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Chiral CO_2-Synthons via Catalytic Asymmetric Hetero-Diels−Alder Reactions of Ketomalonate and Dienes

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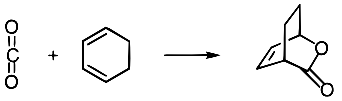
A catalytic enantioselective approach for the formation of chiral CO_2-synthons is presented. The described methodology is based on the reaction of dienes with diethyl ketomalonate using C_2-symmetric bisoxazolines as the chiral ligands and copper(II) and zinc(II) as the Lewis acids. For cyclic dienes the reaction proceeds in good yield and with up to 93% ee for 1,3-cyclohexadiene, while for cyclopentadiene the reaction also proceeds well at low temperature, but increasing the temperature leads to a retro-Diels−Alder reaction. The reaction has been studied under different conditions and for various dienes, and it has been found that for activated dienes both the hetero-Diels−Alder and Mukaiyama aldol products are isolated. The compound formed by the enantioselective hetero-Diels−Alder reaction of 1,3-cyclohexadiene with ketomalonate has been converted to both the CO_2-synthon formed in principle from the [2+4] cycloaddition reaction of CO_2 and 1,3-cyclohexadiene, and attractive optically active 1,4-disubstituted cyclohexene diols. The absolute configuration of the hetero-Diels−Alder adduct has been assigned on the basis of the structure of (1*S*)-camphanic ester of a 1,4-disubstituted cyclohexene diol which gave suitable crystals for X-ray analysis. The reactions have also been analyzed from a theoretical point of view. First, the [2+4] cycloaddition reaction of CO_2 with 1,3-cyclohexadiene has been investigated, and then the relative stability of the two major isomers of bidentate ketomalonate coordinated to a copper(II) or zinc(II) Lewis acid dication was investigated applying density functional theory calculations. Finally, the energetics of the [2+4] hetero-Diels−Alder addition mechanisms typical of the reaction with normal dienes catalyzed by C_2-symmetric bisoxazoline−zinc(II) complexes using semiempirical calculations are presented.

Introduction

The hetero-Diels−Alder reaction of carbon dioxide with conjugated dienes, such as 1,3-cyclohexadiene, would principally afford a [2+4] cycloadduct containing a CO_2-synthon (eq 1). The reaction has, to the best of our knowledge, not yet been achieved because of the large energy barrier (vide infra),[1,2] and recently it has been stated that the product of this reaction could not possibly be obtained.[2b] If this reaction could be performed in an easy manner, it would lead to CO_2-synthons which could have great potential[1,3] in organic synthesis. Such a CO_2-synthon can easily be converted into synthetically important intermediates, e.g., diols of 1,4-disubstituted 2,3-cyclohexenes which can be used for the synthesis of highly valuable compounds such as cyclohexenyl -carbinols,[3a] anticapsin,[3b] etc. Furthermore, if the [2+4] cycloaddition product formed in this reaction could be prepared in an enantioselective manner, it would significantly enhance the potential of the reaction.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The CO_2-synthon theoretically derived from the [2+4] cycloaddition of carbon dioxide with 1,3-cyclohexadiene as outlined in eq 1 can be synthesized by an indirect approach, e.g., by the reaction of 1,3-cyclohexadiene (**1a**) with diethyl ketomalonate (**2**) serving as a CO_2-equivalent. Ruden and Bonjouklian were able to perform the initial hetero-Diels−Alder reaction between **2** and several dienes, and the cycloadducts were transformed into CO_2-synthons, such as **5**, by a Curtius degradation (Scheme 1).[2a,4a] However, the studied compounds were mainly of an achiral nature, and the reaction was generally conducted in a racemic fashion. Moreover, the reaction of diene **1a** afforded **5** in a poor overall yield of only 4%. Salomon et al. showed that a homodienophilic equivalent of carbon dioxide could be achieved via a thermal [2π+2π+2π] cycloaddition reaction of bicyclo[2.2.1]hepta-2,7-diene with **2** and subsequent oxidative bisdecarboxylation of α-alkoxymalonic acids into carboxylic esters.[5]

The crucial step for the formation of optically pure CO_2-synthons using ketomalonate **2** is the catalytic enantioselective hetero-Diels−Alder reaction of ketones with

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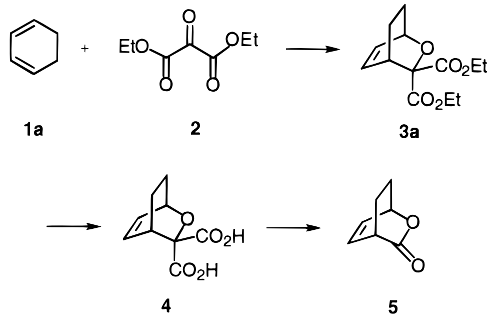
Scheme 1



dienes. The catalytic asymmetric hetero-Diels−Alder reaction between aldehydes and dienes has been available for some time.[6] The analogous reaction of ketones, which can lead to the formation of a chiral quaternary carbon center, however, has only been achieved very recently.[7] High yields and very high ee's were obtained using C_2-symmetric copper(II)−bisoxazolines as catalysts for the hetero-Diels−Alder reaction of α-diketones and α-keto esters with activated dienes applying a reaction protocol which shows very high activity and selectivity.[7b] Pioneering investigations of ketone hetero-Diels−Alder reactions using chiral Lewis acid catalysts were made by Jankowski et al. in 1987,[8a] and for the reaction of **2** with 1-methoxy-1,3-butadiene, the corresponding hetero-Diels−Alder adduct was formed in 100% yield but with only 15% ee employing menthoxyaluminum dichloride as the catalyst. Moreover, no attempts were made to transform the hetero-Diels−Alder product to the CO_2-synthon.

In this paper we describe the development of catalytic enantioselective hetero-Diels−Alder reactions of ketomalonate **2** with both activated and unactivated conjugated dienes leading to adducts with high ee. Furthermore, it will be shown that the cycloadduct can be transformed into a chiral CO_2-synthon. It is notable that the present catalytic enantioselective hetero-Diels−Alder reaction also gives a simple approach to highly valuable optically active 1,4-disubstituted 2,3-cyclohexenes. The reaction and intermediates are analyzed from a theoretical point of view in an attempt to obtain insight into the reaction mechanism, as well as structural and electronic information about the reaction intermediates. If a Danishefsky type diene is used, the reaction pathway proceeds initially as a Mukaiyama aldol reaction[9] and results finally in the formal hetero-Diels−Alder product in good yield and enantioselectivity. The intermediate, corresponding to the aldol step, has been isolated and characterized.

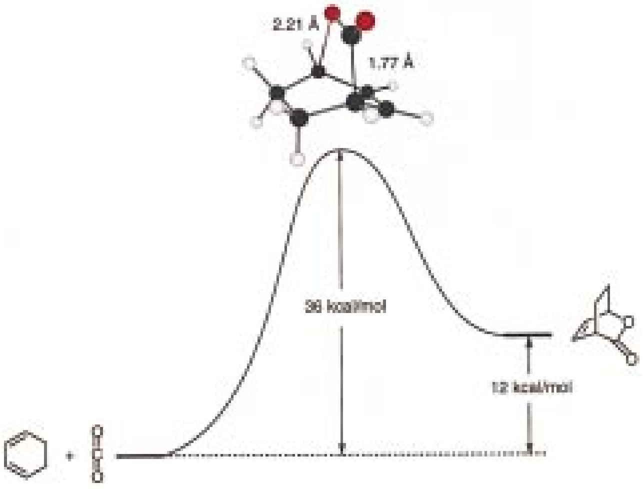


Figure 1. The reaction energy profile for the [2+4] cycloaddition reaction of CO_2 with 1,3-cyclohexadiene obtained by DFT calculations. The bond lengths for the forming bonds in the transition state are also shown.

Results and Discussion

Theoretical Analysis of the [2+4] Cycloaddition Reaction of Carbon Dioxide with 1,3-Cyclohexadiene. We will start with a theoretical investigation of the [2+4] cycloaddition reaction of carbon dioxide with 1,3-cyclohexadiene (eq 1) to determine the energetics of the basic reaction leading to the CO_2-synthon. This reaction has been studied by DFT calculations, using the GAUSSIAN 94 program,[10] with the BLYP gradient-corrected exchange-correlation functional and applying full optimization of substrates and products as well as characterization of the transition state for the reaction using a BLYP/6-31G* basis set.

The total energy of the optimized structures of carbon dioxide and cyclohexadiene are calculated to be −421.8499 au. The transition state for the [2+4] cycloaddition reaction has been localized, and the transition state energy is calculated to be 36 kcal·mol^{-1} relative to the substrates. The calculated transition state structure is shown in Figure 1 together with the reaction energy profile for the reaction outlined in eq 1. Besides the energy changes for the reaction, only the forming C−O and C−C bond lengths calculated to be 2.21 and 1.77 Å, respectively, in the transition state are given in Figure 1. The product of the reaction is calculated to be 12 kcal·mol^{-1} less stable than the substrates. The theoretical calculations show that the direct [2+4] cycloaddition reaction of carbon dioxide with 1,3-cyclohexadiene re-

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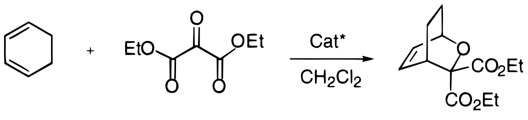
Table 1. Hetero-Diels–Alder Reaction between 1,3-Cyclohexadiene (1a) and Ketomalonate 2 Catalyzed by Different Chiral Lewis Acids



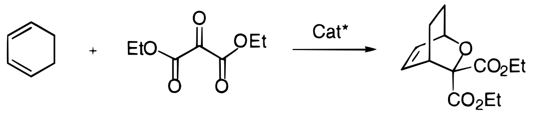
1a **2** **3a**

entry	catalyst	cat. load. (mol %)	temp/time (°C/h)	yield (%)[a]	ee (%)[b]
1	(*S*)-**6a**–$Cu(OTf)_2$	5	rt/18	40	27
2	(*S*)-**6a**–$Cu(OTf)_2$	5	−40/70	20	40
3	(*S*)-**6a**–$Cu(SbF_6)_2$	5	rt/17	48	21
4	(*S*)-**6a**–$Cu(SbF_6)_2$	5	−40/70	11	64
5	(*S*)-**6a**–$Cu(OTf)_2$	20	−35/18	75	24
6	(*R*)-**6b**–$Zn(OTf)_2$	5	rt/17	52	77
7	(*R*)-**6b**–$Zn(OTf)_2$	10	rt/22	68	76
8	(*R*)-**6b**–$Zn(OTf)_2$	20	rt/17	76	77
9	(*R*)-**6b**–$Zn(OTf)_2$	10	−25/4 d	31	91
10	(*R*)-**6b**–$Zn(SbF_6)_2$	10	rt/36	65	27
11	(*R*)-**6b**–$Cu(OTf)_2$	10	rt/19	76	84
12	(4*R*,5*R*)-**6c**–$Zn(OTf)_2$	10	rt/18	64	34
13	(4*R*,5*S*)-**6d**–$Zn(OTf)_2$	10	rt/18	66	75
14	(*S*)-**7a**–$AlMe_3$	10	rt/18	–	–
15	(*R*)-**7b**–$AlMe_3$	10	rt/18	13	33

[a] Isolated yield. [b] Ee determined by HPLC using a Chiralpak AD column or by chiral GC using a Chrompack Chirasil-DEX CB column.

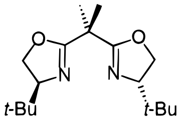
quires a relatively high activation energy, but also that the product might be expected to be fairly unstable compared with the substrates.

Development of the Catalytic Enantioselective Hetero-Diels–Alder Reaction of Conjugated Dienes with Ketomalonate 2 Leading to Optically Active CO_2-Synthons. To achieve the synthesis of optically active CO_2-synthons, the hetero-Diels–Alder reaction of dienes with ketomalonate **2** has to be conducted in an enantioselective manner. Initially, we utilized the 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]–$Cu(OTf)_2$ [(*S*)-**6a**–$Cu(OTf)_2$] as catalyst for the reaction (eq 2), since this complex has recently been found to promote very efficiently the hetero-Diels–Alder reaction between α-diketones and α-keto esters with activated dienes, resulting in excellent ee's.[7b] However, only a yield of 40% with 27% ee of **3a** was achieved by employing catalyst (*S*)-**6a**–$Cu(OTf)_2$ for the reaction between **1a** and **2**. Attempts to improve the results on the basis of the use of this ligand were not successful (Table 1, entries 1–5). The reason might be that **2** is a C_2-symmetric substrate and the reaction site keto carbonyl functionality lies along the C_2-axis, which makes it difficult to achieve good asymmetric induction using a chiral Lewis acid with a distorted square planar structure[6g,7g,11] in the intermediate.

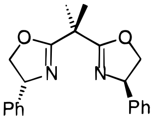


(2)

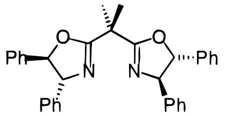
1a **2** **3a**



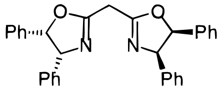
(*S*)-**6a**



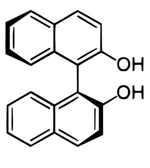
(*R*)-**6b**



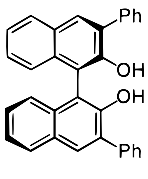
(4*R*,5*R*)-**6c**



(4*R*,5*S*)-**6d**



(*S*)-**7a**



(*R*)-**7b**

We then investigated other bisoxazoline type ligands[12] such as (*R*)-**6b**, (4*R*,5*R*)-**6c**, and (4*R*,5*S*)-**6d** in combination with zinc(II) and copper(II) salts as the catalysts for their ability to catalyze the studied reaction (eq 2). Fortunately, we found that phenyl-substituted bisoxazoline type ligands in combination with $Zn(OTf)_2$ or $Cu(OTf)_2$ are good catalysts for the reaction between 1,3-cyclohexadiene (**1a**) and ketomalonate **2**. The best result, i.e., 76% yield with 84% ee of **3a**, was obtained when (*R*)-**6b**–$Cu(OTf)_2$ was used as the catalyst (entry 11). Catalyst (*R*)-**6b**–$Zn(OTf)_2$ was also found to be very promising for the above reaction as **3a** was formed in 68% yield with 76% ee in the presence of 10 mol % of catalyst (entry 7). On the other hand, performing the reaction at −25 °C leads to a significant increase in ee of up to 91% (entry 9). However, the yield was reduced to only 31% in the latter case. A similarly good yield and ee of **3a** were obtained when the (4*R*,5*S*)-**6d** ligand was employed in combination with $Zn(OTf)_2$ as the Lewis acid (entry

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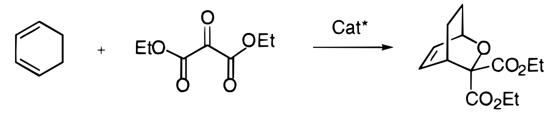
Table 2. Influence of Solvent, Temperature, and Catalyst Loading on the Hetero-Diels−Alder Reaction between 1,3-Cyclohexadiene (1a) and Ketomalonate 2 Catalyzed by (*R*)-4b−Zn(OTf)$_2$ and (*R*)-4b−Cu(OTf)$_2$, Respectively



1a **2** **3a**

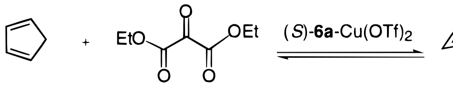
entry	catalyst	solvent	cat. load. (mol %)	temp/time (°C/h)	yield (%)[a]	ee (%)[b]
1	(*R*)-**6b**−Zn(OTf)$_2$	CH$_2$Cl$_2$	10	rt/22	68	72
2	(*R*)-**6b**−Zn(OTf)$_2$	CH$_2$Cl$_2$	10	−10/84	39	86
3	(*R*)-**6b**−Zn(OTf)$_2$	Et$_2$O	10	rt/144	94	91
4	(*R*)-**6b**−Zn(OTf)$_2$	Et$_2$O	10	−10/106	40	91
5	(*R*)-**6b**−Zn(OTf)$_2$	Et$_2$O	5	rt/115	60	91
6	(*R*)-**6b**−Zn(OTf)$_2$	Et$_2$O/CH$_2$Cl$_2$ (1:1, v/v)	10	rt/120	59	72
7	(*R*)-**6b**−Zn(OTf)$_2$	PhMe	10	rt/120	59	90
8	(*R*)-**6b**−Zn(OTf)$_2$	PhMe	10	rt/240	68	90
9	(*R*)-**6b**−Zn(OTf)$_2$	THF	10	rt/32	15	86
10	(*R*)-**6b**−Zn(OTf)$_2$	MeCN	10	rt/52	17	23
11	(*R*)-**6b**−Cu(OTf)$_2$	THF	10	rt/18	70	72
12	(*R*)-**6b**−Cu(OTf)$_2$	CH$_2$Cl$_2$	10	rt/19	70	72
13	(*R*)-**6b**−Cu(OTf)$_2$	Et$_2$O	10	rt/18	78	86
14	(*R*)-**6b**−Cu(OTf)$_2$	Et$_2$O	10	−20/89	64	93
15	(*R*)-**6b**−Cu(OTf)$_2$	Et$_2$O	5	rt/18	63	86
16	(*R*)-**6b**−Cu(OTf)$_2$	Et$_2$O	1	rt/66	68	85

[a] Isolated yield. [b] Ee determined by HPLC using a Chiralpak AD column or by chiral GC using a Chrompack Chirasil-DEX CB column.

13), while (4*R*,5*R*)-**6c**−Zn(OTf)$_2$ induced a reaction leading to good yield of **3a**, but with only moderate ee (entry 12). The BINOL ligands (*S*)-**7a** and (*R*)-**7b** in combination with AlMe$_3$ were also tested for their ability to catalyze the studied reaction since such catalysts have been found to give good results for hetero-Diels−Alder reactions of glyoxylate esters.[6h] However, using (*S*)-**7a**−AlMe$_3$ as the catalyst, no product was isolated after the reaction was kept at room temperature for 18 h (entry 14), whereas the phenyl-substituted (*R*)-**7b**−AlMe$_3$ catalyzed the hetero-Diels−Alder reaction between **1a** and **2**, affording **3a** in very low yield and modest ee (entry 15).

It was therefore decided to investigate optimal conditions using (*R*)-**6b**−Zn(OTf)$_2$ and (*R*)-**6b**−Cu(OTf)$_2$ as the catalysts for the reaction described in eq 2, and the results are presented in Table 2. It became evident that in both cases the asymmetric induction was best using Et$_2$O as the solvent (entries 3−5 and 13−16), although the reaction performed in Et$_2$O was slower than in CH$_2$Cl$_2$ when (*R*)-**6b**−Zn(OTf)$_2$ was used as the catalyst (entries 1−4). THF and PhMe also afforded good ee, but the reaction became sluggish, and therefore, the yield was lower than in the case of Et$_2$O, or a much longer reaction time was needed (entries 7−9). More polar solvents, e.g., MeCN, appear to be unfavorable as both yield (17%) and ee (23%) are low (entry 10). Using (*R*)-**6b**−Cu(OTf)$_2$ as the catalyst and performing the reaction at −20 °C, the highest ee (93%) of **3a** was obtained with a catalyst loading of 10 mol % (entry 14). The catalyst loading could be reduced to 5 mol % and further to 1 mol %, and still high ee was achieved while the yield dropped to 60−68% (entries 5, 15, and 16). Under the optimized reaction conditions, both (*R*)-**6b**−Cu(OTf)$_2$ and (*R*)-**6b**−Zn(OTf)$_2$ are suitable as catalysts for the reaction of 1,3-cyclohexadiene (**1a**) with ketomalonate **2** leading to the formation of **3a** with high ee. Compared to the copper(II)-derived catalyst which affords a much faster reaction, the use of the zinc(II)-derived catalyst is more convenient as the reaction could be conducted at room temperature to achieve an ee of 91% and a yield of 94% (entry 3).

The reactions of ketomalonate **2** with other dienes, i.e., **1b**−**d**, have also been investigated. For the reaction of 1,3-cyclopentadiene (**1b**) and **2**, previous attempts to perform this reaction under thermal conditions at various temperatures ranging from −20 to +135 °C failed, and the supposed hetero-Diels−Alder adduct **3b** has, according to our knowledge, never been isolated,[4a,13] and no evidence for the formation of **3b** has been reported. However, in our investigation, the reaction of **1b** with **2** in the presence of (*S*)-**6a**−Cu(OTf)$_2$ as the catalyst (eq 3) showed some very interesting behavior. When the reaction was performed at room temperature, no hetero-Diels−Alder adduct **3b** was observed. However, when the reaction temperature was lowered to −40 to −78 °C, both TLC and ^{1}H NMR spectra showed that **3b** was formed with high conversion, but upon removal of solvent using a conventional rotary evaporator in vacuo, no product could be detected in the residue either by TLC or by NMR spectroscopy. Further investigation of the reaction monitored by ^{1}H NMR spectroscopy showed that a retro-hetero-Diels−Alder reaction[14] probably took place when the reaction temperature was increased to above −30 °C, since the formed product **3b** disappeared gradually with the increase of temperature, while substrates could be recognized (see the Experimental Section for details and Supporting Information for ^{1}H NMR spectroscopic evidence). Thus, no further investigation of the catalytic hetero-Diels−Alder reaction of 1,3-cyclopentadiene (**1b**) with ketomalonate **2** was undertaken.



1b **2** **3b** (3)

For the reaction of ketomalonate **2** with activated dienes such as the Danishefsky type diene **1c**, good ee

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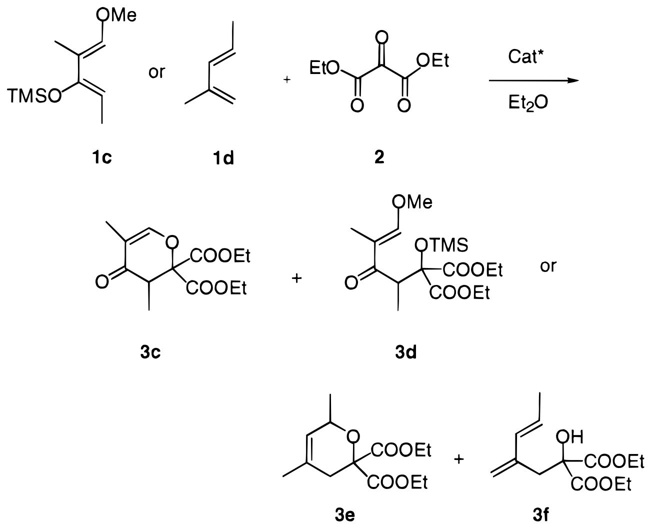
[13] (a) Achmatowicz, O.; Zamojski, A. *Rocz. Chim.* **1961**, *35*, 125. (b) Zamojski, A.; Jankowski, K. *Rocz. Chim.* **1964**, *38*, 707.

[14] Prasad, J. V. N.; Iyer, P.; Pillai, C. N. *J. Org. Chem.* **1982**, *47*, 1381.

Table 3. Results of the Hetero-Diels−Alder Reaction of Dienes 1c,d with Ketomalonate 2 in the Presence of 10 Mol % Catalyst

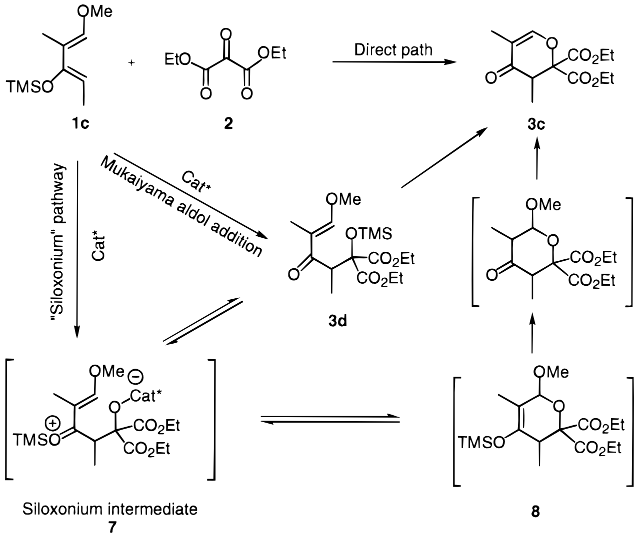


entry	catalyst	diene	product	temp/time (°C/h)	yield (%)[a]	ee (%)[b]
1	(*R*)-**6b**−Zn(OTf)$_2$	**1c**	**3c**/**3d** (7:1)	rt/21	82 (**3c**) 12 (**3d**)	84 (**3c**)
2	(*R*)-**6b**−Zn(OTf)$_2$	**1c**	**3c**/**3d** (24:1)	rt/139	94 (**3c**) 4 (**3d**)	84 (**3c**)
3	(*R*)-**6b**−Cu(OTf)$_2$	**1c**	**3c**/**3d** (40:1)	rt/19	79 (**3c**) 2 (**3d**)	9 (**3c**)
4	(*R*)-**6b**−Cu(OTf)$_2$	**1c**	**3c**/**3d** (1:1)	−20/43	43 (**3c**,**3d**)	9 (**3c**)
5	(*R*)-**6b**−Zn(OTf)$_2$	**1d**	**3e**/**3f** (1:1.3)	rt/24	30 (**3e**) 39 (**3f**)	25 (**3e**)
6	(*R*)-**6b**−Cu(OTf)$_2$	**1d**	**3e**/**3f** (1:15)	−20/48	5 (**3e**) 74 (**3f**)	33 (**3e**)

[a] Isolated yield. [b] Ee determined by HPLC using a Chiralpak AD column or by chiral GC using a Chrompack Chirasil-DEX CB column.

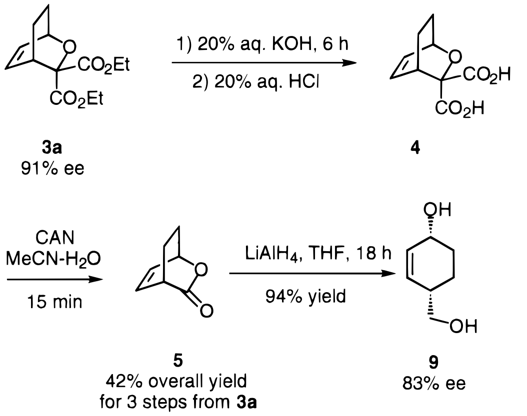
and yield of the hetero-Diels−Alder adduct **3c** were achieved with (*R*)-**6b**−Zn(OTf)$_2$ as the catalyst (Table 3, entries 1 and 2). Surprisingly, the copper(II)-derived catalyst (*R*)-**6b**−Cu(OTf)$_2$ afforded only a 9% ee of **3c** even by performing the reaction at −20 °C (entries 3 and 4). The reason for the occurrence of a nearly racemic reaction between **2** and **1c** in the latter case is not clear at present. Besides the formal hetero-Diels−Alder product **3c**, the Mukaiyama aldol product **3d** was also isolated. It is established that Danishefsky type dienes can undergo a Mukaiyama aldol reaction in the presence of various catalysts.[9] However, in most cases the formal hetero-Diels−Alder adduct is the isolated product only after prolonged acidic treatment of the reaction mixture.[6a,b,7a,b] A “siloxonium” pathway may explain the early appearance of the pyrone besides the aldol product (Scheme 2). We were able to isolate both formal hetero-Diels−Alder product **3c** and the Mukaiyama aldol product **3d** simply by quenching the reaction without adding any additional acid. The ratio of the two products is easily influenced by prolonging the reaction time. Thus, a ratio of 24:1 is achieved after 139 h at room temperature using catalyst (*R*)-**6b**−Zn(OTf)$_2$, while **3c** was predominant by only 7:1 after 21 h (entries 1 and 2). When the reaction was performed at room temperature using the more acidic Cu(OTf)$_2$ as the Lewis acid, a ratio of 40:1 of the ring-closed hetero-Diels−Alder product **3c** to the ring-opened aldol adduct **3d** was obtained, but when the reaction was run at −20 °C, equal amounts of both products were observed (entries 3 and 4). Thus, it may be speculated whether the siloxonium pathway is predominant, leading to both the Mukaiyama aldol and formal hetero-Diels−Alder product, where the latter one is the thermodynamically more stable one. The mechanism suggested is outlined in Scheme 2.[9]

Scheme 2



In the case of the unactivated diene 2-methyl-1,3-pentadiene, **1d**, a competition between the hetero-Diels−Alder reaction and the ene reaction was observed. Both catalysts (*R*)-**6b**−Zn(OTf)$_2$ and (*R*)-**6b**−Cu(OTf)$_2$ led to only moderate ee, but they influenced the ratio of hetero-Diels−Alder product **3e**:ene product **3f** in very different ways. The zinc(II)-derived catalyst afforded a nearly 1:1 ratio with a slight excess of the ene product (entry 5),

Scheme 3



while (R)-**6b**−Cu(OTf)$_2$ afforded a 1:15 ratio in favor of the ene product **3f** (entry 6).

To achieve the synthesis of the chiral CO$_2$-synthon **5**, diester **3a** has to be hydrolyzed, and the resulting dicarboxylic acid has to be bisdecarboxylated. Bonjouklian and Ruden have reported the transformation of different diesters into lactones via a Curtius degradation process which proved to be superior over the Pb(OAc)$_4$ method studied by the same authors.[2a,4a] In their investigation the studied diacids were achiral, and although the enantioselectivity was not an issue, the transformation into the corresponding lactones as in the case of compound **5** was achieved with very poor overall yield (4%). We present here a methodology which applies a decarboxylation method using cerium ammonium nitrate (CAN) as a very mild oxidant[5] (Scheme 3). It has been found that the isolated yield of **5** can be improved significantly if the transformation of diester **3a** to **5** is performed in a one-pot procedure without isolation of diacid **4**. Thus, diester **3a** was treated with KOH, and after neutralization of the reaction mixture, treatment with CAN and purification by column chromatography afforded lactone **5** in a 42% overall yield. The ^{1}H NMR spectroscopic data of the isolated compound **5** were in accordance with the literature data,[4a] and ^{13}C NMR spectroscopy exhibited the presence of only one carbonyl functionality. However, the expected instability of **5** made ee determination by GC analysis impossible as only 1,3-cyclohexadiene was detected by GC−MS. Also HPLC analysis using a Chiracel OD or OJ column or Chiralpak AD column did not result in separation of the two enantiomers of **5**. Thus, lactone **5** was transformed into diol **9** by treatment with LiAlH$_4$. This synthetically very interesting compound containing a primary and a secondary hydroxyl group on the cyclohexene ring was obtained in an isolated yield of 94% from **5**. The ee of **9** from a sample of **3a** with 91% ee was found to be 83% as determined by HPLC using a Chiralpak AD column. Thus, 8% ee was lost during the transformation of diester **3a** to diol **9**. It is notable that the diol **9** might be used as an important optically active building block in organic synthesis.

Assignment of the Absolute Configuration of the Hetero-Diels−Alder Adduct 3a. To account for the reaction mechanism in the present catalytic enantioselective reactions, the absolute configuration of the adduct has to be assigned. In relation to the mechanism for the present reaction, one of the crucial questions is, how does the ketomalonate coordinate to the Lewis acid complex catalyst (vide infra)?

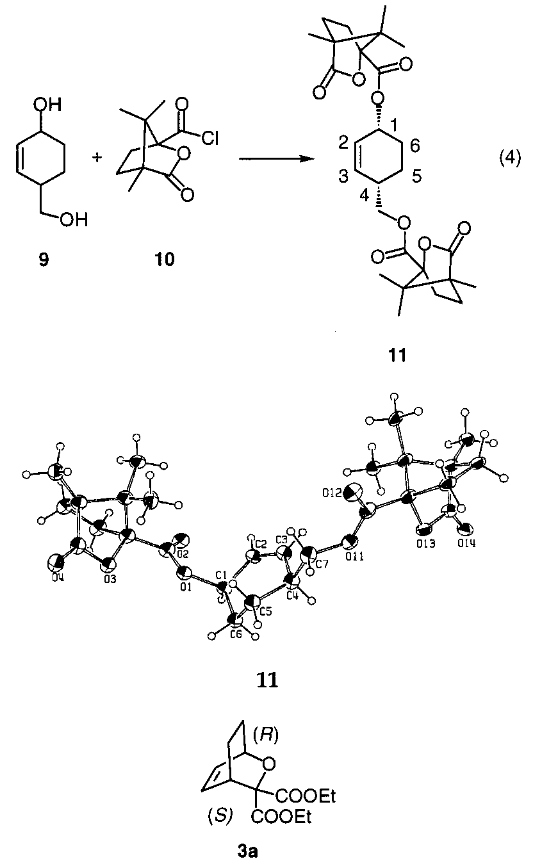


Figure 2. (top) The reaction of diol **9** with (1S)-camphanic chloride (**10**) (eq 4). (middle) The X-ray structure of **11** used for the assignment of the absolute configuration of the cyclohexene ring. (bottom) The assignment of the absolute configuration of hetero-Diels−Alder adduct **3a** formed from the reaction of 1,3-cyclohexadiene (**1a**) with ketomalonate **2** catalyzed by (R)-**6b**−Zn(OTf)$_2$.

The absolute configuration of the hetero-Diels−Alder adduct **3a** formed in the reaction of ketomalonate **2** with 1,3-cyclohexadiene (**1a**) in the presence of (R)-**6b**−Zn(OTf)$_2$ as the catalyst has been assigned by the following procedure: Compound **3a** was transformed to 1,4-disubstituted 2,3-cyclohexene diol **9**, followed by reaction with (1S)-camphanic chloride (**10**) to give the diester **11** (eq 4, Figure 2) which gave suitable crystals for X-ray analysis.

The X-ray structure of **11** in Figure 2 shows that both hydroxy groups in **9** have reacted with (1S)-camphanic chloride (**10**). On the basis of the X-ray structure analysis of **11**, the absolute configuration of the two formed chiral centers in the cyclohexene ring of **9** have been assigned as (1R,4S). Having this assignment in hand, it was concluded that chiral centers formed in the hetero-Diels−Alder adduct **3a** using (R)-**6b**−Zn(OTf)$_2$ as the catalyst had the absolute configuration (1R,4S) as shown in Figure 2. With the absolute configuration of **3a** known, the possible structures of the intermediates and the mechanism of the addition reaction have been studied, and the results are presented below.

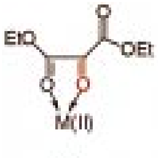
Theoretical Calculations of the Intermediates and Mechanistic Aspects. Several interesting aspects of the coordination of ketomalonate **2** to the Lewis acids emerge. It is generally accepted that α-dicarbonyl com-

Table 4. Calculated Relative Stability of Five- and Six-Membered-Ring Intermediates, Charge of the Reacting Carbonyl Functionality, and LUMO Energy of Ketomalonate Coordinated to Cu(II) and Zn(II) Model Systems

entry	ring size	metal	relative energy (kcal·mol^{-1})	charge (C)	charge (O)	LUMO energy (eV)
1[a]	5 (**12**)	Cu	4.6[b]	0.49	−0.58	−6.8[c]
2[a]	6 (**13**)	Cu	0.0[d]	0.32	−0.26	−6.1[c]
3[e]	5 (**12**)	Zn	5.3	0.52	−0.53	−10.3
4[e]	6 (**13**)	Zn	0.0[f]	0.47	−0.38	−10.0
5[g]	5 (**12**)	Zn	17.2	0.37	−0.30	−9.0
6[g]	6 (**13**)	Zn	0.0	0.26	−0.30	−8.2

[a] DFT calculations/UHF. [b] Relative to six-membered ring. [c] Average of α and β energies. [d] Total energy −1072.1067 au. [e] DFT calculations. [f] Total energy −1101.7848 au. [g] MNDO calculations.

pounds use both carbonyl functionalities to coordinate in a bidentate fashion to the Lewis acid. Assuming that **2** behaves in the same way for the coordination to either copper(II) or zinc(II) Lewis acids, two different intermediates can be formed, i.e., a five-membered-ring system **12** or a six-membered-ring system **13** (the reacting carbonyl functionality is shown in red).



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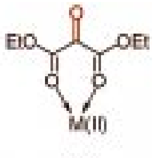

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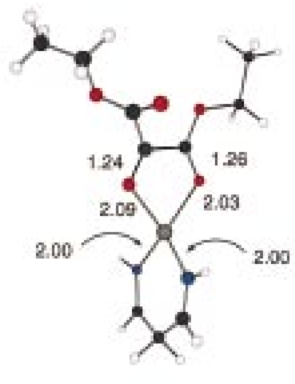
Theoretical investigations of several compounds have been undertaken to elucidate the structure of the catalytic species and to provide insight into underlying mechanisms. This work falls into two broad areas: the relative stabilities of the two isomers of bidentate ketomalonate coordinated with a copper(II) or zinc(II) Lewis acid dication and the energetics of the [2+4] hetero-Diels−Alder addition mechanisms of the reaction with dienes. Due to the large size of the full catalytic system, the bulk of the mechanistic work has been performed using the MNDO semiempirical technique; while certainly not of chemical accuracy, we believe that this method incorporates the aspects of electronic structure theory most essential for the qualitative description of the chemical transformations under study so that the computational results provide not proof, but useful evidence for interpreting the accompanying experimental results. Certain model systems are presented as well, which are amenable to the treatment by more powerful density functionality theory methods and serve to calibrate and check the semiempirical work.

We have optimized the structures **12** and **13** for copper(II) and zinc(II) using DFT calculations.[10] Furthermore, we have added a small C_2-ligand to model the bisoxazoline system used in the catalytic enantioselective reactions. The copper(II) and the zinc(II) complexes lead to two different electron counts. Four-coordinate 18-electron Zn(II) complexes are found to be tetrahedral, as is typical of such complexes, and this has also been postulated for reactions catalyzed by the zinc(II) bisoxazolines.[6g,12b,e] Four-coordinate 17-electron Cu(II) complexes stand intermediate between the classical limits of 18-electron tetrahedral and 16-electron square planar complexes, and are found in the calculations to take the square planar form.



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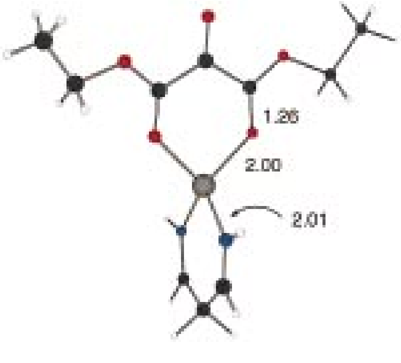

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Table 4 gives the important results for the present investigation of the optimized structures of **12** and **13**. The DFT optimized structures of the zinc(II) complexes are shown in **14** and **15** together with the calculated bond lengths at the metal center. These calculated bond lengths are only slightly dependent on whether it is the five- or six-membered complex. The square planar structure found for the Cu(II) is in accordance with X-ray structures of related complexes which have been discussed in relation to reactions catalyzed by C_2-symmetric bisoxazoline complexes,[7g,15] although other structural types of intermediates have also been invoked.

On the basis of the results presented in Table 4 for both metals, the six-membered ring **13** is more stable than the five-membered ring **12** by a modest number in kilocalories per mole (entries 1−4). Entries 5 and 6 are replications of the DFT calculations, using the MNDO semiempirical method, but only for the zinc complex. The stabilization trend is in agreement with the DFT calculations, but a comparison of the relative energies suggests that the semiempirical calculations “overestimate” the stability of **13** relative to **12** if compared with the DFT method. It is interesting to compare the electronic differences of the reacting carbonyl functionality in the two types of intermediates. For **12** the carbonyl functionality

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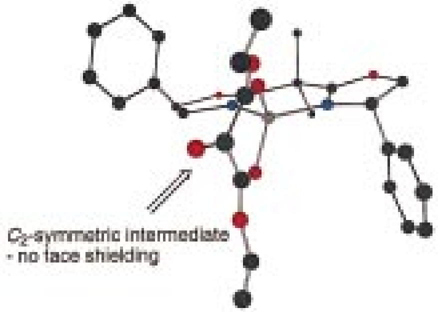
(15) See e.g. (a) Evans, D. A.; Rovis, T. Kozlowski, M. C.; Tedrow, J. *J. Am. Chem. Soc.* **1999**, *121* 1994.

is much more polarized compared with **13** (compare charges at carbon and oxygen atoms), indicating a more reactive carbonyl group in the former complex. Moreover, the LUMO energies of **12** and **13** indicate that the five-membered intermediate should be expected to be more reactive than the six-membered intermediate, as the LUMO energy of the former is lower than the latter by using a frontier orbital theory way of reasoning.

We are facing a classic dilemma in catalytic chemistry by looking at the results in Table 4. One intermediate, the six-membered-ring system, is slightly more stable than the five-membered-ring system, while the five-membered-ring system should, on the basis of the electronic data, be expected to be more reactive than the six-membered-ring system. Therefore, we have calculated the transition state energy for the reaction of 1,3-cyclohexadiene (**1a**) with ketomalonate **2** in the presence of (*S*)-**6b**−Zn(II) as the catalyst (please observe that it is the other enantiomer of the chiral ligand which has been used in the following calculations compared with the experimental results above).

Before proceeding with the theoretical investigations of the hetero-Diels−Alder reaction, we will focus on the structure of the actual intermediate(s) in the present reactions. The structure of the two coordination modes of ketomalonate—a five- and six-membered-ring system—to the (*S*)-**6b**−Zn(II) catalyst has been optimized using MNDO calculations, and the two structures are shown in **16** and **17** (hydrogen atoms omitted for clarity). For the six-membered ketomalonate−(*S*)-**6b**−Zn(II) intermediate **16**, the bidentate coordination of ketomalonate leads to a C_2-symmetric intermediate, and inspection of intermediate **16** reveals that there is no obvious face shielding of the reacting carbonyl functionality of ketomalonate **2** as it lies along the C_2-axis and is placed pointing away from the chiral ligand. The five-membered ketomalonate−(*S*)-**6b**−Zn(II) intermediate **17** is an asymmetric intermediate with one face of the reacting carbonyl functionality shielded by one of the phenyl substituents. The reason for face shielding in this case is that the reacting carbonyl functionality of **2** is now coordinated to the Lewis acid. If both intermediates **16** and **17** are present during the catalytic cycle, the former intermediate will lead to a racemic reaction, while the latter will introduce enantioselectivity in the addition step. The enantioselelectivity in the reaction is thus very dependent on the reactivity of the two intermediates **16** and **17**.



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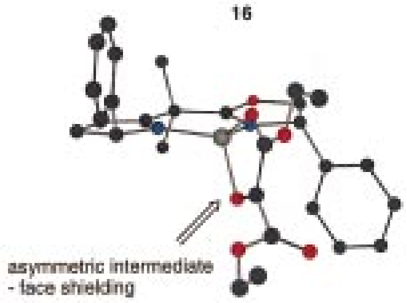

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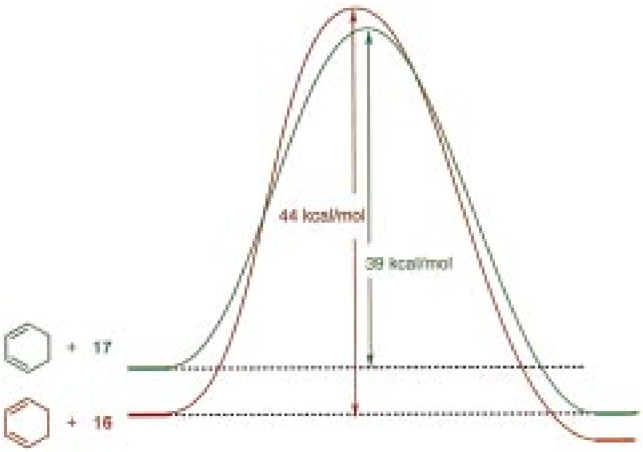
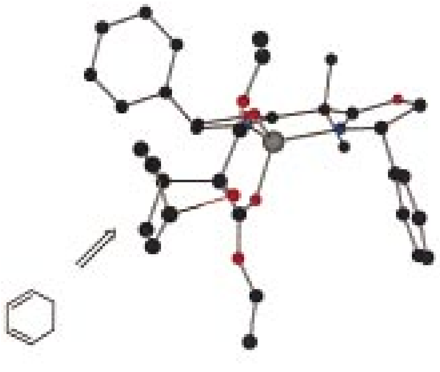


Figure 3. Reaction profile for the reaction of 1,3-cyclohexadiene with ketomalonate coordinated in a bidentate fashion to (*S*)-**6b**−Zn(II). The reaction and results in red are for the reaction which proceeds via the six-membered intermediate **16**, while the reaction and results in green are for the reaction proceeding via the five-membered intermediate **17**.

We have therefore studied the reaction of the two intermediates **16** and **17** with 1,3-cyclohexadiene (**1a**) by calculating the transition state for both the endo and exo approach of **1a** to ketomalonate **2** coordinated for both the five- and six-membered-ring intermediates. The reaction energy profile for the endo approach of **1a** to the reacting carbonyl functionality of **16** and **17** is outlined in Figure 3.

The calculated transition state energies for the hetero-Diels−Alder reaction of 1,3-cyclohexadiene (**1a**) with the intermediates **16** and **17** reveal that the activation energy for the reaction with the latter intermediate—the five membered-ring system—is 5 kcal·mol^{-1} lower in energy compared with the activation energy of the six-membered-ring system. The calculated transition state energies are 44 and 39 kcal·mol^{-1}, respectively (please note that the total energy of **1a** + **17** is higher than the total energy of **1a** + **16**). The calculated transition state energies for the two reaction paths are probably exaggerated because the MNDO calculations tend to overestimate the stability of **16** and **17** compared with the DFT calculations. However, we believe that the semiempirical calculations are able, in a qualitative way, to describe the difference in reaction paths in such a way that it allows one to begin to understand these reactions from a more detailed point of view.

A comparison of the calculated geometry of the transition state for the reaction of **1a** with intermediate **17** with the geometry for the [2+4] cycloaddition of carbon dioxide with **2** (vide supra) gives nearly the same bond lengths for the bonds being formed. The C−O and C−C bond lengths in the transition state for the catalytic reaction are 2.11 and 1.61 Å, respectively, compared with 2.21 and 1.77 Å for the carbon dioxide reaction. The results of the calculated transition state energies, relative to starting materials, point to a mechanism in which the more reactive intermediate is the one which has **2** coordinated to the catalyst in a bidentate fashion using the reacting carbonyl functionality and one of the ester carbonyls, leading to a five-membered-ring system. The calculated transition state structures for the approach of **1a** to the two intermediates **16** and **17** corresponding to the reaction profile in Figure 3 are shown in **18** and **19** (hydrogen atoms omitted for clarity), respectively.



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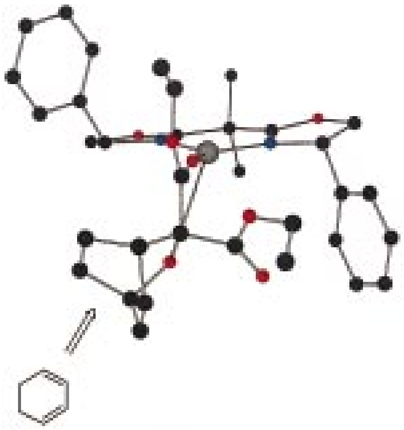

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The calculated transition states shown in **18** and **19** can account for the observed experimental results of the reaction between 1,3-cyclohexadiene and ketomalonate since the absolute configuration of the product **3a** using (*R*)-**3b**−Zn(II) is (1*R*,4*S*). For transition state **18** there is no obvious face shielding when **1a** approaches the reacting carbonyl functionality of **2** due to the C_2-symmetric intermediate **16**. However, for the calculated transition state structure **19** (please note that (*S*)-**6b** was used in the calculations), the phenyl substituent of the chiral ligand shields the *si*-face of the reacting carbonyl functionality, allowing the diene to approach from the *re*-face, and therefore a product with absolute configuration of (1*S*,4*R*) could be formed. Thus, the calculations are in accordance with the experimental results.

In relation to our proposal of the intermediate in the catalytic enantioselective reaction of ketomalonate **2** with dienes being a five-membered-ring system, it should be noted that Evans et al. in a very recent investigation of the catalytic enantioselective Michael addition of silylketene to alkylidene malonates has found evidence for a six-membered-ring system intermediate in reactions catalyzed by (*S*)-**6a**−Cu(II).[15]

The calculated transition state structure for the reaction of 1,3-cyclohexadiene **1a** with ketomalonate **2** in the presence of bisoxazoline−zinc(II) catalyst presented in **19** indicates that the reaction proceeds with simultaneous bond formation of the C−C and C−O bonds corresponding to the direct path in Scheme 2, although we cannot exclude that the reaction might also take place as a stepwise mechanism. The reaction of cyclopentadiene proceeds in a similar manner. However, for the reaction of activated dienes the results in Table 3 show that another reaction path probably also takes place as the Mukaiyama aldol product has also been isolated. We have therefore also investigated the reaction of **2** catalyzed by the bisoxazoline−zinc(II) catalyst (*S*)-**6b**−Zn(II) with the Danishefsky type diene **1c**. The transition state for the reaction of **1c** with five- and six-membered ketomalonate−(*S*)-**6b**−Zn(II) intermediates **17** and **16** has been calculated, and here only the trends of these calculations will be presented. These calculations also show that intermediate **17** is the more reactive one by reaction with diene **1c**. However, in this case the reaction does not take place with simultaneous formation of the C−C and C−O bonds. The first step is the formation of the siloxonium intermediate **7** (Scheme 2) formed by a nucleophilic-like attack of **1c** on the carbonyl functionality of **2** when coordinated to the catalyst. However, in this case, we have not been able to characterize a transition state for the direct path for the formation of the hetero-Diels−Alder adduct. The calculations thus support the experimental observations that for the activated dienes the reaction probably takes place as a stepwise mechanism, via the siloxonium intermediate **7** or **3d** in the first step. We cannot, on the basis of the calculations, distinguish whether **7** is formed in the first step followed by a rearrangement of the TMS substituent leading to **3d**, or if it is **3d** which is formed directly in a simultaneous catalytic addition step with formation of the carbon−carbon bond and rearrangement of the TMS substituent. However, on the basis of the calculations, we have been able to account for, and understand, the experimental results.

Conclusion

In conclusion, we have presented a high-yielding synthesis of CO_2-synthons, which was, for the first time, described in a catalytic enantioselective fashion with very good ee based on the reaction of diethyl ketomalonate with conjugated dienes. This novel methodology provides an attractive approach to optically active building blocks useful in organic synthesis. Moreover, the possible pathways, hetero-Diels−Alder and Mukaiyama aldol reactions of Danishefsky type dienes in the bisoxazoline−Lewis acid-catalyzed reactions, were further elucidated by the experimental and theoretical evidence presented. Theoretical calculations of various modes of the coordination of diethyl ketomalonate to the Lewis acids Cu(II) and Zn(II) and the calculation of transition state energies for the reaction of 1,3-cyclohexadiene were performed for the catalytic system. On the basis of the absolute configuration of the products obtained and the theoretical calculations, it is suggested that the reaction proceeds via a five-membered-ring intermediate.

Experimental Section

General Methods. All reactions under anhydrous conditions were carried out in a flame-dried Schlenk tube under

N_2. CH_2Cl_2 and CH_3CN were dried over CaH_2, and toluene, THF, and Et_2O over sodium/benzophenone, and they were all distilled prior to use. Merck silica gel (230−400 mesh) was used for flash chromatography (FC). ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as the deuterated solvent. Enantiomeric excess (ee) was determined by GC using a Chrompack Chirasil-DEX CB column or by HPLC using a Daicel Chiralpak AD column as stated in the experimental procedures. Optical rotations were measured with a sodium lamp at room temperature and reported as follows: $[\alpha]^{rt}_{D} = (c$, g/100 mL, solvent).

Materials. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] [(*S*)-**6a**], (*R*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline) [(*R*)-**6b**], 4,4′-methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] [(4*R*,5*S*)-**6d**], (*S*)-1,1′-bi-2-naphthol [(*S*)-**7a**], and dienes **1a** and **1d** were purchased from Aldrich, diethyl ketomalonate (**2**) was purchased from Lancaster, and they were all used as received. $Cu(OTf)_2$ and $Zn(OTf)_2$ from Aldrich were stored in a glovebox and used without further purification. 4,4′-Isopropylidenebis-[(4*R*,5*R*)-4,5-diphenyl-2-oxazoline] [(4*R*,5*R*)-**6c**],[16] (*R*)-1,1′-bi-3,3′-diphenyl-2-naphthol [(*R*)-**7b**],[17] and diene **1c**[18] were prepared as described in the literature.

General Procedure for the Hetero-Diels−Alder Reactions of Diethyl Ketomalonate 2 with Dienes Catalyzed by 10 mol % (*R*)-6b−Zn(OTf)$_2$. To a flame dried Schlenk tube were added $Zn(OTf)_2$ (18 mg, 0.05 mmol) and (*R*)-**6b** (16 mg, 0.055 mmol). The mixture was dried under vacuum for 1−2 h, freshly distilled anhydrous solvent (1.5 mL) was added, and the solution was stirred for 0.5−1 h. Subsequently, diethyl ketomalonate (**2**) (76 μL, 0.5 mmol) and diene **1** (1 mmol) were added. After being stirred for the required reaction time, the reaction mixture was filtered over a pad of silica and concentrated in vacuo, and the crude product was directly purified by flash column chromatography (FC) (20% EtOAc in pentane) to afford compound **3**. Ee was detected by chiral GC or HPLC using a Chiralpak AD column.

Preparation of 2-Oxa-3,3-dicarboethoxybicyclo[2.2.2]-oct-5-ene (3a). According to the general procedure, reaction between diethyl ketomalonate (**2**) (1.37 mL, 9.0 mmol) and 1,3-cyclohexadiene (**1a**) (1.72 mL, 18 mmol) using 10 mol % (*R*)-**6b**−$Zn(OTf)_2$ afforded, after purification by FC (20% EtOAc in pentane), compound **3a** (2.1474 g, 8.45 mmol, 94%) as a colorless viscous oil: 91% ee according to chiral GC or HPLC using a Chiralpak AD column (*i*-PrOH−hexane, 1:99, 0.5 mL/min); R_f 0.46 (20% EtOAc in pentane); $[\alpha]^{rt}_{D} = +55.5°$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 6.56−6.35 (m, 2H), 4.70−4.60 (m, 1H), 4.32−4.05 (m, 4H), 3.41−3.24 (m, 1H), 2.21−2.13 (m, 1H), 1.66−1.56 (m, 1H), 1.32−1.16 (m, 8H); ^{13}C NMR δ 169.5, 168.8, 133.7, 133.3, 82.9, 68.0, 61.9, 61.6, 34.6, 24.5, 17.5, 14.1, 14.0.

Reaction of 1,3-Cyclopentadiene 1b and Diethyl Ketomalonate (2). Evidence for Formation of 2-Oxabicyclo-[2.2.1]hept-5-ene-3,3-dicarboxylic Acid Diethyl Ester 3b. According to the general procedure, reaction of ketomalonate **2** (76 μL, 0.5 mmol) and 1,3-cyclopentadiene (**1b**) (1 mmol) was run at −78 °C in CH_2Cl_2. After 18 h at −78 °C, TLC analysis showed a clear spot with $R_f = 0.65$ (20% EtOAc in pentane). To an NMR tube was added 0.7 mL of $CDCl_3$, and the tube was placed at −78 °C for several minutes. Subsequently, an aliquot of the reaction mixture (0.1 mL) was added, and immediately a ^1H NMR spectrum was recorded. The ^1H NMR spectrum of the reaction mixture clearly showed the formation of **3b**: ^1H NMR δ 6.25−6.45 (m, 2H), 5.98 (br s, 1H), 4.32−4.05 (m, 4H), 3.86 (br s, 1H), 2.05−1.85 (m, 1H), 1.62−1.45 (m, 1H), 1.32−1.16 (m, 6H). After the NMR sample was kept at −78 °C for 2 h and further at −30 to −35 °C for 1 h, similar NMR spectra were obtained in both cases. However, keeping the NMR sample at room temperature overnight, both TLC and ^1H NMR spectroscopy showed only a trace of **3b**, but both 1,3-cyclopentadiene (**1b**) and diethyl ketomalonate (**2**) could be recognized from the ^1H NMR spectrum. The same reaction was run at −40 °C, and the formation of **3b** was also observed by TLC and ^1H NMR spectroscopy, but once the solvent was evaporated by a conventional rotary evaporator in vacuo, no **3b** in the residue could be detected by TLC and/or ^1H NMR spectroscopy.

3,5-Dimethyl-4-oxo-3,4-dihydro-2*H*-pyran-2-dicarboxylic Acid Ethyl Ester (3c). According to the general procedure, reaction between diethyl ketomalonate (**2**) (76 μL, 0.5 mmol) and diene **1c** (150 mL, 0.66 mmol) using 10 mol % (*R*)-**6b**−$Zn(OTf)_2$ afforded, after purification by FC (20% EtOAc in pentane), compounds **3c** (110 mg, 0.41 mmol, 82%) and **3d** as colorless viscous oils. Compund **3c**: 84% ee according to chiral GC; $R_f = 0.52$ (20% EtOAc in pentane); $[\alpha]^{rt}_{D} = -145.6$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 7.18 (q, $J = 0.9$ Hz, 1H), 4.33−4.19 (m, 4H), 3.29 (q, $J = 7.3$ Hz, 1H), 1.63 (d, $J = 0.9$ Hz, 3H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.16 (d, $J = 7.8$ Hz, $3H_3$); ^{13}C NMR δ 193.2, 166.0, 164.7, 154.9, 113.6, 87.6, 63.0, 62.7, 43.9, 14.0, 13.8, 12.1, 10.2. Compound **3d**: $R_f = 0.67$ (20% EtOAc in pentane); ^1H NMR δ 7.23 (q, $J = 1.1$ Hz, 1H), 4.28−4.11 (m, 4H), 3.85 (s, 3H), 3.68 (q, $J = 11.6$ Hz, 1H), 1.68 (d, $J = 1.1$ Hz, 3H), 1.32−1.16 (m, 9H), 0.0 (s, 9H); ^{13}C NMR δ 199.5, 170.0, 169.4, 159.8, 116.6, 82.7, 61.8, 61.7, 61.3, 47.3, 14.1, 14.0, 13.9, 8.6, 1.7.

4,6-Dimethyl-2,3-dihydro-5*H*-2-dicarboxylic Acid Ethyl Ester (3e) and 1-Hydroxy-3-methylenehex-4-ene-1-dicarboxylic Acid Ethyl Ester (3f). According to the general procedure, reaction between diethyl ketomalonate (**2**) (76 μL, 0.5 mmol) and diene **1c** (115 μL, 1 mmol) using 10 mol % (*R*)-**6b**−$Zn(OTf)_2$ afforded, after purification by FC (20% EtOAc in pentane), a mixture of **3e** and **3f** (89 mg) in a ratio as determined by ^1H NMR and given in Table 3: R_f (**3e** and **3f**) 0.6 (20% EtOAc in pentane); ^1H NMR δ 6.03 (d, $J = 14.8$ Hz, 1H) (**3f**), 5.86−5.72 (m, 1H) (**3f**), 5.28 (br s, 1H) (**3e**), 5.03 (s, 1H) (**3f**), 4.94 (s, 1H) (**3f**), 4.39 (br s, 1H) (**3f**), 4.30−4.13 (m, 8H) (**3e** + **3f**), 3.67 (s, 1H) (**3e**), 2.95 (s, 2H) (**3f**), 2.63 (dd, $J = 2.2$, 17.0 Hz, 1H) (**3e**), 2.40 (d, $J = 17.0$ Hz, 1H) (**3e**), 1.74 (s, 3H) (**3e**), 1.72 (s, 3H) (**3f**), 1.31−1.21 (m, 15H); ^{13}C NMR δ 169.9, 168.5, 168.3, 139.7, 133.3, 129.3, 125.9, 123.6, 116.8, 80.4, 78.6, 69.0, 62.3, 62.0, 61.8, 36.2, 33.3, 22.7, 21.5, 18.2, 14.0, 13.9, 13.9.

2-Oxabicyclo[2.2.2]oct-5-en-3-one (5). Diester **3a** (300 mg, 1.18 mmol) was suspended in aqueous KOH (20%, 5.6 mL) and stirred for 6 h. The mixture was extracted with ether (2 × 1.5 mL) and subsequently adjusted to pH 6−7 by addition of aqueous HCl (20%). The resulting solution was cooled to 0 °C, and CAN (3.3 g, 6.02 mmol) in CH_3CN/H_2O (3/1, v/v, 20 mL) was added dropwise. The reaction was allowed to warm to room temperature, and stirring was continued for 15 min. Subsequently, the reaction was quenched by addition of brine (100 mL) and extracted with Et_2O (6 × 10 mL). The combined organic layers were washed with brine (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by FC (40% EtOAc in pentane) to afford lactone **5** (61 mg, 0.49 mmol, 42%) as a colorless oil: R_f 0.4 (40% EtOAc in pentane); $[\alpha]^{rt}_{D} = -29.8$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 6.55−6.41 (m, 2H), 5.24−5.19 (m, 1H), 3.52−3.47 (m, 1H), 2.33−2.10 (m, 1H), 1.96−1.84 (m, 1H), 1.70−1.43 (m, 2H); ^{13}C NMR δ 174.2, 132.3, 131.6, 74.2, 40.7, 24.9, 19.2.

***cis*-4-(Hydroxymethyl)cyclohex-2-enol (9).** $LiAlH_4$ (15 mg, 0.39 mmol) was suspended in THF (5 mL), and a solution of **5** (40 mg, 0.32 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 18 h, subsequently quenched with NaOH (10%), and filtered over Celite. The resulting clear solution was diluted with EtOAc (10 mL), washed with brine (3 × 3 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by FC (3 g of silica gel, 10% MeOH in CH_2Cl_2) to afford **9** (38 mg, 0.3 mmol, 94%) as a colorless viscous oil: 83% ee according to HPLC using a Chiralpak AD column (*i*-PrOH−hexane, 1:99, 0.5 mL/min); $R_f = 0.34$ (10% MeOH in CH_2Cl_2); $[\alpha]^{rt}_{D} = +13.0$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 5.93−5.84 (m, 1H), 5.75 (dd, $J = 2.3$ Hz, $J = 10.2$ Hz, 1H), 4.12 (dd, $J = 3.8$ Hz, $J = 7.7$ Hz, 1H), 3.56 (m, 2H), 2.80 (br s,

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2H), 2.28−2.14 (m, 1H), 1.84−1.70 (m, 4H); ^{13}C NMR δ 131.9, 130.7, 65.8, 64.1, 38.1, 29.9, 20.5.

(1*R*,4*S*)-Camphanic Acid 4-(Camphanoxymethyl)cyclohex-2-enyl Ester (11). To a dried flask containing diol **9** (20 mg, 0.16 mmol), (1*S*)−(−)-camphanic chloride (250 mg, 1.16 mmol) and several crystals of DMAP were added dry CH_2Cl_2 (5 mL) and Et_3N (0.3 mL), and the mixture was cooled to 0 °C. After the reaction mixture was stirred at 0 °C for 10 min and at room temperature for 2 h, the solvent was evaporated and the crude product was purified by FC (25% EtOAc in pentane) to afford ester **11** as a white solid (70 mg, 95% yield). Recrystallization from EtOAc and hexane gave crystals suitable for X-ray analysis: ^1H NMR δ 5.89 (br s, 2H), 5.36 (br s, 1H), 4.23 (dd, J = Hz, 1H), 4.12 (dd, J = Hz, 1H), 2.50−1.55 (m, 13H), 1.10−0.93 (m, 18H); ^{13}C NMR δ 178.2, 178.1, 167.4, 166.9, 133.4, 126.5, 91.1, 91.0, 67.9, 54.7, 54.1, 35.1, 30.7, 30.4, 28.8, 26.8, 21.3, 16.8, 16.7, 9.6.

X-ray Structure Determination of 11. Compound **11** forms hexagonal or trigonal, colorless plates. A hemisphere of data (21 833 reflections) were collected on a SIEMENS SMART diffractometer using Mo Kα radiation ($\lambda = 0.710\ 73$ Å). **11** is trigonal, space group $P3_2$, $a = b = 6.529(2)$ Å, $c = 49.54(2)$ Å. The reflections were hardly resolved in the *c*-direction, necessitating the use of extra narrow frames and a narrow integration box to minimize overlap. The internal agreement indicated space group $P3_2$ (3315 unique reflections), but space group $P3_212$ gave only moderately higher R_{int} than $P3_2$ (0.174 against 0.127). The structure solved with no trouble in $P3_2$ (SIR97)[19a] and showed the expected stereochemistry of the camphanic moieties (it could not be solved in space group $P3_212$). Isotropic refinement stopped at $R = 0.15$, and anisotropic displacement parameters gave no improvement. It was realized that the crystal was a twin, causing the near-2-fold symmetry of the data. The program for least squares refinement using Pawley[19b] constraints was consequently modified to include the contributions from both twins to each intensity, with separate scale factors refined. Severe constraints had to be applied: the two camphanic cages held identical; atomic displacement parameters constrained to the rigid body TLS model, with extra rotations allowed around single bond chains. The final agreement was $R = 0.065$, $R_w = 0.073$, for 101 parameters refined against 2385 significant reflections.

Theoretical Calculations. All calculations were performed using the Gaussian 94 suite of codes[10] and visualized with the Chem3D program from Cambridge Software. Hessians were computed at all stationary points, to confirm the proper local behavior of the potential energy surface as local minima or first-order saddle points. The hetero-Diels−Alder reaction of CO_2 with 1,3-cyclohexadiene was studied using the BLYP gradient-corrected density functional and the 6-31G* basis set. Binding of ketomalonate and a simple bidentate nitrogen ligand was studied using the B3LYP gradient-corrected density functional, and general basis set: the SBK pseudopotential and associate triple-ζ valence basis on copper and zinc, the 6-31G* polarized double-ζ valence basis on nitrogen and oxygen, and the 6-31G double-ζ valence basis on carbon and hydrogen.

Semiempirical calculations on the full Zn(II)−ketomalonate−bisoxazoline−cyclohexadiene reaction path were performed using the MNDO Hamiltonian.

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Supporting Information Available: NMR and X-ray structure data of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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