Catalytic Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes Catalyzed by Well-Defined Chiral Ru Amido Complexes

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The asymmetric Michael addition to nitroalkenes has been developed as a powerful tool in organic synthesis,[1–6] because Michael adducts, optically active nitroalkanes, are versatile building blocks for agricultural and pharmaceutical compounds.[1] Although there have been many reports of enantioselective Michael additions with chiral catalysts, including metal-based catalysts and multi-metallic catalysts as well as organic catalysts,[7] practical Michael additions of 1,3-dicarbonyl compounds to nitroalkenes remain largely unexplored except for reactions with chiral Mg catalysts[4] and optically active thioureas as efficient catalysts.[6d] We have recently developed practical asymmetric Michael reactions of 1,3-dicarbonyl compounds with cyclic enones catalyzed by chiral Ru amido complexes (**1**)[8] in which the Brønsted basic chiral Ru amido catalyst may be responsible for high reactivity and selectivity in the enantioselective C−C bond formation.[9] We have expanded the scope of the reaction catalyzed by chiral Ru amido complex and found that the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes proceeds smoothly to provide the corresponding Michael adducts in high yields and with excellent ees as shown in Scheme 1. Fine-tuning the structures of the arene and N-sulfonyl diamine ligands in the chiral amido complexes leads to the achievement of the highly efficient catalytic enantioselective reaction of nitroalkenes.

The well-defined chiral Ru catalyst, Ru[(S,S)-Msdpen](η^6-hexa-methylbenzene) ((S,S)-MsDPEN = (1S,2S)-N-(methanesulfonyl)-1,2-diphenylethylenediamine)[9] (**1c**), which is an excellent catalyst for the Michael addition of malonates to cyclic enones, effected asymmetric Michael reaction of *trans*-β-nitrostyrene (**2a**) with dimethyl malonate (**3a**) (nitroalkene/malonate/Ru = 50:50−60:1) at 30 °C in toluene to produce the corresponding Michael adduct (R)-**4aa** with 77% ee and in a good yield (45%). Table 1 lists the experimental results.

The outcome of the reaction with the amido complex **1** was significantly influenced by the structures of the amido catalysts as well as the reaction conditions. Noticeably, the reactivity and enantioselectivity of the Ru[(S,S)-N-sulfonylated dpen](η^6-hmb) (HMB = η^6-hexamethylbenzene, $(CH_3)_6C_6$) tend to increase with the increase of the electron-donating ability of the N-substituents of the sulfonyl groups, namely, in the order p-CH₃C₆H₄SO₂ (**1b**) > 3,5-(CH₃)₂C₆H₃SO₂ (**1d**) > 2,4,6-(CH₃)₃C₆H₂SO₂ (**1e**) > 2,3,4,5,6-(CH₃)₅C₆SO₂ (Ps) (**1f**) as a sulfonyl group in a DPEN ligand; Ru-[(S,S)-Psdpen](η^6-hmb) (**1f**) gave the best catalyst performance in terms of the reactivity and selectivity, reaching up to 99% yield and 90% ee, respectively. Even at the lower temperature, −20 °C, the reaction of **2a** and **3a** with an alkene/catalyst molar ratio (S/C) of 100 proceeded smoothly to give the Michael adduct **4aa** with 95% ee and in 99% yield. The p-cymene complex (**1g**) gave unsatisfactory results (34% yield, 15% ee at 30 °C). These results indicate that the balance of the electronic and steric effect of the arene and the sulfonyl group is crucial in determining the reactivity.
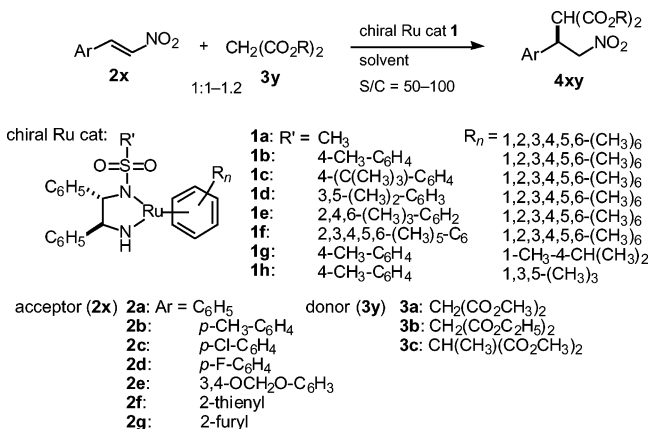
Scheme 1

Table 1. Asymmetric Michael Reaction of Nitroalkenes (**2a**−**g**) with Malonates (**3a**−**c**) Catalyzed by Chiral Ru Amido Complexes[a]

acceptor	donor	Ru catalyst	solvent	temp, °C	time, h	yield, %[b] (isolated[c])	% ee[d]
2a	**3a**	**1a**	toluene	30	24	45	77
2a	**3a**	**1b**	toluene	30	24	50	72
2a	**3a**	**1c**	toluene	30	24	43	70
2a	**3a**	**1d**	toluene	30	24	53	73
2a	**3a**	**1e**	toluene	30	24	99	87
2a	**3a**	**1f**	toluene	30	24	99	90
2a	**3a**	**1f**	toluene	−20	48	99 (97)	95
2a	**3b**	**1f**	toluene	−20	48	92 (90)	93
2a	**3a**	**1f**	THF	30	24	32	30
2a	**3a**	**1f**	CHCl₃	30	24	26	49
2a	**3a**	**1f**	DMF	30	24	5	
2b	**3a**	**1f**	toluene	−20	48	96	92
2c	**3a**	**1f**	toluene	−20	48	93	93
2d	**3a**	**1f**	toluene	−20	48	98	93
2e	**3a**	**1f**	toluene	−20	48	99 (98)	95
2f	**3a**	**1f**	toluene	−20	48	99 (91)	97
2g	**3a**	**1f**	toluene	−20	48	99 (91)	98
2a	**3c**	**1f**	toluene	−20	48	99 (95)	97

[a] Unless otherwise noted, the reaction was carried out using 1.0 mmol of Michael acceptors and donors (1:1−1.2) in 1.0 mL of solvent. The molar ratio of acceptor/donor/Ru is 50:50−60:1. [b] Determined by ¹H NMR analysis. [c] Isolated yield after flash chromatography on the silica gel. [d] Determined by HPLC analysis; see Supporting Information.

Similarly, the reaction of diethyl malonate (**3b**) with **2a** in the presence of **1f** gave the Michael adduct with 93% ee in 92% yield. Toluene is the best choice of the solvent for the present reaction, while the conjugate addition in CHCl₃, THF, DMF, or CH₃CN gave unsatisfactory results.[10]

The aromatic ring-substituted *trans*-β-nitrostyrenes (**2b**−**e**) reacted with **3a** in toluene containing the chiral catalyst **1f** at −20 °C for 48 h to give the optically active nitro compounds (**4ba**−**ea**) with 92−95% ee in excellent yields regardless of the electronic effect of the substituent. The reaction of p-methyl-, p-chloro-

3d: CH$_3$	CH$_3$	95	58
3e: C$_2$H$_5$	CH$_3$	97	89
3f: CH(CH$_3$)$_2$	CH$_3$	97	94
3g: C$_6$H$_5$	C$_2$H$_5$	96	92

3h: CH$_3$	90	7
3i: C$_2$H$_5$	98	97
3j: CH(CH$_3$)$_2$	99	97

Figure 1. Effect of the structures of the Michael donors. The reaction of β-keto esters gave a 1:1−1.5 mixture of diastereomers with a single stereogenic center on benzylic carbon of the Michael adducts.

p-fluoro-, and dioxolane-substituted β-nitrostyrene gave the Michael adducts with 92, 93, 93, and 95% ee, respectively. Similarly, the nitroalkenes with hetero aromatic rings, thienyl (**2f**) and furyl (**2g**), provided the Michael adducts (**4fa**, **4ga**) in almost quantitative yield with 97 and 98% ee, respectively, as shown in Table 1.

The stereochemical outcome of the conjugate addition was found to be significantly influenced by the structure of the Michael donors. The sterically more congested methyl-substituted dimethyl malonate **3c** readily reacted with *trans*-β-nitrostyrene **2a** in toluene containing **1f** to give the corresponding adduct (**4ac**) with 97% ee and in 99% yield (Table 1). When β-keto esters (**3d−g**) (**2a**/keto ester/Ru = 50:60:1, −20 °C, 24 h) were used, the conjugate addition to **2a** gave the corresponding adducts in 95−97% yield as shown in Figure 1. The enantioselectivity of the reaction was markedly improved by increasing the bulkiness of the acyl group in the keto esters. The reaction of acetoacetate **3d** gave the product (**4ad**) with 58% ee, while the enantiomeric purity of the Michael adducts increased in the order CH$_3$ < C$_2$H$_5$ < C$_6$H$_5$ < CH(CH$_3$)$_2$, the ee value reaching up to 94% with the keto ester **3f**. This conjugate addition to **2a** became even more appealing when 1,3-diketones were used as donors. The reaction of acetylacetone **3h** gave the Michael adduct in a reasonably high yield but with a poor ee, while sterically bulkier diketone **3j** provided satisfactory results in terms of the yield and enantioselectivity, the ee value reaching to 97% (Figure 1).

Although we have shown the possibility of the *C*-bound Ru malonate complex (**5a**, R = OCH$_3$) as catalytic active intermediates for the conjugate addition of malonates to cyclic enones, on the basis of the X-ray crystallographic analysis and NMR investigation of the Ru malonato complex derived from the complex **1h**,[9a,c] the reaction mechanism of the Michael reaction with the chiral Ru amido complex is still controversial. A marked positive effect of the steric hindrance in the β-keto esters and 1,3-diketones on the stereochemical outcome of the reaction as discussed above suggests that the reaction may proceed through *C*-bound or *O*-bound Ru enolato intermediates (**5a** or **5b**) depending on the structures of
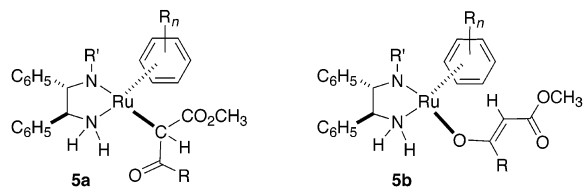
the Michael donors.[11] Further investigation, including isolation of *O*-bound Ru enolato complexes as the possible catalyst intermediates, as well as computational analysis on the reaction pathways, is still required.

In summary, we have successfully developed a practical enantio-selective Michael addition of 1,3-dicarbonyl compounds with nitro-alkenes to the optically active nitroalkanes with up to 98% ee. This reaction is applicable to the synthesis of the intermediate of the chiral drug, rolipram.[4b,12] A large-scale reaction of 3-cyclopentyl-oxy-4-methoxy-β-nitrostyrene[4b] (2.1 g) with **3a** with the chiral Ru catalyst (**1f**) (alkene/**3a**/Ru = 100:120:1) at −20 °C gave the optically active (*R*)-nitro compound[4b] in 94% yield (2.97 g) with 95% ee.

Supporting Information Available: Experimental procedures of the catalytic Michael reaction and spectroscopic data for compounds **4xy** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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