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Enantioselective carbonyl-ene-type cyclization of α-ketoester and 2-substituted vinylsilane catalyzed by a chiral Cu-BOX complex

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ABSTRACT

We developed an enantioselective carbonyl-ene-type cyclization using 2-substituted vinylsilane as a nucleophilic ene moiety catalyzed by a chiral copper-BOX complex. This reaction is the first example of enantioselective carbonyl-ene cyclization using a 1,2-disubstituted olefin. This methodology gave chiral indenols with a tetrasubstituted carbon.

Introduction

The carbonyl-ene reaction is an important carbon-carbon bond-forming reaction, and catalytic and enantioselective variants have been reported with a variety of chiral catalysts.[1] The ene component is considered to act as a nucleophile. Thus, 1,1-disubstituted or trisubstituted olefins were generally used in past reports, and less reactive 1,2-disubstituted olefins[1b] were rarely utilized. As far as we know, there has been no successful example on catalytic and enantioselective carbonyl-ene *cyclization* of 1,2-disubstituted olefins. Evans's group reported the use of 2-substituted vinylsilanes as a 1,2-disubstituted ene moiety, taking advantage of the β-silyl cationic effect of the intermediate (Scheme 1-A).[2–4] The enophile component is preferably electron-deficient, and thus aldehydes or glyoxylates have generally been used. When ketones or their derivatives were used as an enophile, a tertiary alcohol would be constructed.[5] Yang's group first used α-ketoester as an enophile in enantioselective carbonyl-ene *cyclization* using a chiral Cu-bis(oxazoline) (BOX) catalyst (Scheme 1-B).[6,7] Although they achieved the construction of carbocycles with a chiral tetrasubstituted carbon, 20 mol% of the catalyst was required.

Here, we report the catalytic and enantioselective carbonyl-ene-type *cyclization* between α-ketoester and 2-substituted vinylsilane (Scheme 1-C). (*E*)-2-oxo-2-(2-(2-(trimethylsilyl)vinyl)phenyl)acetate (**1**) should have good reactivity in carbonyl-ene cyclization since the cationic intermediate **2** would be stable as β-silyl cation along with benzyl cation. According to Mikami's report,[4] two products are presumed in this reaction. Compound **3** would be formed via silyl transfer of **2**, and **4** would be generated by desilylation of **3**. These two products are chiral indenol with a tetrasubstituted carbon, which is seen as a core skeleton in biologically active compounds.[8]

Results and discussion

We set ethyl (*E*)-2-oxo-2-(2-(2-(trimethylsilyl)vinyl)phenyl)acetate (**1a**) as a substrate and screened catalysts using various metal triflic imidates, since we have been focusing on demonstrating the synthetic utility of metal triflic imidates ($M_m(NTf_2)_n$) as a Lewis acid.[9,10] By a concise metal screening, $Cu(NTf_2)_2$ gave the highest yield.[11] Before starting chiral ligand screening, we tried Yang's catalyst ($Cu(OTf)_2$-**L1**),[6] but it was not effective in this reaction (entry 1, Table 1). With 20 mol% of $Cu(NTf_2)_2$ and **L1**, the yield and ee of **4a** were both increased compared to those of entry 1 (entry 2). Next, we screened chiral BOX ligands **L2**-**7**. Among them, ligands **L2**, **L6**, and **L7** with benzyl substituents at the methylene bridge[12] improved the yield of the product (entries 3, 7, and 8). We chose **L2**

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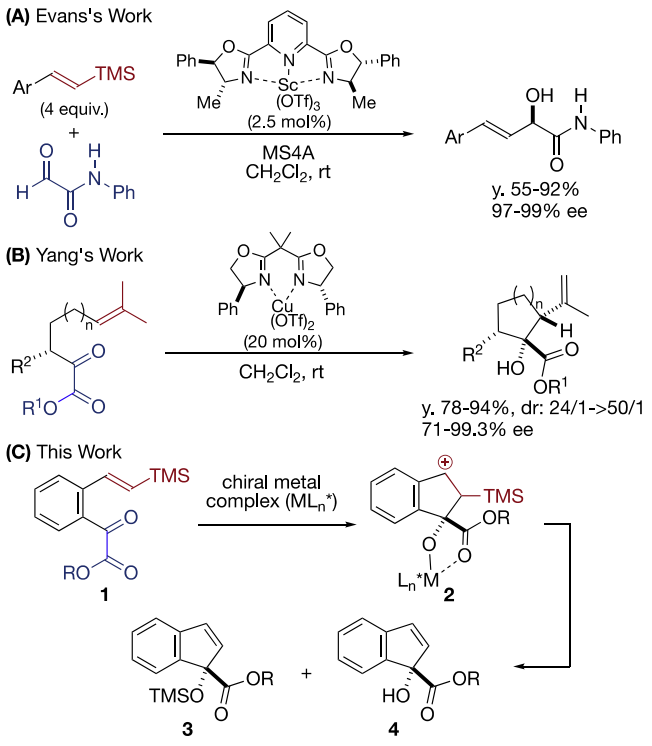


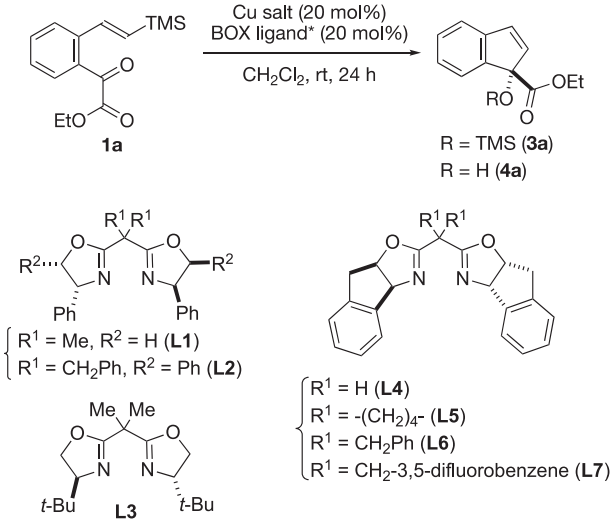
Scheme 1. Catalytic and enantioselective carbonyl-ene reactions.

as the optimal ligand for the enantioselective carbonyl-ene-type cyclization, because it gave the products in the highest yield (totally 95%) with the highest enantioselectivity (93% ee for **4a**). 10 mol% of $Cu(NTf_2)_2$-**L2** catalyst gave a result similar to the reaction using 20 mol% catalyst, except for the ratio of **3a** and **4a** (entry 9).[13,14]

We then examined the substituent effects on the ketoester moiety. With $Cu(NTf_2)_2$-**L2** catalyst, we found that 5 mol% of the catalyst was enough for completion of the reaction. The reaction procedure was simplified by the treatment of the reaction mixture with aqueous HCl to converge the mixture of products **3** and **4** to the single product **4** (entry 1, Table 2). Methyl ester **1b** gave **4b** in excellent yield and enantioselectivity (entry 2). Ethyl thioester **1c** decreased the yield and enantioselectivity (entry 3). Using methyl ester derivatives, substituent effects on the benzene ring were then investigated. Substrates with a methyl group at the C4, C5, or C6 position afforded the corresponding products in good yields and ees (entries 4 to 6). Substrates with electron-withdrawing groups, F or Cl, at the C4 position had relatively low reactivity, and thus a higher temperature was required for completion of the reaction (entries 7 and 8). On the other hand, an electron-donating group at the C5 position increased the reactivity, and **4i** was obtained in excellent yield even for 30 min with moderate enantioselectivity (entries 9 and 10). Substrate **1j** with a bulky silyl group (*Si* = TBS) gave **4a** in 3% yield with 41% ee (entry 11), since it might not be preferable to form $Cu(NTf_2)_2$-**L2**-**1j** complex due to steric repulsion between a chiral Cu complex and a bulky TBS group.

We also examined the catalytic and enantioselective double carbonyl-ene-type cyclization with **5** (Scheme 2). With 10 mol% of chiral $Cu(NTf_2)_2$-**L2** complex, indacene derivative *cis*-diol-**6** was obtained in 89% yield with >99% ee in excellent diastereoselectivity. Compound **7** was also obtained in 11% yield as a mixture of keto- and enol-forms. The relative and absolute configurations of **6** were unambiguously determined by X-ray crystallographic analysis.[15]

Table 1
Screening of chiral copper catalyst.



Entry	Cu salt	BOX ligand	**3a** (%)	**4a** (%)	% ee of **4a**	**1a** (%)
1	$Cu(OTf)_2$	**L1**	0	9	54	83
2	$Cu(NTf_2)_2$	**L1**	0	15	65	79
3	$Cu(NTf_2)_2$	**L2**	13[a]	82	93	5[a]
4	$Cu(NTf_2)_2$	**L3**	0	15	−29	85
5	$Cu(NTf_2)_2$	**L4**	0	24	−22	76
6	$Cu(NTf_2)_2$	**L5**	0	25	−16	65
7	$Cu(NTf_2)_2$	**L6**	12[a]	61	−52	20[a]
8	$Cu(NTf_2)_2$	**L7**	1[a]	47	−24	47[a]
9	$Cu(NTf_2)_2$[b]	**L2**[b]	72	28	93	0

[a] Determined by ^{1}H NMR of the mixture of **3a** and **1a**.
[b] 10 mol% of the reagent was used.