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Asymmetric Catalysis

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Catalytic Enantioselective Inverse Electron Demand Hetero-Diels–Alder Reaction with Allylsilanes**

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Abstract: *The first diastereo- and enantioselective inverse electron demand hetero-Diels–Alder reaction of β,γ-unsaturated α-ketoesters with allylsilanes is described. Chiral copper(II) catalysts successfully activate the β,γ-unsaturated α-ketoesters and promote the reaction with allylsilanes with excellent enantioselectivities. This process represents a new entry to chiral oxanes.*

We have developed chiral copper(II) catalysts (**1**·CuX$_2$; Figure 1), which show higher catalytic activities than conventional bis(oxazoline)/copper(II) complexes in the enantioselective Diels–Alder reaction with acrylamides.[1,2] The sulfonamide groups of **1** interact with the copper(II) cation (*n*–cation interaction), and results in high catalytic activity for a wide range of substrates and a high level of enantioselective induction.[3] Thus, the *n*–cation catalysts may also be applicable to other asymmetric carbon–carbon bond-forming reactions of α,β-unsaturated carbonyl compounds. We report herein the first enantioselective hetero-Diels–Alder (HDA) reaction of β,γ-unsaturated α-ketoesters with allylsilanes.

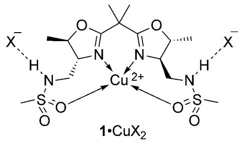
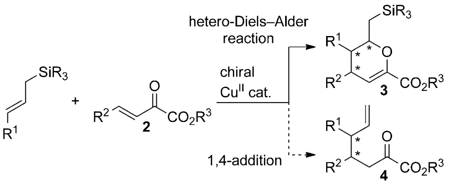


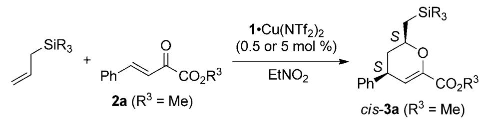
Figure 1. Chiral *n*–cation catalysts **1**·CuX$_2$.

During the course of our extensive studies on **1**·CuX$_2$-catalyzed asymmetric carbon–carbon bond-forming reactions, we examined the reaction of the β,γ-unsaturated α-ketoesters **2** with allylsilanes (Scheme 1). Although β,γ-unsaturated α-ketoesters[4,5] are good Michael acceptors, allylsilanes[6] are less nucleophilic alkenes than vinyl ethers and silyl enol ethers.[7] Therefore, strong Lewis acid catalysts are generally required to promote the reaction of allylsilanes. We expected that our *n*–cation catalysts would promote the reaction of the β,γ-unsaturated α-ketoesters **2** with allylsilanes to give the corresponding 1,4-adducts **4**. Indeed, the chiral complex **1**·Cu(NTf$_2$)$_2$ successfully catalyzed the reaction of **2a** with allyltrimethylsilane (Table 1). However, the reaction surprisingly gave the corresponding HDA adduct **3a** (65% yield) with excellent enantioselectivity, along with a small amount of the 1,4-adduct **4a** (12% yield, 27% *ee*; entry 1). The absolute configuration of *cis*-**3a** (R = Me) was determined to be 2*S*,4*S* by X-ray crystallographic analysis after conversion into the amide with (*S*)-α-methyl-4-nitrobenzylamine.[8] The asymmetric HDA reaction of carbonyl compounds is one of the most powerful methods for the construction of optically



Scheme 1. HDA reaction versus 1,4-addition with allylsilanes.

Table 1: HDA reaction of **2a** with allylsilanes promoted by *n*-cation catalyst.[a]



Entry	R	*T* [°C]	*t* [h]	Yield [%][b] **3a** (**4a**)	*cis*/*trans*	*ee* [%][c] *cis*-**3a**	 *trans*-**3a**
1	Me	−20	14	65 (12)	75:25	98	99
2	Et	−20	2	57 (37)	61:39	98	99
3	*i*Pr	−20	25	83 (0)	54:46	81	68
4[d]	Ph	RT	3	89 (0)	65:35	99	99
5[d]	TMS	0	20	71 (0)	29:71	84	71

[a] Unless otherwise noted, the reaction of **2a** (0.2 mmol) and an allylsilane (5 equiv) was conducted in EtNO$_2$ (1 mL) in the presence of **1**·Cu(NTf$_2$)$_2$ (5 mol%). [b] Yield of isolated product **3a**. Data within parentheses represent the yield of **4a**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 2 equiv of allylsilane were used. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

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active heterocycles.[9,10] Although numerous chiral Lewis acid catalysts have been developed for the asymmetric inverse electron demand HDA reaction of α,β-unsaturated carbonyl compounds, dienophiles are limited to highly electron-rich alkenes such as vinyl ethers. To the best of our knowledge, this is the first successful example of the enantioselective inverse electron demand HDA reaction of β,γ-unsaturated α-ketoesters with allylsilanes.[11–13]

Based on this promising result, we next examined the reactivities of various allylsilanes for the **1**$\cdot$Cu(NTf$_2$)$_2$-catalyzed reaction of **2a** (R^3 = Me). As a result, the use of sterically hindered allylsilanes such as allyltriisopropylsilane, allyltriphenylsilane, and allyltris(trimethylsilyl)silane suppressed the generation of **4a** and improved the yield of **3a**, although the diastereoselectivities were moderate (Table 1, entries 2–5). Allyltriphenylsilane gave the best result (entry 4).[14] The major isomer **3a** (R = Ph) could be separated as a single isomer by chromatography on silica gel. Interestingly, the use of sterically hindered allyltris(trimethylsilyl)silane preferentially gave the corresponding *trans*-**3a** (entry 5). Notably, in contrast to the **1**$\cdot$Cu(NTf$_2$)$_2$-catalyzed reaction (entry 4), the use of a conventional bis(oxazoline)$\cdot$copper(II) complex, (*S*,*S*)-*t*Bu-bis(oxazoline)$\cdot$Cu(NTf$_2$)$_2$, as a catalyst gave **3a** in only 51 % yield with significant decomposition of **2a**, even after 17 hours at ambient temperature.

We propose here a mechanism for the present inverse electron demand HDA reaction with allylsilanes based on the absolute configuration of **3a** and our previous studies.[2] The *n*–cation interaction would create an efficient asymmetric environment around the copper(II) cation and preferentially shield the Cβ-*Re* face of the coordinated **2a** (Figure 2b). Allyltriphenylsilane would approach the Cβ-*Si* face of **2a** via the *endo* transition state to give *cis* adducts as major products. The predominance of *endo* transition state can be explained in terms of a secondary orbital interaction between the allylsilane HOMO and the β,γ-unsaturated α-ketoester LUMO[15,16] (Figure 2a). Indeed, an achiral copper(II) catalyst also preferentially gave *cis*-**3a** (ca. 8:2).[8] However, the steric repulsion between the sulfonamide group and the triphenylsilyl group decreases the *endo*/*exo* selectivity, which resulted in the moderate *cis*/*trans* ratio of the adducts. This consideration is consistent with the fact that the sterically less hindered allyltrimethylsilane showed good *cis* selectivity, while the sterically hindered allyltris(trimethylsilyl)silane preferentially gave *trans* adducts (Table 1).

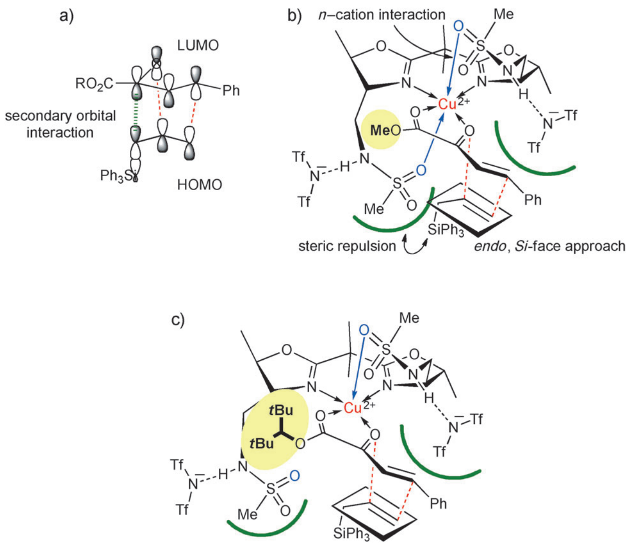
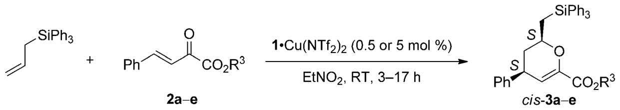


Figure 2. Proposed transition-state assembly for the **1**$\cdot$Cu(NTf$_2$)$_2$-catalyzed HDA reaction of **2**.

To improve the *cis*/*trans* selectivity of the present HDA reaction, we next investigated the ester moiety of **2** (Table 2).

Table 2: Effect of the ester moiety on the *cis*/*trans* selectivity.[a]



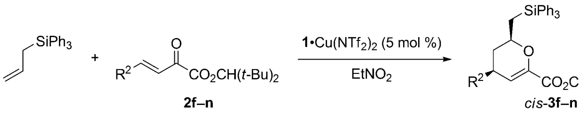
Entry	**2** (R^3)	Yield [%][b]	*cis*/*trans*	*ee* [%][c]	
				cis-**3**	*trans*-**3**
1	**2a** (Me)	89	65:35	99	99
2	**2b** (*i*Pr)	89	80:20	95	92
3	**2c** [CH(*i*Pr)$_2$]	99	89:11	96	99
4	**2d** [CH(*t*Bu)$_2$]	99	90:10	99	99
5[d]	**2d** [CH(*t*Bu)$_2$]	99	90:10	97	96
6	**2e** (*t*Bu)	20[e]	97:3[e]	n.d.	

[a] Unless otherwise noted, the reaction of **2** (0.4 mmol) and an allylsilane (2 equiv) was conducted in EtNO$_2$ (2 mL) in the presence of **1**$\cdot$Cu(NTf$_2$)$_2$ (5 mol %) at ambient temperature for 3–17 h. [b] Yield of isolated product **3**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction of **2d** (4 mmol) and allylsilane (2 equiv) was conducted in the presence of **1**$\cdot$Cu(NTf$_2$)$_2$ (0.5 mol %) in EtNO$_2$ (4 mL). [e] Yield and *cis*/*trans* ratio of the corresponding carboxylic acid (R^3 = H).

As a result, we found that the use of **2** bearing a bulky R^3 group improved the *cis*/*trans* ratio (entries 2–4). Especially, the use of a di(*tert*-butyl)methyl group gave the best results (entry 4). In contrast, the *tert*-butyl ester (**2e**) was unstable under the reaction conditions and gave the carboxylic acid derivatives of **3e** in low yield (20 %), although the diastereoselectivity was high (*cis*/*trans* 97:3). The improved diastereoselectivity can be explained by the structure of the transition-state assembly (Figure 2c). The sterically hindered di(*tert*-butyl)methyl group of **2d** would make the sulfonamide group move toward the left back side. This change in conformation would release the steric repulsion between the sulfonamide group and the triphenylsilyl group to improve the diastereoselectivity. Only 0.5 mol % of **1**$\cdot$Cu(NTf$_2$)$_2$ efficiently promoted the reaction of **2d** (4 mmol) to give the corresponding adduct **3d** in 99 % yield with excellent selectivity (entry 5). The major *cis*-isomer of **3d** could be separated as a single isomer by chromatography on silica gel.

With the highly diastereo- and enantioselective reaction conditions in hand, we next explored the generality and scope of the present HDA reaction with allyltriphenylsilane. The reactions of the various β,γ-unsaturated α-ketoesters **2** were conducted in the presence of **1**$\cdot$Cu(NTf$_2$)$_2$ (5 mol %) at −20 °C to ambient temperature (Table 3). As a result, **2f–i**, bearing

Table 3: Catalytic HDA reaction with allyltriphenylsilane.[a]

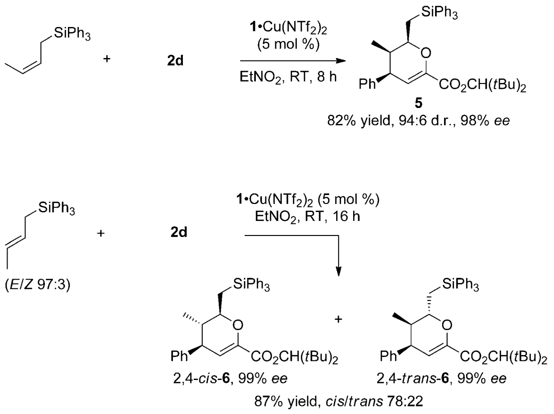


Entry	**2** (R^2)	Yield [%][b]	*cis*/*trans*	*ee* [%][c]
1	**2f** (4-MeOC$_6$H$_4$)	99	92:8	99
2[d]	**2f** (4-MeOC$_6$H$_4$)	94	91:9	98
3	**2g** (4-BrC$_6$H$_4$)	97	91:9	99
4[d]	**2g** (4-BrC$_6$H$_4$)	99	90:10	99
5	**2h** (3-BrC$_6$H$_4$)	98	90:10	99
6	**2i** (2-BrC$_6$H$_4$)	96	90:10	98
7	**2j** (2-naphthyl)	98	91:9	99
8	**2k** (*N*-acetyl-3-indolyl)	77	91:9	99
9	**2l** [(*E*)-PhCH=CH]	86	90:10	99
10[e]	**2m** (Me)	99	92:8	99
11[f]	**2n** (*i*Pr)	64	79:21	92

[a] The reaction of **2** (0.4 mmol) and allyltriphenylsilane (2 equiv) was conducted in EtNO$_2$ (2 mL) in the presence of **1**·Cu(NTf$_2$)$_2$ (5 mol%) at ambient temperature. [b] Yield of isolated product **3**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction of **2** (4 mmol) and allyltriphenylsilane (2 equiv) was conducted in EtNO$_2$ (4 mL) in the presence of **1**·Cu(NTf$_2$)$_2$ (0.5 mol%) at ambient temperature. [e] At −20 °C. [f] At 0 °C.

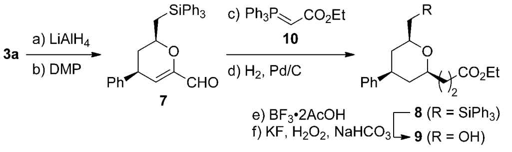
an electron-donating methoxy group or electron-withdrawing bromine group on the phenyl ring, were smoothly converted into the corresponding adducts **3f–i** in almost quantitative yield with high diastereo- and enantioselectivity (entries 1–6). The use of only 0.5 mol% of **1**·Cu(NTf$_2$)$_2$ successfully gave excellent results (entries 2 and 4). The reaction of **2j–n**, bearing a 2-naphthyl, *N*-acetyl-3-indolyl, cinnamyl, and alkyl group at the γ-position also gave the corresponding adducts **3j–n** with high diastereo- and enantioselectivity (entries 7–11).

We next examined the enantioselective HDA reaction of **2d** with *E*- and *Z*-crotyltriphenylsilanes catalyzed by **1**·Cu(NTf$_2$)$_2$ (Scheme 2). The reaction with *Z*-crotyltriphenylsilane gave the corresponding 2,4-*cis*-adduct **5** (82% yield) with excellent enantioselectivity (98% *ee*) and diastereoselectivity (94:6 d.r.). The configuration of *Z*-crotylsilane was completely retained during the reaction. In the same way, the reaction with *E*-crotyltriphenylsilane gave a mixture of the corresponding 2,4-*cis*-adducts **6** (87% yield) with excellent enantioselectivity (99% *ee*) and good diastereoselectivity (78:22 d.r.). These results clearly indicated that the reaction proceeded through a concerted pathway.



Scheme 2. HDA reaction with crotylsilanes.

The triphenylsilyl group in adduct **3d** could be converted into a hydroxy group by the following reaction sequence (Scheme 3). Reduction of the ester group of **3d** (99% *ee*) and subsequent Dess–Martin oxidation gave the aldehyde **7** in 84% yield. Wittig reaction of **7** with the ylide **10**[17] followed by hydrogenation gave the ethyl ester **8** in 91% yield as a single isomer. Subsequent oxidative conversion[18] of the triphenylsilyl group gave the hydroxycarboxylic ester **9** in 70% yield without any loss of enantiomeric excess (99% *ee*).



Scheme 3. Oxidative conversion of a triphenylsilyl group: a) LiAlH$_4$ (5 equiv), THF, 0 °C, 85%; b) Dess–Martin periodinane (DMP; 1.1 equiv), EtOAc, RT, 99%; c) Ph$_3$P=CHCO$_2$Et (**10**, 1.1 equiv), THF, RT, 97%; d) H$_2$, 10% Pd/C (10% w/w), EtOAc, 50 °C, 94%; e) BF$_3$·2AcOH (10 equiv), CH$_2$Cl$_2$, reflux; f) KF (3 equiv), 30% aq. H$_2$O$_2$ (10 equiv), NaHCO$_3$ (1 equiv), MeOH/THF (1:1 v/v), reflux, 70% for two steps. THF = tetrahydrofuran.

In conclusion, we have achieved the first diastereo- and enantioselective inverse electron demand HDA reaction of β,γ-unsaturated α-ketoesters with allylsilanes using *π*–cation catalysts. In contrast to the conventional inverse electron demand HDA reactions with vinyl ethers which give cyclic acetals, the present reaction represents a new entry to chiral oxanes, which can serve as useful building blocks.

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Communications

Asymmetric Catalysis

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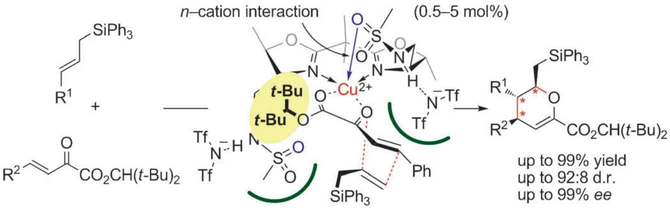
K. Ishihara* ________ ■■■■–■■■■

Catalytic Enantioselective Inverse Electron Demand Hetero-Diels–Alder Reaction with Allylsilanes



New on the block: The first diastereo- and enantioselective title reaction of β,γ-unsaturated α-ketoesters with allylsilanes is described. Chiral copper(II) catalysts successfully activate the β,γ-unsaturated α-ketoesters and promote the reaction with allylsilanes with excellent enantioselectivities. This process represents a new entry to chiral oxanes, which are useful building blocks. Tf = trifluoromethanesulfonyl.