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Direct evidence for a ruthenium(IV) oxo complex-mediated oxidation of a hydroxamic acid in the presence of phosphine oxide donors

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

[a] *UMIST, Department of Chemistry, PO Box 88, Manchester, UK M60 1QD. E-mail: a.whiting@umist.ac.uk*

[b] *GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*

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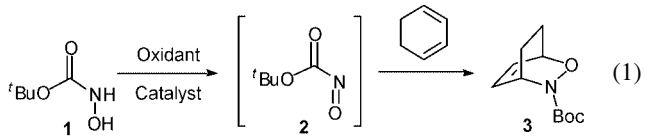
Ruthenium(II) complexes can be used to oxidise *N*-Boc hydroxylamine in the presence of *tert*-butylhydroperoxide to the corresponding nitroso dienophile, which is trapped using cyclohexa-1,3-diene as the hetero-Diels–Alder adduct; direct evidence has been obtained for the intervention of a triphenylphosphine oxide-stabilised ruthenium(IV) oxo-complex as the catalytically active species.

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 have 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 (liable to dimerisation) 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] In this communication, we report a new ruthenium(IV)-based method for the *in situ* generation of an acyl nitroso dienophile, identified from a combinatorial screening approach.†

A diversity-based screening strategy was used to search for new *in situ* oxidation methods for the generation of the Boc-nitroso dienophile **2** for use in a subsequent hetero-Diels–Alder cycloaddition with cyclohexadiene to produce adduct **3** [eqn. (1)]. Of several metal complex–oxidant combinations screened (*i.e.* including complexes derived from manganese, chromium, osmium, ruthenium, titanium and vanadium and various peroxide oxidants), $[RuCl_2(PPh_3)_4]$ and ^{t}BuOOH was found to be highly effective as shown by the screening results reported in Table 1, entries 1–3. Having established that $[RuCl_2(PPh_3)_4]$ clearly catalysed the *in situ* oxidation of **1**, we investigated the probable mechanism for this process. Since it is well known[9] that triphenylphosphine dissociates from the $[RuCl_2(PPh_3)_4]$ complex in solution, we expected that the dissociated phosphine would be immediately oxidised by *tert*-butylhydroperoxide (TBHP) to give triphenylphosphine oxide. Indeed, ^{31}P NMR studies showed that not only is free triphenylphosphine oxidised, but after 10 min exposure to the TBHP, all triphenylphosphine had been oxidised, which suggests that the $[RuCl_2(PPh_3)_4]$ is a pre-catalyst. From these results, it was hypothesised that catalytic activity was the result of a ruthenium(II)–(IV) couple, where the ruthenium(IV) species was stabilised by the presence of triphenylphosphine oxide ligands. Further support for this hypothesis was obtained by subsequent experiments, as reported in Table 1.



(1)

Entry 10 (Table 1) shows that TBHP alone gives a slow background oxidation of **1**, providing only 30% yield of adduct over 4 d, compared with 60% yield in 30 min using 10 mol% $[RuCl_2(PPh_3)_4]$ (entry 8, Table 1). Ruthenium(III) chloride (entry 9, Table 1) displays little more than background, *i.e.* TBHP-derived activity, even in the presence of $OPPh_3$. In contrast, RuO_2 dissolves slowly in DCM in the presence of $OPPh_3$ and accomplishes a slow oxidation of the hydroxamic acid **1** *in the absence of TBHP* (19% over 4 d) when used stoichiometrically (entry 11, Table 1). However, when the RuO_2 + $OPPh_3$ mixture is used catalytically with 3 equiv. of TBHP, only slight enhancement over the background (TBHP-derived) reaction occurs (compare entries 11 and 12, Table 1). This shows that although a RuO_2-derived complex can effect the oxidation of **1** (entry 12, Table 1), it is not responsible for the catalytic activity observed in, for example, entry 8 (Table 1). It is therefore likely that a mixed ruthenium(IV) oxo-chloride complex stabilised by a phosphine oxide is responsible for the observed catalytic activity, as outlined in Scheme 1.

Table 1 Reaction conditions and yields for the *in-situ* generation of **2** and trapping as **4**

Entry	Catalyst/mol%	Solvent	^{t}BuOOH/mol%	Temp./°C	Time/°C	Yield of **3**[a](%)
1	$RuCl_2(PPh)_4$ (10)	CH_2Cl_2	0	rt	72	0
2	$RuCl_2(PPh)_4$ (10)	CH_2Cl_2	100	−78	8	25
3	$RuCl_2(PPh)_4$ (10)	CH_2Cl_2	100	rt	24	57
4	$RuCl_2(PPh)_4$ (10)	CH_2Cl_2	300	rt	72	69
5	$RuCl_2(PPh)_4$ (10)	CH_2Cl_2	500	rt	72	43[d]
6	$RuCl_2(PPh)_4$ (0.1)	CH_2Cl_2	300	rt	48	39
7	$RuCl_2(PPh)_4$ (1.0)	CH_2Cl_2	300	rt	18	54
8	$RuCl_2(PPh)_4$ (10)	CH_2Cl_2	300	rt	0.5	60
9	$RuCl_3$	MeOH[c]	300	rt	144	20
10	None	CH_2Cl_2	300	rt	96	30
11	$RuCl_2(PPh)_4$ (100) + $OPPh_3$ (400)[b]	CH_2Cl_2	0	rt	96	19
12	RuO_2 (10) + $OPPh_3$ (40)	MeOH[c]	300	rt	72	38

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

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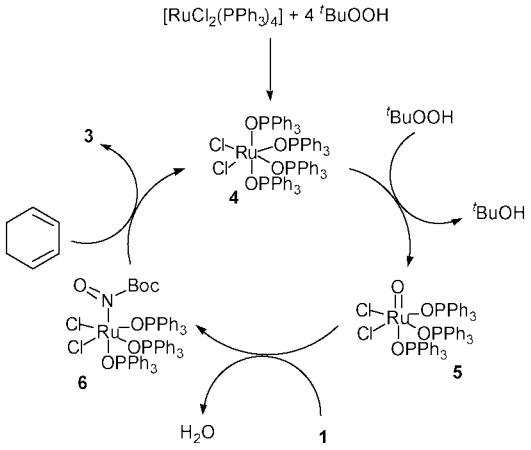

Scheme 1

From the data presented, it is evident that the PPh_3 ligands of $[RuCl_2(PPh_3)_4]$ are oxidised to $OPPh_3$ to give compound **4**, which is then further oxidised to give **5** by TBHP. The presence of an oxo-ligand is inferred from the unprecedented oxidation of the hydroxamic acid, facilitated by RuO_2 in the presence of $OPPh_3$ (note: hydrated RuO_2 is known to catalytically decompose H_2O_2, fully crystalline RuO_2 does not[10]). The oxo-chloride-containing complex **5** then oxidises the hydroxamic acid **1** to give **6**, which contains an N-bound nitroso ligand. Evidence to support the presence of an N-bound nitroso ligand comes from the recent report[11] which clearly demonstrated this bonding mode in ruthenium complexes. The N-bound nitroso complex **6** then undergoes the cycloaddition reaction with cyclohexadiene to give adduct **3** and regenerate **4**. If the cycloaddition does take place directly on the N-bound nitroso complex **6**, the opportunity to carry out an asymmetric version of this reaction is a real possibility; we are actively pursuing this.

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Notes and references

† *Typical procedure*: A solution of $[RuCl_2(PPh_3)_4]$ (92 mg, 0.075 mmol) in DCM (10 ml), *N*-Boc hydroxamic acid **1** (100 mg, 0.751 mmol) and cyclohexa-1,3-diene (0.08 ml, 0.751 mmol) was treated with TBHP (slow, dropwise addition) (5–6 M solution in decane) (0.42 ml, 2.250 mmol). After 30 min, the reaction mixture was washed H_2O (10 ml) (2×) 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 the eluent) gave cycloadduct **3**[12] as a pale yellow oil (100 mg, 63%).

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