A Novel Catalytic and Highly Enantioselective Approach for the Synthesis of Optically Active Carbohydrate Derivatives

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A catalytic enantioselective inverse-electron demand hetero-Diels−Alder reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes catalyzed by chiral bisoxazolines in combination with $Cu(OTf)_2$ as the Lewis acid is presented. The reaction of γ-substituted β,γ-unsaturated α-keto esters with vinyl ethers and various types of *cis*-disubstituted alkenes proceeds in good yield, high diastereoselectivity, and excellent enantioselectivity. The potential of the reaction is demonstrated by the synthesis of optically active carbohydrates such as spiro-carbohydrates, an ethyl β-D-mannoside tetraacetate, and acetal-protected *C*-2-branched carbohydrates. On the basis of X-ray crystallographic data and the absolute configuration of the products, it is proposed that the alkene approaches the *si*-face of the reacting α,β-unsaturated carbonyl functionality when coordinated to the catalyst.

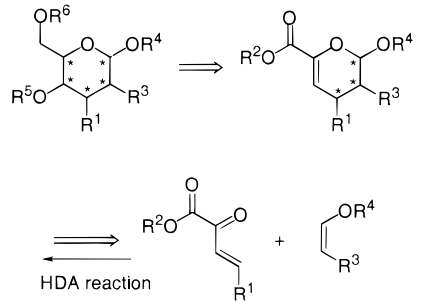
Introduction

The interest in the development of new synthetic procedures for the preparation of natural and unnatural carbohydrates is due to the abundance of carbohydrates in living cells. The most common synthetic approach for the formation of these compounds has been to derivatize naturally occurring carbohydrates. However, there are limitations with this approach: (i) few monosaccharides are readily available from natural sources; (ii) mainly D-sugars are found in the chiral pool; (iii) a large number of protection and deprotection steps makes the synthesis less efficient; and (iv) the choice of substituents is limited. Alternative procedures for the preparation of these carbohydrate analogues from acyclic precursors would therefore be of great value.

An attractive synthetic procedure for the preparation of novel optically active carbohydrate derivatives is the hetero-Diels−Alder (HDA) reaction of α,β-unsaturated carbonyls with electron-rich alkenes, i.e., enol ethers.[1] The retrosynthetic analysis presented in Scheme 1 illustrates this approach for the formation of carbohydrate derivatives. This procedure allows control of up to three stereocenters in a single step, as well as incorporating a broad choice of substituents in the final six-membered ring. Furthermore, the substituents introduced might eventually be transformed into other functional groups allowing coupling reactions.

The type of reaction outlined in Scheme 1 has already been shown to proceed in an achiral environment.[2] However, to obtain optically active carbohydrate derivatives by the HDA approach, either a chiral transformation via the use of a chiral auxiliary or a catalytic

Scheme 1



enantioselective reaction is necessary. The diastereoselective reaction requires an optically active α,β-unsaturated carbonyl compound and/or an optically active alkene. In recent years, several diastereoselective HDA reactions of α,β-unsaturated carbonyl compounds with electron-rich alkenes have appeared, leading to carbohydrate derivatives with good diastereomeric excess.[3] A problem with this process is that it is usual to remove the chiral auxiliary after reaction, which can lead to a lowering of

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(1) For leading references of inverse-electron demand hetero-Diels−Alder reactions, see, for example: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651−692. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (c) Tietze, L. F.; Kettschau, G. *Stereoselective Heterocyclic Synthesis I*; Metz, P., Ed.; Springer: Berlin, 1997; Vol. 189, pp 1−120. (d) Ager, D. J.; East, M. B. *Tetrahedron* **1993**, *49*, 5683−5765.

(2) For references of inverse hetero-Diels−Alder reactions in an achiral environment, see, for example: (a) Tietze, L. F.; Voss, E. *Tetrahedron Lett.* **1986**, *27*, 6181−6184. (b) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373−3377. (c) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793- 5796. (d) Wada, E.; Kanemasa, S.; Tsuge, O. *Chem. Lett.* **1989**, 675−678. (e) Tietze, L. F.; Hartfiel, U. *Tetrahedron Lett.* **1990**, *31*, 1697−1700. (f) Sera, A.; Ohara, M.; Yamada, H.; Egashira, E.; Ueda, N.; Setsune, J. *Chem. Lett.* **1990**, 2043−2046. (g) Tietze, L. F.; Schneider, C. *Synlett*, **1992**, 755−756. (h) Sera, A.; Ohara, M.; Yamada, H.; Egashira, E.; Ueda, N.; Setsune, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1912−1917.

(3) For examples of diastereoselective hetero-Diels−Alder reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes, see, for example: (a) Schmidt, R. R.; Maier, M. *Tetrahedron Lett.* **1985**, *26*, 2065−2068. (b) Schmidt, R. R.; Haag-Zeino, B.; Hoch, M. *Liebigs Ann. Chem.* **1988**, 885−889. (c) Dujardin, G.; Molato, S.; Brown, E. *Tetrahedron: Asymmetry* **1993**, *4*, 193−196. (d) Tietze, L. F.; Montenbruck, A.; Schneider, C. *Synlett* **1994**, 509−510. (e) Tietze, L. F.; Schneider, C.; Grote, A. *Chem. Eur. J.* **1996**, *2*, 139−148. (f) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205−1220. (g) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron* **1996**, *52*, 4007−4010. (h) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 763−770.

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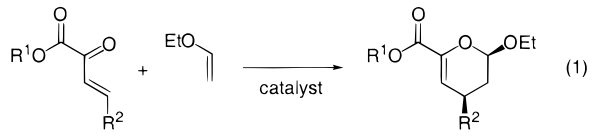
the yield of the desired product. The catalytic enantioselective HDA approach has several advantages compared with the diastereoselective reactions. First, the substrate does not require a chiral auxiliary, so the preparation and cleavage steps associated with this technique are now removed. Second, only catalytic amounts of chiral complex are required to promote the reaction. The only work published until recently using the catalytic enantioselective approach for intermolecular HDA reactions has, according to our knowledge, been published by Wada et al.[4]

The use of chiral Lewis acids for the HDA reaction of dicarbonyl compounds with dienes has recently been shown to be a useful procedure for preparing products with good enantioselectivity.[5,6] Among the chiral Lewis acids used as catalysts, the chiral bisoxazoline copper(II) complexes have been shown to be effective catalysts for addition reactions to α-dicarbonyl compounds.[6−8] The bisoxazoline copper(II) catalysts can catalyze highly diastereo- and enantioselective HDA reactions of activated aldehydes with conjugated dienes or ketones with activated dienes.[6] These reactions can be considered as normal-electron demand HDA reactions where the dienophile, activated by the chiral Lewis acid, interacts by its LUMO, with the HOMO of the diene.[9] Recently, it was communicated that the chiral bisoxazoline copper(II) complexes can catalyze highly enantioselective inverse-electron demand HDA reactions.[10] In two independent communications from Evans et al.[10c] and from us[10b] it was demonstrated that β,γ-unsaturated α-keto esters react with ethyl vinyl ether in the presence of chiral bisoxazoline copper(II) complexes as catalysts leading to enantiomerically enriched dihydropyrans (eq 1).[10b−d]

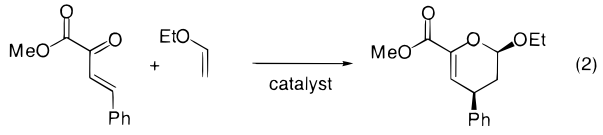


(1)

This paper presents the development of highly diastereo- and enantioselective catalytic HDA reactions of α,β-unsaturated dicarbonyl compounds with electron-rich alkenes. The products of this reaction are carbohydrate precursors which can be converted into attractive carbohydrate derivatives.

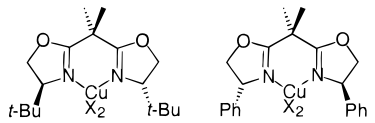
Results and Discussion

Several different chiral bisoxazoline copper(II) complexes can catalyze the HDA reaction of the β,γ-unsaturated α-keto ester **1a** with ethyl vinyl ether **2a** (eq 2) and among them, the *tert*-butyl-substituted bisoxazoline copper(II) triflate catalyst (*t*-Bu-Box-Cu(OTf)$_2$) **4a**, has been found to have the most promising properties.[7,10b] Some representative results for the reaction of (*E*)-2-oxo-4-phenylbut-3-enoic acid methyl ester **1a** with **2a** in the presence of different C_2-bisoxazoline ligands and copper(II) salts are presented in Table 1.



(2)

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



(*S*)-**4a** (*R*)-**4b**

The results in Table 1 show that *t*-Bu-Box-Cu(OTf)$_2$ **4a** catalyzes a highly diastereo- and enantioselective HDA reaction giving the dihydropyran **3a** in very high yield. In THF, compound **3a** is isolated in 95% yield, predominantly as one diastereomer (the diastereoselectivity is >98%) and with a very high ee, 99.5% (entry 1). Changing the solvent from THF to CH_2Cl_2 or Et_2O gives similar results (entries 2, 3). When $MeNO_2$ is the solvent at 0 °C, lower diastereoselectivity of **3a** was observed (entry 4). At ambient temperatures and at 0 °C, the reaction proceeds well in Et_2O with no loss of yield and selectivity even with only 0.5 mol % catalyst loading (entries 5−10). We have previously reported[10b] that THF was the solvent of choice, but in many cases further studies have shown that Et_2O gives better results. By the use of Ph-Box-Cu(OTf)$_2$ **4b** in Et_2O at 0 °C as the

(4) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637−1640.

(5) The use of chiral Lewis acids in HDA reactions, see, for example: (a) Graven, A.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1996**, 2373−2374. (b) Yao, S.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1*. **1997**, 2345−2349. (c) Johannsen, M.; Jørgensen, K. A.; Zheng, X. F.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 299−301. (d) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem.* **1999**, *111*, 2459−2553; *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (e) Desimoni, G.; Faita, G.; Righetti, P.; Sardone, N. *Tetrahedron* **1996**, *52*, 12019−12030. (f) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310−312. (g) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951−1952. (h) Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979−988. (i) Schauss, S.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405. (j) Motoyama, Y.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1563−1564. (k) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060−7067. (l) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427−2430. (m) Li, L.-S.; Wu, Y.; Hu, Y.-J. Xia, L.-J.; Wu, Y.-L. *Tetrahedron: Asymemtry* **1998**, *9*, 2271- 2277. (n) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. (o) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999. (p) Togni, A. *Organometallics* **1990**, *9*, 3106−3113.

(6) Hetero-Diels−Alder reactions of aldehydes/ketones with dienes catalyzed by chiral bisoxazoline-copper(II): (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (b) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321−7328. (c) Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183−1185. (d) Johannsen, M.; Yao, S.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1997**, 2169−2170. (e) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 118−121. (f) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117−1122. (g) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599−8605. (h) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165−2168.

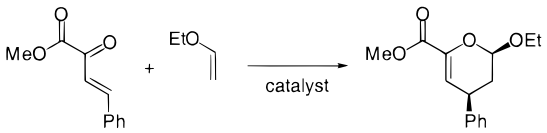
(7) For chiral bisoxazoline copper(II) complex used to catalyze addition to α-dicarbonyls, see, for example: (a) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613. (b) Evans, D. A.; Johnson, J. S. *Acc. Chem. Res.* **2000**, *33*, in press.

(8) For pioneering work using bisoxazoline ligands, see: (a) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A.; Keller, W.; Kratky, C. *Helv. Chim. Acta* **1988**, *71*, 1541−1552. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728.

(9) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinhein, 1970.

(10) (a) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895−4896. (b) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem.* **1998**, *110*, 2543−2546; *Angew. Chem., Int. Ed.* **1998**, *37*, 2404−2406. (c) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem.* **1998**, *110*, 3554−3557; *Angew. Chem., Int. Ed.* **1998**, *37*, 3372−3375. (d) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649.

Table 1. Results for the Reaction of 1a with 2a Giving the Hetero-Diels–Alder Adduct 3a in the Presence of the Catalysts 4a,b



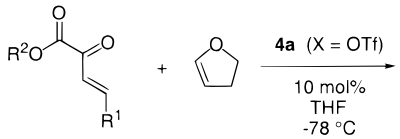
1a **2a** **3a**

entry	catalyst	loading, mol %	solvent	temp, °C	yield,[a] %	de,[b,c] %	ee[b]/% endo/exo
1	(*S*)-**4a** X = OTf	10	THF	−78	95[d]	>98	>99
2	(*S*)-**4a** X = OTf	10	CH_2Cl_2	−78	99	97	99
3	(*S*)-**4a** X = OTf	10	Et_2O	−78	93	99	99
4	(*S*)-**4a** X = OTf	10	CH_3NO_2	0	99	34	87/58
5	(*S*)-**4a** X = OTf	10	Et_2O	0	93	98	99
6	(*S*)-**4a** X = OTf	10	Et_2O	rt	99[e]	97	>99
7	(*S*)-**4a** X = OTf	5	Et_2O	0	96	99	>99
8	(*S*)-**4a** X = OTf	2	Et_2O	0	98	99	>99
9	(*S*)-**4a** X = OTf	1	Et_2O	0	98	99	>99
10	(*S*)-**4a** X = OTf	0.5	Et_2O	0	99	98	99
11	(*R*)-**4b** X = OTf	10	Et_2O	0	99	71[f]	12/5
12	(*S*)-**4a** X = PF_6	10	CH_2Cl_2	0	99	84[f]	−/93

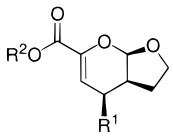
[a] Isolated yield after 1 d. [b] Determined by chiral HPLC. [c] Endo diastereomer major product. [d] Isolated yield after 2 d. [e] Isolated yield after 2 h. [f] Other diastereomer.

catalyst, the diastereoselectivity changed and the enantioselectivity was low (entry 11). The use of the PF_6-salt of the *t*-Bu-Box-CuX_2 **4a** catalyst also changes the de of the reaction (entry 12).

The catalytic enantioselective properties of *t*-Bu-Box-Cu(OTf)$_2$ **4a** for the HDA reaction of *β*,*γ*-unsaturated α-keto esters with activated alkenes leading to precursors for carbohydrates and carbohydrate derivatives will be presented in the following. The reaction of the *β*,*γ*-unsaturated α-keto esters **1a**−**c** with 2,3-dihydrofuran **2b** (eq 3) will be studied first.



1a: R^1 = Ph, R^2 = Me **2b**
1b: R^1 = OEt, R^2 = Et
1c: R^1 = Me, R^2 = Et

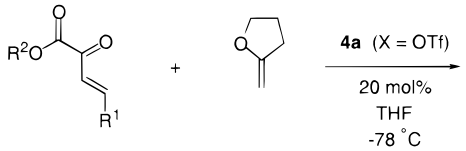


(3)

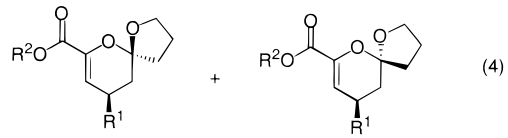
3b: R^1 = Ph, R^2 = Me, yield 96%, >99% ee
3c: R^1 = OEt, R^2 = Et, yield 84%, 98% ee
3d: R^1 = Me, R^2 = Et, yield 51%, >99% ee

2,3-Dihydrofuran **2b** reacts with (*E*)-2-oxo-4-phenylbut-3-enoic acid methyl ester **1a**, (*E*)-4-ethoxy-2-oxobut-3-enoic acid ethyl ester **1b** and (*E*)-2-oxopent-3-enoic ethyl acid ester **1c** in the presence of *t*-Bu-Box-Cu(OTf)$_2$ **4a** (10 mol %) as the catalyst in THF. The bicyclic unsaturated esters products **3b**−**d** are formed in good yield, high diastereoselectivity (de >95%, only traces of the minor diastereomer can be detected by ^{1}H NMR spectroscopy) and enantioselectivity (up to 99.5% ee), results which are similar to those observed by Evans et al.[10c,d] An increase of the enantioselectivity is found for the reaction of **1b** and **2b** in the presence of catalyst **4a**, when performed in Et_2O at −78 °C (>99.5% ee). This correlates well with the findings in Table 1.

The catalytic enantioselective HDA reaction can be used for the preparation of optically active spiro carbohydrates, which are found in a variety of natural products such as pheromones, steroid derivatives, antiparasitic agents or polyether antibiotics.[11] Equation 4 shows the reaction of **1b** and **1d** with the *exo*-cyclic vinyl ether **2c** catalyzed by *t*-Bu-Box-Cu(OTf)$_2$ **4a**. It appears that by the use of the HDA methodology, it is possible to obtain the spiroacetal functionality in a convergent way, avoiding a stepwise spirocyclization.[12,13] The catalytic enantioselective HDA reaction of the *exo*-cyclic vinyl ether **2c** with enone **1b** or **1d** proceeds with moderate yield with the *endo*-**3e** and *endo*-**3f** formed in 74% and 76% ee respectively, as the major product.[14] The minor diastereomers *exo*-**3e** and *exo*-**3f** are formed in 84% and 95% ee, respectively (eq 4).



1b: R^1 = OEt, R^2 = Et **2c**
1d: R^1 = OBn, R^2 = Et



(4)

endo-**3e**: R^1 = OEt, R^2 = Et
yield 63%, 74% ee
endo-**3f**: R^1 = OBn, R^2 = Et
yield 40%, 76% ee

exo-**3e**: R^1 = OEt, R^2 = Et
yield 21%, 84% ee
exo-**3f**: R^1 = OBn, R^2 = Et
yield 12%, 95% ee

To obtain derivatives which more closely resembles a carbohydrate structure, the introduction of an alcohol in an *anti*-Markovnikov sense on the double bond at the carbon-4 position (carbohydrate numbering), as well as the reduction of the ester to an alcohol at the carbon-6 position, are required. The introduction of the alcohol can be achieved in *endo*-**3e** using $TiCl_4$−$NaBH_4$.[15] However, when this approach was used, a mixture of diastereomers was formed in low yield. Using an alternative method developed by Boger et al., we could obtain diastereomer **5**, in which the alcohol at carbon-4 has been introduced anti compared to the substituents on carbon-3 and

(11) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661; see also: Bartolozzi, A.; Capozzi, G.; Falciani, C.; Menichetti, S.; Naitvi, C.; Bacialli, A. P. *J. Org. Chem.* **1999**, *64*, 6490−6494.

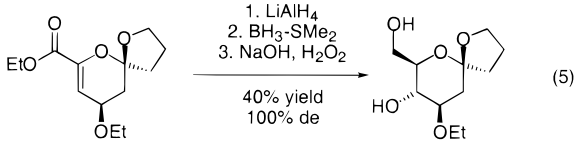
(12) For spirosugars made using HDA, see: Ireland, R. E.; Häbich, D. *Chem. Ber.* **1981**, *114*, 1418−1427.

(13) For other methodes to synthesize spirosugars, see, for example: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362. (b) Martin, A.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1996**, *61*, 3999−4006. (c) Van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061−6064.

(14) The attribution of *endo* and *exo* to the products **3e** and **3f** were made according to previous results where we observed that the *endo* product is the major compound formed under the reaction conditions (see eq 3 and ref 10b, as well as following results in this article (compound *endo*-**3g**)).

(15) Kano, S.; Tanaka, Y.; Hibino, S. *J. Chem. Soc., Chem. Commun.* **1980**, 414−415.

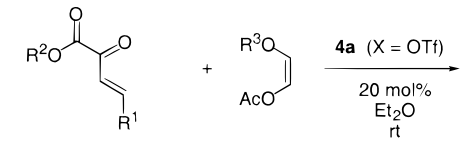
carbon-5 (eq 5) (stereochemistry vide infra).[2c] These reactions, which have not been optimized, proceed well giving the spiro-carbohydrate derivative **5** in satisfactory overall yield. The catalytic enantioselective reaction of β,γ-unsaturated α-keto esters with the *exo*-cyclic vinyl ether catalyzed by *t*-Bu-Box-Cu(OTf)$_2$ **4a** is a convenient new synthetic procedure for the preparation of optically active spiro-carbohydrates.



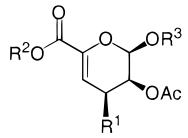
(5)

endo-**3e** **5**

For the catalytic enantioselective reactions of the β,γ-unsaturated α-keto esters presented until now, an oxygen substituent is lacking in the 2-position. In the following we will consider *cis*-dihydroxy-substituted alkenes for the introduction of the oxygen atom in the 2-position. To control the regioselectivity in the HDA step when alkenes with two different oxygen substituents are used, *cis*-1-acetoxy-2-ethoxyethene **2d** and *cis*-1-acetoxy-2-(benzyloxy)ethene **2e** have been chosen. However, a symmetrical *cis*-alkene is also interesting and 2,2-dimethyl-1,3-dioxole **2f** (vide infra) has been used. Both *cis*-alkenes **2d** and **2f** were prepared in gram scale by a retro-Diels−Alder reaction, and alkene **2e** was synthesized following a procedure developed by Boger et al.[2c]



1a: R^1 = Ph, R^2 = Me **2d**: R^3 = Et
1b: R^1 = OEt, R^2 = Et **2e**: R^3 = Bn
1d: R^1 = OBn, R^2 = Et

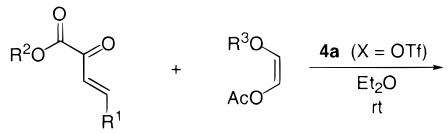


(6)

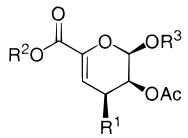
endo-**3g**: R^1 = Ph, R^2 = Me, R^3 = Et
endo-**3h**: R^1 = OEt, R^2 = Et, R^3 = Et
endo-**3l**: R^1 = OBn, R^2 = Et, R^3 = Et
endo-**3j**: R^1 = OEt, R^2 = Et, R^3 = Bn

The results for the reaction of **2d** and **2e** with the β,γ-unsaturated α-keto esters **1a**,**b**,**d** (eq 6) are presented in Table 2. The reaction requires room temperature to proceed and a 20 mol % loading of the *t*-Bu-Box-Cu(OTf)$_2$ **4a** catalyst is necessary, as the reaction proceeds with a decrease of enantioselectivity when only 10 mol % of the catalyst is applied (entry 1). The reason for the higher catalyst loading might be due to the binding of **2d** to the catalyst **4a**, which causes its deactivation. However, using 20 mol % of **4a** as the catalyst leads to a highly regio-, diastereo-, and enantioselective reaction (entry 2). The reaction of **1b** with **2d** gives only one regioisomer of the HDA adduct and only the *endo*-diastereomer, *endo*-**3h**, could be observed by ^{1}H NMR spectroscopy. Changing the solvent to dioxane, CH_2Cl_2, or Et_2O leads to higher enantioselectivity in the reaction, with the best results

Table 2. Results for the Reaction of 1a, 1b and 1d with 2d and 2e in the Presence of (*S*)-*t*-Bu-Box-Cu(OTf)$_2$ 4a as the Catalyst in Et$_2$O at Room Temperature



1a: R^1 = Ph, R^2 = Me **2d**: R^3 = Et
1b: R^1 = OEt, R^2 = Et **2e**: R^3 = Bn
1d: R^1 = OBn, R^2 = Et



endo-**3g**: R^1 = Ph, R^2 = Me, R^3 = Et
endo-**3h**: R^1 = OEt, R^2 = Et, R^3 = Et
endo-**3i**: R^1 = OBn, R^2 = Et, R^3 = Et
endo-**3j**: R^1 = OEt, R^2 = Et, R^3 = Bn

entry	enone	alkene	catalyst load/%	solvent	yield[a]/%	ee[b]/%
1	**1b**	**2d**	10	THF	*endo*-**3h**/nd	7
2	**1b**	**2d**	20	THF	*endo*-**3h**/45	81
3	**1b**	**2d**	20	dioxane	*endo*-**3h**/41	90
4	**1b**	**2d**	20	CH_2Cl_2	*endo*-**3h**/30	94
5	**1b**	**2d**	20	Et_2O	*endo*-**3h**/70	99.5
6	**1b**	**2d**	15	Et_2O	*endo*-**3h**/69	99
7	**1b**	**2d**	10	Et_2O	*endo*-**3h**/69	83
8	**1a**	**2d**	20	Et_2O	*endo*-**3g**/76[c]	99.5
9	**1d**	**2d**	20	Et_2O	*endo*-**3i**/60	96.5
10	**1b**	**2e**	20	Et_2O	*endo*-**3j**/61	66

[a] Isolated yield. [b] Determined by chiral GC or HPLC. [c] 4% of *exo*-diastereomer, no determination of the ee.

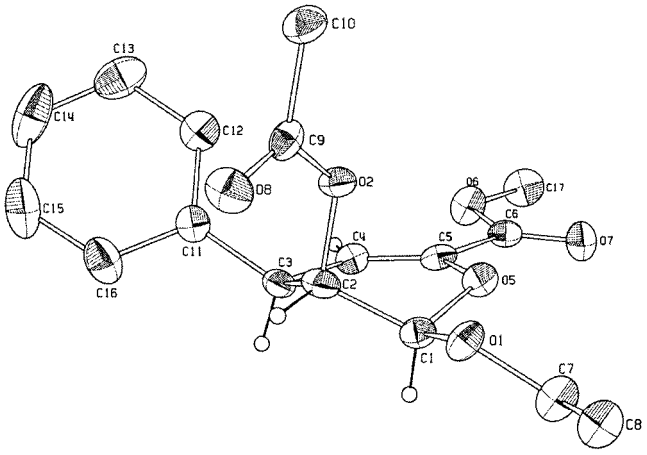
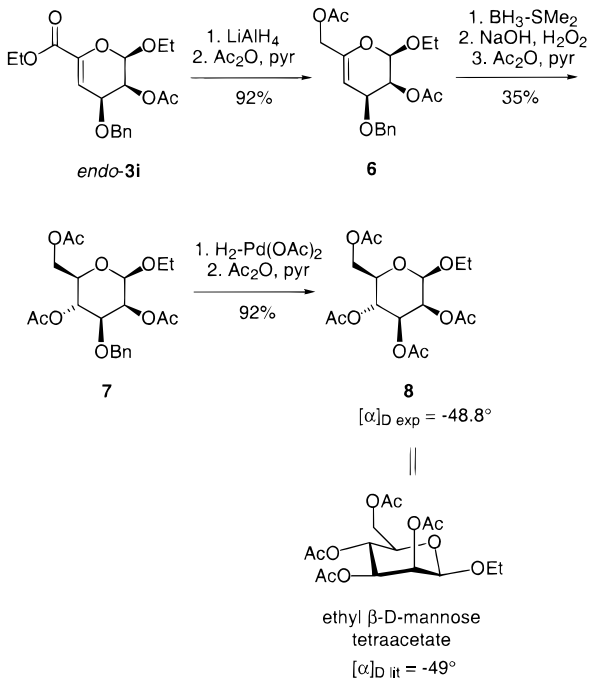


Figure 1. The X-ray structure of *endo*-**3g**.

in Et_2O (entries 3−5). The ee of *endo*-**3h** under these reaction conditions is measured as 99.5% (entry 5). However, trying to reduce the catalyst loading for the reaction in Et_2O from 20 mol % to 15 mol % and 10 mol %, leads to a decrease in enantioselectivity (entries 6, 7). Applying the optimal condition to the phenyl-substituted enone **1a** leads to product *endo*-**3g** in 76% yield and with excellent ee of 99.5% (entry 8). However, in this case, the formation of 4% of the *exo*-product is observed. An X-ray analysis of *endo*-**3g** proved that the major diastereomer has a *cis*-relationship with the three substituents in the ring, corresponding to the *endo*-product (Figure 1).

An exchange of the 4-ethoxy substituent with a benzyloxy substituent in the β,γ-unsaturated α-keto ester, (*E*)-4-(benzyloxy)-2-oxobut-3-enoic acid ethyl ester **1d**,

Scheme 2

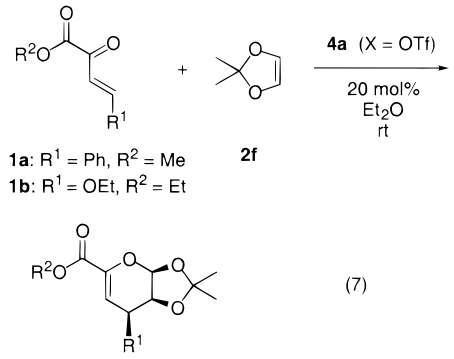


leads to a substrate which contains a protecting group on the C-3 alcohol. The reaction of **1d** with **2d** in the presence of *t*-Bu-Box-Cu(OTf)$_2$ **4a** as the catalyst gave *endo*-**3i** as the only diastereomer in 60% isolated yield and with an ee of 96.5% (entry 9). The three different protecting groups on the three alcohols in *endo*-**3i** are orthogonal and make *endo*-**3i** a useful synthon for carbohydrate derivatives. The reaction of **1b** with **2e** catalyzed by *t*-Bu-Box-Cu(OTf)$_2$ **4a** proceeds also with high diastereoselectivity (only the *endo*-product is observed) and in reasonable yield in Et_2O as the solvent. However, a decrease to 66% ee of *endo*-**3j** was found (entry 10).

The catalytic enantioselective HDA reactions presented in Table 2 can be used for the preparation of β-D-mannopyranosides. The stereoselective synthesis of this class of carbohydrates has been a long standing problem in carbohydrate chemistry[16] which has attracted the attention of numerous groups worldwide and has successfully been carried out by, for example, Crich et al.,[17] Hindsgaul et al.,[18] Stork et al.,[19] Ogawa et al.,[20] and others.[21] We will in the following present the synthesis of ethyl β-D-mannoside tetraacetate **8** using the HDA approach. Furthermore, the synthesis of **8** allows us to assign the absolute stereochemistry of the product by comparison to literature.[22] The synthesis of **8** from *endo*-**3i** is presented in Scheme 2.

The first step in the synthesis of the ethyl β-D-mannoside tetraacetate **8** from *endo*-**3i** is the reduction of the ester followed by protection of the resulting alcohol into an acetate which gives compound **6** with 92% overall yield. Hydroboration of the double bond in **6**, which proceeds in moderate yield, gives the sugar derivative **7** after acetylation of the hydroxyl groups. Finally, compound **8** is obtained after a palladium-catalyzed reduction of the benzyl group and acetylation of the resulting hydroxyl group. After measurement of the optical rotation of **8**, we were able to assign the absolute stereochemistry of this compound by comparison with the optical rotation of ethyl β-D-mannoside tetraacetate found in the literature ($[\alpha]_{D\ exp} = -48.8°$; $[\alpha]_{D\ lit} = -49°$).[22] This stereochemistry is used for the assignment of the absolute configuration of the HDA adducts.

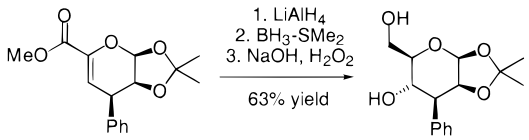
The symmetric activated cyclic alkene 2,2-dimethyl-1,3-dioxole **2f** also reacts smoothly with **1a** and **1b** in the presence of *t*-Bu-Box-Cu(OTf)$_2$ **4a** (20 mol %) (eq 7). When **1a** is the substrate, *endo*-**3k** is isolated in 76% yield having an ee of 99%, while **1b** gives similar results with *endo*-**3l** isolated in 63% yield and 99% ee. *Exo*-**3k** and *exo*-**3l** are also formed in 22% and 16% yield, and with 92% and 82% ee, respectively.



(7)

endo-**3k**: R^1 = Ph, R^2 = Me, yield 76%, 99% ee
endo-**3l**: R^1 = OEt, R^2 = Et, yield 63%, 99% ee

To obtain the carbohydrate derivative, the methodology described in eq 5 was applied to *endo*-**3k** for the introduction of the alcohol at the carbon-4 position and reduction of the ester. The carbohydrate derivative **9** was isolated in 63% overall yield and as an optically pure compound (eq 8). Furthermore, an X-ray structure analysis of **9**



(8)

showed the *anti*-relationship of the alcohol on carbon-4, formed in the hydroboration/oxidation step, with the substituents on carbon-3 and carbon-5 (Figure 2).

To show the potential of the catalytic enantioselective HDA reaction, the enones **1a**, **1b**, and **1d** were reacted

(16) See, for example: Barresi, F.; Hindsgaul, O. *Synthesis of* β-D-mannose Containing Oligosaccharides. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic Publishers: Amsterdam, 1996; pp 251−276.

(17) See, for example: (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506−4508. (c) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199. (d) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.

(18) (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376−9377. (b) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759−761. (c) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447−1465.

(19) (a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. (b) Stork, G.; La Clair J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248.

(20) (a) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767. (b) Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1997**, *119*, 5562−5566.

(21) See also: (a) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335−2336. (b) Srivastava, V. K.; Schuerch, C. *Tetrahedron Lett.* **1979**, *20*, 3269−3272.

(22) Asp, L.; Lindberg, B. *Acta Chem. Scand.* **1952**, *6*, 947−948.

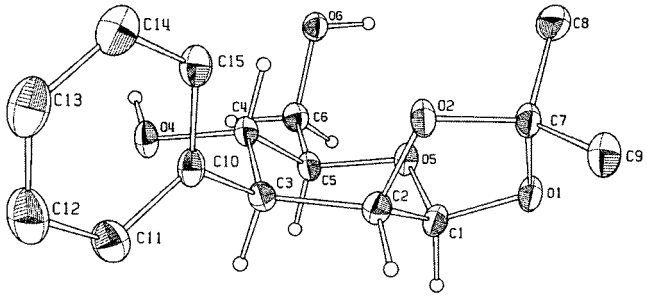
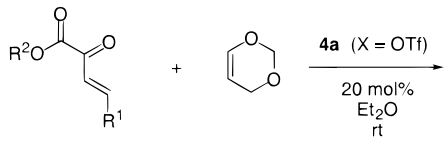


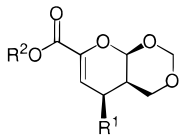
Figure 2. The X-ray structure of **9**.

with 4*H*-1,3-dioxine **2g**[23] catalyzed by *t*-Bu-Box-Cu(OTf)$_2$ **4a** (eq 9). The alkene **2g** can lead to a new procedure for the synthesis of *C*-branched sugars, subunits which are found in numerous natural compounds.[24] The HDA reaction between **1a**,**b**,**d** and **2g** can facilitate the synthesis of 2-*C*-analogues of carbohydrates. Two recent articles showed new methods to get to these particular compounds.[25] The present HDA reaction could be an alternative: it proceeds smoothly, giving the three *endo*-diastereomers **3m**, **3n**, and **3o** in 66%, 65%, and 81% yield, and high ee's 93%, 96%, and 91%, respectively. The formation of the *exo*-diastereomer is also observed, but only for the reaction of enone **1a** where *exo*-**3m** is formed in 11% yield.



1a: R^1 = Ph, R^2 = Me
1b: R^1 = OEt, R^2 = Et
1d: R^1 = OBn, R^2 = Et

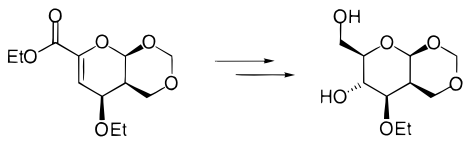
2g



(9)

endo-**3m**: yield 66%, 93% ee
endo-**3n**: yield 65%, 96% ee
endo-**3o**: yield 81%, 91% ee

The reaction presented in eq 9 leads to a synthetic procedure for the preparation of unnatural synthetic acetal-protected 2-*C*-branched carbohydrates **10** as outlined in eq 10. The acetal functionality of compound **10**



(10)

endo-**3m** **10**

can then be removed, forming a CH_2OH group on carbon-2, which is attractive for further coupling reactions, e.g., unnatural oligosaccharide synthesis.

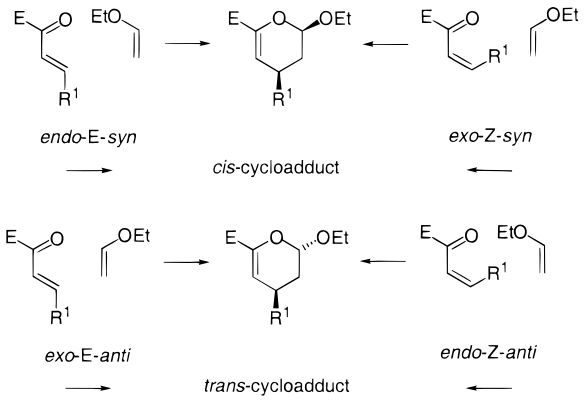


Figure 3. The four different diastereoselective approaches of an alkene such as ethyl vinyl ether to γ-substituted β,γ-unsaturated α-keto ester (E = EtOOC).

The catalytic HDA method developed has a high regio-, diastereo-, and enantioselectivity. The regioselectivity in this reaction is controlled by the electronic effects in the alkene, thus alkenes **2d** and **2e** have been chosen so that the most electron-rich oxygen becomes the one at the anomeric position in the product. The diastereoselectivity is controlled by both electronic and steric factors. Electronic effects favor the formation of the *endo*-product, but when the size and shape of the alkene interact with the enantiodirecting ligand the *exo*-product is formed. This can be rationalized from the different diastereoselectivities obtained by reaction with the different alkenes: ethyl vinyl ether **2a** (99% de), 2,3-dihydro-furan **2b** (96% − locked), 4*H*-1,3-dioxine **2g** (75% − locked and more bulky than **2b**), *tert*-butyl vinyl ether (60% − very bulky),[10b] 2,2-dimethyl-1,3-dioxole **2f** (60% − bulky and locked).

The diastereochemistry of the product formed in the HDA reaction depends on the geometry of the transition structures. There are four different transition states through which the HDA reaction can proceed, the two *endo*- and two *exo*-orientations. The four transition structures[1c] leading to the two diastereomers of the reaction of γ-substituted β,γ-unsaturated α-keto esters with ethyl vinyl ether are outlined in Figure 3. The *cis*-adduct can be formed by either an *endo-E-syn* or *exo-Z-syn* orientation, whereas the *trans*-adduct is obtained by either an *exo-E-anti* or *endo-Z-anti* orientation.

The results for the catalytic enantioselective reactions presented in this paper have shown that the *cis*-cycloadduct is the diastereomer formed, by either an *endo-E-syn* or *exo-Z-syn* orientation of the electron-rich alkene in the transition state. The γ-substituted β,γ-unsaturated α-keto esters substrates all have the γ-substituent *trans* [(*E*)] and therefore the *endo-E-syn* orientation is the preferred orientation of the alkene when approaching the β,γ-unsaturated α-keto ester.

Preparing crystals of dicarbonyl compounds coordinated to the catalyst has proved illusive with only crystals with 2 equiv of water per copper center, which are similar to those published by Evans et al.[10c,d,26] From the X-ray structures it appears that chiral bisoxazoline copper(II) coordinated complexes can have different geometrical structures depending on the coordination number of copper. When the coordination number is four,

(23) Groth, U.; Schöllkopf, U.; Tiller, T. *Tetrahedron* **1991**, *47*, 2835−2842.

(24) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983. (b) Fraser-Reid, B. *Acc. Chem. Res.* **1996**, *29*, 57−66.

(25) (a) Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377−9384. (b) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137−12138.

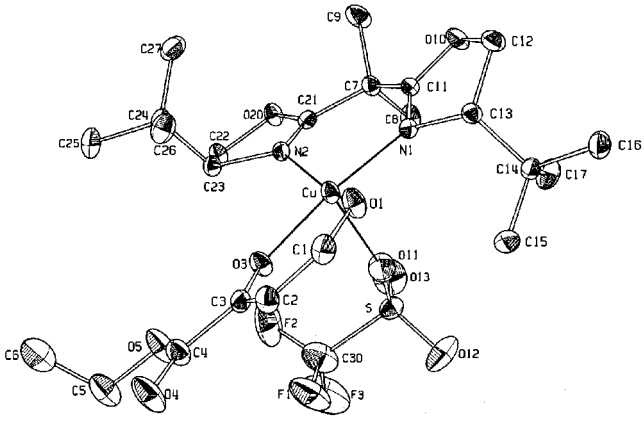


Figure 4. The X-ray structure of the hydrolyzed enone **1b** coordinated to the chiral catalyst (*S*)-t-Bu-Box-Cu(II) **11**.

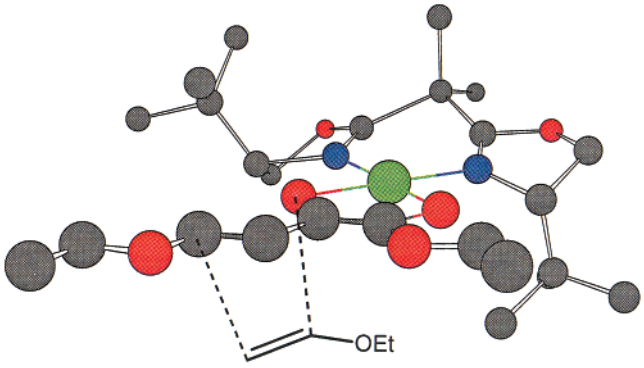


Figure 5. The *endo-E-syn* approach to ethyl vinyl ether to a bidentate coordinated (*E*)-4-ethoxy-2-oxobut-3-enoic acid ethyl ester to the (*S*)-t-Bu-Box-Cu(II) catalyst.

copper(II) exhibits distorted square-planar geometry with a dihedral angle for the O(H_2O)−Cu−N−C(chiral carbon atom in ligand) in the range from +33.3° for *t*-Bu-Box-Cu$(OH_2)_2^{2+}$ to −9.3° for Ph-Box-Cu$(OH_2)_2^{2+}$.[26a] A pentacoordinated complex *t*-Bu-Box-Cu$(OH_2)_2(OTf)_2^+$ has also been characterized and shows a square-pyramidal geometry.[10c,d] A chiral bisoxazoline copper(II) complex, with an alkylidene malonate coordinated to copper, has also been isolated and characterized by X-ray analysis and shows a distorted square-planar geometry.[26b] By chance a failed reaction with enone **1b** gave a crystal of the anion of the hydrolyzed enone bound to the chiral bisoxazoline copper(II) catalyst **11** and is shown in Figure 4. The structure of complex **11** also shows a distorted square-planar geometry at the copper(II) center with a dihedral angle of 16.1° and 14.0° for the O(enol/ketone)−Cu−N−C(chiral carbon atom in the ligand) angles, respectively.

The postulated intermediate presented in Figure 5 is based on the assumption that the γ-substituted β,γ-unsaturated α-keto ester **1b** coordinates in a bidentate fashion by the carbonyl oxygen atoms to the (*S*)-*t*-Bu-Box-Cu(II) catalyst similar to the structure in Figure 4. The approach of the electron-rich alkene to **1b** when coordinated to the catalyst will thus take place toward the *si*-face of the reacting carbonyl, as the *re*-face is shielded by the *tert*-butyl substituent of the chiral ligand.

(26) (a) Evans, D. A.; Johnson, J. A.; Burgey, C. S.; Compos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879−2882. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995.

This approach is in accordance with the absolute configuration of the HDA adduct obtained using the (*S*)-*t*-Bu-Box-Cu(II) (*S*)-**4a** catalyst. The preferred *endo-E-syn* orientation of the electron-rich alkene might be due to a favorable electronic interaction between the oxygen atom of the alkene and the metal center of the catalyst. However, when the steric bulk of the substituent at the oxygen atom of the vinyl ether increases, e.g., from ethyl vinyl ether to *tert*-butyl vinyl ether,[10b] the diastereoselectivity of the reaction is reduced. This reduction might be caused by an increased steric repulsion between the *tert*-butyl substituent of the vinyl ether and the *tert*-butyl of the chiral ligand located on the same side as the alkene approaches.

The reason for the high enantioselectivity is (i) the near perfect shielding of the reacting enone; (ii) the low degree of freedom of the enones due to the bidentate coordination and the required *s-cis* conformation for the reaction to proceed.

Summary

We have shown that it is possible to use a highly enantioselective hetero-Diels−Alder (HDA) reaction catalyzed by the *tert*-butyl-substituted bisoxazoline copper(II) complex (*S*)-**4a** for the synthesis of carbohydrate derivatives. In one reaction step, substituted dihydropyran compounds with useful chemical handles are obtained with high ee from two simple acyclic precursors. The reagents can have different substituents, and the reactions proceed generally in good to high yield. In the HDA step, up to three chiral centers are formed with a high degree of stereoselectivity at each center. The HDA product can be converted in a few steps to interesting derivatives of both natural and unnatural carbohydrates and it is shown how a β-D-mannoside can be synthesized. Other derivatives synthesized include optically active spirosugars and *C*-branched sugars. The absolute configuration of the products, and isolation of a chiral bisoxazoline copper(II)-hydrolyzed enone complex, indicate a reaction mechanism by which the β,γ-unsaturated α-keto ester coordinates to the copper(II) center in a bidentate fashion. This leads to a square-planar intermediate in which the *si*-face of the reacting carbonyl is available for approach of the alkene.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of N_2 using anhydrous solvents and flame-dried glassware. Commercially available compounds were used without further purification, except for the vinyl ethers **2a**,**b** which were distilled over sodium before use. Solvents were dried according to standard procedures. Purification of the products was carried out either by kugelrohr distillation or by flash-chromatography (FC) using Merck silica gel 60 (230−400 mesh). ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively, using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS ($\delta = 0$) for ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.00$) for ^{13}C NMR. The enantiomeric excess (ee) of the products were determined by chiral GC and GC-MS using a Chrompack Chiralsil-Dex CB column, or by HPLC using a Daicel Chiralpak AD column, a Chiralcel OD column, or a Chiralcel OJ column.

Materials. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], (R)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline), $CuBr_2$, $Cu(OTf)_2$, and $AgPF_6$ from Aldrich were stored under an inert

atmosphere and used without further purification. Ethyl oxochloro acetate and the alkenes **2a** and **2b** were commercially available from Aldrich and Fluka. The alkenes **2c**,[12] **2d**, **2e**,[27a,b] **2f**,[2c] and **2g**[27c] were prepared according to literature procedures. The enones (*E*)-4-ethoxy-2-oxobut-3-enoic acid ethyl ester **1b**[28a,b] and (*E*)-2-oxopent-3-enoic acid ethyl ester **1c**[28c,d] were prepared according to literature procedures.

(*E*)-2-Oxo-4-phenylbut-3-enoic Acid Methyl Ester (1a). Acetyl chloride (12 mL) was added dropwise to MeOH (70 mL) cooled in an ice bath to produce dry hydrochloric acid. Potassium benzylidene pyruvate[29] (10.7 g, 50 mmol) was added at 0 °C. The reaction was warmed to room temperature and stirred for 2 h and then refluxed overnight. The solvent was removed by evaporation. Water (25 mL) was added to the crude product which was then extracted with CH_2Cl_2 (25 mL × 2). The combined organic phases were washed with $NaHCO_3$ (25 mL × 2) and then with water (25 mL) to give **1a** in 91% yield. The yellow solid was recrystallized from abs EtOH: mp 70−71 °C; ^{1}H NMR δ 7.88 (d, 1H, J = 16.3 Hz), 7.63 (dd, 2H, J = 7.4, 1.7 Hz), 7.46−7.40 (m, 3H), 7.37 (d, 1H, J = 16.3 Hz), 3.93 (s, 3H); ^{13}C NMR δ 182.4, 162.5, 148.7, 134.0, 131.7, 129.1, 129.1, 120.4, 53.1; mass (TOF ES$^+$): m/z 213 (M + Na)$^+$; HRMS calcd for $C_{11}H_{10}NaO_3$ 213.0528, found 213.0517.

(*E*)-4-(Benzyloxy)-2-oxobut-3-enoic Acid Ethyl Ester (1d). Ethyl oxochloro acetate (20.5 g, 150 mmol) and benzyl vinyl ether[30] (23.5 g, 175 mmol) were mixed and stirred for 1 day at 0 °C. The solution was evaporated and kugelrohr distilled under reduced pressure (0.1 mBar) at 230 °C to give a yellow oil of **1d** in 50% yield (17.6 g). Though **1d** is unstable on silica, the oil could be further purified by flash chromatography (FC) using EtOAc:pentane 1:10 as eluent. The FC of 2.25 g oil gave 1.01 g of a pale yellow oil which crystallized into a white solid in the freezer: ^{1}H NMR δ 7.96 (d, 1H, J = 12.4 Hz), 7.43−7.30 (m, 5H), 6.31 (d, 1H, J = 12.4 Hz), 5.03 (s, 2H), 4.32 (q, 2H, J = 7.1 Hz), 1.37 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 182.2, 166.7, 162.3, 134.5, 128.90, 128.85, 127.9, 102.7, 74.1, 62.4, 14.4; mass (TOF ES$^+$): m/z 257 (M + Na)$^+$; HRMS calcd for $C_{13}H_{14}NaO_4$ 257.0790, found 257.0791.

General Procedure for the Hetero-Diels−Alder Reactions of Enones with Alkenes Catalyzed by (*S*)-4a-Cu(OTf)$_2$. Preparation of 6-Ethoxy-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic Acid Methyl Ester (3a). To a flame-dried Schlenk tube was added $Cu(OTf)_2$ (36.1 mg, 0.1 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (30.9 mg, 0.105 mmol) under N_2. The mixture was dried under vacuum for 1−2 h, anhydrous solvent (2.0 mL) was added, and the resulting suspension was stirred vigorously for 1−5 h. The catalysts are green and homogeneous in all the solvents used except in Et_2O in which the catalysts were heterogeneous. To the catalyst in solution at 0 °C were added the enone **1a** (190 mg, 1.0 mmol) and then 1.5 equiv of ethyl vinyl ether **2a** (143 μL, 1.50 mmol), and the reaction was stirred at 0 °C overnight. Purification by FC on silica gel (CH_2Cl_2) gave *endo*-**3a** as a colorless oil in 93% yield in 98% de with 99% ee detected by HPLC using a Chiralpak OJ column (hexane:*i*-PrOH 98:2), 0.5 mL/min: $[\alpha]^{rt}_D$ = +1.5° (c = 0.0103 g/mL, CH_2Cl_2); ^{1}H NMR δ 7.34−7.20 (m, 5H), 6.16 (dd, 1H, J = 3.2, 1.1 Hz), 5.16 (dd, 1H, J = 7.7, 2.2 Hz), 4.04 (dq, 1H, J = 9.3, 7.1 Hz), 3.81 (s, 3H), 3.73 (ddd, 1H, J = 9.5, 7.0, 3.2 Hz), 3.63 (dq, 1H, J = 9.3, 7.1 Hz), 2.31 (dddd, 1H, J = 13.5, 7.0, 2.2, 1.1 Hz), 1.97 (ddd, 1H, J = 13.5, 9.5, 7.7 Hz), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 163.2, 142.8, 142.3, 128.5, 127.5, 126.8, 114.5, 100.0, 64.7, 52.2, 37.8, 36.0, 15.1; mass (TOF ES$^+$): m/z 285 (M + Na)$^+$; HRMS calcd for $C_{15}H_{18}NaO_4$ 285.1103, found 285.1111.

Preparation of Catalyst (*S*)-4a-Cu(PF$_6$)$_2$. To a flame-dried Schlenk tube were added $CuBr_2$ (22.3 mg, 0.10 mmol), $AgPF_6$ (50.6 mg, 0.20 mmol), and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (30.9 mg, 0.105 mmol) under N_2. The Schlenk tube was kept in darkness, and the mixture was dried under vacuum for 1−2 h. Anhydrous CH_2Cl_2 (2.0 mL) was added, and the resulting suspension was stirred vigorously overnight. The white precipitate was filtered from the green catalyst solution through a Celite plug in a Pasteur pipet with N_2 pressure.

4-Phenyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylic Acid Methyl Ester (3b). According to the general procedure dihydrofuran **2b** (113 μL, 1.50 mmol) was reacted with **1a** (190 mg, 1.0 mmol) in THF (2 mL) at −78 °C in 2 days with 10 mol % catalyst. Purification by FC on silica gel (30% Et_2O in heptane) gave *endo*-**3b** as a colorless oil in 96% yield in 95% de with >99% ee detected by chiral GC. $[\alpha]^{rt}_D$ = −65.7° (c = 0.0127 g/mL, Et_2O); ^{1}H NMR δ 7.37−7.20 (m, 5H), 6.20 (dd, 1H, J = 2.7, 1.1 Hz), 5.64 (d, 1H, J = 3.7 Hz), 4.17 (td, 1H, J = 9.0, 2.0 Hz), 4.16 (dd, 1H, J = 7.6, 2.7 Hz), 3.86 (ddd, 1H, J = 9.7, 9.0, 7.3 Hz), 3.83 (s, 3H), 2.65 (m, 1H), 1.71 (tt, 1H, J = 12.3, 7.3 Hz), 1.34 (dtd, 1H, J = 12.3, 7.3, 2.0 Hz); ^{13}C NMR δ 162.9, 142.4, 141.0, 128.6, 127.5, 127.0, 110.0, 101.3, 68.4, 52.3, 43.9, 38.1, 24.5; mass (TOF ES$^+$): m/z 283 (M + Na)$^+$; HRMS calcd for $C_{15}H_{16}NaO_4$ 283.0946, found 283.0939.

4-Ethoxy-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylic Acid Ethyl Ester (3c). According to the general procedure dihydrofuran **2b** (113 μL, 1.50 mmol) was reacted with **1b** (172 mg, 1.0 mmol) in THF (2 mL) at −45 °C in 2 days with 10 mol % catalyst. Purification by FC on silica gel (30% Et_2O in heptane) gave *endo*-**3c** as a colorless crystalline compound in 84% yield in >98% de with 98% ee detected by chiral GC. $[\alpha]^{rt}_D$ = −32.1° (c = 0.0106 g/mL, $CHCl_3$); ^{1}H NMR δ 6.01 (dd, 1H, J = 2.2, 1.5 Hz), 5.66 (d, 1H, J = 4.0 Hz), 4.50 (dd, 1H, J = 6.6, 2.2 Hz), 4.26 (qd, 2H, J = 7.1, 4.4 Hz), 4.24 (ddd, 1H, J = 17.9, 9.2, 3.5 Hz), 3.97 (dt, 1H, J = 9.2, 8.1 Hz), 3.60 (q, 2H, J = 7.1 Hz), 2.75 (m, 1H), 2.01 (m, 2H), 1.31 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.1, 141.6, 108.6, 102.2, 70.6, 68.4, 64.3, 61.4, 42.5, 23.7, 15.4, 14.2; mass (TOF ES$^+$): m/z 265 (M + Na)$^+$; HRMS calcd for $C_{12}H_{18}NaO_5$ 265.1052, found 265.1042.

4-Methyl-2,3,3a,7a-tetrahydro-4*H*-furo[2,3-*b*]pyran-6-carboxylic Acid Ethyl Ester (3d). According to the general procedure, dihydrofuran **2b** (113 μL, 1.50 mmol) was reacted with **1c** (142 mg, 1.0 mmol) in THF (2 mL) at −78 °C in 2 days with 10 mol % catalyst. Purification by FC on silica gel (25% Et_2O in hexane) gave *endo*-**3d** as an oil in 51% yield in >98% de with >99% ee detected by chiral GC. $[\alpha]^{rt}_D$ = −42.3° (c = 0.0052 g/mL, Et_2O); ^{1}H NMR δ 5.77 (dd, 1H, J = 2.4, 1.4 Hz), 5.47 (d, 1H, J = 3.8 Hz), 4.22 (qd, 2H, J = 7.1, 1.7 Hz), 4.18 (ddd, 1H, J = 9.7, 8.2, 2.3 Hz), 3.93 (ddd, 1H, J = 9.7, 8.2, 7.3 Hz), 2.86 (qd, 1H, J = 7.3, 2.4 Hz), 2.37 (m, 1H), 1.88 (dtd, 1H, J = 12.4, 7.3, 2.3 Hz), 1.67 (tt, 1H, J = 12.4, 9.7 Hz), 1.28 (t, 3H, J = 7.1 Hz), 1.10 (d, 3H, J = 7.3 Hz); ^{13}C NMR δ 162.6, 140.9, 112.8, 101.2, 68.3, 61.2, 43.1, 26.7, 23,5 17.9, 14.2.

9-Ethoxy-1,6-dioxaspiro[4.5]dec-7-ene-7-carboxylic Acid Ethyl Ester (3e). According to the general procedure, the *exo*-cyclic vinyl ether **2c** (84 mg, 1.0 mmol) was reacted with **1b** (86 mg, 0.5 mmol) in Et_2O (2 mL) at −78 °C in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 5:1) gave 2 products: *endo*-**3e** as a colorless oil isolated in 62.5% yield with 74% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 99.5:0.5), 0.2 mL/min: $[\alpha]^{rt}_D$ = +125.31° (c = 0.0113 g/mL; CH_2Cl_2); ^{1}H NMR δ 6.13 (dd, 1H, J = 2.2, 1.6 Hz), 4.29 (ddd, 1H, J = 8.8, 6.1, 2.2 Hz), 4.20 (q, 2H, J = 7.1 Hz), 4.08−3.90 (m, 2H), 3.64−3.48 (m, 2H), 2.34−2.25 (m, 1H), 2.22−2.11 (m, 2H), 2.00−1.77 (m, 3H), 1.27 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.6, 142.4, 110.7, 108.7, 69.1, 68.5, 63.9, 61.1, 36.7, 35.4, 23.59, 15.4, 14.1; mass (TOF ES$^+$): m/z 279 (M + Na)$^+$; HRMS calcd for $C_{13}H_{20}O_5Na$ 279.1208, found 279.1215. *exo*-**3e** as a yellowish

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oil isolated in 21% yield with 84% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 99.5:0.5), 0.3 mL/min: $[\alpha]^{rt}_D = -5.12°$ (c = 0.00508 g/mL; $CHCl_3$); ^{1}H NMR δ 6.24 (d, 1H, J = 4.4 Hz), 4.22 (q, 2H, J = 7.1 Hz), 4.14−3.98 (m, 3H), 3.69−3.50 (m, 2H), 2.26−2.08 (m, 4H), 2.03−1.87 (m, 1H), 1.85−1.74 (m, 1H), 1.28 (t, 3H, J = 7.1 Hz), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.8, 143.1, 109.6, 107.2, 69.0, 68.11, 64.3, 61.2, 36.7, 35.7, 23.0, 15.4, 14.1; mass (TOF ES$^+$): m/z 279 $(M + Na)^+$; HRMS calcd for $C_{13}H_{20}O_5Na$ 279.1208, found 279.1220.

9-(Benzyloxy)-1,6-dioxaspiro[4.5]dec-7-ene-7-carboxylic Acid Ethyl Ester (3f): According to the general procedure the *exo*-cyclic vinyl ether **2c** (84 mg, 1.0 mmol) was reacted with **1d** (117 mg, 0.5 mmol) in Et_2O (2 mL) at −78 °C in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 10:1 then 5:1) gave 2 products: *endo*-**3f** as a colorless oil isolated in 40% yield with 76% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 99.5:0.5), 0.3 mL/min: $[\alpha]^{rt}_D = +114.22°$ (c = 0.00914 g/mL; CH_2Cl_2); ^{1}H NMR δ 7.38−7.28 (m, 5H), 6.21 (dd, 1H, J = 2.7, 1.1 Hz), 4.64 (d, 1H, J = 12.1 Hz), 4.58 (d, 1H, J = 11.5 Hz), 4.43 (ddd, 1H, J = 9.4, 6.6, 2.8 Hz), 4.23 (q, 2H, J = 7.1 Hz), 4.11−4.01 (m, 1H), 4.00−3.91 (m, 1H), 2.40−2.28 (m, 1H), 2.26−2.13 (m, 2H), 2.06 (dd, 1H, J = 12.7, 9.3 Hz), 2.02−1.80 (m, 2H), 1.30 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.6, 142.7, 138.1, 128.4, 127.7, 127.6, 110.3, 108.7, 70.6, 69.1, 68.6, 61.2, 36.6, 35.5, 23.6, 14.1; mass (TOF ES$^+$): m/z 341 $(M + Na)^+$; HRMS calcd for $C_{18}H_{22}O_5Na$ 341.1365, found 341.1343. *exo*-**3f** as a colorless oil isolated in 12% yield with 95% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 99.5:0.5), 0.3 mL/min: $[\alpha]^{rt}_D = +8.43°$ (c = 0.00332 g/mL; CH_2Cl_2); ^{1}H NMR δ 7.42−7.28 (m, 5H), 6.25 (d, 1H, J = 3.9 Hz), 4.68 (d, 1H, J = 12.6 Hz), 4.63 (d, 1H, J = 12.1 Hz), 4.24 (q, 2H, J = 7.1 Hz), 4.17−4.00 (m, 3H), 2.28−2.19 (m, 3H), 2.18−2.09 (dd, 1H, J = 14.2, 6.6 Hz), 2.03−1.89 (m, 1H), 1.87−1.75 (m, 1H), 1.30 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.8, 143.4, 138.2, 128.4, 127.8, 127.7, 109.3, 107.2, 70.3, 69.1, 66.8, 61.2, 36.8, 35.6, 23.1, 14.2; mass (TOF ES$^+$): m/z 341 $(M + Na)^+$; HRMS calcd for $C_{18}H_{22}O_5Na$ 341.1365, found 341.1367.

3-Acetoxy-2-ethoxy-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylic Acid Methyl Ester (3g). According to the general procedure *cis*-1-acetoxy-2-ethoxyethene **2d** (100 mg, 0.75 mmol) was reacted with **1a** (95 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 10:1) gave two products (80% yield): *exo*-**3g** as a colorless oil isolated in 4% yield: ^{1}H NMR δ 7.36−7.19 (m, 5H), 6.17 (d, 1H, J = 2.8 Hz), 5.30 (d, 1H, J = 2.2 Hz), 5.01 (dd, 1H, J = 9.9, 2.2 Hz), 3.98−3.78 (m, 5H), 3.71 (dq, 1H, J = 9.9, 7.2 Hz), 1.97 (s, 3H), 1.25 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 170.1, 162.7, 140.1, 139.4, 128.7, 128.4, 127.5, 113.8, 95.6, 72.1, 64.9, 52.4, 40.1, 20.7, 15.0; mass (EI): m/z 320 ($M^{+\bullet}$), 260, 215, 201, 172. *endo*-**3g** as a white solid isolated in 76% yield with 99.5% ee according to chiral GC: $[\alpha]^{rt}_D = +31.33°$ ($CHCl_3$, c = 0.024 g/mL); ^{1}H NMR δ 7.30−7.16 (m, 5H), 6.19 (d, 1H, J = 3.3 Hz), 5.39 (d, 1H, J = 6.0 Hz), 5.18 (bs, 1H), 4.06−3.93 (m, 2H), 3.83 (s, 3H), 3.65 (dq, 1H, J = 9.9, 7.1 Hz), 1.83 (s, 3H), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 169.9, 162.6, 142.4, 137.0, 129.3, 128.1, 127.4, 112.2, 98.5, 67.7, 65.3, 52.3, 41.6, 20.6, 14.9; mass (EI): m/z 320 ($M^{+\bullet}$), 277, 260, 214, 172.

3-Acetoxy-2,4-diethoxy-3,4-dihydro-2*H*-pyran-6-carboxylic Acid Ethyl Ester (*endo*-3h). According to the general procedure, *cis*-1-acetoxy-2-ethoxyethene **2d** (100 mg, 0.75 mmol) was reacted with **1b** (86 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 7:1) gave the product as a pale yellow oil isolated in 70% yield with 99.5% ee according to chiral GC-MS: $[\alpha]^{rt}_D = -0.31°$ ($CHCl_3$, c = 0.019 g/mL); ^{1}H NMR δ 6.02 (d, 1H, J = 2.7 Hz), 5.33 (d, 1H, J = 3.9 Hz), 5.08 (bs, 1H), 4.29−4.18 (m, 3H), 3.96 (dq, 1H, J = 9.9, 7.2 Hz), 3.70−3.56 (m, 2H), 3.51 (dq, 1H, J = 8.8, 7.2 Hz), 2.14 (s, 3H), 1.29 (t, 3H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 170.6, 161.8, 142.1, 109.6, 97.9, 69.9, 65.8, 65.6, 61.5, 20.9, 15.2, 14.9, 14.1; mass (EI): m/z 302 ($M^{+\bullet}$), 257 (M − OEt), 243 (M − AcO), 173.

3-Acetoxy-4-(benzyloxy)-2-ethoxy-3,4-dihydro-2*H*-pyran-6-carboxylic Acid Ethyl Ester (*endo*-3i). According to the general procedure, *cis*-1-acetoxy-2-ethoxyethene **2d** (100 mg, 0.75 mmol) was reacted with **1d** (117 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 10:1) gave the product as a pale yellow oil isolated in 60% yield with 96.5% ee detected by HPLC using a Chiralcel OJ column (hexane:*i*-PrOH 95:5), 0.4 mL/min: $[\alpha]^{rt}_D = -2.89°$ (CH_2Cl_2, c = 0.0135 g/mL); ^{1}H NMR δ 7.42−7.28 (m, 5H), 6.02 (dd, 1H, J = 2.8, 1.1 Hz), 5.39 (d, 1H, J = 4.9 Hz), 5.09 (s, 1H), 4.69 (d, 1H, J = 12.1 Hz), 4.55 (d, 1H, J = 12.1 Hz), 4.34 (m, 1H), 4.25 (dq, 2H, J = 7.1, 1.6 Hz), 3.99 (dq, 1H, J = 9.9, 7.2 Hz), 3.68 (dq, 1H, J = 9.9, 7.2 Hz), 2.15 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 170.6, 161.8, 142.3, 137.6, 128.5, 127.9, 127.8, 109.3, 97.9, 71.7, 68.8, 65.8, 65.7, 61.6, 21.0, 14.9, 14.2; mass (TOF ES$^+$): m/z 387 $(M + Na)^+$; HRMS calcd for $C_{19}H_{24}O_7Na$ 387.1420, found 387.1370.

3-Acetoxy-2-(benzyloxy)-4-ethoxy-3,4-dihydro-2*H*-pyran-6-carboxylic Acid Ethyl Ester (*endo*-3j). According to the general procedure, *cis*-1-acetoxy-2-(benzyloxy)ethene **2e** (144 mg, 0.75 mmol) was reacted with **1b** (86 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 36 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 10:1) gave the product as a pale yellow oil, isolated in 61% yield with 66% ee detected by HPLC using a Chiralcel OD column (hexane:*i*-PrOH 98:2), 0.6 mL/min; ^{1}H NMR δ 7.40−7.25 (m, 5H), 6.05 (d, 1H, J = 3.3 Hz), 5.32 (dd, 1H, J = 4.9, 1.1 Hz), 5.09 (d, 1H, J = 1.1 Hz), 4.96 (d, 1H, J = 12.6 Hz), 4.76 (d, 1H, J = 12.6 Hz), 4.33−4.17 (m, 3H), 3.65 (dq, 1H, J = 8.8, 7.2 Hz), 3.55 (dq, 1H, J = 8.8, 7.2 Hz), 2.15 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz), 1.18 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 170.5, 161.7, 142.0, 136.6, 128.4, 128.0, 127.9, 109.8, 96.4, 70.6, 69.6, 66.0, 65.9, 61.5, 20.9, 15.3, 14.2; mass (TOF ES$^+$): m/z 387 $(M + Na)^+$; HRMS calcd for $C_{19}H_{24}O_7Na$ 387.1420, found 387.1314.

2,2-Dimethyl-7-phenyl-7,7a-dihydro-3a*H*-[1,3]dioxolo-[4,5-*b*]pyran-5-carboxylic Acid Methyl Ester (3k). According to the general procedure 2,2-dimethyl-1,3-dioxole **2f** (75 mg, 0.75 mmol) was reacted with **1a** (95 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 5:1) gave 2 products: *exo*-**3k** as a colorless oil, isolated in 22% yield with 92% ee according to chiral GC: $[\alpha]^{rt}_D = +166.92°$ (c = 0.0026 g/mL; $CHCl_3$); ^{1}H NMR δ 7.40−7.18 (m, 5H), 6.24 (dd, 1H, J = 5.5, 1.6 Hz), 5.55 (d, 1H, J = 2.7 Hz), 4.25 (ddd, 1H, J = 2.7, 1.6, 1.6 Hz), 3.84 (m, 4H), 1.52 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 162.7, 141.7, 138.8, 129.1, 128.0, 127.7, 111.4, 109.2, 95.3, 78.3, 52.4, 40.3, 27.9, 25.9; mass (EI): m/z 290 $M^{+\bullet}$. *endo*-**3k** was isolated as a white solid in 76% yield with >99% ee detected by HPLC using a Chiralcel OD column (hexane:*i*-PrOH 99.5:0.5), 0.2 mL/min: $[\alpha]^{rt}_D = -69.87°$ (c = 0.008 g/mL; $CHCl_3$); ^{1}H NMR δ 7.40−7.25 (m, 5H), 6.33 (dd, 1H, J = 4.0, 2.2 Hz), 5.87 (d, 1H, J = 3.3 Hz), 4.50 (ddd, 1H, J = 5.0, 3.3, 1.7 Hz), 3.83 (m, 4H), 1.45 (s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 162.5, 142.2, 138.9, 128.7, 128.4, 127.2, 114.0, 111.8, 98.3, 77.4, 52.3, 40.2, 27.4, 25.9; mass (EI): m/z 290 ($M^{+\bullet}$), 275 ($M - CH_3$), 231 ($M - CO_2Me$), 173, 144, 100; HRMS (TOF ES$^+$) calcd for $C_{16}H_{18}O_5Na$ 313.1052, found 313.1045.

7-Ethoxy-2,2-dimethyl-7,7a-dihydro-3a*H*-[1,3]dioxolo-[4,5-*b*]pyran-5-carboxylic Acid Ethyl Ester (3l). According to the general procedure 2,2-dimethyl-1,3-dioxole **2f** (75 mg, 0.75 mmol) was reacted with **1b** (86 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 16 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 5:1) gave 2. products: *Exo*-**3l** as a colorless oil, isolated in 16% yield with 81.5% ee according to chiral GC-MS: $[\alpha]^{rt}_D = +55.95°$ (c = 0.0042 g/mL, $CHCl_3$); ^{1}H NMR δ 6.17 (dd, 1H, J = 4.9, 1.6 Hz), 5.55 (d, 1H, J = 2.7 Hz), 4.27 (q, 2H, J = 7.1 Hz), 4.23 (m, 1H), 4.06 (dd, 1H, J = 4.9, 1.6 Hz), 3.72−3.54 (m, 2H), 1.46 (s, 3H), 1.41 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz), 1.21 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.1, 142.5, 111.3, 106.0, 95.5, 76.7, 68.5, 64.6, 61.6, 27.8, 25.9, 15.4, 14.2; mass (EI): m/z 272 ($M^{+\bullet}$); HRMS (TOF ES$^+$) calcd for $C_{13}H_{20}O_6Na$ 295.1158, found 295.1155. Endo-3l was isolated as a colorless oil in 62.5% yield with >99% ee detected by HPLC using a Chiralcel OD column

(hexane:i-PrOH 99.5:0.5), 0.2 mL/min: $[\alpha]^{rt}_D = -22.93$ (c = 0.015 g/mL, $CHCl_3$); ^{1}H NMR δ 6.25 (dd, 1H, J = 2.2, 1.7 Hz), 5.80 (d, 1H, J = 3.9 Hz), 4.58 (m, 1H), 4.29 (dd, 1H, J = 2.2, 2.2 Hz), 4.24 (q, 2H, J = 7.2 Hz), 3.78−3.58 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 161.6, 141.5, 113.2, 112.5, 98.5, 76.1, 71.4, 65.2, 61.3, 27.1, 26.0, 15.2, 14.1; mass (EI): m/z 272 ($M^{+\bullet}$), 227 ($M^{+\bullet} - OEt$), 199 ($M^{+\bullet} - CO_2Et$); HRMS (TOF ES+) calcd for $C_{13}H_{20}O_6Na$ 295.1158, found 295.1152.

5-Phenyl-4a,8a-dihydro-4*H*,5*H*-pyrano[2,3-*d*][1,3]dioxine-7-carboxylic Acid Methyl Ester (*endo*-3m). According to the general procedure 4*H*-1,3-dioxine **2g** (91 mg, 1.0 mmol) was reacted with **1a** (95 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 36 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 10:1) gave the product as a pale yellow oil in 66% yield with 93% ee detected by HPLC using a Chiralcel OJ column (hexane:*i*-PrOH 92:8), 0.7 mL/min: $[\alpha]^{rt}_D = -5.46°$ (c = 0.0162 g/mL; CH_2Cl_2); ^{1}H NMR δ 7.42−7.06 (m, 5H), 6.19 (dd, 1H, J = 2.8, 1.1 Hz), 5.63 (bs, 1H), 5.16 (d, 1H, J = 5.5 Hz), 4.79 (d, 1H, J = 6.1 Hz), 4.01 (dd, 1H, J = 7.1, 2.7 Hz), 3.86 (s, 3H), 3.55 (dd, 1H, J = 12.1, 12.1 Hz), 3.14 (dd, 1H, J = 11.6, 4.9 Hz), 2.72−2.60 (m, 1H); ^{13}C NMR δ 162.4, 142.7, 137.9, 128.8, 127.5, 127.4, 111.1, 95.9, 87.2, 63.5, 52.5, 39.4, 36.0; mass (TOF ES$^+$): m/z 299 (M + Na)$^+$; HRMS calcd for $C_{15}H_{16}O_5Na$ 299.0895, found 299.0849.

5-Ethoxy-4a,8a-dihydro-4*H*,5*H*-pyrano[2,3-*d*][1,3]dioxine-7-carboxylic Acid Ethyl Ester (*endo*-3n). According to the general procedure 4*H*-1,3-dioxine **2g** (91 mg, 1.0 mmol) was reacted with **1b** (86 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 36 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAc 10:1) gave the product as a pale yellow oil in 65% yield with 96% ee detected by HPLC using a Chiralcel OJ column (hexane:*i*-PrOH 95:5), 0.4 mL/min: $[\alpha]^{rt}_D = -10.93°$ (c = 0.0151 g/mL; CH_2Cl_2); ^{1}H NMR δ 5.96 (dd, 1H, J = 1.6, 1.6 Hz), 5.49 (d, 1H, J = 1.7 Hz), 5.19 (d, 1H, J = 6.1 Hz), 4.83 (d, 1H, J = 6.1 Hz), 4.32 (dd, 1H, J = 6.6, 2.2 Hz), 4.27 (q, 2H, J = 7.2 Hz), 3.98 (dd, 1H, J = 11.5, 4.9 Hz), 3.73 (dd, 1H, J = 12.1, 12.1 Hz), 3.55 (q, 2H, J = 7.2 Hz), 2.78 (m, 1H), 1.31 (t, 3H, J = 7.2 Hz), 1.20 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 161.7, 141.6, 109.2, 95.5, 87.4, 70.8, 64.8, 62.7, 61.6, 34.6, 15.2, 14.2; mass (TOF ES$^+$): m/z 281 (M + Na)$^+$; HRMS calcd for $C_{12}H_{18}O_6Na$ 281.1001, found 281.0984.

5-(Benzyloxy)-4a,8a-dihydro-4*H*,5*H*-pyrano[2,3-*d*][1,3]dioxine-7-carboxylic Acid Ethyl Ester (*endo*-3o). According to the general procedure 4*H*-1,3-dioxine **2g** (91 mg, 1.0 mmol) was reacted with **1d** (117 mg, 0.5 mmol) in Et_2O (2 mL) at room temperature in 36 h with 20 mol % catalyst. Purification by FC on silica gel (pentane:EtOAC, 10:1 then 7:1) gave the product as a pale yellow oil in 81% yield with 91% ee detected by HPLC using a Chiralcel OJ column (hexane:*i*-PrOH 99:1), 0.4 mL/min: $[\alpha]^{rt}_D = +7.31°$ (c = 0.0112 g/mL; CH_2Cl_2); ^{1}H NMR δ 7.42−7.28 (m, 5H), 6.01 (dd, 1H, J = 1.6, 1.6 Hz), 5.48 (d, 1H, J = 1.1 Hz), 5.21 (d, 1H, J = 6.0 Hz), 4.85 (d, 1H, J = 6.0 Hz), 4.59 (s, 2H), 4.42 (dd, 1H, J = 6.6, 2.2 Hz), 4.29 (q, 2H, J = 7.2 Hz), 4.09 (dd, 1H, J = 12.1, 5.0 Hz), 3.80 (dd, 1H, J = 12.1, 12.1 Hz), 2.82 (m, 1H), 1.33 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 161.7, 141.8, 137.2, 128.6, 128.4, 128.1, 127.6, 108.9, 95.5, 87.4, 71.0, 70.0, 62.7, 61.7, 34.5, 14.2; mass (TOF ES$^+$): m/z 343 (M + Na)$^+$; HRMS calcd for $C_{17}H_{20}O_6Na$ 343.1157, found 343.1158.

9-Ethoxy-7-(hydroxymethyl)-1,6-dioxaspiro[4.5]decan-8-ol (5). To the compound *endo*-**3f** (84 mg, 0.33 mmol) in THF (10 mL) at 0 °C was added 2 equiv of LAH (40 mg). The reaction mixture was strirred at 0 °C for 30 min and 1 h at room temperature. Quenching of the reaction was done by careful addition of 0.05 mL of H_2O and then 0.1 mL of NaOH (15% in H_2O) and finally 0.1 mL of H_2O. The resulting mixture was filtered through Celite, and the organic phase was dried over $MgSO_4$. After evaporation of the solvent, the alcohol was used immediately without further purification. A solution of the crude alcohol (0.33 mmol) in dry THF (10 mL) was cooled to 0 °C and was treated with a 2 M solution of $BH_3{\cdot}SMe_2$ in THF (0.41 mL, 0.82 mmol). The resulting solution was stirred for 1 h at 0 °C and overnight at room temperature, after which 0.6 mL of a solution of NaOH (30% in H_2O) and 0.6 mL of H_2O_2 (35% in H_2O) were added. The solution was then heated at 60 °C for 1 h. After the addition of H_2O, the product was extracted with EtOAc (10 mL × 3). The aqueous layer was then saturated with NaCl and extracted with 25% *i*-PrOH/CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude mixture was separated by FC (3% MeOH in CH_2Cl_2) to afford 30 mg of diol **5** (40% yield for two steps) as a colorless oil which crystallized upon standing. ^{1}H NMR δ 3.95−3.84 (m, 2H), 3.83−3.76 (m, 2H), 3.69−3.59 (m, 3H), 3.53−3.39 (m, 2H), 2.91 (bs, 1H), 2.29 (m, 1H), 2.15 (dd, 1H, J = 12.7, 5.0 Hz), 2.10−1.77 (m, 3H), 1.73 (dd, 1H, J = 9.3, 3.8 Hz), 1.67 (dd, 1H, J = 12.6, 11.5 Hz), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 106.6, 78.1, 72.0, 71.4, 67.4, 64.4, 62.9, 37.6, 37.2, 23.3, 15.6.

Acetic Acid 5-Acetoxy-4-(benzyloxy)-6-ethoxy-5,6-dihydro-4*H*-pyran-2-ylmethyl Ester (6). To the compound *endo*-**3i** (510 mg, 1.4 mmol) in THF (45 mL) at 0 °C was added 3.5 equiv of LAH (190 mg). The reaction mixture was strirred at 0 °C for 30 min and 1 h at room temperature. Quenching of the reaction was done by careful addition of 0.3 mL of H_2O and then 0.6 mL of NaOH (30% in H_2O) and finally 0.6 mL of H_2O. The resulting mixture was filtered through Celite, and the organic phase was dried over $MgSO_4$. After evaporation of the solvent, the diol was used immediately in the next step without further purification. To the solution of the crude diol (1.4 mmol) in dry pyridine (10 mL) was added Ac_2O (2 mL). The solution was stirred overnight and then quenched by addition of ice−water. The solution was extracted with CH_2Cl_2 (10 mL × 5); the combined organic phases were washed successively with AcOH 1 N (10 mL × 3), $NaHCO_3$ aq (sat.) (20 mL × 2) and a satd brine solution. The organic phase was dried over $MgSO_4$ and concentrated in a vacuum. The crude was used immediately without further purification: ^{1}H NMR δ 7.35−7.23 (m, 5H), 5.37 (d, 1H, J = 4.9 Hz), 5.01 (bs, 1H), 4.92 (d, 1H, J = 2.7 Hz), 4.65 (d, 1H, J = 12.1 Hz), 4.50 (d, 1H, J = 12.1 Hz), 4.47 (s, 2H), 4.24 (m, 1H), 3.92 (dq, 1H, J = 9.9, 7.2 Hz), 3.63 (dq, 1H, J = 9.9, 7.2 Hz), 2.14 (s, 3H), 2.05 (s, 3H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 170.5, 170.2, 148.0, 137.7, 128.2, 127.6, 127.6, 99.8, 97.4, 71.3, 68.9, 65.9, 65.3, 62.6, 20.9, 20.7, 14.8.

Acetic Acid 3,5-Diacetoxy-4-(benzyloxy)-6-ethoxytetrahydropyran-2-ylmethyl Ester (7). A solution of the crude **6** (1.29 mmol) in dry THF (35 mL) was cooled to 0 °C and was treated with a 2 M solution of $BH_3{\cdot}SMe_2$ in THF (1.6 mL, 3.20 mmol). The resulting solution was stirred 1 h at 0 °C and overnight at room temperature, and then 2.3 mL of a solution of NaOH (30% in H_2O) and 2.3 mL of H_2O_2 (35% in H_2O) were added. The solution was then warmed to 60 °C for 1 h. After the addition of H_2O (5 mL), the product was extracted with EtOAc (10 mL × 3). The aqueous layer was then saturated with NaCl and was extracted with 25% *i*-PrOH/CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude product was used immediately in the next step. To the solution of the crude diol (1.29 mmol) in dry pyridine (9 mL) was added Ac_2O (2 mL). The solution was stirred overnight and quenched by addition of ice−water. Then the solution was extracted with CH_2Cl_2 (10 mL × 5); the combined organic phases were washed successively with AcOH 1 N (10 mL × 3), $NaHCO_3$ aq (satd) (20 mL × 2), and a satd brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by FC (pentane:Et_2O 8:1) to afford 166 mg of compound **7** (35% yield for two steps): ^{1}H NMR δ 7.38−7.23 (m, 5H), 5.61 (d, 1H, J = 3.3 Hz), 5.18 (dd, 1H, J = 9.9 Hz), 4.70 (d, 1H, J = 12.1 Hz), 4.54 (s, 1H), 4.41 (d, 1H, J = 12.1 Hz), 4.27 (dd, 1H, J = 12.1, 6.0 Hz), 4.12 (dd, 1H, J = 12.1, 2.2 Hz), 3.93 (dq, 1H, J = 9.9, 7.2 Hz), 3.63−3.49 (m, 3H), 2.20 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.22 (t, 3H, J = 7.2 Hz); ^{13}C NMR δ 170.7, 170.5, 169.5, 137.2, 128.3, 127.8, 127.7, 98.7, 76.3, 72.2, 70.8, 67.4, 67.4, 65.5, 62.7, 21.0, 20.7, 20.7, 14.8.

Synthesis of Ethyl β-D-Mannoside Tetraacetate (8). Compound **7** (188 mg, 0.44 mmol) was dissolved in EtOH (5 mL) and was set under vacuum and flushed with N_2. This procedure was repeated (3×), and $Pd(OAc)_2$ (40 mg, 0.18 mmol)

was added. The reaction mixture was set under vacuum and flushed with H_2. The reaction mixture was stirred overnight and then filtered through Celite, and the residual $Pd(OAc)_2$ was washed thoroughly with EtOH and pyridine. The filtrate was concentrated in vacuo and coevaporated with toluene (5 mL × 3). The residue was then taken into the next step without further purification. To the solution of the crude alcohol (0.44 mmol) in dry pyridine (4 mL) was added Ac_2O (0.7 mL). The solution was stirred overnight, quenched by addition of ice−water. Next the solution was extracted with CH_2Cl_2 (10 mL × 5); the combined organic phases were washed successively with AcOH 1 N (10 mL × 3), $NaHCO_3$ aq (satd) (20 mL × 2), and a satd brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by FC (pentane:Et_2O 2.5:1) to afford 153 mg of compound **8** (92% yield for two steps): $[\alpha]^{rt}_D$ = −48.8° (*c* = 0.015 g/mL; $CHCl_3$); ^{1}H NMR δ 5.41 (d, 1H, *J* = 2.7 Hz), 5.20 (dd, 1H, *J* = 9.9 Hz), 5.00 (dd, 1H, *J* = 9.9, 3.3 Hz), 4.61 (d, 1H, *J* = 1.1 Hz), 4.26 (dd, 1H, *J* = 12.1, 5.5 Hz), 4.09 (dd, 1H, *J* = 12.1, 2.2 Hz), 3.87 (dq, 1H, *J* = 9.9, 7.2 Hz), 3.65−3.60 (m, 1H), 3.55 (dq, 1H, *J* = 9.9, 7.2 Hz), 2.14 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 1.16 (t, 3H); ^{13}C NMR δ 170.6, 170.4, 169.9, 169.5, 98.4, 72.3, 71.1, 68.9, 66.0, 65.8, 62.5, 20.8, 20.7, 20.6, 20.5, 14.8; mass (EI): *m*/*z* 361 (M − CH_3), 317 (M − CO_2Me).

5-(Hydroxymethyl)-2,2-dimethyl-7-phenyltetrahydro-[1,3]dioxolo[4,5-*b*]pyran-6-ol (9). To *endo*-**3k** (100 mg, 0.34 mmol) in THF (10 mL) at 0 °C was added 2 equiv of LAH (40 mg). The reaction mixture was strirred at 0 °C for 30 min and 1 h at room temperature. Quenching of the reaction was done by careful addition of 0.05 mL of H_2O and then 0.1 mL of NaOH (30% in H_2O) and finally 0.1 mL of H_2O. The resulting mixture was filtered through Celite, and the organic phase was dried over $MgSO_4$. After evaporation of the solvent, the alcohol was used immediately without further purification. A solution of the crude alcohol (0.34 mmol) in dry THF (10 mL) was cooled at 0 °C and treated with a 2 M solution of BH_3·SMe_2 in THF (0.4 mL, 0.80 mmol). The resulting solution was stirred for 1 h at 0 °C and overnight at room temperature, and then 0.6 mL of a solution of NaOH (30% in H_2O) and 0.6 mL of H_2O_2 (35% in H_2O) were added. The solution was heated at 60 °C for 1 h. After the addition of H_2O, the product was extracted with EtOAc (10 mL × 3). The aqueous layer was saturated with NaCl and extracted with 25% i-PrOH/CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude mixture was separated by FC (2% MeOH in CH_2Cl_2) to afford 60 mg of diol **9** (63% yield for two steps) as a colorless oil which crystallized upon standing. ^{1}H NMR δ 7.50−7.30 (m, 5H), 5.32 (d, 1H, *J* = 2.2 Hz), 4.21 (ddd, 1H, *J* = 10.9, 9.3, 3.2 Hz), 4.19 (dd, 1H, *J* = 2.7, 2.7 Hz), 3.91−3.81 (m, 2H), 3.49 (ddd, 1H, *J* = 9.3, 3.9, 3.9 Hz), 2.99 (dd, 1H, *J* = 11.0, 3.3 Hz), 2.27 (dd, 1H, *J* = 6.6, 6.6 Hz), 1.84 (d, 1H, *J* = 3.3 Hz), 1.58 (s, 3H), 1.28 (s, 3H); ^{13}C NMR δ 137.0, 129.7, 128.7, 127.8, 111.8, 97.6, 84.4, 78.7, 77.1, 66.6, 63.0, 50.9, 28.3, 25.8.

X-ray Structure Determination of *endo*-3c, *endo*-3g, 9, and the Complex of Catalyst with Hydrolyzed Enone 11. In all cases at least a hemisphere of data was collected at 120 K on a SIEMENS SMART diffractometer using Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods (SIR97)31 and refined by full matrix least-squares methods.

***endo*-3c:** Tetragonal, $P4_12_12$, *a* = 14.2997(6) Å, *c* = 12.0909-(7) Å; 16880 reflections measured, 3210 unique, 2883 with $I > 3\sigma(I)$ used in refinement of 227 parameters; final R = 0.029, R_w = 0.034.

***endo*-3g:** orthorhombic, $Pca2_1$, *a* = 10.2673(7) Å, *b* = 18.519-(1) Å, *c* = 8.7856(6) Å, 23936 reflections measured, 4039 unique, 1932 with $I > 3\sigma(I)$ used in refinement of 208 parameters, final R = 0.051, R_w = 0.055.

Compound **9**: monoclinic, $P2_1/c$, *a* = 14.420(6) Å, *b* = 5.944-(3) Å, *c* = 17.858(8) Å, β = 113.813(6)°; 12548 reflections measured, 4250 unique, 2645 with $I > 3\sigma(I)$ used in the refinement of 262 parameters, final R = 0.037, R_w = 0.043.

Complex of Catalyst with Hydrolyzed Enone 11: orthorhombic, $P2_12_12_1$, *a* = 9.6416(6) Å, *b* = 14.9091(9) Å, *c* = 20.504(1) Å; 64800 reflections measured, 8639 unique, 7402 with $I > 3\sigma(I)$ used in refinement of 511 parameters; final R = 0.023, R_w = 0.028.

In all structures the distances and angles fit the formulas given in the text. All crystallographic data have been deposited with the Cambridge Structural Database 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for products **1a**,**d**, *endo*-**3a**−**o**, *exo*-**3e**−**g**,**k**,**l**,**5**−**7**,**9** and X-ray data for *endo*-**3c**, *endo*-**3g**, **9**, and complex of catalyst with hydrolyzed enone **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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