5 mL) under N_2, DIBALH (1.6 mL, 1M in hexanes) was added dropwise at −78 °C. Stirring was continued for 6 hours, while the temperature slowly increased to −20 °C. Methanol (5 mL) was carefully added at −78 °C, the reaction mixture was allowed to warm up to room temperature, and the solvents evaporated. The residue was purified by column chromatography on silica gel (hexanes / AcOEt 95:5) to afford **3a** (0.252 g, 68% yield) as an amorphous solid. Data for **3a**: $[\alpha]_D^{22}$ = -48.8 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24 (m, 6H), 2.32 (m, 4H), 3.08 (m, 1H), 3.35 (m, 2H), 4.21 (d, J = 7Hz, 1H), 7.12-7.50 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.6, 26.6, 44.3, 51.7, 61.1, 70.6, 87.1, 125.6, 126.9, 127.6, 127.7, 127.8, 128.7, 142.6, 143.9; HRMS (CI, NH_3): Calcd for $C_{33}H_{36}NOS$: 494.2518; Found: 494.2505.

(15) **Typical experimental procedure:** 10 mg (0.02 mmol) of **3a** was dissolved in 1 mL of anhydrous toluene, under nitrogen atmosphere. A 1 M diethylzinc solution in hexanes (0.8 mL, 0.80 mmol) was added dropwise, and, after cooling the mixture at 0 °C, benzaldehyde (42 mg, 0.40 mmol) was added via syringe. Five hours later, the reaction was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases dried over Na_2SO_4. After filtration, the organic solution was analyzed by GC (β-DEX™ 120): Conversion was found to be 98%, selectivity was higher than 99%, and ee was 99%.

Article Identifier:
1437-2096,E;2001,0,07,1155,1157,ftx,en;G05301ST.pdf