JOC Article

Direct Asymmetric Michael Reactions of Cyclic 1,3-Dicarbonyl Compounds and Enamines Catalyzed by Chiral Bisoxazoline−Copper(II) Complexes

Nis Halland, Thomas Velgaard, and Karl Anker Jørgensen*

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

kaj@chem.au.dk

Received March 7, 2003

The catalytic direct Michael addition of cyclic 1,3-dicarbonyl compounds and enamines to unsaturated 2-ketoesters is presented. A series of different 4-hydroxycoumarins, 4-hydroxy-6-methyl-2-pyrone, 3-hydroxy-1*H*-phenalene-1-one, 2-hydroxy-1,4-naphthoquinone, 5,5-dimethyl-1,3-cyclohexanedione, and various enamines of cyclic 1,3-diketones all add to unsaturated 4-substituted 2-ketoesters in an enantioselective manner. The reaction is catalyzed by chiral bisoxazoline−copper(II) complexes and proceeds in the absence of base to afford Michael adducts in good to high yields and with up to 98% ee. The products formed are substructures found in skeletons of important biological and pharmaceutical molecules. The scope and potential of the new reaction are discussed as well as the mechanism for the catalytic enantioselective reaction.

Introduction

The Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds is an important reaction in organic synthesis, as the products obtained can have biological and pharmaceutical activities.[1,2] Several synthetic procedures have been developed for the addition of cyclic 1,3-dicarbonyl compounds, and in particular enol lactones, to α,β-unsaturated carbonyl systems; however, these methods often require harsh reactions conditions, the use of strong acids or bases or heat.[3] Very recently, Kanemasa et al. have shown that especially nickel(II) perchlorate hexahydrate can catalyze the addition−cyclization of cyclic 1,3-dicarbonyl compounds to 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles.[4] However, to our knowledge, no catalytic asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl systems has been developed.[5]

The development of a catalytic enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl systems can afford optically active products containing substructure functionalities such as neoflavonoids and coumarins. These compounds are widely distributed in nature; many have interesting biological and pharmaceutical activities,[2] and several are related to anticoagulant agents.[6]

Recently, we have shown that chiral bisoxazoline−copper(II) complexes[7] are useful catalysts for a Friedel−Crafts-type alkylation reaction in which heteroaromatic and aromatic C−H bonds add in an enantioselective manner to 4-substituted 2-oxo-3-butenoate esters and alkylidene malonates.[8] We envisioned that this approach could also be applied to the addition of other types of activated C−H bonds to α,β-unsaturated systems, and in this paper the catalytic enantioselective Michael

(1) For reviews of enantioselective conjugate addition reactions, see: (a) Yamaguchi, M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 31.2. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

(2) For biological and pharmaceutical activities see, e.g.: (a) Murray, R. D. H.; Medez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley: New York, 1982. (b) *The Handbook of Natural Flavonoids*; Harborne, J. B., Baxter, H., Eds.; Wiley: Chichester, UK, 1999. (c) Manolov, I.; Danchev, N. D. *Eur. J. Med. Chem.* **1995**, *30*, 531. (d) Mouli, C.; Giridhar, T.; Rao. D. M.; Reddy, R. B. *J. Heterocycl. Chem.* **1996**, *33*, 5. (e) Rehse, K.; Schinkel, W. *Arch. Pharm.* **1983**, 988.

(3) (a) Ikawa, M.; Stahmann, M. A.; Link, K. P. *J. Am. Chem. Soc.* **1944**, *66*, 902. (b) Ivanov, I. C.; Manolov, I.; Alexandrova, L. A. *Arch. Pharm.* **1990**, 521. (c) Talapatra, S. K.; Chakrabarti, R.; Mukhopadhyay, P. K.; Das, P. K.; Talapatra, B. *Heterocycles* **1984**, *22*, 519.

(4) Itoh, K.; Kanemasa, S. *Tetrahedron Lett.* **2003**, *44*, 1799.

(5) For examples of Lewis-acid-catalyzed enantioselective Michael additions of 1,3-dicarbonyls to acyclic substrates, see: (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (b) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818. (c) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215. (d) Barnes, D. M.; Ji, J.; Fickles, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097. (e) Christoffers, J.; Rößler, U.; Werner, T. *Eur.*

(6) (a) O'Reilly, R. A. *N. Engl. J. Med.* **1976**, *295*, 354. (b) Wingard, L. B.; O'Reilly, R. A.; Levy, G. *Clin. Pharmacol. Ther.* **1978**, *23*, 212. (c) Bardsley, H. J.; Daly, A. K. PCT Patent WO 00/43003. (d) Li, H.-Y.; Robinson, A. J. U.S. Patent 5,856,525, January 5, 1999. (e) Li, H.-Y.; Robinson, A. J.; Feaster, J. *Tetrahedron Lett.* **1996**, *37*, 8321. (f) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707. (g) Demir, A. S.; Tanyeli, C.; Gulbeyaz, V.; Akgun, H. *Turk. J. Chem.* **1996**, *20*, 139. (h) Druzgala, P.; Zhang, X.; Pfister, J. R. PCT Pat. Appl. WO 02/085882.

(7) For reviews of C_2-bisoxazoline−Lewis acid complexes as catalysts, see e.g.: (a) Ghosh, A. K.; Mathivanen, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(8) (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (b) Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347.

10.1021/jo0343026 CCC: $25.00
Published on Web 05/28/2003

TABLE 1. Screening of Reaction Conditions for the Chiral Lewis Acid-Catalyzed Enantioselective Michael Addition of 4-Hydroxycoumarin 1a with 4-Phenyl-2-Oxo-3-Butenoate Methyl Ester 2a[a]

entry	Lewis acid	ligand	solvent	time (h)	temp (°C)	yield[b] (%)	Ee[c] (%)
1	$Cu(OTf)_2$	(*S*)-*t*-Bu-BOX	CH_2Cl_2	15	rt	98	60 (*R*)
2	$Cu(OTf)_2$	(*S*)-*t*-Bu-BOX	THF	15	rt	98	13 (*R*)
3	$Cu(OTf)_2$	(*S*)-*t*-Bu-BOX	Et_2O	15	rt	98	84 (*R*)
4	$Cu(OTf)_2$	(*S*)-*t*-Bu-BOX	Et_2O	15	0	98	61 (*R*)
5	$Cu(OTf)_2$	(*S*)-*t*-Bu-BOX	Et_2O	15	reflux	98	86 (*R*)[d]
6	$Cu(SbF_6)_2$	(*S*)-*t*-Bu-BOX	Et_2O	20	rt	34	28 (*R*)
7	$Cu(OTf)_2$	(*S*)-*t*-Bu-BOX	*t*-BuOMe	24	rt	74	65 (*R*)
8	$Cu(OTf)_2$	(*R*)-Ph-BOX	Et_2O	10	rt	85	77 (*S*)
9	$Zn(OTf)_2$	(*S*)-Ph-BOX	Et_2O	15	rt	98	0
10	$Zn(OTf)_2$	(*S*)-Ph-BOX	CH_2Cl_2	15	rt	98	25 (*S*)
11	$Ni(ClO_4)_26H_2O$	(*R*)-Ph-DBFOX	CH_2Cl_2	15	rt	98	29 (*S*)

[a] Catalyst loading = 10 mol %. [b] Isolated yield. [c] Ee measured by HPLC using a chiral stationary phase. Absolute configuration assigned by analogy to compound **3b**. [d] Catalyst loading = 3 mol %.

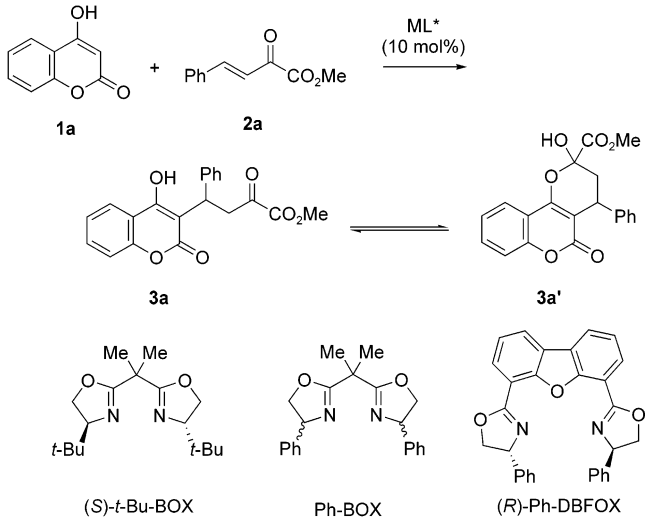
addition of cyclic 1,3-dicarbonyl compounds and enamines to activated α,*β*-unsaturated carbonyl compounds under base-free conditions is presented (eq 1).

Results and Discussion

A variety of different Lewis acids can catalyze the Michael addition of 4-hydroxycoumarins to 4-substituted 2-oxo-3-butenoate esters. However, to obtain optically active Michael adducts, the combination of chiral bisoxazolines and copper(II) turned out to be the best choice under the reaction conditions investigated.[9] Table 1 shows the screening results of the Michael addition of 4-hydroxycoumarin **1a** to 4-phenyl-2-oxo-3-butenoate methyl ester **2a** catalyzed by mainly chiral bisoxazolines and copper(II) salts.

The optimal combination for the catalytic enantioselective Michael reaction of 4-hydroxycoumarin **1a** to 4-phenyl-2-oxo-3-butenoate methyl ester **2a** is application of (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ as the catalyst in Et_2O, as 98% yield of **3a** is isolated (Table 1, entries 1−5). It is notable that the reaction takes place under base-free conditions. Furthermore, it should be pointed out that the Michael addition adduct **3** is in a rapid equilibrium with the cyclic hemiketal **3′** (Scheme 1).[10] An interesting temperature effect is observed for the enantioselectivity of the reaction: at room temperature, 84% ee is obtained (entry 3), while performing the reaction at 0 °C gave only 61% ee (entry 4); also, an improvement to 86% ee is found at reflux using 3 mol % of the catalyst (entry 5). The reaction is very dependent on the copper(II) counterion: a change from triflate (entry 3) to hexafluoroantimonate (entry 6) leads to a significant reduction in the yield of the reaction as well as the enantiomeric excess of the Michael adduct. The Ph-BOX-$Cu(OTf)_2$ is also applicable as a catalyst for the reaction; however, the yield and enantiomeric excess of **3a** is reduced (entry 8) compared to that obtained with

SCHEME 1



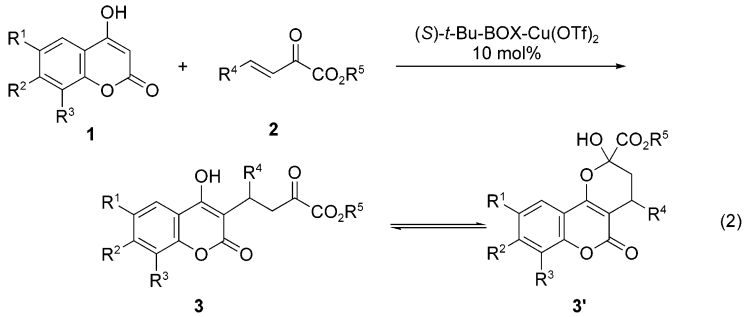
the (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ catalyst. Other Lewis acid catalysts have also been employed for the reaction. For example, (*S*)-Ph-BOX-$Zn(OTf)_2$ is an effective catalyst in terms of yield; unfortunately, however, **3a** was formed as a racemate in Et_2O (entry 9), while the reaction in CH_2Cl_2 afforded 25% ee (entry 10). The use of the (*R*)-Ph-DBFOX-$Ni(ClO_4)6H_2O$ catalyst, which has been found to be very useful as a chiral catalyst for Michael addition reactions, afforded only a low enantiomeric excess of **3a** (entry 11).[11]

To expand the scope of the Michael reaction of 4-hydroxycoumarins **1a**−**e** and 4-substituted 2-oxo-3-butenoate esters **2a**−**f** using (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ as the catalyst, several reactions were performed (eq 2) and the results are presented in Table 2.

The catalytic enantioselective reactions of 4-hydroxycoumarin **1a** with the different 4-aromatic- and 4-(2-furyl)-2-oxo-3-butenoate esters **2a**−**e** using (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ as the catalyst in Et_2O all proceeded in moderate to excellent isolated yields and with good enantioselectivity (up to 86% ee) (Table 2, entries 1−5). The reaction takes place with only 1−3 mol % of the catalyst and very high yields of the Michael adducts (**3a**,**b**), and good enantioselectivities are still obtained (entries 1 and 2). 4-Hydroxy coumarins having different electron-donating and electron-withdrawing substituents (**1b**−**e**) also undergo an enantioselective reaction with 4-phenyl-2-oxo-3-butenoate methyl ester **2a** to give the Michael adducts

(9) Use of chiral bisoxazoline−Lewis acid complexes for enantioselective Michael additions, see e.g.: (a) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (d) Sibi. M. P.; Chen, J. *Org. Lett.* **2002**, *4*, 2933 and refs 5c and 5d.

TABLE 2. Catalytic Enantioselective Michael Addition of Substituted 4-Hydroxycoumarins to 4-Substituted 2-Oxo-3-butenoate Esters in the Presence of (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ as the Catalyst in Et$_2$O



(2)

	4-hydroxycoumarin				4-substituted 2-ketoester				
entry		R^1	R^2	R^3		R^4	R^5	yield[a] (%)	Ee[b] (%)
1	**1a**	H	H	H	**2a**	Ph	Me	**3a** 98	86[c] (*R*)[e]
2	**1a**	H	H	H	**2b**	4-ClC_6H_4	Me	**3b** 98	73 (>99.5)[d] (*R*)
3	**1a**	H	H	H	**2c**	4-MeOC_6H_4	Me	**3c** 98	64 (*R*)[e]
4	**1a**	H	H	H	**2d**	4-MeC_6H_4	Me	**3d** 95	78 (*R*)[e]
5	**1a**	H	H	H	**2e**	2-furyl	Et	**3e** 95	81 (*S*)[e]
6	**1b**	Cl	H	H	**2a**	Ph	Me	**3f** 83	84[f] (*R*)[e]
7	**1c**	Cl	H	Cl	**2a**	Ph	Me	**3g** 98	78 (*R*)[e]
8	**1d**	H	OMe	H	**2a**	Ph	Me	**3h** 47	91 (*R*)[e]
9	**1e**	H	F	H	**2a**	Ph	Me	**3i** 45	91 (*R*)[e]
10	**1a**	H	H	H	**2f**	Me	Et	**3j** 98	90
11	**1e**	H	F	H	**2f**	Me	Et	**3k** 45	92

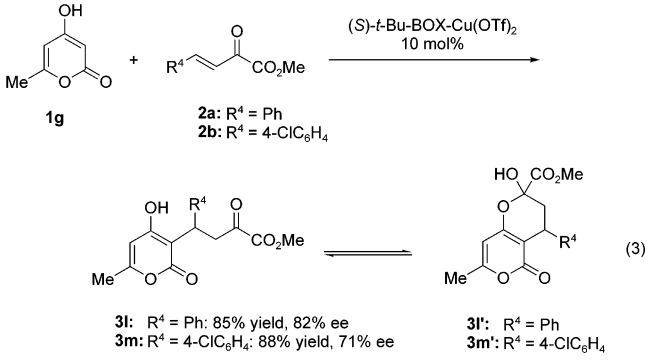
[a] Isolated yield. [b] Ee measured by HPLC using a chiral stationary phase. [c] Catalyst loading = 3 mol %. [d] Catalyst loading = 1 mol %; the product was recrystallized to be >99.5% ee in EtOAc/hexane, and the absolute stereochemistry was assigned by X-ray analysis. [e] Absolute configuration assigned by analogy to compound **3b**. [f] Performing this reaction in CH_2Cl_2 as the solvent gives >98% yield of **3f** having 77% ee.

3f−**i** in moderate to excellent yield and enantioselectivity (entries 6−9). The two 4-hydroxycoumarins **1a**,**e** react with 4-alkyl-2-oxo-3-butenoate esters in a highly enantioselective fashion; Michael adducts **3j** and **3k** were obtained in 98 and 45% yields and 90 and 92% ee, respectively (entries 10 and 11), while the Michael addition of 4-hydroxycoumarin to 4-benzyloxy-2-oxo-3-butenoate methyl ester afforded Michael products that had eliminated benzyl alcohol.

The optically active 3-substituted 4-hydroxycoumarins obtained represent a common structural unit found in a number of naturally occurring biologically active compounds,[2] the most important of these being the anticoagulant dicoumarol and the antibiotics novobiocin and coumermycin. A very large number of the more than 2000 existing 3-substituted 4-hydroxycoumarins have been prepared synthetically, and without doubt the single most important one is the anticoagulant warfarin that has been marketed as a racemate for more than 40 years.

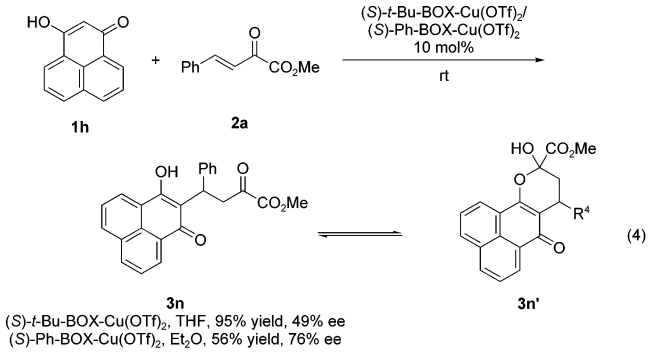
The scope of the reaction was extended to other 1,3-dicarbonyl compounds acting as Michael donors in the reaction with 4-substituted 2-oxo-3-butenoate esters **2**. (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol %) in Et$_2$O catalyzes the enantioselective addition of 4-hydroxy-6-methyl-2-pyrone **1g** to the 4-substituted 2-oxo-3-butenoate esters **2a**,**b** (eq 3), and the optically active Michael adducts **3l**,**m** are formed in high yields and in 82 and 71% ee, respectively.

3-Hydroxy-1*H*-phenalene **1h** reacts with the 4-phenyl-2-oxo-3-butenoate methyl ester **2a** catalyzed by both (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ and (*S*)-Ph-BOX-Cu(OTf)$_2$ (10 mol %), and excellent yields of Michael adduct **3n** can be obtained (eq 4). The former catalyst gave the best yield of **3n** (95%)



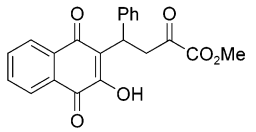
(3)

in CH_2Cl_2 and THF with enantiomeric excesses of 31 and 49%, respectively, and an improvement to 64% ee could be obtained in Et$_2$O; however, only 20% of **3n** was isolated. For the latter catalysts CH_2Cl_2 and THF were the best solvents in terms of yields, as up to 95% was isolated of **3n** having 49% ee, while performing the reaction in Et$_2$O afforded **3n** in 56% yield and 76% ee.

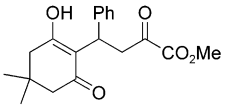


(4)

SCHEME 2



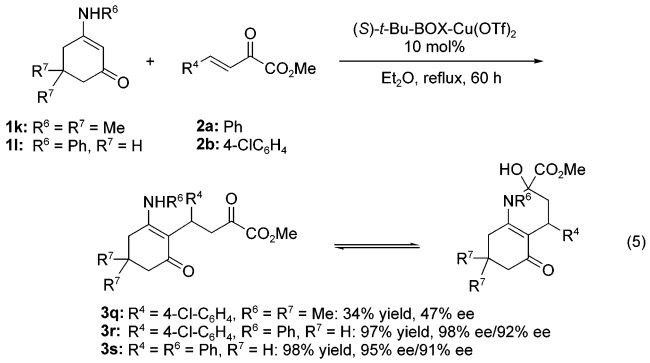
3o
92% yield, 50% ee



3p
85% yield, 45% ee

Several other compounds such as 2-hydroxy-1,4-naphthoquinone **1i** and 5,5-dimethyl-1,3-cyclohexanedione **1j** also react with 4-substituted 2-oxo-3-butenoate esters. Compound **1i** reacted with 4-phenyl-2-oxo-3-butenoate methyl ester **2a** to give the corresponding Michael adduct **3o** in 92% yield and 50% ee using (*S*)-Ph-BOX-Cu(OTf)$_2$ (10 mol %) as the catalyst in CH_2Cl_2. In the same solvent, but using 10 mol % (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ as the catalyst, **1j** reacted with **2a** and the Michael adduct **3p** was formed in 85% yield and 45% ee (Scheme 2).

The present catalytic enantioselective approach can be extended to enamines of 1,3-dicarbonyl compounds. The *N*-methylenamine of 5,5-dimethyl-1,3-cyclohexanedione, **1k**, reacted with 4-(4-chloro-phenyl)-2-oxo-3-butenoate methyl ester **2b** catalyzed by (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol %) very slowly, and only a moderate yield (34%) and enantiomeric excess (47%) of the Michael adduct **3q** were obtained (eq 5). The discouraging results obtained for **1k** prompted us to exchange the *N*-methyl substituent with a *N*-phenyl group, which was expected to be more reactive because conjugation to the phenyl group would stabilize the imine intermediate formed in the reaction. To our delight, it was found that the reaction of the *N*-phenylenamine of 1,3-cyclohexanedione **1l** with **2a** and **2b** catalyzed by (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol %) in Et_2O (eq 5) proceeded in high yield and with excellent enantiomeric excess of **3r** and **3s**. The reactivity of the enamines **1k**,**l** are much lower compared to the 1,3-dicarbonyl compounds, but even though 60 h of reflux was required to obtain full conversion, up to 98% ee was obtained. Similar to the Michael adducts **3a**−**n**, which exist predominantly in their hemiketal form, **3r**,**s** exist as a mixture of slowly equilibrating hemiaminals **3r′**,**s′**. Unlike the hemiketals **3a′**−**n′**, the equilibrium for the hemiaminals **3r′**,**s′** is very slow, and thus the diastereomers could be isolated by column chromatography and kept for several hours in solution before the other diastereomer was observed.



Absolute Configuration and Mechanistic Aspects. The absolute configuration of the Michael adduct **3b** obtained from the reaction of 4-hydroxycoumarin **1a** and 4-(4-chlorophenyl)-2-oxo-3-butenoate methyl ester **2b** using (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ as the catalyst was assigned by X-ray analysis (See Supporting Information). The X-ray crystal structure of **3b** reveals that the absolute configuration of the chiral center formed in the reaction is (*R*). The observed stereochemistry can be rationalized from the transition state model in Figure 1 where it is proposed that the unsaturated 4-substituted 2-oxo-3-butenoate esters **2** coordinate in a bidentate fashion to the Lewis acid.

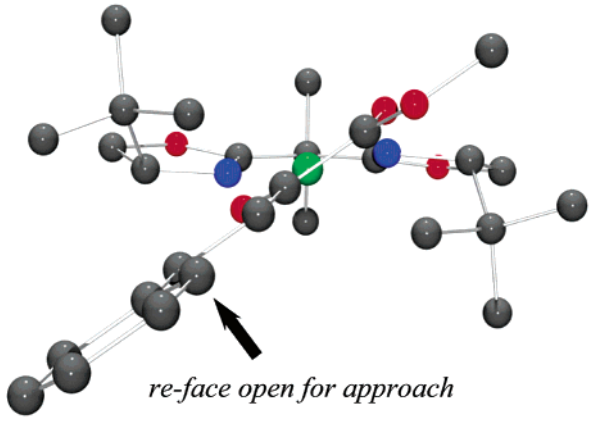


FIGURE 1. Proposed intermediate and approach of the 1,3-dicarbonyl compound in the (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$-catalyzed Michael reaction.

In the transition state model, the *Si*-face of the alkene double bond is shielded by the ligand, leaving the *Re*-face open for attack to afford an (*R*)-configuration at the chiral center formed in the reaction. The observed stereochemistry of the product agrees well with previous conjugate addition reactions to 4-substituted 2-oxo-3-butenoate esters **2** using (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ as the catalyst.[8a] The geometry of the catalyst−substrate complex is proposed to be intermediate between square−planar and tetrahedral as shown in Figure 1 and is in accordance with previous studies of the complex in various reactions.[14]

In summary, we have developed a novel base-free catalytic asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds and enamines catalyzed by chiral bisoxazoline−copper(II) complexes. The addition to a number of unsaturated 4-substituted 2-ketoesters proceeds smoothly using various 1,3-dicarbonyl compounds and quantitative yields, and up to 92% ee was obtained. The reaction was extended to cyclic enamine Michael donors, and these also afforded practically quantitative yields and up to 98% ee. Furthermore, the structure of the products was discussed and an intermediate for the

(10) Equilibrium is sufficiently rapid so that only enantiomers are detected upon CSP-HPLC, and no diastereomers are observed. For equilibrium studies on related compounds, see: (a) Heimark, L. D.; Trager, W. F. *J. Med. Chem.* **1984**, *27*, 1092. (b) Porter, W. R.; Trager, W. F. *J. Heterocycl. Chem.* **1982**, *19*, 475.

(11) (a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (b) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett.* **2002**, *43*, 829.

(12) Li, H.-Y.; Boswell, G. A. *Tetrahedron Lett.* **1996**, *37*, 1551.

(13) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487.

(14) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888.

reaction has been proposed to account for the observed stereochemistry of the products.

Experimental Section

Materials. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], 2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline], methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline], $Cu(OTf)_2$, and $Zn(OTf)_2$ were purchased commercially and used without further purification. 4-Hydroxycoumarins **1a**−**d**, 4-hydroxy-6-methyl-2-pyrone **1g**, dimedone **1l**, 3-hydroxy-1*H*-phenalene **1h**, 5,5-dimethyl-3-methylamino-cyclohex-2-enone **1k**, and 3-phenylamino-cyclohex-2-enone **1l** were also purchased commercially and used as received. 7-Fluoro-4-hydroxycoumarin **1e**[12] and 4-substituted 2-oxo-3-butenoate esters **2a**,**b** were prepared according to reported methods,[13] and 4-substituted 2-oxo-3-butenoate esters **2c**,**d**,**f** were prepared by the same procedure. 2-Oxo-pent-3-enoic acid ethyl ester **2f** was prepared according to literature procedures,[8a] and 4-furan-2-yl-2-oxo-but-3-enoic acid ethyl ester **2e** was prepared by a Wittig reaction as described below.

4-Furan-2-yl-2-oxo-but-3-enoic Acid Ethyl Ester (2e). Ethyl-bromopyruvate (5 g, 0.026 mol) in 25 mL of toluene was stirred with Ph_3P (5.7 g, 0.022 mol) in 50 mL of toluene at ambient temperature overnight. After evaporation of the toluene, the residue was dissolved in 30 mL of MeOH and 1 M Na_2CO_3 was added until pH 10 was reached. The precipitate was filtered, washed several times with water, dissolved in CH_2Cl_2, and dried over Na_2SO_4. After evaporation of the solvent, the phosphine was dissolved in 100 mL of toluene; 2-furaldehyde (2.0 mL, 0.024 mol) was added, and the mixture was refluxed for 3 days. After removal of the solvent, the precipitate was dissolved in CH_2Cl_2 and flushed through silica using CH_2Cl_2 as the eluent to remove Ph_3PO. The compound was recrystallized in EtOH/hexane to afford 1.7 g (40%) of 4-furan-2-yl-2-oxo-but-3-enoic acid ethyl ester **2e** as brown crystals: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.4 Hz, 3H), 4.29 (k, J = 7.4 Hz, 2H), 6.46 (dd, J = 2.0, 3.5 Hz, 1H), 6.75 (d, J = 3.5 Hz, 1H), 7.12 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 62.2, 113.0, 117.7, 118.5, 133.3, 146.2, 150.8, 161.8, 182.1; HRMS (TOF ES$^+$) m/z 217.0487 (M + Na$^+$), calcd for $C_{10}H_{10}O_4Na^+$ 217.0477.

General Procedure for the Catalytic Asymmetric Michael Reaction. To a flame-dried Schlenk tube equipped with a magnetic stirrer were added $Cu(OTf)_2$ (18.1 mg, 0.050 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (16.2 mg, 0.055 mmol). The mixture was stirred under vacuum for 2 h and filled with N_2. Dry, freshly distilled Et_2O (2 mL) was added, and the solution was stirred for 1 h. The 2-oxo-3-butenoate ester (0.5 mmol) was added followed by the addition of the 1,3-dicarbonyl compound. The crude reaction mixture was stirred for the indicated time under N_2 and then purified by FC to give the optically active Michael adduct.

4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3a) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D$ = −20.4° (c = 1.0 g/100 mL, CH_2Cl_2, 84% ee); ^{1}H NMR ($CDCl_3$) δ 2.45 (d, J = 9.0 Hz, 1.34H), 2.55 (dd, J = 14.4, 3.1 Hz, 0.33H), 2.80 (ddd, J = 14.4, 7.4, 1.2 Hz, 0.33H), 3.89 (s, 2.04H), 3.92 (s, 0.96H), 4.2 (t, J = 9.1 Hz, 0.67H), 4.36 (dd, J = 7.4, 3.1 Hz, 0.33H), 4.45 (d, J = 1.6 Hz, 0.33H, OH, position is concentration dependent), 4.65 (s, 0.67H, OH, position is concentration dependent), 7.15−7.34 (m, 7H), 7.48−7.55 (m, 1H), 7.78 (dd, J = 7.8, 1.2 Hz, 0.67H), 7.83 (dd, J = 7.8, 1.6 Hz, 0.33H); ^{13}C NMR ($(CD_3)_2SO$) δ 34.3, 35.2, 38.1, 38.5, 52.5, 53.3, 96.7, 98.1, 102.3, 103.0, 115.0, 116.5, 122.7, 124.4, 126.1, 126.3, 127.3, 127.5, 128.2, 132.4, 141.8, 143.1, 152.3, 152.4, 158.7, 158.9, 160.4, 160.5, 168.1, 168.5; HRMS (TOF ES$^+$) m/z 375.0844 (M + Na$^+$), calcd for $C_{20}H_{16}O_6Na^+$ 375.0845.

4-(4-Chloro-phenyl)-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric Acid Methyl Ester (3b) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a partly hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D$ = −42.3° (c = 1.0 g/100 mL, CH_2Cl_2, 91% ee); repeated recrystallizations in ^{1}H NMR ($CDCl_3$) δ 2.29−2.39 (m, 1.3H), 2.41 (dd, J = 2.7, 14.3 Hz, 0.35H), 2.72 (dd, J = 7.8, 14.3 Hz, 0.35H), 3.84 (s, 1.95H), 3.86 (s, 1.05H), 4.11 (dd, J = 7.4, 11.3 Hz, 0.65H), 4.23 (dd, J = 2.7, 7.8 Hz, 0.35H), 4.52 (s, 0.35H, OH position is concentration dependent), 4.72 (s, 0.65H, OH position is concentration dependent), 7.09−7.31 (m, 6H), 7.45−7.54 (m, 1H), 7.70 (dd, J = 1.1, 7.8 Hz, 0.65H), 7.75 (dd, J = 1.6, 8.2 Hz, 0.35H); ^{13}C NMR ($CDCl_3$) δ 33.1, 34.0, 35.1, 37.8, 53.9, 54.1, 95.3, 95.9, 102.4, 104.3, 114.9, 115.1, 116.5, 116.7, 122.8, 122.9, 123.9, 124.1, 128.3, 128.4, 128.8, 128.9, 132.0, 132.1, 132.2, 132.3, 140.2, 140.8, 152.7, 152,8, 158.2, 158.6, 160.7, 161.6, 168.7, 168.9; HRMS (TOF ES$^+$) m/z 409.0462 (M + Na$^+$), calcd for $C_{20}H_{15}ClO_6Na^+$ 409.0455.

4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-4-(4-methoxy-phenyl)-2-oxo-butyric Acid Methyl Ester (3c) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D$ = −22.6° (c = 1.0 g/100 mL, CH_2Cl_2, 64% ee); ^{1}H NMR ($CDCl_3$) δ 2.44 (d, J = 9.2 Hz, 1.28H), 2.51 (dd, J = 3.1, 14.4 Hz, 0.36H), 2.76 (ddd, J = 1.2, 7.4, 14.4 Hz, 0.36H), 3.76 (s, 1.08H, CH_3), 3.78 (s, 1.92H), 3.89 (s, 1.92H), 3.92 (s, 1.08H), 4.16 (t, J = 9.2 Hz, 0.64H), 4.31 (dd, J = 3.1, 7.4 Hz, 0.36H), 4.50 (d, J = 1.2 Hz, 0.36H, OH position is concentration dependent), 4.68 (s, 0.64H, OH position is concentration dependent), 6.80−6.86 (m, 2H), 7.14−7.19 (m, 2H), 7.25−7.38 (m, 2H), 7.50−7.62 (m, 1H), 7.77 (dd, J = 1.6, 7.8 Hz, 0.64H), 7.83 (dd, J = 1.6, 7.8 Hz, 0.36H); ^{13}C NMR ($CDCl_3$) δ 32.7, 33.7, 35.5, 38.1, 53.9, 54.0, 55.1, 55.2, 95.5, 96.1, 103.0, 105.0, 113.8, 114.1, 115.0, 115.2, 116.5, 116.6, 122.7, 122.8, 123.7, 124.0, 128.0, 128.3, 131.8, 132.0, 133.3, 134.1, 152.7, 152.8, 157.8, 158.2, 158.3, 160.6, 161.6, 168.9; HRMS (TOF ES$^+$) m/z 405.0947 (M + Na$^+$), calcd for $C_{21}H_{18}O_7Na^+$ 405.0950.

4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-p-tolyl-butyric Acid Methyl Ester (3d) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D$ = −20.3° (c = 1.0 g/100 mL, CH_2Cl_2, 78% ee); ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 0.96H), 2.23 (s, 2.04H), 2.35 (d, J = 8.6 Hz, 1.36H), 2.43 (dd, J = 3.5, 14.0 Hz, 0.32H), 2.68 (dd, J = 7.8, 14.0 Hz, 0.32H), 3.75 (s, 2.04H), 3.82 (s, 0.96H), 4.08 (t, J = 8.6 Hz, 0.68H), 4.21 (dd, J = 3.5, 7.8 Hz, 0.32H), 4.58 (s, 0.32H, OH position is concentration dependent), 4.93 (s, 0.68H, OH position is concentration dependent), 6.98−7.08 (m, 4H), 7.13−7.28 (m, 2H), 7.39−7.49 (m, 1H), 7.69 (dd, J = 1.2, 7.8 Hz, 0.68H), 7.75 (dd, J = 1.5, 8.2 Hz, 0.32H); ^{13}C NMR ($CDCl_3$) δ 20.1, 32.2, 33.1, 34.6, 37.2, 52.8, 52.9, 94.5, 95.1, 101.9, 103.9, 114.0, 114.2, 115.5, 115.6, 121.7, 121.9, 122.8, 123.0, 125.9, 126.2, 128.2, 128.4, 130.8, 131.1, 135.2, 135.2, 137.4, 138.2, 151.6, 151.7, 157.0, 157.4, 159.8, 160.7, 168.0; HRMS (TOF ES$^+$) m/z 389.1015 (M + Na$^+$), calcd for $C_{21}H_{18}O_6Na^+$ 389.1001.

4-Furan-2-yl-4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-butyric Acid Ethyl Ester (3e) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers.

The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D = -4.9°$ (c = 1.0 g/100 mL, CH_2Cl_2, 81% ee); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 1.47H), 1.31 (t, J = 7.0 Hz, 1.53H), 2.31 (dd, J = 6.2, 13.6 Hz, 0.49H), 2.53−2.68 (m, 1H), 2.72 (dd, J = 14.0, 2.0 Hz, 1.02H), 4.23−4.37 (m, 3H), 4.68 (s, 0.49H, OH position is concentration dependent), 4.73 (s, 0.51H, OH position is concentration dependent), 6.01 (d, J = 3.1 Hz, 0.51H), 6.15 (d, J = 3.5 Hz, 0.49H), 6.24 (dd, J = 2.0, 3.1 Hz, 0.51H), 6.27 (dd, J = 2.0, 3.5 Hz, 0.49H), 7.18−7.30 (m, 3H), 7.43−7.52 (m, 1H), 7.69 (dd, J = 1.6, 8.2 Hz, 0.49H), 7.73 (dd, J = 1.6, 7.8 Hz, 0.51H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 27.3, 28.3, 31.4, 34.2, 63.5, 63.6, 95.3, 95.5, 100.7, 102.5, 106.1, 106.5, 110.5, 110.7,115.0, 115.2, 116.5, 116.7, 122.8, 123.0, 123.8, 124.1, 132.0, 132.3, 141.2, 141.3, 152.7, 153.4, 153.6, 157.9, 158.2, 160.6, 162.7, 168.2, 168.3; HRMS (TOF ES$^+$) m/z 379.0801 (M + Na$^+$), calcd for $C_{19}H_{16}O_7Na^+$ 379.0794.

4-(6-Chloro-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3f) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA; $[\alpha]^{23}_D = -44.7°$ (c = 1.0 g/100 mL, CH_2Cl_2, 84% ee); ^{1}H NMR ($CDCl_3$) δ 2.46 (d, J = 9.0 Hz, 1.36H), 2.54 (dd, J = 3.4, 14.4 Hz, 0.32H), 2.80 (dd, J = 7.4, 14.4 Hz, 0.32H), 3.92 (s, 2.04H), 3.94 (s, 0.96H), 4.19 (t, J = 9.0 Hz, 0.68H), 4.34 (dd, J = 3.4, 7.4 Hz, 0.32H), 4.51 (s, 0.32H, OH position is concentration dependent), 4.71 (s, 0.68H, OH position is concentration dependent), 7.15−7.39 (m, 6H), 7.48 (dd, J = 2.7, 9.0 Hz, 0.68H), 7.52 (dd, J = 2.3, 8.6 Hz, 0.32H), 7.74 (d, J = 2.3 Hz, 0.68H), 7.79 (d, J = 2.3 Hz, 0.32H); ^{13}C NMR ($CDCl_3$) δ 33.8, 34.5, 35.6, 37.9, 53.9, 95.7, 96.3, 105.6, 116.4, 118.0, 118.1, 122.3, 122.4, 126.8, 127.1, 127.3, 128.4, 128.7, 129.3, 131.8, 132.1, 141.2, 141.8, 151.1, 157.1, 160.3, 168.6; HRMS (TOF ES$^+$) m/z 409.0458 (M + Na$^+$), calcd for $C_{20}H_{15}ClO_6Na^+$ 409.0455.

4-(6,8-Dichloro-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3g) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a partly hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D = -8.2°$ (c = 1.0 g/100 mL, CH_2Cl_2, 72% ee); ^{1}H NMR ($CDCl_3$) δ 2.40 (d, J = 9.0 Hz, 1.40H), 2.46 (dd, J = 3.1, 14.4 Hz, 0.30H), 2.71 (dd, J = 7.4, 14.4 Hz, 0.30H), 3.80 (s, 2.10H), 3.85 (s, 0.90H), 4.12 (dd, J = 7.8, 9.0 Hz, 0.7H), 4.25 (dd, J = 3.1, 7.4 Hz, 0.30H), 4.60 (s, 0.30H, OH position is concentration dependent), 4.92 (s, 0.70H, OH position is concentration dependent), 7.13−7.23 (m, 5H), 7.48 (d, J = 2.3 Hz, 0.70H), 7.53 (d, J = 2.3 Hz, 0.30H), 7.58 (d, J = 2.3 Hz, 0.70H), 7.18 (d, J = 2.3 Hz, 0.30H); ^{13}C NMR ($CDCl_3$) δ 33.8, 34.7, 35.5, 37.9, 54.1, 54.3, 95.9, 96.5, 104.5, 106.5, 117.2, 117.4, 121.0, 121.2, 122.4, 122.6, 126.9, 127.0, 127.2, 127.4, 128.5, 128.8, 129.2, 129.4, 131.9, 132.1, 140.9, 141.5, 147.3, 156.6, 157.1, 159.0, 159.9, 168.6, 168.7; HRMS (TOF ES$^+$) m/z 443.0067 (M + Na$^+$), calcd for $C_{20}H_{14}Cl_2O_6Na$ 443.0065.

4-(4-Hydroxy-7-methoxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3h) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D = +6.4°$ (c = 1.0 g/100 mL, CH_2Cl_2, 91% ee); ^{1}H NMR ($CDCl_3$) δ 2.37 (d, J = 9.0 Hz, 1.32H), 2.46 (dd, J = 3.1, 14.2 Hz, 0.34H), 2.71 (dd, J = 7.3, 14.2 Hz, 0.34H), 3.71 (s, 1.98H), 3.76 (s, 1.98H), 3.78 (s, 1.02H), 3.80 (s, 1.02H), 4.10 (t, J = 9.0 Hz, 0.66H), 4.24 (dd, J = 3.1, 7.3 Hz, 0.34H), 4.42 (s, 0.34H, OH position is concentration dependent), 4.70 (s, 0.66H, OH position is concentration dependent), 6.69−6.78 (m, 2H), 7.09−7.28 (m, 5H), 7.57 (d, J = 9.0 Hz, 0.66H), 7.62 (d, J = 8.6 Hz, 0.34H); ^{13}C NMR ($(CD_3)_2SO$) δ 34.1, 35.0, 38.2, 38.6, 52.4, 53.2, 56.0, 96.6, 97.9, 99.4, 100.1, 100.6, 108.1, 112.4, 123.9, 126.0, 126.2, 127.3, 127.5, 128.1, 142.0, 143.3, 154.3, 159.2, 159.3, 160.7, 160.8, 162.7, 168.2, 168.6; HRMS (TOF ES$^+$) m/z 405.0953 (M + Na$^+$), calcd for $C_{21}H_{18}O_7Na^+$ 405.0950.

4-(7-Fluoro-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3i) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D = -19.3°$ (c = 1.0 g/100 mL, CH_2Cl_2, 91% ee); ^{1}H NMR ($CDCl_3$) δ 2.38 (d, J = 9.0 Hz, 1.40H, 2.47 (d, J = 14.4 Hz, 0.30H), 2.72 (dd, J = 7.0, 14.4 Hz, 0.30H), 3.82 (s, 2.10H), 3.85 (s, 0.90H), 4.11 (t, J = 9.0 Hz, 0.70H), 4.26 (d, J = 7 Hz, 0.30H), 4.44 (s, 0.30H, OH position is concentration dependent), 4.67 (s, 0.70H, OH position is concentration dependent), 6.90−7.03 (m, 2H), 7.15−7.27 (m, 5H), 7.70−7.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 33.4, 34.4, 35.4, 38.0, 53.9, 54.0, 95.4, 96.0, 104.0 (d, J = 25.2 Hz, C−F), 104.1 (d, J = 25.9 Hz, C−F), 111.9 (d, J = 22.8 Hz, C−F), 112.0 (d, J = 39.9 Hz, C−F), 124.5, 124.6, 124.7, 124.8, 126.8, 126.9, 127.0, 127.3, 128.4, 128.7, 141.2, 142.0, 153.9, 154.0, 157.6, 158.1, 160.3, 161.3, 164.5, (d, J = 252.4 Hz, C−F), 164.7 (d, J = 252.4 Hz, C−F), 168.8; HRMS (TOF ES$^+$) m/z 393.0757 (M + Na$^+$), calcd for $C_{20}H_{15}FO_6Na^+$ 393.0750.

4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-pentanoic Acid Methyl Ester (3j) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/2-propanol 97/3 containing 0.3% TFA: $[\alpha]^{23}_D = +12.1°$ (c = 1.0 g/100 mL, CH_2Cl_2, 90% ee); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 1.83H), 1.34 (t, J = 7.0 Hz, 1.17H), 1.43 (t, J = 7.8 Hz, 3H), 2.02−2.12 (m, 1H), 2.21 (dd, J = 6.6, 13.7 Hz, 0.39H), 2.47 (dd, J = 7.4, 13.6 Hz, 0.61H), 3.01−3.10 (m, 1H), 4.28−4.38 (m, 2H), 4.65 (br s, 0.39H, OH position is concentration dependent), 4.77 (br s, 0.61H, OH position is concentration dependent), 7.14−7.28 (m, 2H), 7.41−7.53 (m, 1H), 7.65 (dt, J = 1.6, 9.4 Hz, 0.61H), 7.87 (dd, J = 1.1, 7.8 Hz, 0.39H, minor ds); ^{13}C NMR ($CDCl_3$) δ 13.9, 18.2, 18.8, 22.7, 23.3, 33.0, 36.6, 63.2, 63.3, 95.4, 96.0, 106.0, 106.4, 115.1, 115.3, 116.1, 116.3, 122.5, 122.6, 123.7, 123.8, 131.5, 132.3, 152.1, 152.2, 156.5, 157.1, 161.8, 162.5, 168.7, 169.1; HRMS (TOF ES$^+$) m/z 327.0848 (M + Na$^+$), calcd for $C_{16}H_{16}O_6Na^+$ 327.0845.

4-(7-Fluoro-4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-oxo-pentanoic Acid Methyl Ester (3k) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AS chiral stationary phase in hexane/2-propanol 97/3 containing 0.15% TFA: $[\alpha]^{23}_D = +17.2°$ (c = 1.0 g/100 mL, CH_2Cl_2, 92% ee); ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 1.77H), 1.41 (t, J = 7.0 Hz, 1.23H), 1.48 (dd, J = 7.0, 7.0 Hz, 3H), 2.01−2.24 (m, 1H), 2.26 (dd, J = 6.2, 13.7 Hz, 0.41H, CH), 2.52 (ddd, J = 1.6, 7.0, 13.7 Hz, 0.59H), 3.04−3.12 (m, 1H, CH), 4.31−4.48 (m, 2H), 4.66 (d, J = 1.6 Hz, 0.41H, OH concentration dependent), 4.80 (d, J = 2.0 Hz, 0.59H, OH concentration dependent), 6.87−7.09 (m, 2H), 7.63−7.74 (m, 1H); ^{13}C NMR ($(CD_3)_2SO$) δ 13.9, 17.9, 18.7, 23.2, 23.9, 35.5, 37.0, 62.0, 96.6, 97.6, 103.8, 104.0, 104.4, 112.0, 112.1, 112.4, 124.6, 124.66, 124.7, 124.8, 153.1 (d, CF), 153.2 (d, CF), 156.4, 156.7, 160.7, 160.9, 162.6, 165.1, 168.2, 168.4; HRMS (TOF ES$^+$) m/z 345.0753 (M + Na$^+$), calcd for $C_{16}H_{15}FO_6Na^+$ 345.0750.

4-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-4-phenyl-butyric Acid Methyl Eter (3l) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers.

The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30: ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 2.04H), 2.20 (s, 0.96H), 2.27 (d, J = 8.6 Hz, 1.36H), 2.38 (dd, J = 3.5, 14.4 Hz, 0.32H), 2.61 (dd, J = 7.4, 14.4 Hz, 0.32H), 3.77 (s, 2.04H), 3.81 (s, 0.96H), 3.97 (t, J = 8.6 Hz, 0.68H), 4.12 (br dd, J = 3.5, 7.4 Hz, 0.32H), 4.22 (br s, 0.32H, OH position is concentration dependent), 4.45 (br s, 0.68H, OH position is concentration dependent), 5.75 (d, J = 0.8 Hz, 0.68H), 5.81 (s, 0.32H), 7.12−7.41 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.8, 19.9, 32.4, 33.2, 35.2, 37.8, 53.8, 53.9, 95.2, 95.8, 99.8, 100.3, 100.7, 127.7, 128.0, 128.6, 128.8, 129.0, 129.1, 131.8, 132.0, 140.3, 140.5, 161.7, 162.8, 163.2, 163.4, 163.5, 168.5, 168.7; HRMS (TOF ES$^+$) m/z 339.0847 (M + Na^+), calcd for $C_{17}H_{16}O_6Na^+$ 339.0845.

4-(4-Chloro-phenyl)-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-oxo-butyric Acid Methyl Ester (3m) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 80/20: $[\alpha]^{23}_D$ = +13.6° (c = 1.0 g/100 mL, CH_2Cl_2, 48% ee): ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 1.95H), 2.26 (s, 1.05H), 2.23−2.33 (m, 1.30H), 2.37 (dd, J = 3.1, 14.4 Hz, 0.35H), 2.67 (dd, 7.0, 14.4 Hz, 0.35H), 3.86 (s, 1.95H), 3.89 (s, 1.05H), 4.02 (dd, J = 7.4, 10.9 Hz, 0.65H), 4.14 (dd, 3.1, 7.0 Hz, 0.35), 4.34 (s, 0.35H, OH position is concentration dependent), 4.53 (s, 0.65H, OH position is concentration dependent), 5.80 (d, J = 0.7 Hz, 0.65H, alkene), 5.86 (s, 0.35H), 7.12−7.18 (m, 2H), 7.24−7.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.8, 19.9, 32.4, 33.2, 35.2, 37.8, 53.8, 53.9, 95.2, 95.8, 99.8, 100.3, 100.7, 127.7, 128.0, 128.6, 128.8, 129.0, 129.1, 131.8, 132.0, 140.3, 140.5, 161.7, 162.8, 163.2, 163.4, 163.5, 168.5, 168.7; HRMS (TOF ES$^+$) m/z 373.0449 (M + Na^+), calcd for $C_{17}H_{15}ClO_6Na^+$ 373.0455.

4-(3-Hydroxy-1-oxo-1*H*-phenalen-2-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3n) was isolated as a yellow solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: $[\alpha]^{23}_D$ = +101.0° (c = 1.0 g/100 mL, CH_2Cl_2, 76% ee); ^{1}H NMR ($CDCl_3$) δ 2.49 (d, J = 9.0 Hz, 1.20H), 2.56 (dd, J = 3.1, 14.4 Hz, 0.40H), 2.79 (dd, J = 7.4, 14.4 Hz, 0.40H), 3.83 (s, 1.80H), 3.91 (s, 1.20H), 4.36 (t, J = 9.0 Hz, 0.60H), 4.44 (s, 0.40H, OH position is concentration dependent), 4.55 (dd, J = 3.1, 7.4 Hz, 0.40H), 4.93 (s, 0.60H, OH position is concentration dependent), 7.14−7.32 (m, 5H), 7.54−7.72 (m, 2H), 7.98−8.26 (m, 3H), 8.40 (dd, J = 1.2, 7.4 Hz, 0.60H), 8.54 (dd, J = 1.2, 7.4 Hz, 0.40H); ^{13}C NMR ($CDCl_3$) δ 32.7, 34.5, 35.5, 38.4, 53.7, 53.8, 95.1, 95.8, 114.8, 116.9, 123.7, 124.0, 126.1, 126.2, 126.3.126.4, 126.5, 126.7, 126.8, 127.1, 127.4, 128.1, 128.3, 128.4, 128.5, 129.9, 130.2, 131.5, 131.7, 131.9, 132.2, 134.0, 134.3, 142.8, 144.2, 158.0, 158.5, 169.5, 169.6, 183.3, 183.4; HRMS (TOF ES$^+$) m/z 409.1050 (M + Na^+), calcd for $C_{24}H_{18}O_5Na^+$ 409.1052.

4-(3-Hydroxy-1,4-dioxo-1,4-dihydro-naphthalen-2-yl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3o) was isolated as a yellow solid after FC in CH_2Cl_2/Et_2O and was found to exist in both a hemiketalized form that gives rise to pseudodiastereomers as well as the keto form. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30 containing 0.15% TFA: ^{1}H NMR ($CDCl_3$, 60 °C) δ 2.09 (br s, 0.18H), 2.34−2.51 (m, 1.60H), 2.73 (br dd, J = 7.4, 14.1 Hz, 0.22H), 3.82 (br s, 2.67H), 3.86 (s, 0.33H), 4.15 (br dd, J = 9.4, 18.7 Hz, 0.28H), 4.28 (br t, J = 8.2 Hz, 0.53H), 4.42 (br s, 0.19H), 4.91 (br s, 0.19H), 5.00 (br s, 0.28H, OH), 5.18 (br s, 0.53H), 7.15−7.50 (m, 5H), 7.59−8.12 (m, 4H); HRMS (TOF ES$^+$) m/z 387.0839 (M + Na^+), calcd for $C_{21}H_{16}O_6Na^+$ 387.0845.

4-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3p) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiketalized form that gives rise to pseudodiastereomers. The enantiomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 80/20 containing 0.20% TFA: $[\alpha]^{23}_D$ = −6.4° (c = 1.0 g/100 mL, CH_2Cl_2, 45% ee): ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 1.89H), 1.04 (s, 1.11H), 1.10 (s, 1.89H), 1.13 (s, 1.11H), 2.12−2.52 (m, 6H), 3.65 (s, 1.89H), 3.77 (s, 1.11H), 3.81 (t, J = 9.0 Hz, 0.63H), 4.01 (br s, 0.37H), 4.27 (br s, 0.37H, OH position is concentration dependent), 4.62 (br s, 0.63H, OH position is concentration dependent), 7.02−7.12 (m, 3H), 7.16−7.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.5, 29.0, 29.5, 31.9, 32.2, 32.3, 33.5, 36.4, 38.5, 42.6, 42.7, 51.0, 51.1, 53.7, 53.8, 94.9, 95.8, 112.0, 113.7, 126.0, 126.2, 127.0, 127.2, 128.2, 128.3, 142.9, 143.8, 167.1, 167.7, 169.3, 196.4, 196.9; HRMS (TOF ES$^+$) m/z 353.1367 (M + Na^+), calcd for $C_{19}H_{22}O_5Na^+$ 353.1365.

4-(4,4-Dimethyl-2-methylamino-6-oxo-cyclohex-1-enyl)-2-oxo-4-phenyl-butyric Acid Methyl Ester (3q) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiaminal form that gives rise to pseudodiastereomers. The pseudodiastereomers were separated by FC, and the enantiomers of both diastereomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30: $[\alpha]^{23}_D$ = −17.1° (c = 1.0 g/100 mL, CH_2Cl_2, 47% ee); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 3H), 1.11 (s, 3H), 2.15−2.29 (m, 4H), 2.34 (d, J = 16.8 Hz, 1H), 2.51 (d, J = 16.8 Hz, 1H), 2.79 (s, 3H), 3.27 (s, 1H, OH position is concentration dependent), 3.78 (s, 3H), 4.19 (br t, J = 5.1 Hz, 1H), 7.01−7.05 (m, 2H), 7.11−7.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2, 29.3, 31.9, 32.1, 32.6, 39.8, 40.9, 49.2, 53.7, 85.6, 108.0, 128.2, 128.6, 131.4, 142.1, 158.1, 172.5, 193.6; HRMS (TOF ES$^+$) m/z, 400.1287 (M + Na^+), calcd for $C_{20}H_{24}ClNO_4Na^+$ 400.1292.

4-(4-Chloro-phenyl)-2-oxo-4-(6-oxo-2-phenylamino-cyclohex-1-enyl)-butyric Acid Methyl ester (3r) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiaminal form that gives rise to pseudodiastereomers. The pseudodiastereomers were separated by FC, and the enantiomers of both diastereomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30. **Diastereomer a.** Isolated in 92% ee: $[\alpha]^{23}_D$ = −28.1° (c = 1.0 g/100 mL, CH_2Cl_2, 92% ee); ^{1}H NMR ($CDCl_3$) δ 1.88−1.98 (m, 2H), 2.06−2.15 (m, 1H), 2.21−2.32 (m, 1H), 2.32−2.45 (m, 3H), 2.71 (dd, J = 7.0, 13.9 Hz, 1H), 3.62 (s, 3H), 3.87 (s, 1H, OH position is concentration dependent), 4.35 (br d, J = 7.0 Hz, 1H), 7.03−7.10 (m, 1H), 7.15−7.28 (m, 4H), 7.32−7.41 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.7, 29.0, 31.0, 36.4, 38.8, 53.4, 85.2, 109.4, 128.1, 128.7, 128.8, 129.0, 129.4, 129.6, 131.1, 131.3, 139.2, 142.5, 158.7, 171.8, 195.0; HRMS m/z 434.1132 (M + Na^+), calcd for $C_{23}H_{22}ClNO_4Na^+$ 434.1135. **Diastereomer b.** Isolated in 98% ee: $[\alpha]^{23}_D$ = −64.0° (c = 1.0 g/100 mL, CH_2Cl_2, 98% ee): ^{1}H NMR ($CDCl_3$) δ 1.75−1.93 (m, 3H), 2.04−2.15 (m, 3H), 2.19−2.26 (m, 1H), 2.33 (t, J = 12.3 Hz, 1H), 3.43 (s, 3H, CH_3), 3.99 (br dd, J = 6.2, 12.3), 4.44 (s, 1H, OH position is concentration dependent), 7.11−7.19 (m, 5H), 7.25−7.28 (m, 1H), 7.30−7.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.2, 29.5, 34.2, 36.4, 41.9, 53.2, 84.7, 112.2, 128.3, 128.3, 128.8, 129.0, 129.4, 130.1, 130.7, 131.0, 139.5, 144.3, 159.2, 171.4, 194.4; HRMS (TOF ES$^+$) m/z 434.1136, calcd for $C_{23}H_{22}ClNO_4Na^+$ 434.1135.

2-Oxo-4-(6-oxo-2-phenylamino-cyclohex-1-enyl)-4-phenyl-butyric Acid Methyl Ester (3s) was isolated as a colorless solid after FC in CH_2Cl_2/Et_2O and was found to exist in a hemiaminal form that gives rise to pseudodiastereomers. The pseudodiastereomers were separated by FC, and the enantiomers of both diastereomers were separated by HPLC using a Chiralpak AD chiral stationary phase in hexane/2-propanol 70/30. **Diastereomer a.** Isolated in 91% ee: $[\alpha]^{23}_D$ = −7.1° (c = 1.0 g/100 mL, CH_2Cl_2, 91% ee); ^{1}H NMR ($CDCl_3$) δ 1.82−1.94 (m, 2H), 2.01−2.08 (m, 1H), 2.15−2.41 (m, 3H), 2.43 (dd, J = 2.7, 13.7 Hz, 1H), 2.68 (dd, J = 7.0, 13.7 Hz, 1H), 3.52 (s, 3H), 3.58 (s, 1H, OH position is concentration dependent), 4.37 (br d, J = 7.0 Hz, 1H), 6.98−7.02 (m, 1H),

7.08−7.14 (m, 1H), 7.20−7.24 (m, 4H), 7.26−7.34 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.7, 29.0, 32.0, 36.4, 39.0, 53.2, 85.5, 109.5, 126.0, 127.2, 128.2, 128.7, 128.9, 129.4, 129.7, 131.2, 139.4, 143.3, 158.4, 171.6, 195.0; HRMS *m*/*z* 400.1532 (M + Na^+), calcd for $C_{23}H_{23}NO_4Na^+$ 400.1525. **Diastereomer b.** Isolated in 95% ee: $[\alpha]^{23}_D = -47.2°$ (*c* = 1.0 g/100 mL, CH_2Cl_2, 95% ee); ^{1}H NMR ($CDCl_3$) δ 1.75−1.94 (m, 3H), 2.04−2.29 (m, 4H), 2.39 (t, *J* = 12.7 Hz, 1H), 3.42 (s, 3H), 4.02 (br dd, *J* = 6.6, 11.7 Hz, 1H), 4.28 (s, 1H, OH position is concentration dependent), 7.07−7.11 (m, 1H), 7.11−7.16 (m, 1H), 7.18−7.24 (m, 4H), 7.26−7.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.2, 29.4, 34.4, 36.2, 41.8, 52.8, 84.8, 111.8, 125.4, 126.9, 128.0, 128.5, 128.8, 129.1, 130.1, 130.8, 149.6, 145.5, 159.1, 171.2, 194.5; HRMS (TOF ES$^+$) *m*/*z* 400.1526 (M + Na^+), calcd for $C_{23}H_{23}NO_4Na^+$ 400.1525.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation. Thanks are expressed to Dr. Rita G. Hazell for solving the X-ray structure of **3b**.

Supporting Information Available: Complete X-ray data for compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0343026