PERKIN 1

The development and application of ruthenium catalysed oxidations of a hydroxamic acid and *in situ* Diels–Alder trapping of the acyl nitroso derivative

Kevin R. Flower,[a] Andrew P. Lightfoot,[b] Hayley Wan[c] and Andrew Whiting*[c]

[a] *UMIST, Department of Chemistry, PO Box 88, Manchester, UK M60 1QD*
[b] *GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*
[c] *Department of Chemistry, Science Laboratories, University of Durham, South Road, Durham, UK DH1 3LE*

Received (in Cambridge, UK) 3rd July 2002, Accepted 30th July 2002
First published as an Advance Article on the web 22nd August 2002

Ruthenium(II) complexes can be used to oxidise *N*-Boc-hydroxylamine in the presence of *tert*-butyl hydroperoxide (TBHP) to the corresponding nitroso dienophile, which is trapped by cyclohexa-1,3-diene as the hetero-Diels–Alder adduct. Direct evidence has been obtained for the intervention of a triphenylphosphine oxide-stabilised ruthenium(IV) oxo-complex as the catalytically active species. Use of a chiral bidentate bis-phosphine derived ruthenium ligand (BINAP or PROPHOS) results in very low asymmetric induction (8 and 11%). Ruthenium(II) salen complexes also catalyse the oxidation of *N*-Boc-hydroxylamine in the presence of TBHP, to give the *N*-Boc-nitroso compound which can be efficiently trapped with a range of dienes. However, use of an enantiopure ruthenium salen complex does not produce asymmetric induction *via* the trapping of the intermediate acyl nitroso dienophile with cyclohexadiene, which strongly suggests that the intermediate dissociates readily from the chiral ruthenium complex involved in the oxidation step prior to Diels–Alder cycloaddition.

Introduction

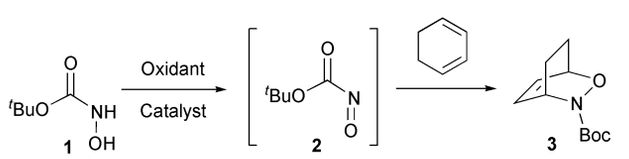
The use of acyl nitroso compounds as efficient hetero dienophiles in the [4 + 2]-cycloaddition reaction with conjugated 1,3-dienes to produce 3,6-dihydro-1,2-oxazines has been studied since the 1940s.[1] These types of hetero Diels–Alder reactions have been used as powerful synthetic tools in the formation of natural products such as polyhydroxylated alkaloids and their derivatives.[2–5]

The formation of acyl nitroso dienophiles is usually achieved *via* an *in situ* oxidation of a hydroxamic acid[6] and the unstable dienophiles (which readily form dimers) are usually trapped by reaction with a diene *via* a hetero-Diels–Alder reaction.[7] Apart from the common periodate oxidation of hydroxamic acids, the only other oxidants reported are Swern and lead(IV) oxide-based oxidants.[8] However, there has been recent interest in the development of new methods for the mild preparation of such intermediates.[9] In parallel with Iwasa *et al.*,[10] we recently reported[11] that ruthenium complexes are capable of catalysing the oxidation of hydroxamic acids to the corresponding nitroso compound, which can be trapped with conjugated dienes to yield 3,6-dihydro-1,2-oxazines. In this paper, we report the full details of this work, mechanistic implications, and the development and application of efficient salen-based ruthenium complexes for the oxidation of a hydroxamic acid and *in situ* trapping with various dienes.

Results and discussion

Cycloadduct **3**[12] is a potentially useful chiral synthon for the synthesis of piperidine alkaloids, aza-sugars and related natural products.[13] It is readily available from the cycloaddition of acyl nitroso dienophile **2**, which in turn is generated *in situ* from hydroxamic acid **1**.

We previously reported the discovery that catalytic $RuCl_2(PPh_3)_4$ and ^tBuOOH (TBHP) was an efficient catalyst–oxidant system for the *in situ* oxidation of hydroxamic acid **1** to the corresponding nitroso dienophile **2** and its subsequent cycloaddition reaction with cyclohexa-1,3-diene.[11] This discovery was achieved by using combinatorial screening methods, after which, optimisation of the reaction conditions produced improved conditions, *i.e.* 10 mol% $RuCl_2(PPh_3)_4$ and 300 mol% TBHP in dichloromethane, giving the corresponding cycloadduct in 69% yield (Scheme 1). In order to understand the



Scheme 1

mechanism of the ruthenium-based oxidation, we carried out a series of reactions summarised in Table 1.

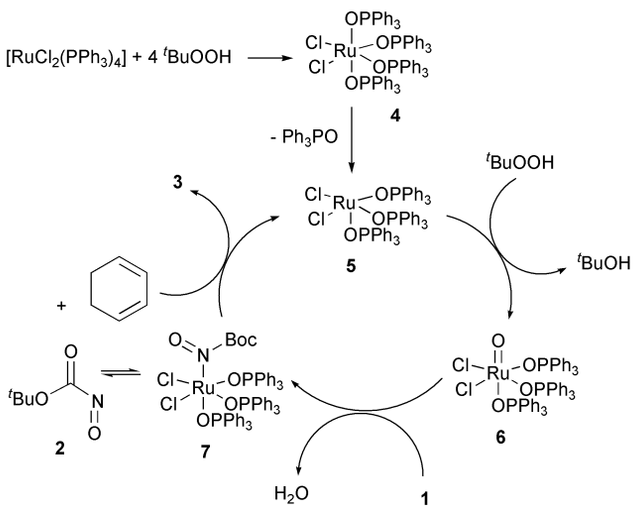
From these results, we can propose a mechanism for the oxidation reaction shown in Scheme 1, involving a ruthenium(IV) oxo complex of type **5**, which oxidizes the hydroxamic acid **1** to the corresponding nitroso dienophile **2**, as shown in Scheme 2. The key findings are: 1) that the background reaction with TBHP is considerably less efficient than the ruthenium-based process (compare entries 4 and 10, Table 1); 2) that a ruthenium(III) catalyst precursor is not involved, since the ruthenium(III) chloride–TBHP system fails to cause oxidation at a higher level than the background TBHP oxidation (compare entries 9 and 10, Table 1); 3) that triphenylphosphine oxide activates ruthenium(IV) oxide, by solubilisation of the insoluble ruthenium oxide and producing a catalyst with low activity, but greater than the background TBHP-alone process (compare entries 10 and 12, Table 1); 4) entry 1 (Table 1) shows that there

 DOI: 10.1039/b206430h

Table 1 The effect of different ruthenium(II), (III) and (IV) sources upon the oxidation and Diels–Alder trapping of hydroxamic acid **1** to give adduct **3**

Entry	Catalyst (mol%)	Solvent	^{t}BuOOH (mol%)	Temp./° C	Time/h	Yield of **3**[c] (%)
1	$RuCl_2(PPh_3)_4$ (10)	CH_2Cl_2	0	rt	72	0
2	$RuCl_2(PPh_3)_4$ (10)	CH_2Cl_2	100	−78	8	25
3	$RuCl_2(PPh_3)_4$ (10)	CH_2Cl_2	100	rt	24	57
4	$RuCl_2(PPh_3)_4$ (10)	CH_2Cl_2	300	rt	72	69
5	$RuCl_2(PPh_3)_4$ (10)	CH_2Cl_2	500	rt	72	43[a]
6	$RuCl_2(PPh_3)_4$ (0.1)	CH_2Cl_2	300	rt	48	39
7	$RuCl_2(PPh_3)_4$ (1.0)	CH_2Cl_2	300	rt	18	54
8	$RuCl_2(PPh_3)_4$ (10)	CH_2Cl_2	300	rt	0.5	60
9	$RuCl_3$ (10) + $OPPh_3$ (30)	MeOH[d]	100	rt	96	28
10	None	CH_2Cl_2	100	rt	96	30
11	$RuCl_2(PPh_3)_4$ (100) + $OPPh_3$ (400)	CH_2Cl_2	0	rt	168	19
12	RuO_2 (10) + $OPPh_3$ (40)[b]	CH_2Cl_2	300	rt	72	38

[a] Effervescence during addition of TBHP. [b] No RuO_2 solubility until addition of $OPPh_3$. [c] Isolated yields after silica gel chromatography. [d] MeOH was used due to the insolubility of $RuCl_3$ in CH_2Cl_2.

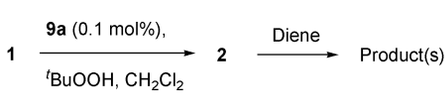


Scheme 2

is no oxidation in the absence of both triphenylphosphine oxide and TBHP; and 5) entry 11 (Table 1) shows that stoichiometric application of a dichloro ruthenium(II) phosphine oxide complex over **1a** long reaction period (168 hours) fails to cause appreciable oxidation. Indeed, this result suggests that the hydroxamic acid itself is a poor self-oxidant; a possibility which is reinforced by the experiments described herein, using ruthenium-salen systems (*vide infra*).

Examination of the proposed catalytic process outlined in Scheme 2 leads us to speculate that after binding and oxidation of hydroxamic acid **1**, by complex **6**, the product complex **7** could stay bound to the nitroso dienophile long enough to allow direct delivery to the diene or dissociate to release nitroso dienophile **2**. Since the ruthenium complexes involved in the catalytic process shown in Scheme 2 (*i.e.* **5**, **6**, and **7**) are all phosphine oxide stabilized, use of a chiral phosphine oxide ligand, bound to ruthenium, could result in the first example of a catalytic asymmetric nitroso cycloaddition reaction. We therefore examined this strategy by using chiral phosphine oxides generated *in situ* by rapid oxidation of the corresponding phosphines by TBHP under the reaction conditions. This was achieved by attempted replacement of the phosphine source with a variety of chiral phosphine sources ([(*R*)-Tol-BINAP, (*R*)-BINAP, (−)-DIOP, (*R*)-PROPHOS])† either by *in situ* reaction of $RuCl_2(PPh_3)_4$ with the diphosphine or by direct preparation of the corresponding bidentate ruthenium(II) complex in a parallel screening approach. Although this approach provided similarly reactive catalyst systems to those reported in Table 1, it failed to provide any asymmetric induction (determined by chiral HPLC). In some cases (BINAP and PROPHOS), the discrete chiral ruthenium(II) complexes were either prepared according to the literature for the BINAP complex,[14] or obtained commercially and applied to the oxidation–cycloaddition reaction (Scheme 1) resulting in 0, 11 and 8% ee (error < 2%) for two different BINAP [$RuCl_2$(*R*)-BINAP)(PPh_3) and $RuCl_2$(*R*)-BINAP)(cymene)] and one PROPHOS [$RuCl_2$(*R*)-PROPHOS)(PPh_3)] complex respectively (isolated yields 27, 63 and 54% respectively). There was a marginal increase in ee to 10% when the $RuCl_2$(*R*)-PROPHOS)(PPh_3)-catalysed reaction was run at −60 °C; however, the reaction was considerably more efficient, producing the cyclohexadiene adduct **3** in 80% yield after 3 hours. This very low level of asymmetric induction may be explained due to that fact the conditions used for these oxidation reactions fail to provide discrete, stable diastereomerically pure ruthenium complexes, hence, the discovery of any asymmetric induction could be viewed as fortuitous. In order to test therefore, that an intermediate ruthenium nitroso complex could possibly be involved in the cycloaddition step to induce asymmetric induction, we proposed that an alternative ruthenium ligand set was required in which all the equatorial ligand positions were fixed and enantiomerically pure. The resulting complexes could therefore be prepared knowing that the resulting complexes could be obtained in a stable and enantiomerically pure form. Thus, ruthenium salen ligands of type **8** were chosen as likely candidates, with the first complex being the achiral Ru-salen complex **9a**, which was prepared using procedures reported by Zheng *et al.*,[15] from $RuCl_2(PPh_3)_4$ and the salen ligand **8a** [eqn. (1)].

Application of achiral Ru(II)-salen complex **9a** in the oxidation–cycloaddition reaction with cyclohexadiene (*i.e.* as in Scheme 1, catalyst = **9a**, oxidant = TBHP), resulted in a considerable improvement over the best systems reported in Table 1: optimum conditions were 0.1 mol% of the Ru-salen complex **9a**, 100 mol% TBHP, 1 hour in dichloromethane at room temperature, giving the cycloadduct in 81% yield after silica gel chromatography. Furthermore, the use of this catalyst system could be demonstrated by application of these same optimum conditions used with cyclohexadiene for a series of other dienes, as reported in Scheme 3 and Table 2. In all cases,

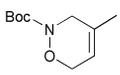
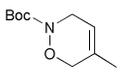
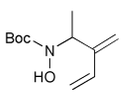
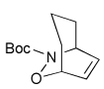
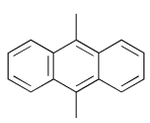
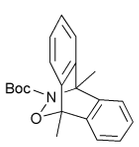
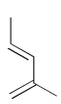
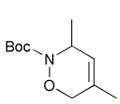
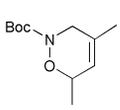
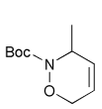
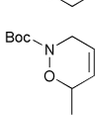
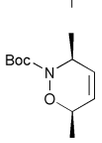
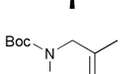
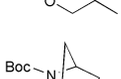


Scheme 3

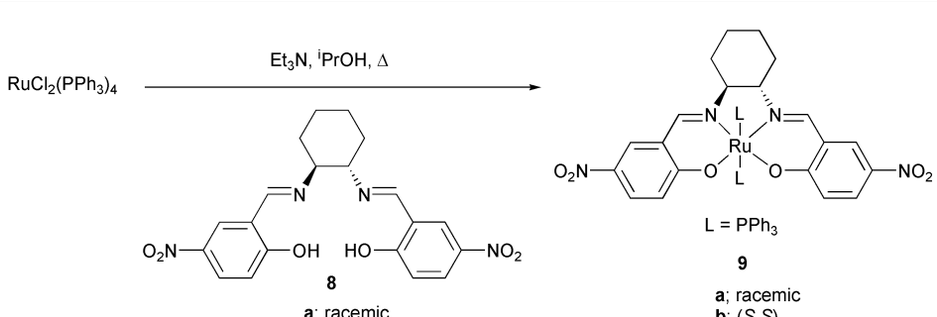
cycloadducts were produced in moderate to good yields, except in the case of 3-methylpenta-1,3-diene (Entry 2, Table 2), from which only product **11** could be isolated, albeit in only 19%

† BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DIOP = 4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane; PROPHOS = (*R*)-1,2-bis(diphenylphosphino)propane.

Table 2 Product structures and corresponding yields for the *in situ* generation of dienophile **2** using ruthenium complex **8a**

Entry	Diene	Time/h	Product(s)		Yield (%)[a]
1		2		**10a**[b]	25[c]
				**10b**[b]	
2		96		**11**	19
3		1		**12**[d]	71
4		96		**13**[e]	36
5		2		**14a**	38[f]
				**14b**	
6		2		**15a**	40[f]
				**15b**	
7		1		**16**[g]	38
8		1		**17**	42
9		1		**18**[h]	69
10		1	**3**		81

[a] All yields are quoted after purification by silica gel chromatography. [b] See ref. 17 [c] 1 : 1 Mixture of inseparable regioisomers. [d] See ref. 18 [e] See ref. 9a. [f] 2 : 1 Mixture of inseparable regioisomers. [g] See ref. 19 [h] See ref. 20



yield, which is derived by a direct ene-reaction of nitroso compound **2** with the diene.[16]

In terms of regiocontrol in Table 2, it is interesting that a 2-methyl substituent on butadiene (Entry 1) fails to exert any polarising effect upon the Diels–Alder reaction. However, a terminal methyl group does produce weak diene polarisation,

Table 3 Effect of air and hydroxamic acid **1** on the salen-complex **9a**-catalysed oxidation of hydroxamic acid **1** and subsequent generation of product **3**

Entry	Salen complex **9a** (mol equiv.)	Oxidation and reaction conditions	Time/d	Isolated yield **3** (%)
1	0.1	Air, DCM	6	10
2	0.1	Argon, DCM	6	3
3	0.1	0.2 mol equiv. TBHP, air, DCM	6	27
4	0.1	0.2 mol equiv. TBHP, argon, DCM	6	15

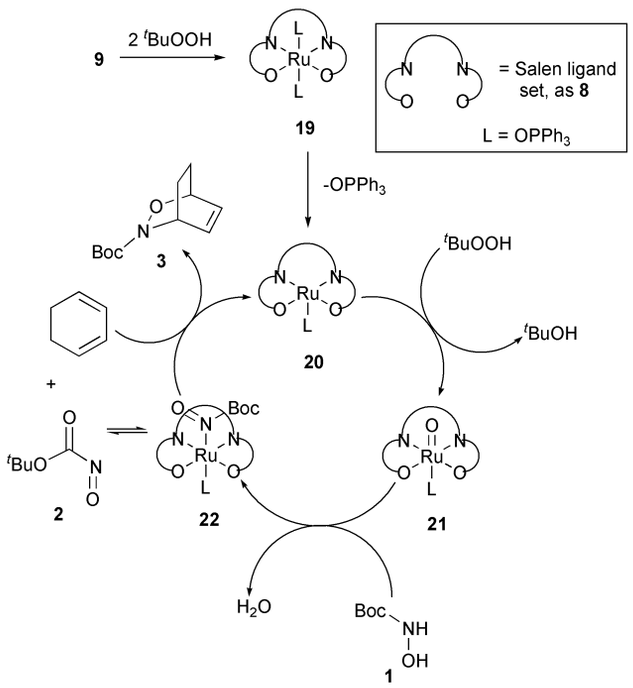
as demonstrated by Entries 5 and 6 (Table 2). The fact that the reactions are essentially concerted is also demonstrated by Entry 7, in which only stereoisomer **16** was isolated.

In addition to the results reported in Table 2, the efficiency of possible background or alternative oxidation reactions catalysed by salen complexes **9** was also examined. Thus, ruthenium complex **9a** (0.1 equivalent) was employed in the absence of TBHP for the oxidation of hydroxamic acid **1**, followed by *in situ* trapping with cyclohexadiene to give adduct **3**. The results, shown in Table 3, demonstrate that salen complex **9a** undergoes slow aerial oxidation of the phosphine ligands to generate an active catalyst, which produces a low (10%) yield of cycloadduct after six days (Entry 1, Table 3). The fact that aerial oxidation is implicated, is shown by the fact that when the identical reaction is carried out under argon (Entry 2, Table 3), little cycloadduct is produced (3%). However, the fact that any adduct is obtained suggests that the hydroxamic acid **1** alone could act as a weak self-oxidant for the reaction, presumably producing Boc-amide and water as by-products. These results are indeed reinforced by the fact that if the salen complex **9a** was first oxidised with TBHP (0.2 equivalents) to solely oxidise each triphenylphosphine unit, a more efficient reaction ensued. Thus, in air, the resulting reaction proceeded to 27% completion after 6 days, *versus* 15% in the absence of air (compare Entries 3 and 4, Table 3). These results clearly show that air is capable of acting as a weaker oxidant than TBHP in the reaction shown in eqn. (1), as is hydroxamic acid **1**, although this is a poor oxidant.

These results outlined in Tables 2 and 3 led us to propose a mechanism for the TBHP ruthenium-salen complex catalysed oxidation of *N*-BocNHOH **1** to the nitroso dienophile **2**, which closely parallels that outlined in Scheme 2 for the corresponding phosphine oxide systems, *i.e.* as outlined in Scheme 4 (the two PPh_3 ligands are rapidly oxidised to Ph_3PO by TBHP, followed by dissociation and further oxidation to give complex **21**), which in turn is expected to transform into complex **22** upon oxidation of the hydroxamic acid. Hence, as long as a complex of type **22** is involved in the cycloaddition step to derive product **3**, asymmetric induction is expected to ensue when using an enantiomerically pure version of complex **21**. Therefore, the equivalent chiral Ru-salen complex **9b** was prepared [eqn. (1)] and used in the reaction involving cyclohexadiene. Unfortunately, no enantioselectivity was observed by chiral HPLC, despite a highly efficient reaction. It is therefore likely that although an N-bound ruthenium complex of type **22** is probably generated after oxidation of hydroxamic acid **1**, this complex is *not* sufficiently stable to directly deliver the dienophile to the diene due to rapid dissociation, and hence no asymmetric induction is obtained. Thus, acylnitroso compounds seem to be poor ligands for ruthenium(II) complexes; once generated they rapidly dissociate into solution and undergo thermal Diels–Alder cycloaddition reactions.

Conclusions

We have discovered that ruthenium(II) complexes, stabilised with phosphine oxide ligands are efficient pre-catalysts for the oxidation of hydroxamic acid **1**, to provide the intermediate nitroso dienophile **2**. In turn, this is efficiently trapped with, for example, cyclohexa-1,3-diene to provide cycloadduct **3**. The



Scheme 4

intermediacy of a ruthenium(IV) oxo complex, also stabilised by phosphine oxide ligands, is inferred from a series of reactions, including a reaction which shows that ruthenium(III) complexes are not involved. The catalytic activation of ruthenium(IV) complexes towards oxidative reactions *via* phosphine oxide ligands is reinforced by the finding that ruthenium(IV) oxide can be solubilised in dichloromethane and is an inefficient but active catalyst for the hydroxamic acid oxidation. Preliminary attempts to use chiral phosphine oxide ligands with the ruthenium(II) oxidants provided only poor levels of asymmetric induction. Hence, we examined the use of salen-like ruthenium(II) with phosphine oxide ligands; these complexes can form the basis of highly efficient catalysts for the mild, TBHP-mediated oxidation of hydroxamic acids to provide acyl nitroso dienophiles. However, we believe that these dienophiles rapidly dissociate from the ruthenium centre and are efficiently trapped by thermal cycloaddition (hetero-Diels–Alder) or ene-reactions. This is demonstrated by the lack of asymmetric induction when using chiral salen ligands on the ruthenium. In order to circumvent the lack of control provided by these ruthenium(II) catalysts as asymmetric controllers in hetero-Diels–Alder reactions, new approaches to tackling this problem are being developed.

Experimental

All starting materials were obtained commercially from Aldrich and used as received, or prepared by known methods. Salen ligands **8** and the subsequent ruthenium complexes **9** were prepared according to literature procedures.[15] Solvents were used as received, unless otherwise stated. Purification by column chromatography was performed using Lancaster silica gel with pore size 60 Å. TLC was carried out using Merck glass-

backed pre-coated plates. ^{1}H NMR spectra were recorded at 200 or 300 MHz using a Varian Mercury 200 MHz spectrometer or a Varian Unity 300 MHz, respectively. ^{13}C NMR spectra were recorded at 125.5 MHz on a Varian Inova AS500 NMR spectrometer. $CDCl_3$ was used as the solvent, unless otherwise stated, and tetramethylsilane as internal standard. Electrospray (ES) mass spectra and accurate mass were recorded using a Micromass LCT spectrometer. Infrared spectra were obtained using FT1600 series spectrometer. HPLC were recorded on a Varian Star HPLC system or a Gilson HPLC system. Evaporations were carried out at 20 mmHg using a Buchi rotary evaporator and water bath, followed by evaporation to dryness (<2 mmHg).

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3.

To a solution of $[RuCl_2(PPh_3)_4]$ (92 mg, 0.075 mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (10 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.42 ml, 2.250 mmol of a 5–6 M solution in decane). After 72 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (279 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as eluent) gave the cycloadduct **3** as a pale yellow oil (100 mg, 69%). All spectroscopic and analytical details were identical to those reported by Miller *et al.*[12]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3

To a solution of $RuCl_3$ (16.0 mg, 0.075 mmol), Ph_3PO (63 mg, 0.225 mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in methanol (10 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 0.751 mmol of a 5–6 M solution in decane). After 96 hours, the solvent was evaporated, the residue redissolved in EtOAc; the resulting solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (252 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (45 mg, 28%). All spectroscopic and analytical details were identical to those reported by Miller *et al.*[12]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3.

To a solution of RuO_2 (10 mg, 0.075 mmol), PPh_3O (83 mg, 0.300 mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (10 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.42 ml, 2.250 mmol of a 5–6 M solution in decane). After 72 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (210 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (60 mg, 38%). All spectroscopic and analytical details were identical to those reported by Miller *et al.*[12]

Preparation of $RuCl_2$(*R*)-PROPHOS)(PPh_3)

To a solution of $RuCl_2(PPh_3)_3$ (120 mg, 0.13 mmol) in anhydrous DCM (30 ml) was added (*R*)-(+)-PROPHOS (52 mg, 0.13 mmol). After 3 days stirring under an argon atmosphere at room temperature, the mixture was concentrated to approx. 2 ml of solvent. Diethyl ether (30 ml) was then added and the mixture allowed to stir at room temperature. After 4 hours, the mixture was filtered, the resulting solid washed with diethyl ether (15 ml) and hexane (15 ml), giving the catalyst as a pale brown solid (60 mg, 57%). Mp 252–254 °C; δ_H (200 MHz, $CDCl_3$) 0.90–1.10 [3H, m, CH_3], 2.52–2.90 (2H, m, CH_2), 3.43–3.65 (1H, m, CH); δ_P (100 MHz, $CDCl_3$) 30.30, 31.56, 31.87, 32.19, 32.51, 49.95, 50.27, 50.57, 56.41 [Found: C, 63.5; H, 4.6; Cl, 8.3; P, 9.9%. Calc. for $C_{45}H_{41}P_3Cl_2Ru$: C, 63.8; H, 4.8; Cl, 8.3; P, 11.0%]

a) Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3 using $RuCl_2$(*R*)-PROPHOS)(PPh_3)

To a solution of catalyst $RuCl_2$(*R*)-PROPHOS)(PPh_3) (32 mg, 3.8×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (50 mg, 0.038 mmol) and cyclohexadiene (0.04 ml, 0.038 mmol) in anhydrous DCM (10 ml), inside a glovebox, was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.11 ml, 0.114 mmol of a 5–6 M solution in decane). After 3 hours stirring at room temperature, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (88 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (43 mg, 54%) with an ee of 8%. Analysis identical to that reported by Miller *et al.*[12]

b) Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3 using $RuCl_2$(*R*)-PROPHOS)(PPh_3)

To a solution of catalyst $RuCl_2$(*R*)-PROPHOS)(PPh_3) (32 mg, 3.8×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (50 mg, 0.038 mmol) and cyclohexadiene (0.04 ml, 0.038 mmol) in DCM (10 ml), was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.11 ml, 0.114 mmol of a 5–6 M solution in decane). After 3 hours stirring at −60 °C, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (121 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (63 mg, 80%) with an ee of 10%. Analysis identical to that reported by Miller *et al.*[12]

Preparation of *tert*-butyl 4-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate and *tert*-butyl 5-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate 10

To a solution of Ru-salen catalyst **9a** (1.6 mg, 1.54×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (200 mg, 1.502 mmol) and isoprene (0.16 ml, 1.652 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.28 ml, 1.502 mmol of a 5–6 M solution in decane). After 2 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (209 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadducts **10** as a pale yellow oil (75 mg, 25%). Analysis identical to that reported by Tolman *et al.*[17]

Preparation of *tert*-butyl *N*-hydroxy-*N*-(1-methyl-2-methylene-but-3-enyl)carbamate 11

To a solution of Ru-salen catalyst **9a** (1.6 mg, 1.54×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (200 mg, 1.502 mmol) and 3-methylpenta-1,3-diene (0.18 ml, 1.652 mmol) in DCM (5 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 1.502 mmol of a 5–6 M solution in decane). After 96 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (323 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the ene product **11** as a pale yellow oil (59 mg,

19%): δ_H (200 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6 Hz, CH_3), 1.36 [9H, s, $(CH_3)_3$], 4.86 (1H, q, *J* 6 Hz, C*H*CH_3,), 5.03 (1H, d, *J* 11.2 Hz, RCH–CH_2), 5.20 (2H, d, *J* 3.2 Hz, R_2C–CH_2), 6.31 (1H, d, *J* 18.0 Hz, CH–CH_2), 6.28 (1H, dd, *J* 11.2 and 11.0 Hz, C*H*–CH_2); δ_C (125.5 MHz; $CDCl_3$) 14.3, 27.3, 52.6, 80.9, 113.1, 115.7, 136.2, 144.0, 155.2; ν_{max} (neat)/cm^{-1} 3320, 2976, 2361, 1654, 1393, 1367, 1257, 1166, 1117; *m*/*z* (ES^+) 236.9419 (M^+ + Na).

Preparation of *tert*-butyl 6-oxa-7-azabicyclo[3.2.2]non-8-ene-7-carboxylate 12

To a solution of Ru-salen catalyst **9a** (1.6 mg, 1.54×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (200 mg, 1.502 mmol) and cyclohepta-1,3-diene (0.18 ml, 1.652 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.28 ml, 1.502 mmol of a 5–6 M solution in decane). After 1 hour, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (295 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **12** as a white solid (241 mg, 71%). Analysis identical to that reported by Bailey *et al*.[18]

Preparation of *tert*-butyl 1,8-dimethyl-15-oxa-16-azatetracyclo[6.6.2.0.^{2,7}0^{9,14}]hexadeca-2,4,6,9,11,13-hexaene-16-carboxylate 13

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 1.502 mmol) and 9,10-dimethylanthracene (170 mg, 0.826 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 0.751 mmol of a 5–6 M solution in decane). After 96 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil. Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **13** as a yellow solid (147 mg, 36%). Analysis identical to that reported by King *et al*.[9a]

Preparation of *tert*-butyl 3,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate and *tert*-butyl 4,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate 14

To a solution of Ru-salen catalyst **9a** (1.6 mg, 1.54×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (200 mg, 1.502 mmol) and *trans*-2-methylpenta-1,3-diene (0.18 ml, 1.652 mmol) in DCM (5 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 1.502 mmol of a 5–6 M solution in decane). After 2 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (287 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadducts **14** as a pale yellow oil (120 mg, 38%): δ_H (200 MHz, $CDCl_3$) major regioisomer 1.20 (3H, d, *J* 6.6 Hz, CHCH_3), 1.41 [9H, s, $(CH_3)_3$], 1.58 (3H, br s, R_2CCH_3), 3.92 and 4.38 (each 1H, br d, *J* 15.8 Hz, OCH_2), 4.32 (1H, br s, NCH), 5.40–5.46 (1H, m, CH=C), minor regioisomer 1.18 (3H, d, *J* 6.6 Hz, XCHCH_3), 1.41 [9H, s, $(CH_3)_3$], 1.65 (3H, br s, R_2CCH_3), 3.83 (2H, br ABq, *J* 17.1 Hz, sep. 58 Hz, NCH_2), 4.44–4.54 (1H, m, OCH), 5.32–5.38 (1H, m, CH=C); δ_C (125.5 MHz; $CDCl_3$) major regioisomer 18.4, 19.9, 28.6, 50.3, 71.5, 81.4, 122.5, 131.0, 154.7, minor regioisomer 18.2, 19.2, 28.6, 48.2, 73.6, 81.5, 123.8, 130.2, 155.0; ν_{max} (neat)/cm^{-1} 2976, 2932, 2361, 1725, 1701, 1679, 1391, 1367, 1168, 1117,1100, 1066; *m*/*z* (ES^+) 236.9374 (M^+ + Na).

Preparation of *tert*-butyl 3-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate and *tert*-butyl 6-methyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate 15

To a solution of Ru-salen catalyst **9a** (1.6 mg, 1.54×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (200 mg, 1.502 mmol) and *cis*-piperylene [(*Z*)-penta-1,3-diene] (0.16 ml, 1.652 mmol) in DCM (5 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 1.502 mmol of a 5–6 M solution in decane). After 2 hours, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and the solvent evaporated to give the crude cycloadduct as a brown oil (240 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadducts **15** as a pale yellow oil (120 mg, 40%): δ_H (200 MHz, $CDCl_3$) major regioisomer 1.26 (3H, d, *J* 6.8 Hz, CHCH_3), 1.45 [9H, s, $(CH_3)_3$], 4.08–4.18 (1H, m, OC*H*H),4.30–4.44 (1H, m, NCH), 4.48–4.57 (1H, m, OCH*H*), 5.75–5.76 (2H, m, CH=CH), minor regioisomer 1.22 (3H, d, *J* 7.0 Hz, CHCH_3), 1.44 [9H, s, $(CH_3)_3$], 3.84–4.18 (2H, m, NCH_2), 4.52–4.66 (1H, m, OCH), 5.53–5.55 (2H, m, CH=CH); δ_C (125.5 MHz; $CDCl_3$) major regioisomer 18.0, 28.6, 50.9, 68.6, 81.6, 123.7, 128.5, 154.7, minor regioisomer 20.0, 31.8, 44.4, 73.9, 81.6, 122.4, 129.8, 154.8; ν_{max} (neat)/cm^{-1} 2977, 1700, 1367, 1313, 1170, 1111; *m*/*z* (ES^+) 222.1128 (M^+ + Na).

Preparation of *tert*-butyl 3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate 16

To a solution of Ru-salen catalyst **9a** (1.6 mg, 1.54×10^{-3} mmol), *tert*-butyl *N*-hydroxycarbamate (200 mg, 1.502 mmol) and hexa-2,4-diene (0.19 ml, 1.652 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.28 ml, 1.502 mmol of a 5–6 M solution in decane). After 1 hour, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (268 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **16** as a clear oil (120 mg, 38%). Analysis identical to that reported by Defoin *et al*.[19]

Preparation of *tert*-butyl 4,5-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate 17

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and 2,3-dimethylbutadiene (0.09 ml, 0.826 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 0.751 mmol of a 5–6 M solution in decane). After 1 hour, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (141 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **17** as a pale yellow oil (67 mg, 42%): δ_H (200 MHz, $CDCl_3$) 1.49 [9H, s, $(CH_3)_3$], 1.58 (3H, s, OCH_2-CCH_3), 1.66 (3H, s, NCH_2CCH_3), 3.89 (2H, s, NCH_2), 4.19 (2H, s, OCH_2); δ_C (125.5 MHz, $CDCl_3$) 13.8, 15.2, 28.3, 48.4, 71.2, 81.4, 121.9, 123.1, 155.0; ν_{max} (neat)/ cm^{-1} 2977, 2929, 1727, 1707, 1477, 1453, 1391, 1367, 1238, 1171, 1140, 1089; *m*/*z* (ES^+) 236.1272 (M^+ + Na).

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate 18

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 1.502 mmol) and cyclopentadiene (55 mg, 0.826 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 0.751 mmol of a 5–6 M solution in decane). After 1 hour, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (176 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **18** as a pale yellow oil (102 mg, 69%). Analysis identical to that reported by Cowart *et al*.[21]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.14 ml, 0.751 mmol of a 5–6 M solution in decane). After 60 minutes, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil (260 mg). Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (128 mg, 81%). Analysis identical to that reported by Miller *et al*.[12]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) was added cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (2 ml). After 6 days stirring in air, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil. Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as eluent) gave the cycloadduct **3** as a pale yellow oil (15 mg, 10%). All spectroscopic and analytical details were identical to those reported by Miller *et al*.[12]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) was added cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (2 ml). After 6 days stirring in an argon atmosphere, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil. Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as eluent) gave the cycloadduct **3** as a pale yellow oil (5 mg, 3%). All spectroscopic and analytical details were identical to those reported by Miller *et al*.[12]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.02 ml, 0.150 mmol of a 5–6 M solution in decane). After 6 days stirring in air, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil. Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (43 mg, 27%). Analysis identical to that reported by Miller *et al*.[12]

Preparation of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 3

To a solution of Ru-salen catalyst **9a** (0.8 mg, 7.71×10^{-4} mmol), *tert*-butyl *N*-hydroxycarbamate (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) in DCM (2 ml) was added *tert*-butyl hydroperoxide (slow, dropwise addition) (0.02 ml, 0.150 mmol of a 5–6 M solution in decane). After 6 days stirring in an argon atmosphere, the solution was washed with distilled water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give the crude cycloadduct as a brown oil. Purification by silica gel chromatography (hexane–ethyl acetate, 6 : 1 as the eluent) gave the cycloadduct **3** as a pale yellow oil (24 mg, 15%). Analysis identical to that reported by Miller *et al*.[12]

HPLC enantiomer separation conditions for *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate

ChiralCel OD column, 254 nm UV detector, 10% isopropyl alcohol in hexane as eluent. $R_f = 7$ and 9 min.

Acknowledgements

We thank EPSRC and GlaxoSmithKline for an industrial CASE studentship (to HW) (Ref. no. 9931546X).

References

1 G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1.
2 O. Wichterle, *Collect. Czech. Chem. Commun.*, 1947, **12**, 292.
3 Y. A. Arbuzov, *Dokl. Akad. Nauk S.S.S.R.*, 1948, **60**, 993.
4 J. Hamer, A. Ahmad and R. E. Holliday, *J. Org. Chem.*, 1963, **28**, 3034.
5 G. Kresze, J. Firl, H. Zimmer and U. Wollnik, *Tetrahedron*, 1964, **20**, 1605.
6 G. W. Kirby, J. W. M. Mackinnon and R. P. Sharma, *Tetrahedron Lett.*, 1977, 215.
7 G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Chem. Commun.*, 1973, 704.
8 L. H. Dao, J. M. Dust, D. Mackay and K. N. Watson, *Can. J. Chem.*, 1979, **57**, 1712.
9 (*a*) N. E. Jenkins, R. W. Ware Jr, R. N. Atkinson and S. B. King, *Synth. Commun.*, 2000, **30**, 947; (*b*) M. H. Davey, V. Y. Lee, R. D. Miller and T. J. Marks, *J. Org. Chem*, 1999, **64**, 4976; (*c*) P. Bach and M. Bols, *Tetrahedron Lett.*, 1999, **40**, 17–3461; (*d*) W. W. Wood and J. A. Wilkin, *Synth. Commun.*, 1992, **22**, 1683; (*e*) P. Quadrelli, A. G. Invernizzi and P. Caramella, *Tetrahedron Lett.*, 1996, **37**, 1909; (*f*) Z. Zhu and J. H. Espenson, *J. Org. Chem.*, 1995, **60**, 1326; (*g*) S. F. Martin, M. Hartmann and J. A. Josey, *Tetrahedron Lett.*, 1992, **33**, 3583.
10 S. Iwasa, K. Tajima, S. Tsushima and H. Nishiyama, *Tetrahedron Lett.*, 2001, **42**, 5897.
11 K. R. Flower, A. P. Lightfoot, H. Wan and A. Whiting, *Chem. Commun.*, 2001, 1812.
12 D. Zhang, C. Sueling and M. J. Miller, *J. Org. Chem.*, 1998, **63**, 885.
13 (*a*) J. Streith and A. Defoin, *Synthesis*, 1994, 1107; (*b*) C. Kibayashi and S. Aoyagi, *Synlett*, 1995, 873; (*c*) J. Streith and A. Defoin, *Synlett*, 1996, 189.
14 B. R. James, A. M. Joshi, I. S. Thorburn and S. J. Rettig, *Inorg. Chim. Acta*, 1992, **198–200**, 283.
15 X. Yao, M. Qui, W. Lü, H. Chen and Z. Zheng, *Tetrahedron: Asymmetry*, 2001, **12**, 197.
16 (*a*) R. E. Banks, M. G. Barlow and R. N. Hazeldine, *J. Chem. Soc.*, 1965, 4714; (*b*) W. Adam, N. Bottke, B. Engels and O. Krebs, *J. Am. Chem. Soc.*, 2001, **123**, 5542.
17 V. Tolman, J. Hanus and P. Sedmera, *Collect. Czech. Chem. Commun.*, 1999, **64**, 696.
18 A. Hall, P. D. Bailey, D. C. Rees, G. M. Rosair and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 2000, 329.
19 A. Defoin, M. Joubert, J-M. Heuchel, C. Strehler and J. Streith, *Synthesis*, 2000, 1719.
20 J. P. Muxworthy, J. A. Wilkinson and G. Proctor, *Tetrahedron Lett.*, 1995, **36**, 7541.
21 M. Cowart, M. J. Bennett and J. F. Kerwin, *J. Org. Chem.*, 1999, **64**, 2240.