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Highly efficient chiral copper Schiff-base catalyst for asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene

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Abstract—A remarkable increase in catalytic activity is found for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with diazoacetate by use of the chiral copper Schiff-base complexes, which are derived from substituted salicylaldehydes, chiral aminoalcohols, and copper acetate monohydrate. Furthermore, a combination of a chiral copper Schiff-base with a Lewis acid showed an increase in yield (up to 90%) and in enantioselectivity (up to 90% ee) for the asymmetric cyclopropanation of the diene with *t*-butyl diazoacetate at 20 °C.

1. Introduction

Catalytic asymmetric cyclopropanation of alkenes with diazoacetate has been a powerful tool in the synthesis of chiral cyclopropyl esters, which are very important intermediates for biologically active compounds.[1–4] 3-(1-Isobutenyl)-2,2-dimethyl cyclopropanecarboxylate (chrysanthemate) is of particular importance as an intermediate of pyrethroid insecticides, and the (1*R*,3*R*) isomer ((+)-*trans* isomer) shows the most insecticidal activity among the four isomers of the chrysanthemate.[5] Among the efficient catalysts which have been developed, copper Schiff-base complexes derived from chiral aminoalcohols are very attractive catalysts. Using this kind of catalysts, Aratani first achieved a high ee (94%) and *trans*/*cis* ratio (93/7) for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate to give the chrysanthemate, and Aratani's asymmetric process leads to successful industrial application in the synthesis of chiral 2,2-dimethylcyclopropane carboxylic acid, by asymmetric cyclopropanation of isobutene with ethyl diazoacetate.[5–7]

To the best of our knowledge, only a few successful reports, in which high *trans* selectivity and high enatioselectivity were achieved, have been presented in the asymmetric cyclopropanation of the diene as a substrate, although many asymmetric cyclopropanations of styrene with diazoacetate have been reported over the last 20 years (Scheme 1).[1–4,8–10]

In Aratani's catalyst, the structure of the chiral aminoalcohol part played an important role on the enantioselectivity,[6,7] so that the modification of the aminoalcohol has been tried to achieve higher enantioselectivity up to 1999. In 2000, Li et al. reported an investigation on the framework of the benzene ring of salicylaldehyde in the copper Schiff-base complex for the asymmetric cyclopropanation of styrene, and more than 98% ee of the *cis* product was obtained with *i*-butyl diazoacetate using the copper Schiff-base catalyst **3b** derived from 5-nitrosalicylaldehyde.[11] They also applied the copper Schiff-base catalyst **3b** to the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate with 1 mol% catalyst loading. However the enantioselectivity of the *trans* product and the *trans*/*cis* ratio were moderate (74% ee, *t*/*c*=72/28), and the catalytic amount used in their report (1 mol%) should increase the cost of the cyclopropane products (Scheme 2).[12]

Therefore, we have developed new highly efficient catalysts for the cyclopropanation of the dienes with a simple alkyl diazoacetate such as ethyl or *t*-butyl diazoacetate, which means that the formed chrysanthemate would be easy to convert to the chiral chrysanthemic acid as the intermediate for pyrethroid insecticides. Here, we report that the copper Schiff-base catalysts derived from 5-substituted salicylaldehyde with an electron-withdrawing group remarkably

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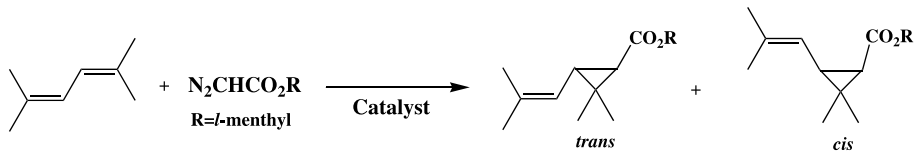
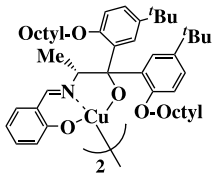
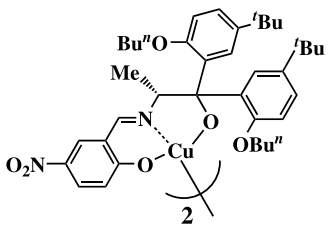




Aratani's catalyst (R-1648)

Yield 75%
t/c = 93/7
94%ee (*trans*)

Scheme 1. The structures of Aratani's catalysts R-1648, and the results of the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate with 1 mol% catalyst loading.



Li 's catalyst (3b)

t/c = 72/28
74% ee (*trans*)

Scheme 2. Structures of Li's catalyst **3b**, and the results of the cyclopropanation of 2,5-dimethyl-2,4-hexadine with *l*-menthyl diazoacetate with 1 mol% catalyst loading.

enhanced the catalytic efficiency for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene. Furthermore, we found that a combination of a copper Schiff-base complex with a Lewis acid achieved 90% yield and more than 90% ee with *t*-butyl diazoacetate at 20 °C with 0.1 mol% catalyst loading.

2. Results and discussion

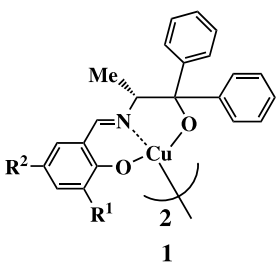
2.1. Effect of substituents of aminoalcohol framework and salicylaldehyde framework on the stereoselectivity and the catalytic efficiency

The results of the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) with ethyl diazoacetate (EDA) are shown in Table 1, using the copper Schiff-base complexes as catalysts as shown in Scheme 3. They were synthesized from chiral aminoalcohols, salicylaldehyde derivatives, and copper(II) acetate hydrate (Scheme 4). In the order of **1a**, **2a**, and **3a**, the enantioselectivety of the *trans* product was enhanced, while the *trans*/*cis* ratio of the product was lowered in the presence of 0.5 mol% catalyst loading (entries 1, 5, 9).[7] The results are consistent with those of Aratani,[7] although the presence of a nitrogen group on the salicylaldehyde framework did not show a remarkable difference with 0.5 mol% catalyst (entries 3, 7, 11). All cases with 0.1 mol% catalysts **1a**, **2a**, and **3a** decreased not only in the yield but also in enantioselectivity, compared to those with 0.5 mol% (entries 1 vs. 2, 5 vs. 6, 9 vs. 10). However, almost the same yield and ee were retained in each case with 0.1 mol% catalysts **1b**, **2b**, and **3b** as those with 0.5 mol% catalyst (entries 3 vs. 4, 7 vs. 8, 11 vs. 12). These results clearly indicated that the copper Schiff-base catalysts derived from salicylaldehyde lose catalytic activity faster than those derived with 5-nitrosalicylaldehyde. Actually, we analyzed the reaction mixture based on the structure of the used catalyst **2a** after the cyclopropanation by HPLC. We found that not only the original copper complex **2a** but also the corresponding Schiff-base ligand

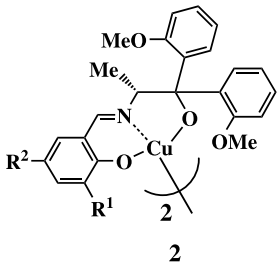
Table 1. Asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) with EDA[a]

Entry	Catalyst	mol%[b]	Yield (%)[c]	*trans*/*cis*[d]	ee (%)[e]	
					trans[f]	*cis*[g]
1	**1a**	0.5	95	61/39	60	59
2	**1a**	0.1	80	63/37	32	30
3	**1b**	0.5	97	61/39	59	50
4	**1b**	0.1	96	61/39	58	48
5	**2a**	0.5	96	58/42	65	69
6	**2a**	0.1	83	60/40	40	39
7	**2b**	0.5	97	58/42	67	65
8	**2b**	0.1	96	58/42	65	60
9	**3a**	0.5	96	55/45	80	61
10	**3a**	0.1	82	58/42	44	39
11	**3b**	0.5	96	54/46	80	60
12	**3b**	0.1	95	54/46	78	56

[a] Reaction conditions: 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate, 80 °C, 0.01 mmol of the monomerized copper complex with 0.5 mol of phenylhydrazine to the binuclear complex as shown in Scheme 4.
[b] Mol% of the mononuclear complex based on EDA.
[c] Based on EDA and determined by GC analysis with *n*-decane as internal standard.
[d] Determined by GC analysis (DB-1, 30 m×0.25 mm ID, 0.25 mm film, column temp. 100 °C).
[e] Determined by LC analysis (Sumichiral OA-2500 (25 cm×4 mm ID, 5 μm film)×2, UV 220 nm, *n*-hexane 0.7 mL/min).
[f] 1*R*,3*R* as a major enantiomer.
[g] 1*R*,3*S* as a major enantiomer.



1



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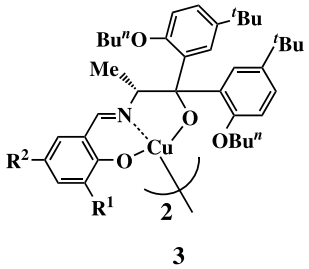
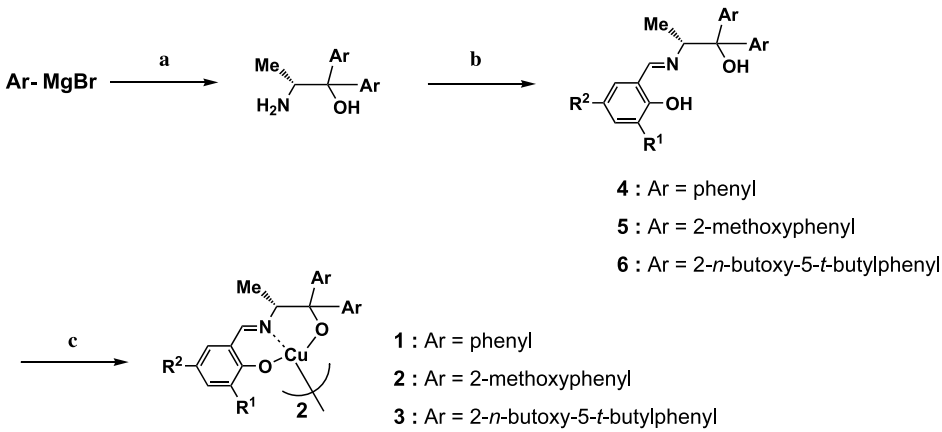


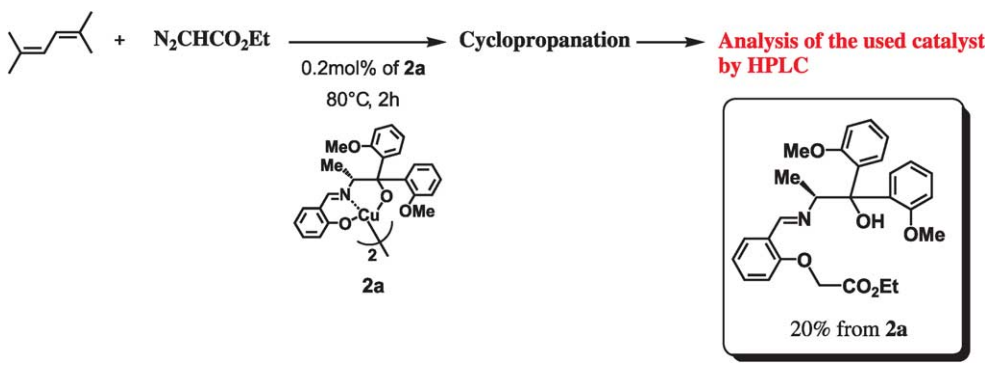
3

	R^1	R^2
1a	H	H
1b	H	NO_2
2a	H	H
2b	H	NO_2
3a	H	H
3b	H	NO_2

Scheme 3. Structures of the copper Schiff-base catalysts **1a**-**1b**, **2a**-**2b**, **3a**-**3b**.



Scheme 4. Synthesis of copper Schiff-base complexes **1**-**3**. (a) *D*-alanine methyl ester hydrochloride; (b) substituted salicylaldehyde; (c) copper acetate monohydrate, NaOH.

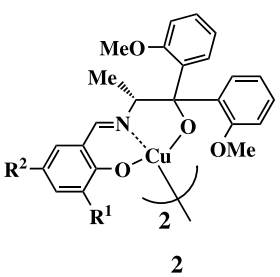


Scheme 5. The structure of the used catalyst **2a** after the cyclopropanation.

did not exist in the reaction mixture any more, and an adduct of ethyl diazoacetate with the phenol oxygen of the Schiff-base ligand was detected as shown in Scheme 5.

Li et al. described that reducing the electron density on the salicylaldehyde framework by the introduction of a nitro group favors the enantioselectivity for the cyclopropanation of styrene. Although our results above suggest that the introduction of a nitro group does not affect the enantioselectivity, the catalytic robustness can be enhanced more strongly with the Cu–O bond from the phenol.

Therefore, several Schiff-bases with various electron-withdrawing substituents on the salicylaldehyde framework in copper complex **2** were examined (Scheme 6). We found that 5-substituted copper complexes with an



2

	R^1	R^2
2a	H	H
2b	H	NO_2
2c	NO_2	H
2d	NO_2	NO_2
2e	H	CO_2Me
2f	CO_2Me	H
2g	H	CN
2h	H	CF_3
2i	H	F
2j	F	H

Scheme 6. Structures of the copper catalysts **2a**-**2k**.

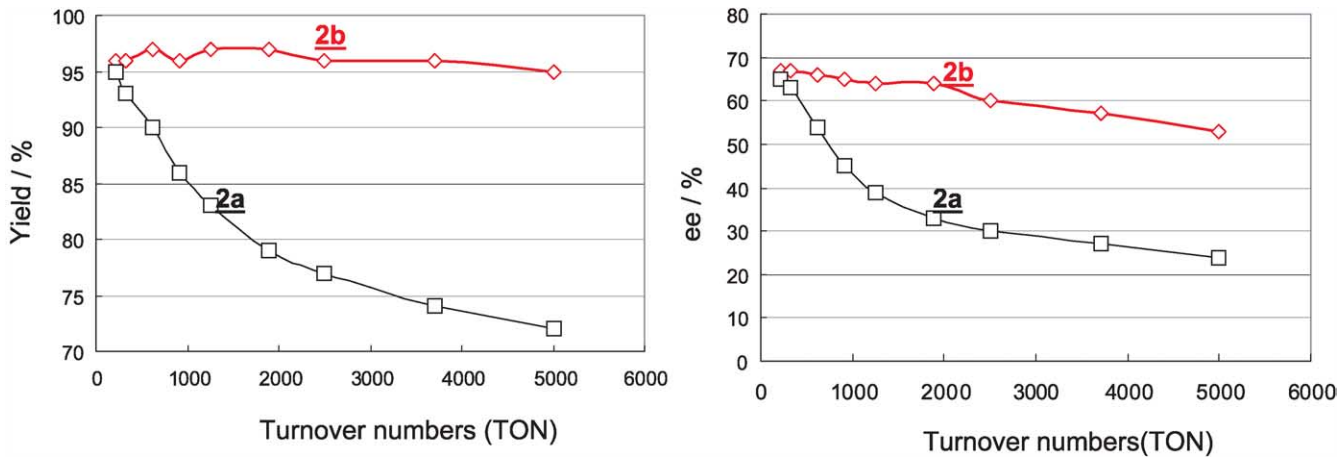


Figure 1. Comparison of catalytic efficiency between **2a** and **2b** at 80 °C.

electron-withdrawing group were more effective for the enantioselectivity than 3-substituted ones, except for the fluorine substituted complex.

Comparison of turnover numbers between **2a** and **2b** is shown in Figure 1. A remarkable decrease in both the yield and ee was observed with higher turnover numbers in the case of **2a**, while in the case of catalyst **2b**, the ratio of the decrease in the yield and the ee is much smaller than that by **2a**.

These results suggested that the copper Schiff-base catalyst derived from the 5-substituted salicylaldehyde with an electron-withdrawing group becomes more efficient for the asymmetric cyclopropanation of the diene, although the same performance is essentially exhibited in enantioselectivity as the unsubstituted copper complex on the salicylaldehyde moiety. This point is also different from the introduction of a nitro group in salicylaldehyde at the 5-position in the copper complex which enhanced the enantioselectivity for the cyclopropanation of styrene by Li et al. (Table 2).

Table 2. Asymmetric cyclopropanation of DMHD with EDA using **2** as the catalyst[a]

Entry	Catalyst	mol%[b]	Yield (%)	*trans*/*cis*	ee (%)	
					trans[c]	*cis*[d]
1	**2a**	0.1	83	60/40	40	39
2	**2b**	0.1	96	58/42	65	60
3	**2c**	0.1	97	59/41	55	48
4	**2d**	0.1	98	60/40	42	33
5	**2e**	0.1	97	58/42	65	58
6	**2f**	0.1	94	60/40	46	40
7	**2g**	0.1	97	58/42	63	57
8	**2h**	0.1	97	58/42	62	58
9	**2i**	0.1	96	60/40	43	41
10	**2j**	0.1	97	59/41	62	57

[a] Reaction conditions: 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate, 80 °C, 0.01 mmol of the monomerized copper complex with 0.5 mol phenylhydrazine to the binuclear complex as shown in Scheme 6.
[b] Mol% of the mononuclear complex based on EDA.
[c] 1*R*,3*R* as a major enantiomer.
[d] 1*R*,3*S* as a major enantiomer.

2.2. Effect of temperatures on the selectivity

Under lower temperatures for the reaction, higher enantiomeric excesses of the product were obtained, but the yield of the product was lowered with the catalyst **2b** or **3b**, as shown in Table 3.

Table 3. The influence of reaction temperature and alkyls in diazoacetate (RDA) in the presence of 0.1mol%[a] of the catalysts[b]

Entry	Catalyst	R in RDA	Temp (°C)	Yield (%)	*trans*/*cis*	ee (%)[c]	
						trans[d]	*cis*[e]
1	**2b**	Et	80	96	58/42	65	60
2	**2b**	Et	20	58	58/42	75	70
3	**2b**	Et	0	35	57/43	83	78
4	**2b**	*t*-Bu	80	88	72/28	83	55
5	**2b**	*t*-Bu	20	27	78/22	91	63
6	**2b**	*t*-Bu	0	6	79/21	93	64
7	**3b**	Et	80	95	54/46	78	56
8	**3b**	Et	0	56	50/50	82	67
9	**3b**	*t*-Bu	80	87	72/28	84	20
10	**3b**	*t*-Bu	20	11	77/23	93	23

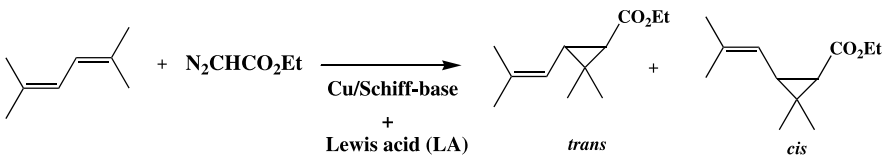
[a] Mol% of mononuclear complex based on RDA.
[b] Reaction conditions: 0.01 mmol of catalyst as the monomeric copper complex, 10 mmol of RDA, 70 mmol of DMHD, 5 mL of ethyl acetate.
[c] Determined by LC analysis (Chiral AGP (25 cm×4 mm ID, 5 μm film) ×2, UV 210 nm, 20 mM KH_2PO_4/CH_3CN=87/13 (v/v), 0.5 mL/min) in the case where $N_2CHCO_2^tBu$ was used.
[d] 1*R*,3*R* as a major enantiomer.
[e] 1*R*,3*S* as a major enantiomer.

A bulky group in the diazoacetate was reported to increase the enantioselectivity and *trans*/*cis* ratio.[5] When *t*-butyl diazoacetate was used, the enantiomeric excesses for the *trans* product reached 93% in the case of both catalysts **2b** and **3b** at 0 °C, although the yield was low. The *trans*/*cis* ratio was slightly better with **2b** than **3b**. The slow rate of the process and the low yield of the product could be dramatically improved by addition of a Lewis acid.

2.3. Effect of a Lewis acid on the selectivity

In order to achieve high yields and high enantioselectivities, addition of an equimolar amount of a Lewis acid was examined with 0.1 mol% catalyst **2b** at 0 or 20 °C. The results are shown in Table 4. It is noteworthy that addition of

Table 4. Asymmetric cyclopropanation of DMHD with EDA using the new catalyst system, consistent for the copper Schiff-base complex and various Lewis acids (LA)[a]



Entry	Cu-complex	LA	Temp (°C)	Yield (%)	*trans*/*cis*	ee (%) *trans*[b]	ee (%) *cis*[c]
1	**2b**	None	20	58	58/42	75	70
2	**2b**	None	0	35	57/43	83	78
3	**2b**	$HfCl_4$	20	84	58/42	76	71
4	**2b**	$B(C_6F_5)_4$	20	91	58/42	76	71
5	**2b**	$Al(OC_6F_5)_3$	20	91	58/42	72	68
6	**2b**	$Ti(O-^iPr)_4$	20	85	58/42	76	70
7	**2b**	$Al(OEt)_3$	20	95	58/42	77	71
8	**2b**	$Al(OEt)_3$	0	86	57/43	84	79
9	**3b**	None	0	56	50/50	82	67
10	**3b**	$Al(OEt)_3$	0	83	49/51	83	68

[a] Reaction conditions: 0.01 mmol of the copper Schiff-base complex as the monomeric copper complex, 0.01 mmol of Lewis acid, 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate.
[b] 1*R*,3*R* as a major enantiomer.
[c] 1*R*,3*S* as a major enantiomer.

Table 5. The effect of adding $Al(OEt)_3$ to the copper Schiff-base catalyst on the asymmetric cyclopropanation of DMHD with RDA[a]

Entry	Cu-complex	LA	R in RDA	Temp (°C)	Yield (%)	*trans*/*cis*	ee (%) *trans*[b]	ee (%) *cis*[c]
1	**2b**	None	*t*-Bu	20	27	78/22	91	63
2	**2b**	$Al(OEt)_3$	*t*-Bu	20	90	78/22	91	62
3	**3b**	None	*t*-Bu	20	11	77/23	93	23
4	**3b**	$Al(OEt)_3$	*t*-Bu	20	86	77/23	93	24

[a] Reaction conditions: 0.01 mmol of copper Schiff-base as the monomeric copper complex, 0.01 mmol of Lewis acid, 10 mmol of RDA, 70 mmol of DMHD, 5 mL of ethyl acetate.
[b] 1*R*,3*R* as a major enantiomer.
[c] 1*R*,3*S* as a major enantiomer.

a Lewis acid increased the reaction rate, and even at 20 °C a 95% yield was obtained in the presence of $Al(OEt)_3$ (77% ee, entries 7 vs. 1); the reaction proceeded smoothly at 0 °C to give 86% yield and 84% ee (entries 8 vs. 2). The combination of the copper complex **3b** with $Al(OEt)_3$ was also examined with EDA, and enhancement of the yield was observed (entries 9 vs. 10).

Furthermore, when *t*-butyl diazoacetate was used instead of ethyl diazoacetate, 91% yield and 91%ee for the *trans* product were obtained at 20 °C in the presence of 0.1 mol% of **2b** combined with $Al(OEt)_3$ (entries 1 vs. 2, in Table 5). The use of the catalyst composed of **3b** and $Al(OEt)_3$ also achieved 86% yield and 93% ee.

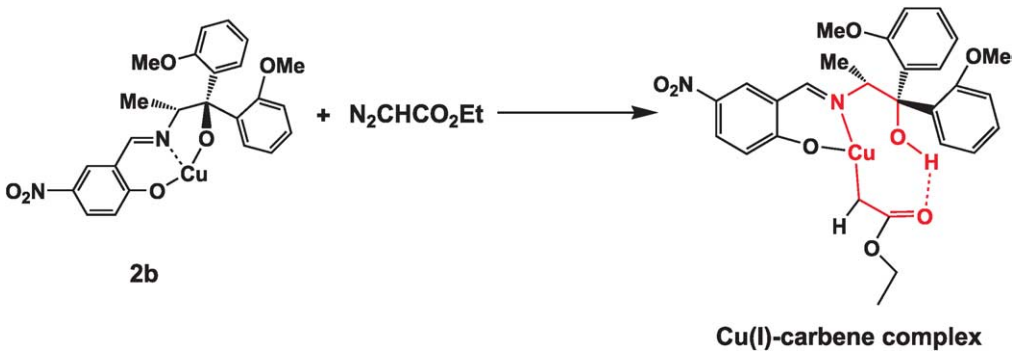
Aratani achieved more than 90% ee for the *trans* product with 1 mol% of a chiral [(*R*)-*N*-salicylidene-2-amino-1,1-di(2-*n*-octyloxy-5-*t*-butylphenyl)-1-propanol] copper complex as a catalyst in the asymmetric cyclopropanation of DMHD with *l*-menthyl diazoacetate, while more than 90% ee for the *trans* product was achieved using 2,6-*t*-butyl-4-methylphenyl diazocetate catalyzed by a copper-chiral-bisoxazoline complex.

To the best of our knowledge, the achievement of more than 90% ee is the first case of the asymmetric cyclopropanation of DMHD with *t*-butyl diazoacetate. It should be noted the *t*-butyl chrysanthemate formed is easy to hydrolyze to convert to chrysanthemic acid by an acid catalyst, which is a key intermediate for synthetic pyrethroids.

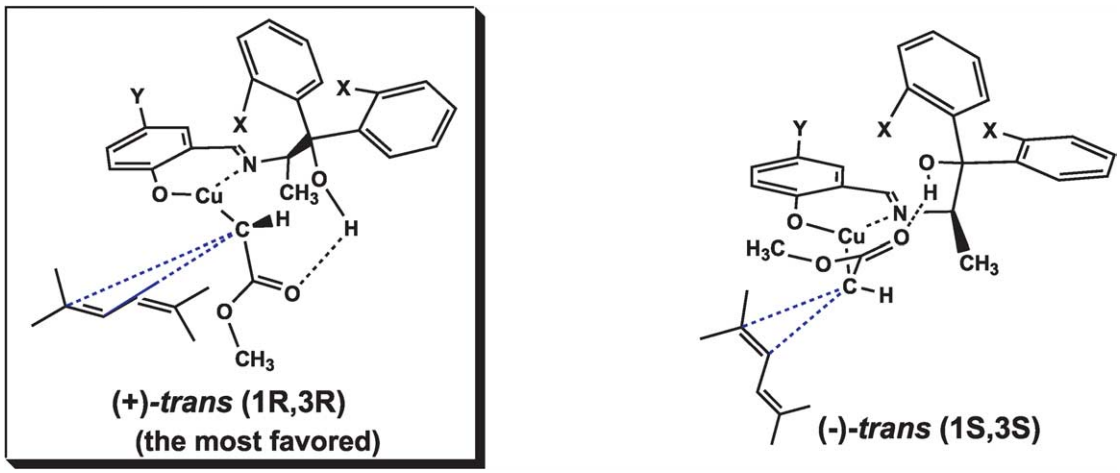
2.4. Study of the possible mechanism based on the calculations

In order to probe the possible mechanism of the asymmetric induction, hybrid density functional calculations were carried out. As the details of the calculation were reported elsewhere,[13] these calculations suggested that the catalytic key intermediate can be the copper(I) carbene complex bearing the intramolecular hydrogen bond between the hydrogen of the hydroxyl group and the carbonyl oxygen of the ester group in the case of catalyst **2b** as shown in Scheme 7.

The reaction proceeds by the [2+1] addition from DMHD to the carbene carbon of the Cu(I)–carbene complex. The enantioselectivity of the chrysanthemate calculated from the Boltzmann distribution of the nine transition states was qualitatively consistent with the experimental result that the (+)-*trans*(1*R*,3*R*) isomer is predominantly



Scheme 7. Structures of the copper(I) carbene complex from catalyst **2b**.



Scheme 8. Schematic representation of the possible orientation of DMHD, which approaches the carbene carbon of the Cu(I)–carbenoid complex for methyl chrysanthemate.

produced. Scheme 8 shows the most favorable transition state for the (+)-*trans*(1*R*,3*R*) isomer and the (−)-*trans*(1*S*,3*S*) isomer, respectively. The conformations of the 9-ring-members bearing the intramolecular hydrogen bond in the copper(I) carbene complex are different from each other, leading the formation of the enantio-isomer of the *trans* chrysanthemate. The *trans*/*cis* ratio should depend on the steric repulsion among the isobutenyl group of DMHD, the ester group on the Cu(I)–carbene complex, and a substituent X on the phenyl group.

The introduction of the electron-withdrawing substituents on the benzene ring of the salicylaldehyde moiety in the copper complex enhances the electrophilicity of the carbene carbon through the copper atom. This enhancement should bring about the high reactivity of the Cu(I)–carbene complex toward the diene.

2.5. Possible mechanism for effect of addition of Lewis acids

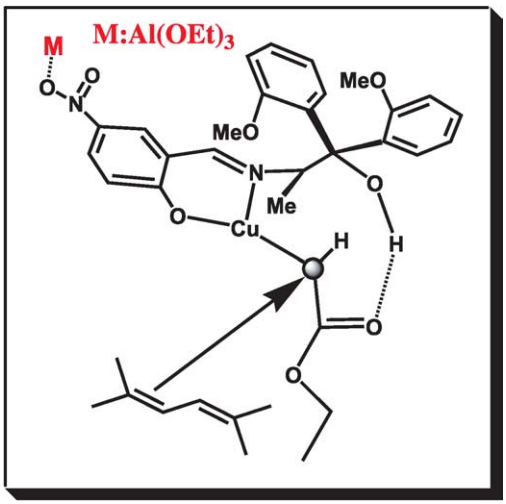
The effect of Lewis acids can also be explained based on the following experimental results in Table 6. Although the effect of $Al(OEt)_3$ is not observed in **2a** and **2h** (entries 1 vs 2, 9 vs. 10), remarkable enhancement of the yield of the product was observed at 0 °C in **2e** as well as **2b** (entries 3 vs. 4, 5 vs. 6). In the case of **2g**, a slight enhancement of the yield was observed (entries 7 vs. 8).

These results suggested that $Al(OEt)_3$ coordinates with the oxygen atom of the nitro group on the salicylaldehyde moiety in the copper carbene complex in the use of the complex **2b** and $Al(OEt)_3$, and that lowered the electron density on the carbene carbon of the carbene complex to enhance the reactivity toward DMHD as shown in Scheme 9.

Table 6. The effect of substituents at the 5-position on the salicylaldehyde group in copper Schiff-base **2** with $Al(OEt)_3$ as the catalyst on the asymmetric cyclopropanation of DMHD with EDA[a]

Entry	Cu-complex	Lewis acid	Yield (%)	*trans*/*cis*	ee (%) *trans*[b]	ee (%) *cis*[c]
1	**2a**	None	5	60/40	38	36
2	**2a**	$Al(OEt)_3$	6	60/40	36	35
3	**2b**	None	35	57/43	83	78
4	**2b**	$Al(OEt)_3$	86	57/43	84	79
5	**2e**	None	35	57/43	84	81
6	**2e**	$Al(OEt)_3$	72	57/43	83	76
7	**2g**	None	29	58/42	84	79
8	**2g**	$Al(OEt)_3$	37	57/43	85	80
9	**2h**	None	32	58/42	84	78
10	**2h**	$Al(OEt)_3$	33	58/42	85	80

[a] Reaction conditions: 0.01 mmol of copper Schiff-base as the monomeric copper complex, 0.01 mmol of $Al(OEt)_3$, 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate, 0 °C, 3h.
[b] 1*R*,3*R* as a major enantiomer.
[c] 1*R*,3*S* as a major enantiomer.



Scheme 9. Tentative scheme for the addition to the copper complex **2b**.

3. Conclusions

New copper Schiff-base complexes derived from substituted salicylaldehydes bearing an electron-withdrawing group at the 5-position were found to be highly efficient for asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with diazoacetate. These compounds demonstrated much more remarkable enhancement of the turnover number than the copper catalyst derived from the salicylaldehyde. In addition, we found that high yield and high enantioselectivity with highly catalytic efficiency using *t*-butyl diazoacetate was achieved by addition of a Lewis acid such as $Al(OEt)_3$. The products were easily converted to chrysanthemic acid.

4. Experimental

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere. Optical rotations were measured on a JASCO DIP-370. Melting points were measured with a METTLER TOLEDO TYPE FP62. NMR spectra were recorded by a Bruker DPX-300NMR spectrometer with trimethyl silane as an internal standard (δ value in $CDCl_3$). The yields and ee values were determined by GC analyses with a capillary column and LC analyses with a chiral column in the cyclopropanation, respectively.

4.1. Aminoalcohol

4.1.1. (*R*)-2-Amino-1,1-diphenyl-1-propanol. The methyl ester hydrochloride of *D*-alanine (7.0 g, 50.1 mmol) was added to a cooled Grignard solution derived from bromobenzene (41.6 g, 265 mmol) and magnesium (6.7 g, 276 mmol) in THF at 0 °C. The mixture was stirred for 3 h at room temperature and then added to cooled 2% hydrochloric acid (200 mL) at 0 °C. 150 mL of toluene was added to the mixture, and the aqueous phase was separated. The aqueous solution was neutralized with ammonium hydroxide, and 150 mL of toluene was added to the mixture. The organic phase was separated, washed with saturated brine, dried, and concentrated. The pale yellow solid was obtained, recrystallized from CH_2Cl_2-*n*-hexane and gave the product as a white solid (8.1 g, 71%). $[\alpha]_D$=87.2 (*c*=1, $CHCl_3$); mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 7.63 (d, *J*=1.7 Hz, 2H), 7.60 (d, *J*=1.3 Hz, 2H), 7.50–7.12 (m, 6H), 4.14 (q, *J*=6.4 Hz, 1H), 0.94 (d, *J*=6.6 Hz, 3H).

4.1.2. (*R*)-2-Amino-1,1-di(2-methoxyphenyl)-1-propanol. Yield 75%, white solid; $[\alpha]_D$=35.5 (*c*=1, $CHCl_3$); mp 89–90 °C; ^1H NMR ($CDCl_3$) δ 7,66 (d, *J*=1.3 Hz, 2H), 7.19–6.73 (m, 6H), 5.31 (s, 1H), 4.33 (q, *J*=6.5 Hz, 1H), 3.58 (s, 3H), 3.52 (s, 3H), 1.01 (d, *J*=6.6 Hz, 3H).

4.1.3. (*R*)-Amino-1,1-di(2-*n*-butoxy-5-*t*-butylphenyl)-1-propanol. Purified by column chromatography (SiO_2, *n*-hexane/AcOEt=10/1→MeOH). Yield 55%, pale yellow viscous oil; $[\alpha]_D$=35.3 (*c*=1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.70 (s, 2H), 7.24–7.12 (m, 2H), 6.73–6.64 (m, 2H), 5.24 (s, 1H), 4.27 (q, *J*=6.5 Hz, 1H), 3.81–3.67 (m, 4H), 1.59–1.43 (m, 6H), 1.38–1.23 (m, 2H), 1.34 (s, 9H), 1.33 (s, 9H), 1.03 (d, *J*=6.3 Hz, 3H), 0.89 (t, *J*=7.3 Hz, 6H).

4.2. The Schiff bases. General procedure for 4a, 5a, and 6a

4.2.1. (*R*)-(*N*-Salicylidene)-2-amino-1,1-diphenyl-1-propanol 4a. (*R*)-2-Amino-1,1-diphenyl-1-propanol (5.00 g, 22.0 mmol) and salicylaldehyde (2.69 g, 22.0 mmol) were dissolved in toluene (30 mL), and the mixture was refluxed for 1 h. Methanol was removed under vacuum and the residue was purified by column chromatography (SiO_2, *n*-hexane:ethyl acetate=1:1) to afford the pure Schiff base **4a** (7.09 g, 97%) as yellow solid. $[\alpha]_D$=−36.8 (*c*=1, $CHCl_3$); mp 112–113 °C; ^1H NMR ($CDCl_3$) δ 12.63 (s, 1H), 8.37 (s, 1H), 7.56–7.48 (m, 4H), 7.35–7.15 (m, 8H), 6.89–6.81 (m, 2H), 4.57 (q, *J*=6.5 Hz, 1H), 2.67 (s, 1H), 1.25 (d, *J*=6.6 Hz, 3H).

Compound **5a**. Yield 96%, yellow solid; $[\alpha]_D$=−166 (*c*=1, $CHCl_3$); mp 141–142 °C; ^1H NMR ($CDCl_3$) δ 13.91 (s, 1H), 8.29 (s, 1H), 7.72–7.61 (m, 2H), 7.26–6.72 (m, 10H), 5.37 (s, 1H), 5.06 (q, *J*=6.4 Hz, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 1.33 (d, *J*=6.6 Hz, 3H).

Compound **6a**. Yield 95%, yellow viscous oil; $[\alpha]_D$=−135 (*c*=1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.69–7.66 (m, 2H), 7.21–6.61 (m, 7H), 5.21 (s, 1H), 4.84(q, *J*=6.4 Hz, 1H), 3.78–3.61 (m, 4H), 1.51–1.18 (m, 8H), 1.41 (d, *J*=6.5 Hz, 3H), 1.34 (s, 9H), 1.20 (s, 9H), 0.86 (t, *J*=7.3 Hz, 6H).

4.3. General procedure for 4b, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j, and 6b

4.3.1. (*R*)-(*N*-5-Nitrosalicylidene)-2-amino-1,1-diphenyl-1-propanol 4b. (*R*)-2-Amino-1,1-diphenyl-1-propanol (2.00 g, 8.80 mmol) and 5-nitrosalicylaldehyde (1.47 g, 8.80 mmol) were dissolved in toluene (20 mL) and the mixture was refluxed for 1 h. The reaction mixture was then cooled to room temperature, and the precipitated Schiff-base was filtered and washed with heptane/toluene (=2/1 (v/v)) to yield the pure Schiff base **4b** (3.22 g, 97%) as a yellow solid. [Anal. Found: C, 70.1%; H, 5.4%; N, 7.4%. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.21%; H, 5.32%; N, 7.45%];

$[\alpha]_D$=−85.0 (c=1, $CHCl_3$); mp 208–209 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 8.15–8.12 (m, 2H), 7.54–7.20 (m, 10H), 6.89–6.82 (m, 1H), 4.65 (q, J=6.6 Hz, 1H), 2.61 (s, 1H), 1.29 (d, J=6.6 Hz, 3H).

Compound **5b**. Yield 95%, yellow solid; [Anal. Found: C, 68.1%; H, 5.8%; N, 5.6%. Calcd for $C_{22}H_{20}N_2O_4{\cdot}0.5C_7H_8$: C, 68.45%; H, 5.85%; N, 5.85%]; $[\alpha]_D$=−131 (c=1, $CHCl_3$); mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 8.10–8.03 (m, 3H), 7.67–7.52 (m, 2H), 7.27–6.65 (m, 8H), 5.66 (s, 1H), 5.26 (q, J=6.5 Hz, 1H), 3.62 (s, 6H), 1.41 (d, J=6.6 Hz, 3H).

Compound **5c**. Yield 91%, yellow solid; [Anal. Found: C, 68.2%; H, 5.8%; N, 5.6%. Calcd for $C_{22}H_{20}N_2O_4{\cdot}0.5C_7H_8$: C, 68.45%; H, 5.85%; N, 5.85%]; $[\alpha]_D$=−389 (c=1, $CHCl_3$); mp 132–135 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.72–7.61 (m, 2H), 7.23–6.69 (m, 9H), 5.33 (s, 1H), 5.03 (q, J=6.5 Hz, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 2.23 (s, 3H), 1.31 (d, J=6.5 Hz, 3H).

Compound **5d**. Yield 96%, yellow solid; [Anal. Found: C, 62.3%; H, 5.1%; N, 7.8%. Calcd for $C_{24}H_{23}N_3O_8{\cdot}0.5C_7H_8$: C, 62.61%; H, 5.16%; N, 7.97%]; $[\alpha]_D$=−242 (c=1, $CHCl_3$); mp 144–147 °C; ^{1}H NMR ($CDCl_3$) δ 8.92 (d, J=3.0 Hz, 1H), 8.30 (d, J=3.1 Hz, 1H), 8.25–8.21 (m, 1H), 7.63 (d, J=7.8 Hz, 1H), 7.50 (d, J=7.9 Hz, 1H), 7.29–6.78 (m, 6H), 5.81 (s, 1H), 5.41(bs, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 1.41 (t, J=6.6 Hz, 3H).

Compound **5e**. Yield 94%, yellow solid; [Anal. Found: C, 71.2%; H, 6.2%; N, 2.6%. Calcd for $C_{26}H_{27}NO_6{\cdot}0.5C_7H_8$: C, 71.50%; H, 6.31%; N, 2.83%]; $[\alpha]_D$=−122 (c=1, $CHCl_3$); mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J=4.5 Hz, 1H), 7.86 (s, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.59 (d, J=7.8 Hz, 1H), 7.28–6.72 (m, 7H), 5.53 (s, 1H), 5.35 (bs, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 1.36 (t, J=6.6 Hz, 3H).

Compound **5f**. Yield 93%, yellow solid; [Anal. Found: C, 69.1%; H, 6.0%; N, 2.9%. Calcd for $C_{26}H_{27}NO_6$: C, 69.47%; H, 6.06%; N, 3.12%]; $[\alpha]_D$=−235 (c=1, $CHCl_3$); mp 135–138 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.26–6.62 (m, 7H), 5.44 (s, 1H), 5.10 (bs, 1H), 3.89 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 1.33 (t, J=6.6 Hz, 3H).

Compound **5g**. Yield 62%, yellow solid; [Anal. Found: C, 73.4%; H, 6.1%; N, 5.9%. Calcd for $C_{25}H_{24}N_2O_4{\cdot}0.5C_7H_8$: C, 74.00%; H, 6.11%; N, 6.06%]; $[\alpha]_D$=−142 (c=1, $CHCl_3$); mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.67 (d, J=7.8 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.38–6.74 (m, 8H), 5.57 (s, 1H), 5.21 (q, J=6.6 Hz, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 1.37 (t, J=6.6 Hz, 3H).

Compound **5h**. Yield 94%, yellow solid; [Anal. Found: C, 67.3%; H, 5.6%; N, 2.6%. Calcd for $C_{25}F_3H_{24}NO_4{\cdot}0.5C_7H_8$: C, 67.71%; H, 5.59%; N, 2.77%]; $[\alpha]_D$=−103 (c=1, $CHCl_3$); mp 108–110 °C, ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.42–6.72 (m, 8H), 5.47 (s, 1H), 5.16 (q, J=6.3 Hz, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 1.34 (t, J=6.6 Hz, 3H).

Compound **5i**. Yield 97%, yellow solid; [Anal. Found: C, 72.0%; H, 6.2%; N, 2.9%. Calcd for $C_{24}FH_{24}NO_4{\cdot}0.5C_7H_8$: C, 72.51%; H, 6.20%; N, 3.08%]; $[\alpha]_D$=−105 (c=1, $CHCl_3$); mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.25–6.70 (m, 8H), 5.42 (s, 1H), 5.09 (q, J=6.5 Hz, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 1.29 (t, J=6.5 Hz, 3H).

Compound **5j**. Yield 78%, yellow solid; [Anal. Found: C, 70.1%; H, 6.0%; N, 3.4%. Calcd for $C_{24}FH_{24}NO_4$: C, 70.40%; H, 5.91%; N, 3.42%]; $[\alpha]_D$=−168 (c=1, $CHCl_3$); mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.25–6.71 (m, 7H), 6.51–6.45 (m, 1H), 5.49 (s, 1H), 5.13 (q, J=6.5 Hz, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 1.34 (t, J=6.6 Hz, 3H).

Compound **6b**. Yield 95%, yellow solid; [Anal. Found: C, 72.2%; H, 8.1%; N, 4.6%. Calcd for $C_{38}H_{52}N_2O_6$: C, 72.15%; H, 8.23%; N, 4.43%]; $[\alpha]_D$=−153 (c=1, $CHCl_3$); m.p. 67–69 °C; ^{1}H NMR ($CDCl_3$) δ 8.05–7.98 (m, 2H), 7.84 (s, 1H), 7.61 (s, 1H), 7.55 (m, 1H), 7.25–7.21 (m, 1H), 7.25–7.21 (m, 1H), 7.12–7.08 (m, 1H), 6.76–6.64 (m, 3H), 5.49 (s, 1H), 5.08 (m, 1H), 3.84–3.72 (m, 4H), 1.53–1.46 (m, 7H), 1.35 (s, 9H), 1.33–1.26 (m, 4H), 1.16 (s, 9H), 0.93–0.87 (m, 6H).

4.4. The copper complex

General procedure. 4.90 g (11.2 mmol) of the Schiff-base **2b** was dissolved in 250 g of ethyl acetate, and 2.24 g (11.2 mmol) of copper acetate monohydrate was added to the above solution. The mixture was refluxed for 1 h, and aqueous sodium hydroxide was then added and further stirred for 30 min at room temperature. The organic layer was separated, washed with water, dried, concentrated in vacuo, and 5.47 g of the copper Schiff-base complex was obtained as a deep green solid. Yield 98%. The copper complex was used without further purification. [LC-MS (positive mode); m/z=997]; $[\alpha]_D$=546 (c=0.1%, $CHCl_3$); mp 160–163 °C (dec.).

4.5. Cyclopropanation

Under a nitrogen atmosphere, 4.96 mg (0.010 mmol) of the copper complex **2b** was dissolved in 5 mL of ethyl acetate, and 7.71 g (70.0 mmol) of 2,5-dimethyl-2,4-hexadiene was added to the solution. 1 μL (0.01 mmol) of phenylhydrazine was added by a microsyringe and the temperature of the reaction mixture was then raised to 80 °C. 8 mL of a solution of ethyl diazoacetate (1.14 g, 10 mmol) in ethyl acetate was added dropwise over 2 h using a syringe pump at 80 °C. After further stirring for 30 min at 80 °C, the reaction mixture was analyzed by GC (DB-1, 30 m×0.25 mm ID, 0.25 mm film, column temp. 100 °C–10 min to 250 °C) using the internal method with *n*-decane as a standard for determining the yield and *trans*/*cis* ratio, and LC Sumichiral OA-2500 (25 cm×4 mm ID, 5 μm film)×2, UV 220 nm hexane 0.7 mL/min) for determining the enantioselectivity. Products were determined by comparison of the LC elution order of the enantiomers with authentic samples.

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