Development of new transition metal catalysts for the oxidation of a hydroxamic acid with *in situ* Diels–Alder trapping of the acyl nitroso derivative†

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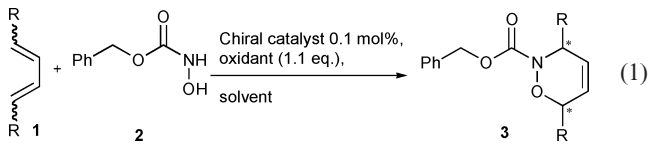
New transition metal catalysts have been prepared and applied for *in situ* formation of acyl nitroso dienophiles.

The use of nitroso compounds as efficient hetero dienophiles in [4 + 2]-cycloaddition reactions with conjugated dienes to produce 3,6-dihydro-1,2-oxazines has been studied for over half a century.[1] These types of hetero Diels–Alder (DA) reactions have been used as powerful synthetic tools in the formation of natural products such as polyhydroxylated alkaloids and their derivatives.[2–7]

The formation of acyl nitroso dienophiles is usually achieved by the oxidation of hydroxamic acid *via* potentially toxic processes involving *n*-Bu_4IO_4, Swern or lead(IV) based oxidants.[8,9] These unstable dienophiles are usually trapped *via* a DA reaction with a diene to result in the heterocyclic adducts.[10,11] However, the toxicity and inefficient economy of atom transfer in these oxidations processes means that there is a need to develop novel clean, catalytic methods for the conversion of hydroxamic acids to acyl nitroso derivatives. To this end, both us[12] and Iwasa *et al.*[13] have independently reported different ruthenium based catalyst systems that are capable of promoting the oxidation of hydroxamic acids to the corresponding nitroso intermediates, which were subsequently able to be trapped by several dienes. In the system described by Iwasa *et al.*,[13] high catalytic loadings of more than 10 mol% and 4 equivalents of oxidant were required to achieve good yields. In contrast, the salen-based ruthenium system of Whiting *et al.*[12] required only very small catalyst loadings (0.1 mol%) and could be used in conjunction with various dienes. Unfortunately, with a few exceptions, the yields were generally poor to moderate. Adamo and Bruschi recently reported[14] that copper, iron and nickel in conjunction with an achiral amine can also be used to catalyse the oxidation of *N*-Boc-hydroxyamine with hydrogen peroxide, in a similar fashion to that of the Iwasa's system. Again, high yields were only obtained when using catalytic loadings of up to 10 mol% and over long reaction times of up to 8 days.

Recently, Chow and Shea reported an asymmetric version of acyl nitroso DA[15] based on our ruthenium–salen system. In this case, the chiral ruthenium–salen complex was shown to catalyse oxidation of a hydroxamic acid to give the nitroso species, which was trapped intramolecularly by a directly attached diene moiety to give the intramolecular cycloadduct in up to an 82% chemical yield with 75% e.e.[15] This intramolecular reaction is to date the only reported example of an asymmetric acyl nitroso DA reaction; there are still no catalytic systems available for an asymmetric intermolecular acyl nitroso DA reaction with the necessary *in situ* generation of the acyl nitroso species. It is within this context that we present the results obtained for the three novel catalytic systems which were designed to produce efficient oxidation of hydroxamic acids and potentially give asymmetric induction in such intermolecular acyl nitroso DA reactions (eqn (1)).



(1)

The lack of asymmetric induction in the intermolecular cases[12] and good e.e.s recorded for the intramolecular reaction[15] can be explained in terms of the relative rates of cyclisation *versus* dissociation of the acyl nitroso species from the catalyst. It is known that intramolecular reactions generally proceed faster than their intermolecular counterparts;[16] and it is therefore expected to be the case here. Based on the assumption that the rate of dissociation of the acyl nitroso species from the catalyst controls the e.e. of the final product, we can postulate that in order to efficiently transfer chirality from the catalyst to the product it is necessary to extend the lifetime of the acyl nitroso species–catalyst complex. In order to try and achieve this, we decided to use commercially available *N*-(benzyloxycarbonyl)hydroxylamine **2**, which can be viewed as a potential bidentate ligand as shown in Fig. 1 through chelation to the nitroso-oxygen and either the urethane-oxygen, or more likely the oxygen atom of the carbonyl group.

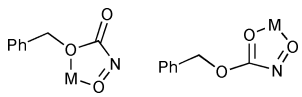


Fig. 1 Binding of *N*-(benzyloxycarbonyl)hydroxylamine **2** to a metal centre.

In addition to the binding modes illustrated in Fig. 1, hydroxylamine **2** and the resulting acyl nitroso species may also form π-donor, *hapto*-complexes *via* the benzene ring. In order to achieve any of these types of binding mode, however, the metal centre requires at least two vacant coordination sites *cis* to each other. We therefore looked to develop new transition metal complexes which would retain the ability to carry out the oxidation of a hydroxamic acid to an acyl nitroso derivative *in situ*, but which did not have the problems associated with the salen-ligands, *i.e.* the lack of

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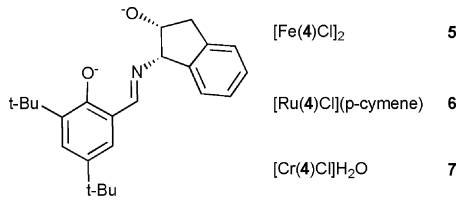
vacant *cis*-coordination sites. A study was therefore undertaken to examine metal complexes of the ligand system **4**, since these would be likely to contain vacant *cis*-oriented sites which would be suitable for acyl nitroso coordination. Furthermore, transition metals complexes derived from ligand **4** should have an asymmetric three dimensional structure which might restrict the approach of the diene to the bound and activated acyl nitroso species in a manner similar to that which has been elegantly demonstrated in the not unrelated hetero-DA reactions.[17] In order to fine-tune the reactivity and selectivity, if required, analogues of the commercially available ligand **4** can be readily synthesized through the use of simple imine formations between arylaldehyde and chiral 1,2-aminoalcohols. Ruthenium, iron and chromium were chosen for this study into the complexation of ligand **4** to a metal because of their rich redox and Lewis acid chemistry.



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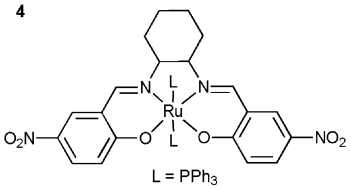
[Fe(**4**)Cl]$_2$ **5**

[Ru(**4**)Cl](p-cymene) **6**

[Cr(**4**)Cl]H_2O **7**



8

The complexes **5** and **6** were prepared by reacting ligand **4** with the metal salt [$FeCl_3$ and $RuCl_2$(*p*-cymene), respectively] in the presence of Et_3N; the complexes were isolated after an aqueous work up in yields of 82% and 48%, respectively. Chromium complex **7** was prepared using literature methods,[12] while ruthenium complex **8** was prepared according to previously reported procedures[17] to act as a comparative model catalyst with systems **5**–**7**.

The molecular structure of complex **5** was confirmed by single crystal X-ray crystallography[18] and is shown in Fig. 2, with relevant bond lengths and angles listed in Table 1. The complex **5** consists

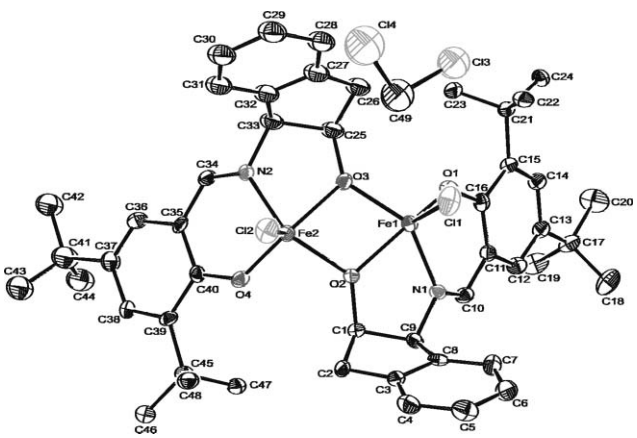


Fig. 2 ORTEP plot of complex **5** with ellipsoids depicted at the 30% probability level. Hydrogen atoms are omitted for clarity.

Table 1 Representative bond lengths and angles for the iron complex **5**

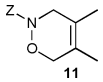
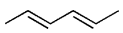
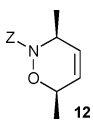
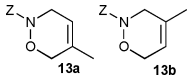
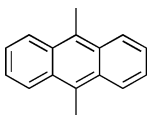
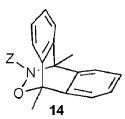
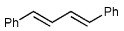
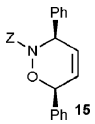
Bond length/Å		Angle/°	
Fe_1–O_1	1.874(3)	O(1)–Fe(1)–O(2)	148.54(13)
Fe_1–O_2	2.008(3)	O(1)–Fe(1)–O(3)	102.11(14)
Fe_1–O_3	1.971(3)	O(2)–Fe(1)–O(3)	74.98(13)
Fe_1–N_1	2.078(4)	O(1)–Fe(1)–N(1)	86.76(15)
Fe_1–Cl_1	2.206(1)	O(2)–Fe(1)–N(1)	77.34(14)
Fe_2–O_2	1.950(3)	O(3)–Fe(1)–N(1)	139.53(14)
Fe_2–O_3	2.023(3)	O(3)–Fe(2)–O(4)	137.72(14)
Fe_2–O_4	1.882(3)	O(2)–Fe(2)–O(4)	98.83(14)
Fe_2–N_2	2.086(4)	O(2)–Fe(2)–O(3)	75.11(12)
Fe_2–Cl_2	2.219(2)	O(4)–Fe(2)–N(2)	86.68(15)
		O(3)–Fe(2)–N(2)	76.31(14)
		O(2)–Fe(2)–N(2)	142.77(14)
		Fe(1)–O(2)–Fe(2)	105.38(14)
		Fe(1)–O(3)–Fe(2)	104.03(14)

of two iron centers which are bridged by the oxygen atoms of the aminoalcohol part of the ligand, with the metal atoms separated by 3.149(1) Å. Each metal centre is elevated above the least squares plane created by their respective bound nitrogen and three oxygen atoms forming an approximately square pyramidal geometry. This elevation, combined with the steric bulk of the ligand, forces the complex to adopt a saddle-like structure. The separation of the metal centers and their arrangement also appears to be almost ideal for **5** to act as a binuclear catalyst,[19] assuming that the structure remains the same in the solution. This complex, along with complexes **6** and **7** were screened for catalytic activity and compared with the salen–ruthenium system **8** in the reaction described in eqn (1) through a series of parallel reactions carried out over a 16 h period at room temperature. The results are presented in Table 2.

Unlike the ruthenium(salen) based system **8**, complexes **5**–**7** did not oxidize the substrate **2** to the corresponding acyl nitroso compound when employing *tert*-butyl hydroperoxide, however, the more environmentally friendly and atom economic hydrogen peroxide proved to be a successful co-oxidant. This route also avoids the use of chlorinated solvents which provides further benefit from the clean catalysis point of view. When complexes **6** and **7** were used for the reaction outlined in eqn (1), the reaction yields were lower than those recorded with the ruthenium–salen complex **8**. However, complex **5** shows activity which is comparable to that of the ruthenium–salen system **8**. Though increasing the catalytic loadings to 1 mol% improved the overall yields and decreased the reaction times, it also increased the formation of undesired side products, presumably due to over oxidation. The low yields in entries 6–9 (Table 2) can be attributed to a competing retro-DA reaction; reversible behaviour that is well documented.[20,21] Unfortunately, none of these catalysts were capable of inducing asymmetric induction in any of the isolated cycloadducts, which is not contradictory with our previous results.[12] It seems likely that this is due to the transition metal–acyl nitroso complex having insufficient stability to control the subsequent Diels–Alder reaction. Therefore, although acyl nitroso dienophiles can be viewed as potentially bidentate metal ligands (Fig. 1), there is no evidence that they behave this way in intermolecular cycloadditions,[12] and only intramolecular reactions demonstrate the potential for these types of processes.[15]

Three novel catalytic systems were designed and tested for activity in asymmetric acyl nitroso DA reactions. Despite the

Table 2 Catalytic results of DA reactions between a series of dienes and acyl nitroso derivative

			Yields[b] of Diels–Alder adducts (%)			
				Catalyst		
Entry	Diene	Product[a]	**5**[d]	**6**[d]	**7**[d]	**8**[e]
1		 **9**	49	32	25	95
2		 **10**	50; 98[c]	45	23	53
3		 **11**	42	40	22	69
4		 **12**	22	7	28	25
5		 **13a** **13b**	10[f]	14[f]	9[f]	14[f]
6		 **14**	11	5	6	15
7		 **15**	23	6	10	16
8		 **16**	0	0	0	0[g]
9		 **17**	0	0	0	0[g]

[a] All compounds are known (see ref. 22). [b] Isolated yields. [c] Yields obtained from HPLC. [d] H_2O_2/Acetone. [e] BuOOH/DCM. [f] Mixture of inseparable isomers. [g] 1 mol% of catalyst used.

low yields and lack of e.e., these new systems have comparable activity to previously reported catalysts. Moreover, because these systems employ stoichiometric amounts of hydrogen peroxide and non-chlorinated solvent, they are environmentally more benign than any previously reported. Further investigations into the mechanistic aspects of the reaction are currently ongoing in our laboratory and any further results or optimisations will be reported in due course.

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Notes and references

1 G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1–24.
2 O. Wichterle, *Collect. Czech. Chem. Commun.*, 1947, **12**, 292.
3 Y. A. Arbuzov, *Dokl. Akad. Nauk SSSR*, 1948, **60**, 993.
4 J. Hammer, A. Ahmad and R. E. Holliday, *J. Org. Chem.*, 1963, **28**, 3034–3036.
5 G. Kresze, J. Firl, H. Zimmer and U. Wollnik, *Tetrahedron*, 1964, **20**, 1605–1611.
6 H. Yamamoto and N. Momiyama, *Chem. Commun.*, 2005, 3514–3525.
7 Y. Yamamoto and H. Yamamoto, *Eur. J. Org. Chem.*, 2006, 2031–2043.
8 L. H. Dao, J. M. Dusk, D. Mackay and K. N. Watson, *Can. J. Chem.*, 1979, **57**, 1712–1719.
9 N. E. Jenkins, R. W. Ware, Jr., R. N. Atkinson and S. B. King, *Synth. Commun.*, 2000, **30**, 947–953.
10 G. W. Kirby, J. W. M. Mackinnon and R. P. Sharma, *Tetrahedron Lett.*, 1977, **18**, 215–218.
11 G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Chem. Commun.*, 1973, 704–705.
12 K. R. Flower, A. P. Lightfoot, H. Wan and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2058–2064.

13 S. Iwasa, K. Tajima, S. Tsushima and H. Nishiyama, *Tetrahedron Lett.*, 2001, **42**, 5897–5899.
14 M. F. A. Adamo and S. Bruschi, *J. Org. Chem.*, 2007, **72**, 2666–2669.
15 C. P. Chow and K. J. Shea, *J. Am. Chem. Soc.*, 2005, **127**, 3678–3679.
16 J. Clayden, N. Greeves, S. Warren and P. Wothers, in *Organic Chemistry*, Oxford University Press, New York, 1st edn, 2005, ch. 6, p. 145.
17 E. R. Jarvo, B. M. Lawrence and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 6043–6046.
18 CCDC reference number 642155. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704728b; G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **A46**, 467–473; G. M. Sheldrick, *Computer Program for Crystal Structure Refinement*, University of Göttingen.
19 E. K. van der Beuken and B. L. Feringa, *Tetrahedron*, 1998, **54**, 12985.
20 G. W. Kirby, H. McGuigan, J. W. M. Machinnon, D. McLean and R. P. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1437–1442.
21 G. W. Kirby, H. McGuigan and D. McLean, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1961–1966.
22 See ref. 9 and 20; and (*a*) A. Defoin, M. Joubert, J.-M. Heuchel, C. Strehler and J. Streith, *Synthesis*, 2000, **12**, 1719–1726; (*b*) V. Tolman, J. Hanus and P. Sedmera, *Collect. Czech. Chem. Commun.*, 1999, **64**, 696–702.