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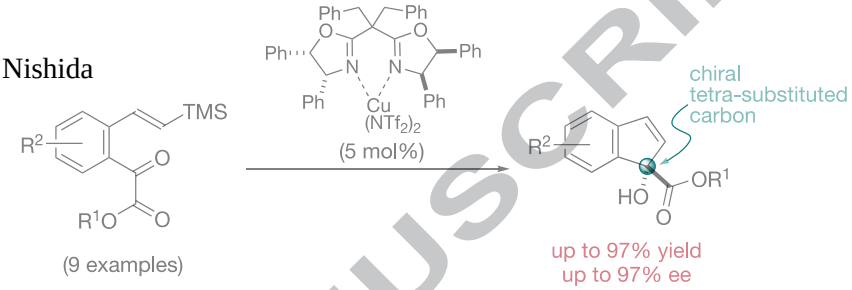

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Enantioselective carbonyl-ene-type cyclization of α-ketoester and 2-substituted vinylsilane catalyzed by a chiral Cu-BOX complex

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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.

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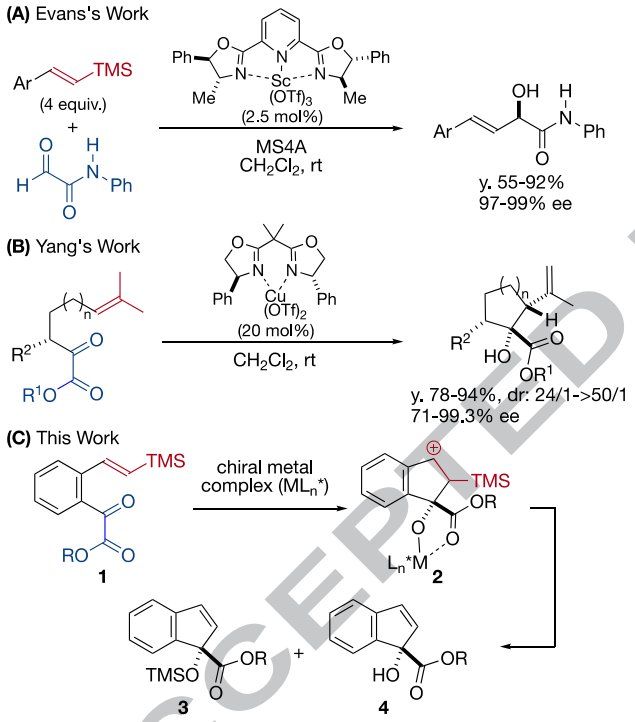
Introduction

The carbonyl-ene reaction is an important C-C 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.



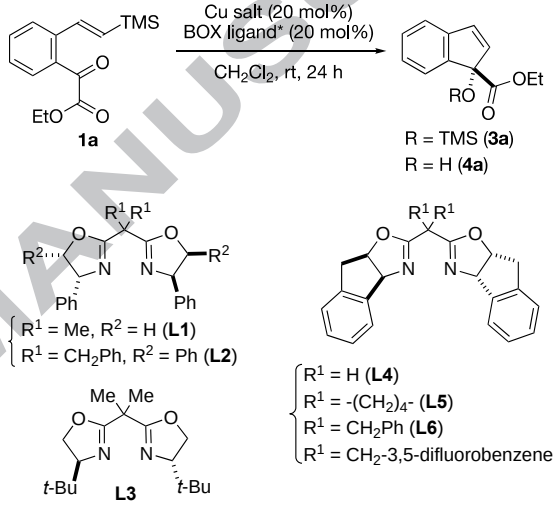
Scheme 1. Catalytic and enantioselective carbonyl-ene reactions

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** 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]

Table 1. Screening of chiral copper catalyst



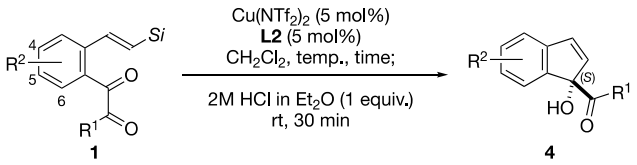
entry	Cu salt	BOX ligand	**3a** (%)	**4a** (%)	% ee of **4a**	**1a** (%)
1	$Cu(OTf)_2$	**L1**	0	9	54	83
2	$Cu(NTf_2)_2$	**L1**	0	15	65	79
3	$Cu(NTf_2)_2$	**L2**	13[a]	82	93	5[a]
4	$Cu(NTf_2)_2$	**L3**	0	15	-29	85
5	$Cu(NTf_2)_2$	**L4**	0	24	-22	76
6	$Cu(NTf_2)_2$	**L5**	0	25	-16	65
7	$Cu(NTf_2)_2$	**L6**	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.

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.

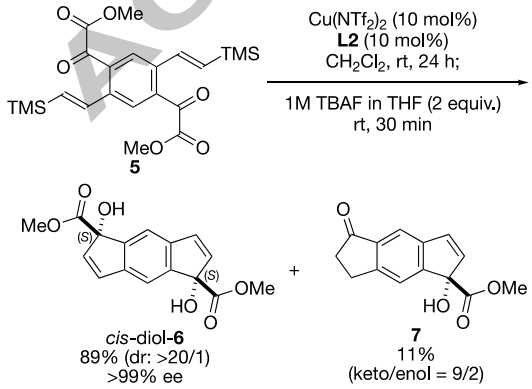
Table 2. Substituent effects



entry	substrate 1	[*Si*,	R^1,	R^2]	temp.	time (h)	yield (%)	% ee
1	**1a**	TMS	OEt	H	rt	24	92	94
2	**1b**	TMS	OMe	H	rt	24	96	96
3	**1c**	TMS	SEt	H	rt	24	76	76
4	**1d**	TMS	OMe	4-Me	rt	21	86	95
5	**1e**	TMS	OMe	5-Me	rt	16	92[a]	96
6	**1f**	TMS	OMe	6-Me	rt	19	82[a]	97
7	**1g**	TMS	OMe	4-F	40 °C	24	95	96
8	**1h**	TMS	OMe	4-Cl	40 °C	24	90	96
9[b]	**1i**	TMS	OMe	5-MeO	rt	0.5	91	71
10[b]	**1i**	TMS	OMe	5-MeO	0 °C	0.5	97	77
11	**1j**	TBS	OEt	H	rt	24	3[a]	41

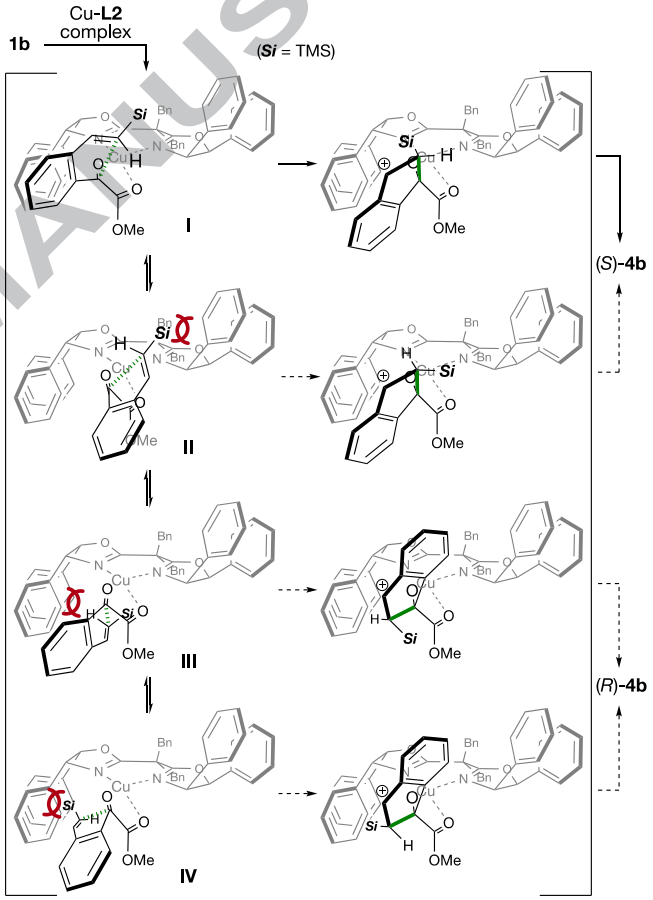
[a] Determined by ^{1}H NMR of the mixture of **4** and **L2**. [b] Reaction mixture was treated with 1M TBAF in THF (1 equiv.) instead of HCl solution.

We also examined the catalytic and enantioselective double carbonyl-ene-type cyclization with **5** (Scheme 2). With 10 mol% of chiral Cu-**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]



Scheme 2. Catalytic and enantioselective double carbonyl-ene-type cyclization

We could propose four configurations **I** to **IV** for the $Cu(NTf_2)_2$-**L2**-**1b** complex, which would lead to different transition states (Scheme 3). The dicarbonyl moiety of **1b** would coordinate in a bidentate manner to Cu(II) with a tetrahedral-like coordination mode.[5a, 16] Each configuration was distinguished by how the ketoester and vinylsilane approach each other. In configurations **I** and **II**, the vinylsilane approaches the ketoester from its *Re*-face. From **I**, a new carbon-carbon bond would be formed at the *Re*-face of the vinylsilane. From **II**, bond-formation would occur at the *Si*-face of the vinylsilane. As a result, both patterns would afford (*S*)-**4b**, because the stereochemistry adjacent to the silyl group would disappear after the formation of a double bond. On the other hand, in **III** and **IV**, the vinylsilane approaches the ketoester from its *Si*-face, and (*R*)-**4b** would be generated in either event. In the structures of **II** and **IV**, there should be considerable steric repulsion between the TMS group of **1b** and the phenyl group of **L2**. In the case of **III**, hydrogen atom of the vinylsilane would be located on the phenyl group of **L2**. Therefore, configuration **I** should have the least steric repulsion, and cyclization preferably proceeded via **I** to give (*S*)-**4b**.



Scheme 3. Proposed reaction pathways

Conclusion

In summary, we have developed a catalytic and enantioselective carbonyl-ene-type cyclization of α-ketoester and 2-substituted vinylsilane, which is the first example of 1,2-disubstituted olefin as a nucleophilic ene moiety in the enantioselective carbonyl-ene cyclization. Using this reaction, we synthesized nine chiral indenols with a tetrasubstituted carbon. We also demonstrated double-cyclization to give a chiral indacene derivative with two tetrasubstituted carbons. The further extension and application of this methodology are being studied.

Acknowledgments

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Supplementary Material

Supplementary data (substrate syntheses, experimental details, NMR data, and HPLC charts) associated with this article can be found in the online version.

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13. For every entry, compound **3** was obtained with a stereoselectivity comparable to that of **4**.
14. The absolute configuration of **4a** was unambiguously assigned by X-ray crystallographic analysis. The supplementary crystallographic data for **4a** can be found at CCDC 1838477. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. This result, together with the X-ray analysis of **6**, was used to establish the absolute configuration of our compounds.
15. The supplementary crystallographic data for **6** can be found at CCDC 1838478. The structure of **7** was also confirmed by X-ray crystallographic analysis, see CCDC 1838495.
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Highlights:

• development of catalytic and enantioselective carbonyl-ene-type *cyclization* between α-ketoester and 2-substituted vinylsilane

• construction of chiral indenol with a tetrasubstituted carbon

• construction of chiral indacene derivative with two tetrasubstituted carbons

• utility of metal triflic imidates as a Lewis acidic catalyst