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Enantioselective Michael addition of β-keto esters to methyl vinyl ketone employing a chiral *N,N′*-dioxide–scandium trifluoromethanesulfonate complex as a catalyst

Makoto Nakajima,* Yukiko Yamaguchi and Shunichi Hashimoto

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060–0812, Japan. E-mail: nakajima@pharm.hokudai.ac.jp

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An enantioselective Michael addition of β-keto esters to methyl vinyl ketone exploiting a chiral *N,N′*-dioxide–scandium trifluoromethanesulfonate complex as a catalyst affords the corresponding Michael adducts in high yields and with enantioselectivities of up to 80% ee.

Enantioselective catalytic Michael additions are one of the most important carbon–carbon bond formation reactions because of the versatility of the products as chiral building blocks.[1] Various chiral catalysts have been reported for the Michael addition of prochiral β-keto esters to α,β-unsaturated carbonyl compounds including cinchona alkaloids,[2a–c] chiral crown ether–metal alkoxide complexes,[2d] chiral amine–transition metal complexes,[2e–g] chiral alkoxide complexes,[2h] and chiral bimetallic lanthanoid complexes[1b].

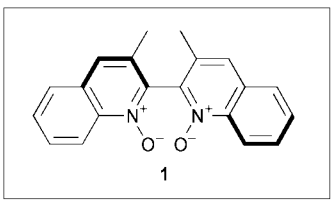
The *N*-oxide functional group is known to form complexes with a variety of metals[3] due to its strong electron donating ability, and as such could be considered useful in potential catalysts. However, only a limited number of attempts to employ *N*-oxides in chiral catalysts have been reported.[4] As part of our program of developing *N*-oxide-mediated reactions,[5] herein we describe an enantioselective Michael addition of β-keto esters to methyl vinyl ketone catalyzed by a chiral *N,N′*-dioxide–scandium trifluoromethanesulfonate complex.

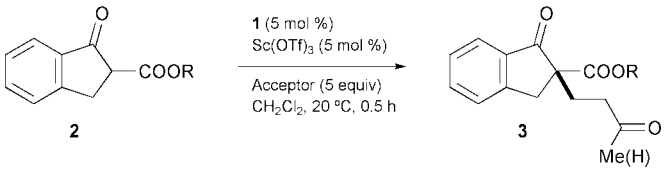
We have recently reported enantioselective conjugate addition of thiols to cyclic enones and acyclic enals catalyzed by the complex between **1** and cadmium iodide.[6] This prompted an investigation of the Michael addition of dimethyl malonate to cyclohexenone employing the **1**–cadmium complex, however, no Michael adduct was obtained with the cadmium complex. A study of the Michael addition of methyl 1-oxoindan-2-carboxylate (**2a**) to methyl vinyl ketone, a reaction frequently investigated as a probe for enantioselective Michael addition, was then undertaken. The reaction proceeded smoothly with the **1**–cadmium iodide complex, but the observed enantiomeric excess of the adduct was low (75% yield, 13% ee). After screening complexes prepared *in situ* from **1** and various metal salts, we found that 5 mol % of a 1:1 complex of **1** and scandium trifluoromethanesulfonate in dichloromethane at room temperature catalyzed the Michael addition to generate the adduct **3a** in quantitative yield with moderate enantioselectivity of 39% ee (Table 1, entry 1).

Introduced by Kobayashi *et al.*, scandium trifluoromethanesulfonate[7] is known as a versatile Lewis acid, yet only a few chiral scandium complexes as catalysts for enantioselective reactions have been reported, scandium trifluoromethanesulfonate–BINOL–amine complexes[8,9] and bimetallic complexes.[1b] Scandium trifluoromethanesulfonate is not soluble in dichloromethane, while its complex with **1** and **2a** dissolves in dichloromethane to give a yellow solution. Other solvents examined in the Michael addition were found to generate products in lower enantiomeric excess than dichloromethane (toluene: 99% yield, 8% ee; propionitrile: 99% yield, 19% ee, tetrahydrofuran: 99% yield, 10% ee). Lower selectivities were obtained at both higher and lower temperatures (0 °C: 91% yield, 5% ee; 40 °C: 98% yield, 20% ee). The enantioselectivity also strongly depended on the ratio of *N*-oxide to scandium (2.5; 99% yield, 19% ee, 1.0: 99% yield, 39% ee, 0.5: 94% yield, 30% ee with 0.5 mM scandium trifluoromethanesulfonate), as well as the catalyst concentration (0.1 mM: 85% yield, 35% ee; 0.5 mM: 99% yield, 39% ee; 2.5 mM: 93% yield, 6% ee with the ratio of *N*-oxide to scandium 1.0). These results suggest a variety of aggregation states for the complexes of scandium and *N*-oxide, though the details of these complexes are beyond the scope of this work.

As a Michael acceptor, acrolein generates a product with similar enantioselectivity (rt, 2 h, 75% yield, 30% ee after conversion of aldehyde into methyl ester), while chalcone

Table 1 Enantioselective Michael addition of β-keto ester **2** to methyl vinyl ketone catalyzed by **1**–$Sc(OTf)_3$ complex





Entry	Donor	R	Acceptor	Adduct	Yield(%)	Ee (%)[a]	Confgn	$[\alpha]_D^{25}$ (*c* 1, benzene)
1	**2a**	Me	CH_2=CHCOMe	**3a**	98	39	*R*[b]	+27.1
2	**2b**	CH_2Ph	CH_2=CHCOMe	**3b**	85	38	*R*[c]	+17.5
3	**2c**	*i*-Pr	CH_2=CHCOMe	**3c**	94	47	*R*[d]	+31.9
4	**2d**	$CH(i\text{-Pr})_2$	CH_2=CHCOMe	**3d**	98	69	*R*[d]	+20.4
5	**2e**	*t*-Bu	CH_2=CHCOMe	**3e**	93	80	*R*[e]	+46.6
6	**2e**	*t*-Bu	CH_2=CHCHO	**3f**	73[f]	75[f]	*R*[d]	+38.3[g]

[a] Determined by HPLC analysis employing Daicel Chiralpak AD or Chiralcel OJ (hexane–isopropyl alcohol = 9:1, 1 mL min^{-1}). [b] Assigned by optical rotation ($[\alpha]_{577}^{25}$+29.8 (*c* 1, benzene), lit. 2*b*: $[\alpha]_{578}^{rt}$ −77 (*c* 2, benzene) for (*S*)-**3a**). [c] Assigned by optical rotation of **3b** prepared from **3a**. [d] Assigned by analogy. [e] Assigned by optical rotation after conversion to **3a**. [f] Determined after conversion of aldehyde into methyl ester. [g] Optical rotation of diester.

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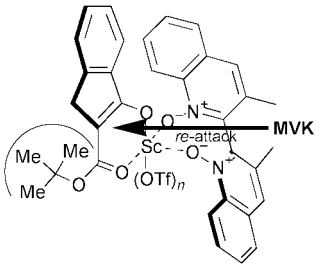

Fig. 1

generates a complex mixture of products. No reaction was observed using methyl acrylate as an acceptor. A variety of β-keto esters were then evaluated as Michael donors employing methyl vinyl ketone as an acceptor. Benzyl 2-oxocyclopentanecarboxylate, methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate, and methyl 2-methyl-3-oxopropanoate produced racemic mixtures, which suggests the importance of the indan skeleton in directing the enantiocontrol.

Enantioselective Michael additions of various esters of 1-oxoindan-2-carboxylic acid to methyl vinyl ketone were then investigated. The bulkiness of the ester substituent was found to have a pronounced effect on the observed enantioselectivity. As shown in Table 1, the enantioselectivities increased with the bulkiness of the ester. *tert*-Butyl ester **2e** exhibits the highest enantioselectivity of 80% ee (entry 5), while the Michael addition of *tert*-butyl ester **2e** to acrolein also produces notably better enantioselectivity (entry 6) than that of methyl ester **2a**.

The predominant formation of (*R*)-**3e** may be explained by the transition state model shown in Fig. 1. The bulky *tert*-butyl ester moiety should be located on the *si*-face of the keto ester plane in order to avoid steric repulsion with the quinoline moiety, which leads the attack of methyl vinyl ketone at the *re*-face preferentially.

A representative procedure for the enantioselective Michael addition catalyzed by the scandium trifluoromethanesulfonate–**1** complex is as follows. A mixture of *N*,*N*′-dioxide **1** (8.0 mg, 0.026 mmol), scandium trifluoromethanesulfonate (15 mg, 0.026 mmol) and β-keto ester **2e** (120 mg, 0.52 mmol) in dichloromethane (5 ml) was sonicated for 5 min to generate a yellow solution. Methyl vinyl ketone (0.2 mL, 2.6 mmol) was added to the solution and the mixture was stirred at room temperature for 0.5 h. After standard work-up followed by silica gel chromatography, **3e** (145 mg, 93%) was isolated as needles. *N*,*N*′-Dioxide **1** was recovered by elution with 10% ethanol in dichloromethane without a loss of optical purity. The enantiomeric excess of the adduct was determined by chiral HPLC.

In conclusion, we have demonstrated the potentiality of a chiral *N*,*N*′-dioxide–scandium trifluoromethanesulfonate complex to act as a catalyst for enantioselective Michael additions of β-keto esters to methyl vinyl ketone. The present reaction provides the first example of a chiral *N*-oxide–scandium complex acting as a catalyst in an enantioselective reaction. Studies into design modifications of chiral *N*,*N*′-oxides to further enhance enantioselectivity, and into the refinement of the mechanism of the reaction are currently in progress.

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