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Practical Copper-Catalyzed Asymmetric Synthesis of Chiral Chrysanthemic Acid Esters

Makoto Itagaki*,† and Katsuhiro Suenobu‡

Organic Synthesis Research Laboratory, Sumitomo Chemical Co., Ltd., 3-1-98, Kasugade-naka, Konohana-ku, Osaka 554-8558, Japan, and Tsukuba Research Laboratory, Sumitomo Chemical Co., Ltd., 6, Kitahara, Tsukuba, Ibaraki 300-3294, Japan

Abstract:

Practical copper salicylaldimine complex catalysts have been developed for the asymmetric synthesis of chiral chrysanthemic acid esters by the cyclopropanation reaction of 2,5-dimethyl-2,4-hexadiene with *tert*-butyl diazoacetate. First, the effects of the substituents on the salicylaldehyde moiety in the copper salicylaldimine complex (copper Schiff base complex) on the catalytic activity and the stereoselectivities were investigated. As a result, a substitution of hydrogen at the 5-position with the nitro group on the salicylaldehyde moiety was found to enhance the catalytic efficiency. In addtition, a combination catalyst of the copper Schiff base complex with Lewis acid was found to also enhance the catalytic efficiency and achieved 90% chemical yield and 91% ee at 20 °C with 0.1 mol % catalyst loading. Furthermore, the asymmetric induction mechanism of the cyclopropanation reaction catalyzed by the copper Schiff base complex was studied using density functional calculations.

1. Introduction

It is well-known that optically pure cyclopropane carboxylates show biological activities as intermediates for insecticides or pharmaceuticals.[1−4] Synthetic pyrethroids have long been the most favored insecticides because of their high efficacy against insect pests and their low mammalian and environmental toxicities. Shown in Figure 1 are some examples of synthetic pyrethroids for household use containing the chiral 3-(1-isobutenyl)-2,2-dimethylcyclopropanecarboxylic acid ((+)-*trans*-chrysanthemic acid) as the acid moiety. Chrysanthemic acid has two chiral centers. Therefore, there are four stereoisomers of chrysanthemic acid, and the ester of the (+)-*trans* isomer generally shows the highest insecticidal activity followed by the (+)-*cis* isomer, whereas the (−)-*trans* and (−)-*cis* isomers are almost ineffective as shown in Figure 2.[5]

The catalytic asymmetric cyclopropanation of alkenes with diazoacetate is a powerful tool for the synthesis of chiral cyclopropyl esters such as chrysanthemic acid esters. Aratani's group first achieved a high ee (94%) and *trans*/*cis* ratio (93/7) for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) with *l*-menthyl diazoacetate to give the chrysanthemate catalyzed by a chiral copper salicylaldimine complex (R-1648 shown in Scheme 1), and Aratani's asymmetric process has led to the successful industrial application for the synthesis of chiral 2,2-dimethylcyclopro-

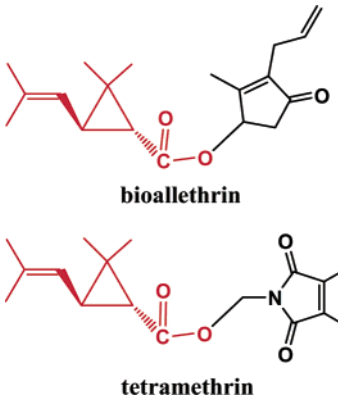

Figure 1. **Examples of synthetic pyrethroids containing chrysanthemate moiety.**

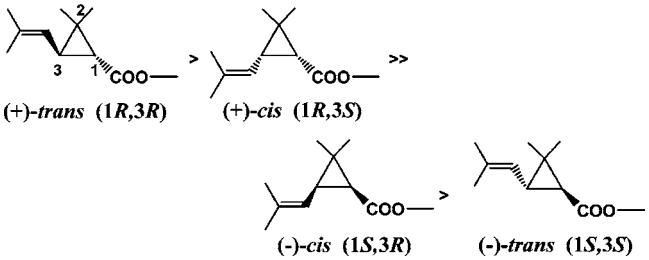

Figure 2. **A comparison of the insecticidal activity among the four isomers of the chrysanthemate moiety.**

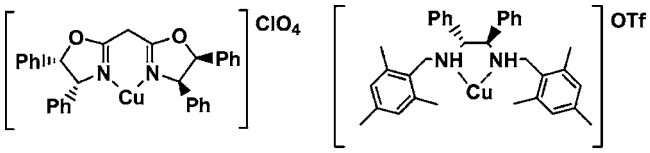

Figure 3. **Effective catalysts for the cyclopropanation of DMHD other than the R-1648 catalyst.**

* Corresponding author. Fax: +81-6-6466-5427. E-mail: itagakim@sc.sumitomo-chem.co.jp.
† Organic Synthesis Research Laboratory, Sumitomo Chemical Co.
‡ Tsukuba Research Laboratory, Sumitomo Chemical Co.

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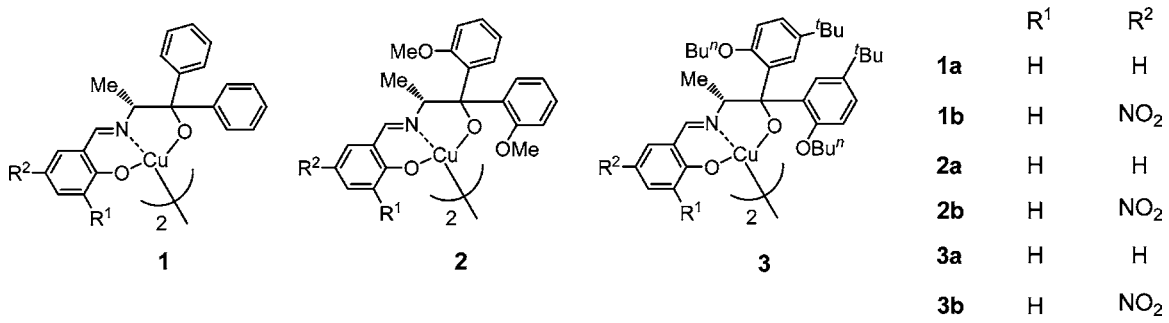
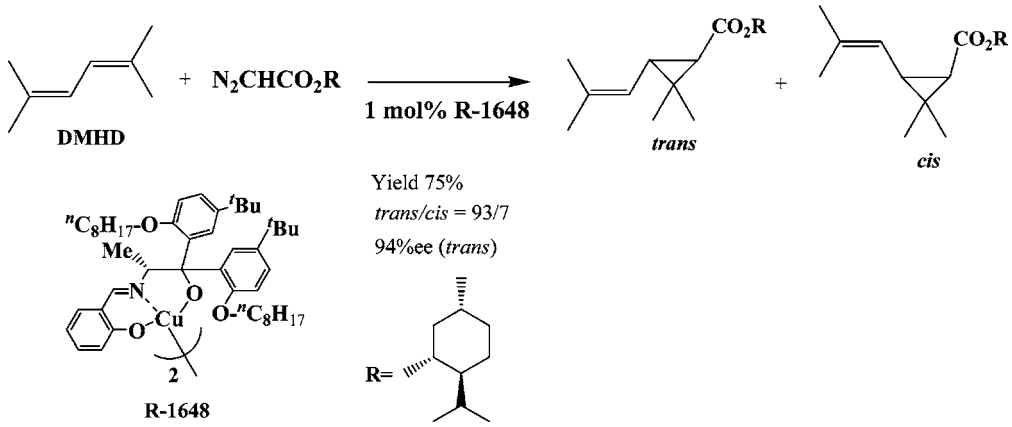


Figure 4. **Structures of the copper Schiff base catalysts 1a and b, 2a and b, 3a and b.**

Scheme 1. **Structure of Aratani's catalyst R-1648 and the results of the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate**



pane carboxylic acid, by the asymmetric cyclopropanation of isobutene with ethyl diazoacetate.[4−7]

After Aratani's successful reports, many kinds of catalysts for the asymmetric cyclopropanation were demonstrated.[1−3,8] However, most of the alkenes used in the reports were styrene and its derivertives. At the present time, to the best of our knowledge, only a few reports have described the successful asymmetric cyclopropanation of DMHD. Shown in Figure 3 are the two highly effective catalysts for the asymmetric cyclopropanation of DMHD, aside from Aratani's catalyst.

These are the copper bisoxazoline catalyst by Masamune[9] and the copper diamine catalyst by Kanemasa.[10] In all these catalyst systems, high stereoselectivities can be achieved using diazoacetates containing a bulky group as the ester moiety such as *l*-menthyl diazoacetate or dicyclohexyl diazoacetate with 1 mol % catalyst. However, these systems are not industrially applicable, because the diazoacetates are too expensive for industrial use and difficult to hydrolyze into chrysanthemic acid from the corresponding chrysanthemic acid ester. Meanwhile, Scott et al. reported the asymmetric cyclopropanation of DMHD using the useful *tert*-butyl diazoacetate catalyzed by the copper complexes with biaryl Schiff base ligands, but the *trans* selectivity and the enantioselectivity were moderate (*trans*/*cis* = 75/25, 72% ee for *trans* isomer).[11] In addition, in the case of these chiral catalysts, 1 mol % catalyst loading was too high and would be expensive for the production of chrysanthemic acid.

Therefore, we have developed highly efficient catalysts for the cyclopropanation of DMHD using a simple alkyl diazoacetate such as ethyl or *tert*-butyl diazoacetate, which means that the formed chrysanthemate would be easy to convert into the chiral chrysanthemic acid as the intermediate for pyrethroid insecticides. As a result, we recently found two practical chiral catalysts using *tert*-butyl diazoacetate to achieve >90% ee.[12−14]

In this paper, we describe several issues concerning our development of such new catalysts for the cyclopropanation of DMHD in our laboratory. First, we present the development of new copper salicylaldimine complex catalysts (copper Schiff base complex catalysts) derived from the 5-substituted salicylaldehyde with an electron-withdrawing group. Some of these catalysts compared to unsubstituted catalysts achieved a higher reactivity and enantioselectivity.[12] Then, we present density functional studies to understand the asymmetric induction mechanism when using these catalysts.[15] Finally, we show that the combination of such copper Schiff base complexes with a Lewis acid further

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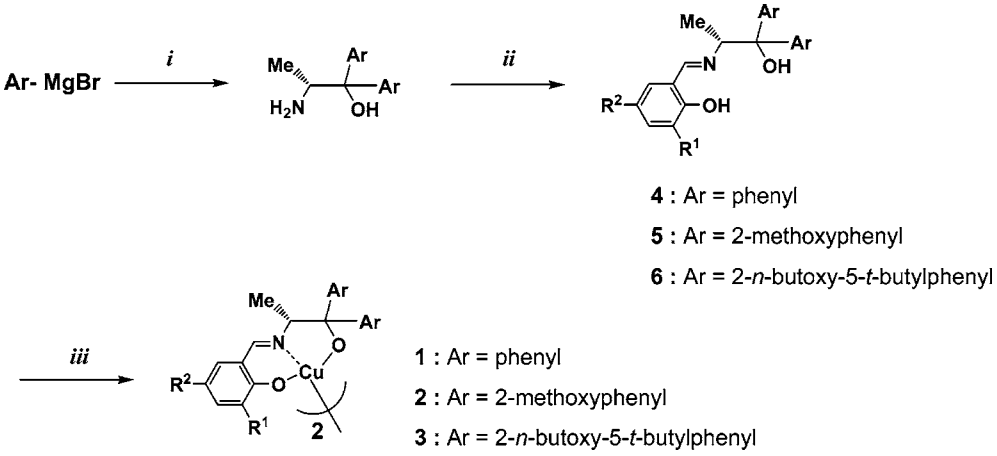
Scheme 2. **Synthesis of copper Schiff base complexes 1−3**[a]



[a] (i) D-Alanine methyl ester hydrochloride in THF, 0 °C, 3 h, then H_3O^+, followed by NH_4OH, 55−75%, (ii) substituted salicylaldehyde in toluene, reflux 1 h, 62−97%; (iii) copper acetate monohydrate in AcOEt, reflux, 1 h, then NaOH−H_2O, 95−98%.

Table 1. **Asymmetric cyclopropanation DMHD with ethyl diazoacetate (EDA)**[a]

					ee[e] (%)	
entry	catalyst	mol %[b]	yield[c] (%)	*trans*/*cis*[d]	*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, 0.01 mmol of the copper complex as the monomeric complex, and 0.01 mmol of phenylhydrazine, 80 °C, 2 h. [b] Mol % of the mononuclear complex based on EDA. [c] Based on EDA and determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C) with *n*-decane as the 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.

enhances the reactivity and enantioselectivity, i.e., 90% yield and more than 90% ee when using *tert*-butyl diazoacetate at 20 °C with 0.1 mol % catalyst loading.[12]

2. Results and Discussion

2.1. Effects of Substituents of Aminoalcohol Framework and Salicylaldehyde Framework on the Stereoselectivity and the Catalytic Efficiency. Copper Schiff base complexes **1**−**3** shown in Figure 4 were synthesized from chiral aminoalcohols, salicylaldehyde derivatives, and copper(II) acetate hydrate (Scheme 2) in order to examine effects of the 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.

As described in Aratani's report, phenylhydrazine was used to convert the binuclear copper complex into the mononuclear copper complex that is considered to be the active form for the cyclopropanation.[4] In the order of **1a**, **2a**, and **3a**, the enantioselectivity of the *trans* product was enhanced, while the *trans*/*cis* ratio of the product was reduced in the presence of a 0.5 mol % catalyst loading (entries 1, 5, 9). The results are consistent with those of Aratani,[4] although the presence of a nitro group on the salicylaldehyde framework did not show a remarkable difference with the 0.5 mol % catalyst (entries 3, 7, 11). Meanwhile, all cases with the 0.1 mol % catalysts **1a**, **2a**, and **3a** decreased not only in the yields but also in enantioselectivity, compared to those with the 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 the 0.1 mol% catalysts **1b**, **2b**, and **3b** as those with the 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 the catalytic activity faster than those derived from 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 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 3.

Therefore, in order to interrupt the attack of the diazoacetate on the copper−oxygen bond (Cu−O−Aryl), a methyl or *tert*-butyl group was introduced at the 3-position on the benzene ring in the salicylaldehyde moiety of the copper complex **2**. However, no enhancements of the chemical yield and stereoselectivities (*trans*/*cis* ratio and ee) were observed. Subsequently, several Schiff bases with various electron-withdrawing substituents on the salicylaldehyde framework in the copper complex **2** were examined (Figure 5). We found that the 5-substituted copper complexes with an electron-withdrawing group were more effective for the enantioselectivity than the 3-substituted ones, except for the fluorine substituted complex **2j** as shown in Table 2.

A comparison of the turnover numbers between **2a** and **2b** is shown in Figure 6. A remarkable decrease in both the yield and ee was observed with the higher turnover numbers

Scheme 3. **Structure of the used catalyst 2a after the cyclopropanation**

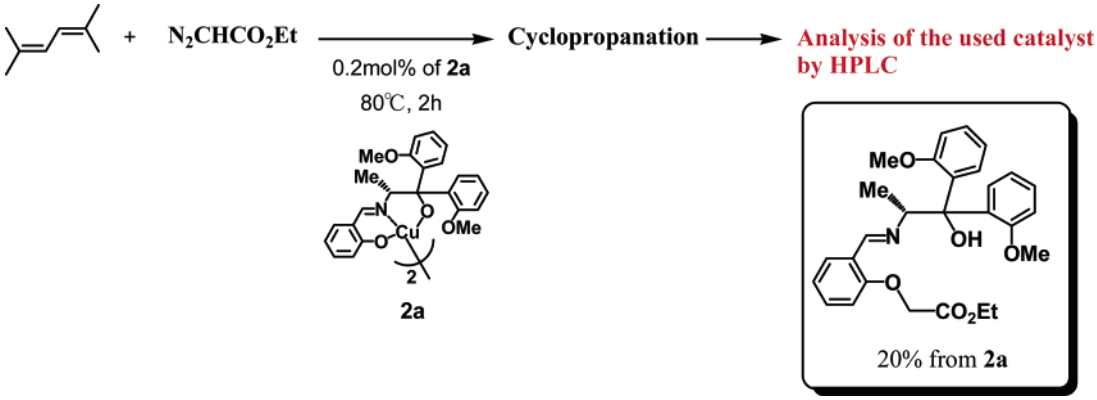
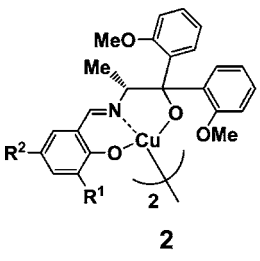


Table 2. **Asymmetric cyclopropanation of DMHD with EDA using 2 as the catalyst**[a]

					ee[e] (%)	
entry	catalyst	mol %[b]	yield[c] (%)	*trans*/*cis*[d]	*trans*[f]	*cis*[g]
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, 0.01 mmol of the copper complex as the monomeric complex, and 0.01 mmol of phenylhydrazine, 80 °C, 2 h. [b] Mol % of the mononuclear complex based on EDA. [c] Based on EDA and determined by GC analysis analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C) with *n*-decane as the 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.

for **2a**, while, in the case of catalyst **2b**, the degree of decrease in the yield and the ee is much lower than that by **2a**. These results suggested that the copper Schiff base catalyst **2b** derived from the 5-substituted salicylaldehyde with an electron-withdrawing group becomes more efficient than the unsubstituted copper complex **2a** on the salicylaldehyde moiety for the asymmetric cyclopropanation of DMHD.



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

Figure 5. **Structures of the copper catalysts 2a−j.**

2.2. Effect of Temperatures on the Selectivity. At lower reaction temperatures, higher enantiomeric excesses of the product were obtained, but the yield of the product was lowered with catalyst **2b** or **3b**, as shown in Table 3.

A bulky group in the diazoacetate was reported to increase the enantioselectivity and *trans*/*cis* ratio.[4,7] When *tert*-butyl diazoacetate was used, the enantiomeric excesses for the *trans* product reached 91% and 93% for both catalysts **2b** and **3b** at 20 °C, respectively, 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 the addition of a Lewis acid.

2.3. Effect of a Lewis Acid on the Selectivities. In order to achieve a high yield and a high enantioselectivity, the addition of an equimolar amount of a Lewis acid was examined with 0.1 mol % catalyst **2b** at 0 °C or 20 °C. The results are shown in Table 4. It is noteworthy that the addition of a Lewis acid increased the reaction rate, and even at 20 °C, 95% yield was obtained in the presence of $Al(OEt)_3$ (77%

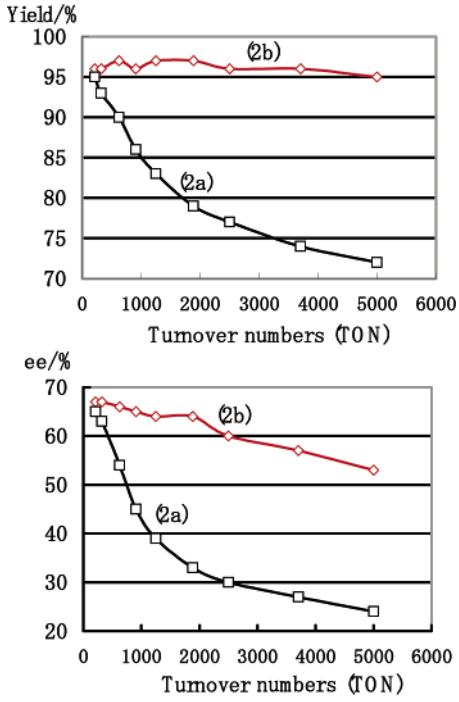


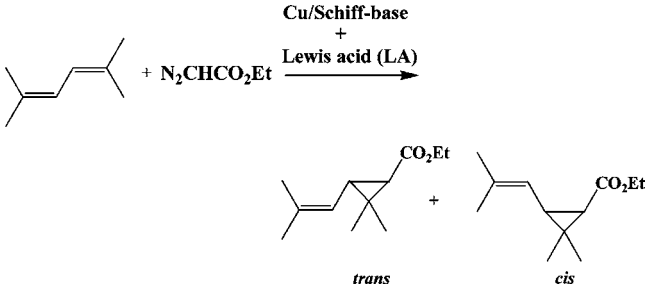
Figure 6. **Comparison of catalytic efficiency between 2a and 2b at 80 °C.**

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

entry	catalyst	R in RDA	*T* (°C)	yield[c] (%)	*trans*/*cis*[d]	ee[e] (%) *trans*[f]	ee[e] (%) *cis*[g]
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	3
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 monomeric complex based on RDA. [b] Reaction conditions: 0.01 mmol of the catalyst as the monomeric compelx, 0.01 mmol of phenylhydradine, 5 mL of ethyl acetate, 10 mmol of RDA, and 70 mmol of DMHD. [c] Based on RDA and determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C) with *n*-decane as the 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) when N_2CHCO_2Et was used. [e] Determined by GC analysis (DB-210, 30 m × 0.25 mm ID, 0.25 mm film, column temp 115 °C) after transformation into *l*-menthyl chrysanthemate when $N_2CHCO_2{}^tBu$ was used. [f] 1*R*,3*R* as the major enantiomer. [g] 1*R*,3*S* as the major enantiomer.

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



entry	Cu complex	LA	*T* (°C)	yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*[e]	ee[d] (%) *cis*[f]
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**	$Ti(O\text{-}^iPr)_4$	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 complex as the monomeric copper complex, 0.01 mmol of phenylhydradine, 0.01 mmol of Lewis acid, 10 mmol of EDA, 70 mmol of DMHD, and 5 mL of ethyl acetate. [b] Based on EDA and determined by GC analysis analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C) with *n*-decane as the internal standard. [c] Determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C). [d] 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). [e] 1*R*,3*R* as the major enantiomer. [f] 1*R*,3*S* as the major enantiomer.

ee, entry 7 vs 1); the reaction smoothly proceeded at 0 °C to produce 86% yield and 84% ee (entry 8 vs 2). The combination of the copper complex **3b** with $Al(OEt)_3$ was also examined with EDA, and an enhancement in the yield was observed (entry 9 vs 10).

Table 5. **Effect of adding $Al(OEt)_3$ to the copper Schiff base catalyst on the asymmetric cyclopropanation of DMHD with $N_2CHCO_2{}^tBu$[a] (DATB)**

entry	Cu complex	Lewis acid	*T* (°C)	yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*[e]	ee[d] (%) *cis*[f]
1	**2b**	none	20	27	78/22	91	63
2	**2b**	$Al(OEt)_3$	20	90	78/22	91	62
3	**3b**	none	20	11	77/23	93	23
4	**3b**	Al(OEt)	20	86	77/23	93	24

[a] Reaction conditions: 0.01 mmol of the copper complex as the monomeric complex, 0.01 mol of Lewis acid, 10 mmol of DATB, 70 mmol of DMHD, and 5 mL of ethyl acetate. [b] Based on TBDA and determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C) with *n*-decane as the internal standard. [c] Determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C). [d] Determined by GC analysis (DB-210, 30 m × 0.25 mm ID, 0.25 mm film, column temp 115 °C) after transformation into *l*-menthyl chrysanthemate when $N_2CHCO_2{}^tBu$ was used. [e] 1*R*,3*R* as the major enantiomer. [f] 1*R*,3*S* as the major enantiomer.

Furthermore, when *tert*-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 $Al(OEt)_3$ (entry 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 a higher than 90% ee for the *trans* product with 1 mol % of the chiral [(*R*)-*N*-salicylidene-2-amino-1,1-di(2-*n*-octyloxy-5-*tert*-butylphenyl)-1-propanol] copper complex (R-1648) as the catalyst in the asymmetric cyclopropanation of DMHD with *l*-menthyl diazoacetate, while Masamune reported higher than 90% ee for the *trans* product with 1 mol % of the chiral copper−bisoxazoline complex using 2,6-*tert*-butyl-4-methylphenyl diazocetate.

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

2.4. Study of the Possible Mechanism Based on Density Functional Calculations. Aratani proposed that the original copper(II) Schiff base complexes have a dimer structure and that the catalytically active species is likely to be a monomeric copper(I) complex as shown in Figure 7.[4] This copper(I) complex can be prepared in situ by addition of phenylhydrazine. The diazo compound then reacts with the copper(I) complex to give a copper(I)−carbene complex, which introduces the cyclopropane product via a metallacyclobutane intermediate as shown in Figure 7. In order to probe the possible mechanism of the asymmetric induction catalyzed by the copper Schiff base complex, hybrid density functional calculations were carried out using simplified models.[15,16]

(16) Theoretical studies for the copper-catalyzed cyclopropanation with C_2-symmetric ligands were also reported by other research groups. (a) Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616−7625. (b) Rasmusen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O. *Chem.—Eur. J.* **2002**, *8*, 177−184. (c) Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Chem.—Eur. J.* **2004**, *10*, 758−765.

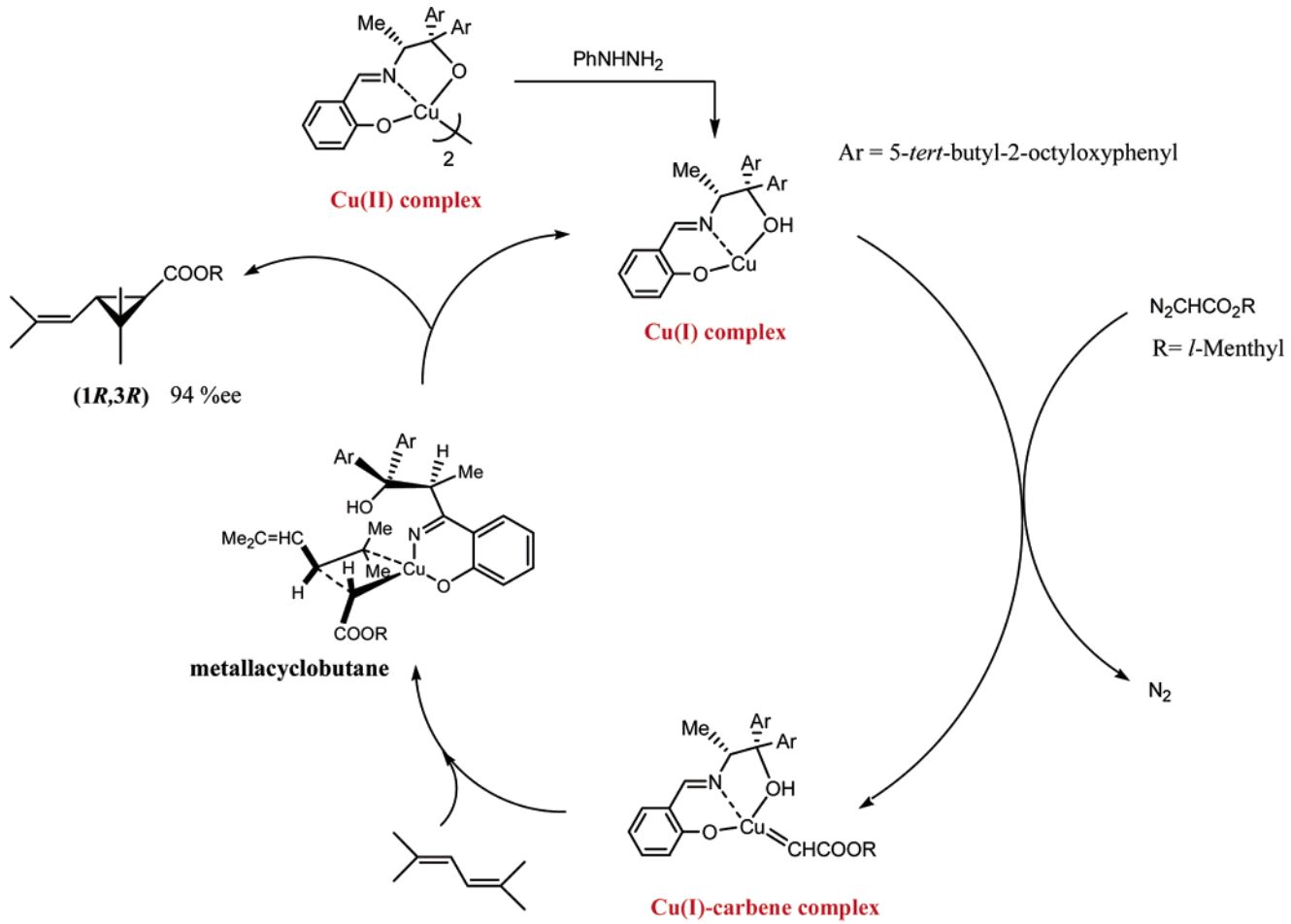
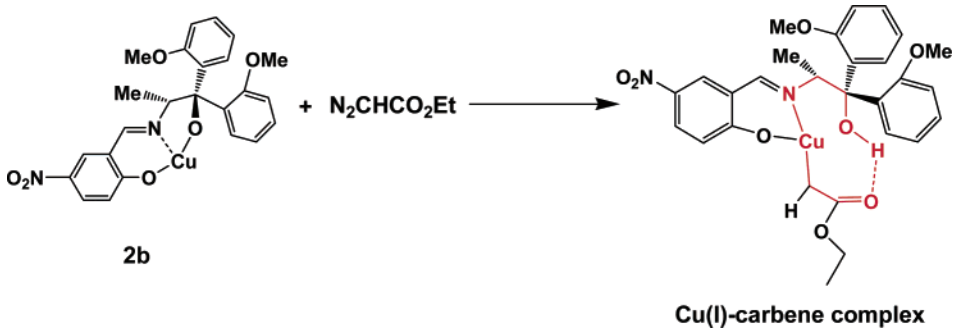


Figure 7. **Aratani's proposed mechanism.**

Scheme 4. **Structures of the copper(I) carbene Complex from catalyst 2b**



As the details of the calculations were reported elsewhere,[15] the catalytic key intermediate involved in the catalyst **2b** 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 as shown in Scheme 4.

Figure 8 shows a schematic representation of the orbital interactions that are important for determining the orientation of the carbene carbon center.[15] This carbene complex is chiral since the plane of the sp^2 carbene carbon center lies orthogonal to the plane of the salicyaldimine. The orthogonal nature arises from the orbital interaction between the occupied $3d_{xz}$ orbital of the copper(I) atom and the vacant $2p_x$ orbital of the carbene carbon atom. If a stereogenic center exists in the imine side chain, the orientation of the ester carbonyl group relative to the stereogenic center in the transition states (TSs) of the cyclopropanation determines

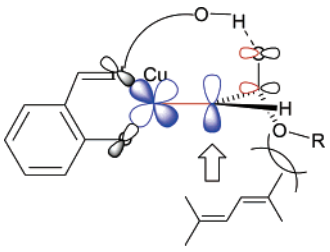
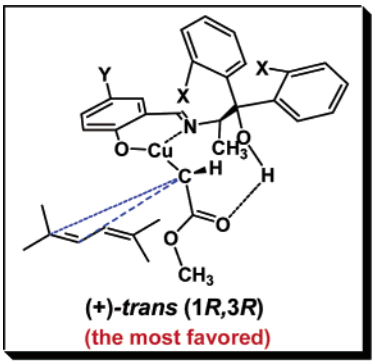
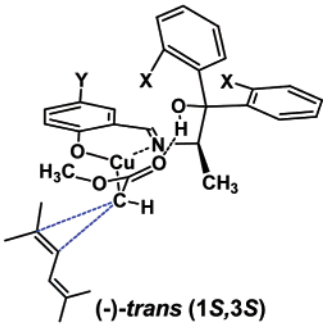
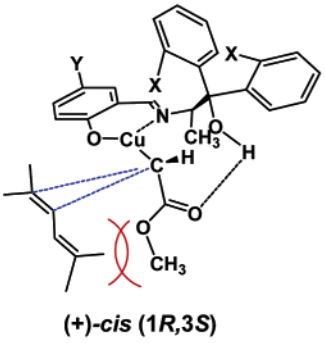


Figure 8. **Orbital interactions that fix the orientation of the carbene center and the carbonyl group (back-donation (blue) and conjugation between the Cu−$C_{carbene}$ σ-bond and carbonyl π-orbital (red)).**







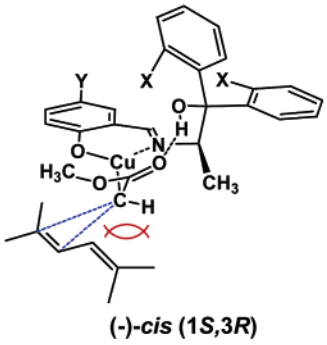


Figure 9. **Schematic representation of the transition states.**

the absolute stereochemistry of the C_1 carbon atom in the cyclopropane products.

The approach of DMHD to the carbene carbon atom in the TSs is limited to only one enantioface, which is opposite to the imine side chain. In addition, the orientation of DMHD is limited to be the one shown in Figure 8. Although we could locate the TSs in an alternative conformation where the $Me_2C{=}CH$ moiety is closer to the salicylaldimine ligand, the free energies of activation for these TSs were found to be quite higher than that for the TSs that have the conformation as described in Figure 8.

After all, the most probable TSs can be selected like those shown in Figure 9. Our calculations showed that the transition states are the [2 + 1] addition from DMHD to the carbene carbon of the Cu(I)−carbene complex. The enantioselectivity of the *trans*-chrysanthemate calculated from the Boltzmann distribution of several TSs was in qualitative agreement with the experimental results that the (+)-*trans* (1*R*,3*R*) isomer is predominantly produced.[15,17] In addition, the *trans*/*cis* ratio was able to be explained by the steric interaction among the isobutenyl group of DMHD and the ester carbonyl group on the Cu(I)−carbene complex.

A comparison of the LUMO energies, which are mainly composed of the 2p orbital of the carbene carbon, was then performed between the unsubstituted copper carbene complex **4a** and the 5-nitro-substituted carbene complex **4b** in Figure 10. As a result, the LUMO energies of **4b** (−2.98 eV) were found to be lower than that of **4a** (−2.57 eV).

Therefore, the introduction of the electron-withdrawing substituents on the benzene ring of the salicylaldehyde moiety in the copper complex enhances the electrophilicity of the

(17) Nine trasition states were obtained by the calculations in ref 15.

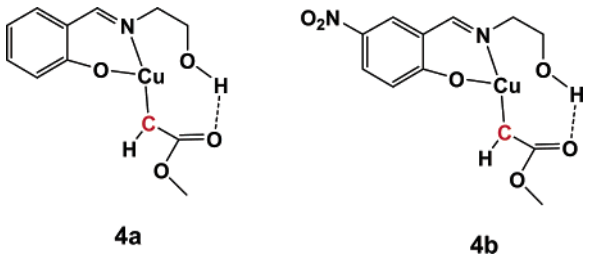


Figure 10. **Simplified carbene complexes for the calculations of LUMO energies.**

carbene carbon through the copper atom. This enhancement should bring about a high reactivity of the Cu(I)−carbene complex toward DMHD.

2.5. Possible Mechanism for Effects of Addition of Lewis Acids. The effects of Lewis acids can also be explained on the basis of the following experimental results listed in Table 6. Although the effect of $Al(OEt)_3$ is not observed in **2a** and **2h** (entries 1 vs 2, 9 vs 10), a remarkable enhancement of the product yield 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 (entry 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 when using the complex **2b** and $Al(OEt)_3$ as shown in Figure 11. In order to examine the effects of the coordination to the nitro group, the LUMO energy of the copper carbene complex **4b** coordinated by $Al(OEt)_3$ was calculated. As a result, the-LUMO energy of the carbene complex coodinated by Al-$(OEt)_3$ (**4b-Al(OEt)$_3$**, −3.33 eV) was found to be lower than that of the uncoordinated one (**4b**, −2.98 eV), which

Table 6. **Effects of substituents at the 5-position on the salicylaldehyde group in the copper Schiff base 2 with $Al(OEt)_3$[a]**

entry	Cu complex	Lewis acid	yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*[b]	ee[d] (%) *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 complex as the monomeric complex, 0.01 mmol of phenylhydradine, 0.01 mmol of $Al(OEt)_3$, 10 mmol of EDA, 70 mmol of DMHD, and 5 mL of ethyl acetate, 0 °C, 3 h. [b] Based on EDA and determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C) with *n*-decane as the internal standard. [c] Determined by GC analysis (DB-1, 30 m × 0.25 mm ID, 0.25 mm film, column temp 100 °C). [d] 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). [e] 1*R*,3*R* as the major enantiomer. [f] 1*R*,3*S* as the major enantiomer.

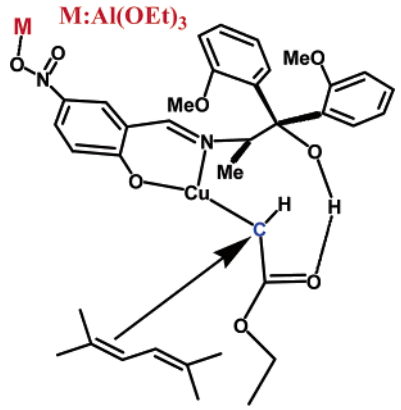


Figure 11. **Tentative scheme for the addition of $Al(OEt)_3$ to the copper complex 2b.**

reasonably explains the enhancement of the reactivity by Lewis acids.

3. Conclusions

New copper salicylaldimine complex catalysts (copper Schiff base complex catalysts) derived from substituted salicylaldehydes bearing an electron-withdrawing group at the 5-position demonstrated a greater enhancement of the turnover number than the copper catalysts derived from the salicylaldehyde for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with diazoacetate. In addition, a high yield (90%) and high enantioselectivity (91% ee) using *tert*-butyl diazoacetate were first achieved by the addition of a Lewis acid such as $Al(OEt)_3$ under 0.1 mol % catalyst loading. Although the current reaction system with *tert*-butyl diazoacetate lowered the *trans*/*cis* ratio compared with *l*-menthyl or dicyclohexyl diazoacetate, it is more practical for industrial production of the chiral chrysanthemate than Aratani's or the Masamune's catalyst due to low loading of the cheap copper catalysts and the use of *tert*-butyl diazoacetate. The products were easily converted into chrysanthemic acid using an acid catalyst. Furthermore, a reasoning for the mechanism of the asymmetric induction in the copper Schiff base catalyzed cyclopropanation mechanism has been provided on the basis of the density functional calculations.

4. Experimental Section

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere. The optical rotations were measured using a JASCO DIP-370. The melting points were measured using a Mettler Toledo Type FP62. The NMR spectra were recorded using a Bruker DPX-300NMR spectrometer with trimethyl silane as the internal standard (δ value in $CDCl_3$). Ethyl diazoacetate and *tert*-butyl diazoacetate were prepared according to literature procedure.[18] The yields were determined by GC analyses with a capillary column for the cyclopropanation. Ee values were then determined by LC analyses with a chiral column in the case of ethyl chrysanthemate and by GC analyses with a capillary column in the case of *tert*-butyl chrysanthemate after transformation into the *l*-menthyl chrysanthemate with $SOCl_2$, pyridine, and *l*-menthol.

4.1. Typical Procedure for Synthesis of Aminoalcohols. (*R*)-2-Amino-1,1-di(2-methoxyphenyl)-1-propanol. The methyl ester hydrochloride of D-alanine (7.0 g, 50.1 mmol) was added to a cooled Grignard solution derived from *o*-bromoanisole (49.6 g, 265 mmol) and magnesium (6.7 g, 276 mmol) in THF at 0 °C. The mixture was stirred for 3 h at room temparature and then added to cooled 2% hydrochloric acid (200 mL) at 0 °C. 150 mL of toluene were added to the mixture, and the aqueous phase was separated. The aqueous solution was neutralized with ammonium hydroxide, and 150 mL of toluene were added to the mixture. The organic phase was separated, washed with saturated brine, dried, and concentrated. A pale yellow solid was obtained, recrystallized from CH_2Cl_2−*n*-hexane which provided the product as a white solid (10.8 g, 75%). $[\alpha]_D = 35.5$ ($c = 1$, $CHCl_3$); mp 89−90 °C; ^{1}H 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).

4.2. Typical Procedure for Synthesis of Schiff Bases. (*R*)-(*N*-5-Nitrosalicylidene)-2-amino-1,1-diphenyl-1-propanol (5b). (*R*)-2-Amino-1,1-di(2-methoxyphenyl)-1-propanol (6.32 g, 22.0 mmol) and 5-nitrosalicylaldehyde (3.68 g, 22.0 mmol) were dissolved in toluene (40 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 **5b** (9.12 g, 95%) as a 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).

(18) (a) For ethyl diazoacetate: *Organic Synthesis Collective Volumes 3*; Horning, E. C., Ed.; John Wiley & Sons, Inc: New York, 1955. (b) For *tert*-butyl diazoacetate: Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906−1912.

4.3. Typical Procedure for Synthesis of the Copper Schiff Base Complexes. The Copper Complex (2b). *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 were then added to this solution. The mixture was refluxed for 1 h, and aqueous sodium hydroxide was next added and further stirred for 30 min at room temparature. The organic layer was separated, washed with water, dried, and concentrated in vacuo, and 5.47 g of the copper Schiff base complex were 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).

4.4. Typical Procedure for the Cyclopropanation Catalyzed by (2b) with Ethyl Diazoacetate. Under a nitrogen atmosphere, 498 mg (1.0 mmol) of the copper complex **2b** were dissolved in 15 mL of ethyl acetate, and 771 g (7.0 mol) of 2,5-dimethyl-2,4-hexadiene were then added to the solution. 100 μL (1.0 mmol) of phenylhydrazine were added by a microsyringe, and the temparature of the reaction mixture was then raised to 80 °C. To the mixture solution were added 500 mL of a solution of ethyl diazoacetate (114 g, 1.0 mol) in ethyl acetate at a constant rate over 2 h using a 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 the 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. The products were determined by comparison of the LC elution order of the enantiomers with authentic samples. Part of the reaction mixture containing 167 g of ethyl chrysanthemate (0.85 mol) was concentrated under reduced pressure, and then ethyl chrysanthemate was obtained as a colorless oil (152 g, purity = 98.5% by GC, the *trans*/*cis* ratio = 58/42, 65% ee for *trans* isomer, 60% ee for *cis* isomer) by distillation (107−112 °C, 13 kPa). The NMR spectra of the obtained ethyl chrysanthemate was identical to that reported by literature.[11]

4.5. Typical Procedure for the Cyclopropanation Catalyzed by (2b)−Al(OEt)$_3$ with *tert*-Butyl Diazoacetate. Under a nitrogen atmosphere, 9.96 mg (0.020 mmol) of the copper complex **2b** and 3.24 mg (0.020 mmol) of triethoxy aluminium were added to 5 mL of ethyl acetate, and 15.4 g (140 mmol) of 2,5-dimethyl-2,4-hexadiene were then added to the solution. 2 μL (0.02 mmol) of phenylhydrazine were added by a microsyringe, and the temparature of the reaction mixture was then set to 20 °C. A solution of *tert*-butyl diazoacetate (2.82 g, 20 mmol) in 10 mL of ethyl acetate was added dropwise to the solution at a constant rate over a period of 3 h at 20 °C, and the mixture was then further stirred at the same temperature for 0.5 h. The reaction mixture was filtered through silica gel and then 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 *n*-decane as an internal standard for determining the yield and *trans*/*cis* ratio. After concentration of the reaction mixture under reduced pressure, a pale yellow oil containing 4.03 g of *tert*-butyl chrysanthemate (18 mmol) was obtained and the NMR spectra were identical to those reported by literature.[11] Afterwards, the resulting pale yellow oil was dissolved in 50 mL of toluene. Trifluoroacetic acid (205 mg, 1.8 mmol) was then added to the solution, and the solution was refluxed for 3 h. After cooling the reaction mixture to 40 °C, 20 mL of water and 20 mL of 1 N sodium hydroxide were added, and the pH of the aqueous phase showed >12. The phases were separated, and the pH of the aqueous phase was adjusted to <2 with 6 N hydrochloric acid. To the aqueous phase were added 50 mL of toluene, and the organic phase was washed with 30 mL of water. The organic phase was then concentrated under reduced pressure to obtain chrysanthemic acid (colorless oil, 2.90 g, yield 96%, purity = 99.0% by GC, *trans*/*cis* ratio = 78/22), which was analyzed by GC (DB-210, 30 m × 0.25 mm ID, 0.25 mm film, column temp 115 °C) after transformation into the *l*-menthyl chrysanthemate with $SOCl_2$, pyridine, and *l*-menthol. The NMR spectra of the obtained chrysanthemic acid were identical to those reported by literature.[19] The absolute configurations of the products were determined by comparison of the GC elution order of the enantiomers with authentic samples.

5. Computational Methods

The density functional studies reported here were performed using the B3LYP hybrid density functional method[20] implemented in the Gaussian98 and Gaussian03 programs.[21] The LUMO energies shown above were calculated at the B3LYP/6-31G(d) level. The more detailed procedure for the calculations was reported elsewhere.[15]

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