Asymmetric Hetero Diels–Alder Reactions and Ene Reactions Catalyzed by Chiral Copper(II) Complexes

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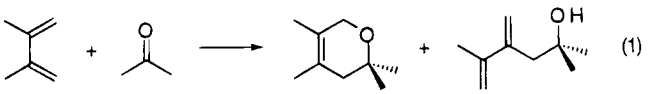
A new copper(II) bisoxazoline-catalyzed reaction of glyoxylate esters with dienes leading to the hetero Diels–Alder product and the ene product in high yield and with a high enantiomeric excess (ee) has been developed. The hetero Diels–Alder product:ene product ratio is in the range 1:0.6 to 1:1.8 and is dependent on both the chiral ligand attached to the metal, the glyoxylate ester, and the reaction temperature. The scope of the copper(II) bisoxazoline-catalyzed reaction of glyoxylate esters with dienes is demonstrated by the reaction of a variety of different dienes with ethyl and isopropyl glyoxylate, and it is shown that a simple substrate such as 1,3-butadiene reacts to give the hetero Diels–Alder product in 55% yield with an ee of 87%. Furthermore, the synthetic application of the reaction is demonstrated by the synthesis of a highly interesting synthon for sesquiterpene lactones in high yield and diastereoselectivity, and with a very high ee from 1,3-cyclohexadiene and ethyl glyoxylate using a copper(II) bisoxazoline as the catalyst. A mechanism for the hetero Diels–Alder reaction, which accounts for the enantioselectivity in the reactions, is proposed.

Introduction

One of the fundamental reactions in organic chemistry is the Diels–Alder (DA) reaction as it allows one, in an efficient and elegant manner, to obtain carbo- and heterocycles in a highly regio- and stereospecific way.[1–4] Although tremendous progress has been made in the field of metal catalyzed enantioselective C–C bond formation,[5] the control of the regio- and stereochemistry of the DA reaction is still far from developed. It is therefore not surprising that considerable attention has been focused on the development of metal-catalyzed asymmetric variants of the DA reaction.[2]

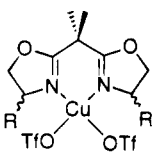
The reaction between a diene, such as 2,3-dimethyl-1,3-butadiene, and a carbonyl compound can lead to the formation of both the hetero DA product and the ene product [reaction 1].



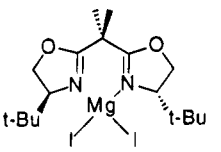
(1)

By using chiral binol titanium complexes, impressive results have been obtained by Nakai et al.[6–9] and Mikami et al.[6–12] in the glyoxylate ene reaction and the hetero DA reaction. These titanium-catalyzed reactions lead to a high degree of ene selectivity by using isoprene as the substrate.[6] However, no catalyst has, according to our knowledge, yet been able to change the reaction course, *i.e.* to improve the amount of hetero DA product, relative to the ene product, formed. It should also be noted that attempts to use vanadium- and lanthanide complexes, and Kogas catalyst, for the hetero DA reaction have been tried.[13,14] More recently a hetero DA reaction using Danishefsky's diene and methyl glyoxylate as the substrates and a chiral boron Lewis acid as catalyst has also been published.[15]

In this paper we present the metal-catalyzed asymmetric reaction of dienes with glyoxylate esters using the metal bisoxazolines (*S*)-**1a**, (*R*)-**1b**, (*S*)-**1b**, and (*S*)-**2** as catalysts. The catalysts have previously been used in asymmetric Diels–Alder reactions.[16,17]



(*S*)-**1a** (R = *t*-Bu)
(*R*)-**1b** (R = Ph)
(*S*)-**1b** (R = Ph)



(*S*)-**2**

The present work is mainly devoted to new catalytic systems for the hetero DA reaction in an attempt to increase the hetero DA product to ene product ratio, and it will be shown that the copper catalysts (*S*)-**1a** and (*R*)-**1b** give a significant higher hetero DA product:ene product ratio compared with the chiral binol titanium catalysts. It will also be shown that especially the copper catalyst (*R*)-**1b** can catalyze the hetero DA reaction of dienes which has proven to fail in the chiral binol titanium-catalyzed reactions.[18] The scope of the reaction will be demonstrated by the synthesis of a synthon for

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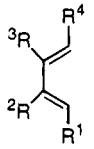
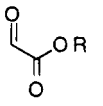
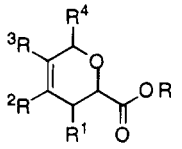
Chart 1



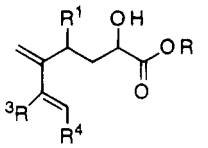
3a: $R^1 = R^2 = R^3 = R^4 = H$
3b: $R^1 = R^3 = R^4 = H$; $R^2 = Me$
3c: $R^1 = R^4 = H$; $R^2 = R^3 = Me$
3d: $R^1 = R^4 = (CH_2)_2$; $R^2 = R^3 = H$



4a: R = Me
4b: R = Et
4c: R = *iso*-Pr



5a: $R^1 = R^2 = R^3 = R^4 = H$, R = *iso*-Pr
5b: $R^1 = R^3 = R^4 = H$; $R^2 = Me$, R = Et
5c: $R^1 = R^4 = H$; $R^2 = R^3 = Me$, R = Me
5d: $R^1 = R^4 = H$; $R^2 = R^3 = Me$, R = Et
5e: $R^1 = R^4 = H$; $R^2 = R^3 = Me$, R = *iso*-Pr
5f: $R^1 = R^4 = (CH_2)_2$; $R^2 = R^3 = H$, R = Et



6a: $R^1 = R^3 = R^4 = H$, R = Et
6b: $R^1 = R^4 = H$; $R^3 = Me$, R = Me
6c: $R^1 = R^4 = H$; $R^3 = Me$, R = Et
6d: $R^1 = R^4 = H$; $R^3 = Me$, R = *iso*-Pr

Table 1. Hetero Diels–Alder reactions and Ene Reactions of 2,3-Dimethyl-1,3-butadiene (3c) with Ethyl Glyoxylate (4b) in the Presence of Different Catalysts (*S*)-1a, (*R*)-1b, and (*S*)-2

		Diels–Alder product **5d**		ene product **6c**		
entry	catalyst	yield/ %[a]	ee/%[b] (config)	yield/ %[a]	ee/ %[b,c]	**5d**:**6c** ratio
1	(*S*)-**1a**	20	85 (*S*)	36	83	1:1.8
2	(*R*)-**1b**	31	83 (*S*)	50	88	1:1.6
3	(*S*)-**2**	10	5 (*S*)	20	10	1:2

[a] Isolated yield. [b] Ee determined by GC on a Chrompack Chirasil-DEX CB column. [c] Absolute stereochemistry not assigned.

sesquiterpene lactones with high diastereoselectivity and enantiomeric excess (ee). Furthermore, a mechanism accounting for the stereochemical outcome of the hetero DA reaction will be presented.

Results and Discussion

The metal-catalyzed asymmetric reaction of the dienes **3a–d** with glyoxylate esters **4a–c** has been studied.

The diene **3c** is chosen as a model substrate since it would be possible to investigate both the hetero DA reaction and the ene reaction at the same time. The reaction of **3c** with ethyl glyoxylate **4b** has been studied in the presence of (*S*)-**1a**, (*R*)-**1b**, and (*S*)-**2** as the catalysts. The results are shown in Table 1 and the experimental details are given in the Experimental Section.

It appears from the results in Table 1 that copper(II) triflate coordinated with bisoxazolines (*S*)-**1a** and (*R*)-**1b** are much better catalysts than the magnesium(II) iodine bisoxazoline complex (*S*)-**2**, both in terms of yield and ee (Table 1, entries 1–3). Comparing the properties of the copper catalysts, such as (*R*)-**1b**, with the chiral binol titanium complexes as catalyst for the present reactions, it appears that using isoprene as the substrate and (*R*)-**1b** as the catalyst gives a hetero DA product:ene product ratio of 1:1 (*vide infra*), whereas the chiral binol titanium complexes give a 1:4 ratio.[6] The present copper(II) bisoxazoline catalysts thus have a significantly better hetero DA selectivity compared with the chiral binol titanium complexes. The catalyst (*R*)-**1b** gives a high ee for both the hetero DA reaction and the ene reaction (entry 2). It is surprising that the absolute configuration of product **5d** is (*S*) for catalysts with *opposite* stereochemistry at the chiral ligand, *i.e.* the catalysts (*R*)-**1b** and (*S*)-**1a** give the same absolute induction (entries 1, 2) (*vide infra*). It should be noted that the reaction of **3c** with **4b** in the presence of (*S*)-**1b** as the catalyst leads to the expected products **5d** and **6c** with opposite stereochemistry compared with (*R*)-**1b** as the catalyst.

The alkyl group of the glyoxylate ester proved to have an apparent influence on the hetero DA product:ene product ratio, but only a relatively small influence on the ee of the reaction. The results are presented in Table 2 for the reaction of **3c** with different glyoxylate esters **4a–c** in the presence of (*S*)-**1a** and (*R*)-**1b**.

The highest hetero DA product:ene product ratio is 1:1 and is obtained with (*S*)-**1a** as the catalyst and **4c** as the alkyl glyoxylate (Table 2, entry 3). The hetero DA product:ene product ratio does not change significantly for the two catalysts (*S*)-**1a** and (R)-**1b**. The highest ee (90%) for the hetero DA product **5a** is obtained with (*S*)-**1a** as the catalyst and **4a** (entry 1). The same ee (90%) is also obtained for the ene product **6d** using (*R*)-**1b** as the catalyst and **4c** as the glyoxylate ester (entry 6). It is interesting to note that the least steric hindered glyoxylate ester **4a** gives the highest ee in the hetero DA reaction when (*S*)-**1a** is the catalyst, while the most sterically hindered glyoxylate ester **4c** gives the highest ee applying (*R*)-**1b** as the catalyst for the same reaction. The highest yield in the reaction is found in the case of the glyoxylate ester **4a** and (*R*)-**1b** as catalyst (entry 4) and this combination also gives a very good hetero DA product:ene product ratio (1:1.4).

The influence of the temperature on the ee has also been studied for the reaction of **3c** with **4b** in the

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Table 2. Hetero Diels–Alder Reactions and Ene Reactions of 2,3-Dimethyl-1,3-butadiene (3c) and Different Alkyl Glyoxylates 4a–c Catalyzed by (*S*)-1a and (*R*)-1b

entry	catalyst	glyoxylate	Diels–Alder product: yield/%[a] (ee/%)[b] (confg)	ene product: yield/%[a] (ee)[b,c]	Diels–Alder product:ene product ratio
1	(*S*)-**1a**	**4a**	**5a**, 25 (90) (*S*)	**6d**, 39 (85)	1:1.6
2	–	**4b**	**5d**, 20 (85) (*S*)	**6c**, 36 (83)	1:1.8
3	–	**4c**	**5e**, 12 (77) (*S*)	**6d**, 12 (83)	1:1
4	(*R*)-**1b**	**4a**	**5c**, 36 (81) (*S*)	**6b**, 50 (85)	1:1.4
5	–	**4b**	**5d**, 31 (83) (*S*)	**6c**, 50 (88)	1:1.6
6	–	**4c**	**5c**, 31 (87) (*S*)	**6d**, 40 (90)	1:1.3

[a] Isolated yield. [b] Ee determined by GC on a Chrompack Chirasil-DEX CB column. [c] Absolute stereochemistry not assigned.

Table 3. Reaction of 2,3-Dimethyl-1,3-butadiene (3c) with Ethyl Glyoxylate 4b in the Presence of (*S*)-1a or (*R*)-1b as the Catalysts at Different Temperatures

entry	catalyst	temp/°C	Diels–Alder product **5d**: yield/%[a] (ee/%)[b] (config)	ene product **6c**: yield/%[a] (ee/%)[b,c]	**5d**:**6c** product ratio
1	(*S*)-**1a**	20	20 (85) (*S*)	36 (83)	1:1.8
2	(*S*)-**1a**	−30	5 (95) (*S*)	4 (94)	1:0.8
3	(*R*)-**1b**	20	31 (83) (*S*)	50 (88)	1:1.6
4	(*R*)-**1b**	0	22 (85) (*S*)	32 (89)	1:1.5
5	(*R*)-**1b**	−30	13 (85) (*S*)	7 (90)	1:0.6

[a] Isolated yield. [b] Ee determined by GC on a Chrompack Chirasil-DEX CB column. [c] Absolute stereochemistry not assigned.

Table 4. Reaction of Different Dienes 3a–d with Glyoxylates 4b,c in the Presence of (*R*)-1b as the Catalyst

			Diels–Alder product		ene product		
entry	diene	glyoxylate	yield/%[a]	ee/%[b] (config)	yield/%[a]	ee/%[b,c]	DA:ene product ratio
1	**3a**	**4c**	**5a**, 55	87 (*S*)	–		–
2	**3b**	**4b**	**5b**, 33	80[c]	**6a**, 34	91	1:1
3	**3c**	**4c**	**5c**, 31	87 (*S*)	**6d**, 40	90	1:1.3
4	**3d**	**4b**	**5f**, 72	60 (*1R,3S,4S*)	–		–

[a] Isolated yield. [b] Ee determined by GC on a Chrompack Chirasil-DEX CB column. [c] Absolute stereochemistry not assigned.

presence of (*S*)-**1a** and (*R*)-**1b** as the catalyst. The results for the temperature study are given in Table 3.

It appears from the results in Table 3 that reducing the temperature from 20 °C to −30 °C and using (*S*)-**1a** as the catalyst leads to a significant increase in ee. At 20 °C the ee for the hetero DA product and ene product are 85% and 83%, respectively, whereas at −30 °C 95% and 94% ee are formed (Table 3, entries 1,2). The temperature also has a significant influence on the hetero DA product:ene product ratio as this ratio is 1:1.8 at 20 °C, while it is 1:0.8 at −30 °C (entry 1,2), *i.e.* a lowering of the reaction temperature increases the amount of hetero DA product relative to the ene product. The increase in ee and the hetero DA product:ene product ratio is unfortunately accompanied by an unacceptably low yield after 8 h reaction time (entry 2). Conversely, the other bisoxazoline catalyst (*R*)-**1b** shows no significant increase in ee by lowering the temperature in the interval 20 °C to −30 °C, as only an increase of 2% in ee is found. However, a high hetero DA product:ene product (1:0.6) is found at −30 °C, compared with the reaction taking place at higher temperature. The temperature study shows that the reaction of **3c** with **4b** in the presence of the copper(II) triflate coordinated by bisoxazoline (*S*)-**1a** at 20 °C and (*R*)-**1b** at 20 °C or 0 °C affords a relatively good yield of the products and with a high ee. Overall (*R*)-**1b** seems to be the catalyst of choice in combination with **4c** as eno- or dienophile.

The reaction of different dienes **3a–d** with the glyoxylate esters **4b,c** has been studied in the presence of (*R*)-**1b** as the catalyst. The results are presented in Table 4.

To our surprise the simplest 1,3-butadiene **3a**, which has been found to be inert to cycloaddition reaction with glyoxylate ester in the presence of chiral binol titanium complexes as the catalyst,[18] underwent a smooth hetero DA reaction at 20 °C, affording the cycloaddition product **5a** in relatively good yield (55%) and with a high ee (87%), though with a prolonged reaction time (120 h) (Table 4, entry 1). This low reactivity of **3a** is probably due to the *s-trans* conformation of free **3a**.[19] The reaction of 2-methyl-1,3-butadiene (isoprene) (**3b**) demonstrates the high hetero DA product selectivity in the present reactions (entry 2) compared with the results described by Mikami et al. who obtained a hetero DA product:ene product ratio of 1:4 by using the chiral binol titanium complexes as the catalyst.[6] The ee for the hetero DA product is 80%, while 91% is found in the ene product (entry 2). The high regioselectivity of this reaction should also be noted (entry 2). The same hetero DA product preference is also seen in the reaction of **3c** (entry 3). An analogous behavior has recently been observed using trifluoroactaldehyde as eno- and dienophile and different achiral Lewis acid catalysts.[20]

Reaction of 1,3-cyclohexadiene **3d** with **4b** in the presence of (*R*)-**1b** as the catalyst produces a highly interesting bicyclic product **5f** (entry 4). According to NMR spectroscopy the endo isomer is the only one formed having an ee of 60%. Alkaline hydrolysis of **5f** followed by acidification induces a stereospecific rearrangement to a valuable bicyclic hydroxy lactone **7**.[21] Recrystallization of **7** from $(i\text{-Pr})_2O$ gives an almost enantiopure lactone (>99.5% ee), which is a highly interesting synthon for natural products synthesis.[22–25] The reaction se-

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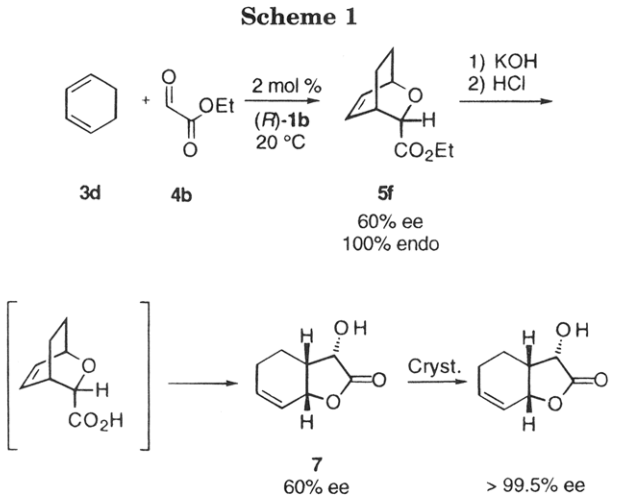
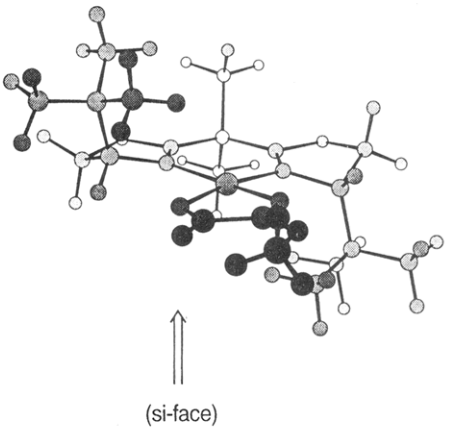
(22) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occuring Compounds*; Academic Press: New York, 1972; Vol. II.

Scheme 1





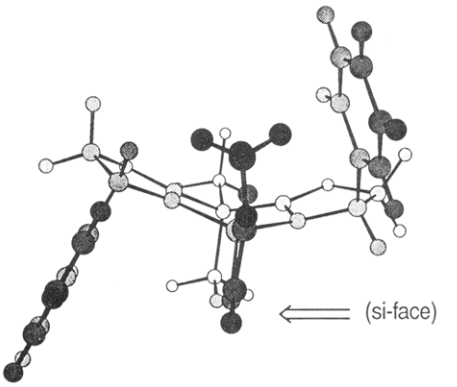
8

quence is outlined in Scheme 1. The synthesis of the bicyclic hydroxy lactone has recently been described using a yeast-induced resolution method,[25] but the present method is superior because of the high endo selectivity giving only one diastereomer, solving the problem of diastereomer separation, and the easy recrystallization procedure (Scheme 1).

The mechanism for the copper(II) bisoxazoline-catalyzed reactions of glyoxylate esters with dienes will be discussed in the following. Coordination of **4a** to copper(II) bisoxazoline (*S*)-**1a** can lead to complex **8** where it is assumed that **4a** is L_2-coordinated to (*S*)-**1a** and the copper-, nitrogen-, and oxygen atoms are in the same plane, as the majority of d^2-copper(II) complexes with similar atoms attached to the metal are found to be square planar.[26] However, it should be noted that significant deviations from planarity to other structural arrangements at the copper centers has also been observed.[26,27] Theoretical calculations of a reaction mechanism for the reaction of a 1,3-diene with the carbonyl group in **8** is probably beyond the present stage of reliability mainly due to the difficulty in obtaining an appropriate electronic description of the open shell d^2-copper bisoxazoline−glyoxylate complex. We will therefore try to present a mechanism for the present hetero DA reaction based on the assumption that the glyoxylate ester is L_2-coordinated to the copper(II) bisoxazoline complex and applying the stereochemical outcome of the reaction to account for the approach of the 1,3-diene to the carbonyl group. Let us start with the reaction of a 1,3-diene with **4a** coordinated to (*S*)-**1a** (**8**).

Intermediate **8** has the *si*-face of the carbonyl group of the glyoxylate ester available for a hetero DA reaction as the other face is sterically blocked by the *tert*-butyl substituent of the bisoxazoline ligand. The stereochemical outcome of the hetero DA product by the approach of the 1,3-diene at the *si*-face in **8** is in nice agreement with the present results.

How can we then account for the fact that an exchange of the *tert*-butyl substituent with a phenyl substituent in the ligand leads to the opposite stereochemical induction in the hetero DA reaction? To explain this observation we propose that the coordination of the glyoxylate ester to (*R*)-**1b** leads to a tetrahedral geometry rather than a planar copper center. With a tetrahedral arrangement at the copper center the *si*-face of the carbonyl group is now again available for reaction with the 1,3-diene leading to a hetero DA product with the observed stereochemistry. The approach is outlined below in **9**.



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There is another experimental indication for a structural change when moving from (*S*)-**1a** to (*R*)-**1b** as the catalyst for the reaction as the ee of both the hetero DA and the ene reaction decreases when the bulkiness of the glyoxylate ester increases using the former as the catalyst, whereas applying the latter as the catalyst leads to the reverse obervation.

We are fully aware of the fact that the proposed geometrical modification from a planar to a tetrahedral structure at the copper center by an exchange of the *tert*-butyl substituent with the phenyl substituent is a major change of the geometry, but at the present time we are not able to explain the observed experimental results in other ways. However, it should be noted that an arrangement of the bisoxazoline ligand and the glyoxylate ester as in **9** is not an unlikely proposal from a structural point of view. It is also remarkable that Evans et al.[18] observed a drastic decrease in their enantioselective Diels−Alder reactions catalyzed by copper(II) bisoxazoline complexes when substituting the *tert*-butyl group with a phenyl group. Is this also due to a structural change of the complex?

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(27) See *e.g.*: (a) Guss, J. M.; Bartunik, H. D.; Freeman, H. C. *Acta Crystallogr.* **1992**, *B48*, 790. (b) Solomon, E. I.; Baldwin, M. J.; Lowery, M. D. *Chem. Rev.* **1992**, *92*, 521.

Summary

It has been shown that copper(II) bisoxazolines are very useful catalysts for the reaction of glyoxylate esters with dienes giving highly valuable hetero DA and ene products. The reaction of dienes having the possibility for both the hetero DA and ene product leads to a mixture of both products. 2-Methyl-1,3-butadiene reacts to give a 1:1 ratio of the DA product:ene product in good yield with an ee of 80% and 91%, respectively, and 2,3-dimethyl-1,3-butadiene as the substrate gives a ratio of 1:1.3, also in high yield and with an ee of 87% and 90%. Simple dienes such as 1,3-butadiene and 1,3-cyclohexadiene reacts smoothly with the glyoxylate ester in the presence of the cooper(II) bisoxazoline as the catalyst to give the hetero DA products in good yield, and, especially for 1,3-butadiene, with a very high ee. For the DA reaction of 1,3-cyclohexadiene the synthetic application of the reaction is demonstrated by the synthesis of a highly interesting synthon for sesquiterpene lactones in high yield and diastereoselectivity, and with a very high ee. The absolute chemistry of the reaction is dependent on the catalyst applied; choosing a bisoxazoline ligand with a *tert*-butyl substituent at the chiral center gives the opposite stereochemistry in the hetero DA product compared with a bisoxazoline ligand having a phenyl substituent at the chiral center. This difference in enantioselectivity is probably caused by a geometrical change at the copper atom. In the case of a bisoxazoline ligand having a *tert*-butyl substituent as the chiral auxiliary and the glyoxylate ester coordinated to the copper atom a planar complex is proposed as the intermediate, whereas a tetrahedral arrangement at the metal is suggested to be involved for the hetero DA reaction when the bisoxazoline ligand is substituted with a phenyl group at the chiral atom. The alkyl group of the glyoxylate ester has both an influence on the hetero DA product:ene product ratio and the ee of the reaction. In the case of a *tert*-butyl-substituted bisoxazoline ligand catalyst the methyl glyoxylate gives the highest ee in the hetero DA and the ene reaction, whereas for the bisoxazoline ligand with a phenyl substituent the isopropyl glyoxylate gives the highest ee. In both the cases the best hetero DA product:ene product ratio is obtained for the isopropyl glyoxylate. It has also been found that a reduction of the reaction temperature leads to an increase of the hetero DA product:ene product ratio in favor of the hetero DA product. The mechanism for the reaction of dienes is proposed to proceed with the glyoxylate ester L_2-coordinated to the copper(II) bisoxazoline catalyst. In the case of the copper(II) bisoxazoline complex having a *tert*-butyl substituent a planar intermediate is proposed, while a tetrahedral intermediate is proposed to account for the reaction course when the the copper(II) bisoxazoline complex has a phenyl substituent.

Experimental Section

General. 2,3-Dimethyl-1,3-butadiene, 2-methyl-1,3-butadiene, 1,3-cyclohexadiene, 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (ligand **a**), (*R*)-2,2′-Isopropylidenebis(4-phenyl-2-oxazoline) (ligand **b**), and $Cu(OTf)_2$ were purchased from Aldrich Chemical Co. and used without further purification. $Cu(OTf)_2$ was stored under N_2. 1,3-Butadiene were purchased from Fluka and used as received. $Eu(hfc)_3$ was purchased from Aldrich Chemical Co. and used as a 0.075 M solution in $CDCl_3$. Solvents were dried according to standard procedures. The alkyl glyoxylates **4a–c** were prepared as described in the literature,[28,29] stored over P_2O_5 at −18 °C and distilled prior to use. Purification of reaction products was carried out by flash chromatography (FC) using Merck silica gel 60 (230–400 mesh). TLC was performed on Merck analytical silica gel 60 F_{254} plates and visualized with a basic $KMnO_4$ solution. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS. Enantiomeric excess (ee) was determined by GC using a Chrompack Chirasil-DEX CB column. For compound **5b** the ee was measured by NMR spectroscopy using $Eu(hfc)_3$ as chemical shift reagent.

General Procedure for the Catalytic DA Reaction and Ene Reaction: Preparation of (*S*)-(−)-Ethyl 4,5-Dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate (5d) and (+)-Ethyl 2-Hydroxy-5-methyl-4-methylene-5-hexenoate (6c). $Cu(OTf)_2$ (36 mg, 0.1 mmol) and ligand **b** (35 mg, 0.105 mmol) were combined in a glove box under N_2. A 1 mL volume of CH_2Cl_2 was added under an N_2 stream, and mechanical stirring was performed for 1–2 h. A 1.0 mmol amount of ethyl glyoxylate (0.102 g) dissolved in 1 mL of CH_2Cl_2 and 1.5 mmol of 2,3-dimethyl-1,3-butadiene (0.17 mL) were added by cannula and stirred for 8 h. A 5 mL volume of heptane was added, and the solution was filtered through a plug of silica gel (2 cm × 2 cm) using 100 mL of 2:8 ethyl acetate/heptane as the eluent. FC (18 cm × 1.5 cm silica gel, 2:8 ethyl acetate/heptane) yields the DA product (57 mg, 31%) and the ene product (91 mg, 50%) as colorless oils.

5d: ^1H NMR: 4.28–4.03 (m, 5H, 2 OCH_2, OCH), 2.36–2.15 (br m, 2H, CH_2), 1.67 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.33–1.28 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR: 171.6, 124.2, 122.5, 72.9, 69.2, 61.0, 33.0, 18.2, 14.2, 13.8. $[\alpha]^{20}_D$ −138° (*c* 1.7, $CHCl_3$) 83% ee.

6c: ^1H NMR: 5.25 (s, 1H, C=CH), 5.14 (s, 1H, C=CH), 5.11 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.37–4.30 (m, 1H, OCH), 4.27–4.19 (m, 2H, OCH_2), 2.90–2.84 (dd, 1H, J = 3.3, 14.3 Hz, CH), 2.67–2.65 (d, 1H, J = 6.6 Hz, OH), 2.59–2.51 (dd, 1H, J = 8.2, 14.3 Hz, CH), 1.94 (s, 3H, CH_3), 1.33–1.28 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR: 174.6, 142.7, 142.1, 115.7, 113.4, 69.5, 61.6, 39.2, 21.2, 14.2. $[\alpha]^{20}_D$ +1° (*c* 1.7, $CHCl_3$) 88% ee.

Reaction of Ethyl Glyoxylate and Isoprene (2-Methyl-1,3-butadiene). The reaction was carried out according to the standard procedure above.

(−)-Ethyl 4-methyl-3,6-dihydro-2*H*-pyran-2-carboxylate (5b): ^1H NMR: 5.43 (br s, 1H, C=CH), 4.29–4.17 (m, 5H, 2 OCH_2, OCH), 2.36–2.17 (br m, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.33–1.28 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR: 171.4, 130.6, 119.4, 72.4, 65.6, 61.0, 32.2, 22.8, 14.2. $[\alpha]^{20}_D$ −90° (*c* 1.8, $CHCl_3$) 80% ee.

(+)-Ethyl 2-hydroxy-4-methylene-5-hexenoate (6a): ^1H NMR: 6.46–6.36 (dd, 1H, J = 10.4, 17.6 Hz, C=CH), 5.32–5.11 (m, 4H, 2 $C=CH_2$), 4.38–4.34 (m, 1H, OCH), 4.28–4.20 (m, 2H, OCH_2), 2.83–2.76 (dd, 1H, J = 1.1, 14.3 Hz, CH), 2.69 (br s, 1H, OH), 2.55–2.48 (dd, 1H, J = 8.2, 14.3 Hz, CH), 1.33–1.29 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR: 174.5, 141.1, 138.2, 119.1, 114.0, 69.2, 61.6, 36.7, 14.1. $[\alpha]^{20}_D$ +2° (*c* 0.9, $CHCl_3$) 91% ee.

Reaction of Ethyl Glyoxylate and 1,3-Cyclohexadiene (Synthesis of the Bicyclic Lactone 7). $Cu(OTf)_2$ (72 mg, 0.2 mmol) and ligand **b** (70 mg, 0.21 mmol) were combined in a glove box under N_2. A 2 mL volume of CH_2Cl_2 was added under a N_2 stream and mechanical stirring was performed for 1–2 h. A 10.0 mmol amount of ethyl glyoxylate (1.02 g) dissolved in 3 mL of CH_2Cl_2 and 15.0 mmol of cyclohexadiene (1.43 mL) were added by cannula and stirred for 20 h. CH_2Cl_2 was removed *in vacuo* and the residue was filtered through silica gel (8.5 cm × 2.5 cm) using 250 mL of 3:2 petroleum ether/ether. Yield: 1.305 g (72%) after concentration *in vacuo*. To 1.2 g (6.6 mmol) of the cycloadduct was added a solution of 2 mL of H_2O, 3.3 mL of EtOH, and 0.74 g (18.2 mmol) of KOH. The solution was stirred under a gentle reflux for 90 min. and partly evaporated (2–3 mL total volume) *in vacuo*. A 5 mL

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volume of H_2O was added and after 5 min stirring, 3 mL of 6 M HCl was added and the solution became bright yellow with some insoluble matter. After 14 h with stirring at 50–60 °C the product was extracted from the aqueous phase with ether (5 × 10–15 mL of Et_2O). The combined ethereal phases were dried with $MgSO_4$ and evaporated until dryness. Yield: 66% (60% ee). The raw product contained only small amounts of impurities according to NMR spectroscopy. To times recrystallization from *i*-Pr_2O gave the almost enantiopure (> 99.5%) bicyclic lactone in 34% yield. The procedure was not optimized.

Ethyl 2-oxabicyclo[2.2.2]oct-5-ene-3-carboxylate (5f): ^{1}H NMR: 6.54–6.50 (m, 1H, C=CH), 6.28–6.24 (m, 1H, C=CH), 4.59–4.56 (m, 1H, OCH), 4.29 (br s, 1H, OCH), 4.18–4.13 (q, 2H, J = 7.1 Hz, OCH_2), 3.10–3.08 (m, 1H, CH), 2.10–2.01 (m, 1H, CH), 1.78–1.70 (m, 1H, CH), 1.43–1.26 (m, 2H, 2 CH), 1.21–1.26 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR: 172.2, 134.6, 130.5, 74.1, 66.4, 60.7, 33.2, 25.6, 20.8, 14.2. $[\alpha]^{20}_D$ −3.4° (*c* 3.0 $CHCl_3$) 60% ee.

(*1R,3S,4S*)-9-Hydroxy-7-oxabicyclo[4.3.0]non-4-en-8-one (7): ^{1}H NMR: 6.28–6.22 (m, 1H, C=CH), 5.97–5.92 (m, 1H, C=CH), 4.73–4.68 (m, 2H, 2 OCH), 2.93 (br s, 1H, OH), 2.77–2.67 (m, 1H, CH), 2.28–2.17 (m, 1H, CH), 2.08–1.98 (m, 1H, CH), 1.96–1.91 (m, 1H, CH), 1.29–1.13 (m, 1H, CH). ^{13}C NMR: 177.3, 136.6, 121.6, 71.8, 71.5, 39.1, 23.1, 17.3. $[\alpha]^{20}_D$ −140.1° (*c* 1.2 $CHCl_3$) >99.5% ee.

Reaction of Isopropyl Glyoxylate and 1,3-Butadiene. The catalyst solution was prepared according to the standard procedure above. Ethyl glyoxylate was added, and 5–10 equiv of 1,3-butadiene was bubbled into the solution. After 5 days stirring at rt, 5 mL of heptane was added and the solution was filtered through a plug of silica gel (2 cm × 2 cm) using 100 mL of 2:8 ethyl acetate/heptane as the eluent. FC (18 cm × 1.5 cm silica gel, 2:8 ethyl acetate/heptane) yields the DA product in 55% yield and 87% ee.

(*S*)-(−)-Isopropyl 3,6-dihydro-2*H*-pyran-2-carboxylate (5a): ^{1}H NMR: 5.88–5.71 (m, 2H, 2 C=CH), 5.16–5.08 (m, 1H, OCH), 4.42–4.16 (m, 3H, OCH, OCH_2), 2.39–2.33 (m, 2H, CH_2), 1.29–1.26 (m, 6H, 2 CH_3). ^{13}C NMR: 171.0, 126.0, 122.9, 72.1, 68.5, 65.5, 27.7, 21.7. $[\alpha]^{20}_D$ −124° (*c* 0.9, $CHCl_3$) 87% ee.

Reduction of (*S*)-(−)-Isopropyl 3,6-Dihydro-2*H*-pyran-2-carboxylate (5a). Determination of Absolute Configuration. An 89 mg (0.52 mmol) amount of the isopropyl ester in 0.5 mL of Et_2O was added with cannula to a slurry of 11 mg (0.29 mmol) of $LiAlH_4$ in 1 mL of Et_2O. The mixture was stirred 2 h at rt and 1 h at gentle reflux. The solution was quenched with 1 mL of H_2O, and 10% H_2SO_4 was added until $Al(OH)_3$ was gone into solution. Extraction with Et_2O followed by FC (18 cm × 1.5 cm silica gel, Et_2O) gave the alcohol in 40% yield. The levorotatory alcohol produced has (*S*) configuration according ref 30.

(*S*)-(−)-(3,6-Dihydro-2H-pyran-2-yl)methanol: ^{1}H NMR: 5.86–5.70 (m, 2H, 2 C=CH), 4.24–4.21 (m, 2H, OCH_2), 3.71–3.53 (m, 3H, OCH_2, OCH), 2.31 (br s, 1H, OH), 2.15–2.04 (m, 2H, CH_2), 1.93–1.85 (m, 2H, CH_2). ^{13}C NMR: 126.2, 123.6, 74.0, 65.7, 65.6, 26.4. $[\alpha]^{20}_D$ −130° (*c* 0.7, $CHCl_3$) 87% ee (determined by GC as the trifluoroacetate derivative).

Reduction of (*S*)-(−)-Ethyl 4,5-Dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate (5d). Determination of Absolute Configuration. Standard $LiAlH_4$ reduction of 45 mg of ester yields 27 mg of levorotatory alcohol (79%). According to ref 30 does the ester have an (*S*) configuration.

(*S*)-(−)-(4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-methanol: ^{1}H NMR: 4.10–3.95 (br dd, 2H, OCH_2), 3.71–3.52 (m, 3H, OCH_2, OCH), 2.20–2.16 (m, 1H, CH), 2.07–1.99 (m, 1H, CH), 1.75–1.69 (br d, 1H, OH), 1.66 (br s, 3H, CH_3), 1.55 (br s, 3H, CH_3). ^{13}C NMR: 124.4, 122.9, 74.6, 69.5, 65.7, 32.0, 18.4, 13.9. $[\alpha]^{20}_D$ −139° (*c* 1.2, $CHCl_3$).

Reduction of *endo*-DA Product 5f of Ethyl Glyoxylate and 1,3-Cyclohexadiene. Determination of Absolute Configuration. Standard $LiAlH_4$ reduction of 100 mg of ester yields 48 mg of dextrorotatory alcohol (62%). According to ref 30, the ester has a (*1R,3S,4S*) configuration.

(*1R,3S,4S*)-(2-oxabicyclo[2.2.2]oct-5-en-3-yl)methanol: ^{1}H NMR: 6.49–6.45 (m, 1H, C=CH), 6.35–6.30 (m, 1H, C=CH), 4.39 (br s, 1H, OCH), 3.89–3.85 (br t, 1H, OCH), 3.40–3.29 (m, 2H, OCH_2), 2.65–2.63 (br d, 1H, CH), 2.09–1.98 (m, 2H, CH, OH), 1.74–1.67 (m, 1H, CH), 1.42–1.30 (m, 2H, CH_2). ^{13}C NMR: 134.1, 132.2, 76.5, 66.2, 65.8, 32.0, 25.7, 22.1. $[\alpha]^{20}_D$ +38° (*c* 0.4 $CHCl_3$).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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