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Asymmetric 1,4-addition of β-keto esters to cyclic enones catalyzed by Ru amido complexes

Hui Wang, Masahito Watanabe and Takao Ikariya*

Graduate School of Science and Engineering, Tokyo Institute of Technology and Frontier Collaborative Research Center, O-okayama, Meguro-ku, Tokyo 152-8552, Japan

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Abstract—Well-defined Ru amido complexes effected asymmetric Michael addition of β-keto esters to 2-cyclopenten-1-one to give quantitatively the corresponding Michael adducts with excellent ee although with a 1:1 diastereomer ratio. The stereochemical outcome of the reaction was significantly influenced by the structures of the catalysts and the structures of the β-keto esters; the ee value reaching up to 97%.

We have recently reported that well-defined chiral Ru amido complexes, Ru[(*S*,*S*)-Tsdpen](η^6-arene) (**1**)[1] and Ru[(*S*,*S*)-Msdpen](η^6-arene) (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, MsDPEN = *N*-methanesulfonyl-1,2-diphenylethylenediamine), efficiently initiate the catalytic enantioselective Michael addition of 1,3-dicarbonyl compounds to cyclic enones[2] and nitroalkenes[3] to provide the corresponding Michael adducts in high yields with excellent ee's. The reversible deprotonation of Michael donors with the Ru amido complex bearing sufficient Brønsted basicity based on the M/NH bifunctional effect was found to be a crucial step for the catalytic C–C bond formation.[2–4] Particularly, in the reaction of β-keto esters with nitroalkenes, we found that an increase in the steric bulkiness of the acyl group in the keto esters caused a significant improvement in the ee value of the product, reaching up to 94% with the reaction of benzoylacetate.[3] These results prompted us to re-examine the reaction of β-keto esters with cyclic enones because asymmetric Michael reaction of β-keto esters to enones remained insufficient in terms of enantioselectivity,[5–7] except for Shibasaki's La-NR-linked-BINOL complexes catalyzed Michael reaction, giving the corresponding adducts in moderate to good yields with good to excellent ees.[8] We now describe Ru[(*S*,*S*)-diamine](η^6-arene) catalyzed asymmetric Michael reaction of β-keto esters having bulky substituents on the acyl group to cyclic enones giving the corresponding Michael adducts in high yields with excellent ee's.

Enantioselective Michael reaction of 2-cyclopentene-1-one **2** and isobutyrylacetic acid methyl ester **3d** catalyzed by Ru[(*S*,*S*)-diamine](η^6-arene) **1** was examined.[9] The outcome of the reaction was found to be delicately influenced by the structures of the diamine ligands in the Ru amido complexes as well as reaction conditions.[2,3,5] Table 1 lists some representative results. When Ru[(*S*,*S*)-Msdpen](hmb) (hmb = hexamethylbenzene) **1a**, which exhibited the best catalyst performance for the Michael addition of dimethyl malonate to **2**, was used for the reaction of **2** and **3d** in *tert*-butyl alcohol (**2**:**3d**:**1a** = 50:50:1) at 30 °C, (*R*)-4-methyl-3-oxo-2-(3-oxocyclopentyl)pentanoic acid methyl ester **4d** was obtained in 96% yield with 92% ee, as a 1:1 mixture of two diastereomeric pairs (Scheme 1). Instead of *tert*-butyl alcohol, the reaction in toluene containing the catalyst **1a** gave the product with relatively low ee. While, in the reaction with Ru[(*S*,*S*)-Tsdpen](hmb) **1b**, toluene provided better results compared with those attained in *tert*-butyl alcohol; the ee value reaching up to 95% ee. When 2-cyclohexen-1-one was used as a Michael acceptor, the reaction of **3b** with catalyst **1b** under conditions similar to those described in Table 1 gave unsatisfactory results, 45% yield and 47% ee. These results indicate that the balance of the steric effect of the ligands in the Ru complexes and the reactants, β-keto esters and cyclic enones, is crucial in determining reactivity and selectivity.

Keywords: Multifunctional catalyst; Ru amido complex; Michael reaction; Asymmetric C–C bond formation.
* Corresponding author. Tel.: +81 357342636; fax: +81 357342637; e-mail: tikariya@apc.titech.ac.jp

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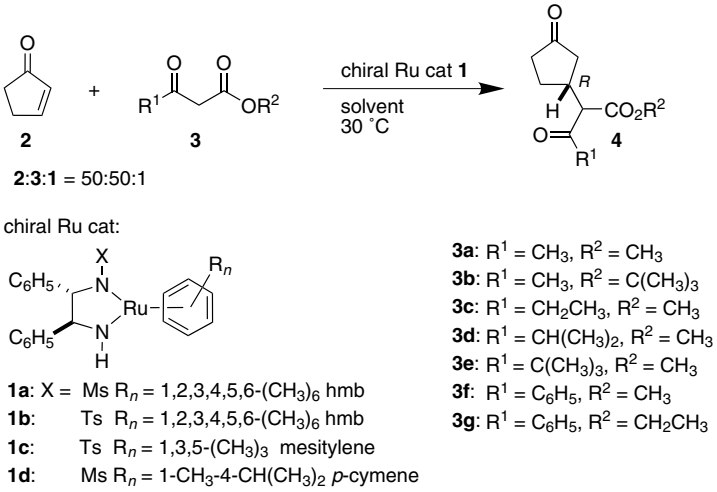


Scheme 1.

Table 1. Asymmetric Michael reactions of 2-cyclopentene-1-one **2** and isobutyrylacetic acid methyl ester **3d** catalyzed by chiral Ru amido complexes[a]

Entry	Cat	Temp (°C)	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**	30	$(CH_3)_3COH$	96	92
2	**1a**	30	Toluene	97	88
3	**1b**	30	Toluene	95	95
4	**1b**	30	$(CH_3)_3COH$	94	86
3	**1b**	0	Toluene	82	91
4	**1b**	−20	Toluene	62	86
5	**1c**	30	Toluene	100	90
6	**1d**	30	Toluene	53	72

[a] Unless otherwise noted, the reaction was carried out using 1.0 mmol of Michael acceptors and donors (1:1) in 1.0 mL of the corresponding solvent. The molar ratio of acceptor:donor:Ru is 50:50:1 (S/C = 50). Products were obtained as a 1:1 mixture of two diastereomeric pairs.
[b] Isolated yield after flash chromatography on the silica gel.
[c] Enantiomeric excesses were determined by HPLC analysis. See Supplementary data.

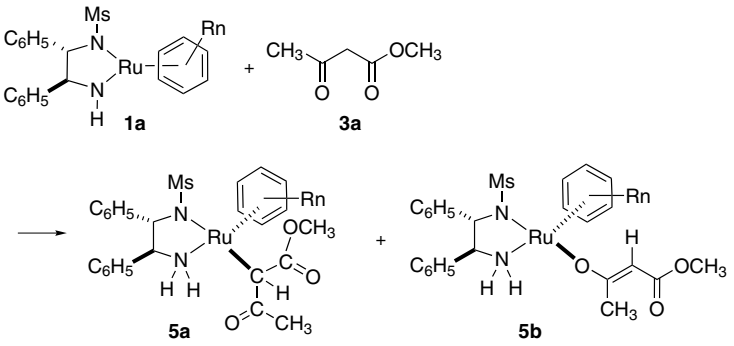
The effect of the reaction temperature on the enantioselectivity is worthy to be noted. The decrease in the temperature of the reaction of **3d** with the catalyst **1b** resulted in a marked decrease in the ee value of the product from 95% at 30 °C to 86% at −20 °C, possibly because of kinetic reasons discussed later.

Noticeably, an increase in the steric bulkiness of the acyl group in the β-keto esters caused an increase in the ee value of the products obtained from the reaction with the catalyst **1a** in the order $CH_3 < CH(CH_3)_2 < C(CH_3)_3$ except for the C_2H_5 substituted keto ester as summarized in Table 2. The reaction of pivaloylacetic acid methyl ester **3e** bearing the *tert*-butyl substituent in the acyl group in toluene gave quantitatively the corresponding Michael adduct **4e** with up to 97% ee. The Michael addition of methyl benzoylacetate and ethyl benzoylacetate to **2** with the catalyst **1a** provided the corresponding adducts with 96% and 97% ee, respec-

Table 2. Asymmetric Michael reactions of 2-cyclopenten-1-one **2** and β-keto esters **3** catalyzed by Ru amido complexes[a]

Entry	Keto ester	R^1	R^2	Cat	Product	Yield[b] (%)	ee[c] (%)	Config[d]
1	**3a**	CH_3	CH_3	**1a**	**4a**	100	85	*R*
2[e]	**3a**	CH_3	CH_3	**1b**	**4a**	99	91	*R*
3[e]	**3b**	CH_3	$C(CH_3)_3$	**1a**	**4b**	93	72	*R*
4	**3c**	CH_2CH_3	CH_3	**1a**	**4c**	92	80	*R*
5	**3c**	CH_2CH_3	CH_3	**1b**	**4c**	99	89	*R*
6	**3d**	$CH(CH_3)_2$	CH_3	**1a**	**4d**	97	88	*R*[f]
7	**3e**	$C(CH_3)_3$	CH_3	**1a**	**4e**	100	97	nd[g]
8	**3e**	$C(CH_3)_3$	CH_3	**1b**	**4e**	92	87	nd[g]
9	**3f**	C_6H_5	CH_3	**1a**	**4f**	91	96	*R*[f]
10	**3g**	C_6H_5	CH_2CH_3	**1a**	**4g**	99	97	*R*[f]

[a] Unless otherwise noted, the reaction was carried out using 1.0 mmol of Michael acceptors and donors (1:1) in 1.0 mL of toluene. The molar ratio of acceptor:donor:Ru is 50:50:1 (S/C = 50). Products were obtained as a 1:1 mixture of two diastereomeric pairs.
[b] Isolated yield after flash chromatography on the silica gel.
[c] Enantiomeric excesses were determined by HPLC analysis. See Supplementary data.
[d] Determined after derivatization to known compounds (Ref. 8).
[e] See Ref. 5.
[f] Determined by comparison of sign of its optical rotation with that of the one derived from the Michael adduct of dimethyl malonate to cyclopentenone (Ref. 8).
[g] Not determined.



Scheme 2.

tively. While, the steric bulkiness of ester part in the β-keto esters showed negative effect on the enantioselectivity of the reaction. For example, *tert*-butyl acetoacetate **3b** gave the adduct with only 72% ee although in good chemical yield.[5] In the reaction with catalyst **1b** in toluene, the outcome of the reaction was not strongly influenced by change in the structure of the substrate; the ee value of the products ranging from 87% (for **3d**) to 91% (for **3a**) (Table 2).

Although we have demonstrated the possibility of the *C*-bound Ru malonato complex as a possible catalytic active intermediate for Michael addition of malonates to cyclic enones,[2] another possible reaction pathway through the *O*-bound Ru enolato intermediate cannot be ruled out. In contrast to the reaction with malonates,[3] the chiral Ru complex having η^6-HMB (**1a**) was found to react with methyl acetoacetate **3a** even at lower temperature (−30 °C) to give a mixture of *C*-bound Ru acetate complex, Ru[$CH(COCH_3)$-$(COOCH_3)$][(*S*,*S*)-Msdpen](η^6-hmb) (**5a**), and *O*-bound Ru enolate complex, Ru[$OC(CH_3)$=$CHCOOCH_3$]-[(*S*,*S*)-Msdpen](η^6-hmb) (**5b**) (**5a**:**5b** = 1:1.1 at −30 °C), as shown in Scheme 2.[10] The ^{1}H VTNMR spectra of a 1:1 mixture of **1a** and **3a** in CD_2Cl_2 revealed that no appreciable change in a molar ratio of **5a** to **5b** was observed by the increase in the temperature and that both complexes **5** existed in a temperature-dependent equilibrium with the amido complex **1a** and free acetoacetate. As discussed above, a positive effect of the steric hindrance in the acyl group of β-keto esters and an apparent negative effect of the temperature on the stereochemical outcome of the reaction suggest that the reaction may proceed through *C*-bound or *O*-bound Ru enolato intermediates (**5a** or **5b**) depending on the structures of the Michael donors and the reaction temperature. However, only with these experimental data and NMR studies, any precise reaction mechanism for the Michael reaction with the chiral amido catalyst cannot be envisaged.[11] Further investigation including computational analysis on the reaction pathways should be required.

In summary, we have developed an efficient asymmetric Michael addition of β-keto esters to 2-cyclopenten-1-one to give quantitatively the corresponding Michael adducts with excellent ee although with a 1:1 diastereomer ratio. The present 1,4-addition reaction is characterized by high reactivity and practicability. A large-scale reaction of **3d** (1.02 g) with **2** promoted by chiral Ru catalyst (**2**:**3d**:**1b** = 50:50:1) at 30 °C for 48 h gave the optically active adduct **4d** in 99% yield (1.60 g) with 96% ee. The stereochemical outcome of the reaction was significantly influenced by the structures of the catalysts and the β-keto esters as well as the reaction conditions.

Acknowledgements

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Supplementary data

Experimental procedure for the Michael reaction catalyzed by chiral amide catalysts and spectroscopic data of the Michael adducts. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.026.

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9. Typical experimental procedure for Michael reaction of cyclic enones with β-keto esters catalyzed by chiral Ru amido complexes. Isobutyrylacetic acid methyl ester **3d** (142 μL, 1.0 mmol), 2-cyclopentene-1-one **2** (84 μL, 1.0 mmol), and toluene (1.0 mL) were added to Ru[(1*S*,2*S*)-Tsdpen](hmb) **1b** (13.0 mg, 0.02 mmol) and the mixture was degassed by freeze-thaw cycles. The mixture was stirred at 30 °C for 24 h, then was evaporated with a vacuum pump and purified with flash column chromatography (silica gel, eluent:hexane/acetone = 9/1) to give (*R*)-4-methyl-3-oxo-2-(3-oxocyclopentyl)pentanoic acid methyl ester **4d** in 95% isolated yield with 95% ee. See Supplementary data.
10. NMR data of the products obtained from the 1:1 reaction mixture of Ru[(*S*,*S*)-Msdpen](hmb) **1a** and methyl acetoacetate **3a** in CD_2Cl_2 at −30 °C. Although reaction products could not be isolated, the chemical shifts of the reaction products were assigned by comparison with those of the isolable Ru–malonate complex[3] and reported *O*-bound or *C*-bound metal enolate complexes.[12] ^{13}C NMR, δ 16.46, 16.55 (CH_3 of the HMB ligand in **5a** and **5b**), 17.18, 24.84, 27.46 (Ru–OC(CH_3)=CH in **5b**, Ru–CH($COCH_3$)(CO_2CH_3) or Ru–CH($COCH_3$)(CO_2CH_3) in **5a**), 44.80 (two CH_3 of the methanesulfonyl group in **5a** and **5b**), 49.74, 49.85 (OCH_3 in **5a** and **5b**), 68.27, 71.03 (strong), 68.81, 71.75 (weak) (two *C*H of the DPEN ligand in **5a** and **5b**), 89.90 (vinyl carbon in **5b**), 90.20, 91.49 (the HMB ligand in **5a** and **5b**), 169.60, 170.81, 185.88, 189.30 (*C*=O in **5a** and O–*C*=C in **5b**). ^1H NMR, full assignment of chemical shifts of the reaction mixture could not be performed because of overlapping of the signals due to **5a**,**5b**, and the Ru amido complex **1a**. Some selected peaks; ^1H NMR (300 MHz, $CDCl_3$): δ, ppm 4.09 (s, 1H, Ru–CH in **5a**), 4.81 (s, 1H, R–OC*H*(CH_3)=CH in **5b**).
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