A Catalytic Michael Addition of Thiols to α,β-Unsaturated Carbonyl Compounds: Asymmetric Michael Additions and Asymmetric Protonations

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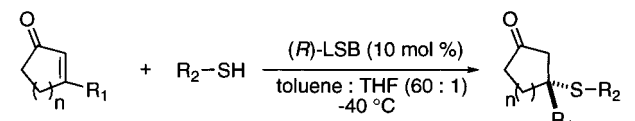
In recent years, the catalytic asymmetric Michael addition promoted by chiral metal complexes has been recognized as an efficient method for enantioselective carbon−carbon bond formations. We[2] and others[3] have already achieved quite efficient catalytic asymmetric Michael additions using malonate derivatives or organometallic reagents. In contrast to these results, a catalytic asymmetric Michael addition using thiols has not yet been developed to a synthetically useful level.[3c,4] Moreover, the development of an effective method for the catalytic asymmetric protonation in Michael additions of thiols to α,β-unsaturated carbonyl compounds has also not been achieved.[5] We have found that heterobimetallic asymmetric complexes,[6] in particular $LaNa_3$-tris(binaphthoxide) (LSB) and $SmNa_3$tris(binaphthoxide) complexes (SmSB), are very useful catalysts for both above-mentioned types of asymmetric reactions. In this communication we report an efficient catalytic asymmetric Michael addition of thiols to cycloalkenones and an effective catalytic asymmetric protonation in Michael additions of thiols.

First, the catalytic asymmetric Michael addition of 4-*tert*-butyl(thiophenol) (**2a**) to cyclohexenone (**1a**) was examined in detail. Among a variety of heterobimetallic asymmetric complexes,[6] it was found that the use of (*R*)-LSB gave the best result.[7] That is, treatment of **1a** with **2a** (1.0 equiv) in the presence of LSB (10 mol %) in toluene containing a small amount of THF (60:1) at −40 °C for 20 min afforded the Michael adduct **3a** in 84% ee and in 93% yield. The use of THF as the only solvent furnished **3a** in 94% yield and only in 2% ee. Although the use of thiophenol (**2b**) in the best solvent system gave **3b** in 87% yield and in 68% ee, we were pleased to find that the use of benzyl mercaptan (**2c**) afforded **3c** in 90% ee and in 86% yield. Having developed an efficient method for the catalytic asymmetric Michael addition of a thiol to cyclohexenone (**1a**), we next investigated catalytic asymmetric Michael additions using other cycloalkenones. The results are summarized in Table 1.[8,9] To the best of our knowledge, this is the most efficient catalytic asymmetric Michael addition of thiols to cycloalkenones.[10] In an attempt to clarify the mechanism for the catalytic asymmetric Michael addition of thiols, the Michael adduct **4** in 52% ee was subjected to essentially similar conditions as applied for the Michael additions to result in the recovery of **4** with 49% ee, suggesting that the present asymmetric Michael addition is a kinetically controlled reaction. The proposed catalytic cycle is shown in Scheme 1. The $LaNa_3$tris(binaphthoxide) complex (LSB) is a multifunctional asymmetric catalyst. That is, a sodium naphthoxide moiety should function as a Brønsted base to activate the thiol, and the center metal (La) should function as a Lewis acid to control the direction of the cycloalkenone as well as activate the cycloalkenone, thereby making possible an effective catalytic asymmetric Michael addition of a thiol to a cycloalkenone. Actually, we have obtained several proofs for the above-mentioned type of mechanism in other reactions.[6]

Next we paid attention to the intermediate **II** with an acidic naphthol moiety. Is it possible to utilize this OH group as an asymmetric protonation source? This concept led us to the development of a catalytic asymmetric protonation in Michael additions of thiols to α,β-unsaturated carbonyl compounds. First

Table 1. Catalytic Asymmetric Michael Additions of Thiols to Enones Promoted by LSB



1a-d **2a-c** **3-6**

enone	R_2−SH	product	time	yield (%)	ee (%)
n = 2, R_1 = H (**1a**)	4-*t*-BuPhSH (**2a**)	**3a**	20 min	93	84
1a	PhSH (**2b**)	**3b**	20 min	87	68
1a	$PhCH_2SH$ (**2c**)	**3c**	14 h	86	90
n = 1, R_1 = H (**1b**)	**2c**	**4**	4 h	94	56
n = 3, R_1 = H (**1c**)	**2c**	**5**[a]	41 h	87	83
n = 2, R_1 = Me (**1d**)	**2c**	**6**[a,b]	43 h	56	85

[a] 20 mol % of LSB was used and the solvent ratio (toluene : THF) was 60 : 2. [b] Carried out at -20 °C.

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(4) (a) Kobayashi, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071. (b) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (c) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363. (d) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H. *J. Org. Chem.* **1988**, *53*, 1157. During the preparation of this manuscript, Tomioka et al. reported an impressive catalytic asymmetric Michael addition of thiols to, in particular, acyclic α,β-unsaturated esters. See: Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974.

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(7) The results using other heterobimetallic asymmetric complexes were as follows: AlLibis(binaphthoxide), 29% ee; GaNabis(binaphthoxide), 3% ee; $LaLi_3$tris(binaphthoxide), 10% ee; LaK_3tris(binaphthoxide), 39% ee; the alkali metal free La−BINOL complex, see ref 2a, 22% ee.

(8) The enantiomeric excesses of **3a**, **3b**, **3c**, **4**, and **6** were determined by chiral stationary phase HPLC (DAICEL CHIRALPAK AS, *i*-PrOH−hexane, 1: 4). The enantiomeric excesses of **5**, **8** and **10a** were determined by chiral stationary phase HPLC (DAICEL CHIRALCEL OJ, *i*-PrOH−hexane, 2:98).

(9) The absolute configurations of **3a** and **3b** were determined by comparison with authentic samples.[4b] The absolute configuration of **3c** was determined by preparing an authentic sample. See: Gawronski, J.; Gawronska, K.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1981**, 307. The absolute configurations of **4**−**6** were tentatively determined based on the result of **3c**.

(10) The use of ethyl *trans*-cinnamate gave the adduct in 56% ee and in 41% yield.

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Scheme 1. Proposed Catalytic Cycle for the Catalytic Asymmetric Michael Addition of Thiols to Cycloalkenones

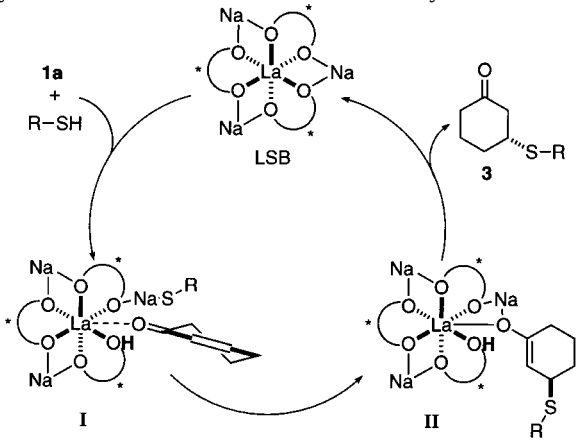
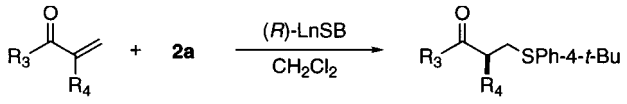


Table 2. Catalytic Asymmetric Protonations in Michael Additions of Thiols to α,β-Unsaturated Carbonyl Compounds[a]



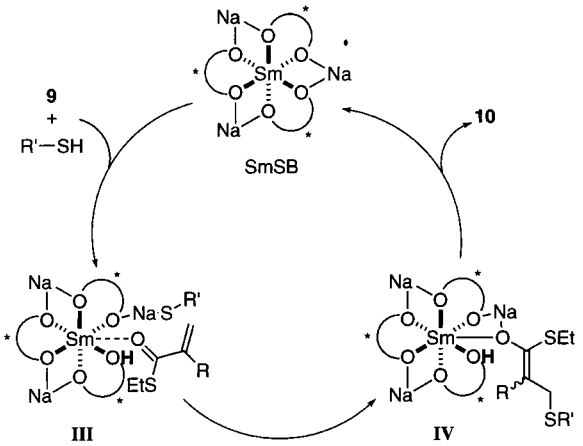
7, 9a-d 8, 10a-d

R_3	substrate R_4		adduct	Ln	catalyst amount (mol %)	temp. (°C)	time (h)	yield (%)	ee (%)
EtO	Me	(**7**)	**8**[b]	La	20	-20	48	44	75
EtO	Me	(**7**)	**8**	La	20	-20	48	50	82
EtS	Me	(**9a**)	**10a**	La	20	-78	2	93	90
EtS	Me	(**9a**)	**10a**	La	10	-78	8	90	88
EtS	Me	(**9a**)	**10a**	Sm	10	-78	7	86	93
EtS	Me	(**9a**)[c]	**10a**	Sm	2	-78	6	89	88
EtS	*i*-Pr	(**9b**)	**10b**	Sm	10	-78	7	78	90
EtS	$PhCH_2$	(**9c**)	**10c**	Sm	10	-78	7	89	87
EtS	Ph	(**9d**)	**10d**	Sm	10	-93	1	98	84

[a] The reactions were carried out by using 65 mg of **9a** (0.5 mmol). [b] Toluene was used as solvent. [c] 1.3 g of **9a** (10 mmol) was used.

of all, a catalytic asymmetric reaction using ethyl methacrylate (**7**) was examined in detail. As expected, treatment of ethyl methacrylate (**7**) with 4-*tert*-butyl(thiophenol) (**2a**) (1.0 equiv) and (*R*)-LSB (20 mol %) in toluene at −20 °C for 48 h was found to furnish **8** in 75% ee and in 44% yield. Moreover, the use of CH_2Cl_2 as a solvent gave **8** in 82% ee and in 50% yield (Table 2).[8,11] We made an effort to optimize the above catalytic asymmetric reaction. Unfortunately, however, more satisfactory chemical yields were not obtained. This drawback to the reaction was finally overcome by the use of a thioester. We were pleased to find that treatment of the thioester **9a** with 4-*tert*-butyl(thiophenol) (**2a**) and (*R*)-LSB (20 mol %) in CH_2Cl_2 at −78 °C for 2 h furnished **10a** in 90% ee and in 93% yield. Even after reducing the amount of catalyst to 10 mol % (*R*)-LSB, excellent results could still be obtained (88% ee, 90% yield). Moreover, the use of (*R*)-SmSB as a catalyst gave **10a** in 93% ee and in 86% yield.[8,12] In a larger scale experiment (1.3 g of starting material **9a**), we could actually decrease the catalyst amount to 2 mol %, affording **10a** in 88% ee and 89% yield. These results together with results using other thioesters are summarized in Table 2.[13] To the best of our knowledge, this is the most satisfactory method for the catalytic asymmetric protonation in Michael additions of thiols to α,β-unsaturated carbonyl compounds.[5] A probable mechanism is shown in Scheme 2. We believe that the high enantiomeric excesses mentioned above can be ascribed to the presence of an acidic OH moiety in a well-organized asymmetric space (see the intermediate **IV**). This OH proton stems from the thiol, being transferred during the formation of **III**. On the other hand, it is well-known that perfect self-assembly of heterobimetallic complexes and reactive nucleophiles such as lithium nitronates and sodium malonates takes place readily.[2c,6a] Thus, ready self-assembly of SmSB and the sodium salt of **2a** can be expected by analogy.[14] In a catalytic asymmetric protonation in the presence of a small amount of the sodium salt of **2a**, at least part of the protons would come from thiol **2a** directly, thereby causing a decrease in the resulting ee. Actually, reaction of **9a** with **2a** in the presence of (*R*)-SmSB (10 mol %) and sodium salt of **2a** (9 mol % or 20 mol %) gave **10a** with lower ee (91% yield, 69% ee and 89% yield, 45% ee, respectively), indicating that high ee's can indeed be ascribed to the acidic OH BINOL moiety.

Scheme 2. Proposed Mechanism for the Catalytic Asymmetric Protonation in Michael Additions of Thiols to α,β-Unsaturated Thioesters



In conclusion, we have developed the most efficient catalytic asymmetric Michael addition of thiols to cycloalkenones and the most satisfactory catalytic asymmetric protonation in Michael additions of thiols to α,β-unsaturated thioesters using LnSB.[15] In particular, we believe that the latter catalytic asymmetric synthesis offers a very efficient methodology for the synthesis of a variety of biologically significant compounds such as captopril, a therapeutically useful hypotensive drug.[16,17] Moreover, with our success in developing the latter reaction we could prove a new capacity of heterobimetallic asymmetric catalysts. Further studies are currently under investigation.

Supporting Information Available: Experimental procedures and characterization data (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) The absolute configuration of **8** was unequivocally determined by comparison with an authentic sample prepared from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate.

(12) The absolute configuration of **10a** was unequivocally determined by converting **10a** to **8** on treatment with *p*-toluenesulfonic acid in ethanol. The absolute configurations of other adducts were tentatively determined on the basis of the result of **10a**.

(13) Other thiols gave less satisfactory results.

(14) The Michael addition of **2c** to **1a** using the catalyst derived from (*R*)-LSB (10 mol %) and the sodium sodium salt of **2c** (9 mol %) gave **3c** in 90% ee, strongly supporting perfect self-assembly of (*R*)-LSB and the sodium salt of **2c**.

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