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Catalytic Enantioselective Hosomi–Sakurai Reaction of α-Ketoesters Promoted by Chiral Copper(II) Complexes

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A catalytic enantioselective Hosomi–Sakurai reaction of α-ketoesters has been developed. A copper(II) complex with a chiral bis(oxazoline) ligand bearing methanesulfonamide groups shows excellent catalytic activity to give α,α-disubstituted α-hydroxyesters in high yields with high enantioselectivities. This is the first successful method for the catalytic enantioselective 1,2-addition of α-ketoesters with allylic silanes.

Catalytic asymmetric allylations of ketones are useful methods for the synthesis of chiral tertiary alcohols.[1] Several effective methods that use chiral catalysts have been developed. Among these methods, the Hosomi–Sakurai reaction[2,3] is promising, since it employs inexpensive and nontoxic allylic silanes as carbon nucleophiles. However, little is known about the catalytic enantioselective Hosomi–Sakurai reaction of ketones,[4,5] because ketones generally show lower reactivity and selectivity than aldehydes. In addition, the use of a chiral Lewis acid catalyst sometimes initiates undesired background reactions through a non-enantioselective silylium ion catalysis to decrease the enantioselectivity.[6]

α-Ketoesters are useful substrates for asymmetric 1,2-addition with a carbon nucleophile, since the reaction affords optically active α,α-disubstituted α-hydroxyesters, which are important structural motifs in biologically active compounds. Accordingly, methods for the catalytic asymmetric allylation of α-ketoesters have been reported.[7] For example, Feng and colleagues reported asymmetric addition with tetraallylstannane catalyzed by N,N'-dioxide–In(III) complexes.[7a] Yoda and colleagues developed an asymmetric addition with β-amido-functionalized allylstannanes catalyzed by chiral In(III) complexes.[7b] Aminophenol-catalyzed asymmetric addition with allylboronates was also reported by Hoveyda and colleagues.[7c] However, to the best of our knowledge, an efficient method for the asymmetric addition of α-ketoesters

with allylic silanes has not yet been reported.

Previously, Ishihara and Sakakura's group developed a new chiral bis(oxazoline) ligand **1a** bearing methanesulfonamide groups (Table 1).[8] A copper(II) complex of **1a**, which is called n-cation catalyst, catalytically promotes the hetero-Diels–Alder reaction of β,γ-unsaturated α-ketoesters with allylsilanes to give the corresponding adducts in high yields with high diastereo- and enantioselectivities.[8c] Since **1a**·CuX$_2$ successfully activates β,γ-unsaturated α-ketoesters, this catalyst may also be suitable for promoting the asymmetric 1,2-addition of α-ketoesters. We report herein the first catalytic enantioselective Hosomi–Sakurai reaction of α-ketoesters.

Our study commenced with an examination of the catalytic activities of **1a**·Cu(NTf$_2$)$_2$ in the Hosomi–Sakurai reaction of α-ketoester **2a** (Table 1). The reaction of **2a** with an allyltrimethylsilane was conducted in the presence of **1a**·Cu(NTf$_2$)$_2$ (5 mol%) at ambient temperature. Since the crude product included a small amount of TMS ether of **3a**,[‡] the crude product was treated with TBAF to remove the TMS group. As a result, the reaction proceeded smoothly in EtNO$_2$ at ambient temperature to give **3a** in 78% yield with 74% ee (entry 1). In sharp contrast, the reaction in other solvents such as dichloromethane, acetonitrile, THF and isopropyl alcohol did not proceed at all even under heating conditions.[‡] The use of allyltriisopropylsilane gave **3a** with a slightly better enantioselectivity (80% ee), but the yield of **3a** was significantly decreased (50%) (entry 2). We next evaluated other chiral bis(oxazoline) ligands.[9] Ligand **1b** bearing trifluoromethanesulfonamide groups is also effective for the Diels–Alder reaction of N-acryloyloxazolidinones.[8a] However, the use of **1b** in the present reaction significantly decreased the enantioselectivity (53% ee), although the reactivity was improved (90% yield) (entry 3). When the reaction was conducted in the presence of ligand **1c**, which has sterically bulky tert-butyl groups at the 4,4'-positions, only a trace amount of **3a** was obtained (entry 4). In contrast, the use of **1d** bearing benzyl groups at the 4,4'-positions gave **3a** in 83% yield, while the enantioselectivity was poor (−7% ee)[§] (entry 5).

The use of ligand **1e** or **1f**, which have four phenyl groups at the 4,4',5,5'-positions, gave **3a** in moderate yields (68 and 67%) in low enantioselectivity (−16 and −35% ee)[§] (entries 6 and 7).

Table 1 Catalytic activities of chiral copper(II) complexes in the addition reaction of **2a** with allylsilanes[a]
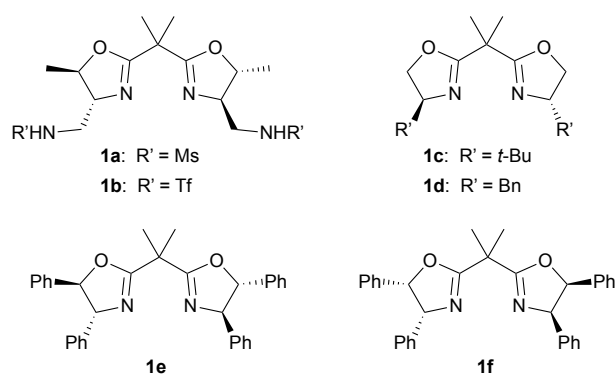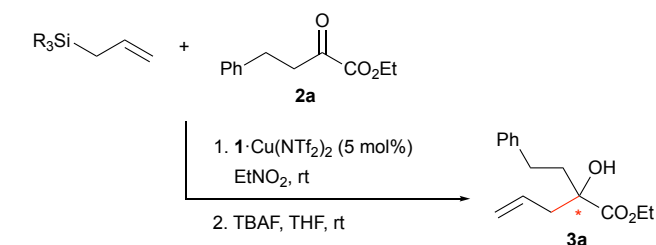
| Entry	1	R	Yield (%)[b]	Ee (%)[c]
1	1a	Me	78	74
2	1a	i-Pr	50	80
3	1b	Me	90	53
4	1c	Me	3	ND
5	1d	Me	83	−7
6	1e	Me	68	−16
7	1f	Me	67	−35

[a] The reaction of **2a** (0.2 mmol) was conducted with allylsilane (3 equiv) in the presence of **1**·Cu(NTf$_2$)$_2$ (5 mol%) in EtNO$_2$ at ambient temperature for 20 h. The crude product was treated with TBAF (1 equiv) in THF at ambient temperature for 0.5 h. [b] Isolated yield. [c] Evaluated by chiral HPLC analysis.

The optimized reaction conditions could be applied to the allylation of various α-ketoesters **2** (Table 2). The reaction of benzyl pyruvate **2b** gave the corresponding adduct **3b** in 71% yield with 65% ee (entry 1). The absolute configuration of **3b** was assigned to be *R* from the sign of the measured optical rotation, compared to that of the reported *S*-isomer.[7a] This enantioselectivity could be explained by the proposed transition state assembly (Scheme 1). Intramolecular interaction of the sulfonamide groups of **1a** with copper(II) cation would preferentially shield the *Si* face of the coordinated **2b**.[8] Allyltrimethylsilane would approach the *Re* face of **2b** to give (*R*)-**3b** as the major enantiomer.

Table 2 **1a**·Cu(NTf$_2$)$_2$-catalyzed Hosomi–Sakurai reaction of **2** with allyltrimethylsilane[a]

Entry	2	R^1	R^2	Yield (%)[b]	Ee (%)[c]
1	2b	Me	Bn	3b, 71	65 (R)
2	2c	CH$_3$(CH$_2$)$_5$	Et	3c, 74	74
3	2d	CH$_2$=CH(CH$_2$)$_2$	Et	3d, 41	74
4	2e	BnO(CH$_2$)$_3$	Et	3e, 75	73
5	2f	c-C$_5$H$_9$	Et	3f, 67	69
6	2g	c-C$_6$H$_{11}$	Et	3g, 0	—
7	2h	Ph	Me	3h, 0	—
8	2i	4-CF$_3$C$_6$H$_4$	Et	3j, 72	79

[a] The reaction of **2** (0.2 mmol) was conducted with allyltrimethylsilane (3 equiv) in the presence of **1**·Cu(NTf$_2$)$_2$ (5 mol%) in EtNO$_2$ at ambient temperature for 1–24 h. The crude product was treated with TBAF (1 equiv) in THF at ambient temperature. [b] Isolated yield. [c] Evaluated by chiral HPLC analysis.
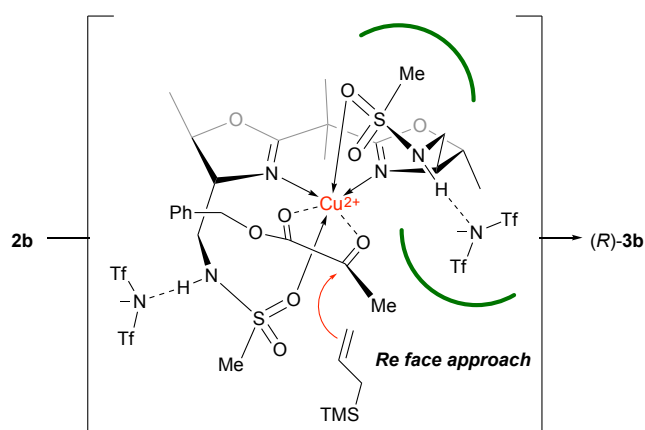

Scheme 1 Proposed transition state assembly for the **1a**·Cu(NTf$_2$)$_2$-catalyzed allylation of **2b**

The reaction of primary alkyl-substituted α-ketoesters such as **2c** [R^1 = CH$_3$(CH$_2$)$_5$], **2d** [R^1 = CH$_2$=CH(CH$_2$)$_2$] and **2e** [R^1 = BnO(CH$_2$)$_2$] also gave the corresponding adducts **3c**–**e** in moderate to good yields (41–75%) with good enantioselectivities (73–74% ee) (entries 2–4).

The reactivity of the present allylation highly depended on the size of the R^1 group. For example, the reaction of cyclopentyl-substituted α-ketoester **2f** gave the corresponding adduct **3f** in 67% yield with 69% ee (entry 5), while cyclohexyl-substituted α-ketoester **2g** (R^1 = c-C$_6$H$_{11}$) and methyl benzoylformate (**2h**, R^1 = Ph) were inert under the present reaction conditions, and the starting materials were completely recovered (entries 6 and 7). The introduction of an electron-withdrawing CF$_3$ group on the phenyl group of **2h** successfully improved the reactivity to give **3i** in 72% yield with 79% ee (entry 8).

We next examined the catalytic enantioselective Hosomi–Sakurai reaction with methallyltrimethylsilane, which is more nucleophilic than allyltrimethylsilane[10] (Scheme 2). As a result, the reaction proceeded rapidly even at −30 °C to give the corresponding adduct **4a** with high enantioselectivity (97% ee).

However, the yield of **4a** was low (48%) and a significant amount (32%) of **5a** was also formed as a byproduct. This byproduct should be generated via deprotonation of the tertiary cation intermediate, while desilylation of the same cationic intermediate gives the desired product **4a**. According to previous reports,[11] **5a** could be converted into **4a** under acidic conditions via formation of the tertiary cation intermediate. Indeed, treatment of **5a** with 5 mol% of **1a**·Cu(NTf$_2$)$_2$ at ambient temperature gave **4a** in 75% yield without any loss of enantiomeric excess (97% ee) (Scheme 2).
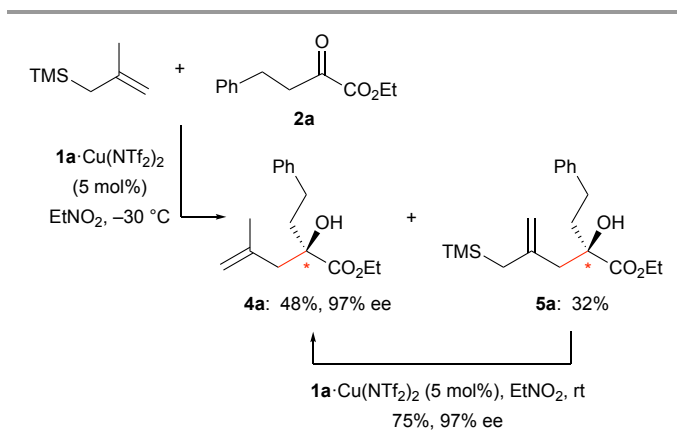
**Scheme 2** **1a**·Cu(NTf$_2$)$_2$-catalyzed addition reaction of **2a** with methallyltrimethylsilane

The above results implied that when the reaction mixture, which was obtained from the reaction of **2a** with methallyltrimethylsilane at –30 °C, was allowed to warm to ambient temperature, then the corresponding adducts **4a** would be formed as a single product. As we expected, the reaction of **2a** with methallyltrimethylsilane under these conditions (–30 °C, 1 h; then rt, 2 h) gave **4a** in 90% yield with 96% ee (Table 3, entry 1).

Since adduct **4a** was obtained in high yield with high enantioselectivity, we next examined the substrate scope and limitations. As in the reaction with allyltrimethylsilane, the crude products included a small amount of TMS ether of **4**, so the crude products were treated with TBAF to remove the TMS group. The reaction of **2b**–**f** gave the corresponding adducts **4b**–**f** in good yields (53–79%) with high enantioselectivity (88–98% ee) (entries 2–6). However, the reaction of **2g**, which has a rather bulky cyclohexyl group, showed a slightly low enantioselectivity (78% ee), although the yield of **4g** was good (81%) (entry 7). The aryl-substituted α-ketoesters **2h**–**l** were also good substrates for the reaction with methallyltrimethylsilane, and gave the corresponding adducts **4h**–**l** in high yields (78–99%) with high enantioselectivity (93–98% ee) (entries 8–12). The introduction of a methyl group at the ortho-position of the phenyl group significantly decreased the reactivity, probably due to steric hindrance (14% yield, entry 13). In contrast to the 2-methylphenyl substituted **2m**, 2-fluoro-derivative **2n** showed good reactivity (75% yield) and high enantioselectivity (97% ee) (entry 14).

Table 3 Enantioselective addition reaction of **2** with methallyltrimethylsilane[a]

Entry	2	R^1	R^2	Yield (%)[b]	Ee (%)[c]
1	**2a**	Ph(CH$_2$)$_2$	Et	**4a**, 90	96
2	**2b**	Me	Bn	**4b**, 73	94
3	**2c**	CH$_3$(CH$_2$)$_5$	Et	**4c**, 79	94
4[d]	**2d**	CH$_2$=CH(CH$_2$)$_2$	Et	**4d**, 75	96
5	**2e**	BnO(CH$_2$)$_3$	Et	**4e**, 53	98
6	**2f**	c-C$_5$H$_9$	Et	**4f**, 53	88
7	**2g**	c-C$_6$H$_{11}$	Et	**4g**, 81	78
8	**2h**	Ph	Me	**4h**, 99	98
9	**2i**	4-CF$_3$C$_6$H$_4$	Et	**4i**, 81	97
10	**2j**	4-MeOC$_6$H$_4$	Et	**4j**, 95	93
11	**2k**	4-MeC$_6$H$_4$	Et	**4k**, 80	96
12	**2l**	3-MeC$_6$H$_4$	Et	**4l**, 78	95
13[e]	**2m**	2-MeC$_6$H$_4$	Et	**4m**, 14	ND
14	**2n**	2-FC$_6$H$_4$	Et	**4n**, 75	97

[a] The reaction of **2** (0.2 mmol) with methallyltrimethylsilane (3 equiv) was conducted in EtNO$_2$ (1 mL) in the presence of **1a**·Cu(NTf$_2$)$_2$ at –30 °C for 1 h, and then the reaction mixture was warmed to ambient temperature. The crude product was treated with TBAF (0.5–3 equiv) in THF at 0 °C. [b] Isolated yield. [c] Evaluated by chiral HPLC analysis. [d] The reaction in the first step was conducted at –50 °C. [e] The reaction in the first step was conducted at 60 °C.
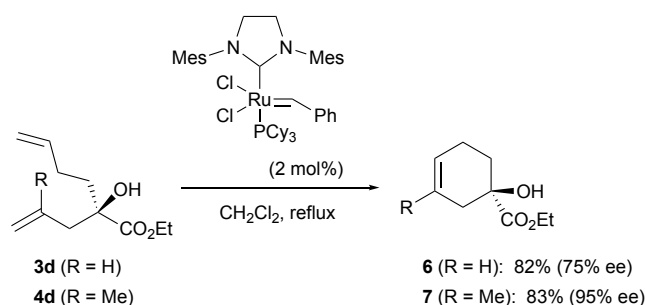
Scheme 3 Ring-closing metathesis of adducts **3d** and **4d**.

α,α-Disubstituted α-hydroxyesters **3** and **4**, the adducts of the present Hosomi–Sakurai reaction, are synthetically useful chiral building blocks. For example, ring-closing metathesis of **3d** and **4d** using Grubbs' 2nd-generation catalyst (2 mol%) gave the corresponding cyclohexenes **6** and **7** in respective yields of 82 and 83% without loss of enantiomeric excess (Scheme 2). Compound **6** is a key chiral intermediate for the synthesis of quinic acid.[12]

In conclusion, we developed a catalytic enantioselective Hosomi–Sakurai reaction of α-ketoesters **2**. Chiral copper(II) complex with bis(oxazoline) ligand **1a** showed high catalytic activity, and chiral α,α-disubstituted α-hydroxyesters **3** and **4** were obtained in high yields with high enantioselectivities.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ See the Electronic Supplementary Information for details.
§ The minus sign indicates that the opposite enantiomer was obtained as a major product.

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