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Mn(salen)-catalyzed sulfimidation: what are the real active species in sulfimidation?

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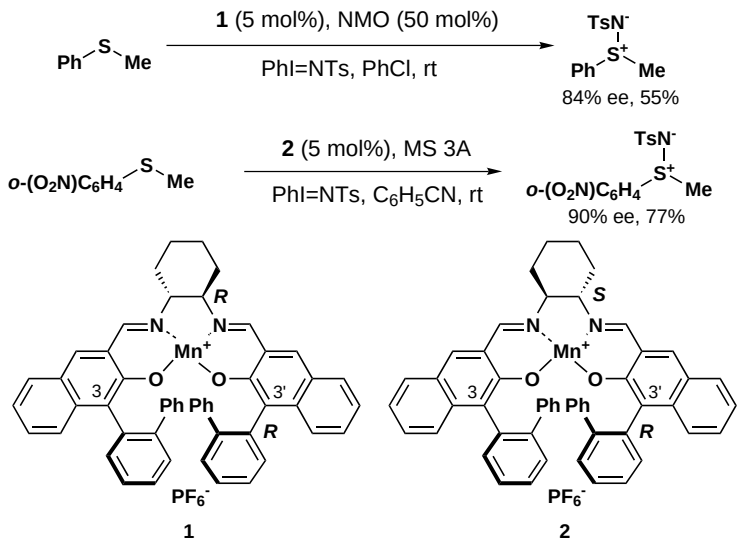
Abstract—An unusual temperature effect on enantioselectivity was found in a study of Mn(salen)-catalyzed sulfimidation. The phenomenon was considered to be attributable to the following reasons: the reaction of Mn(salen) and a nitrenoid precursor (ArI=NTs) provides primarily an Mn–ArINTs adduct which undergoes sulfimidation and transformation to an Mn–nitrenoid species competitively; however, the rates of sulfimidation by the Mn–ArINTs adduct and the Mn–nitrenoid species and of the transformation are dependent on the structure of the catalyst, the nature of ArI=NTs and the presence or absence of a donor ligand.

We recently disclosed that chiral (salen)manganese(III) complexes [hereafter referred to as Mn(salen)] served as catalysts for asymmetric sulfimidation.[1] However, the optimized reaction conditions for the sulfimidation were found to vary with the substrates used. For example, asymmetric sulfimidation of methyl phenyl sulfide was well effected in chlorobenzene by using (*R*,*R*)-Mn(salen) **1** as the catalyst in the presence of *N*-methylmorpholine *N*-oxide (NMO), while that of methyl *o*-nitrophenyl sulfide in benzonitrile was well effected by using (*R*,*S*)-Mn(salen) **2** in the absence of a donor ligand (Scheme 1). On the other hand, sulfimidation of



Scheme 1.

Keywords: (salen)manganese(III) complex; asymmetric catalysis; asymmetric sulfimidation; nonlinear effect.

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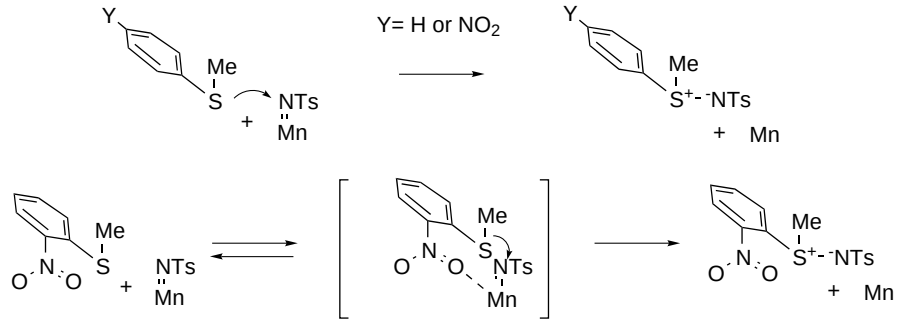


Scheme 2.

methyl *p*-nitrophenyl sulfide with (*R*,*S*)-**2** as the catalyst showed moderate enantioselectivity (55% ee). To understand the mechanism of these sulfimidation reactions, we studied the enantioselectivity–temperature relationship in the reactions using (*R*,*R*)-**1** and (*R*,*S*)-**2** as catalysts.

We had reasoned that methyl *o*-nitrophenyl sulfide is a better substrate for sulfimidation with (*R*,*S*)-**2** as catalyst, as the *p*-nitro group serves simply as an electron-withdrawing group but the *o*-nitro group serves as a coordinating group as well as an electron-withdrawing group.[1] Accordingly, we had also expected that methyl phenyl sulfide and methyl *p*-nitrophenyl sulfide should attack the Mn–nitrenoid species nucleophilically (Scheme 2), and the enantiomer ratio of the resulting sulfimide (p = major enantiomer/minor enantiomer) would correlate linearly with the reaction temperature through the Eyring equation ($\ln p = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R$). On the other hand, methyl *o*-nitrophenyl sulfide had been expected to make a complex with an Mn–nitrenoid species which undergoes subsequent sulfimidation. If this consideration is correct, there is some chance for the latter reaction to show a non-linear relationship between $\ln p$ and $1/T$, because the formation of the Mn(nitrenoid)–sulfide complex is considered to be reversible.[2,3] Thus, we studied the relationship between one enantiomer ratio and the reaction temperature in these reactions using (*R*,*R*)-**1** and (*R*,*S*)-**2** as the catalyst and PhI=NTs **3** and *p*-$CH_3OC_6H_4I$=NTs **4** as the nitrenoid precursors.

Different from the above expectation, however, the relationship between the enantiomer ratio and the reaction temperature was found to depend not only on the substrate, but also on the catalyst, the nitrenoid precursor (ArI=NTs) and the presence or absence of a donor ligand.

All sulfimidations of methyl phenyl sulfide in chlorobenzene in the presence of NMO, irrespective of the catalyst and the nitrenoid precursor, showed a linear relationship between the enantiomer ratio and the reaction temperature, though the reaction with (*R*,*R*)-**1** as the catalyst exhibited higher enantioselectivity than that with (*R*,*S*)-**2** as the catalyst (Fig. 1). A different type of relationship was observed in the sulfimidation of methyl *p*-nitrophenyl sulfide in benzonitrile in the absence of a donor ligand: almost the same enantiomer ratio was obtained at every temperature in the reactions with (*R*,*S*)-**2** as the catalyst and **3** and **4** as the nitrenoid precursors and the ee-break was observed at 40°C, while the enantiomer ratios observed in the reactions with (*R*,*R*)-**1** depended on the nitrenoid precursor used, that is, the ee-break was observed at ca. 27°C in the reaction with **3** and no ee-break in the reaction with **4** (Fig. 2). Reactions of methyl *o*-nitrophenyl sulfide with (*R*,*S*)-**2** as the catalyst and **3** and **4**

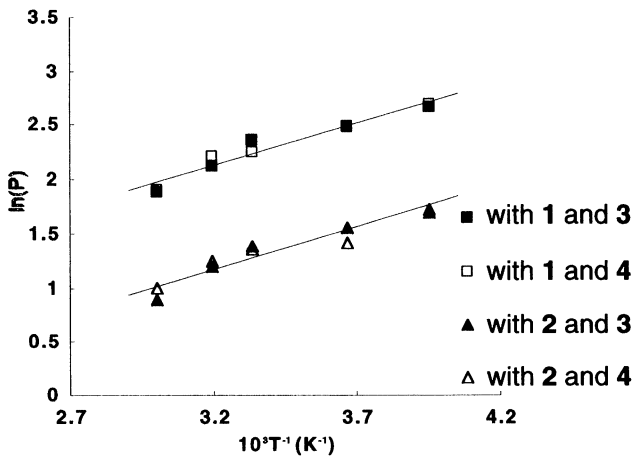


Figure 1. Reactions of methyl pheny sulfide in chlorobenzene in the presence of NMO.

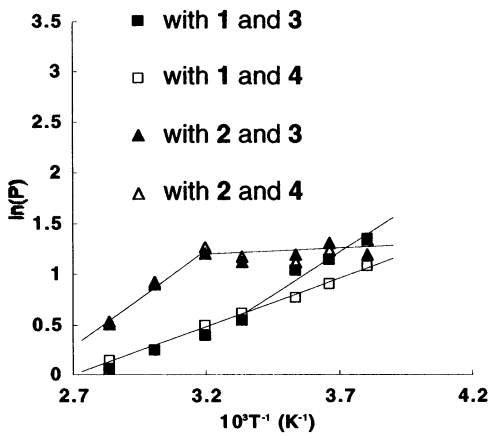


Figure 2. Reactions of methyl *p*-nitrophenyl sulifide in benzonitrile.

as the nitrenoid precursors in benzonitrile also showed almost the same enantiomer ratios at every temperature and showed the ee-break at ca. 40°C, while the enantiomer ratio–temperature relationship in the reactions with (*R*,*R*)-**1** depended on the nitrenoid precursor: the reaction using **3** showed the ee-break at ca. 10°C, but the reaction using **4** did not (Fig. 3). These results indicated that the reactions of (*R*,*R*)-**1** and the nitrenoid precursors **3** and **4**, in benzonitrile in the absence of NMO, did not give the common nitrenoid species but a different active species, respectively, below some temperature (Figs. 2 and 3) (Scheme 3).[4,5] Furthermore, both the reactions of methyl *o*- and *p*-nitrophenyl sulfides with (*R*,*S*)-**2** as the catalyst showed the ee-break. This suggested that the ee-break was not attributable to the reversible formation of the Mn(nitrenoid)–sulfide complexes but to some other factor(s), though we could not completely rule out the possibility of the complex formation.

We also examined the sulfimidation of methyl phenyl sulfide in benzonitrile in the absence of NMO (Fig. 4). The reactions with (*R*,*S*)-**2** and nitrenoid precursors **3** and **4** exhibited almost the same enantiomer ratios at every reaction temperature, though the enantioselectivities of the reactions were depressed considerably as compared with those of the reactions in chlorobenzene in the presence of NMO. On the other hand, the enantioselectivities of the reactions with (*R*,*R*)-**1** depended on the nitrenoid precursor used: the reaction with **3** showed higher enantioselectivity than the reaction with **4** at temperatures of −10 to 80°C.[6] This result suggested that the reactive intermediates generated by treating (*R*,*R*)-**1** with **3** and **4** in benzonitrile in the absence of NMO were not the same ones. The reactions in chlorobenzene in the absence of NMO also showed similar results: the enantioselectivities of the reactions with (*R*,*R*)-**1** depended on the nitrenoid precursor used: the reaction with **3** showed higher enantioselectivity than the reaction with **4** at temperatures of −20 to 60°C, though the enantiomer ratio correlated linearly with the temperature (Fig. 5). On the other hand, the reactions with (*R*,*S*)-**2** and nitrenoid precursors **3** and **4**

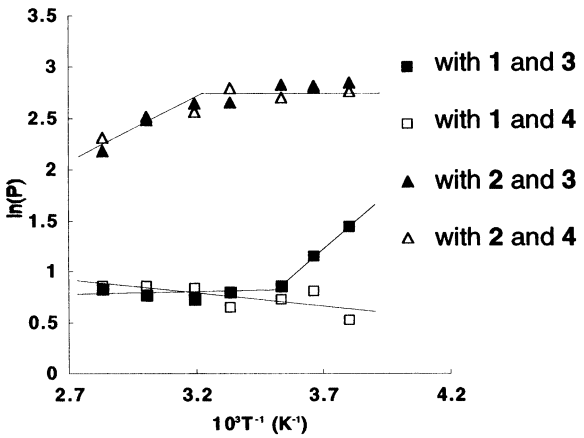
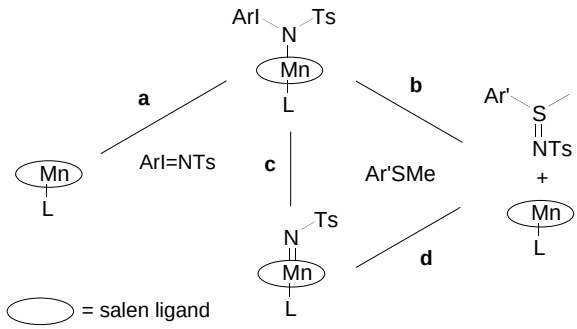


Figure 3. Reactions of methyl *o*-nitrophenyl sulfide in benzonitrile.



Scheme 3.

showed the ee-break at ca. 20°C. Although the enantiomer ratios observed in chlorobenzene and benzonitrile in the absence of NMO are different, this is considered to be partly attributable to the difference in coordinating ability of these solvents.

Based on these results, we propose the following reaction pathway for Mn(salen)-catalyzed sulfimidation, in which both the Mn–ArINTs adduct and the nitrenoid species take part (Scheme 3): the reaction of Mn(salen) and ArI=NTs first provides the Mn–ArINTs adduct (path **a**), which undergoes sulfimidation (path **b**) and transformation to an Mn–nitrenoid species (path **c**)

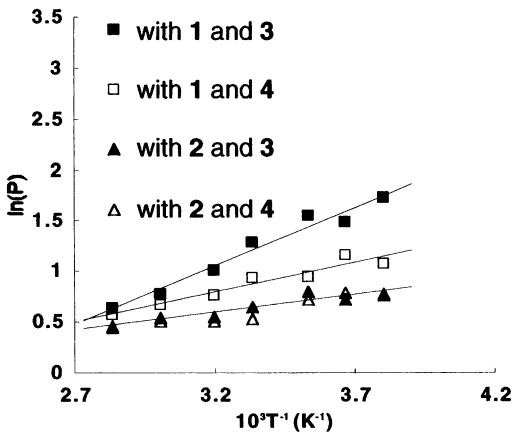


Figure 4. Reactions of methyl phenyl sulfide in benzonitrile.

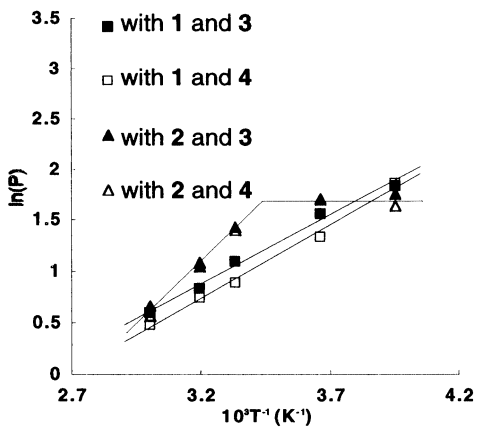


Figure 5. Reaction of methyl phenyl sulfide in chlorobenzene in the absence of NMO.

competitively. At lower temperature, sulfimidation by the Mn–ArINTs adduct (path **b**) is the major pathway and the enantioselectivity of the reactions with **2** is dependent on the nitrenoid precursors used, while the adduct transforms to the Mn–nitrenoid species (path **c**) preferentially at higher temperature and the enantioselectivity becomes independent of the precursors (Figs. 2 and 3). As described above, the reactions of methyl phenyl sulfide in the presence of NMO showed a linear relationship, regardless of the catalysts used. This suggests that coordination of NMO at an apical position accelerates the conversion of the Mn–ArINTs adduct to the nitrenoid species (path **c**).[7]

Although ee-breaks were observed in both the reactions with (*R*,*R*)-**1** and (*R*,*S*)-**2** as catalysts in the absence of NMO, ln *p* difference between the reactions with **3** and **4** at lower temperature was observed mostly when (*R*,*R*)-**1** was used as catalyst. This suggests that the aryliodo moiety of the Mn–ArINTs adduct derived from (*R*,*R*)-**1** is probably located close to the 3(3′)-substituents of the salen ligand, while the aryliodo moiety of the adduct derived from **2** is distal from the 3(3′)-substituents. However, more information on the structures of Mn–ArINTs adducts is required for further discussion.

Typical experimental procedures were exemplified by sulfimidation of methyl phenyl sulfide with (*R*,*R*)-**1** and that of methyl *o*-nitrophenyl sulfide with (*R*,*S*)-**2**.

Sulfimidation of methyl phenyl sulfide: Complex (*R*,*R*)-**1** (2.3 mg, 2.5 μmol) and *N*-methylmorpholine *N*-oxide (3 mg, 25 μmol) were suspended in dry toluene (0.5 ml), azeotropically concentrated in vacuo, and resuspended in chlorobenzene (0.25 ml). To this suspension was added methyl phenyl sulfide (11.7 μl, 0.1 ml) and it was allowed to cool or warm to the appropriate temperature. [*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane (18.6 mg, 0.05 mmol) was added to the mixture and stirred for 6 h at the temperature (60, 40 and 27°C, respectively) [for 12 h at 0 and −20°C]. The reaction mixture was directly subjected to silica-gel column chromatography (hexane:ethyl acetate = 7:3–3:7) to give the corresponding sulfimide. The enantiomeric excess of the product was determined by HPLC analysis using Daicel Chiralcel OD-H, (hexane/2-propanol = 1/1).

Sulfimidation of methyl o-nitrophenyl sulfide: Complex (*R*,*S*)-**2** (2.3 mg, 2.5 μmol) was dissolved in dry toluene (0.5 ml), azeotropically concentrated in vacuo, and re-dissolved in benzonitrile (0.25 ml). To this solution were added methyl *o*-nitrophenyl sulfide (16.9 mg, 0.1 mmol) and MS-3A (25 mg) and stirred for half an hour at room temperature. After the reaction temperature of the mixture was adjusted to the appropriate one, [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (18.6 mg, 0.05 mmol) was added under nitrogen and stirred for 3 h at the temperature (80, 60, 40 and 27°C, respectively) [for 6 h at 10 and 0°C; for 12 h at −10°C]. The reaction mixture was directly subjected to silica-gel column chromatography (hexane:ethyl acetate = 7:3–3:7) to give the corresponding sulfimide. The enantiomeric excess of the product was determined by HPLC analysis using Daicel Chiralpak AD, (hexane/2-propanol = 1/1).

The reaction of methyl *p*-nitrophenyl sulfide was performed under the same conditions as methyl *o*-nitrophenyl sulfide and the enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OJ, (hexane/2-propanol = 1:1).

The same reaction was repeated three times at each measurement point and the average ln *p* values are given in Figs. 1–5. The scattering of the measured ln *p* values was within ±0.1.

In conclusion, we were able to demonstrate that two active species, Mn–ArINTs adduct and Mn–nitrenoid, take part in the Mn(salen)-catalyzed sulfimidation, depending on the reaction conditions used.

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