Pergamon

Tetrahedron Letters 43 (2002) 2107–2110

TETRAHEDRON LETTERS

Asymmetric alkene epoxidation with chromium oxo salen complexes. Effect of added phosphoryl ligands

Nessan J. Kerrigan, Ivan J. Langan, Cormac T. Dalton, Adrian M. Daly, Claudine Bousquet and Declan G. Gilheany*

Chemistry Department and Conway Institute of Biomolecular and Biomedical Sciences, University College Dublin, Belfield, Dublin 4, Ireland

Received 5 December 2001; accepted 24 January 2002

Abstract—In the stoichiometric asymmetric epoxidation of *E*-β-methylstyrene with cationic chromium–salen oxo complexes, enantioselectivity is elevated by the addition of many different types of phosphoryl compounds. Triarylphosphine oxides are the most effective, and, amongst them, tris(3,5-dimethylphenyl)phosphine oxide gave the highest ee to date (93%). There is a ceiling effect of additive, bulky additives are ineffective, there is no substituent electronic effect within the additive and there is a saturation of its effect with increasing concentration.

The use of metal complexes of chiral salen ligands in catalytic asymmetric synthesis has been widespread in recent years.[1] Especially useful is the manganese–salen catalyzed asymmetric epoxidation of conjugated *Z*-alkenes (Fig. 1, M = Mn) studied extensively by Jacobsen[2] and Katsuki.[3] We have reported[4] on the complementary chiral chromium salen complexes which give good selectivity for *E*-alkenes (Fig. 1, M = Cr) and have the useful feature that the SalCr(V)=O species is stable,[5] unlike the SalMn(V)=O species which is a fleeting intermediate.[6,7] Use of the isolated Cr(V)=O species (stoichiometric reaction) then enables separate study of the stereoselectivity and catalysis issues. We have shown that the high ees obtained stoichiometrically were not fully maintained in the catalytic version of the reaction, although the latter gave a higher yield.[4b,c,e] We proposed an explanation[4e] based on reaction of the Cr(V)=O with its reduced Cr(III) form to give an unreactive μ-oxo dimer, Cr(IV)–O–Cr(IV) (Fig. 1), the manganese version of which is considered to be the resting state of the catalyst in the manganese series.[6,8]

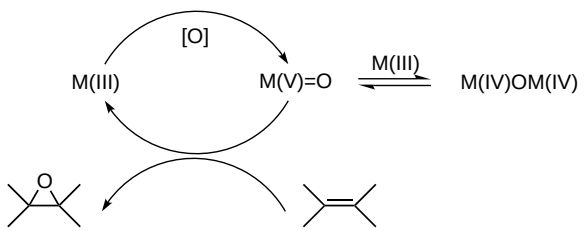
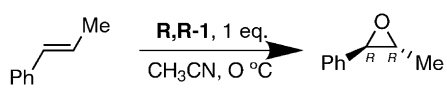


Figure 1. The catalytic cycle for chromium and manganese salen epoxidation.

A notable aspect of our system was the change in enantiomeric excess (ee) by as much as 30% on addition of certain achiral oxo-type ligands (L), such as phosphine oxides and amine *N*-oxides.[4b,c,f] In the case of chromium salen complexes, it was known[5,9] that such additives are coordinated by the oxygen atom in the apical position (L in complex **1**, Scheme 1), which weakens the Cr=O bond and increases epoxidation rate. We are not aware of any other studies of additives in the chromium series. In contrast, additives have a wide range of reported effects on the chiral manganese–salen epoxidation.[2,3] We hoped that the stoichiometric variant of the reaction available in the chromium series might provide an understanding of the manganese system. Our first studies showed that there is a complex relationship between the effect of L addition and the salen substituents W–Z in **1**. Thus, ee can be increased

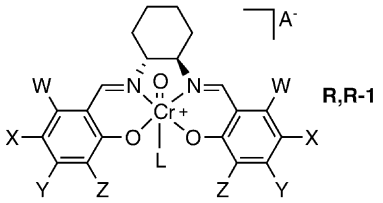


Scheme 1.

Keywords: asymmetric epoxidation; chromium; salen; phosphine oxide; *meta*-effect.

* Corresponding author. Tel.: +353-1-7162308; fax: +353-1-7162127; e-mail: declan.gilheany@ucd.ie

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00193-4



R,R-1

when substituents are present at X/Z but not at W/Y.[4f] Since then we have embarked on more comprehensive studies and we now report on phosphorus-containing additives. Variations in nitrogen-containing and other additives will be the subject of future reports. The studies show that a very large range of ligands can influence the observed selectivities. Included in the work reported here are a series of triarylphosphine oxides, one of which provided an improvement to give our highest ee to date (93%) with our test substrate, *E*-β-methylstyrene (Scheme 1).

The additive triphenylphosphine oxide (TPPO) had previously been most consistent in raising yield and ee.[4b,c,e,f] Therefore, we examined a range of substituted tertiary phosphine oxides with the hope of optimizing the selectivity and of gaining an understanding of their mode of action. Table 1 shows results for the epoxidation[10,11] of β-methylstyrene using five of our oxo-chromium(V) salen complexes[12] in combination with (1 equiv. of) various types of mostly triarylphosphine oxides,[13] according to Scheme 1. The presence of additive usually decreased the reaction time, but only by as much as half at best, and it usually increased epoxide yield. However, the best yields were still those obtained with TPPO, except in the case of complex **1**:W = H, X = Z = Br (with the additive at entry 11). All complexes gave very low yields (<5%) with at least one additive. Note that the best yields only approach 50% because the Cr(V)=O species reacts with the Cr(III) product;[4e] the reaction time does not reflect the true rate of epoxidation for the same reason.

Table 1. Results of stoichiometric epoxidation[a] of *E*-β-methylstyrene according to Scheme 1 with various chiral non-racemic substituted oxo-chromium(V) salen complexes[b] in the presence of various substituted triarylphosphine oxides L[c] as added ligands

Complex	**W** **X** **Y**	**H** **H** **H**	**H** **Cl** **Cl**	**H** **Br** **Br**	**H** **H** **Cl**	**H** **H** **CF_3**
	Reaction time[d]	12 h	60 min	10 min	60 min	90 min
	Yield with no additive (%)	22	18	2	20	25
	Highest yield with additive (%)	46	40	24	35	33
	ee with no additive	58	67	71	80/81[f]	88[g]/90[f]
Entry	Additive L	Increase in ee with additive				
1	Ph_3PO[e]	14	16	8	6/7[f]	2[g]/2[f]
2	Ph_3PO[h]	14[i]	16[i]		6	
3	$(4\text{-MeOPh})_3PO$	11	16[h]	6	6/6[f]	−5
4	$(3\text{-MeOPh})_3PO$	16	11	7	6[i]/7[f]	−5
5	$(2\text{-MeOPh})_3PO$	6		5	2	
6	$(2,4,6\text{-triMeOPh})_3PO$	−2		−23	−3	
7	$(4\text{-FPh})_3PO$		15		5	−3
8	$(3\text{-FPh})_3PO$	11	13	5	1	
9	$(\text{pentaFPh})_3PO$	6	8	−12	−1	
10	$(3,5\text{-diFPh})_3PO$	3			−3	
11	$(3,5\text{-diMePh})_3PO$	14		7	4	3[f]
12	$(2,4\text{-diMePh})_3PO$	4			−12	
13	$(2,6\text{-diMePh})_3PO$	−7		1	−2	
14	$(2,4,6\text{-triMePh})_3PO$	4[h]			−2[h]	
15	Oct_3PO	11[h]			1[h]	
16	$^tBu_3PO$	5[h]			3[h]	
17	$(EtO)_3PO$	7[h]			0[h]	
18	$(4\text{-MePhO})_3PO$	7[h]			0[h]	
19	$(C_4H_8N)_3PO$[j]				0	0

[a] Procedure (CAUTION) as described in Ref. 10, all at 0°C; ee determined by CSP GC.
[b] A = hexafluorophosphate unless noted otherwise and Y = H in all cases.
[c] 1 equivalent added, unless noted otherwise.
[d] Time to discharge of green colour to orange.
[e] Previously reported by us, Ref. 4.
[f] A = nitrate.
[g] Incorrectly reported as 86% (no additive) and 88% (TPPO as additive) in Ref. 4e.
[h] 2 equiv. of additive.
[i] The (*SS*)-chromium complex was also used and gave the same ee of opposite enantiomer of epoxide.
[j] Tris(1-pyrrolidinyl)phosphine oxide.

A general trend in enantioselectivity is visible in Table 1. The five complexes are arranged in order of increasing ee without additive, and it can be seen very clearly that the beneficial effect of additive becomes less as the ee without additive increases. Thus, the values of the entries become smaller or go negative to the right in Table 1. This confirms previous observations with our earlier more limited additive set. We refer to it as a *ceiling effect of additive*. It can be explained if changes in the salen-substitution pattern produce the same effect as addition of ligand L, but with the latter giving the weaker effect. Our working hypothesis is that both Z-substituents[4c] and additives L can favorably influence the conformation of complex **1** to give better selectivity. In complexes with suitable Z-substituents, the conformation without L reaches an optimum and the effect of L is thus minimal. However, the same effects could be produced by variations in the equilibrium involving complex with and without additive (vide infra).

Table 1 also shows the effects on enantioselectivity of substitution within the aryl rings of TPPO. The most immediately obvious, and disappointing, observation is that substitution mostly does not lead to increased selectivity. Thus, of the approximately 50 new data points in Table 1, only three are higher than obtained with TPPO. *ortho*-Substitution leads to lower, sometimes much lower, selectivity (compare: entries 5/6 to 3/4; 12/13/14 to 11; 16 to 1), assumed to be a steric effect. It is also noticeable that electronic effects are small, with electron donating groups (EDGs) only marginally better for selection than electron withdrawing groups (EWGs) (compare entries 3/7 and 4/8: five examples, two counter examples). Both EWGs and EDGs are usually worse than TPPO itself, again this is less noticeable with the EDGs (one example greater). It is not clear at this time why EDGs and EWGs should give similar changes in selectivity.

More encouraging was the observation that an EDG at the *meta*-position appears to be mostly beneficial (entries 4/11) and leads to our best ee to date (93%) for complex **1** (W = X = H, Z = CF_3) with L = tris(3,5-dimethylphenyl)phosphine oxide, marginally better than with TPPO. This additive also provides the best selectivity with other salen complexes that we have studied, for example with **1** (W = Cl, X = Z = H, not in Table 1) it gives an ee of 80%, again marginally better than with TPPO. This effect appears to be a combination of electronic and steric factors and has good precedence in the recent literature of enantioselective catalysis.[14–16]

Many other types of phosphoryl compound can lead to an increase in selectivity (Table 1 and Ref. 17). However, none are as good as TPPO. Indeed introduction of any non-aryl group in TPPO reduces the ee elevation.[17b] Symmetrical trialkylphosphine oxides (entry 15; Ref. 17c,d,e) do mostly give some reasonable ee elevation so long as they are not bulky (entry 16). Unsymmetrical[17a] and asymmetric cases[17f] are similar so long as they are not bulky[17g] as are phosphinate[17h] and phosphates (entries 17, 18, Ref. 17i,j,k) but tris(amino)phosphine oxide has no effect (entry 19). Phosphoryl chloride destroys selection.[17l]

In all cases examined, addition of a second (or further) equivalent of TPPO had no extra effect, giving the same ee elevation as the first equivalent (Table 1, entry 2). Indeed we found that maximum ee elevation is already attained at substantially less than one equivalent of additive. For example, with TPPO and complex **1**: W = X = H, Z = Cl, the maximum elevation (6) is achieved at 0.2 equivalents. A similar result was obtained with TPPO and complex **1**: W = X = Z = Cl. On the other hand, for the case of tris(3,5-dimethylphenyl)phosphine oxide as additive with complex **1**: W = H, X = Z = Br, the maximum elevation (8) was not achieved until approximately 0.5 equivalents of additive were present.

It is clear that addition of tertiary phosphine oxide increases rate and enantioselectivity. The latter, in turn, could mean that the presence of L changes the conformation of the complex. This would be in accord with and support similar recent proposals by Wiest, Plattner and co-workers in the manganese series.[7] However, it could also be that the presence of L affects the balance between the epoxidation rates of two different oxidants. We have previously had to postulate a second oxidant in the catalytic version of the reaction.[4e] Also, there are other aspects of the results that present a dilemma in analysis. With rate acceleration at less than one equivalent of L, these effects are examples of ligand-accelerated catalysis.[18] However, they are lower than expected from the work of Kochi and co-workers,[5] who found orders of magnitude accelerations with similar L and achiral SalCr(V)=O. On the other hand, the observed ee elevations, especially at lower L concentrations, *require* a substantially higher rate for LSalCr(V)=O over SalCr(V)=O. This is because the formation constant for LsalCr(V)=O is not very high. Kochi and co-workers[5] estimated it at approx. 13 M^{-1} for L = Et_3PO with achiral SalCr(V)=O. They also noted that it decreased as the bulk of the additive increased. With one equiv. of L, this corresponds to a ratio of LSalCr(V)=O to SalCr(V)=O of about 3. In addition, as the product SalCr(III) species builds up, it should sequester L as $L_2Cr(III)$.[5] These considerations lead us to suspect that the role of L in the chromium series is more complex than previously envisaged[5] and we are engaged in further experiments to investigate this.

In summary, we have found that, in epoxidations by SalCr(V)=O complexes, many phosphoryl additives give ee elevation, subject to a ceiling with the more beneficial salen substituents. The effect falls off with increasingly bulky substituents but there is almost no electronic effect of the substituents. The elevation saturates at less than one equivalent of additive.

Acknowledgements

The authors are grateful to Professor O. Wiest for helpful discussions. C.B. acknowledges a Marie Curie

Fellowship (No ERB4001GTR921129) from the European Commission. We thank Enterprise Ireland (Grants SC/93/213, SC/94/569 and SC/97/536, Scholarships for N.J.K., I.J.L.), University College Dublin for Demonstratorships (N.J.K., I.J.L., A.M.D.), and Schering Plough (Avondale) Ltd. for an Irish American Partnership Scholarship (C.T.D.). We also thank Drs. Kenneth Ryan, Valerie Wall, Marie Renehan and Colm O'Mahony for additional experiments.

References

1. Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85–93.
2. Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 18.2, pp. 649–677.
3. Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6B, pp. 287–325.
4. (a) Dalton, C. T.; Ryan, K. M.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Top. Catal.* **1998**, *5*, 75–91; (b) Bousquet, C.; Gilheany, D. G. *Tetrahedron Lett.* **1995**, *36*, 7739–7742; (c) Ryan, K. M.; Bousquet, C.; Gilheany, D. G. *Tetrahedron Lett.* **1999**, *40*, 3613–3616; (d) Daly, A. M.; Dalton, C. T.; Renehan, M. F.; Gilheany, D. G. *Tetrahedron Lett.* **1999**, *40*, 3617–3620; (e) Daly, A. M.; Renehan, M. F.; Gilheany, D. G. *Org. Lett.* **2001**, *3*, 663–666; (f) O'Mahony, C. P.; McGarrigle, E. M.; Renehan, M. F.; Ryan, K. M.; Kerrigan, N. J.; Bousquet, C.; Gilheany, D. G. *Org. Lett.* **2001**, *3*, 3435–3438.
5. Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606–7617.
6. Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309–2320.
7. (a) Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1718–1719; (b) Plattner, D. A.; Feichtinger, D.; El-Bahraoui, J.; Wiest, O. *Int. J. Mass Spectrom.* **2000**, *195/196*, 351–362; (c) Feichtinger, D.; Plattner, D. A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1023–1028; (d) Feichtinger, D.; Plattner, D. A. *Chem. Eur. J.* **2001**, *7*, 591–599; (e) El-Bahraoui, J.; Wiest, O.; Feichtinger, D.; Plattner, D. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2073–2076.
8. Bryliakov, K. P.; Babushkin, D. E.; Talsi, E. P. *J. Mol. Catal. A: Chem.* **2000**, *158*, 19–35.
9. Sidall, T. L.; Miyaura, N.; Huffmann, J. C.; Kochi, J. K. *J. Chem. Soc., Chem. Commun.* **1983**, 1185.
10. Experimental procedure. CAUTION: Cr(V)=O species are known carcinogens, all complexes were generated in situ. To the appropriate precursor (salen)Cr(III) complex (30–50 mg, 1 equiv.) in CH_3CN (5 mL) was added iodosylbenzene (1–2 equiv.). A deep green/black colour appeared almost immediately. After stirring for 30 min this solution was filtered and the filtrate was cooled to 0°C. The donor ligand (L) (1 equiv.) was added followed 5 min later by the alkene substrate (9–12 μl, 1 equiv.) and the solution was left until an orange/brown colour persisted. After evaporation and short path chromatography (alumina, Et_2O), analysis was by GLC on a Supelco α-cyclodextrin capillary column with *n*-decane as internal standard. As discussed previously (Ref. 4e), reduced yields are partially accounted for by recovered alkene, along with some benzaldehyde and benzyl methyl ketone. Burn ratios used and determination of absolute configurations have been given previously (Ref. 4e).
11. We confirmed that the influence of small amounts of water and atmospheric oxygen on the reaction was minimal. We have previously shown that the effects of extended reaction times and possible kinetic resolution effects are not significant under these conditions (Ref. 4e). The solvent used was acetonitrile but similar results were obtained in more limited studies using dichloromethane: O'Mahony, C. P.; Gilheany, D. G.; unpublished results.
12. We have previously described in detail (Ref. 4e) the synthesis of the precursor Cr(III) trifluoromethyl complexes. The other precursor Cr(III) complexes used in this work were synthesized in an analogous manner.
13. Most L are known compounds, prepared in short synthetic sequences, while a few were available commercially.
14. (a) Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315–6323; (b) Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A.; Eisentrager, F. *Organometallics* **2000**, *19*, 1299–1307 and references cited therein.
15. RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429–3447 and references cited therein.
16. (a) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441–1449; (b) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *Chem. Lett.* **2000**, 1272–1273; (c) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852–6856; (d) Blaser, H. U.; Buser, H. P.; Hausel, R.; Jalett, H. P.; Spindler, F. *J. Organomet. Chem.* **2001**, *621*, 34–38; (e) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499–1505 and references cited in this account.
17. Other ee results for **1**: L, W,X,Z, ee increase %: (a) 1-NapPh$_2$PO, H,H,Cl, 3; (b) Ph$_2$MePO, H,H,Cl, −1; (c) Et$_3$PO, H,H,Cl: 11; (d) ^{n}Bu$_3$PO: Cl,Cl,Cl, 4; (e) Oct$_3$PO, Cl,Cl,Cl, −1; (f) (±)-oAnMePhPO, H,H,H, 11; H,H,Cl, 6; (g) (±)-1-NapMePhPO, H,H,Cl, −2; (h) (±)-MeOMePhPO, H,H,H, 8; (i) (^{n}HexO)$_3$PO, H,HH, 12; H,H,Cl, −4; (j) (Me$_3$CH(CH$_2$)$_4$O)$_3$PO, H,H,H, 7; H,H,Cl, 3; Cl,Cl,Cl, 7; (k) (EtO)$_3$PO, Cl,Cl,Cl, 7; (l) Cl$_3$PO, Cl,C,Cl, −32.
18. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059–1070.