Catalytic Asymmetric Addition Reactions of Carbonyls. A Common Catalytic Approach

KARL ANKER JØRGENSEN,*
MOGENS JOHANNSEN, SULAN YAO,
HÉLÈNE AUDRAIN, AND JACOB THORHAUGE

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

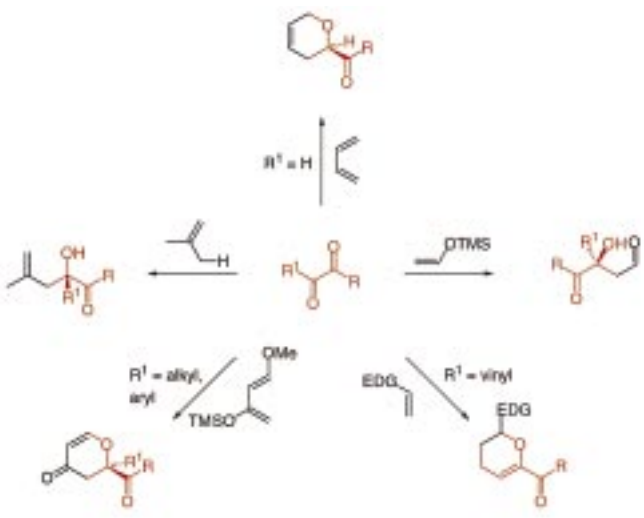
Received August 26, 1998

Asymmetric catalysis has become an interdisciplinary and internationally competitive research field in chemistry.[1] The prospects of asymmetric catalysis for both academia and industry are enormous, and the demand for nonracemic compounds from the society will probably not decrease in the future.

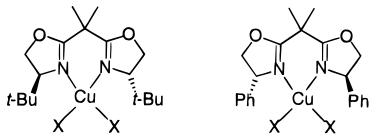
Many asymmetric catalytic reactions which have been used with great success only give excellent enantioselectivity for a narrow range of substrates. A very attractive goal in asymmetric catalysis is to develop general synthetic methodologies based on chiral catalysis which shows large substrate tolerance, i.e., allowing a variety of different substrates to react with various reactants in a highly stereoselective manner. Furthermore, if the chiral catalyst can catalyze more than just one type of reaction, the prospects will be even further enlarged.

In this Account we intend to present such a common catalytic system, which can catalyze, in a highly stereoselective manner, a variety of important organic addition reactions. The reactions which will be considered are outlined in Scheme 1. This approach for the enantioselective addition reactions takes its starting point from α-dicarbonyl compounds (marked in red). For α-dicarbonyl compounds having R^1 = H, reaction with conjugated dienes can give the hetero-Diels−Alder adduct. However, for reaction of substrates having allylic C−H bonds, application of the same catalysts can lead to the ene reaction. Ketones (R^1 = alkyl, aryl) can also be substrates for a hetero-Diels−Alder reaction by reaction with activated conjugated dienes. The first two hetero-Diels−Alder reactions in Scheme 1 are normal electron demand reactions. The catalytic approach can furthermore be applied for the inverse electron demand hetero-Diels−Alder reactions (R^1 = vinyl) with alkenes substituted with electron-donating groups (EDG) as the dienophile. Finally, the approach can be used to catalyze the aldol reaction with enol silanes.

Scheme 1



The key element in the common catalytic approach in Scheme 1 is the use of the chiral C_2-symmetric bisoxazolines (*S*)-**1a** and (*R*)-**1b** in combination with copper(II) salts as the Lewis acid. C_2-symmetric bisoxazoline−metal complexes as chiral catalysts, which are structurally related to the C_2-symmetric semicorrins pioneered by Pfaltz et al.,[2] have received a great deal of attention in different catalytic reactions in recent years.[3] A variety of chiral bisoxazoline ligands with a great deal of structural diversity have been introduced since the early 1990s,[3] when several research groups introduced these ligands in combination with metal salts as catalysts for different enantioselective reactions, such as the Diels−Alder reaction,[4] cyclopropanation,[5] aziridination of alkenes and imines,[6] allylic substitution[7] and oxidation,[8] free radical additions,[9] nucleophilic addition to aldehydes[10] and imines,[11] and 1,3-dipolar cycloaddition reactions.[12]



The reason for us, in this Account, to involve only α-dicarbonyl compounds and the chiral C_2-symmetric

Karl Anker Jørgensen (b. 1955) is Professor at Aarhus University. Following a Ph.D. from Aarhus University (1984) and a postdoctoral period with R. Hoffmann, Cornell University, he joined the Aarhus University faculty. The development and understanding of metal-catalyzed reactions in organic chemistry is the main goal of his research.

Mogens Johannsen (b. 1969) received his Ph.D. (1997) from Aarhus University. He has been a research fellow in Heidelberg with G. Helmchen. Currently he is Assistant Professor at The Technical University of Denmark, Copenhagen.

Sulan Yao (b. 1963) obtained her M.Sc. from Jiangxi University, China (1991), and started her Ph.D. study with K. A. Jørgensen (1996). She is currently working with asymmetric catalytic hetero-Diels−Alder and ene reactions.

Hélène Audrain (b. 1968) received her Ph.D. (1994) from the University of Paris XI, Orsay, France, under the direction of D. S. Grierson. After a first postdoctoral position (1995) at the University of Ottawa, Canada, in A. G. Fallis's group, she is currently working as a postdoctoral fellow in K. A. Jørgensen's group.

Jacob Thorhauge (b. 1975) was educated at Aarhus University and has started his Ph.D. study with K. A. Jørgensen (1997). He is currently working with inverse electron demand Diels−Alder reactions.

10.1021/ar970347f CCC: $18.00
Published on Web 05/13/1999

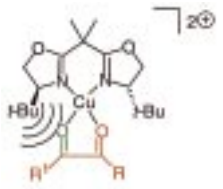
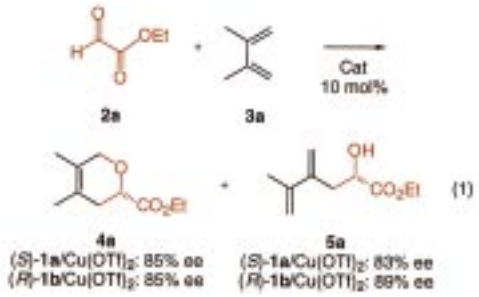


FIGURE 1. The idea behind the use of C_2-symmetric bisoxazoline−copper(II) complexes as the catalyst. The α-dicarbonyl compound coordinates to the catalyst in a bidentate fashion by which the "green" carbonyl functionality is activated and shielded from above.

bisoxazolines (*S*)-**1a** and (*R*)-**1b** is that the catalysts provide, for the reactions presented in Scheme 1, a chiral environment at the Lewis acid center, leading to highly selective reactions. This basic idea is illustrated in Figure 1. For (*S*)-**1a** the α-dicarbonyl compound coordinates to the copper cation in a bidentate fashion with the two carbonyl oxygen atoms by which the reacting carbonyl functionality (the one in green) is activated, by lowering the energy of the $\pi_{C=O^*}$ orbital (LUMO) compared with the unactivated substrate. The function of the chiral bisoxazoline fragment is to shield one of the faces of the carbonyl functionalities; in the model presented in Figure 1, the *re* face of the "green" carbonyl functionality is shielded by the *tert*-butyl group.

Hetero-Diels−Alder Reactions of Aldehydes

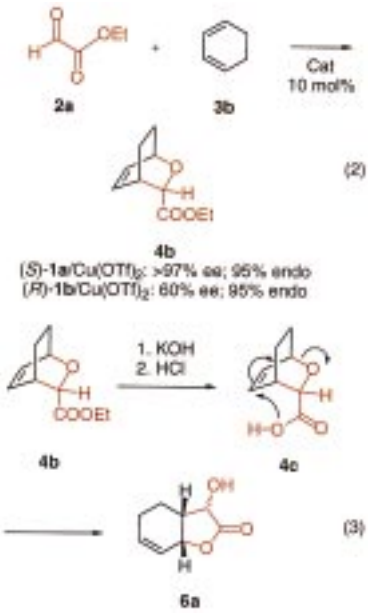
The use of chiral bisoxazolines in combination with copper(II) salts, (*S*)-**1a** and (*R*)-**1b**, as the catalysts for the hetero-Diels−Alder (HDA) and ene reactions of glyoxylates with conjugated dienes was introduced in 1995 in our laboratory,[13a,14] inspired by the work of Evans et al. on carbo-Diels−Alder reactions.[4b] The application of (*S*)-**1a**/$Cu(OTf)_2$ and (*R*)-**1b**/$Cu(OTf)_2$ as catalysts (10 mol %) for the reaction of ethyl glyoxylate **2a** with 2,3-dimethyl-1,3-butadiene **3a** (eq 1) leads to a HDA:ene ratio of 1:1.5



(**4a**:**5a**) compared with a 1:9 ratio when using BINOL−TiX_2 complexes.[14] The HDA adduct **4a** was formed in up to 85% enantiomeric excess (ee) using the two catalysts (*S*)-**1a**/$Cu(OTf)_2$ and (*R*)-**1b**/$Cu(OTf)_2$. It is notable that the application of the catalysts (*S*)-**1a**/$Cu(OTf)_2$ and (*R*)-**1b**/$Cu(OTf)_2$ leads to the same enantiomer (*R*) in the HDA adduct (vide infra). Other conjugated dienes, such as isoprene and 1,3-butadiene, also react with ethyl glyoxylate in the presence of (*R*)-**1b**/$Cu(OTf)_2$ as catalyst, giving the HDA adducts in reasonable yields and 80% and 87% ee, respectively.[13a]

The reaction rate, chemoselectivity, and ee using the copper(II)−bisoxazolines (*S*)-**1a** and (*R*)-**1b** as catalysts are dependent on the solvents and counterions.[4c,15] The HDA:ene ratio, and ee of the HDA adducts, can be improved by changing the solvent from CH_2Cl_2 to $MeNO_2$.[15] For the reaction outlined in eq 1 the HDA:ene ratio is improved to 1:0.8 and the ee to 90%. It should be mentioned that this ratio, and the enantioselectivity, can be improved significantly using BINOL−AlMe[16] as the catalyst.

Cyclic conjugated dienes, such as 1,3-cyclohexadiene **3b**, are also excellent substrates for the HDA reaction with ethyl glyoxylate **2a** catalyzed by the copper(II)−bisoxazolines (eq 2).[13,15] The reaction rate is dependent on both counterion and solvent. A highly diastereo- and enantioselective reaction is obtained using (*S*)-**1a**/$Cu(OTf)_2$ as catalyst in $MeNO_2$ as the solvent, giving exclusively the *endo* adduct **4b** in more than 90% isolated yield with >97% ee.[13,15]



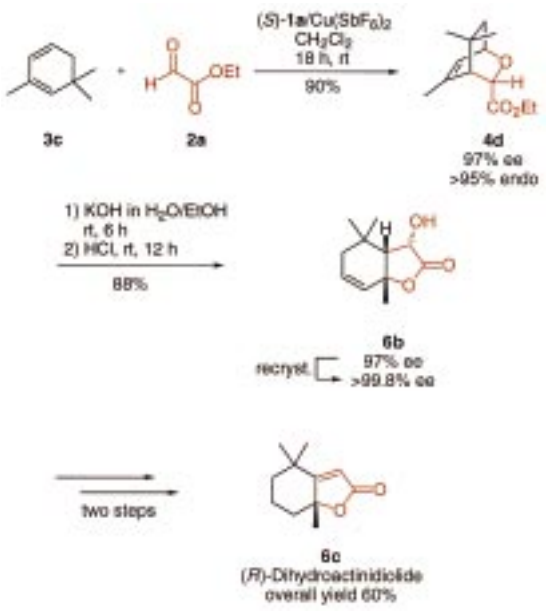
The HDA adduct **4b** formed by reaction of ethyl glyoxylate with cyclic dienes catalyzed by (*S*)-**1a** and (*R*)-**1b** in combination with copper(II) salts was used in a simple synthetic approach for the preparation of enantiopure synthons for natural products (eq 3). By treatment of **4b** successively with base, and then acid, intermediate **4c** is formed, which undergoes an intramolecular rearrangement, leading to the enantiopure bicyclic lactone **6a** after recrystallization (eq 3).[13a,15a]

This HDA approach has, e.g., been used for the total synthesis of (*R*)-dihydroactinidiolide **6c**, one of the main components of the pheromone for the queen recognition of the workers of the red fire ant, *Soleneopsis invicta*.[17] The total synthesis starting from 2,6,6-trimethyl-1,3-cyclohexadiene **3c** and ethyl glyoxylate **2a** is outlined in Scheme 2 and shows for the HDA reaction the highly regio-, diastereo-, and enantioselective catalytic properties of (*S*)-**1a**/$Cu(SbF_6)_2$.

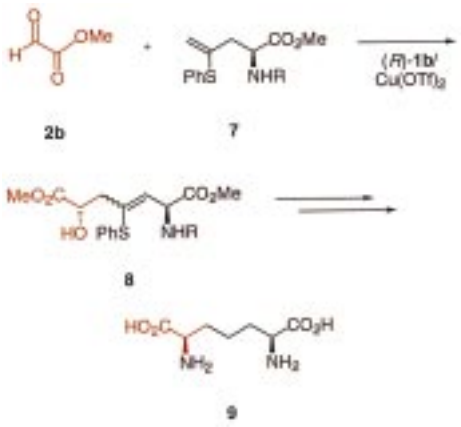
Ene Reactions

The fact that the copper(II)−bisoxazoline-catalyzed reaction of alkyl glyoxylates with substrates having allylic C−H

Scheme 2



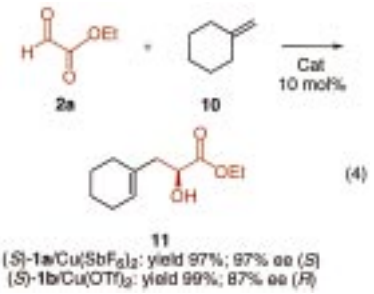
Scheme 3



bonds can give both the HDA and ene adducts has been applied in organic synthesis[13,18] and more recently been developed as a highly enantioselective reaction.[19] For the synthesis of *meso*-diaminopimelic acid **9**, a key constituent of bacterial peptidoglycan, the use of BINOL−TiX_2 complexes[14] as catalysts for the ene reaction failed, whereas (*R*)-**1b**/$Cu(OTf)_2$ catalyzed the desired ene reaction between methyl glyoxylate **2b** and **7** to give the alcohol **8** in modest yield (42%) (Scheme 3).[18] The alcohol **8** was transformed into the desired acid **9** in a few steps.

Evans et al. have recently increased the potential for the use of (*S*)-**1a** and (*R*)-**1b** as catalysts for ene reactions.[19] Ethyl glyoxylate **2a** reacts with methylenecyclohexane **10** in the presence of (*S*)-**1a**/$Cu(SbF_6)_2$ as the catalyst (10 mol %), giving the ene product **11** in 97% yield and 97% ee, while (*S*)-**1b**/$Cu(OTf)_2$ gives 99% yield and 87% ee of the other enantiomer of **11** (eq 4).

This ene reaction has the practical advantage that a bis(aqua) complex (*S*)-**1a**/$Cu(H_2O)_2(SbF_6)_2$, readily prepared as a bench-stable solid, can be used as catalyst with loadings as low as 0.1 mol % without significant loss of yield and enantioselectivity. A variety of substrates can

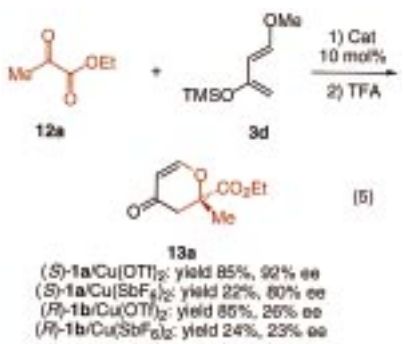


be applied in this ene reaction. Besides the symmetrical 1,1-disubstituted alkenes, unsymmetrical 1,1-disubstituted, 1,2-disubstituted, and monosubstituted alkenes also react in a highly enantioselective manner applying the copper(II)−bisoxazoline complexes as catalysts, which shows the potential of this reaction.[19] The ene reaction of 2-methyl-1-heptene with **2a** catalyzed by (*S*)-**1b**/$Cu(OTf)_2$ shows that the catalytic system can discriminate between the methyl and methylene groups in the substrate as the ene reaction proceeds in a 90:10 ratio at the methyl rather than the methylene group. After determination of the absolute configuration of the products, it was shown that the use of the ligands (*S*)-**1a** and (*S*)-**1b** gives products with opposite configuration.

Hetero-Diels−Alder Reactions of Ketones

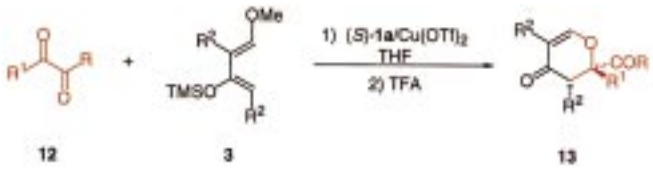
Ketones are generally less reactive compared to aldehydes. Therefore, addition reactions to ketones should be expected to be more difficult to achieve. This is reflected in the very few asymmetric catalytic HDA reactions of ketones compared with the many different catalysts which can catalyze enantioselective HDA reactions of various types of aldehydes.

Ketonic substrates, such as ethyl pyruvate **12a**, do not react with simple dienes such as 2,3-dimethyl-1,3-butadiene **3a** and cyclohexadiene **3b** in the presence of (*S*)-**1a** and (*R*)-**1b** as catalysts. However, using activated dienes, such as *trans*-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene) **3d**, we found that a smooth HDA reaction with **12a** in the presence of both (*S*)-**1a** and (*R*)-**1b** as catalysts (10 mol %) took place (eq 5).[20] The results in eq 4 for the reaction of **12a** with **3d** illustrate the influence of the chiral ligand and counterion on the yield and ee of **13a**.



The reaction conditions for the HDA reaction of ethyl pyruvate **12a** with activated dienes in the presence of (*S*)-

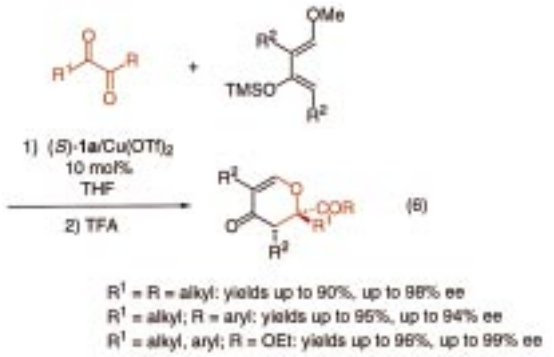
Table 1. Results for the Asymmetric HDA Reaction of Some α-Keto Esters and α-Diketones 12b−g with Dienes 3d,e Using Low Catalyst Loading of (*S*)-1a/Cu(OTf)$_2$



				hetero-Diels−Alder product **13**	
entry	ketone **12** R^1/R	diene **3** R^2	catalyst load (%)	yield (%)[a]	ee (%)
1	Me/OMe (**b**)	H (**d**)	0.05	(**b**) 90	98.4
2	Me/Me (**c**)	H (**d**)	0.05	(**c**) 88	93.9
3	Me/Et (**d**)	H (**d**)	0.05	(**d**) 76	97.8
4	Me/Ph (**e**)	H (**d**)	0.05	(**e**) 25	96.4
5	Et/OMe (**f**)	H (**d**)	0.5	(**f**) 70	96.8
6	Me/OMe (**b**)	Me (**e**)	2.5	(**g**) 85	97.4
7	Ph/OEt (**g**)	Me (**e**)	2.5	(**h**) 65	98.7
8	Me/Me (**c**)	Me (**e**)	2.5	(**j**) 81	97.1

[a] Isolated yield.

1a/Cu(OTf)$_2$ as the catalyst in THF as the solvent turned out to be the optimal conditions for a general reaction for both alkyl and aryl α-diketones and α-keto esters reacting with activated dienes.[20b] Some representative results showing the generality of the HDA reaction of ketones are presented in eq 6.



From a synthetic point of view the catalytic enantioselective HDA reaction of ketones in eq 6 allows one to prepare, from simple commercially available substrates, a chiral quaternary carbon center in one step. Formation of such a center is a particularly demanding task in organic synthesis.[21]

In an attempt to obtain insight into the mechanism for the catalytic enantioselective HDA reaction of ketones, a kinetic study was undertaken. However, this took a highly unexpected direction, as a very fast reaction took place within a few minutes in the presence of 10 mol % (*S*)-**1a**/Cu(OTf)$_2$ as the catalyst. It turned out that it was possible to reduce the catalyst loading to only 0.05 mol % without affecting the yield of the HDA adduct, and in some cases even improving the ee. Some representative results for the reaction of various α-diketones and α-keto esters **12b−g** with the activated dienes **3d**,**e** catalyzed by very low loadings of (*S*)-**1a**/Cu(OTf)$_2$ are presented in Table 1.

From the results in Table 1, we show that this HDA reaction proceeds in high yield and with excellent enantioselectivities with a catalyst loading down to 0.05 mol %, one of the lowest loadings in Lewis acid-catalyzed asymmetric reactions observed. Of the results in Table 1, in particular two will be addressed here: the reactions of 2,3-pentanedione **12d** (entry 3) and 3-phenyl-2,3-propanedione **12e** (entry 4). 2,3-Pentanedione **12d** reacts with **3d** in the presence of only 0.05 mol % (*S*)-**1a**/Cu(OTf)$_2$ as the catalyst with a high regioselective preference for the methyl fragment relative to the ethyl fragment (91:9) and gives 97.8% ee of HDA adduct **13d**. For 3-phenyl-2,3-propanedione **12e** reacting with **3d** an even higher regioselectivity is observed as the methyl fragment now reacts in a 98:2 ratio relative to the phenyl fragment and again with high enantioselectivity. These results are schematically outlined in Figure 2.

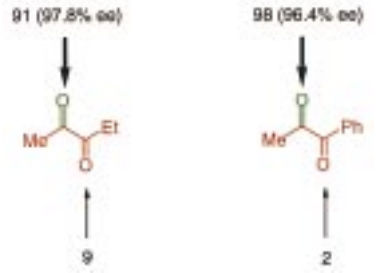
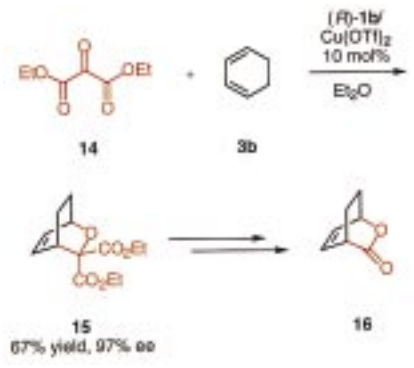


FIGURE 2. A schematic representation of the regio- and enantioselective HDA reactions of 2,3-pentadione (to the left) and 3-phenyl-2,3-propanedione (to the right) with dienes catalyzed by (*S*)-**1a**/Cu(OTf)$_2$. The green color indicates the most reactive carbonyl functionality, and the numbers refer to regioselectivity with ee in the brackets.

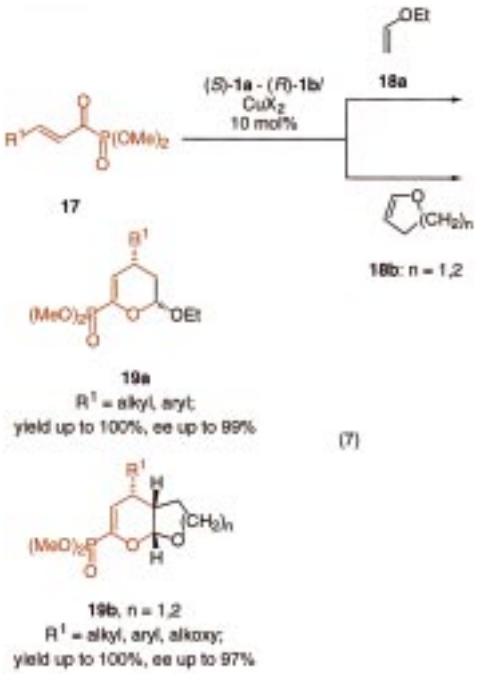
One preliminary result, using the catalytic enantioselective HDA reaction of ketones will be presented here—the formation of chiral CO_2 cycloadduct.[22] A chiral CO_2 cycloadduct is in principle a [2 + 4] cycloaddition reaction between CO_2 and a diene, and from a theoretical point of view this is a very unfavorable reaction in terms of both activation energy and enthalpy.[22] However, this unfavorable process can be overcome by applying an alternative procedure using (*R*)-**1b**/Cu(OTf)$_2$ as the catalyst for the HDA reaction of ethyl ketomalonate **14** with 1,3-cyclohexadiene **3b**, giving the HDA adduct **15** in 67% yield and 97% ee (Sheme 4). Further transformations of **15** give the enantiopure chiral CO_2 cycloadduct **16**.

Scheme 4



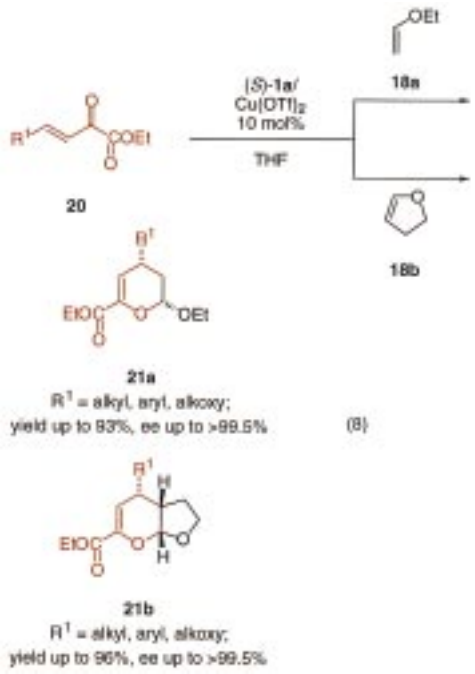
Hetero-Diels–Alder Reactions with Inverse Electron Demand

The HDA reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes provides a simple synthetic approach to substituted 3,4-dihydro-*2H*-pyrans, which are very useful precursors for the synthesis of carbohydrates and natural products. Before proceeding to the inverse electron demand HDA reaction outlined in Scheme 1, the work by Evans et al.,[23] which was developed simultaneously with our work,[24] will be presented. The catalysts (*S*)-**1a**/CuX_2 and (*R*)-**1b**/CuX_2 (X = OTf, SbF_6) are effective for an enantioselective HDA reaction of α,β-unsaturated acyl phosphonates **17** with ethyl vinyl ether **18a** and the cyclic enol ethers **18b**, giving the HDA adducts **19a**,**b** in very high yield and ee (eq 7).



It is notable that the acyclic and cyclic enol ethers react in a highly stereoselective manner and that the same antipode of **19a** (R^1 = Me) is formed using (*S*)-**1a**/CuX_2 and (*R*)-**1b**/CuX_2 as the catalyst for the reaction in eq 7.[23] Furthermore, it is also of practical importance that the HDA reaction of **17** (R^1 = Me) can react with ethyl vinyl ether **18a** using a catalytic load of only 0.2 mol % (*R*)-**1b**/$Cu(SbF_6)_2$ with minimal reduction in the yield of the HDA adduct and no loss of enantioselectivity (93% ee).[23]

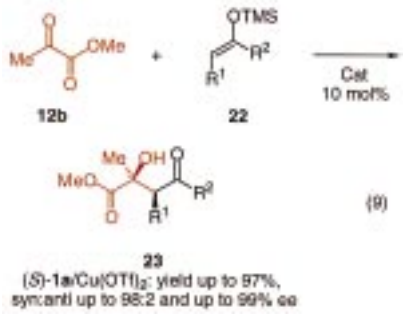
Our development of the catalytic enantioselective inverse electron demand HDA reaction focuses on the reaction of β,γ-unsaturated α-keto esters **20** with ethyl vinyl ether **18a** and 2,3-dihydrofuran **18b** (eq 8).[24] The generality and potential of the highly enantioselective HDA reaction of the β,γ-unsaturated α-keto esters **20** with ethyl vinyl ether **18a** and 2,3-dihydrofuran **18b** catalyzed by (*S*)-**1a**/$Cu(OTf)_2$ is obvious from the results in eq 8.[24] Very high yields and ee's are obtained for the various substrates as both alkyl, aryl, and alkoxy substituents might be present in the oxadiene, while for the dienophile,



both acyclic and cyclic compounds are usable. The present reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes catalyzed by chiral copper(II)–bisoxazolines offers a new and promising methodology for the construction of natural compounds, as well as novel carbohydrate derivatives.

Aldol Reactions

The catalytic enantioselective aldol reaction has also received considerable interest in recent years, and several reviews are available.[3,25] Though our laboratory has not contributed to this particular reaction type, we include it for completeness, and only reactions related to the approach in Scheme 1 will be considered. Evans et al. have developed highly enantioselective aldol reactions of glyoxylate and pyruvate esters to enol silanes catalyzed by mainly chiral copper(II)– and tin(II)–bisoxazolines.[26] The reaction of methyl pyruvate **12b** with various enol silanes **22** proceeds well in the presence of (*S*)-**1a**/$Cu(OTf)_2$ as the catalyst, giving the *syn*-aldol products **23** with high diastereo- and enantioselectivity (eq 9). The catalyst (*S*)-



1a/$Cu(OTf)_2$ can also be employed to catalyze additions to α-diketones, and as observed in the HDA reaction, the catalyst can also for the aldol reaction differentiate

between a methyl and ethyl substitution as 2,3-pentanedione reacts with the (*Z*)-silylketene acetal derived from *tert*-butyl thiopropionate with high regio- (98:2), diastereo- (93:7), and enantioselectivity (97% ee).[26a]

By changing the metal from copper(II) to tin(II) and the chiral bisoxazoline to one having a benzyl substituent at the chiral center, Evans et al. were able to perform catalytic enantioselective *anti*-aldol additions of enol silanes to glyoxylate, methyl pyruvate, and an α-diketone.[26b] The selectivities for the tin(II)−bisoxazoline-catalyzed aldol reactions are also very high and comparable to those obtained when (*S*)-**1a**/$Cu(OTf)_2$ is applied as the catalyst, but the tin(II) catalyst leads to opposite diastereoselectivity compared with the copper(II) catalyst.

Mechanistic Aspects

Several questions arise with regard to the mechanism for the reactions of the α-dicarbonyl compounds discussed in this Account. In the following we address two of these questions: (i) How does the α-dicarbonylic fragment coordinate to catalyst? (ii) What is the structure(s) of the α-dicarbonyl-copper(II)−bisoxazoline intermediate. The mechanistic discussion of other copper(II)−bisoxazoline-catalyzed reactions is also available.[3]

Let us start with the formation of the catalysts (*S*)-**1a** and (*R*)-**1b**. The X-ray structures of two copper(II)−bisoxazoline−aqua complexes characterized are outlined in Figure 3.[19,27] The structure of the catalyst (*S*)-**1a**/$Cu(H_2O)_2(SbF_6)_2$ **24** shows that it contains two water molecules coordinated to the copper(II) center and that the SbF_6 counterions are noncoordinating.[27] Of particular interest is that the coordinated water molecules are distorted an average of 33° out of the copper(II)−ligand plane and that the complex exhibits a distorted square-planar geometry. Changing the counterion in **24** to triflate leads to a complex with one triflate counterion coordinated,[28] while (*S*)-**1a**/$CuCl_2$ has the chlorides coordinated to the metal similar to the water molecules in **24**.[29] For the aqua complex of (*R*)-**1b**/$Cu(H_2O)_2(OTf)_2$ **25** in Figure 3, the triflate counterions coordinate to the metal. This complex is octahedral with the two water molecules coordinated to copper(II) in the equatorial plane, the same plane as the chiral bisoxazoline ligand, while the two triflate counterions occupy the axial positions.

These X-ray structures, **24** and **25** in Figure 3, might serve as a structural guideline for the coordination of the α-dicarbonyl compounds to the catalyst. Furthermore, the stereochemical outcome of the reactions adds further information about the geometrical arrangement of the chiral bisoxazoline ligand and the α-dicarbonyl compound at the copper(II) center.

After the formation of the copper(II)−bisoxazoline catalyst, the next reaction step is coordination of the α-dicarbonyl compound to the catalyst. It is generally accepted that the α-dicarbonyl compound utilizes both carbonyl functionalities for coordination to copper(II). This view has been invoked in the mechanistic approaches for the enantioselective catalytic reactions using (*S*)-**1a** and

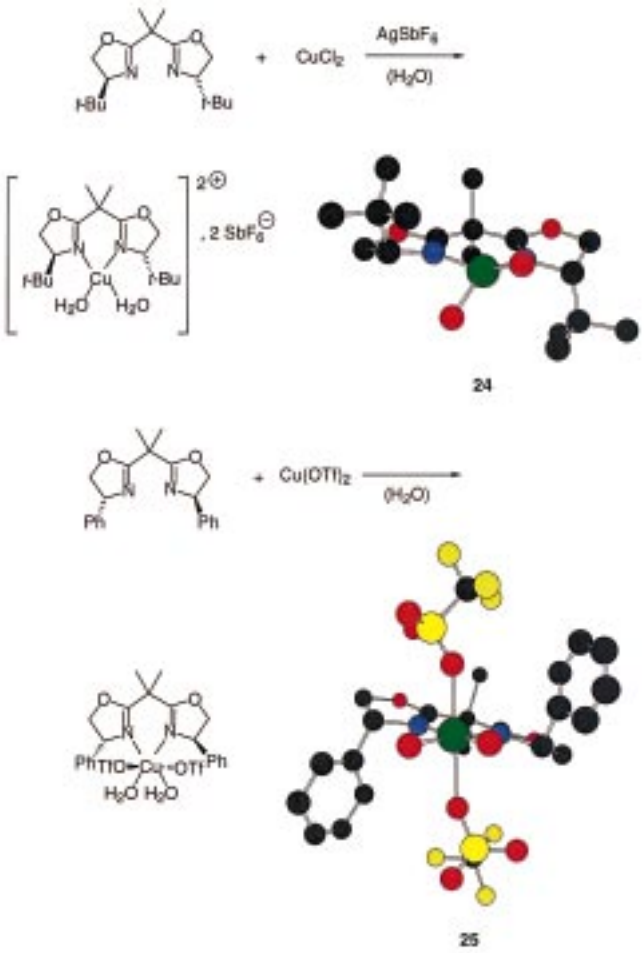


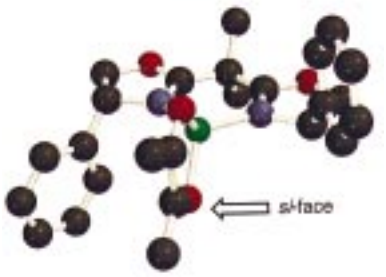
FIGURE 3. Reactions of chiral bisoxazoline ligands with copper(II) salts leading to the aqua complexes of (*S*)-**1a** and (*R*)-**1b**.[19,27] The X-ray strucure of (*S*)-**1a**/$Cu(H_2O)_2(SbF_6)_2$ **24** is shown without the noncoordinating SbF_6 counterions, while for (*R*)-**1b**/$Cu(H_2O)_2(OTf)_2$ the coordinating OTf counterions are shown.[19,27]

(*R*)-**1b**. EPR spectroscopic studies of (*S*)-**1a**/$Cu(OTf)_2$ and methyl pyruvate **12b** have supported a square-planar copper(II)−bisoxazoline−pyruvate intermediate in which the two pyruvate carbonyl oxygen atoms chelate to the metal.[26a] A square-planar copper(II) bisoxazoline intermediate was first postulated by Evans et al. in Diels−Alder reactions of acryloyloxazolidinone-catalyzed by (*S*)-**1a**/$Cu(OTf)_2$ using double stereodifferentiating experiments.[4b]

The absolute configuration of the different addition products formed by reaction of the various α-dicarbonyl compounds catalyzed by (*S*)-**1a** outlined in Scheme 1 points to an intermediate in which the α-dicarbonyl compound "substitutes" the two water molecules (Figure 3) by coordination to the copper(II) center, leading to a square-planar intermediate, **26**.[4b,13,17,19,20b,27] Intermediate **26** has the α-dicarbonyl compound 2,3-butanedione coordinated to the catalyst and causes a shielding of the *re* face of the reacting carbonyl functionality, leaving the *si* face available for attack by the various reagents. Intermediate **26** is presented as a square-planar complex, and it might be appropriate to compare it with the structure of (*S*)-**1a**/$Cu(H_2O)_2(SbF_6)_2$ (**24**; Figure 3). A distortion of the α-dicarbonyl fragment out of the copper-

(II)−bisoxazoline plane similar to the distortion of the two water molecules in **24** does not change the face shielding of the carbonyl functionality, and **26** can account for the stereochemical outcome of the reactions catalyzed by (*S*)-**1a**.

26



27

The use of (*R*)-**1b** as the catalyst leads generally to the same absolute configuration in the products formed as applying (*S*)-**1a** as the catalyst. The absolute stereochemical outcome of the reactions catalyzed by the copper(II)−bisoxazoline complexes indicates that different geometrical intermediates are involved. To account for this change, we initially proposed a tetrahedral intermediate, **27**, for the hetero-Diels−Alder reactions of glyoxylates with conjugated dienes catalyzed by the copper(II)−bisoxazoline catalyst having phenyl substituents in the chiral ligand.[14a,30] Such an intermediate, **27**, has the same face (*si* face) of the carbonyl functionality of the α-dicarbonyl compound available for attack by the various reagents. More recently Evans et al. have proposed an intermediate in which the geometry at the copper center is trigonal pyramidal, which also can accounts for the absolute configuration.[19] The intermediates can be interchanged by a minor distortion of the coordinated substrate. The proposal of the intermediate in the (*R*)-**1b**/(*S*)-**1b**-catalyzed reactions being tetrahedral or trigonal pyramidal has until now been based on mainly the absolute configuration of the products of the addition reactions. However, neither the tetrahedral nor the trigonal pyramidal intermediate is in accordance with the structure of (*R*)-**1b**/$Cu(H_2O)_2(OTf)_2$, **25**, Figure 3.

At the present stage one can only guess about the reason for this structure of the intermediate compared with the structure of the characterized copper(II)−bisoxazoline. Two reasons for the change from a square-planar intermediate in the case of (*S*)-**1a** as the catalyst to a tetrahedral or trigonal-pyramidal intermediate for reactions catalyzed by (*R*)-**1b** ((*S*)-**1b**) might be that in the latter case the intermediate is stabilized by $\pi-\pi$ interactions between the phenyl substituent of the chiral ligand and the π-orbital of the carbonyl functionality, or less destabilized by steric repulsion of the phenyl substituents in this geometry.

Probably the most important question in relation to the mechanism for the copper(II)−bisoxazoline-catalyzed reactions is why these catalysts are so highly efficent for the addition reactions to α-dicarbonyl compounds. This is probably because the bidentate coordination of the α-dicarbonyl compound to the metal center leads to a chiral enviroment with efficient shielding of one of the carbonyl faces (hopefully) visible in **26** and **27**, and that the Lewis acidity of copper(II) is optimal for this class of substrates.

Conclusion

The ultimate goal for asymmetric catalysis is to create general reactions which can be promoted by simple and easily available catalysts showing very high activity and stereoselectivity. If this challenge can be met with success, a new era for this methodology will emerge and asymmetric catalysis will be an even stronger tool useful even for industrial synthesis. In this Account we have presented the potential of copper(II)−bisoxazolines as catalysts for addition reactions to α-dicarbonyl compounds. The catalytic reactions discussed, normal and inverse electron demand hetero-Diels−Alder-, ene-, and aldol reactions, which are among the most fundamental reactions in organic chemistry, all proceed in high yields and very high enantiomeric excess for a variety of different substrates, leading to highly valuable compounds.

This work was made possible by a grant from The Danish National Research Foundation. Thanks are expressed to Professor David E. Evans for providing us with X-ray data.

References

(1) See, e.g.: (a) *Advances in Catalytic Processes: Asymmetric Chemical Transformations*; Doyle, M., Ed.; JAI: Greenwich, CT, 1995; Vol. 1. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Verlagsgesellschaft: Weinheim, 1993. (c) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1995. (d) Boger, D. L.; Weinreb, S. N. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press: San Diego, 1987; Vol. 47. (e) Tietze, L. F.; Kettschau, G. In *Stereoselective Heterocyclic Synthesis I*; Metz, P., Ed.; Springer-Verlag: Berlin, 1997; Vol. 189, pp 1−120. (g) *Transition Metals for Fine Chemicals and Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-Interscience: Chichester, U.K., 1998.

(2) Pfaltz, A. Chiral Semicorrins and Related Nitrogen Heterocycles as Ligands in Asymmetric Catalysis. *Acc. Chem. Res.* **1993**, *26*, 339.

(3) Ghosh, A. K.; Mathivanen, P.; Cappiello, J. C_2-symmetric bis(oxazoline)-metal complexes in catalytic asymmetric synthesis. *Tetrahedron: Asymmetry* **1998**, *9*, 1.

(4) See, e.g.: (a) Corey, E. J.; Imai, N.; Zhang, H. Designed Catalyst for Enantioselective Diels−Alder Addition from a C_2−Symmetric Chiral Bis(oxazoline)-Fe(III) Complex. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Evans, D. A.; Miller, S. J.; Lectka, T. Bis(oxazoline)copper(II) Complexes as Chiral Catalysts for the Enantioselective Diels−Alder Reaction. *J. Am. Chem. Soc.* **1993**, *115*, 6469. (c) Evans, D. A.; Murry, J. A.; Matt, P.; Norcross, R. D.; Miller, S. J. C_2-Symmetric Cationic Copper(II) Complexes as Chiral Lewis Acids: Counterion Effects in the Enantioselective Diels−Alder Reaction. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

(5) See, e.g.: (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. Asymmetric Catalytic Cyclopropanation of Olefins: Bis-Oxazoline Copper Complexes. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. C_2-Symmetric 4,4′,5,5′-Tetrahydrobi(oxazoles) and 4,4′,5,5′-Tetrahydro-2,2′-methylenebis[oxazoles] as Chiral Ligands for Enantioselective Catalysis. *Helv. Chim. Acta* **1991**, *74*, 232. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. Bis(oxazolines) as Chiral Ligands in Metal-Catalyzed Asymmetric Reactions. Catalytic Asymmetric Cyclopropanation of Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 726. (d) Evans, D. A.; Woerpel, K. A.; Scott, M. J. "Bis(oxazoline)" als Liganden für sich selbst organisierende, chirale Koordinations polymere; Struktur eines kupfer(I)-Katalysators für die enantio selektive Cyclopropanierung von Olefinen. *Angew. Chem., Int. Ed. Engl.* **1992**, *32*, 430.

(6) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. Bis(oxazoline)-Copper Complexes as Chiral Catalysts for the Enantioselective Aziridination of Olefins. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (b) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. Carbenoid Transfer to Imines: A New Asymmetric Catalytic Synthesis of Aziridines. *Angew. Chem., Int. Ed. Engl.* **1995**, *36*, 676.

(7) See, e.g.: van Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H. Pregosin, P. S. Enantioselective Allylic Substitution Catalyzed by Chiral [Bis(dihydrooxazole)]palladium Complexes: Catalyst Structure and Possible Mechanism of Enantioselection. *Helv. Chim. Acta* **1995**, *78*, 265.

(8) See, e.g.: Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. Enantioselective Allylic Oxidation catalyzed by Chiral Bisoxazoline-Copper Complexes. *Tetrahedron Lett.* **1995**, *36*, 1831.

(9) See, e.g.: (a) Wu, J. H.; Radinov, R.; Porter, N. A. Enantioselective Free Radical Carbon−Carbon Bond Forming Reactions: Chiral Lewis Acid Promoted Acyclic Additions. *J. Am. Chem. Soc.* **1995**, *117*, 11029. (b) Sibi, M. P. Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. Chiral Lewis Acid Catalysis in Radical Reactions: Enantioselective Conjugate Radical Additions. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

(10) See, e.g.: Corey, E. J.; Wang, Z. Enantioselective Conversion of Aldehydes to Cyanohydrins by a Catalytic System with Separate Chiral Binding Sites for Aldehyde and Cyanide Components. *Tetrahedron Lett.* **1993**, *34*, 4001.

(11) See, e.g.: Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. Asymmetric Addition of Organolithium Reagents to Imines. *J. Am. Chem. Soc.* **1994**, *116*, 8797.

(12) See, e.g.: Gothelf, K. G.; Hazell, R. G.; Jørgensen, K. A. Control of Diastereo- and Enantioselectivity in Metal-Catalyzed 1,3-Dipolar Cycloaddition Reactions of Nitrones with Alkenes. Experimental and Theoretical Investigations. *J. Org. Chem.* **1996**, *61*, 346.

(13) (a) Johannsen, M.; Jørgensen, K. A. Asymmetric Hetero Diels−Alder Reactions and Ene Reactions Catalyzed by Chiral Copper(II) Complexes. *J. Org. Chem.* **1995**, *60*, 5757. (b) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. Metal-catalyzed Hetero-Diels−Alder Reactions of Unactivated dienes with Glyoxylates. *Pure Appl. Chem.* **1998**, *79*, 1117.

(14) It should be noted that highly selective ene reactions of glyoxylates with alkenes and dienes catalyzed by BINOL−TIX_2 have been developed: Mikami, K.; Shimizu, M. Asymmetric Ene Reactions in Organic Synthesis. *Chem. Rev.* **1992**, *92*, 1021.

(15) (a) Johannsen, M.; Jørgensen, K. A. Solvent Effects in Asymmetric Hetero Diels−Alder and Ene Reactions. *Tetrahedron* **1996**, *52*, 7321. (b) Johannsen, M.; Jørgensen, K. A. Solvent vs. Counterion Acceleration of Enantioselective Carbo and Diels−Alder Reactions. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183.

(16) Graven, A.; Johannsen, M.; Jørgensen, K. A. A Highly Chemo- and Enantioselective Hetero-Diels−Alder Reaction Catalysed by Chiral Aluminium Complexes. *J. Chem. Soc., Chem. Commun.* **1996**, 2373.

(17) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. Total Synthesis of (*R*)-Dihydroactinidiolide and (*R*)-Actinidiolide Using Asymmetric Catalytic Hetero-Diels−Alder Methodology. *J. Org. Chem.* **1998**, *63*, 118.

(18) Gao, Y.; Lane-Bell, P.; Vederas, J. C. Stereoselective Synthesis of *meso*- 2,6-Diaminopimelic Acid and Its Selectively Protected Derivatives. *J. Org. Chem.* **1998**, *63*, 2133.

(19) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojlovsky, T.; Tregay, S. W. C_2−Symmetric Copper(II) Complexes as Chiral Lewis Acids. Enantioselective Catalysis of the Glyoxylate-Ene Reaction. *J. Am. Chem. Soc.* **1998**, *120*, 5824.

(20) (a) Johannsen, M.; Yao, S.; Jørgensen, K. A. The First Highly Enantioselective Catalytic Hetero Diels−Alder Reaction of Ketones. *J. Chem. Soc., Chem. Commun.* **1997**, 2169. (b) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. Catalytic Asymmetric Hetero-Diels−Alder Reactions of Ketones: Chemzymatic Reactions. *J. Am. Chem. Soc.* **1998**, *120*, 8599.

(21) Corey, E. J.; Guzman-Perez, A. The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

(22) Yao, S.; Roberson, M.; Reichel, F.; Jørgensen, K. A. to be submitted.

(23) Evans, D. A.; Johnson, J. S. Catalytic Enantioselective Hetero Diels- Alder Reactions of α,β-Unsaturated Acyl Phosphonates with Enol Ethers. *J. Am. Chem. Soc.* **1998**, *120*, 4895.

(24) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. Highly Enantioselective Catalytic Hetero-Diels−Alder Reaction with Inverse Electron Demand. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2404.

(25) See, e.g.: (a) Nelson, S. G. Catalyzed Enantioselective Aldol Additions of Latent Enolate Equivalents. *Tetrahedron: Asymmetry* **1998**, *9*, 357.

(26) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. C_2−Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enan-

tioselective Aldol Additions of Enolsilanes to Pyruvate Esters. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (b) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. C_2-Symmetric Tin(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Anti Aldol Additions of Enolsilanes to Glyoxylate and Pyruvate Esters. *J. Am. Chem. Soc.* **1997**, *119*, 10859.

(27) Evans, D. A.; Peterson, G. S.; Johnson, J. J.; Barnes, D. M.; Canpos, K. R.; Woerpel, K. A. An Improved Procedure for the Preparation of 2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane[(*S*,*S*)-tert-Butyl-bis(oxazoline)] and Derived Copper(II) Complexes. *J. Org. Chem.* **1998**, *63*, 4541.

(28) Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. Unpublished results.

(29) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. Cationic Bis(oxazoline) and Pyridyl-bis(oxazoline)Cu(II) and Zn(II) Lewis Acid Catalysts. A Comparative Study in Catalysis of Diels−Alder and Aldol Reactions. *Tetrahedron Lett.* **1996**, *37*, 7481.

(30) See also: Desmoni, G.; Faita, G.; Righetti, P. P. The First Enantio selective Synthesis of Both Diels−Alder Enantiomers with the Same bis(oxazoline)-Magnesium Perchlorate Catalyst. *Tetrahedron Lett.* **1996**, *37*, 3027.

AR970347F