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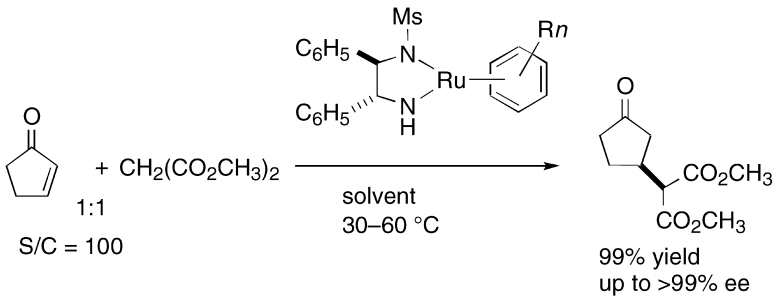

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Enantioselective Michael Reaction Catalyzed by Well-Defined Chiral Ru Amido Complexes: Isolation and Characterization of the Catalyst Intermediate, Ru Malonato Complex Having a Metal−Carbon Bond

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We have recently developed a well-defined chiral ruthenium amido complex, Ru[(*R*,*R*)-Tsdpen](η^6-arene) ((*R*,*R*)-TsDPEN = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) (**1**), which has sufficient Brønsted basicity to effectively deprotonate hydrogen donors such as 2-propanol or formic acid and acidic organic compounds, leading to a hydrido amino complex and amino complexes bearing a metal bonded *C*-nucleophile, respectively, in a highly diastereoselective manner.[1,2] Since the hydrido amido complex stereoselectively reacts with ketonic substrates through a pericyclic six-membered transition state to give optically active alcohols and the amido complex, enantioselective reduction of ketones can be catalytically performed in a highly efficient manner.[1d] These results prompted us to extend the conceptual metal−NH bifunctional effect to enantioselective C−C bond formation, Michael reaction, catalyzed by the amido complexes.

The catalytic asymmetric Michael reaction is one of the most important organic synthetic procedures for a stereoselective C−C bond forming reaction partly due to its high atom economy; therefore, there are many reports on enantioselective Michael type reactions catalyzed by chiral metal catalyst systems.[3] We now disclose that chiral Ru amido complexes promote asymmetric Michael addition of malonates to cyclic enones, leading to Michael adducts with excellent ee's (Scheme 1) in which the chiral Ru amido complexes react with malonates to give isolable catalyst intermediates, new organometallic complexes bearing a metal-bound *C*-nucleophile.

A well-defined chiral Ru catalyst, Ru[(*R*,*R*)-Tsdpen](η^6-arene) (**1a**−**e**), efficiently effected enantioselective reactions of cyclic enones (**2a**−**d**) and malonates or acetoacetate (**3a**−**d**), giving the corresponding Michael adducts with excellent ee's. For example, the reaction of dimethyl malonate **3a** and cyclopentenone **2a** in a 1:1 molar ratio in 1 mL of *tert*-butyl alcohol containing the amido complex **1b** (malonate:enone:Ru = 50:50:1) proceeds smoothly at 40 °C to provide the corresponding (*S*)-Michael adduct in 99% yield and with 89% ee. The outcome of the reaction was delicately influenced by the structure of the arene and diamine ligands as well as the reaction conditions. As shown in Table 1, the *p*-cymene complex **1a**, which is an excellent catalyst for the transfer hydrogenation of ketones,[1a] worked but with unsatisfactory enantioselectivity. Noticeably, enantioselection increases in the order of **1a** < **1b** < **1c** < **1d** and **1e**, and a more sterically congested complex with pentamethyl- (**1d**) or hexamethylbenzene (**1e**) displays a better reactivity than the *p*-cymene complex, indicating the electron-donating ability of the multisubstituted arene ligands should cause the increase in a nucleophilicity of the metal-bonded Michael donors. *tert*-Butyl alcohol, toluene, and THF worked equally well, while CH_2Cl_2 gave a reasonably high ee albeit a slightly lower activity. In particular, the methanesulfonyl-substituted diamine (MsDPEN) complex (**1f**) exhibited much better catalyst performance

Scheme 1

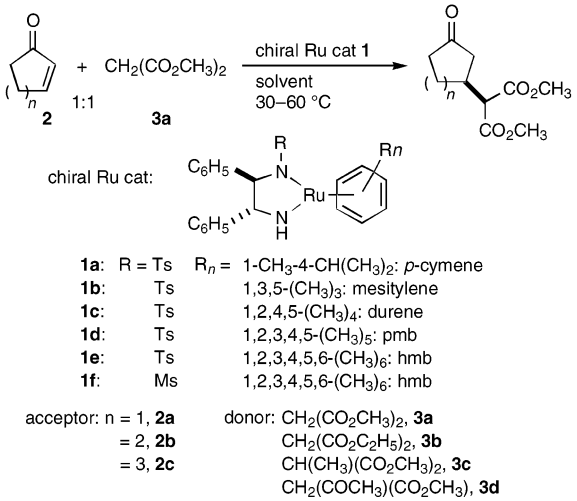

Table 1. Asymmetric Michael Reaction of Enones and Malonates or Acetoacetates Catalyzed by Chiral Ru Amido Complexes[a]

enone	Michael donor	catalyst	solvent	temp, °C	time, h	yield, %[b]	ee, %[c] (config)
2a	**3a**	**1a**	$(CH_3)_3COH$	40	24	87	82 (*S*)
2a	**3a**	**1b**	$(CH_3)_3COH$	40	24	99	89 (*S*)
2a	**3a**	**1c**	$(CH_3)_3COH$	40	24	99	95 (*S*)
2a	**3a**	**1d**	$(CH_3)_3COH$	40	24	99	97 (*S*)
2a	**3a**	**1e**	$(CH_3)_3COH$	40	24	98	98 (*S*)
2a	**3a**	**1c**	toluene	30	24	99	95 (*S*)
2a	**3a**	**1c**	THF	30	24	99	95 (*S*)
2a	**3a**	**1c**	CH_2Cl_2	30	24	88	93 (*S*)
2a	**3a**	**1f**	$(CH_3)_3COH$	40	24	99	98 (*S*)
2a	**3a**	**1f**[d]	$(CH_3)_3COH$	60	24	99	97 (*S*)
2a	**3b**	**1e**	$(CH_3)_3COH$	40	24	96	96 (*S*)
2b	**3a**	**1e**	$(CH_3)_3COH$	30	48	93	96 (*S*)
2b	**3a**	**1f**	$(CH_3)_3COH$	30	48	99	98 (*S*)
2c	**3a**	**1e**	$(CH_3)_3COH$	30	48	53	>99[e] (*S*)
2c	**3a**	**1f**	$(CH_3)_3COH$	30	72	75	>99[e] (*S*)
2d	**3a**	**1f**	$(CH_3)_3COH$	30	72	83	>99 (-)[f]
2a	**3c**	**1f**	toluene	30	48	51	97 (-)[f]
2a	**3d**	**1e**	toluene	40	24	99	91[g] (*S*)

[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 solvent. The molar ratio of acceptor:donor:Ru is 50:50:1 (S/C = 50). [b] Isolated yield after flash chromatography on the silica gel. [c] Determined by HPLC analysis, see Supporting Information. [d] S/C = 100. [e] Determined by ^{13}C NMR of corresponding ketals derived from the products and (2*R*,3*R*)-butanediol. [f] Not determined. [g] Obtained as a 1:1 mixture of diastereomers with a single stereogenic center on cyclopentanone ring.

in terms of activity and enantioselectivity as well as thermal stability.[4] The reaction at 60 °C with **1f** proceeded faster without serious loss of the ee values to give the products even at an S/C = 100.

A variety of cyclic enones, **2b**−**d**, and Michael donors, malonates **3a**−**c** and acetoacetate **3d**, can be successfully transformed with **1** to corresponding optically active Michael adducts with high ee's

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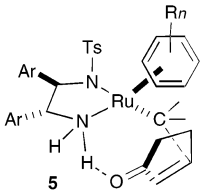
as shown in Table 1. Cyclohexenone and cycloheptenone reacted with **3a** in the presence of **1f** to give 1,4-adducts in 99% (98% ee) and 75% yields (>99% ee), respectively. The reaction of 4,4-dimethylcyclopentenone **2d** with **3a** gave the product with >99% ee and in 83% yield. α-Methyl-substituted malonate **3c** readily reacted with **2a** to give the Michael adduct with 97% ee and in a moderate yield. Acetoacetate **3d** can be used as a donor, giving the Michael adducts of **2a** in 99% yield and with 91% ee, although with a 1:1 diastereomer ratio. The reaction of linear α,β-unsaturated ketones gave unsatisfactory results.

A stoichiometric reaction of the amido complex **1** with malonates can provide information on the reaction mechanism.[5] Dimethyl malonate **3a** has been proven to react rapidly with **1b** (malonate: **1b** = 8:1) in acetone below −30 °C to give a yellow crystalline complex, Ru[CH(CO_2CH_3)$_2$][(*R*,*R*)-Tsdpen](η^6-mesitylene) (**4**), as a single diastereomer. The single-crystal X-ray analysis of **4** confirmed that it has a three-legged piano stool coordination environment with mesitylene, amino, sulfonamido, and a *C*-bound malonato ligand, as observed in the metal hydrido and chlorido complexes.[1b,2,6] The ^{1}H NMR spectra of **4** exhibited the dynamic behavior of the complexes in solution. At −50 °C, one of two inequivalent acidic NH protons appeared downfield at δ 6.59 ppm, possibly due to hydrogen bonding between an oxygen atom of malonate and the acidic NH proton as observed in the related complexes.[1b] On raising the temperature to 0 °C, a set of signals attributed to **1b** in addition to the free malonate resonance was observed, showing that **4** existed in a temperature-dependent equilibrium with **1b** and free malonate ($K_{eq} = 2.9 \times 10^2$ at 0 °C) (Scheme 2). No detectable formation of the metal enolato complex, *O*-bound Ru complex, was observed in these NMR studies.[2,5b,7]

These structural analyses and NMR studies as well as recently reported results[8] imply that the reaction of the amido complex **1** with Michael donors proceeds diastereoselectively to give the *C*-bound malonato complex **4**, which further reacts with enones, possibly through a similar transition state (**5**) as postulated for the transfer hydrogenation.[1b,c]



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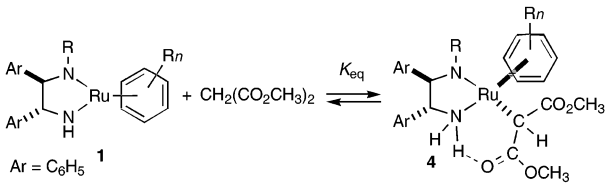
This work presents the first successful application of chiral amido complex **1** with a M/NH bifunctional unit to asymmetric catalytic Michael reactions. The Brønsted basicity of the amido group in complex **1** is responsible for the excellent catalyst performance in terms of high reactivity and practicability.[9] We are now working on expansion of the scope of the reaction and further studies aimed at clarifying the mechanism.

Scheme 2



Ar = C_6H_5 **1** **4**

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Supporting Information Available: Experimental procedure of the catalytic Michael reaction, Ortep view of complex **4**, and spectroscopic data and an X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The catalysts **1c**−**e** were found to be deactivated during the reaction at a higher temperature of 40−60 °C, leading to pale yellow crystalline complexes, which were structurally determined to be new type of Ru complexes bearing an M−C bond by X-ray crystallographic analysis. A detailed structure and formation mechanism will be reported in a separate paper.

(5) For the mechanism of a Michael type reaction catalyzed by chiral transition metal complexes, see: (a) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052−5058. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241. (c) Michael reaction of 1-oxoindanecarboxylate and methyl vinyl ketone with chiral Rh amido complexes was reported independently by Suzuki et al. Suzuki, T.; Torii, T. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1077−1081.

(6) Crystal and structure refinement parameters of **4**: $C_{35}H_{40}N_2O_6SRu$ T = 293 K, $P2_1$ (No. 4), Z = 4, a = 8.098(2), b = 22.593(6), and c = 17.761(5) Å, β = 90.575(5)°, V = 3249.4(15) Å^3, D_c = 1.467 g/cm^3, R_1 = 0.090, wR_2 = 0. See Supporting Information.

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(9) The reaction of 1.07 g of **2a** and 1.72 g of **3a** in *tert*-butyl alcohol containing 72 mg of the catalyst **1f** gave 2.76 g of the Michael adduct with 98% ee and in 99% yield.

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