Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8135–8138

TETRAHEDRON LETTERS

$Co(thd)_2$: a superior catalyst for aerobic epoxidation and hydroperoxysilylation of unactivated alkenes: application to the synthesis of spiro-1,2,4-trioxanes

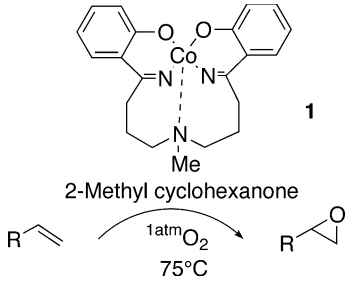
Paul M. O'Neill,[a,b,*] Stephen Hindley,[a] Matthew D. Pugh,[a] Jill Davies,[c] Patrick G. Bray,[c] B. Kevin Park,[b] Dauda S. Kapu,[c] Stephen A. Ward[c] and Paul A. Stocks[a]

[a]*Department of Chemistry, The Robert Robinson Laboratories, University of Liverpool, Liverpool L69 7ZD, UK*
[b]*Department of Pharmacology, University of Liverpool, Liverpool L69 3GE, UK*
[c]*School of Tropical Medicine, Pembroke Place, University of Liverpool, Liverpool L3 5QA, UK*

Received 21 July 2003; revised 12 August 2003; accepted 3 September 2003

Abstract—Bis(2,2,6,6-tetramethyl-3,5-heptanedionato)cobalt(II) ($Co(thd)_2$), a β-diketonate prepared in a simple one-step procedure, is an excellent catalyst for aerobic epoxidation and Mukaiyama–Isayama hydroperoxysilylation of unactivated alkenes. For hydroperoxysilylation, $Co(thd)_2$ is superior to $Co(acac)_2$ and can catalyse oxidation of cyclic alkenes in excellent yield. Chiral β-diketonate or keto iminato catalysts failed to catalyse this reaction in an enantioselective manner and a free radical mechanism consistent with this observation is proposed. Hydroperoxysilylation of cyclohex-1-enylmethanol by $Co(thd)_2$ followed by addition of a ketone/TsOH provides a simple one-pot procedure for the synthesis of spiro-1,2,4-trioxane antimalarials.

The selective monooxygenation of various organic compounds utilising molecular oxygen is one of the most challenging topics in synthetic organic chemistry.[1] Recently, a great deal of effort has been directed towards monooxygenation of olefins via single oxygen atom transfer by combined use of molecular oxygen and an appropriate reducing agent.[2] In 1992 Mukaiyama described conditions for the aerobic epoxidation of a range of alkenes by employing Co(II) Schiff base catalysts, e.g. **1** in the presence of ketones as reducing agents (Scheme 1).[3]



Scheme 1. Aerobic epoxidation of alkenes.

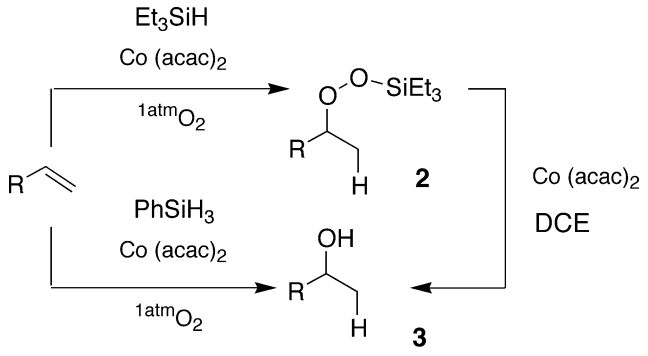
The yields for epoxidation were excellent (up to 98%). Equally impressive, was the discovery that several bis-(diketonato)Co(II) derivatives, e.g. $Co(acac)_2$ could effect aerobic epoxidation of alkenes in the presence of propionaldehyde diethyl acetal as the reducing agent.[4]

Further advances in this field have led to the development of aerobic asymmetric epoxidation, using either Co(II) salen derived Jacobsen type ligands[5] or chiral Mn(III) β-diketonate derivatives.[6] Both systems give reasonable yields of epoxide with excellent enantiomeric excesses.

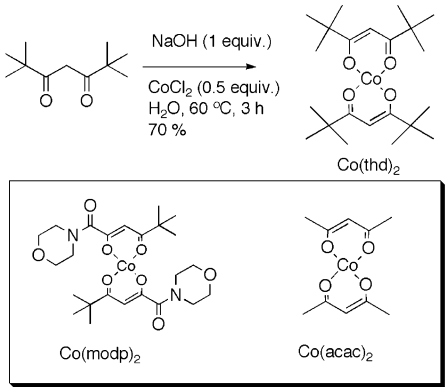
In parallel with this research, Isayama reported that modification of the above reaction conditions by replacement of the ketone with triethylsilane, as the reducing agent, enabled the smooth and regioselective conversion of alkenes into the corresponding triethylsilylperoxide derivatives **2** in good yield (Scheme 2).[7] Replacement of triethylsilane with phenylsilane in this reaction, gave the corresponding alcohol **3** as the product under neutral conditions. Further work demonstrated that silyl peroxides **2** could be smoothly reduced to alcohols **3** by reduction with catalytic quantities of $Co(acac)_2$ under an atmosphere of argon (Scheme 2, B).[8]

* Corresponding author.

0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.09.033



Scheme 2. Aerobic hydroperoxysilylation and hydration.



Scheme 3. Synthesis of $Co(thd)_2$ and structures of Co(II) β-diketonates.

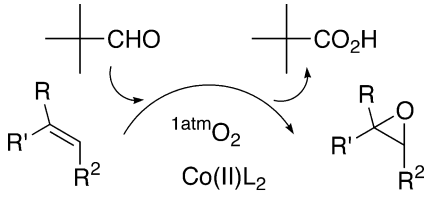
One of the best catalysts that has been employed in aerobic oxidation reactions of the type described in this report is bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedio-nato)cobalt(II) $Co(modp)_2$ (Scheme 3).[8] This catalyst is superior to $Co(acac)_2$ but requires a three-step synthesis. The overall yield for the synthesis of this catalyst is low. We reasoned that the corresponding catalyst derived from the ligand 2,2,6,6-tetramethylheptane-3,5-dione would have similar structural and electronic properties to $Co(modp)_2$. In this letter, we describe the synthesis and use of this catalyst in aerobic epoxidation and hydroperoxysilylation reactions on a variety of different alkene substrates. Results are compared with $Co(acac)_2$. We also describe the application of this catalyst to the synthesis of some simplified spiro 1,2,4-trioxane analogues of artemisinin by a simple one-pot operation.

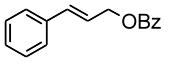
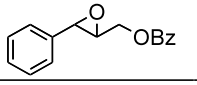
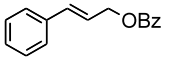
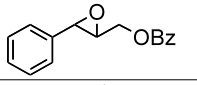
Bis(2,2,6,6 - tetramethyl - 3,5 - heptanedionato)cobalt(II) was prepared in 70% yield from the 1,3-diketone as shown in Scheme 3.

Several epoxidation reactions were carried out under a positive oxygen atmosphere using pivaldehyde as co-reducing agent. In all cases, $Co(thd)_2$ gave good to excellent yields of epoxide, with significant improvements over $Co(acac)_2$. The yields recorded in Table 1 correspond to isolated yields after column chromatography on silica gel. All reactions were complete after 4 h. A number of mechanisms have been proposed for the Mukaiyama aerobic epoxidation ranging from the generation of oxo-metal intermediates[9] to the metal catalysed formation of a per-acid.[10] More recent studies by Nolte and co-workers, suggest that for nickel-β-diketonates, the mechanism of the observed epoxidation is radical in nature with the formation of a nickel-bound acylperoxy radical which stays bound to the metal complex for stabilisation.[11] Evidence for distinct radical intermediates was provided by EPR studies. Whether this mechanism is involved in $Co(thd)_2$-mediated oxidations reported here remains to be established by appropriate additional experiments.

In addition to being a superior catalyst for epoxidation, $Co(thd)_2$ is also an excellent catalyst for effecting hydroperoxysilylation of alkenes. Substituting pivaldehyde for triethylsilane, we carried out hydroperoxysilylation on a number of different alkenes. Table 2 lists five examples which clearly show that this catalyst is superior to $Co(acac)_2$. Indeed, the final two entries show that $Co(acac)_2$ is a very poor catalyst for effecting oxidation of cyclic alkenes and allylic alcohols. In contrast, $Co(thd)_2$ can effect peroxysilylation in excellent yield. In all cases, the reactions proceed with high Markovnikov regioselectivity The solvent of choice in these reactions was found to be 1,2-dichloroethane (DCE).

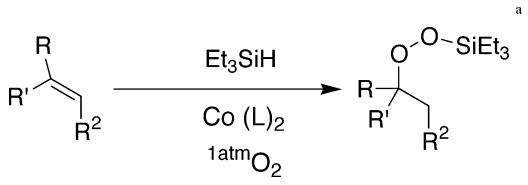
Table 1. Co(II)-mediated aerobic epoxidation of alkenes

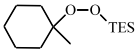
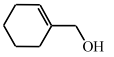
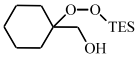


Catalyst/ equiv.	Alkene	Epoxide	Yield/%
$Co(thd)_2$/ 0.1	Styrene (R^1 = Ph, R, R^2 = H)	Styrene oxide (R^1 = Ph, R, R^2 = H)	74
$Co(thd)_2$/ 0.1	1,2-Dihydro-naphthalene	1,2-Dihydro-naphthalene epoxide	71
$Co(thd)_2$/ 0.1	R=Ph, R^1=H, R^2 = CH_2OH	R=Ph, R^1=H, R^2 = CH_2OH	79
$Co(thd)_2$/ 0.1			85
$Co(acac)_2$/ 0.1	Styrene	Styrene Epoxide	40
$Co(acac)_2$/ 0.1	1,2-Dihydro-naphthalene	1,2-Dihydro-naphthalene epoxide	56
$Co(acac)_2$/ 0.1	R=Ph, R^1=H, R^2 = CH_2OH	R=Ph, R^1=H, R^2 = CH_2OH	35
$Co(acac)_2$/ 0.1			37

[a] Reactions were carried out in benzene under an atmosphere of O_2 using pivaldehyde as the sacrificial reductant. The temperature in all cases was 30 °C.

Table 2. Co(II)-mediated aerobic hydroperoxysilylation of alkenes[a]



Entry	Alkene	Silylperoxide	$Co(acac)_2$ Yield/%	$Co(thd)_2$ Yield/%
1	Styrene	**2**, R = Ph	35	72
2	R=Bu, R^1=CH_3, R^2 = H	R=Bu, R^1=CH_3, R^2 = H	57	80
3	R=CH_3, R^1=Ph, R^2 = H	R=CH_3, R^1=Ph, R^2 = H	69	79
4	R=Ph, R^1=H, R^2 = CH_2OH	R=Ph, R^1=H, R^2 = CH_2OH	80	88
5	R=Ph, R^1=H, R^2 = CH_2OBz	R=Ph, R^1=H, R^2 = CH_2OBz	76	85
6	R=CH_3, R^1=CH_2OH, R^2=H	R=CH_3, R^1=CH_2OH, R^2=H	45	90
7			5	68
8			15	72

[a] TES = triethylsilyl, All reactions were carried out in 1,2-dichloroethane

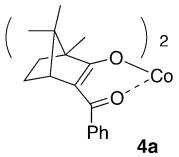
Until recently, the mechanism for this useful transformation was poorly understood. Based on this fact and several recent reports on the asymmetric aerobic epoxidation using cobalt Schiff base complexes, we examined the possibility of carrying out hydroperoxysilylation in an enantioselective manner.

Table 3 summarises our attempts at carrying out asymmetric hydroperoxysilylation chemistry using different chiral Co(II) complexes. From Table 3, it is clear that the best catalysts for effecting this transformation are analogues of $Co(acac)_2$. Thus the camphor derived chiral complex **4a** provided target peroxysilyl alkanes in good yield.

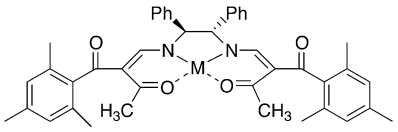
The ketoiminato catalyst **4b** was also capable of catalysing these reactions, albeit in lower yields than **4a**. Disappointingly, there was no asymmetric induction in any of these oxidation reactions.

Mechanism of the hydroperoxysilylation reaction—In contrast to the reported use of chiral cobalt complexes for aerobic asymmetric epoxidation it is clear that the Mukaiyama hydroperoxysilylation reaction proceeds through a mechanism that leads to optically inactive products (Scheme 4). Based on a mechanism proposed by Magnus for tandem $Mn(dpm)_3$ mediated aerobic enone reduction/alpha hydroxylation,[12] we reasoned that a similar Co(III) hydride species may be involved in the key step. A proposed mechanism that would account for the lack of asymmetric induction was recently proposed by Nojima and co-workers and provides a rationale for the results in Table 3.[13]

Table 3. Chiral Co(II) complex mediated aerobic hydroperoxysilylation of alkenes[a]



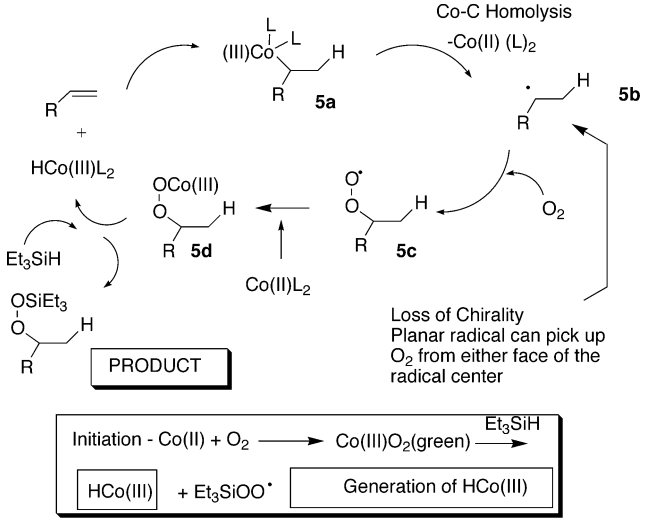
4a



4b

Entry	Alkene	Silylperoxide/ Yield %	**4a** Yield/%	**4b** Yield/%
1	Styrene	**2**, R = Ph (see Table 2)	55	25
2	R=CH_3, R^1=Ph, R^2 = H	R=CH_3, R^1=Ph, R^2 = H	69	39
3	R=Ph, R^1=H, R^2 = CH_2OH	R=Ph, R^1=H, R^2 = CH_2OH	80	39

[a] No asymmetric induction was observed in these reactions.

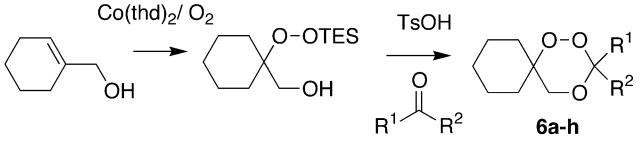


Scheme 4. Mechanism of the Isayama–Mukaiyama peroxygenation of alkenes.

Addition of the Co(III)-H across the double bond of the alkene provides the chiral cobalt species **5a**. Homolysis of the Co–carbon bond then ensues to produce a carbon centred radical **5b** that can capture triplet oxygen from either face of the radical centre. It is this process that is responsible for the complete lack of asymmetric induction using chiral complexes **4a** and **4b**. The final stage of the proposed mechanism involves a metal exchange between **5d** and triethylsilane to give the observed product **2**.

We recently reported on a simple synthesis of 1,2,4-trioxanes using $Co(acac)_2$.[14] In contrast to $Co(acac)_2$, the key finding that $Co(thd)_2$ can catalyse the regioselective hydroperoxysilylation of cyclic allylic alcohols has enabled us to broaden this methodology to the synthesis of some potent spiro 1,2,4-trioxane antimalarials (Table 4). The allylic alcohol prepared in 72% yield from cyclohex-1-enyl-methanol was allowed to react under the standard conditions and the resulting silica gel purified peroxysilyl species was then cyclised with

Table 4. Synthesis of spiro 1,2,4-trioxanes



Entry	Carbonyl	Trioxane (R^1, R^2)	Yield /%	IC50 (nM)[b]
1	acetone	**6a**, R^1=R^2= Me	85	>1000
2	cyclohexanone	**6b**, R^1=R^2= -$(CH_2)_5$-	62	145
3[a]	cyclododecanone[15]	**6c**, R^1=R^2= -$(CH_2)_{11}$-	40	55
4[a]	phenanthrene-9-carbaldehyde	**6d**, R^1=H R^2= 9-phenanthryl	50	>1000
5	4-fluoro benzaldehyde	**6f**, R^1=H R^2= *p*-F-phenyl	55	764
6	4-trifluoromethyl benzaldehdye	**6g**, R^1=H R^2= *p*-CF_3-phenyl	65	790
7	acetophenone[16]	**6h**, R^1=CH_3 R^2= phenyl	54	35
8	4-trifluoromethyl acetophenone	**6i**, R^1=CH_3 R^2= *p*-CF_3-phenyl	61	28
9	artemisinin		NA	14

[a] The yields recorded are for a one-pot procedure where silyl peroxide intermediate is not isolated.

[b] Testing was carried out *in vitro* versus the K1 strain of *Plasmodium falciparum*.[14] This is a chloroquine resistant strain.

the appropriate aldehyde or ketone in the presence of tosic acid (catalytic amounts). As in our previous communication, the procedure can also be adopted to a one-pot procedure, whereby the silyl alcohol is not isolated but used crude for the cyclisation step.

Table 4 summarises the results for the synthesis of some simple 1,2,4-trioxanes. Significantly, some of these compounds that can be synthesised in a one-pot procedure are active in the low nanomolar region. It is also clear that the structure of the 1,2,4-trioxane has a huge bearing on the pharmacological activity of these endoperoxides. In a full paper, we will subsequently describe SAR and mechanistic ferrous mediated degradation studies for this class of antimalarial.

Summary

Bis(2,2,6,6 - tetramethyl - 3,5 - heptanedionato)cobalt(II) (Co(II)$(thd)_2$) was found to be an excellent catalyst for both aerobic epoxidation and hydroperoxysilylation of unactivated alkenes. In all cases, the yields for oxidation reactions were superior to Co$(acac)_2$. A mechanism for hydroperoxysilylation is provided that is consistent with the fact that chiral Co(II) complex catalysed reactions proceed without asymmetric induction. An important application of Co$(thd)_2$ is outlined which involves a one-pot procedure for the synthesis of antimalarially active spiro 1,2,4-trioxanes. This procedure provides a simple and cost-effective route to potential new antimalarial drugs.

Acknowledgements

We thank the EPSRC (SH, PON) (GR/N65875/01) and BBSRC (PAS, PON, SAW) (26/B13581) for financial support of this work. The authors also thank Pfizer, Sandwich, Kent, UK for a CASE award to MDP.

References

1. Proc. 6th Int. Symp. Activation of Dioxygen, *J. Mol. Catal. A., Chemical* **1997**, 117.
2. Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2109.
3. Takai, T.; Hata, E.; Yorozu, K.; Mukaiyama, T. *Chem. Lett.* **1992**, 2077.
4. Mukaiyama, T.; Yorozu, K.; Takai, T.; Yamada, T. *Chem. Lett.* **1993**, 439.
5. Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Bhatt, A. K.; Iyer, P. *J. Mol. Catal. A.* **1997**, *121*, 25.
6. Mukaiyama, T.; Yamada, Y.; Nagata, T.; Imagawa, K. *Chem. Lett.* **1993**, 327.
7. Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573.
8. Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071.
9. Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401.
10. Kaneda, K.; Haruna, S.; Imanaka, T.; Hamamoto, M. *Tetrahedron Lett.* **1992**, *45*, 6827.
11. Wentzel, B. B.; Gosling, P. A.; Feiters, M. C.; Nolte, R. J. M. *J. Chem. Soc., Dalton Trans.* **1998**, 2241.
12. Magnus, P.; Fielding, M. R. *Tetrahedron Lett.* **2001**, *42*, 6633.
13. Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, 3595.
14. O'Neill, P. M.; Pugh, M. D.; Davies, J. D.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569.
15. Compound **6c**: mp 70–72°C; IR ν_{max} (Nujol mull)/cm^{-1} 2928.0 (C-H), 1086.0 (C-O), 874.0 (O-O), 851.0 (O-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (2H, brm, C(22)$\underline{H}_2$), 2.37–1.25 (32H, brm); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.21, 77.23, 66.22, 26.10, 26.03, 25.95, 22.35; MS *m*/*z* (CI) $[M+H]^+$ 311 (56), 295 (26), 200 (21), 183 (27), 129 (100), 95 (22). HRMS. Found 311.25935. $C_{19}H_{35}0_3$ $[M+H]^+$ requires 311.25861; found: C, 74.12; H, 11.17; requires C, 73.50; H, 11.04%.
16. Compound **6h**: IR ν_{max} (neat)/cm^{-1} 2923.9 (C-H), 1452.5 (Ar), 1094.3 (C-O), 868.4 (O-O), 820.2 (O-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (5H, m, Ar), 4.21 (2H, brm, C(4)$\underline{H}_2$), 1.86–0.92 (13H, brm); MS *m*/*z* (CI) $[M+NH_4]^+$ 266 (27), $[M+H]^+$ 249 (7), 233 (35), 151 (100), 138 (52), 116 (61), 105 (37). HRMS. Found 249.14971. $C_{15}H_{21}0_3$ $[M+H]^+$requires 249.14907; found: C, 72.70; H, 8.18; requires C, 72.55; H, 8.12%.