Effect of the neighbouring oxygenated substituent on asymmetric reduction with Hantzsch-type 1,4-dihydropyridines having a chiral sulfinyl group

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Introduction of the oxygen substituent at C-6 of the Hantzsch-type compound having a sulfinyl group at C-5 affects the reduction of ketones with respect to both reactivity and stereoselectivity.

The significant role of the metal ion in the reduction of ketones with NADH or with its mimics[1] has been suggested and some possible structures of the ternary complex composed from the model compound, metal ion and ketone have been proposed.[2] Recently the amido-carbonyl oxygen was reported to be responsible for the formation of the metal complex from a molecular orbital approach.[3] However, little experimental evidence clearly indicating the relation between the metal coordination and the reaction has been reported. We have previously reported the effective asymmetric reduction with the NADH model compound having a sulfinyl group as a chiral auxiliary[4] and also revealed that the stereospecific transfer of the hydrogen at C-4, which is *syn* to the S–O bond of the sulfinyl group, is involved in this reduction.[5] From these results, we expected that in our compound the sulfinyl group would act in place of a planar amide group and were interested in the ionophilic effect around the sulfinyl group on this reaction. Here we show experimentally that both the reactivity and the stereoselectivity depend on the oxygen substituent proximity to the sulfinyl group by using the sulfinylated Hantzsch-type compounds **1–3**, which were synthesized previously.[6]

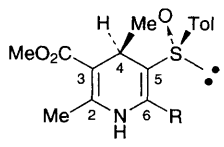
The reduction of methyl benzoylformate **4** and 1-benzoylisoquinoline **5** with Hantzsch-type 1,4-dihydropyridines **1–3**† were studied, the results are summarized in Table 1. Methyl benzoylformate **4** was successfully reduced to methyl (*R*)-mandelate **6** with compounds **1–3**. Introduction of the one oxygen-unit to the C-6 methyl group of **1** (**2**, methoxyethyl group at C-6) increased both the chemical and optical yields (*cf.* entries 1 and 2). In contrast, although the stereoselectivity obtained by **3** bearing two oxygen units (methoxyethoxyethyl group at C-6) was almost the same as that from **2**, the reactivity of **3** was unexpectedly lower than that of the methoxyethyl derivative **2** and seems to be a little higher than that of **1** (entry 3). A similar but more remarkable tendency was observed in the reduction of 1-benzoylisoquinoline **5**. Taking into account the bulkiness of its chelation structure as shown in Fig. 2, **5** was expected to be more difficult to reduce than benzoylformate **4**, and was hardly reduced using **1** (entry 4). However, **2** could reduce **5** to the corresponding alcohol **7** (entry 5). Further reduction with **3** afforded **7** but in a poor yield (entry 6). The stereochemistry of **7** was determined to be *R* by X-ray crystallography of the corresponding (1*S*)-camphanate ester (Fig. 3),‡ showing that the reaction proceeded in a similar manner to that of **4**.

^{13}C NMR analyses of **1–3** in the absence and presence of Mg^{2+} salt revealed that Mg^{2+} similarly interacts with these compounds. The sulfinyl oxygen was found to be responsible for coordination with Mg^{2+} in these compounds since the chemical shifts of the carbons around the sulfinyl group (C-5 and C-6 of the 1,4-dihydropyridine ring and C-4′ of the tolyl group) of **1–3** were changed similarly by the addition of Mg^{2+} salt as shown in Fig. 4. These results show that the enhancement of both reactivity and stereoselectivity induced by the introduction of the one oxygen-unit at C-6 is most likely to be due to the

Table 1 Reduction of methyl benzoylformate **4** and 1-benzoylisoquinoline **5** with **1–3**[a]

Entry	Ketone	Hantzsch compound	Reaction time/h	Yield[b] (%)	Ee[c] (%)
1	**4**	**1**	156	63	67
2	**4**	**2**	15	67	93
3	**4**	**3**	36	52	95
4	**5**	**1**	168	trace	nd[d]
5	**5**	**2**	96	40	73
6	**5**	**3**	96	< 10[e]	nd[d]

[a] Reaction was carried out in the presence of 1 equiv. $Mg(ClO_4)_2$ in MeCN under reflux. [b] Isolated yield. [c] Determined from ^1H NMR of the corresponding MTPA ester. [d] Nd = not determined. [e] Obtained from ^1H NMR spectrum of the crude product.



1 R = Me
2 R = $(CH_2)_2OMe$
3 R = $(CH_2)_2O(CH_2)_2OMe$

Fig. 1

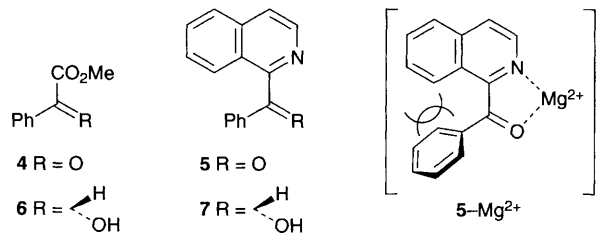


Fig. 2

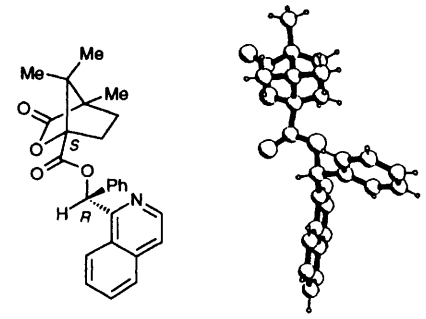


Fig. 3 Molecular structure of (1*S*)-camphanate ester of **7**

assistance of the 6-methoxyethyl group for metal coordination with the sulfinyl oxygen. The fact that the stereoselectivity of **3** was as high as that of **2** but the reactivity of **3** was lower than that of **2** suggests that the second oxygen in **3** competes with the substrate in coordination with Mg^{2+}. These findings clearly indicate that formation of the ternary complex mediated by the metal ion is vital for this type of reaction.

Based on the results described above and the fact that the *syn*-orientation between the 4-hydrogen and the sulfinyl oxygen is essentially required, we propose the structure of the ternary complex as illustrated in Fig. 5. In the NAD(P)H reduction, coordination of the substrate and the amido-carbonyl oxygen in place of the sulfinyl group with metal ion should allow the reduction to proceed. This phenomenon is thought to be true in the naturally occurring NAD(P)H reduction system as well and is also expected to be of great use for the design of novel NADH mimics.

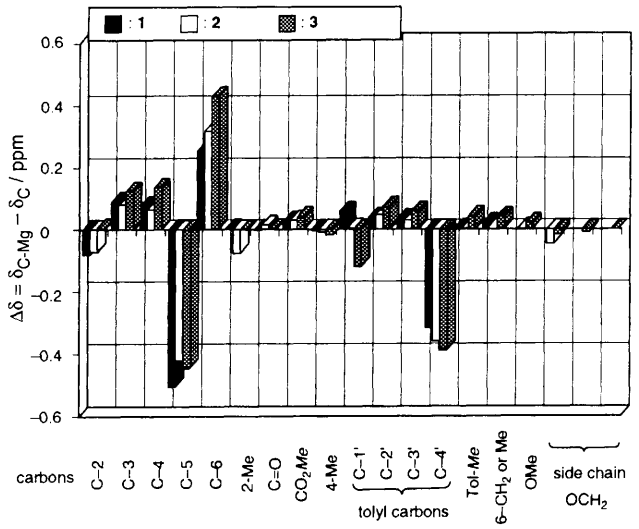


Fig. 4 Differences of the ^{13}C NMR data for **1–3** between with and without Mg^{2+}

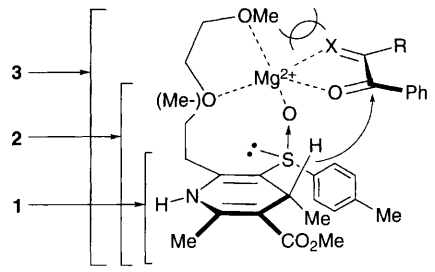


Fig. 5 Possible structure of the ternary complex

Footnote

† We also examined the reduction of **4** with 4*S*-isomer of **1**, which proceeded quite slowly and afforded (*S*)-mandelate with low stereoselectivity.

‡ *Crystal data* for (*R*)-α-(1-isoquinolyl)benzyl (1*S*)-camphanate: crystal dimensions 0.5 × 0.2 × 0.5 mm, $C_{26}H_{25}NO_4$, M = 415.47, monoclinic, space group $P2_1$, a = 9.094(1), b = 13.608(2), c = 9.420(1) Å, β = 107.46(1)°, V = 1112.0(2) Å^3, Dc = 1.241 g cm^{-3}, z = 2, μ(Cu-K$_\alpha$) = 0.67 cm^{-1}, $F(000)$ = 440. Intensity data were collected at 20 °C using an ω-2θ scan technique to a maximum 2θ value of 130°. no. of unique reflections, 1832. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares using SHELXL93.[7] Goodness of fit on F^2 0.806. The final agreement indices for 1766 reflections [$I > 4\sigma(I)$] were R = 0.057, R_w = 0.152. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/243.

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