Catalytic Asymmetric Hetero-Diels−Alder Reactions of Ketones: Chemzymatic Reactions

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Abstract: A general catalytic hetero-Diels−Alder reaction for ketones has been developed, and for the first time a general reaction protocol is disclosed where the selectivity and activity of a chiral Lewis acid are approaching the ones displayed by enzymes. A variety of combinations of different C_2-symmetric ligands and Lewis acids have been tested as catalysts for the hetero-Diels−Alder reaction between ethyl pyruvate and an activated diene, and it has been found that the readily accessible copper(II) bisoxazolines are very effective catalysts for the reaction, leading to products with very high enantiomeric enrichment (up to 99.8% enantiomeric excess) using the lowest loading of a chiral Lewis acid catalyst observed (down to 0.05 mol %). The catalytic hetero-Diels−Alder reaction of ketones has been developed to be a general reaction which proceeds well with very high turnover numbers, isolated yield, and regio-, diastereo-, and enantioselectivity for various α-diketones and α-keto esters. The potential and scope of the reaction are demonstrated by the reaction of various ketones, and it is shown that α-diketones, such as 2,3-pentanedione and 3-phenyl-2,3-propanedione, react primarily at the methyl ketone fragment, giving 97.8% and 96.4% ee, respectively, in the presence of only 0.05 mol % of the catalyst. Furthermore, both aliphatic and aromatic α-keto esters react smoothly, giving very high ee of the hetero-Diels−Alder product. On the basis of the synthesis of a hetero-Diels−Alder product with known absolute stereochemistry, a model for the approach of the diene to the copper(II) bisoxazoline−α-diketone intermediate is proposed and the mechanism for the reaction discussed.

Introduction

The ultimate challenge for asymmetric catalysis[1] is to create reactions which can be promoted by simple and easily available catalysts showing very high activity and stereoselectivity, i.e., chemzymatic reactions.[2,3] If this goal can be achieved for chiral Lewis acids, a new era for these catalysts will emerge. From an academic but also from a commercial point of view, asymmetric Lewis acid catalysis will no longer be a chemical curiosity but rather a strong tool useful even for industrial synthesis.

The hetero-Diels−Alder reaction of carbonyl compounds is a very important reaction in chemistry, and compounds of fundamental importance for the society have been prepared using asymmetric Diels−Alder chemistry.[1,4] Recently, the development of hetero-Diels−Alder chemistry has entered a new stage using chiral Lewis acids as catalyst for the reaction. Though the catalytic asymmetric hetero-Diels−Alder reaction of aldehydes with conjugated dienes has been developed with success for various types of aldehydes,[5] the catalytic asymmetric hetero-Diels−Alder reaction of ketones (eq 1) has not yet been achieved.[6]

(1)

The activity of the Lewis acid (chemzyme) in the hetero-Diels−Alder reactions we present here is hitherto unprecedented,

(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) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley-Interscience: New York, 1993.

(2) Chemzyme, a specific molecule or complex which can catalyze a single chemical reaction for a particular chemical substrate with very high enantioselectivity and enantiospecificity at rates which approach "catalytic perfection". See, e.g.: Bugg, T. *An Introduction to Enzyme and Coenzyme Chemistry*; Blackwell Science: Oxford, 1997.

(3) According to our knowledge, the term "chemzyme" has only been used very few times in relation to asymmetric catalysis. Two examples are the following: (a) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207. (b) Sasai, H.; Takayoshi, A.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. In the latter case, the word "chemzyme" was used only in the Introduction.

(4) (a) See, e.g.: Boger, D. L.; Weinreb, S. N. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press: San Diego, CA, 1987; Vol. 47. (b) Tietze, L. F.; Kettschau, G. *Stereoselective Heterocyclic Synthesis I*; Metz, P., Ed.; Springer-Verlag: Berlin, 1997; Vol. 189, pp 1−120. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(5) (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 0, 5998. (c) Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979. (d) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951. (e) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060 and references therein. (f) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (g) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (h) Graven, A.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1996**, 2372.

(6) (a) Recently, we disclosed the enantioselective catalytic hetero-Diels−Alder reaction of ketones: Johannsen, M.; Yao, S.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1997**, 2169. (b) A previous attempt on asymmetric hetero-Diels−Alder reactions of ketones with chiral Lewis acids: Quimpère, M.; Jankowski, K. *J. Chem. Soc., Chem. Commun.* **1987**, 676.

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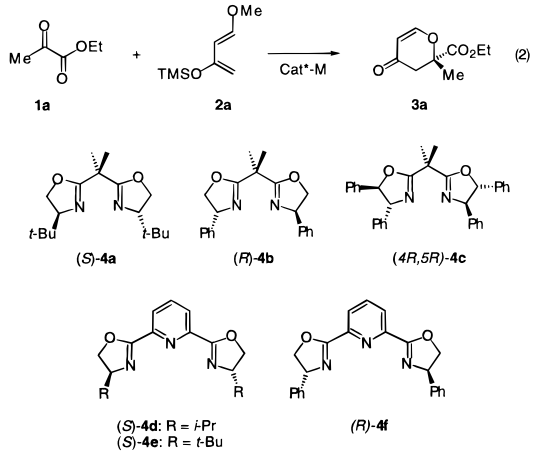
and the selectivity is, in some cases, almost perfect, i.e., being enzyme-like.[7] The hetero-Diels−Alder reaction protocol presented here offers some features which make it very attractive for synthetic purpose: (i) the chemicals are all inexpensive and easily available; (ii) the protocol has a very broad scope, as both aliphatic and aromatic carbonyl compounds are excellent substrates; (iii) the reactions are very easy to carry out and are highly reliable; (iv) in some cases the reactions show enhanced enantioselectivity when the amount of chemzyme is reduced; and, most notably, (v) even as little as 0.05 mol % catalyst is sufficient to achieve high yield and optical purity of the hetero-Diels−Alder product when using commercially available chemicals. The hetero-Diels−Alder products obtained are highly valuable for organic synthesis in general and for the construction of heterocyclic building blocks in particular.[4] It is notable that the adducts contain a chiral quaternary carbon center, the formation of which is a particularly demanding task in organic synthesis.[8]

Results and Discussion

A variety of different C_2-symmetric bisoxazoline-type ligands[9,10] and Lewis acids have been tested as catalysts for the hetero-Diels−Alder reaction of ethyl pyruvate (**1a**) with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene, **2a**) (eq 2).



It has been found that the hetero-Diels−Alder product **3a** was formed in highly varying yields and enantioselectivities depending on the catalyst used. Some representative results are given in Table 1.

From Table 1, it appears that the combination of 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] ((*S*)-**4a**) with copper(II) salts gives the hetero-Diels−Alder product **3a** in reasonable yields and with high ee, when especially triflate is used as the anion (entries 1−4). The use of (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst gives 78% isolated yield of **3a** with an ee of 99% (entry 4), while only 37% yield and 89% ee of **3a** is obtained when (*S*)-**4a**-Cu(SbF$_6$)$_2$ is applied (entry 3). This effect on the ee of the anion is opposite to the previous observations using (*S*)-**4a**-Cu^{II} salts as the catalyst for the hetero-Diels−Alder reaction of ethyl glyoxylate with dienes.[11a] Evans et al. have also observed that antimonate leads to a faster and more selective reaction compared with triflate as the anion for carbo-Diels−Alder reaction catalyzed by copper(II) salts in combination with (*S*)-**4a**,[9c] whereas for aldol reaction of pyruvate, triflate was again the anion of choice.[11b] The use of catalyst (*R*)-**4b**-Cu(OTf)$_2$ leads to the formation of **3a** in reasonable yield, but the ee of the product is low (entry 6). Although the absolute stereochemistry of the two ligands [(*S*)-**4a** and (*R*)-**4b**] is opposite, the same absolute stereochemistry is found in product **3a**.[10k,12] The results for the application of ligand (4*R*,5*R*)-**4c** in combination with the metal salts Cu(OTf)$_2$, Zn(OTf)$_2$, and Mg(OTf)$_2$ (entries 7−9) show that, for this ligand, the Zn(OTf)$_2$ has the best catalytic properties, in terms of both yield and ee of **3a**. The tridentate ligands **4d**−**f** and Cu(OTf)$_2$ as the Lewis acid all led to low yields and enantioenrichments of **3a** (entries 10−12).

Table 1. Influence of Bisoxazoline Ligand **4a**−**f**, Metal, Counterion, and Temperature on the Hetero-Diels−Alder Reaction of Ethyl Pyruvate (**1a**) with *trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's Diene) (**2a**)

		react. temp		hetero-Diels−Alder product **3a**	
entry	catalyst (10 mol %)	(°C)	solvent	yield (%)[a]	ee (%)[b]
1	(*S*)-**4a**-Cu(SbF$_6$)$_2$	rt	CH_2Cl_2	22	80
2	(*S*)-**4a**-Cu(OTf)$_2$	rt	CH_2Cl_2	85	92
3	(*S*)-**4a**-Cu(SbF$_6$)$_2$	−40	CH_2Cl_2	37	89
4	(*S*)-**4a**-Cu(OTf)$_2$	−40	CH_2Cl_2	78	99
5	(*R*)-**4b**-Cu(SbF$_6$)$_2$	rt	CH_2Cl_2	24	23
6	(*R*)-**4b**-Cu(OTf)$_2$	rt	CH_2Cl_2	85	26
7	(4*R*,5*R*)-**4c**-Cu(OTf)$_2$	−40	THF	4	23
8	(4*R*,5*R*)-**4c**-Zn(OTf)$_2$	−40	THF	86	63
9	(4*R*,5*R*)-**4c**-Mg(OTf)$_2$	−40	THF	20	
10	(*S*)-**4d**-Cu(OTf)$_2$	rt	CH_2Cl_2	29	9
11	(*S*)-**4e**-Cu(OTf)$_2$	rt	CH_2Cl_2	15	27
12	(*S*)-**4f**-Cu(OTf)$_2$	rt	CH_2Cl_2	23	55

[a] Isolated yield. [b] Ee determined by chiral GC on a Chrompack Chirasil-DEX CB column.

The reaction of methyl pyruvate (**1b**) with diene **2a** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %) as the catalyst has been

(7) The Lewis acid- or chemzyme-catalyzed reactions should most adequately be considered as a kind of three-component coupling, as no covalent bonding between the substrates and catalyst occurs. This means that small catalyst loadings are very hard to obtain, and normal loadings are de facto in the range of 5−10 mol %. We are aware of one example of a chiral Lewis acid-catalyzed ene reaction where as little as 0.2 mol % of the Lewis acid was employed. However, only a single substrate was shown to react: Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 833.

(8) For a review about the catalytic formation of molecules with quaternary carbon centers, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

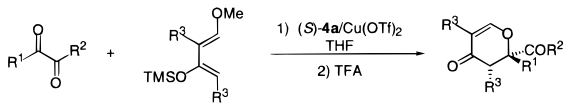
(9) For pioneering work using bisoxazolines and copper Lewis acids, see: (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (c) Evans, D. A.; Murry, J. A.; Matt, P.; Norcross, R. D.; Miller, S. *J. Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

(10) For bisoxazoline-catalyzed asymmetric carbo-Diels−Alder reactions, see, e.g.: (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Ishihara, K.; Corey, E. J. *Tetrahedron Lett.* **1992**, *33*, 6807. (c) Evans D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481. (d) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815. (e) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165. (f) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1753. (g) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 1725. (h) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (i) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454. (j) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.-i.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074. (k) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1 and references therein.

(11) (a) Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893.

(12) For the particular effect of the bisoxazoline ligands on the absolute stereochemistry of the products, see, e.g.: Yao, S.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2345 and references therein.

Table 2. Results for the Hetero-Diels−Alder Reaction (eq 3) of α-Keto Esters **1a**−**e** and α-Diketones **1f**−**i** with the Activated Dienes **2a**,**b** in the Presence of (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %)



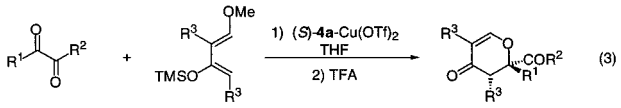
1 **2** **3**

entry	ketone **1**, R^1/R^2	diene **2**, R^3	catalyst load (%)	react. temp/ react. time (°C/h)	hetero-Diels−Alder product yield (%)[a]	hetero-Diels−Alder product ee (%)
1	Me/OEt-**1a**	H-**2a**	10	−78 to −40/30	**3a**, 96	99[b]
2	Me/OMe-**1b**	H-**2a**	10	−78 to −40/30	**3b**, 96	99[b]
3	Et/OMe-**1c**	H-**2a**	10	−78/30	**3c**, 80	94[b]
4	i-Pr/OEt-**1d**	H-**2a**	10	−78/40	**3d**, 42	37[b]
5	Ph/OEt-**1e**	H-**2a**	10	rt/20	**3e**, 77	77[c]
6	Me/Me-**1f**	H-**2a**	10	−40/30	**3f**, 90	94[b]
7	Me/Et-**1g**	H-**2a**	10	−40/30	**3g**, 77	98[b]
8	Et/Et-**1h**	H-**2a**	10	−40/30	**3h**, 84	90[b]
9	Me/Ph-**1i**	H-**2a**	10	−40/30	**3i**, 95	94[c]
10	Me/OMe-**1b**	Me-**2b**	10	−40/30	**3j**, 75[d]	96[c]
11	Ph/OEt-**1e**	Me-**2b**	10	−40/30	**3k**, 57[d]	99[c]
12	Me/Me-**1f**	Me-**2b**	10	−40/30	**3l**, 60[d]	91[c]

[a] Isolated yield. [b] Ee determined by chiral GC on a Chrompack Chirasil-DEX CB column. [c] Ee determined by using HPLC on a Daicel Chiralpak AD column. [d] Isolated yield of the major diastereomer.

studied in different solvents. The optimal solvent is THF in terms of yield and ee of **3b**, as the reaction in this solvent gives 96% yield of **3b** and 99% ee. The same ee (99%) of **3b** is obtained in CH_2Cl_2 as the solvent, with a slightly lower yield. The use of Et_2O as the solvent for the reaction leads to formation of **3b** in 42% yield with an ee of 98%, whereas in nitromethane 75% of **3b** is isolated having 66% ee.

The reaction has been developed to a general reaction between various α-dicarbonyl compounds **1a**−**i** and the dienes **2a**,**b** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst (10 mol %) (eq 3).



(3)

1a: R^1 = Me, R^2 = OEt
1b: R^1 = Me, R^2 = OMe
1c: R^1 = Et, R^2 = OMe
1d: R^1 = *i*-Pr, R^2 = OEt
1e: R^1 = Ph, R^2 = OEt
1f: R^1 = Me, R^2 = Me
1g: R^1 = Me, R^2 = Et
1h: R^1 = Et, R^2 = Et
1i: R^1 = Me, R^2 = Ph

2a: R^3 = H
2b: R^3 = Me

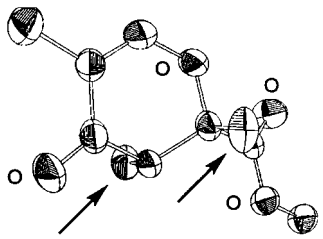
3a: R^1 = Me, R^2 = OEt, R^3 = H
3b: R^1 = Me, R^2 = OMe, R^3 = H
3c: R^1 = Et, R^2 = OMe, R^3 = H
3d: R^1 = *i*-Pr, R^2 = OEt, R^3 = H
3e: R^1 = Ph, R^2 = OEt, R^3 = H
3f: R^1 = Me, R^2 = Me, R^3 = H
3g: R^1 = Me, R^2 = Et, R^3 = H
3h: R^1 = Et, R^2 = Et, R^3 = H
3i: R^1 = Me, R^2 = Ph, R^3 = H
3j: R^1 = Me, R^2 = OMe, R^3 = Me
3k: R^1 = Ph, R^2 = OEt, R^3 = Me
3l: R^1 = Me, R^2 = Me, R^3 = Me

By inspection of the results obtained using the optimized conditions on a range of different α-keto esters **1a**−**e** and α-diketones **1f**−**i**, the scope of the reaction becomes evident (Table 2).

Both ethyl and methyl pyruvate (**1a**,**b**) react with **2a**, giving high isolated yields of **3a**,**b**, and for both substrates 99% ee is obtained (entries 1 and 2). An exchange of the methyl ketone fragment in the pyruvates **1a**,**b** with an ethyl fragment, compound **1c**, leads also to a highly selective hetero-Diels−Alder reaction, with 80% isolated yield of **3c** and 94% ee (entry 3), whereas the sterically more demanding isopropyl compound **1d** reacts poorly with diene **2a**, compared with the other substrates, as only 42% yield of **3d** is isolated with 37% ee (entry 4). Aromatic α-keto esters are also substrates for the present hetero-Diels−Alder reaction (entry 5, vide infra) as ethyl benzoylformate (**1e**) reacts with **2a** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$, giving 77% yield of **3e** with 77% ee.

The catalytic hetero-Diels−Alder reaction of ketones can be extended to symmetrical and unsymmetrical α-diketones without loss of selectivity; 2,3-butanedione **1f** reacts with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene **2a**, giving **3f** in 90% yield and 94% ee (entry 6). The (*S*)-**4a**-Cu(OTf)$_2$ catalytic system can distinguish between a methyl and an ethyl fragment, as shown by the reaction of unsymmetrical 2,3-pentanedione (**1g**), which reacts primarily at the methyl fragment, giving the corresponding hetero-Diels−Alder product **3g** in 77% yield and 98% ee (entry 7). The symmetric substrate 4,5-hexanedione (**1h**) also reacts with **2a**, leading to high yield and ee of the Diels−Alder product, 84% and 90%, respectively (entry 8). The high regioselectivity of the reaction is further demonstrated by the reaction of an α-diketone substituted with a methyl and a phenyl subtituent (entry 9). For this substrate, **1i**, the methyl ketone reacts exclusively, and 95% of the corresponding hetero-Diels−Alder product **3i** is isolated, having 94% ee (entry 9).

The hetero-Diels−Alder reaction of the various α-keto esters and α-diketones proceeds well for other dienes too, such as **2b**. Diene **2b** introduces a further selectivity aspect of the reaction, the diastereoselectivity. Methyl pyruvate (**1b**) reacts with **2b** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %) as the catalyst, giving the endo product **3j** in 75% yield and 96% ee (entry 10). The X-ray structure of **3j** was solved to prove that

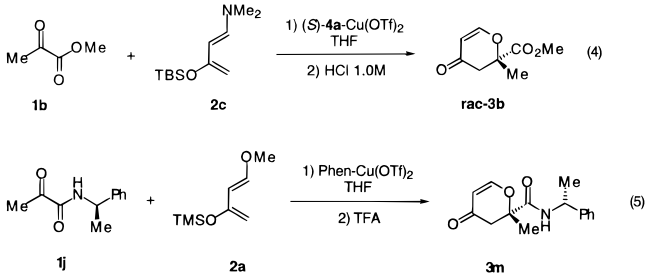


3j

the diastereomer formed is the one with the two methyl substituents trans (indicated with the two arrows), the endo product. The phenyl-substituted α-keto ester **1e** reacts with **2b** with a de of 67%, giving 57% yield of the major diastereomer **3k** formed in 99% ee (entry 11), while 2,3-butanedione (**1f**) reacts with **2b** in a diastereo- (de = 80%) and highly enantioselective manner, giving the hetero-Diels−Alder product **3l** as the major diastereomer in 60% isolated yield and with a high ee (91%) (entry 12).

The reaction of the methyl pyruvate (**1b**) with the amino-substituted diene **2c** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %) as the catalyst (eq 4) leads, unfortunately, only to a racemic mixture of **3b**. The hetero-Diels−Alder reaction catalyzed by copper(II) salts proceeds also for an α-keto amide as shown in eq 5, where the chiral α-keto amide **1j** reacts diastereoselectively (de = 67%) with **2a** to give **3m** in the presence of 1,10-phenanthroline-Cu(OTf)$_2$ (10 mol %) as the catalyst (vide infra).

Careful investigation of the reaction between methyl pyruvate (**1b**) and *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**2a**) in the presence of 10 mol % of (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst revealed that an instant reaction (<2 min) takes place. Reducing the amount of the catalyst to 2 mol % still gave a very fast reaction, as 95% of **3b** (~98% ee) was isolated after a reaction time of 10 min at −78 °C. Further reduction of the



catalyst amount to 0.5 and 0.1 mol % leads to similar observations. The reaction of **1b** with **2a** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ can proceed to complete conversion with only 0.05 mol % of the catalyst present—which, according to our knowledge, is among the lowest catalyst loading in Lewis acid-catalyzed asymmetric reactions observed until now—leading to only one enantiomer detected by chiral GC of the crude reaction mixture, as shown in Figure 1. *The turnover numbers for the (S)-4a-Cu(OTf)$_2$ catalyst in the reaction of **1b** with **2a** using only 0.05 mol % shows that, for the present hetero-Diels−Alder reaction, the catalytic effect is beginning to be enzyme-like*.[2,3,7]

The successful application of a very low catalytic loading of (*S*)-**4a**-Cu(OTf)$_2$ for the hetero-Diels−Alder reaction of **1b** with **2a** turned out to be a general catalytic feature for the reaction of various α-keto esters and α-diketones. To emphasize the broad scope of the protocol, a set of results is presented in Table 3, which summarizes the reactions between the various substrates **1b**,**c**,**e**,**f**,**g**,**i** with the conjugated dienes **2a**,**b**.

As can be seen, a minute amount of chemzyme (*S*)-**4a**-Cu(OTf)$_2$ generally is sufficient to catalyze the additions in a highly selective manner. Reaction of 2,3-butanedione (**1f**) with **2a** catalyzed by 0.05 mol % of the copper(II) bisoxazoline chemzyme complex (*S*)-**4a**-Cu(OTf)$_2$ leads to the hetero-Diels−Alder product **3f** in 88% yield with 93.9% ee (Table 3, entry 2). However, more impressive with regard to the regioselectivity is the reaction of 2,3-pentanedione (**1g**) as **2a** approaches the methyl ketone rather than the ethyl ketone (ratio 9:1), affording product **3g** in 76% yield and 97.8% ee (entry 3). The symmetric substrate 4,5-hexanedione also reacts with **2a**, leading to high yield and ee of the hetero-Diels−Alder product **3h**, 84% and 90.0%, respectively. Substitution of the ethyl substituent in **1g** with a phenyl substituent, compound **1i**, causes a significant improvement in regioselectivity as the only hetero-Diels−Alder product observed, **3i** (25% yield, 96.4% ee), is formed by addition of **2a** exclusively to the methyl ketone fragment in **1i** (entry 4). The yield of **3i** in the latter reaction can be improved by increasing the amount of the catalyst. The α-keto ester **1c** also reacts with diene **2a** using low catalyst loading, giving the corresponding product **3c** in high enantioselectivity and yield, 96.8% and 70%, respectively (entry 5). It is notable that the ee obtained in the reaction of **1c** and **1i** using this low catalyst loading is higher than that obtained employing 10 mol % of the catalyst (compare with Table 2, entries 3 and 9). It should also be noted that, for the reaction of **1b** and **1f** with diene **2b** with low catalyst loading, very high ee of the hetero-Diels−Alder products **3j** and **3l** are also found (entries 6 and 8).

Similarly, aromatic ketones can be substrates for the highly catalytic asymmetric hetero-Diels−Alder reaction with dienes. The aromatic ketones **1** (R^1 = Ph (**1e**), *p*-CF_3-C_6H_4 (**1k**), *p*-CH_3-C_6H_4 (**1l**), *p*-CH_3O-C_6H_4 (**1m**), R^2 = OEt) react with both **2a** and **2b** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ (2.5 mol %) as the catalyst, giving the hetero-Diels−Alder products in reasonable to good yields (50−80%). The reactions with diene **2a** give the lowest ee's (∼80%) of the products, whereas with diene **2b** higher total yields and very high ee's of one of the diastereomers of the hetero-Diels−Alder products are obtained. The results for the reaction of **1e** with **2b** given in entry 7 show the high ee (98.7%) and good yield of the diastereomer obtained (**3k**). The reactions of the other ketones **1k**−**m** with **2b** give similarly high ee of the hetero-Diels−Alder products.

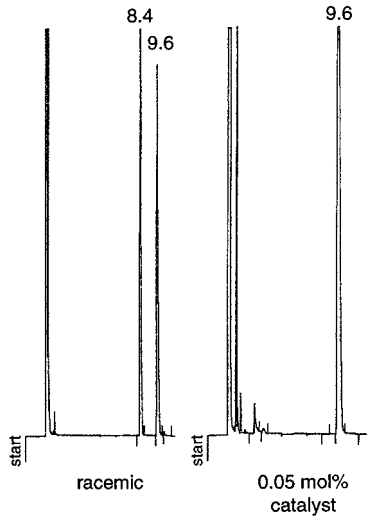
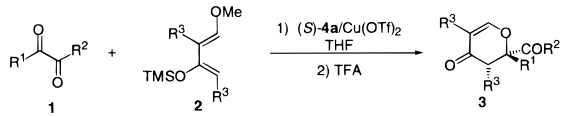


Figure 1. Chiral GC of the hetero-Diels−Alder product of methyl pyruvate (**1b**) with the diene **2a** (eq 3). The GC to the left is of the racemic product, and that to the right is of the crude reaction mixture using 0.05 mol % of (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst. Retention time is given in minutes.

Table 3. Results for the Asymmetric Hetero-Diels−Alder Reaction of α-Keto Esters and α-Diketones **1b**,**c**,**e**,**f**,**g**,**i** with Dienes **2a**,**b** Using Low Catalyst Loading of (*S*)-**4a**-Cu(OTf)$_2$



entry	ketone **1**, R^1/R^2	diene **2**, R^3	catalyst load (%)	react. temp/ react. time (°C/h)	hetero-Diels−Alder product yield (%)[a]	hetero-Diels−Alder product ee (%)
1	Me/OMe-**1b**	H-**2a**	0.05	−78/20	**3b**, 90	98.4[b]
2	Me/Me-**1f**	H-**2a**	0.05	−78 to −40/18	**3f**, 88	93.9[b]
3	Me/Et-**1g**	H-**2a**	0.05	−78/20	**3g**, 76	97.8[b]
4	Me/Ph-**1i**	H-**2a**	0.05	−78/20	**3i**, 25	96.4[c]
5	Et/OMe-**1c**	H-**2a**	0.5	−78/30	**3c**, 70	96.8[b]
6	Me/OMe-**1b**	Me-**2b**	2.5	−40/12	**3j**, 85[d]	97.4[c]
7	Ph/OEt-**1e**	Me-**2b**	2.5	−40/12	**3k**, 65[d]	98.7[c]
8	Me/Me-**1f**	Me-**2b**	2.5	−40/12	**3l**, 81[d]	97.1[c]

[a] Isolated yield. [b] Ee determined by chiral GC on a Chrompack Chirasil-DEX CB column. [c] Ee determined by using HPLC on a Daicel Chiralpak AD column. [d] Isolated yield of the major diastereomer.

To determine the absolute stereochemistry of the major enantiomer **3b** (>99% ee) formed by reaction of methyl pyruvate (**1b**) with diene **2a**, the chiral hetero-Diels−Alder product **3m** was synthesized (Figure 2). The adduct **3b** was first hydrolyzed with lithium hydroxide in a THF/H_2O solution, giving the carboxylic acid **3n**. Condensation with (*R*)-phenylethylamine applying an oxidation−reduction condensation using 2,2′-dipyridyl disulfide as oxidant[13] (eq 6, Figure 2) gave the crystalline diastereomer **3m**. The stereochemistry of **3m** was

(13) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1901.

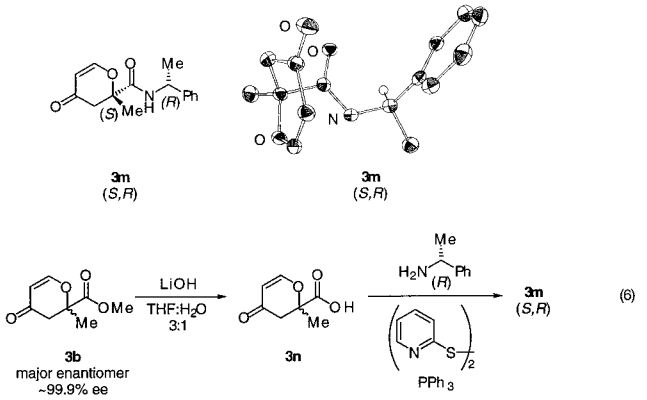


Figure 2. The X-ray structure of **3m**(*S*,*R*) shows also the position of the α-hydrogen atom in the (*R*)-(+)-α-methylbenzylamine fragment, while the other hydrogens are omitted for clearity. Reaction 6 shows the synthetic route for the assignment of the absolute stereochemistry of the major enantiomer of **3b**.

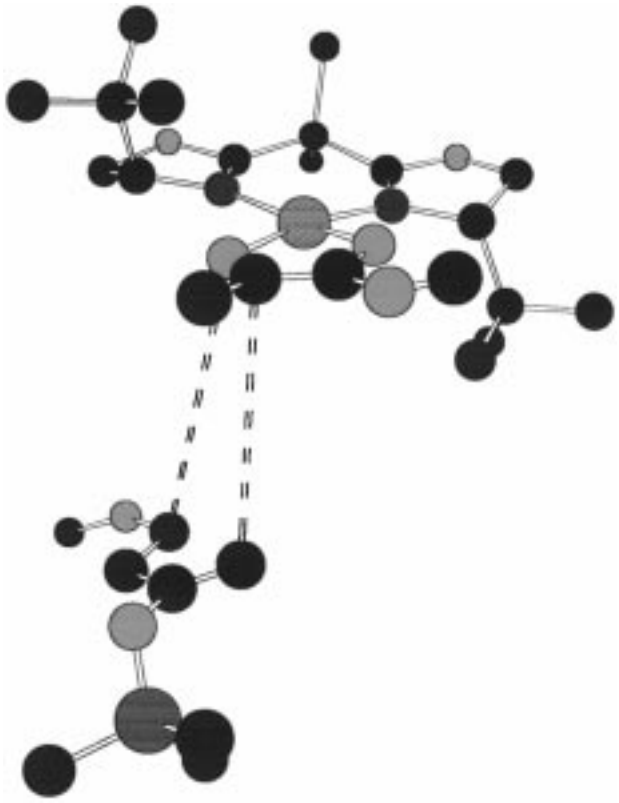


Figure 3. Model for the approach of the diene to methyl pyruvate (**1b**) when coordinated to the asymmetric catalyst. Black, carbon; red, oxygen; blue, nitrogen; gray, copper; and brown, silicon. Hydrogen atoms are omitted for clearity.

assigned by X-ray analysis to be (*S*,*R*); i.e., the absolute stereochemistry of the formed quaternary carbon center of the hetero-Diels−Alder product **3b** is (*S*). We anticipate the outcome of the other reactions to be consistent with this observation, and all adducts, therefore, have the same three-dimensional structure.

In order for (*S*)-**3b** to be formed, the diene has to approach the *si* face of ketone **1b**. A ball-and-stick model for the possible chemzyme−substrate intermediate is presented in Figure 3. It is assumed that both the chiral ligand and methyl pyruvate (**1b**) are bidentate-coordinated to the copper(II) center during the reaction. As evidenced, a square-planar geometrical arrangement at the metal center with the ligand and the substrate in the same plane leads to a complex where the carbonyl *re* face is effectively shielded by the ligand *tert*-butyl groups (Figure 3).[5g,9c,10k,12]

Summary

The results for the highly enantioselective hetero-Diels−Alder reaction of the various aliphatic and aromatic ketones with the dienes catalyzed by the very low amount of the bisoxazoline−copper(II) complex (*S*)-**4a**-Cu(OTf)$_2$ show the potential of the reaction protocol. The reaction can proceed with only 0.05 mol % of the catalyst without loss of selectivity. We anticipate that it might be possible to reduce the loading of the catalyst and enhance the selectivity even further by a careful choice of ligand, anion, and solvent. Moreover, the reaction might be scaled up, which can allow for a further lowering in the amount of the catalyst. The low loading of (*S*)-**4a**-Cu(OTf)$_2$ catalyst is, according to our knowledge, the first example of a chemzymatic reaction using Lewis acids as the catalyst, and we hope that our findings will stimulate further work in this field and that commercial use of this or related protocols will soon emerge.

Experimental Section

General Methods. All reactions were carried out using anhydrous solvents and under N_2 in flame-dried Schlenk tubes. CH_2Cl_2 and CH_3NO_2 were dried over CaH_2, distilled, and stored over 4 Å molecular sieves. Tetrahydrofuran (THF), Et_2O, and toluene were dried and distilled from sodium benzophenone prior to use. Merck silica gel (230−400 mesh) was used for flash chromatography (FC). ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as the solvent and were reported in ppm downfield from TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta =$ 77.00) for ^{13}C NMR. Enantiomeric excess (ee) was determined by GC using a Chrompack Chirasil-DEX CB column or by HPLC using a Daicel Chiralpak AD column or a Chiralcel OD column as stated in the experimental procedures. Optical rotations were measured with a sodium lamp and were reported as follows: $[\alpha]^{rt}_D$ (*c* g/100 mL, solvent).

Materials. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], (*R*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline), 2,6-bis[(4*S*)-isopropyl-2-oxazolin-2-yl]pyridine, $CuBr_2$, Cu(OTf)$_2$, and $AgSbF_6$ from Aldrich were stored in glovebox and used without further purification. 2,2′-Isopropylidenebis[(4*R*,5*R*)-4,5-diphenyl-2-oxazoline], 2,6-bis[(4*S*)-*tert*-butyl-2-oxazolin-2-yl]pyridine, and 2,6-bis[(4*R*)-phenyl-2-oxazolin-2-yl]pyridine were prepared according to literature procedures.[14] Methyl pyruvate, ethyl pyruvate, ethyl benzoylformate, ethyl 3-methyl-2-oxobutyrate, 2,3-butanedione, 2,3-pentanedione, 3,4-hexanedione, and 1-phenyl-1,2-propanedione were purchased from Aldrich and distilled before use. Methyl 2-oxobutyrate was prepared according to the literature procedure.[15] *trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene from Aldrich was used as received without any purification. Dienes **2b** and **2c** were prepared according to the literature procedure.[16]

General Procedure for the Hetero-Diels−Alder Reactions of α-Diketones with Dienes Catalyzed by 10 Mol % (*S*)-4a-Cu(OTf)$_2$. Preparation of 2-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (3b). To a flame-dried Schlenk tube was added

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(15) Weissberger, A.; Kibler, C. J. In *Organic Syntheses*; Horning, E. C., Ed.; John Wiley & Sons: New York, 1955; Collect. Vol. 3, pp 610−613.

(16) (a) Myles, D. C.; Bigham, M. H. In *Organic Syntheses*; Meyers, A. I., Ed.; John Wiley & Sons: New York, 1992; Vol. 70, pp 231−239. (b) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252.

$Cu(OTf)_2$ (36 mg, 0.1 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (31.5 mg, 0.105 mmol) under N_2. The mixture was dried under vacuum for 1−2 h, anhydrous solvent (1.5−2.0 mL) was added, and the resulting suspension was stirred vigorously for 1−5 h. The catalyst solution was then cooled to −78 °C, and methyl pyruvate (90 μL, 1.0 mmol) was added, followed by the addition of diene (240 μL, 1.2 mmol). The reaction was kept stirring at −78 °C for the described time, and then trifluoroacetic acid (TFA) (0.1 mL in CH_2Cl_2 (20 mL) was added, and the mixture was stirred at 0 °C for 1 h. The solution was neutralized with saturated $NaHCO_3$ and filtered through a plug of cotton. The organic phase was separated, and the water phase was extracted twice with CH_2Cl_2. The combined organic phases were dried, filtered, and concentrated to give the crude product. Purification by FC (EtOAc/pentane 20:80) afforded the title compound as a light yellow oil: 164 mg, 96% yield, 99% ee according to chiral GC, $[\alpha]^{rt}_D$ +173.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.34 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.42 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 3.76 (s, 3H, CO_2CH_3), 3.00 (d, *J* = 17.5 Hz, 1H, C*H*H), 2.68 (d, *J* = 16.5 Hz, 1H, C*H*H), 1.65 (s, 3H, CH_3); ^{13}C NMR δ 190.0, 171.4, 161.8, 107.3, 82.8, 53.2, 44.6, 24.2.

Hetero-Diels−Alder Reaction of Methyl Pyruvate (1b) with *trans*-1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (2a) Catalyzed by (*S*)-4a-Cu(OTf)$_2$ (0.05 Mol %). (a) Preparation of Catalyst Solution (0.01 M). $Cu(OTf)_2$ (36 mg, 0.1 mmol) and 2,2′-isopropylidene[(4*S*)-4-*tert*-butyl-2-oxazoline] (31 mg, 0.105 mmol) were added to a flame-dried Schlenk tube under N_2. The mixture was stirred under vacuum for 5 h (10^{-2} mbar). Freshly distilled THF (10 mL) was added with a syringe under N_2. The clear green solution was stirred for 10−15 h until it had become absolutely homogeneous.

(b) Catalytic Reaction. To another flame-dried Schlenk tube was added freshly distilled THF (1 mL) via a syringe under N_2. An aliquot of 50 μL (0.5 μmol) was taken from the catalyst solution under N_2 and transferred to this THF solution. The catalyst solution was cooled to −78 °C, and then methyl pyruvate (90 μL, 1 mmol) and *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (240 μL, 1.2 mmol) were added. The solution was stirred at −78 °C for 20 h before the reaction was quenched with TFA (0.1 mL) dissolved in CH_2Cl_2 (15−20 mL). The solution was allowed to reach 0 °C and was stirred for 1 h. According to chiral GC of the crude product, only one enantiomer has been formed. Separation by FC (EtOAc/pentane 2:8) afforded **3b** as a light yellow oil: 153 mg, 90% yield, 98.4% ee according to chiral GC.

2-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (3a). Purification by FC on silica gel (petroleum ether/EtOAc 8:2) gave the product as a colorless oil in 78% yield with 99% ee according to chiral GC: $[\alpha]^{rt}_D$ +150.3° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.36 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.42 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 4.22 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 3.00 (d, *J* = 16.5 Hz, 1H, CH_2), 2.68 (d, *J* = 17.1 Hz, 1H, CH_2), 1.65 (s, 3H, CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 190.1, 170.9, 161.9, 107.3, 82.8, 62.4, 44.7, 24.1, 14.1.

The results for **3b** are given above.

2-Ethyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (3c). Purification by FC on silica gel (petroleum ether/EtOAc 8:2) gave the product as a colorless oil in 80% yield with 94% ee according to chiral GC: $[\alpha]^{rt}_D$ +148.1° (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 7.37 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.40 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 3.74 (s, 3H, OCH_3), 2.92 (d, *J* = 17.0 Hz, 1H, C*H*H), 2.70 (d, *J* = 17.0 Hz, 1H, C*H*H), 1.96 (q, *J* = 7.7 Hz, 2H, CH_2CH$_3$), 0.95 (t, *J* = 7.7 Hz, 3H, CH_2CH_3); ^{13}C NMR δ 190.2, 170.9, 162.13, 107.3, 86.0, 53.0, 42.9, 30.7, 7.6.

2-Isopropyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (3d). Purification by FC on silica gel (petroleum ether/EtOAc 85:15) gave the product as a colorless oil in 42% yield with 37% ee according to chiral GC: $[\alpha]^{rt}_D$ = −70.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.37 (d, *J* = 6.1 Hz, 1H, CH═C*H*), 5.37 (d, *J* = 6.1 Hz, 1H, CH═C*H*), 4.19 (q, *J* = 6.6 Hz, 2H, OCH_2CH_3), 2.86 (d, *J* = 17.5, 1H, C*H*H), 2.73 (d, *J* = 16.5, 1H, C*H*H), 2.19 (sept, *J* = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$), 1.23 (t, *J* = 6.6 Hz, 3H, OCH_2CH_3), 0.99 (m, *J* = 6.5 Hz, 6H, CH(CH_3)$_2$); ^{13}C NMR δ 190.6, 170.3, 162.3, 107.4, 88.5, 62.0, 40.5, 34.7, 16.7, 16.5, 14.1.

2-Phenyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (3e). Purification by FC on silica gel (petroleum ether/EtOAc 8:2) gave the product as a colorless oil in 77% yield with 77% ee detected by HPLC using a Chiralpak AD column (hexane/*i*-PrOH 99:1), 1.0 mL/min: $[\alpha]^{rt}_D$ = +35.9° (*c* 1.46, $CHCl_3$); ^{1}H NMR δ 7.54−7.37 (m, 6H, C_6H_5 and CH═C*H*), 5.51 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 4.20 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.45 (d, *J* = 16.5 Hz, 1H, C*H*H), 3.06 (d, *J* = 16.5 Hz, 1H, C*H*H), 1.20 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR δ 189.7, 169.5, 161.4, 136.7, 129.1, 128.8, 125.0, 108.4, 85.7, 62.7, 44.3, 13.9.

2-Acetyl-2-methyl-2,3-dihydropyran-4-one (3f). Purification by FC on silica gel (petroleum ether/EtOAc 82:18 to 70:30) gave the product as a colorless oil in 90% yield with 94% ee according to chiral GC: $[\alpha]^{rt}_D$ +171.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.35 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.42 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 2.98 (d, *J* = 16.5 Hz, 1H, C*H*H), 2.56 (d, *J* = 16.5 Hz, 1H, C*H*H), 2.26 (s, 3H, $COCH_3$), 1.50 (s, 3H, CH_3); ^{13}C NMR δ 207.3, 190.1, 160.6, 107.6, 87.6, 43.2, 24.2, 22.5.

2-Methyl-2-propionyl-2,3-dihydropyran-4-one (3g). Purification by FC on silica gel (petroleum ether/EtOAc 75:25) gave the product as a colorless oil in 77% yield with 98% ee according to chiral GC: $[\alpha]^{rt}_D$ +172.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.35 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.42 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 2.53−3.00 (m, 4H, ═CHCOCH_2, $COCH_2CH_3$), 1.50 (s, 3H, CH_3), 1.06 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR δ 210.0, 190.2, 160.7, 107.5, 87.7, 43.4, 29.6, 22.8, 7.4.

2-Ethyl-2-propionyl-2,3-dihydropyran-4-one (3h). Purification by FC on silica gel (petroleum ether/EtOAc 85:15) gave the product as a colorless oil in 84% yield with 90% ee according to chiral GC: $[\alpha]^{rt}_D$ +175.6° (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ 7.35 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.37 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 2.44−2.91 (m, 4H, ═CHCOCH_2, $COCH_2CH_3$), 1.78−1.98 (m, 2H, CH_2CH$_3$), 1.01 (s, 3H, $COCH_2CH_3$), 0.92 (s, 3H, CH_2CH_3); ^{13}C NMR δ 210.2, 190.3, 160.9, 107.5, 90.7, 41.5, 30.5, 29.3, 7.5, 7.3.

2-Methyl-2-benzoyl-2,3-dihydropyran-4-one (3i). Purification by FC on silica gel (petroleum ether/EtOAc 8:2) gave the product as a white solid in 95% yield with 94% ee detected by HPLC using a Chiralpak AD column (hexane/*i*-PrOH 99:1), 1.0 mL/min: $[\alpha]^{rt}_D$ +425.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.11−8.08, 7.58−7.56, 7.48−7.43 (m, 5H, C_6H_5), 7.20 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 5.37 (d, *J* = 6.0 Hz, 1H, CH═C*H*), 3.30 (d, *J* = 16.5 Hz, 1H, C*H*H), 2.68 (d, *J* = 16.5 Hz, 1H, C*H*H), 1.83 (s, 3H, CH_3); ^{13}C NMR δ 199.1, 190.7, 160.6, 133.5, 133.4, 129.9, 128.4, 108.2, 88.8, 45.1, 24.8.

2,3,5-Trimethyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (3j). Purification by FC on silica gel (petroleum ether/EtOAc 10:1) gave the product as a white solid in 98% yield with 86% de and 97.4% ee (major diastereomer) detected by HPLC using a Chiralpak AD column (hexane/*i*-PrOH 99.5:0.5), 1.0 mL/min. Physical data for the major diastereomer: $[\alpha]^{rt}_D$ +16.0° (*c* 0.25, $CHCl_3$); ^{1}H NMR δ 7.09 (bs, 1H, C*H*═C), 3.77 (s, 3H, OCH_3), 2.63 (q, 1H, *J* = 7.2 Hz, $COCHCH_3$), 1.64 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.12 (d, 3H, *J* = 7.7 Hz, $COCHCH_3$); ^{13}C NMR δ 194.5, 170.8, 155.4, 111.8, 85.3, 52.7, 47.2, 21.5, 12.4, 10.4.

3,5-Dimethyl-4-oxo-2-phenyl-3,4-dihydro-2*H*-pyran-2-carboxylic Acid Methyl Ester (3k). Purification by FC on silica gel (petroleum ether/EtOAc 15:1) gave the product as a yellowish solid in 97% yield with 67% de and 98.7% ee (major diastereomer) detected by HPLC using a Chiralpak AD column (hexane/*i*-PrOH 99.5:0.5), 1.0 mL/min. Physical data for the major diastereomer: $[\alpha]^{rt}_D$ +232.32° (*c* 0.43, $CHCl_3$); ^{1}H NMR δ 7.52 (m, 2H, C_6H_5), 7.46 to 7.28 (m, 4H, C_6H_5 and C*H*═C), 4.15 (m, 2H, CH_2O), 3.41 (q, 1H, *J* = 7.3 Hz, $COCHCH_3$), 1.69 (s, 3H, CH_3), 1.15 (t, 3H, *J* = 7.0 Hz, CH_3CH_2O), 0.87 (d, 3H, *J* = 7.1 Hz, $COCHCH_3$); ^{13}C NMR δ 195.6, 170.7, 156.9, 135.5, 128.7, 128.5, 124.7, 113.4, 88.5, 62.4, 46.7, 13.9, 12.1, 10.4.

2-Acetyl-2,3,5-trimethyl-2,3-dihydropyran-4-one (3l). Purification by FC on silica gel (petroleum ether/EtOAc 15:1) gave the product as a yellowish solid in 93% yield with 83% de and 97.1% ee (major diastereomer) detected by HPLC using a Chiralpak AD column (hexane/*i*-PrOH 99.5:0.5), 1.0 mL/min. Physical data for the major diastereomer: $[\alpha]^{rt}_D$ −82.4° (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 7.10 (bs, 1H, C*H*═C), 2.62 (q, 1H, *J* = 7.3 Hz, $COCHCH_3$), 2.29 (s, 3H, CH_3), 1.67 (s,

3H, CH_3), 1.43 (s, 3H, CH_3), 1.07 (d, 3H, J = 7.2 Hz, COCHCH_3); ^{13}C NMR δ 208.2, 195.4, 154.9, 111.9, 89.5, 46.9, 26.6, 20.3, 12.7, 10.4.

2-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic Acid (3n). To the ester **3b** (200 mg, 1.18 mmol) in solution in THF (15 mL) and H_2O (5 mL) at 0 °C was added LiOH (56 mg, 2.35 mmol). The solution was left under stirring at 0 °C for 1 h and at room temperature for another hour. THF was then evaporated, and the resulting water phase was acidified to pH 2. The water phase was extracted twice with EtOAc. The combined organic phases were washed with brine, and the organic phase was dried over $MgSO_4$ and evaporated to dryness in vacuo. The crude compound was used without further purification in the next step (112 mg, 52%): ^{1}H NMR δ 10.18 (bs, 1H, COOH), 7.40 (dd, 1H, J = 1.6, 6.0 Hz, C*H*═CH), 5.51 (d, 1H, J = 6.1 Hz, C*H*═CH), 3.05 (d, 1H, J = 17 Hz, C*H*HCO), 2.72 (dd, 1H, J = 1.6, 17 Hz, C*H*HCO), 1.71 (s, 3H, CH_3).

Preparation of 2-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic-(1(*R*)-phenylethyl) Amide (3m). (*R*)-Phenylethylamine (80 mg, 0.65 mmol) and Ph_3P (170 mg, 0.65 mmol) in CH_2Cl_2 (2 mL) was added at room temperature to a mixture of the acid **3n** (112 mg, 0.61 mmol) and 2,2′-dipyridyl disulfide (137 mg, 0.62 mmol) in solution in 3 mL of CH_2Cl_2. After stirring for 12 h at room temperature, the solution was washed with dilute HCl, aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness in vacuo. FC (petroleum ether/EtOAc 2:1) provided **3m** as a yellowish solid (83 mg, 53%): $[\alpha]^{rt}_D$ +194.2° (*c* 0.83, $CHCl_3$); ^{1}H NMR δ 7.38 to 7.24 (m, 5H, C$_6H_5$), 7.21 (d, 1H, J = 6.6 Hz, C*H*═CH), 6.65 (bd, 1H, NH), 5.43 (d, 1H, J = 6.1 Hz, C*H*═CH), 5.11 (m, 1H, NHC*H*Me), 2.94 (d, 1H, J = 17.0 Hz, C*H*HCO), 2.65 (d, 1H, J = 17.0 Hz, C*H*HCO), 1.62 (s, 3H, CH_3), 1.52 (d, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR δ 190.1, 170.1, 159.4, 142.4, 128.6, 127.4, 125.9, 107.5, 83.6, 48.5, 43.7, 22.7, 21.3.

X-ray Crystallographic Data for Compound 3j: $C_{10}H_{14}O_4$, forms monoclinic crystals, space group $P2_1$, with a = 6.7013(3) Å, b = 6.7255(3) Å, c = 22.8294(9) Å, β = 89.524(1)°, V = 1028.9(1) Å^3; ρ_{calc} = 1.28 g cm^{-3}, Z = 4. A total of 8504 reflections were measured on a Siemens SMART diffractometer at 295 K using Mo Kα radiation (λ = 0.710 73 Å) with θ_{max} = 29°, giving 2475 independent reflections, of which 2273 had $I > 3\sigma I$, R_{int} = 0.066. The structure was solved by direct methods (SIR92) and refined by full matrix least-squares to R = 0.040, R_w = 0.049.

X-ray Crystallographic Data for Compound 3m: $C_{15}H_{17}NO_3$, forms orthorhombic crystals, space group $P2_12_12_1$, with a = 9.5403(5) Å, b = 10.2868(5) Å, c = 13.9304(7) Å, V = 1367.1(1) Å^3; ρ_{calc} = 1.26 g cm^{-3}, Z = 4. A total of 8608 reflections were measured on a Siemens SMART diffractometer at 120 K using Mo Kα radiation (λ = 0.710 73 Å) with θ_{max} = 29.6°, giving 3626 independent reflections, of which 3287 have $I > 3\sigma I$, R_{int} = 0.052. The structure was solved by direct methods (SIR92) and refined by full matrix least-squares to R = 0.035, R_w = 0.036. Atomic coordinates, bond lengths and angles, and thermal parameters for **3j**,**m** have been deposited at the Cambridge Crystallographic Data Center (CCDC).

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Supporting Information Available: Copies of NMR spectra (27 pages). See any current masthead page for ordering information and Web access instructions.

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