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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).

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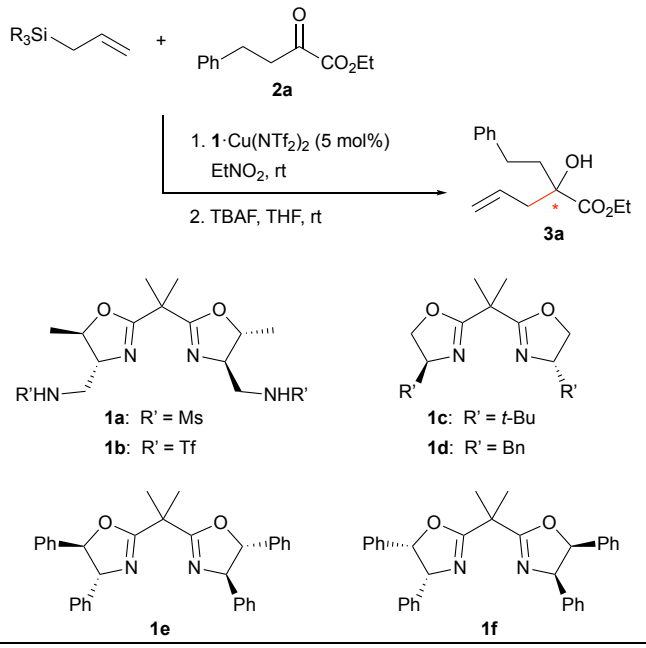
The use of ligand **1e** or **1f**, which have four phenyl groups at the 4,4',5,5'-positions, gave **3a** in moderate yields (68 and 67%) in low enantioselectivity (–16 and –35% ee)[§] (entries 6 and 7).

Table 1 Catalytic activities of chiral copper(II) complexes in the addition reaction of **2a** with allylsilanes[a]

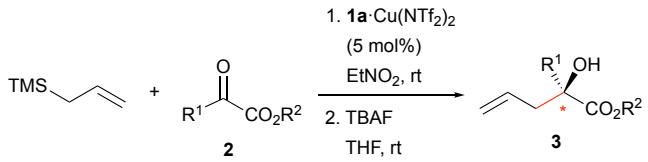


Entry	1	R	Yield (%)[b]	Ee (%)[c]
1	**1a**	Me	78	74
2	**1a**	*i*-Pr	50	80
3	**1b**	Me	90	53
4	**1c**	Me	3	ND
5	**1d**	Me	83	–7
6	**1e**	Me	68	–16
7	**1f**	Me	67	–35

[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.

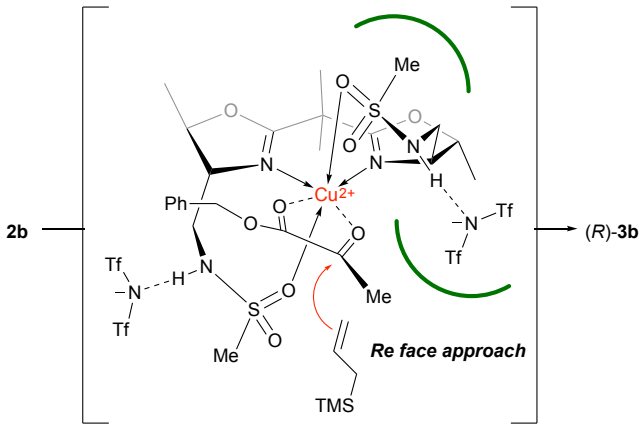
The optimized reaction conditions could be applied to the allylation of various α-ketoesters **2** (Table 2). The reaction of benzyl pyruvate **2b** gave the corresponding adduct **3b** in 71% yield with 65% ee (entry 1). The absolute configuration of **3b** was assigned to be *R* from the sign of the 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_5H_9	Et	**3f**, 67	69
6	**2g**	*c*-C_6H_{11}	Et	**3g**, 0	—
7	**2h**	Ph	Me	**3h**, 0	—
8	**2i**	4-$CF_3C_6H_4$	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.



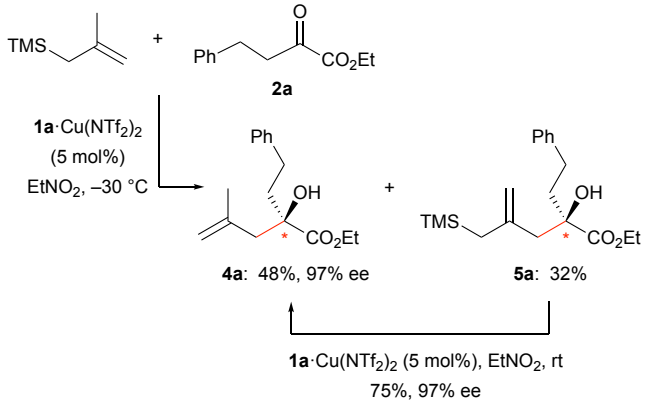
Scheme 1 Proposed transition state assembly for the **1a**·Cu(NTf$_2$)$_2$-catalyzed allylation of **2b**

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_6H_{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).

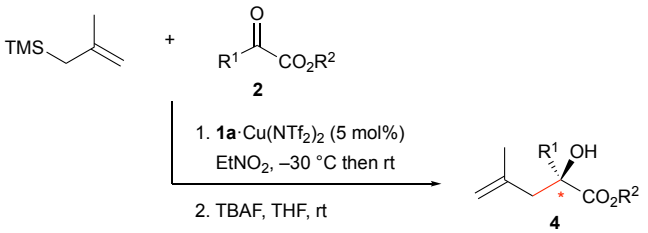


Scheme 2 **1a**·$Cu(NTf_2)_2$-catalyzed addition reaction of **2a** with methallyltrimethylsilane

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).

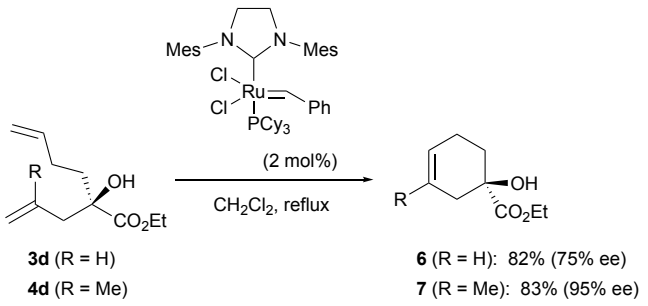
Since adduct **4a** was obtained in high yield with high enantioselectivity, we next examined the substrate scope and limitations. As in the reaction with allyltrimethylsilane, the crude products included a small amount of TMS ether of **4**, so the crude products were treated with TBAF to remove the 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_5H_9	Et	**4f**, 53	88
7	**2g**	*c*-C_6H_{11}	Et	**4g**, 81	78
8	**2h**	Ph	Me	**4h**, 99	98
9	**2i**	4-$CF_3C_6H_4$	Et	**4i**, 81	97
10	**2j**	4-$MeOC_6H_4$	Et	**4j**, 95	93
11	**2k**	4-MeC_6H_4	Et	**4k**, 80	96
12	**2l**	3-MeC_6H_4	Et	**4l**, 78	95
13[e]	**2m**	2-MeC_6H_4	Et	**4m**, 14	ND
14	**2n**	2-FC_6H_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.

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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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