The First Catalytic Asymmetric Nitro-Mannich-Type Reaction Promoted by a New Heterobimetallic Complex[**]

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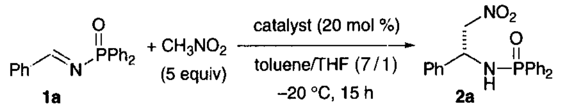
Catalytic enantioselective nucleophilic addition to imines is a challenging area of organic chemistry. Although numerous efficient catalytic asymmetric methods have been developed for the addition of carbon nucleophiles to carbonyl compounds,[1] only a few examples are known for imines. To date, noteworthy and impressive developments in this field have mainly been made using organometallic reagents,[2, 3] silyl ketene acetals,[4] or allylstannanes[5] as nucleophiles, and recently catalytic asymmetric Strecker reactions have been reported.[6] The catalytic asymmetric addition of nitroalkanes to imines, called the catalytic asymmetric nitro-Mannich-type reaction, provides chiral β-nitroamines. This versatile class of compounds can be easily converted into useful chiral building blocks such as α-amino acids and 1,2-diamines. To the best of our knowledge no catalytic asymmetric nitro-Mannich-type reaction has been reported to date.[7] Herein, we report the first example.

We first examined this reaction using heterobimetallic asymmetric complexes containing both Brönsted basic and Lewis acidic functionalities. These complexes have been developed in our laboratory and have proved to be highly efficient catalysts for many types of asymmetric reactions including catalytic asymmetric nitroaldol reactions.[8] We envisioned that development of a catalytic asymmetric nitro-Mannich-type reaction would be feasible. Unexpectedly, the use of usual imines such as *N*-benzylimines gave only unsatisfactory results.[9] However, having discovered in previous work that P=O double bonds can coordinate to the central metal of a heterobimetallic complex,[10] we assumed that *N*-phosphinoylimines **1** might be more suitable substrates for our target reaction. The synthesis of imine **1**, using known literature methods,[11] proved unsatisfactory and led us to develop a modified method for imine preparation.[12]

A screening of catalysts showed us that the complex [YbK$_3$(binaphthoxide)$_3$] (YbPB) was the best heterobimetallic catalyst for the reaction.[13] For example, when 20 mol% of YbPB was used, the addition of nitromethane to imine **1a** afforded the nitroamine **2a** in 64% yield and with 52% *ee* (Table 1, entry 1). After several attempts to improve the *ee* value, we were pleased to find that reducing the amount of potassium in the Yb-containing heterobimetallic catalyst increased the *ee* value of the product (entries 2 and 3). The catalyst prepared from Yb(O*i*Pr)$_3$, KO*t*Bu, and binaphthol in the ratio of 1:1:3 gave the best result, providing the desired product in 62% yield and with 82% *ee*. Importantly, it was necessary to add nitromethane slowly to obtain this result.[14] We initially thought that the reduced amount of potassium resulted in the formation of a complex of Yb, K, and binaphthol in the ratio of 1:1:2[15] along with a free binaphthol, and that the complex [YbK(binaphthoxide)$_2$] was the actual catalyst. However, this possibility was excluded because the complex prepared from Yb(O*i*Pr)$_3$, KO*t*Bu, and binaphthol in the ratio of 1:1:2 did not promote the reaction (entry 4).

Table 1. The effects of the composition of the catalysts on the yield and *ee* value.

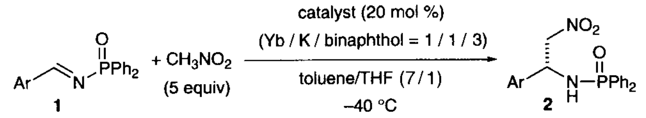


Entry[a]	Catalyst composition (Yb:K:binaphthol)	Yield [%]	*ee* [%]
1	1:3:3(YbPB)	64	52
2	1:2:3	82	75
3	1:1:3	62	82
4	1:1:2	–	–

[a] Nitromethane was added over 14 h.

The best result was obtained when the reaction was carried out at −40 °C with 20 mol% of the catalyst (Yb:K:binaphthol = 1:1:3) and slow addition (over 27 h) of nitromethane (5 equiv) to the imine **1a**. The product **2a** was formed in 79% yield and with 91% *ee* (Table 2, entry 1). With these optimized conditions in hand, we examined the scope and limitations of the reaction (Table 2). As expected the reaction proceeded smoothly with the imine **1b**, which contains an electron-withdrawing substituent, giving the product **2b** in 93% yield and with 87% *ee* (entry 2). In the case of imine **1c**, which contains an electron-donating group, the reaction required a prolonged reaction time and gave the product **2c** in 85% yield and with 89% *ee* (entry 3). The reactions were rather slow with imines **1d** and **1e**, which contain electron-rich aromatic groups, and gave the products with good *ee* values but in only moderate yields[16] (entries 4

Table 2. The scope and limitations of the catalytic asymmetric nitro-Mannich-type reaction.



Entry[a]	Ar	Imine	Product	*t* [h]	Yield [%]	*ee* [%]
1	Ph	**1a**	**2a**	60	79	91
2	4-Cl-C$_6$H$_4$	**1b**	**2b**[b]	60	93	87
3	*p*-tolyl	**1c**	**2c**[b]	168	85	89
4	2-furyl	**1d**	**2d**[b]	168	57	83
5	2-thiophenyl	**1e**	**2e**[b]	168	41	69

[a] Nitromethane was added over 27 h. [b] The absolute configuration was tentatively assigned.

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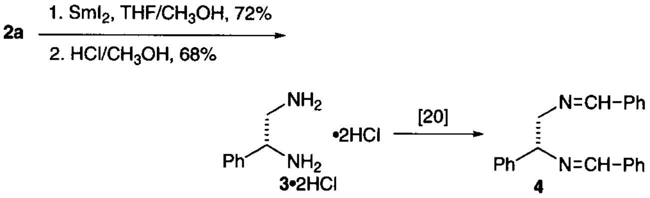
[**] H.G. thanks the Japanese Science and Technology Corporation (JST) for a postdoctoral grant. S.J.H. thanks the Japanese Society for the Promotion of Science (JSPS) for a postdoctoral grant.

and 5). To date, results using imines derived from aliphatic aldehydes such as pivalaldehyde are less satisfactory.[17]

To highlight the importance of the nitroamine products obtained from this reaction, we converted the nitroamine **2a** into the synthetically versatile diamine **3** (Scheme 1). The nitro group was reduced to an amino group using Sm^{II} in 72 % yield,[18] and the diphenylphosphinoyl group was cleaved under mildly acidic conditions[19] to afford the diamine **3** in 68 % yield as the dihydrochloride. The HPLC analysis (chiral stationary phase) of the Schiff base **4**, derived from the dihydrochloride of the diamine **3**, revealed that the absolute configuration of the major enantiomer of nitroamine **2a** was *R* when the catalyst was prepared from (*R*)-binaphthol.[20]



Scheme 1. The transformation of the nitroamine **2a** into the dihydrochloride of diamine **3**.

To determine the structure of the catalyst, we measured laser desorption/ionization time-of-flight (LDI-TOF) mass spectra of the catalyst solution. The main peaks in the positive-ion mode were at *m*/*z* 285, 1602, and 2114, corresponding to $[binaphthol]H^+$, $[YbK(binaphthoxide)_2]_2K^+$, and $[YbK(binaphthoxide)_2]_3K^+$, respectively. The main peaks in the negative-ion mode were *m*/*z* 286, 741, and 1519, corresponding to $[H(binaphthoxide)]^-$, $[Yb(binaphthoxide)_2]^-$, and $K[Yb(binaphthoxide)_2]_2^-$, respectively. Given these observations, the structure of the catalyst could be $[YbK(binaphthoxide)_2]$ (Figure 1, middle) or its aggregated complex $[YbK(binaphthoxide)_2]_n$ (Figure 1, right). However, since the 1:1:2 complex gave poor results for the nitro-Mannich reaction (Table 1, entry 4), it seems unlikely that they represent the structure of the active catalyst. Since the mass spectra reflect the structure of the catalyst in solution, we propose that the active catalyst may be a complex of $[YbK(binaphthoxide)_2]$ and binaphthol, weakly associated to each other by Lewis acid–Lewis base interactions and hydrogen bonding (Figure 1, left).

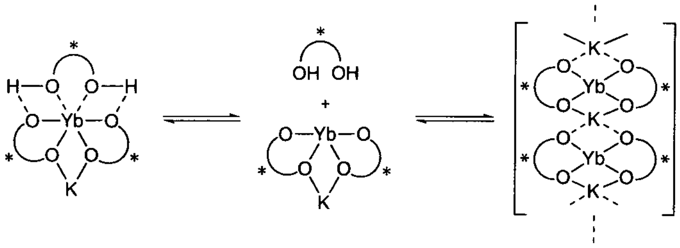


Figure 1. The proposed structure of the new heterobimetallic complex. (The semicircles represent the 1,1′-binaphthyl skeleton of binaphthol).

In conclusion, we have developed the first enantioselective nitro-Mannich-type reaction in a catalytic manner. The best catalyst for this reaction is a new type of heterobimetallic complex, containing Yb, K, and binaphthol in the ratio of 1:1:3, rather than the known heterobimetallic complex YbPB (1:3:3).

Experimental Section

$Yb(OiPr)_3$ was purchased from Kojundo Chemical Co., Ltd.[21] All solvents used in the reactions were dried prior to use. All reagents were purified by standard methods. All reactions were performed under an anhydrous argon atmosphere.

Preparation of the catalyst solution: (*R*)-Binaphthol (86.5 mg, 0.30 mmol; dried at 45 °C for 4 h in vacuo) was dissolved in THF (2.8 mL), and the solution was stirred for 10 min at room temperature. $Yb(OiPr)_3$ (0.1 M solution in THF, 1.0 mL) was added to the solution, and the mixture was stirred for another 10 min. KO*t*Bu (1.0 M solution in THF, 0.10 mL) and then after 10 min H_2O (1.0 M solution in THF, 0.10 mL) were added to the mixture. The mixture was stirred for an additional hour at room temperature before the solvent was removed in vacuo. The residual solid was dried in vacuo for a further hour, and then THF (0.50 mL) and toluene (3.5 mL) were added. The mixture was stirred for 1 h at room temperature and was then used as a 0.025 M catalyst solution (toluene/THF 7/1).

General procedure for the catalytic asymmetric nitro-Mannich-type reaction: (*R*)-*N*-(2-nitro-1-phenylethyl)-*P*,*P*-diphenylphosphinic amide (**2a**): To *N*-benzylidene-*P*,*P*-diphenylphosphinic amide (**1a**; 76 mg, 0.25 mmol) was added the freshly prepared catalyst solution (2.0 mL, 0.20 equiv), and the mixture was stirred for 10 min at room temperature. The mixture was cooled to −40 °C and stirred for 10 min before nitromethane (0.068 mL, 5.0 equiv) was added slowly over 27 h at the same temperature. After the addition of nitromethane was completed, the mixture was stirred for an additional 33 h at the same temperature, and then quenched by the addition of water (ca. 5 drops) and diluted with CH_2Cl_2 (ca. 5 mL). The mixture was allowed to warm up to room temperature, and after further dilution with CH_2Cl_2 (ca. 15 mL) the mixture was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (Si_2O, acetone/hexane 40/60 → 50/50) gave nitroamine **2a** (72 mg, 79 %) with 91 % *ee* as an off-white solid.[22]

Received: May 26, 1999 [Z13470IE]
German version: *Angew. Chem.* **1999**, *111*, 3713–3715

Keywords: asymmetric catalysis · asymmetric synthesis · diamines · imines · nitroalkanes

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[12] *P,P*-Diphenylphosphinic amide (0.22 g, 1.0 mmol) was placed in a flame-dried 25-mL test tube and dissolved in CH$_2$Cl$_2$ (4.4 mL). To the solution was added benzaldehyde (0.20 mL, 2.0 mmol) and triethylamine (0.42 mL, 3.0 mmol), and then the mixture was cooled with an ice-water bath. A solution of TiCl$_4$ in CH$_2$Cl$_2$ (1.0 M, 0.55 mL) was added dropwise to the cooled mixture (over ca. 5 min). After the removal of the ice-water bath, the mixture was stirred for 2 h at room temperature, and then diluted with toluene (ca. 20 mL). The mixture was transferred into a 200-mL flask, and was diluted with further toluene (ca. 75 mL). The suspension was then filtered through celite, and the celite was washed with toluene. Evaporation of the solvent gave a brown oil containing mainly the imine **1a** and benzaldehyde. The excess benzaldehyde was removed under high vacuum, and recrystallization of the resulting solid provided the imine **1a** (0.26 g, 85%).

[13] For example, [LaLi$_3$(binaphthoxide)$_3$] (LLB) at −40 °C gave the product in 29% yield and with 2% *ee*, and [AlLi(binaphthoxide)$_2$] (ALB) gave no product.

[14] When nitromethane was added in one portion, the result was less satisfactory (34% yield, 45% *ee*).

[15] This is a characteristic structure for heterobimetallic complexes with a Group 13 central metal.

[16] To overcome these problems of reactivity, bis(4-trifluoromethylphenyl)phosphinoyl imines were prepared. However, this strategy was unsuccessful, and did not give better results.

[17] Attempts to prepare the corresponding imines starting from enolizable aldehydes, such as isobutyraldehyde, failed due to self-condensation of the aldehydes under the conditions of imine formation.

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[21] Address: 5-1-28, Chiyoda, Sakato, Saitama 350-02 (Japan); Fax: (+81) 492-84-1351.

[22] The enantiomeric excess of **2a** was determined by HPLC analysis on a chiral stationary phase (DAICEL Chiralcel OD, *i*PrOH/hexane 10/90, flow rate: 1.0 mL min^{-1}, retention time: 15 min (*S* isomer) and 27 min (*R* isomer), detection at 254 nm).

Mesoporous Magnetic Materials Based on Rare Earth Oxides[**]

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Since the discovery of the mesoporous silicas MCM-41[1] and FSM-16[2] derived from their surfactant mesocomposites, increasing attention has focused on the synthesis of mesoporous materials by the template method. Mesostructured silicas with surface-modified mesopores have large internal surface areas and narrow pore size distributions, and are effective catalysts and molecular sieves.[3] Mesoporous transition metal oxides are promising not only as catalysts and molecular sieves but also as highly functional materials with shape-specific and/or quantum effects characteristic of their ordered inorganic skeletons. Antonelli et al.[4] and Sun et al.[5] synthesized various micro- and mesoporous transition metal oxides such as niobium and tantalum oxides by the ligand-assisted liquid crystal template method with neutral primary amines. Layered[6] and hexagonal[7] mesostructured titanium oxides were found to be photocatalytically active.

Rare earth oxides and mixed oxides are useful as materials with luminescent, catalytic, electric, and magnetic properties that result from their 4f electrons. Rare earth garnets are applicable as bubble memory materials owing to their small magnetic domains with up or down spins. If such rare earth oxides were obtainable as mesoporous solids, they would be promising as adsorbents or separating agents with a combination of shape- or size-selectivity and magnetic properties. They could also act as electrically, magnetically, or optically functional host materials. We have reported the synthesis of a series of mesostructured metal oxides and demonstrated that the homogeneous precipitation method with urea is effective for the synthesis of aluminum-, gallium-, and yttrium-based dodecyl sulfate mesophases in which layered and hexagonal structures are templated by alkyl sulfate assemblies.[8–13] The hexagonal yttrium-based mesophase was converted into a mesoporous material with a specific surface area of 545 m^2 g^{-1} by anion exchange of the surfactant with acetate ions, although the Al- and Ga-based analogues collapsed on the removal of surfactants.[13] However, the introduction of yttrium species into the inorganic framework of Al- and Ga-based mesophases yielded highly ordered mesoporous Al–Y and Ga–Y mixed oxides with specific surface areas of 798 and 714 m^2 g^{-1}, respectively.[14, 15] Here we report on the first synthesis and characterization of mesoporous rare earth oxides, as well as their anomalous magnetic properties.

The X-ray diffraction (XRD) pattern of the solid erbium-based mesophase isolated after a reaction time *t* of 3 h (see

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[**] This work was supported by a Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Scinence, Sports and Culture of Japan.