Asymmetric Catalysis

A Novel Dinuclear Chiral Niobium Complex for Lewis Acid Catalyzed Enantioselective Reactions: Design of a Tridentate Ligand and Elucidation of the Catalyst Structure**

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Development of chiral catalysts for asymmetric reactions is one of the most important tasks in organic synthesis.[1] While various types of catalysts have been developed, exploitation of novel catalysts, especially those based on unusual metals and novel ligands, applicable to new enantioselective reactions, is still very important. Herein we describe the first highly enantioselective niobium(v) Lewis acid catalyst.

Niobium lies below vanadium in Group 5 and is expected to have high Lewis acidity,[2] there are only a few reports of chiral niobium catalysts, which have been used in asymmetric Diels–Alder reactions and oxidations.[3,4] This situation is in remarkable contrast to many asymmetric transformation catalyzed by the neighboring Group 4 metal complexes of titanium[5] and zirconium.[6] To prepare an efficient chiral pentavalent niobium(v) catalyst for activation of aldehydes or imines, we designed tridentate ligands **4a**–**d** (see Equation (1)),[7] which were synthesized according to conventional methods).[8]

Ligands **4a**–**d** were combined with niobium alkoxides ($Nb(OR)_5$), and were employed as catalysts for the Mannich-type reaction of imines **1** with silicon enolates **2** [Eq. (1)].[9]

For the reaction of **1a** with **2a**, several reaction parameters were examined, and the results are summarized in Table 1. It was found that *N*-methylimidazole (NMI) was effective as an additional ligand.[10] Among the chiral ligands screened, **4c** gave the best enantioselectivity (Table 1, entry 3). The selectivity was further improved in a toluene–CH_2Cl_2 (1:1) mixed solvent system (Table 1, entry 6) and in the presence of 3-Å or 4-Å molecular sieves (MS 3Å or MS 4Å; Table 1, entries 7 and 8). We also examined several niobium alkoxides. When $Nb(OMe)_5$ was combined with ligand **4c**, the desired Mannich-type adduct was obtained in 86% yield with 99% *ee* (Table 1, entry 10). It is noteworthy that almost complete selectivity has been achieved using this novel chiral niobium catalyst.

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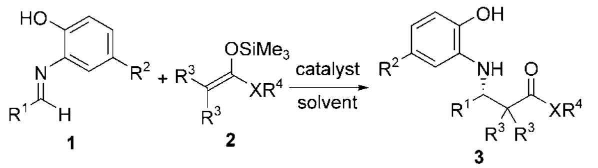
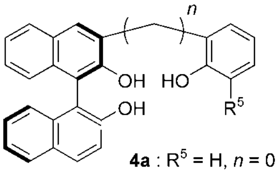


(1)

1a : R^1 = Ph, R^2 = H
1b : R^1 = (4-Cl)C_6H_4, R^2 = H
1c : R^1 = (4-MeO)C_6H_4, R^2 = H
1d : R^1 = 1-Naphthyl, R^2 = H
1e : R^1 = 2-Naphthyl, R^2 = H
1f : R^1 = 3-Thienyl, R^2 = H
1g : R^1 = Ph, R^2 = CF_3
1h : R^1 = 2-Furyl, R^2 = H
2a : R^3 = Me, XR^4 = OMe
2b : R^3 = H, XR^4 = SEt



4a : R^5 = H, n = 0
4b : R^5 = Et, n = 1
4c : R^5 = *i*Pr, n = 1
4d : R^5 = *t*Bu, n = 1

Table 1: Effect of binol derivatives on the reaction of **1a** with **2a** [Eq. (1)].[a]

Entry	Nb(OR)$_5$	Binol	Additive[b]	Yield [%]	*ee* [%]
1	OEt	**4a**	none	64	14
2	OEt	**4b**	none	71	35
3	OEt	**4c**	none	73	67
4	OEt	**4d**	none	34	6
5[c]	OEt	**4c**	none	37	82
6[d]	OEt	**4c**	none	84	85
7[d]	OEt	**4c**	MS 3Å	84	92
8[d]	OEt	**4c**	MS 4Å	74	88
9[d,e]	OEt	**4c**	MS 3Å	87	95
10[d,e]	OMe	**4c**	MS 3Å	86	99
11[d,e]	O*n*Pr	**4c**	MS 3Å	80	90
12[d,e]	O*i*Bu	**4c**	MS 3Å	28	73

[a] The reactions were carried out using 10 mol% of Nb(OR)$_5$, 10–12 mol% of the binol derivative, and 10–12 mol% of NMI in CH_2Cl_2 at 0°C for 18 h. [b] Molecular sieves (100 mg/0.6 mmol substrate) were used. [c] In toluene. [d] In toluene:CH_2Cl_2 = 1:1. [e] −20°C, 48 h.

Several other substrates were tested, and the results are summarized in Table 2. Various imines reacted with **2a** in toluene-CH_2Cl_2 (1:1) between at −10 and −20°C to afford the corresponding Mannich-type adducts in high yields with excellent enantioselectivities. When silicon enolate **2b** was used, the enantioselectivities were good but slightly decreased (Table 2, entries 9–11). The catalyst loading could be reduced from 10 mol% to 5 mol% and 2 mol% without significant loss of the yield and selectivity.[11]

Table 2: Substrate generality [Eq. (1)].[a]

Entry	Imine	Si enolate	Product	Yield [%]	*ee* [%]
1[b,d]	**1a**	**2a**	**3a**	86	99
2[c,d]	**1a**	**2a**	**3a**	69	96
3[e]	**1b**	**2a**	**3b**	82	98
4[f]	**1c**	**2a**	**3c**	79	96
5	**1d**	**2a**	**3d**	40	95
6	**1e**	**2a**	**3e**	77	98
7	**1f**	**2a**	**3f**	85	93
8[f]	**1g**	**2a**	**3g**	75	91
9[f]	**1a**	**2b**	**3h**	69[g]	84
10	**1b**	**2b**	**3i**	44	88
11[f]	**1h**	**2b**	**3j**	70	87

[a] The reactions were performed using 10 mol% of Nb(OMe)$_5$, 12 mol% of **4c**, 12 mol% of NMI, and MS 3Å (100 mg/0.6 mmol substrate) at −20°C for 48 h. [b] 5 mol% of the catalyst was used. [c] 2 mol% of the catalyst was used. [d] MS 3Å (50 mg/0.4 mmol substrate) was added. [e] −10°C, 18 h. [f] −10°C, 48 h. [g] Determined by ^1H NMR spectroscopy.

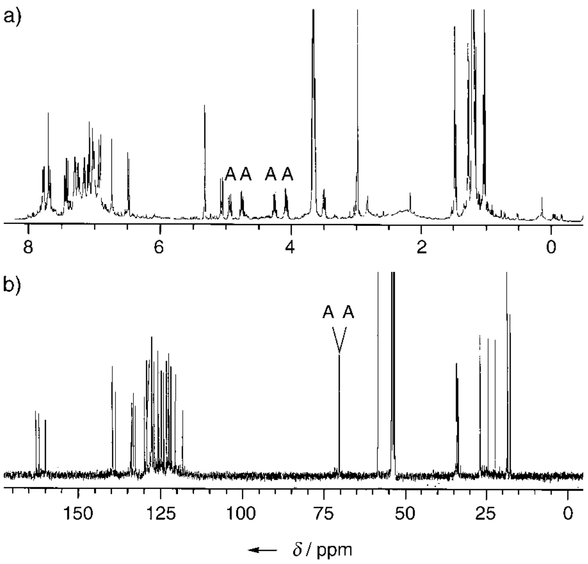
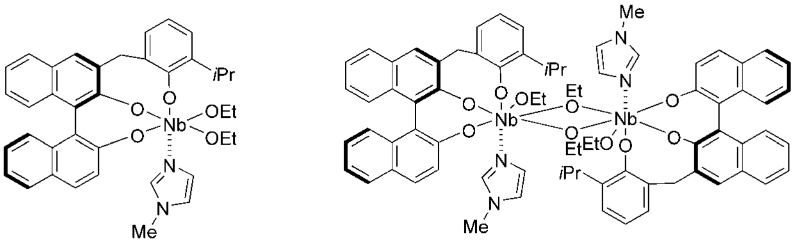


Figure 1. a) ^1H and b) ^{13}C NMR spectra of a catalyst solution of Nb(OEt)$_5$, **4c**, and NMI in CD_2Cl_2. **A**: OCH_2CH_3.

We next turned our attention to the structure of the chiral catalyst. Analysis of the ^1H and ^{13}C NMR spectra of Nb(OEt)$_5$, **4c**, and NMI in CD_2Cl_2 revealed the presence of a single species, in which Nb and **4c** were a 1:1 molar ratio (Figure 1). Since two sets of resonances (**A** in Figure 1) were observed for -OEt, structure **5** was tentatively assigned as a single unit of the catalyst (Figure 2). Since niobium complexes are known to form dimeric structures easily,[12] we then investigated the nonlinear effect (NLE)[13] in the Mannich-type reaction to confirm whether a dimeric structure existed. We conducted the reaction using the ligand with low enantiomeric excess (23% *ee*, 45% *ee*, 73% *ee*), and observed a significant positive NLE (■ in Figure 3). We prepared optically pure *R* and *S* chiral niobium catalysts, then mixed them together to form the catalysts with low enantiomeric excess, and conducted the



5 **6**

Figure 2. Possible structures of the highly selective Nb catalyst in solution.

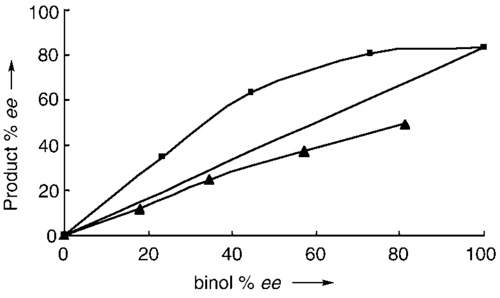


Figure 3. Nonlinear effect. The reactions were performed using **1a** and **2a** as substrates in CH_2Cl_2 at −20 °C in the presence of the Nb catalyst (10 mol %),—— linear, ■ low *ee* value binol ligand, ▲ mixed catalyst solution.

same Mannich-type reaction. Interestingly, in this case a slightly negative nonlinear effect was observed (▲ in Figure 3). These results suggest that a dimeric species such as **6** is formed by combining $Nb(OR)_5$, **4c**, and NMI, and that the *R*,*S* heterodimeric species might be less reactive than the *R*,*R* and *S*,*S* homodimeric species. It is also assumed that no ligand exchange occurred after formation of the dimeric species.

Single crystals of a Nb complex suitable for X-ray analysis were obtained by the addition of petroleum ether to a combination of $Nb(OEt)_5$, **4c**, and NMI in toluene. Crystals formed gradually, and the X-ray structure obtained is shown in Figure 4.[14] Surprisingly, crystal structure **7** was different from the assumed structure in solution (**6**). Characteristic features of **7** are a Nb-(μ_2-O)-Nb unit, and that the binol moiety of **4c** is bound in a bidentate fashion to one niobium atom while the oxygen atom of the pendent phenol moiety is bonded to the other niobium atom (bridged structure).

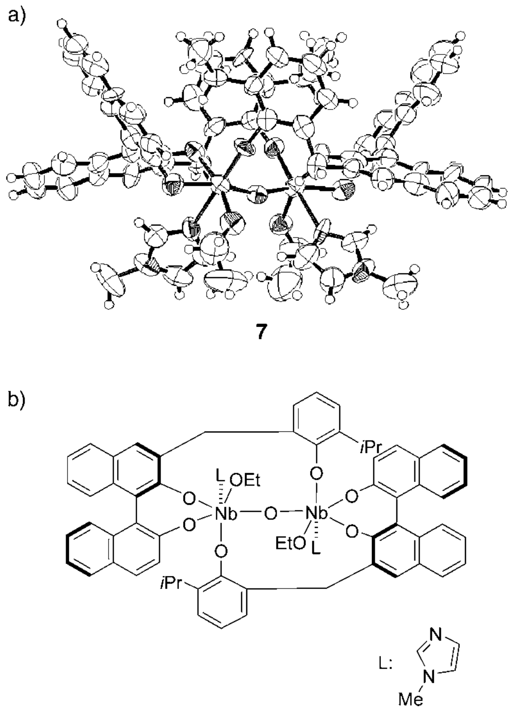


Figure 4. a) Crystal structure and b) structural formula of the niobium complex **7**.

Crystals of **7** thus obtained were also analyzed by ^1H and ^{13}C NMR spectroscopy in CD_2Cl_2 (Figure 5). Of note is that the spectra are quite different from those of the assumed complex **6** (Figure 1). The principle differences are the number of the ethoxy moieties (**B** in Figure 5) and the chemical shifts of the methyl groups in the isopropyl substituents (**C** in Figure 5) in the ^1H NMR spectrum. The chemical shifts of the methyl groups in **7** are at around $\delta =$ 0 ppm, while the chemical shifts of the methyl groups in the assumed complex **6** are observed at around $\delta = 1.2$ ppm. Aromatic shielding effects might be the cause of the significant upfield shift.

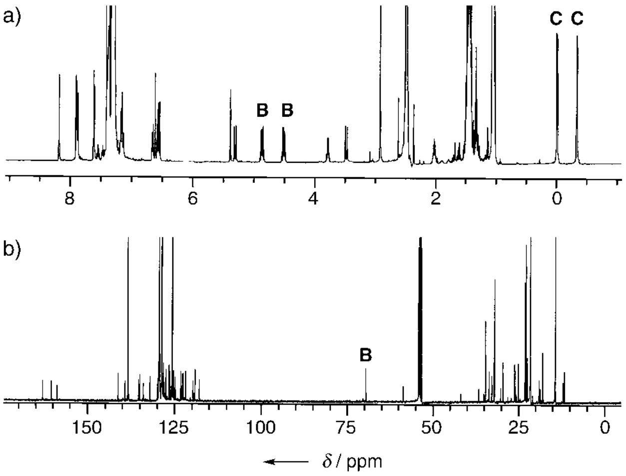


Figure 5. a) ^1H and b) ^{13}C NMR spectra of **7** in CD_2Cl_2. **B**: OCH_2CH_3, **C**: $(CH_3)_2CH$.

Chiral Nb complex **7** displayed lower catalytic activity in the Mannich-type reaction of imine **1a** with silicon enolate **2a** (9 mol % based on Nb atom) of **7**, in dichloromethane at −20 °C for 18 h). The desired product was obtained in 21 % yield with 61 % *ee*, while the same product was obtained in 74 % yield with 83 % *ee* in the presence of 10 mol % of the chiral niobium catalyst prepared in situ.

Since the NLE experiments suggested that no ligand exchange occurred after formation of the dimeric species, we propose **8** as the most plausible structure of the highly enantioselective Nb complex (Figure 6). We assume that **7** was formed from **8** during the crystallization. A key to understanding the mechanism for the formation of **7** from **8** is the origin of the oxygen atom between the niobium atoms in **7**. Contamination of a small amount of water might form **7** from **8**, but this possibility was ruled out by several control experiments. A possible mechanism is the cleavage of the C–O bond of the bridging ethoxy group of **8**, followed by the Nb-O-Nb bond formation accompanied with generation and elimination of diethyl ether. The highly strained structure of **8** might induce the formation of **7**. Further investigations to obtain clear evidence for this mechanism are now in progress.

In summary, we have developed a novel dinuclear chiral niobium catalyst, in which tridentate ligands have been shown

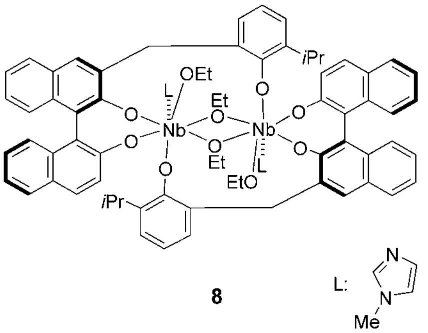


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Figure 6. The most plausible structure of the highly selective niobium catalyst in solution.

to be effective. In the presence of a catalytic amount of this complex, asymmetric Mannich-type reactions proceeded smoothly to afford the desired adducts in high yields with high enantioselectivities. A crystal structure of a chiral binuclear niobium complex, which contains a Nb-(μ_2-O)-Nb unit and a tridentate binol derivative (**4c**) chelates one Nb atom while bridging to another, has been revealed. Furthermore, the most plausible structure of the highly selective niobium complex has been proposed.

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