Metal salts induced improved α-hydroxylation of ketones for the preparation of the key chiral intermediate of azole antifungals

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Abstract: The first example demonstrating the influence of metal salts for an improved synthesis of 2',4'-difluoro-(R)-2-hydroxypropiophenone, (2), a key intermediate for the preparation of azole antifungals such as Sch 42427 (1) in excellent enantiomeric excess and high chemical yield via the use of camphorsulfonyloxaziridines is described. © 1997 Elsevier Science Ltd

Since the report of camphorsulfonyloxaziridines as chiral, selective, aprotic and neutral oxidizing reagents by Davis,[1] several avenues are being simultaneously progressed by researchers to advance their synthetic utilities. These consist of:
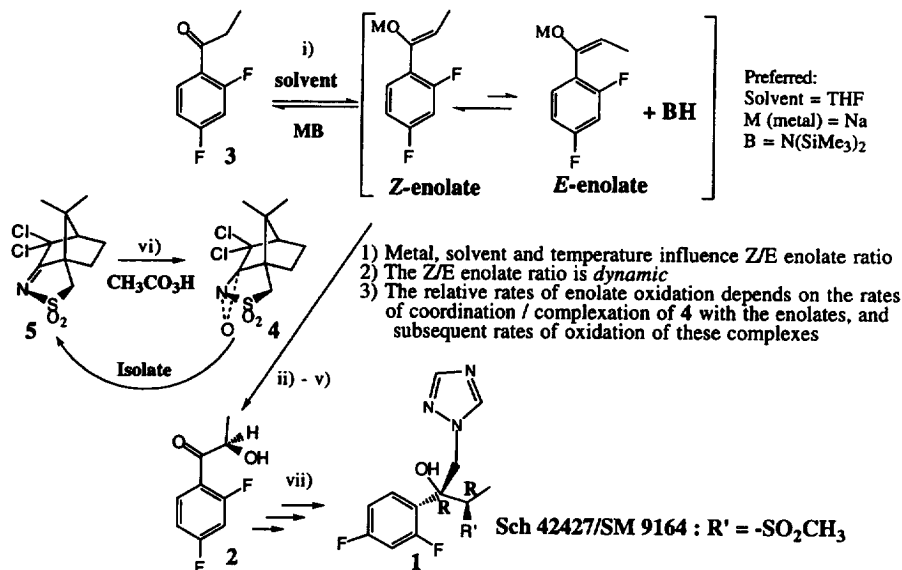
(1) Development of novel camphorsulfonyloxaziridines as more efficient reagents;[2]

(2) Their use for the preparation of chiral hydroxy ketones,[1–3] sulfoxides,[4] hydroxy phosphonates,[5] and selenoxides[6] towards the synthesis of biologically active compounds. In some instances camphorsulfonyloxaziridines have been competitive with the corresponding enzymatic preparations which require resolutions.[7] These reagents have also been used to prepare primary alcohols;[8]

(3) Economical, large scale synthesis and safe use of camphorsulfonyloxaziridines[9] resulting in their commercial availability; and

(4) Mechanistic investigations.[3,10]

In pursuit of making these reagents more accessible with standard laboratory equipment and routinely used procedures, based on our mechanistic studies, we report in this communication the first example of metal salts promoted improved hydroxylation of ketones.

Publications towards the syntheses of potent azole antifungals compounds (1) such as Sch 42427 and ER-30346 indicate that chiral hydroxy ketone 2 is a key intermediate.[3,11] To this end a synthesis of 2 with a yield and *ee* of 95% via chiral hydroxylation of ketone 3 with camphorsulfonyloxaziridine 4 has been reported. The key feature of this along with the NMR based fine tuned mechanism is depicted in Scheme 1.

The low temperature d_8-THF NMR study[3] of the reaction mixture, which allowed for the fine tuning of the mechanism proposed by Davis,[10] suggested an existence of a dynamic *Z/E* enolate ratio[12] which dependent on the metal ion (Li>Na), the substrate (desfluoro-3>3), and the temperature (the lower the temperature, the better the ratio in the range of −40° to −90°) employed. This study also showed that for a set of substrate/metal combination, a certain *Z/E* enolate ratio could be generated at a given temperature regardless of the temperature at which the enolates were formed or the mixture was held previously. Thus the enolate ratio at the time of oxidation determines the *ee*s in the above reactions, and it is influenced by the temperature, the solvent, the base, the metal ion used in the reaction, the substitution pattern of the oxaziridines and of the substrate. The hydroxy phosphonates results reported recently[13] are in agreement with this mechanism proposed for enolates of ketones. The substrate for the above antifungals, 2',4'-difluoropropiophenone (3), is fixed, whereas the optimization of solvent, temperature, and oxaziridines has been described in the above article. Although under similar conditions Li generated a better *Z/E* enolate ratio than Na, the chemical yield for the oxidation

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i) solvent

MB

F **3**

MO

Z-enolate

MO

E-enolate

+ BH

Preferred:
Solvent = THF
M (metal) = Na
B = N(SiMe$_3$)$_2$

Cl
Cl

5   S
O$_2$

vi)
CH$_3$CO$_3$H

Cl
Cl

N   S
O   O$_2$ **4**

Isolate

ii) - v)

1) Metal, solvent and temperature influence Z/E enolate ratio
2) The Z/E enolate ratio is *dynamic*
3) The relative rates of enolate oxidation depends on the rates of coordination / complexation of **4** with the enolates, and subsequent rates of oxidation of these complexes

O
H
OH
F

F   **2**

vii)

N
N
N

OH   R
R
R'   Sch 42427/SM 9164 : R' = -SO$_2$CH$_3$

F   F   **1**

i) Table 1 ii) 1.2 eq. **4**; iii) aq. NH$_4$Cl, warm to r.t.; iv) extract w. EtOAc or CH$_2$Cl$_2$; v) replace solvent w. hexanes or heptanes, cool to 0°C, filter; vi) ref. 9b; vii) ref. 3a.

Scheme 1.

of the Li enolate was poor. This implies that the metal ion not only influences the Z/E ratio, it may also play an important role in other facets of the hydroxylation reaction such as influencing the rate at which the oxaziridines coordinate/complex with the enolates, and/or the rate of subsequent oxidation of the resultant complexes leading to the product. Hence we sought to further influence the yields and *ees* of **2** via manipulation of the remainder of variables, i.e. the metals. Since −90° to −95°C temperature is cumbersome to attain in the laboratory, emphasis was placed on making this reaction more amenable to routine laboratory equipment/techniques such as the use of −78°C temperature which can be attained safely.[14]

For this study, commercially available, non-hydrated metal salts, which can readily be removed at the end of the reaction either with routine workup or with filtration, were used without purification. The use of specially prepared salts would partially deviate from the intent of this work, and hence were excluded. Since oxaziridines are oxidants, the metals, preferably as their oxides in their higher oxidation state, were preferred for this study. To rule out potential mechanistic complications, chiral metal complexes or salts were not used in this proof of principle study. Note that the recycle of sulfonylimine **5** via an extraction of **5** with an organic solvent from the mixture containing **5** and metal salt was not evaluated for this small scale study. Based on the stability study of the oxaziridines[9] it is highly recommended that a thorough evaluation of the influence of the residual metal salt for the recycle of **5** be conducted prior to instituting recycle of either **5** or the metal salt.

Among many[15] metal salts screened, ones which led to either improved yield or more importantly improved *ees* compared to control are listed in Table 1. No straightforward correlation between the properties of the metal or the metal salts (e.g. solubility, radius, electronic nature, etc.) and the improved yield or *ee* is apparent. This favors the hypothesis suggested above where metal is expected to influence several facets of the mechanism outlined above, each facet requiring a selected property of the metal used.

In many cases the added salts resulted in a heterogeneous reaction mixture, yet most of the reactions were complete within three hours. When reactions were conducted at −40°C, the control reaction as well as the reactions where MgO, MgCl$_2$, or TeO$_2$ was added, led to product along with byproducts,

Table 1. Influence of metal salts on *ees* during α-hydroxylation of ketone 3[16,17]

i) THF, -78°C ii) Metal Salt iii) NaHMDS iv) 4	The metal salts, typically 1.1 molar equivalent, were added prior to the addition of 1.1 equivalnet NaHMDS. 1.2 Molar equivalent 4 was used for oxidation. NMR and HPLC[17] were used to determine yields and *ees* of isolated[16] product. Toluene in place of THF typically lowered the *ees*.

#	Periodic Table Group	Additive	Yield %	R:S (%ee)	#	Periodic Table Group	Additive	Yield %	R:S (%ee)
1	Control	--	80	90:10 (80)	10	IIIa	B_2O_3	95	91:9 (82)
2	Ia	RbCl	79	94:6 (88)	11		B_2PO_3	92	90:10 (80)
3		RbBr	85	94:6 (88)	12		EuF_3	84	90:10 (80)
4		RbI	88	94:6 (88)	13		Eu_2O_3	90	90:10 (80)
5		CsCl	90	90:10 (80)	14	IVb	TiO_2	90	90:10 (80)
6		CsBr	92	94:6 (88)	15		ZrO_4	91	90:10 (80)
7	IIa	$MgCl_2$	95	94:6 (88)	16	VIa	TeO_2	82	96.5:3.5(93)
8		MgO	90	93:7 (86)	17		SeO_2	95	92:8 (84)
9		$MgSO_4$	85	90:10 (80)					

hence it was deemed synthetically less useful. Increased amounts of metal salts usually had no beneficial effect. On the contrary, in some cases, the additional salts interfered with the stirring of reaction mixture and lowered yields. Since the reactions were complete in a resonable time at −78°C, for cost/practicality purposes, mixed metal salts that could improve the solubility of these salts were not used. Thus with TeO_2 at −78°C *ees* comparable to the one reported at −90° to −95°C were attained.

For the first time the influence of metals on the *ees* for the chiral hydroxylation of ketones is shown. This finding demonstrates an improved synthesis of the key antifungal intermediate 2 in good yield and excellent enantiomeric excess at −78°C, in place of −90° to −95°C. This finding generates yet another lead towards influencing the chemical and chiral outcome of enolate oxidation by camphorsulfonyloxaziridines. This should be valuable to those interested in improving enantiomeric excesses and yields of chiral compounds for biological or physicochemical studies.

Acknowledgements

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12. This contrast from the enolate trapping experiments with 3 (also shown for desfluoro-3, ref. 10b) where only the Z silyl (TMS or TBDMS) enolethers are formed.

13. See Table 1, p. 3496 of ref. 5.

14. A dry ice/highly flammable diethyl ether bath is typically the combination of choice to obtain a reaction temperature of −90°C to −95°C. Alternatively, liquid nitrogen containing baths may be used to obtain this temperature. On the other hand, a dry ice/acetone bath is a more common, less constraining/flammable laboratory technique to obtain approx. −78°C reaction temperature and hence the latter is more preferable.

15. The following salts led to decreased yields sand/or ees: Al_2O_3, CuCl, CuBr, $CuCl_2$, $CuBr_2$, $ZnCl_2$, $ZnBr_2$, $CeCl_3$, $SmCl_3$, $EuCl_3$, $SnCl_2$, $TeCl_2$. It is possible that in some cases the salts either consumed NaHMDS and/or decomposed the oxaziridine.

16. For instability of 2 see: Gala, D.; Puar, M. S.; Kugelman, M.; DiBenedetto, D. J. *J. Pharm. Sci.* **1992**, *81*, 1199. For high yields, maintain cold (0–10°C) temperature, inert atmosphere and neutral pH during the workup and storage of the product as indicated in ref. 3a.

17. The ees were determined by HPLC (Chiracel OB; 4–7% iPrOH/Hexane, 0.7 to 1.1 mL/min, UV 220nm).