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Norephedrine-derived Oxazolidines as Chiral Auxiliaries– Stereocontrolled Routes to *R* or *S* β-Hydroxy Phosphine Oxides

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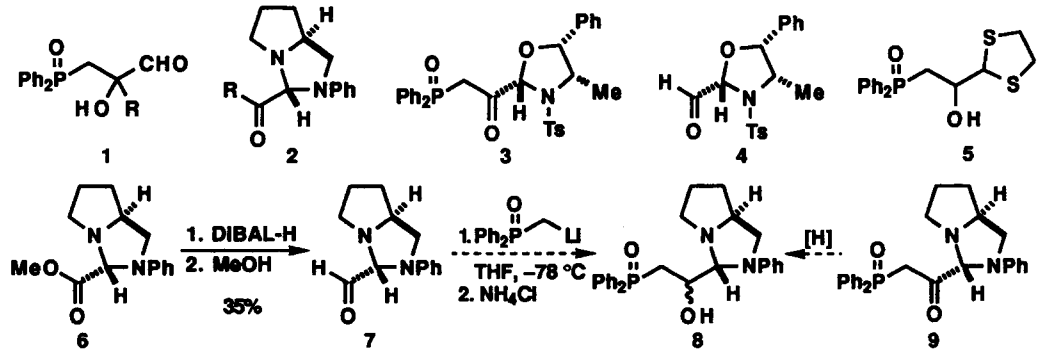
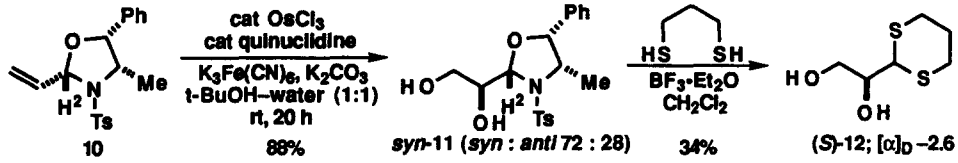
Abstract: Reduction of a β-keto phosphine oxide oxazolidine and reaction of an oxazolidine aldehyde with a lithiated phosphine oxide provide stereoselective routes to *S* or *R* β-hydroxy phosphine oxides.

Recently, we described a stereocontrolled synthesis of both enantiomers of diphenylphosphinoyl hydroxy aldehydes **1** (R = Ph and Me) using the addition of lithiated phosphine oxides to keto aminals **2** as the key step.[1] However, our attempts at extending this aminal methodology to the synthesis of aldehydes **1** in which R = H proved fruitless. In this paper, we wish to describe our failed attempts with the aminal methodology and a solution to this synthetic problem using norephedrine-derived oxazolidines as chiral auxiliaries. In particular, we report how reduction of keto oxazolidine **3** and addition of a lithiated phosphine oxide to aldehyde oxazolidine **4** provide stereocontrolled and complementary routes to either enantiomer of β-hydroxy phosphine oxide **5**.



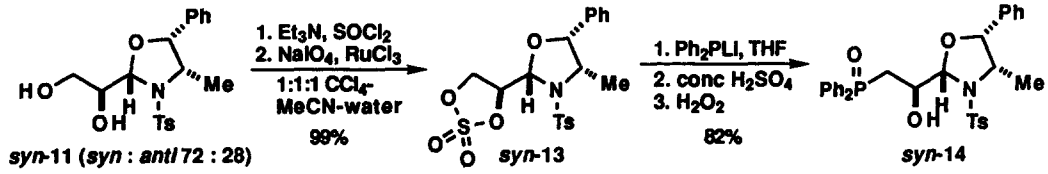
The known[2] aldehyde **7** was synthesised by diisobutylaluminium hydride reduction of methyl ester **6**. However, when we reacted a lithiated phosphine oxide with aldehyde **7** in exactly the same way as we had done with keto aminals **2** (R = Ph and Me), we never observed hydroxy aminals **8** either by isolation or in the ^{1}H NMR of the crude reaction mixture. In a similar manner, reduction of β-keto phosphine oxide **9**[3] with a variety of reducing agents [e.g. $NaBH_4$, $NaBH_4/CeCl_3{\cdot}7H_2O$, $LiAlH_4$, $LiAlH_4/ZnCl_2$, $Zn(BH_4)_2$] failed to generate hydroxy aminals **8**.

Because of the disappointing results of the aminal reactions, attention was switched to finding an alternative chiral auxiliary which was also a masked aldehyde. Apparently, reduction routes to alcohols similar to **8** are most popular: Eliel has described the reduction of keto oxathianes[4] and keto oxazines[5] whilst recent attention has focussed on reductions of *N*-tosyl[6,7] and *N*-Boc[8] protected keto oxazolidines derived from norephedrine. However, we decided to study reactions of keto oxazolidine **3** and aldehyde oxazolidine **4**, oxazolidine analogues of aminals **9** and **7** respectively.

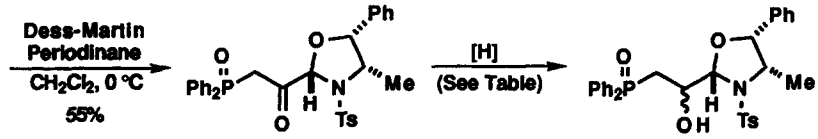


10 — *syn*-**11** (*syn* : *anti* 72 : 28) — (*S*)-**12**; $[\alpha]_D$ –2.6

Our synthesis of β-keto phosphine oxide **3** starts with the known[6] alkenyl oxazolidine **10** which is readily available from the condensation of *N*-tosyl norephedrine[9] with acrolein diethyl acetal.[10] Although conversion of **10** into 1,2 diols **11** has previously[11] been described, we preferred to synthesise 1,2 diols in an improved 88% yield (72:28 mixture of *syn*- and *anti*-**11**[12]) using the racemic dihydroxylation protocol developed recently in our own laboratory.[13] The relative stereochemistry of 1,2 diols **11** was established by conversion into the dithiane (*S*)-**12** {$[\alpha]_D$ –2.6 (*c* 1.2 in MeOH); lit.,[14] $[\alpha]_D$ +6.0 (*c* 1.08 in MeOH) for dithiane (*R*)-**12**}.



syn-**11** (*syn* : *anti* 72 : 28) — *syn*-**13** — *syn*-**14**



3 — **14**

Using Sharpless' conditions,[15] 1,2 diols **11** were transformed via the four cyclic sulfites into the cyclic sulfates **13** (in quantitative yield).[16] This 72:28 mixture of cyclic sulfates *syn*- and *anti*-**13** was then reacted at –30 °C with lithium diphenylphosphide (prepared according to the method of Ashby[17]). Stirring the reaction mixture overnight at room temperature with catalytic concentrated sulfuric acid in water[18] followed by hydrogen peroxide work up gave a very good 82% yield of hydroxy oxazolidines **14** (in a *syn*:*anti* ratio of 70:30). Subsequent Dess-Martin periodinane[19] oxidation of hydroxy oxazolidines **14** afforded the required β-keto phosphine oxide **3** in 55% yield (cf: 18% yield using Swern oxidation).

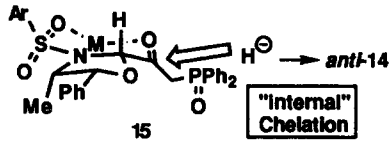
The results obtained from the reductions of β-keto phosphine oxide **3** to hydroxy oxazolidines **14** are presented in the Table. We were able to assign the sense of asymmetric induction because we had already synthesised hydroxy oxazolidines **14** from 1,2 diols **11** of known relative stereochemistry. In the cases where reduction had occurred (entries 2-5), the reactions were always highly *syn* selective. The conversion was low with L-selectride® (entries 2-3) but essentially complete with sodium borohydride (entries 4-5) and, from the Luche[20] reduction (entry 5), a 60% yield of hydroxy oxazolidine *syn*-**14** was obtained after chromatography.

Table: Reduction of β-Keto Phosphine Oxide **3** to Hydroxy Oxazolidines **14**

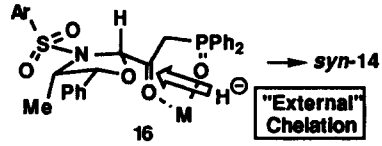
Entry	Reducing Agent	Solvent	Temp (°C)	SM[a] : Products[b]	*syn*-**14** : *anti*-**14**[b]
1	$LiAlH_4$	THF	0	—[c]	—[c]
2	L-selectride®	THF	–78	44 : 56	95 : 5
3	L-selectride® / $MgBr_2 \cdot Et_2O$	THF	–78	85 : 15	95 : 5
4	$NaBH_4$	EtOH	rt	No SM	88 : 12
5	$NaBH_4$ / $CeCl_3 \cdot 7H_2O$	EtOH	–78	No SM	95 : 5

[a] Starting material; [b] By ^1H NMR; [c] Expected alcohols **14** were not observed in the ^1H NMR of the crude reaction mixture.

When we carried out the reductions in the presence of magnesium bromide etherate and cerium (III) chloride (entries 3 and 5), we expected the reactions to proceed via the chelated intermediate **15** (M = Mg or Ce): nucleophilic attack on the less hindered face of the carbonyl group in this chelated form would then give hydroxy oxazolidines *anti*-**14** as the major products. Scolastico[6,7] and Hoppe[21] (*N*-tosyl) as well as Agami[8] (*N*-Boc) have used exactly this argument to explain the selectivity of Grignard reactions and reductions of other keto oxazolidines. In contrast, our reductions of β-keto phosphine oxide **3** in the presence of chelating metals (Mg and Ce) were highly *syn* selective (entries 3 and 5). We suggest that the presence of the diphenylphosphinoyl group interferes with the usual "internal" chelation of sulfonyl and ketone oxygens (e.g. **15**) – instead, "external" chelation between the ketone and phosphinoyl oxygens[22] occurs and the *syn* selectivity can be rationalised by Felkin control[23] (*N*-tosyl group perpendicular to the carbonyl group; transition state **16**) on an "externally" chelated intermediate.

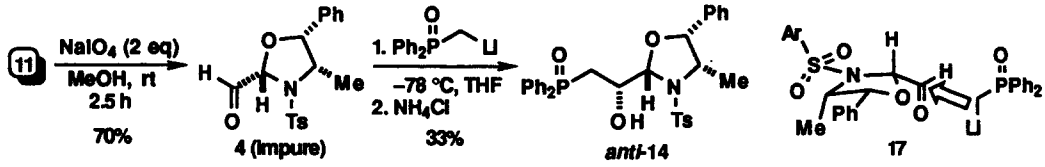


15



16

Although we were unable to find suitable conditions for the reduction of β-keto phosphine oxide **3** to hydroxy oxazolidine *anti*-**14**, we have been able to synthesise hydroxy oxazolidine *anti*-**14** using a different reaction. 1,2 Diol cleavage of a mixture of 1,2 diols **11** afforded aldehyde **4** which, despite repeated chromatography, could not be purified fully. Subsequent reaction (unoptimised) with lithiated methyldiphenylphosphine oxide gave a 33% yield of hydroxy oxazolidine *anti*-**14** after chromatography. The *anti* selectivity of the addition reaction can be rationalised using the Felkin[23] transition state **17**.



To demonstrate the synthetic potential of this methodology, we deprotected a 70:30 mixture of hydroxy oxazolidines *syn*- and *anti*-**14** using ethan-1,2-dithiol and $BF_3 \cdot Et_2O$[10,24] to give a 53% yield of β-hydroxy phosphine oxide (*S*)-**5** (40% ee by 400 MHz ^1H NMR spectroscopy in the presence of Pirkle's chiral shift reagent[25]). In summary, we have described stereoselective syntheses of both hydroxy oxazolidines *syn*- and *anti*-**14** which are direct precursors of optically pure β-hydroxy phosphine oxides (*S*)- and (*R*)-**5**.

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