CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700420

Enantiomer-Selective Carbamoylation of Racemic α-Hydroxy γ-Lactones with Chiral Cu^{II} Catalysts: An Example of a Highly Active Lewis Acid Catalyzed Reaction

Nobuhito Kurono,[a] Tadahiro Kondo,[a] Masanori Wakabayashi,[a] Hirohito Ooka,[a, b] Tsutomu Inoue,[b] Hiroto Tachikawa,[c] and Takeshi Ohkuma*[a]

Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: Enantiomer-selective carbamoylation of racemic α-hydroxy γ-lactones with half equivalents of isocyanates in the presence of chiral Cu^{II} catalysts was studied. Among a series of catalyst bearing chiral bis(oxazoline) (box) and pyridine(bisoxazoline) ligands, [Cu(*t*Bu-box)]X_2 [X = OSO_2CF_3 (**3a**), SbF_6 (**3b**)] showed the highest enantioselectivity in the reaction of pantolactone (**1a**). Use of *n*-C_3H_7NCO, a small alkyl isocyanate, in CH_2Cl_2 solution was important to achieve a high level of enantiomer selection. The *t*Bu-box-Cu^{II} catalyst efficiently differentiated two enantiomers of β-substituted α-hydroxy γ-lactones under the optimized reaction conditions, resulting in a stereoselectivity factor ($s = k_{fast}/k_{slow}$) of up to 209. Furthermore, this catalyst is highly active, so that the carbamoylation can be conducted with a substrate-to-catalyst molar ratio of 2000–3000. A catalytic cycle of this reaction is also proposed.

Keywords: asymmetric catalysis · copper · kinetic resolution · Lewis acids · lactones

Introduction

Asymmetric reactions catalyzed by chiral Lewis acids have provided a wide variety of optically active compounds.[1] Well-organized chiral environments of these catalysts enable one to create optically pure molecules. Compared with the great success of these catalytic reactions on the enantioselectivity, the number of catalyst turnovers or the catalyst lifetime of many reactions seems to be unsatisfactory. The substrate-to-catalyst molar ratio (S/C) is usually less than 100 for completion of reactions within a reasonable period[1] because many Lewis acid catalysts have inherent drawbacks such as high sensitivity to moisture and tendency towards undergoing inhibition by the products. Thus, we propose here four criteria for achieving high reactivity and enantioselectivity in the Lewis acid catalyzed reactions: 1) use of moisture-robust late-transition-metal catalysts for achieving a long life span; 2) choice of well-designed chiral ligands preferably with C_2 symmetry for predicting the stereochemistry of the products; 3) use of substrates to form a rigid chelate intermediate (and/or transition state) with a center metal of the catalyst for achieving efficient enantioselection; and 4) selection of a type of reaction that will form products with only weak binding affinity for the catalyst, thereby avoiding product inhibition. According to these criteria, we planned a kinetic resolution of racemic α-hydroxy lactones by enantiomer-selective carbamoylation with bis(oxazoline)-Cu^{II} (box-Cu^{II}) catalysts, which show high enantioselectivity in a wide range of asymmetric reactions.[2,3]

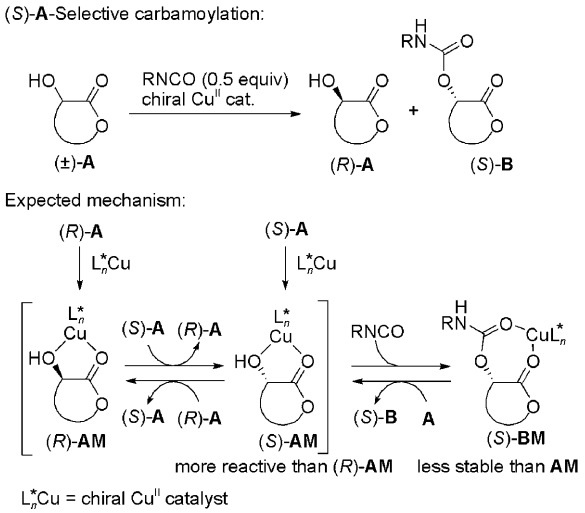
Our scenario for enantiomer-selective carbamoylation of α-hydroxy lactones is depicted in Scheme 1. The *S*-enantiomer-selective reaction is exemplified. Some nonproductive

[a] Dr. N. Kurono, T. Kondo, M. Wakabayashi, H. Ooka, Prof. Dr. T. Ohkuma
Division of Chemical Process Engineering
Graduate School of Engineering
Hokkaido University
Sapporo 060-8628 (Japan)
Fax: (+81) 11-706-6598
E-mail: ohkuma@eng.hokudai.ac.jp

[b] H. Ooka, Dr. T. Inoue
Odawara Research Center
Nippon Soda Co., Ltd.
345 Takada, Odawara 250-0280 (Japan)

[c] Dr. H. Tachikawa
Division of Materials Chemistry
Graduate School of Engineering
Hokkaido University
Sapporo 060-8628 (Japan)

Supporting information for this article is available on the WWW under http://www.chemasianj.org or from the author.



Scheme 1. Enantiomer-selective carbamoylation and expected mechanism.

or minor pathways are omitted for clarity. When a racemic α-hydroxy lactone, (±)-**A**, is mixed with 0.5 equiv of alkylisocyanate, RNCO, in the presence of a chiral box-Cu^{II} catalyst, the unreacted (*R*)-**A** and the *S* carbamate, (*S*)-**B**, are selectively obtained. (*R*)-**A** and (*S*)-**A** with the box-Cu^{II} catalyst form diastereomeric chelate complexes, (*R*)-**AM** and (*S*)-**AM**, respectively. The two diastereomers are in equilibrium. (*S*)-**AM** is more reactive with RNCO than (*R*)-**AM** to give the (*S*)-**B**-Cu^{II} complex, (*S*)-**BM**, selectively. The seven-membered chelate complex, (*S*)-**BM**, is less stable than the five-membered chelate complexes, (*R*)- and (*S*)-**AM**, so that (*S*)-**BM** is easily converted into **AM** with release of the product (*S*)-**B**.

Recently, Matsumura and co-workers reported asymmetric carbamoylation of *meso* 1,2-diols using C_6H_5NCO to the optically active hydroxy carbamates with a Ph-box-Cu^{II} catalyst.[4,5] The reactions were conducted with an S/C ratio of 10 in THF at −40 °C to give the chiral products in up to 93 % *ee*. We describe here our studies on the asymmetric carbamoylation of α-hydroxy γ-lactones in detail. The features are different from Matsumura's desymmetrization of *meso* 1,2-diols. The reactions can be conducted with an S/C ratio of 2000–3000, achieving a stereoselectivity factor ($s = k_{fast}/k_{slow}$)[6,7] of up to 209.

Abstract in Japanese:

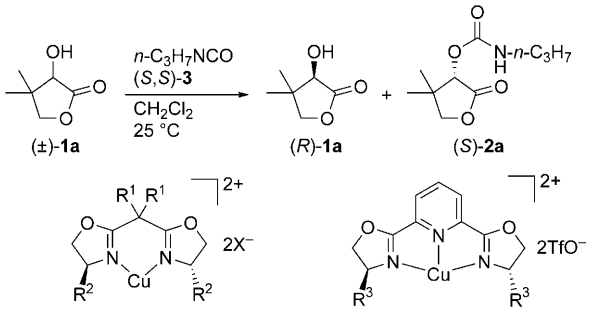
光学活性銅錯体触媒によるラセミ体α-ヒドロキシγ-ラクトン類のエナンチオマー選択的カルバモイル化反応の検討を行った結果、[Cu(*t*Bu-box)]X_2 [X = OSO_2CF_3 (**3a**), SbF_6 (**3b**)]が優れた触媒機能を示すことを見出した。ジクロロメタン溶媒中、基質に対して 0.5 当量の *n*-C_3H_7NCO を作用させることで、効率的な速度論分割を達成した。基質の両エナンチオマーの反応速度比 ($s = k_{fast}/k_{slow}$) は最高 209 に達した。触媒活性も非常に高く、基質/触媒比 2000–3000 で反応させることができた。

Results and Discussion

Screening of Chiral Cu^{II} Catalysts

We first selected the enantiomer-selective carbamoylation of racemic pantolactone [(±)-**1a**][8,9] with *n*-C_3H_7NCO (0.5 equiv to **1a**) to find a chiral Cu^{II} catalyst that showed sufficiently high activity and enantiomer discrimination ability. Optically active pantolactone[10] is a key intermediate for synthesizing biologically active pantothenic acid and its derivatives,[8,11] as well as other naturally occurring compounds.[12] It is also utilized as an efficient chiral auxiliary for many stereoselective transformations.[10,13] The chiral Cu^{II} complexes **3** shown in Table 1 were freshly prepared

Table 1. Carbamoylation of racemic pantolactone [(±)-**1a**] with chiral Cu^{II} catalysts **3**.[a]



(*S*,*S*)-**3a**: $R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$, X = TfO
(*S*,*S*)-**3b**: $R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$, X = SbF_6
(*S*,*S*)-**3c**: $R^1 = CH_3$, $R^2 = i\text{-}C_3H_7$, X = TfO
(*S*,*S*)-**3d**: $R^1 = CH_3$, $R^2 = CH_3$, X = TfO
(*S*,*S*)-**3e**: $R^1 = CH_3$, $R^2 = C_6H_5$, X = TfO
(*S*,*S*)-**3f**: $R^1 = C_2H_5$, $R^2 = t\text{-}C_4H_9$, X = TfO
(*S*,*S*)-**3g**: $R^1 = C_2H_5$, $R^2 = i\text{-}C_3H_7$, X = TfO
(*S*,*S*)-**3h**: $R^1 = C_2H_5$, $R^2 = C_6H_5$, X = TfO
(*S*,*S*)-**3i**: $R^1 = n\text{-}C_3H_7$, $R^2 = t\text{-}C_4H_9$, X = TfO
(*S*,*S*)-**3j**: $R^3 = t\text{-}C_4H_9$
(*S*,*S*)-**3k**: $R^3 = C_6H_5$

3	ee_{1a} [%][b]	ee_{2a} [%][b]	Conv. [%][c]	s[d]
3a	90.9	90.4	50.1	62
3b	86.8	91.5	48.7	64
3c	64.2	86.9	42.5	28
3d	48.5	83.4	36.8	18
3e	32.8	77.0	29.8	11
3f	84.5	89.0	48.7	46
3g	76.3	87.4	46.6	34
3h	54.2	76.6	41.4	13
3i	89.1	87.5	50.5	45
3j	1.1	6.7	14.1	1
3k	2.0[e]	8.1[e]	19.8	1

[a] Reactions were conducted using (±)-**1a** (5.0 mmol) and *n*-C_3H_7NCO (2.5 mmol) in CH_2Cl_2 (10 mL) containing (*S*,*S*)-**3** with an S/C ratio of 2000 at 25 °C for 1 h. [b] Determined by chiral GC analysis. [c] Conv. = $ee_{1a}/(ee_{1a}+ee_{2a})$. [d] $s = \ln[(1-\text{conv.})(1-ee_{1a})]/\ln[(1-\text{conv.})(1+ee_{1a})]$. [e] (*S*)-**1a** and (*R*)-**2a** were the major compounds.

before use according to the procedure reported by Evans et al.[14] with slight modifications. The chiral ligand (26.5 mmol) and $Cu(OTf)_2$ (24 mmol) were dissolved in THF (2 mL). The solution was stirred at ambient temperature for 10 min, and then THF was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), and

insoluble contents were removed by filtration with a membrane filter. The obtained clear solution was used as a catalyst solution (see the Experimental Section). The carbamoylation was carried out with an S/C ratio of 2000 in CH_2Cl_2 at 25 °C for 1 h. The results are listed in Table 1. High reactivity and enantioselectivity were achieved in the reaction using [Cu{(*S*,*S*)-*t*Bu-box}](OTf)$_2$ ($TfO^- =$ trifluoromethanesulfonate) [(*S*,*S*)-**3a**] as a catalyst. The isocyanate was consumed (50.1 % conversion) to afford unreacted (*R*)-**1a** in 90.9 % *ee* and the *S* carbamate, (*S*)-**2a**, in 90.4 % *ee*. The *s* value was calculated to be 62. [Cu(*t*Bu-box)](SbF$_6$)$_2$ (**3b**)[14] showed a comparable efficiency, suggesting that the counteranion has virtually no influence on the catalytic performance.[15] Thus, we used the triflate complex for further screening because of the operational simplicity. When box-Cu^{II} catalysts, **3c**–**3e**, bearing smaller R^2 groups (*i*-C_3H_7, CH_3, and C_6H_5) on the oxazoline ring, were employed, the enantiomer selectivity was decreased. This tendency in the enantioselectivity was also observed in a series of reactions with **3f** ($R^1 =$ C_2H_5, $R^2 =$ *t*-C_4H_9), **3g** ($R^1 = C_2H_5$, $R^2 =$ *i*-C_3H_7), and **3h** ($R^1 = C_2H_5$, $R^2 = C_6H_5$). The alkyl substituent R^1 at the spacer carbon atom also influenced the *s* value. Complex **3a** ($R^1 = CH_3$, $R^2 =$ *t*-C_4H_9) showed better selectivity than **3f** ($R^1 = C_2H_5$, $R^2 =$ *t*-C_4H_9) and **3i** ($R^1 =$ *n*-C_3H_7, $R^2 =$ *t*-C_4H_9). The pyridine(bisoxazoline)-Cu^{II} catalysts,[15–17] **3j** and **3k**, negligibly differentiated two enantiomers of **1a** with relatively low activity.

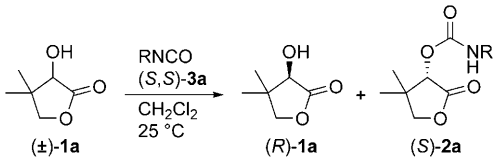
Effect of the Isocyanate Structure

We next surveyed the effect of the isocyanate structure on the catalytic activity and enantioselectivity. Five characteristic and commercially available reagents, *n*-C_3H_7NCO, $C_6H_5CH_2NCO$, *cyclo*-$C_6H_{11}NCO$, *t*-C_4H_9NCO, and C_6H_5NCO, were selected. The more volatile and irritant CH_3NCO and C_2H_5NCO were excluded. As shown in Table 2, the highest enantioselectivity ($s = 62$) was obtained by the use of *n*-C_3H_7NCO (catalyst: **3a**, S/C = 2000; solvent: CH_2Cl_2, 25 °C, 1 h). More bulky alkyl isocyanates (R = $C_6H_5CH_2$, *cyclo*-C_6H_{11}) caused lower stereoselectivity. The reaction with *t*-C_4H_9NCO showed the worst selectivity and reactivity. Use of an aromatic isocyanate, C_6H_5NCO, gave good reactivity and enantioselectivity ($s = 43$). The small alkyl isocyanate **3a** is preferable for this transformation.

Optimization of Reaction Conditions

Screening experiments of catalysts and isocyanate structures revealed that the *t*Bu-box-Cu^{II} complex **3a** exhibits excellent catalytic activity (S/C = 2000) and enantiomer selectivity ($s =$ 62) in the reaction of (±)-**1a** and *n*-C_3H_7NCO in CH_2Cl_2 at 25 °C (Table 3, entry 1). When the carbamoylation was conducted at 0 °C, a higher *s* value of 95 was attained, while it took 4 h to reach 50 % conversion (Table 3, entry 2). The *s* value decreased to 53 in the reaction with an S/C of 3000 (Table 3, entry 3). Employment of a solvent other than CH_2Cl_2 resulted in a decline in the enantiomer selectivity

Table 2. Effect of isocyanate structure in carbamoylation of racemic pantolactone [(±)-**1a**] with chiral Cu^{II} catalyst **3a**.[a]

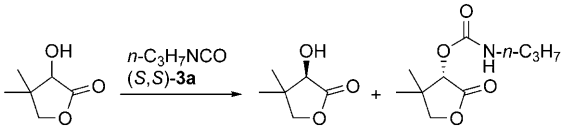


(*S*)-**2a**: R = *n*-C_3H_7
(*S*)-**2aa**: R = $CH_2C_6H_5$
(*S*)-**2ab**: R = *cyclo*-C_6H_{11}
(*S*)-**2ac**: R = *t*-C_4H_9
(*S*)-**2ad**: R = C_6H_5

R	ee_{1a} [%][b]	ee_{2a} [%][b]	Conv. [%][c]	s[c]
n-C_3H_7	90.9	90.4	50.1	62
$C_6H_5CH_2$	62.8	85.9	42.2	25
cyclo-C_6H_{11}	71.7	87.4	45.1	32
t-C_4H_9	32.1	75.6	29.8	10
C_6H_5	88.1	87.5	50.2	43

[a] Reactions were conducted using (±)-**1a** (5.0 mmol) and RNCO (2.5 mmol) in CH_2Cl_2 (10 mL) containing (*S*,*S*)-**3a** with an S/C ratio of 2000 at 25 °C for 1 h. [b] Determined by chiral GC and/or HPLC analysis. [c] See footnotes of Table 1.

Table 3. Carbamoylation of racemic pantolactone [(±)-**1a**] with chiral Cu^{II} catalyst **3a**: optimization of reaction conditions.[a]



Entry	Solvent	T [°C]	t [h]	S/C[b]	ee_{1a} [%][c]	ee_{2a} [%][c]	Conv. [%][d]	s[d]
1	CH_2Cl_2	25	1	2000	90.9	90.4	50.1	62
2	CH_2Cl_2	0	4	2000	93.3	93.0	50.1	95
3	CH_2Cl_2	0	12	3000	86.4	90.0	49.0	53
4	$CHCl_3$	25	1	2000	61.2	83.5	42.4	21
5	$(C_2H_5)_2O$	25	1	2000	63.4	85.2	42.7	24
6	THF	25	1	2000	76.4	85.4	47.2	29
7	DME	25	1	2000	65.1	81.9	44.3	20
8	toluene	25	1	2000	0.3	5.7	4.3	1
9	$CH_3CO_2C_2H_5$	25	1	2000	48.2	85.0	36.2	20
10	CH_3CN	25	1	2000	60.9	87.8	41.0	29

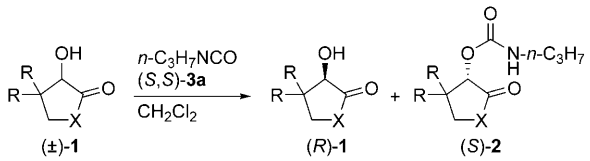
[a] Reactions were conducted using (±)-**1a** (5.0 mmol) and *n*-C_3H_7NCO (2.5 mmol) in solvent (10 mL) containing (*S*,*S*)-**3a**. [b] Substrate/catalyst molar ratio. [c] Determined by chiral GC analysis. [d] See footnotes of Table 1.

(Table 3, entries 4–10). Interestingly, various types of solvents, such as $CHCl_3$, ethers, ethyl acetate, and acetonitrile, resulted in an *s* value in the range of 20–29. The low conversion of the reaction in toluene was caused by the limited solubility of the catalyst (Table 3, entry 8).

Scope of the Reaction

Carbamoylation of racemic β,β-disubstituted α-hydroxy γ-lactones, (±)-**1a**–**e**, with a half equivalent of *n*-C_3H_7NCO in CH_2Cl_2 in the presence of (*S*,*S*)-**3a** at an S/C ratio of 2000 was examined (Table 4). As described above, reaction of

Table 4. Carbamoylation of racemic α-hydroxy carbonyl compounds (±)-**1** with chiral Cu^{II} catalyst **3a**.[a]



a: R = CH_3, X = O **d**: R–R = $(CH_2)_4$, X = O
b: R = C_2H_5, X = O **e**: R = H, X = O
c: R = C_6H_5, X = O **f**: R = CH_3, X = NH

Substrate **1**	*T* [°C]	*t* [h]	ee_1 [%][b]	ee_2 [%][b]	Conv. [%][c]	*s*[c]
1a	25	1	90.9	90.4	50.1	62
1a	0	4	93.3	93.0	50.1	95
1b	25	1	83.4	93.0	47.3	72
1b	0	4	85.2	95.4	45.5	114
1c	25	9	92.7	94.1	49.6	113
1d	0	4	96.7	93.3	50.9	119
1e	0	4	36.2	41.3	46.7	3
1f[d]	25	6	24.3	40.8	37.3	3

[a] Unless otherwise stated, reactions were conducted using (±)-**1** (5.0 mmol) and *n*-C_3H_7NCO (2.5 mmol) in CH_2Cl_2 (10 mL) containing (*S*,*S*)-**3a** with an S/C ratio of 2000. [b] Determined by chiral GC or HPLC analysis. [c] See footnotes of Table 1. [d] This reaction was conducted with **1f** (2.0 mmol) and *n*-C_3H_7NCO (1.0 mmol) in CH_2Cl_2 (16 mL).

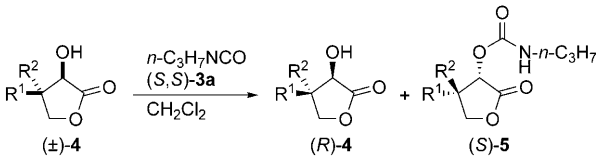
(±)-**1a** (R = CH_3) selectively gave (*S*)-**2a**, leaving unreacted (*R*)-**1a**. The *s* values were 62 at 25 °C and 95 at 0 °C. The reaction of β,β-diethyl substrate **1b** gave even better selectivity (*s* = 72 at 25 °C, 114 at 0 °C) without loss of reactivity. Sterically more hindered **1c** (R = C_6H_5) achieved an *s* value of 113 at 25 °C, while the reaction rate was slowed down. The low solubility of **1c** in CH_2Cl_2 did not allow the reaction at 0 °C. The spiro compound **1d** reacted in the same way (*s* = 119 at 0 °C). The bulkiness around the β position of substrates is crucially important to achieve high enantiomer selectivity. Thus, the two enantiomers of simple α-hydroxy γ-lactone **1e** (R = H) were hardly differentiated by the Cu catalyst **3a**. Racemic pantolactam (R = CH_3, X = NH) [(±)-**1f**] is a difficult substrate for differentiating two enantiomers by this carbamoylation. The *s* value at 25 °C was only 3.

Compound (*R*)-**1a** in greater than 99 % *ee* became available when (±)-**1a** was treated with 0.55 equiv of *n*-C_3H_7NCO in the presence of (*S*,*S*)-**3a** (S/C = 2000, 0 °C, 22 h, 54.0 % conversion). The crude mixture was filtered through a silica-gel pad to remove Cu contents followed by a short-path distillation under reduced pressure to give (*R*)-**1a** in 99.6 % *ee* (99 % chemical purity determined by GC analysis; see the Experimental Section).

Reaction with Diastereomeric Compounds

We next examined the carbamoylation of *cis*- and *trans*-α-hydroxy β-phenyl γ-lactones, (±)-*cis*-**4** and (±)-*trans*-**4**, to reveal the influence of each *cis* and *trans* β substituent on the enantioselectivity. When (±)-*cis*-**4** was treated with *n*-C_3H_7NCO in the presence of (*S*,*S*)-**3a** at 23 °C, unreacted (*R*)-*cis*-**4** in 93.3 % *ee* and (*S*)-*cis*-**5** in 87.1 % *ee* were obtained with 51.6 % conversion (Table 5). The *s* value was calculated to be 50. The enantiomer selectivity was notably increased in the reaction at 0 °C. Thus, the isocyanate was consumed within 2 h (S/C = 2000), resulting in an *s* value of 209. On the other hand, the carbamoylation of (±)-*trans*-**4** with (*S*,*S*)-**3a** at 23 °C resulted in an *s* value of only 3 with much lower reactivity than that of the reaction with (±)-*cis*-**4**. No increment of the enantiomer selectivity was observed under lower-temperature conditions. These results clearly show that the *t*Bu-box-Cu^{II} catalyst **3a** recognizes the *cis*-β substituent of **1a**–**1e** and **4** in the enantiomer discrimination.

Table 5. Carbamoylation of racemic α-hydroxylactones (±)-**4** with chiral Cu^{II} catalyst **3a**.[a]



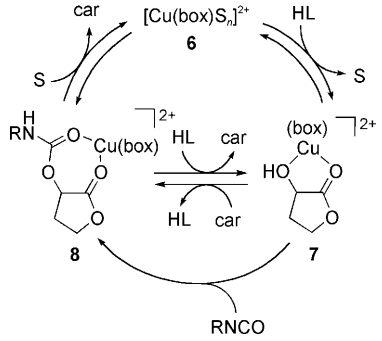
cis: R^1 = C_6H_5, R^2 = H
trans: R^1 = H, R^2 = C_6H_5

Substrate **4**	*T* [°C]	*t* [h]	ee_1 [%][b]	ee_2 [%][b]	Conv. [%][c]	*s*[c]
cis-**4**	23	1	93.3	87.1	51.6	50
cis-**4**	0	2	96.0	96.3	49.9	209
trans-**4**	23	7	31.5	36.5	46.3	3
trans-**4**	0	16	18.3	20.1	47.4	2

[a] Reactions were conducted using (±)-**4** (1.0 mmol) and *n*-C_3H_7NCO (0.50 mmol) in CH_2Cl_2 (2.0 mL) containing (*S*,*S*)-**3a** with an S/C ratio of 2000. [b] Determined by chiral HPLC analysis. [c] See footnotes of Table 1.

Plausible Reaction Mechanism

Our proposed mechanism for the carbamoylation of α-hydroxy γ-lactones catalyzed by box-Cu^{II} complexes is shown in Scheme 2. [Cu(box)]X_2 (**3**; X = OTf, SbF_6) liberates the counteranion, X^-, to be the solvated cationic species [Cu(box)S_n]$^{2+}$ (**6**; S = solvent) in the reaction mixture. The weakly binding solvent molecules (S) are replaced by an α-



Scheme 2. Proposed mechanism for Cu^{II}-catalyzed carbamoylation of α-hydroxy γ-lactones (HL = α-hydroxy lactone, car = carbamate, S = solvent).

hydroxy lactone (HL) to form a chelation complex **7**. The species **7** reacts with RNCO to afford the carbamate-Cu^{II} (car-Cu^{II}) complex **8**. Catalytic species **6** and/or **7** are regenerated with release of the carbamate. Three cationic species **6**, **7**, and **8** could be in equilibrium. The HL-Cu^{II} species **7** with a rigid bicyclo[3.3.0] structure is much more stable than the solvated complex **6** and the car-Cu^{II} complex **8** with a bicyclo[5.3.0] structure, so that this reaction proceeds without serious product inhibition.

No clear spectroscopic data to determine the structures of the HL-Cu^{II} intermediates **7** in Scheme 2 was available. Therefore, we estimated the optimized structures of two diastereomeric species, (*R*)-HL/(*S*,*S*)-*t*Bu-box-Cu^{II} [(*R*/*S*,*S*)-**7**] and (*S*)-HL/(*S*,*S*)-*t*Bu-box-Cu^{II} [(*S*/*S*,*S*)-**7**], by calculation at the B3LYP/LANL2DZ level.[18] The obtained structures are shown in Figure 1. Both species, (*R*/*S*,*S*)-**7** and (*S*/*S*,*S*)-**7**, have highly distorted square-planar structures, of which the dihedral angles are (O1-Cu-N1-C1 35°, O2-Cu-N2-C2 35°) and (O1-Cu-N1-C1 31°, O2-Cu-N2-C2 31°), respectively.[19] As shown in Table 6, the difference of total energy between

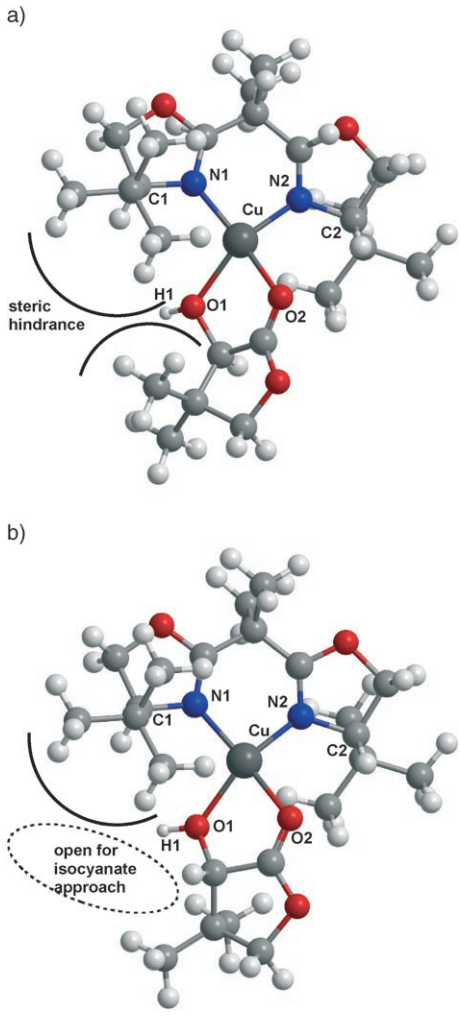


Figure 1. Calculated diastereomeric intermediates, (*R*/*S*,*S*)-**7** (a) and (*S*/*S*,*S*)-**7** (b). Dihedral angles: (*R*/*S*,*S*)-**7**; O1-Cu-N1-C1 35°, O2-Cu-N2-C2 35°. (*S*/*S*,*S*)-**7**; O1-Cu-N1-C1 31°, O2-Cu-N2-C2 31°.

Table 6. Natural atomic charges, and total and relative energies of intermediates (*R*/*S*,*S*)-**7** and (*S*/*S*,*S*)-**7** calculated at the B3LYP/LANL2DZ level.

Atom	(*R*/*S*,*S*)-**7**	(*S*/*S*,*S*)-**7**
O1	−0.86	−0.86
H1	+0.55	+0.55
Cu	+1.38	+1.38
O2	−0.70	−0.70
Total energy [a.u.]	−1581.64378	−1581.64342
Relative energy [kcal mol^{-1}]	0.0	0.2

these two species is only 0.2 kcal mol^{-1}, suggesting that the enantiomer selectivity in this reaction is kinetically determined at the irreversible step **7**→**8** (Scheme 2). The electrophilic RNCO could approach the lone-pair orbital of the hydroxy oxygen atom (O1) from the side opposite the hydroxy proton (H1) that is, from the upper side of **7**. The RNCO molecule may be activated by the Lewis acidic Cu species.[20] Compound (*S*/*S*,*S*)-**7** is much more reactive than the diastereomeric (*R*/*S*,*S*)-**7** because the approach of RNCO to (*R*/*S*,*S*)-**7** is blocked by the *tert*-butyl group of the box ligand and the β-CH_3 moiety connects *cis* to the hydroxy group of the substrate. This view is consistent with the observation that the reaction of *cis*-α-hydroxy β-phenyl γ-lactones, (±)-*cis*-**4**, catalyzed by **3a** showed much higher enantioselectivity than the reaction of (±)-*trans*-**4** (Table 5).

Conclusions

The *t*Bu-box-Cu^{II} complex performs high catalytic activity and enantiomer selectivity in the carbamoylation of racemic α-hydroxy γ-lactones. The reaction is conducted with an S/C ratio of 2000–3000 to achieve an *s* value of up to 209 under the optimized conditions. A reaction mechanism is proposed according to the experimental data and a computational analysis. These results demonstrate that our proposed four criteria for achieving high efficiency in the Lewis acid catalyzed reactions are useful, that is, 1) use of late-transition-metal catalysts, 2) choice of well-designed chiral ligands, 3) use of substrates to form a rigid chelate intermediate, and 4) selection of a reaction that will form products that bind only weakly to the catalyst. We hope these criteria will help in the development of new and efficient asymmetric Lewis acid catalyzed reactions.

Experimental Section

General

Gas chromatographic (GC) analysis was conducted on a Shimadzu GC-17A or Shimadzu GC-2010 instrument with a CP-Chirasil-Dex column (chiral; 0.32 mm inner diameter × 25 m, df = 0.25 μm, VARIAN) using helium carrier gas (72 kPa) with a split ratio of 45:1 or a TC-5 column (achiral; 0.53 mm inner diameter × 30 m, df = 1.50 μm, GL Sciences) using helium carrier gas (80 kPa) under a splitless setting. High-performance liquid chromatographic (HPLC) analysis was conducted on a JASCO PU-980 instrument with CHIRALPAK AD-H, AD-RH, and OD-RH

columns (4.6 mm inner diameter × 150 mm, Daicel Chemical Ind.). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX-270 (270/67.8 MHz) or JNM-400 FT NMR (400/100 MHz) spectrometer. The chemical shifts of ^{1}H and ^{13}C NMR resonances are reported in ppm relative to tetramethylsilane. Optical rotation measurements of chiral products were performed on a JASCO DIP-360 polarimeter using a sodium lamp in the indicated solvent in a 10 mm inner diameter × 10 cm cell.

Materials

Benzyl, *tert*-butyl, cyclohenyl, phenyl, and *n*-propyl isocyanates were purchased from TCI Co., Ltd. Dehydrated solvents (THF, CH_2Cl_2, $CHCl_3$, diethyl ether, DME, toluene, ethyl acetate, and acetonitrile) were purchased from Kanto Chemical Co., Inc. and used without further purification. Racemic hydroxy lactones (±)-**1a** (Aldrich Co., Ltd.) and (±)-**1e** (TCI Co., Ltd.) were used as purchased. Box ligands **3a**–**3i** were prepared as described in the literature.[14,21] Pybox ligands **3j** and **3k** were purchased from Aldrich Co., Ltd. and used without further purification. Anhydrous $Cu(OTf)_2$ (TCI Co., Ltd.) and $AgSbF_6$ (Aldrich Co., Ltd.) were used as purchased. Racemic carbamates **2a**–**2h** were prepared as described in the literature.[22] Argon gas of 99.99% purity (Air Water Inc.) was used. For preparative column chromatography and thin layer chromatography, silica gel 60N (100–210 μm, Kanto Chemical. Co., Inc.) and Merck precoated TLC (silica gel 60 F254 1.0 mm) were used, respectively.

Syntheses

Preparation of [Cu{(*S*,*S*)-bis(*tert*-butyloxazoline)}](OTf)$_2$ [(*S*,*S*)-**3a**]:[14] $Cu(OTf)_2$ (8.65 mg, 24 mmol) and (*S*)-2,2-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (7.80 mg, 26.5 mmol) were placed in an oven-dried 20-mL Schlenk tube equipped with a teflon-coated magnetic stirring bar and a serum rubber cap. After the air in the flask had been replaced with argon, THF (2 mL) was added at ambient temperature to give a light-blue solution. After 10 min of stirring, THF was evaporated under reduced pressure. The light-green residue was dissolved in CH_2Cl_2 (10 mL) at ambient temperature. The obtained green solution of [Cu{(*S*,*S*)-*t*Bu-box}](OTf)$_2$ [(*S*,*S*)-**3a**] was used for asymmetric carbamoylation.

Representative procedure for enantiomer-selective carbamoylation of racemic pantolactone [(±)-**1a**]: Racemic pantolactone [(±)-**1a**] (653 mg, 5.02 mmol) and CH_2Cl_2 (9 mL) were placed in an oven-dried, 25-mL two-necked flask equipped with a teflon-coated magnetic stirring bar, a serum rubber cap, and a rubber balloon filled with argon. The CH_2Cl_2 solution of (*S*,*S*)-**3a** described above (1.0 mL, 2.4 mmol) was added to this flask through a syringe filter unit (pore size of 450 nm; Toyo Roshi Kaisha, Ltd.) to remove unreacted solid $Cu(OTf)_2$. The resulting solution was stirred for 30 min at 0 °C. To this solution was added *n*-C_3H_7NCO (0.23 mL, 2.5 mmol), and the reaction mixture was stirred for 4 h at 0 °C. Methanol (5 mL) was added to the mixture, which was then concentrated under reduced pressure. The residue was passed through a silica gel pad eluted with ethyl acetate to remove metal components, affording a mixture of recovered (*R*)-**1a** and the carbamate (*S*)-**2a**. The *ee* values of **1a** and **2a**, ee_{1a} and ee_{2a}, respectively, were determined by GC analysis. The conversion (conv.) was estimated by the following equation: conv. $= ee_{1a}/(ee_{1a}+ee_{2a})$.[6,7] The estimated conv. value agreed well with that determined by GC analysis using tetralin as an internal standard. The stereoselectivity factor ($s = k_{fast}/k_{slow}$) was calculated by the following equation: $s = \ln[(1-\text{conv.})(1-ee_{1a})]/\ln[(1-\text{conv.})(1+ee_{1a})]$.[6,7]

Isolation of (R)-1a in >99% *ee*

Preparation of catalyst: The CH_2Cl_2 solution of (*S*,*S*)-**3a** was prepared as described above. Conditions: 1) $Cu(OTf)_2$ (30.6 mg, 84.8 mmol), (*S*)-2,2-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (25.0 mg, 84.9 mmol), THF (3 mL), ambient temperature, 30 min; 2) concentration under reduced pressure; 3) dissolution in CH_2Cl_2 (10 mL).

Carbamoylation: Racemic substrate (±)-**1a** (19.3 g, 148 mmol) and CH_2Cl_2 (291 mL) were placed in an oven-dried 300-mL three-necked flask equipped with a teflon-coated magnetic stirring bar, a serum rubber cap, and a rubber balloon filled with argon. The CH_2Cl_2 solution of (*S*,*S*)-**3a** (8.8 mL, 75 mmol) was added to this flask through a syringe filter unit. The resulting solution was stirred for 30 min at 0 °C. To this solution was added *n*-C_3H_7NCO (6.99 g, 82.1 mmol, 0.55 equivalents to **1a**), and the reaction mixture was stirred for 22 h at 0 °C. Methanol (50 mL) was added to the mixture, which was then concentrated under reduced pressure to give the crude product (25.8 g) as a green viscous oil. The yield and *ee* value of (*R*)-**1a** determined by GC analysis were 45% and 99.0% *ee*, respectively. The crude product was passed through a silica gel pad eluted with ethyl acetate to remove metal components, affording a mixture of recovered (*R*)-**1a** and the carbamate (*S*)-**2a**. A short-path distillation of the mixture without water cooling afforded (*R*)-**1a** in 99.6% *ee* (8.19 g, 43% yield based on (±)-**1a**, 99% chemical purity determined by GC analysis). B.p. 64 °C/0.15 mmHg; m.p. 48–49 °C; $[\alpha]_D^{20}$ −50 (*c* = 0.90, H_2O) (reference [23]: $[\alpha]_D^{25}$ −54.0 (*c* = 0.25, H_2O), 94% *ee* (*R*)); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.09 (s, 3H; CH_3C), 1.23 (s, 3H; CH_3C), 3.89 (br, 1H; OH), 3.96 (d, *J* = 8.8 Hz, 1H; C*H*H), 4.03 (d, *J* = 8.8 Hz, 1H; CH*H*), 4.20 ppm (s, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.76, 22.70, 40.71, 75.56, 76.41, 178.04 ppm; GC: column, CP-Chirasil-Dex; column temp., 130 °C; injection temp., 220 °C; retention time (t_R) of (*R*)-**1a**, 7.2 min; t_R of (*S*)-**1a**, 6.6 min.

(*S*)-Dihydro-4,4-dimethyl-3-propylaminocarbonyloxy-2(3*H*)-franone [(*S*)-**2a**] (Table 3): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 44% yield. B.p. 135 °C/0.25 mmHg (bulb-to-bulb); m.p. 37–38 °C; $[\alpha]_D^{20}$ +28 (*c* = 1.30, $CHCl_3$), 93% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, *J* = 7.4 Hz, 3H; CH_3CH$_2$), 1.05 (s, 3H; CH_3C), 1.09 (s, 3H; CH_3C), 1.50–1.63 (sext, *J* = 7.4 Hz, 2H; CH_3CH_2), 3.16–3.23 (q, *J* = 7.4 Hz, 2H; CH_2CH_2NH), 4.02 (s, 2H; CH_2O), 5.00 (br, 1H; NH), 5.29 ppm (s, 1H; CHOCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.05, 19.65, 22.83, 40.09, 42.93, 75.40, 76.0, 154.92, 173.35 ppm; IR (KBr): $\tilde{\nu}$ = 3344, 1793, 1717 cm^{-1}; MS (EI, relative intensity): 215 (4), 186 (58), 113 (40), 99 (23), 86 (45), 71 (100); HRMS (EI): *m*/*z* calcd for $C_{10}H_{17}NO_4$: 215.1157 ($[M]^+$); found: 215.1153; GC: column, CP-Chirasil-Dex; initial column temp., 130 °C (10 min); final column temp., 160 °C (15 min); progress rate, 10 °C min^{-1}; injection temp., 220 °C; t_R of (*R*)-**2a**, 23.6 min; t_R of (*S*)-**2a**, 24.1 min.

(*S*)-3-Benzylaminocarbonyloxy-dihydro-4,4-dimethyl-2(3*H*)-franone [(*S*)-**2aa**] (Table 2): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 41% yield. M.p. 110–113 °C; $[\alpha]_D^{22}$ +26 (*c* = 0.08, $CHCl_3$), 86% *ee*; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.10 (s, 3H; CH_3C), 1.24 (s, 3H; CH_3C), 4.03 (s, 2H; CH_2O), 4.42 (d, *J* = 5.9 Hz, 2H; PhCH_2), 5.27 (bs, 1H; NH), 5.32 (s, 1H; CHOCO), 7.23–7.46 ppm (m, 5H; aromatics); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ = 19.71, 22.85, 40.11, 45.22, 75.72, 76.00, 127.49, 128.64, 137.74, 154.99, 173.15 ppm; IR (KBr): $\tilde{\nu}$ = 3314, 3029, 2969, 2918, 2879, 1786, 1731, 1706, 1538 cm^{-1}; MS (EI, relative intensity): 263 (2.6), 150 (46), 132 (3.3), 114 (20), 106 (100), 99 (48), 91 (80), 79 (7.4), 65 (8.6); HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_4$: 263.1157 ($[M]^+$); found: 263.1159; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 1.0 mL min^{-1}; detection, 254 nm light; t_R of (*R*)-**2aa**, 8.6 min; t_R of (*S*)-**2aa**, 7.6 min.

(*S*)-3-Cyclohexylaminocarbonyloxy-dihydro-4,4-dimethyl-2(3*H*)-franone [(*S*)-**2ab**] (Table 2): Isolation: TLC (eluent, 2:1 diethyl ether/hexane), 43% yield. M.p. 144–145 °C; $[\alpha]_D^{19}$ +25 (*c* = 0.70, $CHCl_3$), 87% *ee*; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.09 (s, 3H; CH_3C), 1.23 (s, 3H; CH_3C), 0.96–2.10 (m, 10H; cyclohexyl CH_2), 3.37–3.61 (m, 1H; cyclohexyl CH), 4.02 (s, 2H; CH_2O), 4.76–4.95 (br s, 1H; NH), 5.27 ppm (s, 1H; CHOCO); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ = 19.73, 22.90, 24.67 (two signals), 25.30, 32.95, 33.09, 40.17, 50.28, 75.35, 76.01, 153.98, 173.37 ppm; IR (KBr): $\tilde{\nu}$ = 3311, 2940, 2856, 1790, 1704, 1546 cm^{-1}; MS (EI, relative intensity): 255 (5.7), 212 (43), 174 (57), 142 (42), 131 (13), 113 (47), 98 (100), 83 (60), 71 (20), 55 (38), 41 (26); HRMS (EI): *m*/*z* calcd for $C_{13}H_{21}NO_4$: 255.1470 ($[M]^+$); found: 255.1467; HPLC: column, AD-RH; eluent, 50:50 H_2O/CH_3CN; flow rate, 0.5 mL min^{-1}; detection, RI; t_R of (*R*)-**2ab**, 9.7 min; t_R of (*S*)-**2ab**, 7.9 min.

(*S*)-3-*tert*-Butylaminocarbonyloxy-dihydro-4,4-dimethyl-2(3*H*)-franone [(*S*)-**2ac**] (Table 2): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 30% yield. M.p. 114–116 °C; $[\alpha]_D^{18}$ +32 (*c* = 0.50, $CHCl_3$), 76% *ee*; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.08 (s, 3H; CH_3C), 1.22 (s, 3H; CH_3C), 1.35 (s, 9H; *tert*-butyl CH_3), 4.02 (s, 2H; CH_2O), 4.93 (br s, 1H; NH), 5.23 ppm (s, 1H; CHOCO); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ = 20.21, 23.46, 29.09 (three signals), 40.65, 51.21, 75.40, 76.52, 153.39, 173.91 ppm;

IR (KBr): $\tilde{\nu}$ = 3327, 2974, 1784, 1709, 1533 cm^{-1}; MS (EI, relative intensity): 230 (1.6), 214 (100), 174 (2.3), 131 (52), 113 (20), 102 (9.0), 84 (61), 72 (12), 57 (78), 43 (15); HRMS (EI): *m/z* calcd for $C_{11}H_{20}NO_4$: 230.1392 ($[M+H]^+$); found: 230.1394; HPLC: column, AD-RH; eluent, 60:40 H_2O/CH_3CN; flow rate, 0.5 mL min^{-1}; detection, RI; t_R of (*R*)-**2ac**, 8.5 min; t_R of (*S*)-**2ab**, 7.4 min.

(*S*)-Dihydro-4,4-dimethyl-3-phenylaminocarbonyloxy-2(3*H*)-franone [(*S*)-**2ad**] (Table 2): Isolation: GPC (eluent, $CHCl_3$), 40% yield. M.p. 149–151 °C: $[\alpha]_D^{22}$ +28 (*c* = 0.80, $CHCl_3$), 88% *ee*; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.15 (s, 3H; CH_3C), 1.28 (s, 3H; CH_3C), 4.07 (s, 2H; CH_2O), 5.39 (s, 1H; CHOCO), 6.95 (br s, 1H; NH), 7.05–7.48 ppm (m, 5H; aromatics); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ = 19.80, 22.85, 40.26, 75.77, 76.17, 118.84, 123.89, 129.01 (three signals), 137.14, 151.95, 173.22 ppm; IR (KBr): $\tilde{\nu}$ = 3365, 3048, 2970, 2912, 1793, 1715, 1604, 1541 cm^{-1}; MS (EI, relative intensity): 249 (74), 177 (12), 137 (9.0), 119 (100), 93 (27); HRMS (EI): *m/z* calcd for $C_{13}H_{15}NO_4$: 249.1001 ($[M]^+$); found: 249.1001; HPLC: column, AD-RH; eluent, 60:40 H_2O/CH_3CN; flow rate, 0.5 mL min^{-1}; detection, 230 nm light; t_R of (*R*)-**2ad**, 14.3 min; t_R of (*S*)-**2ad**, 12.5 min.

(*R*)-4,4-Diethyl-dihydro-3-hydroxy-2(3*H*)-franone [(*R*)-**1b**] (Table 4): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 40% yield. M.p. 48–49 °C; $[\alpha]_D^{21}$ −6.3 (*c* = 0.10, CH_3OH), 85% *ee* (reference [23]: $[\alpha]_D^{25}$ −12.0 (*c* = 0.33, CH_3OH), 95% *ee* (*R*)); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91 (t, *J* = 7.5 Hz, 3H; CH_3), 0.99 (t, *J* = 7.5 Hz, 3H; CH_3), 1.39–1.67 (m, 4H; $2CH_3CH_2$), 2.41 (br, 1H; OH), 3.87 (d, *J* = 9.4 Hz, 1H; C*H*HO), 4.16 (d, *J* = 9.4 Hz, 1H; CH*H*O), 4.20 ppm (s, 1H; CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.04, 8.42, 21.50, 28.05, 46.53, 73.14, 74.63, 178.52 ppm; IR (KBr): $\tilde{\nu}$ = 3434, 1771 cm^{-1}; GC: column, CP-Chirasil-Dex; column temp., 145 °C; injection temp., 220 °C; t_R of (*R*)-**1b**, 10.4 min; t_R of (*S*)-**1b**, 9.5 min.

(*S*)-4,4-Diethyl-dihydro-3-propylaminocarbonyloxy-2(3*H*)-franone [(*S*)-**2b**] (Table 4): 47% yield. M.p. 42–43 °C; $[\alpha]_D^{20}$ +6.1 (*c* = 0.50, $CHCl_3$), 95% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.89–0.97 (m, 9H; $2CH_3CH_2$ and $CH_3CH_2CH_2NH$), 1.45–1.62 (m, 6H; $2CH_3CH_2$ and $CH_3CH_2CH_2NH$), 3.20 (q, *J* = 7.0 Hz, 2H; $CH_3CH_2CH_2NH$), 3.99 (d, *J* = 9.3 Hz, 1H; C*H*HO), 4.15 (d, *J* = 9.3 Hz, 1H; CH*H*O), 4.93 (br, 1H; NH), 5.44 ppm (s, 1H; CHOCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 8.08 (two signals), 11.07, 22.90, 23.12, 27.58, 42.96, 45.69, 72.61, 73.78, 154.84, 174.02 ppm; IR (KBr): $\tilde{\nu}$ = 3435, 3327, 1794, 1702 cm^{-1}; elemental analysis: calcd (%) for $C_{12}H_{21}NO_4$: C 59.24, H 8.70, N 5.76; found: C 59.02, H 8.66, N 5.68; MS (EI, relative intensity): 243 (8), 214 (29), 113 (42), 85 (100), 86 (45); HRMS (EI): *m/z* calcd for $C_{12}H_{21}NO_4$: 243.1470 ($[M]^+$); found: 243.1462; GC: column, CP-Chirasil-Dex; initial column temp., 145 °C (12 min); final column temp., 180 °C (10 min); progress rate, 5 °C min^{-1}; injection temp., 220 °C; t_R of (*R*)-**2b**, 25.5 min; t_R of (*S*)-**2b**, 26.2 min.

(*R*)-Dihydro-3-hydroxy-4,4-diphenyl-2(3*H*)-furanone [(*R*)-**1c**] (Table 4): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 44% yield. M.p. 179–180 °C; $[\alpha]_D^{19}$ +204 (*c* = 0.20, $CHCl_3$), 93% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.25 (d, *J* = 7.8 Hz, 1H; OH), 4.48 (d, *J* = 9.7 Hz, 1H; C*H*HO), 5.11 (d, *J* = 7.8 Hz, 1H; C*H*OH), 5.19 (d, *J* = 9.7 Hz, 1H; CH*H*O), 7.12–7.44 ppm (m, 10H; aromatics); ^{13}C NMR (100 MHz, $[D_6]$DMSO) δ = 55.29, 72.43, 72.93, 126.82, 127.07 (two signals), 127.29, 127.95 (two signals), 128.79 (two signals), 128.94 (two signals), 139.92, 143.56, 176.32 ppm; IR (KBr): $\tilde{\nu}$ = 3435, 1780 cm^{-1}; elemental analysis: calcd (%) for $C_{16}H_{14}O_3$: C 75.58, H 5.55; found: C 75.65, H 5.65; MS (EI, relative intensity): 254 (24), 180 (100), 165 (28); HRMS (EI) *m/z* calcd for $C_{16}H_{14}O_3$: 254.0943 ($[M]^+$); found: 254.0934; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 0.5 mL min^{-1}; detection, 230 nm light; t_R of (*R*)-**1c**, 21.7 min; t_R of (*S*)-**1c**, 15.4 min. The absolute configuration was estimated by ^{1}H NMR analysis after conversion to the (*R*)- and (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters (see the Supporting Information).[24]

(*S*)-Dihydro-4,4-diphenyl-3-propylaminocarbonyloxy-2(3*H*)-franone [(*S*)-**2c**] (Table 4): 50% yield. M.p. 138 °C; $[\alpha]_D^{20}$ −76 (*c* = 0.10, $CHCl_3$), 94% *ee*. The carbamate **2c** existed as an 85:15 mixture of conformational isomers in $CDCl_3$ at ambient temperature: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.68 (br m, 3H; a set of signals of $CH_3CH_2CH_2$), 0.91 (t, *J* = 7.3 Hz, 3H; $CH_3CH_2CH_2$), 1.26 (br m, 2H; a set of signals of $CH_3CH_2CH_2$), 1.53 (sext, *J* = 7.3 Hz, 2H; $CH_3CH_2CH_2$), 2.72 (br m, 2H; a set of signals of $CH_3CH_2CH_2$), 3.19 (q, *J* = 7.3 Hz, 2H; $CH_3CH_2CH_2$), 4.47 (d, *J* = 9.6 Hz, 1H; C*H*H), 4.65 (br s, 1H; NH), 5.11 (d, *J* = 9.6 Hz, 1H; CH*H*), 6.38 (s, 1H; CH), 7.09–7.41 ppm (m, 10H; aromatics). This compound was detected as a single isomer in $[D_6]$DMSO at 80 °C, the NMR behavior of which is described in the Supporting Information. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.09, 22.90, 42.99, 55.14, 72.32, 74.05, 126.69 (two signals), 127.50, 127.78, 128.28 (two signals), 128.47 (two signals), 123.08 (two signals), 139.05, 141.36, 154.49, 172.09 ppm; IR (KBr): $\tilde{\nu}$ = 3320, 2964, 1796, 1721, 1704, 1529 cm^{-1}; elemental analysis: calcd (%) for $C_{20}H_{21}NO_4$: C 70.78, H 6.24, N 4.13; found: C 70.49, H 6.25, N 4.03; MS (EI, relative intensity): 339 (8), 254 (27), 180 (100), 165 (16), 149 (19); HRMS (EI) *m/z* calcd for $C_{20}H_{21}NO_4$: 339.1470 ($[M]^+$); found: 339.1462; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 0.5 mL min^{-1}; detection, 230 nm light; t_R of (*R*)-**2c**, 26.7 min; t_R of (*S*)-**2c**, 23.0 min.

(*R*)-4-Hydroxy-2-oxaspiro[4,4]nonan-3-one [(*R*)-**1d**] (Table 4): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 44% yield. M.p. 74–75 °C; $[\alpha]_D^{22}$ −12 (*c* = 0.19, $CHCl_3$), 97% *ee* (reference [25]: $[\alpha]_D^{25}$ +18.6 ($CHCl_3$), 94% *ee* (*S*)); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.40–2.06 (m, 8H; cyclopentyl), 2.82 (d, *J* = 3.3 Hz, 1H; OH), 4.02 (dd, *J* = 8.9 and 0.7 Hz, 1H; OC*H*H), 4.13 (d, *J* = 8.9 Hz, 1H; OCH*H*), 4.29 ppm (d, *J* = 3.5 Hz, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.76, 24.87, 28.96, 33.35, 51.45, 73.41, 76.00, 178.04 ppm; IR (KBr): $\tilde{\nu}$ = 3389, 2965, 2869, 1765 cm^{-1}; GC: column, CP-Chirasil-Dex; column temp., 160 °C; injection temp., 220 °C; t_R of (*R*)-**1d**, 8.5 min; t_R of (*S*)-**1d**, 7.6 min.

(*S*)-2-Oxa-4-(propylaminocarbonyloxy)spiro[4,4]nonan-3-one [(*S*)-**2d**] (Table 4): 49% yield. B.p. 147 °C/0.14 mmHg (bulb-to-bulb); $[\alpha]_D^{20}$ +26 (*c* = 0.20, $CHCl_3$), 93% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, *J* = 7.3 Hz, 3H; CH_3), 1.49–1.96 (m, 10H; cycropentyl, NCH_2CH_2), 3.15–3.22 (m, 2H; NH_2), 4.08 (d, *J* = 8.9 Hz, 1H; OC*H*H), 4.13 (d, *J* = 9.0 Hz, 1H; C*H*OH), 5.06 (br s, 1H; NH), 5.45 ppm (d, *J* = 9.0 Hz, 1H; CHOCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.15, 22.97, 24.75, 24.78, 30.35, 33.22, 43.04, 50.81, 73.59. 75.63, 154.94, 173.35 ppm; IR (KBr): $\tilde{\nu}$ = 3360, 2963, 2875, 1793, 1725, 1531 cm^{-1}; elemental analysis: calcd (%) for $C_{12}H_{19}NO_4$: C 59.73, H 7.94, N 5.81; found: C 59.47, H 8.02, N 5.80; MS (EI, relative intensity): 241(10), 212 (49), 156 (40), 139 (100), 112 (72), 94 (66), 81 (57); HRMS (EI): *m/z* calcd for $C_{12}H_{19}NO_4$: 241.1314 ($[M]^+$); found: 241.1316; GC: column, CP-Chirasil-Dex; column temp., 180 °C; injection temp., 220 °C; t_R of (*R*)-**2d**, 17.5 min; t_R of (*S*)-**2d**, 18.2 min.

(*R*)-Dihydro-3-hydroxy-2(3*H*)-furanone [(*R*)-**1e**] (Table 4): Isolation: TLC (eluent, Et_2O), 45% yield. B.p. 74 °C/0.25 mmHg (bulb-to-bulb); $[\alpha]_D^{22}$ +32 (*c* = 0.30, $CHCl_3$), 36% *ee* (reference [26]: $[\alpha]_D^{20}$ −60.1 (*c* = 0.67, $CHCl_3$), 99% *ee* (*S*)); ^{1}H NMR (270 MHz, $CDCl_3$) δ = 2.17–2.44 (m, 1H; CHC*H*H), 2.52–2.77 (m, 1H; CHCH*H*), 3.24–3.57 (br, 1H; OH), 4.16–4.34 (m, 1H; C*H*OH), 4.38–4.62 ppm (m, 2H; OCH_2); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ = 30.72, 65.24, 67.25, 178.37 ppm; IR (KBr): $\tilde{\nu}$ = 3377, 1772 cm^{-1}; GC: column, CP-Chirasil-Dex; column temp., 100 °C; injection temp., 220 °C; t_R of (*R*)-**1e**, 17.5 min; t_R of (*S*)-**1e**, 17.0 min.

(*S*)-Dihydro-3-propylaminocarbonyloxy-2(3*H*)-franone [(*S*)-**2e**] (Table 4): 46% yield. B.p. 135 °C/0.18 mmHg (bulb-to-bulb); $[\alpha]_D^{20}$ −2.0 (*c* = 0.40, $CHCl_3$), 41% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.93 (t, *J* = 7.3 Hz, 3H; $CH_3CH_2CH_2$), 1.48–1.62 (sext, *J* = 7.3 Hz, 2H; NCH_2CH_2), 2.22–2.38 (m, 1H; C*H*HCH$_2$O), 2.67–2.78 (m, 1H; CH*H*CH$_2$O), 3.14–3.21(m, 2H; NCH_2), 4.24–4.33 (m, 1H; CH_2CHHO), 4.43–4.50 (m, 1H; CH_2CH*H*O), 4.99 (br s, 1H; NH), 5.36 ppm (dd, *J* = 8.7 and 9.7 Hz, 1H; CHOCO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.14, 22.96, 29.34, 42.97, 64.92, 68.15, 154.85, 173.44, 154.9, 173.4 ppm; IR (KBr): $\tilde{\nu}$ = 3326, 1794, 2971, 1702, 1544 cm^{-1}; MS (EI, relative intensity): 188 ($[M+H]^+$, 6), 158 (100), 86 (59), 58 (37), 43 (57); HRMS (EI): *m/z* calcd for $C_8H_{14}NO_4$: 188.2011 ($[M+H]^+$); found: 188.0923; GC: column, CP-Chirasil-Dex; initial column temp., 100 °C (25 min); final column temp., 170 °C (11 min); progress rate, 10 °C min^{-1}; injection temp., 220 °C; t_R of (*R*)-**2e**, 40.2 min; t_R of (*S*)-**2e**, 40.8 min.

(*R*)-3-Hydroxy-4,4-dimethyl-2-pyrrolidinone [(*R*)-**1f**] (Table 4): Isolation: TLC (eluent, 2:1 ethyl acetate/hexane), 46% yield. M.p. 158–159 °C; $[\alpha]_D^{20}$ +5.0 (*c* = 0.20, CH_3OH), 24% *ee* (reference [27]: $[\alpha]_D^{23}$ +25.6 (*c* = 1.0, C_2H_5OH), (*R*)); ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.07 (s, 3H; CH_3C),

1.24 (s, 3H; CH_3C), 3.08 (dd, $J=9.5$ and 10.5 Hz, 2H; CH_2NH), 3.41 (d, $J=3.6$ Hz, 1H; CHO*H*), 3.95 (d, $J=3.6$ Hz, 1H; C*H*OH), 6.34 ppm (br s, 1H; NH); ^{13}C NMR (67.8 MHz, $CDCl_3$) $\delta=19.86$, 24.86, 40.88, 51.98, 77.07, 177.61 ppm; IR (KBr): $\tilde{\nu}=3355$, 3218, 1705, 1683 cm^{-1}; elemental analysis: calcd (%) for $C_6H_{11}NO_2$: C 55.80, H 8.58, N 10.84; found: C 55.72, H 8.50, N 10.84; MS (EI, relative intensity): 129 (100), 71 (56); HRMS (EI): *m*/*z* calcd for $C_6H_{11}NO_2$: 129.0790 ($[M]^+$); found: 129.0785; HPLC: column, AD-RH; eluent, 5:95 2-propanol/hexane; flow rate, 0.5 mL min^{-1}; detection, 210 nm light) t_R of (*R*)-**1 f**, 11.3 min; t_R of (*S*)-**1 f**, 13.1 min.

(*S*)-4,4-Dimethyl-3-propylaminocarbonyloxy-2-pyrrolidinone [(*S*)-**2 f**] (Table 4): 45% yield. M.p. 95–97 °C; $[\alpha]_D^{20}$ −7.9 ($c=0.50$, CH_3OH), 40.8% *ee*; ^1H NMR (270 MHz, $CDCl_3$) $\delta=0.93$ (t, $J=7.3$ Hz, 3H; $CH_3CH_2CH_2$), 1.07 (s, 3H; CCH_3), 1.24 (s, 3H; CCH_3), 1.55 (sext, $J=7.3$ Hz, 2H; $CH_3CH_2CH_2$), 3.05 (dd, $J=1.3$ and 9.4 Hz, 1H; C*H*H of lactam), 3.17 (t, $J=7.3$ Hz, 2H; $CH_3CH_2CH_2$), 3.20 (d, $J=9.4$ Hz, 1H; CH*H* of lactam), 5.05 (br s, 1H; NH of carbamate), 5.12 ppm (s, 1H; CHOCO), 6.51 (br s, 1H; NH of lactam); ^{13}C NMR (67.8 MHz, $CDCl_3$) $\delta=11.16$, 20.87, 22.96, 25.03, 40.02, 42.92, 52.21, 77.61, 155.66, 174.37 ppm; IR (KBr): $\tilde{\nu}=3422$, 1702 cm^{-1}; elemental analysis: calcd (%) for $C_{10}H_{18}N_2O_3$: C 56.06, H 8.47, N 13.07; found: C 55.82, H 8.13, N 12.8; MS (EI, relative intensity): 214 (3), 185 (12), 156 (12), 129 (45), 111 (100), 98 (31); HRMS (EI): *m*/*z* calcd for $C_{10}H_{18}N_2O_3$: 214.1318 ($[M]^+$); found: 214.1326. The *ee* value was determined after conversion into **1 f**.[28] HPLC: column, AD-RH; eluent, 5:95 2-propanol/hexane; flow rate, 0.5 mL min^{-1}; detection, 210 nm light; t_R of (*R*)-**1 f**, 11.3 min; t_R of (*S*)-**1 f**, 13.1 min.

(3*R*,4*R*)-Dihydro-3-hydroxy-4-phenyl-2(3*H*)-furanone [(*R*)-*cis*-**4**] (Table 5): Isolation: TLC (eluent, ethyl acetate), 45% yield. M.p. 97 °C; $[\alpha]_D^{20}$ −11 ($c=0.10$, $CHCl_3$), 96% ee; ^1H NMR (270 MHz, $CDCl_3$) $\delta=2.14$ (d, $J=6.3$ Hz, 1H; OH), 3.86 (ddd, $J=2.8$, 5.2, and 7.9 Hz, 1H; PhC*H*), 4.63 (dd, $J=2.8$ and 9.7 Hz, 1H; C*H*H), 4.66 (dd, $J=5.2$ and 9.7 Hz, 1H; CH*H*), 4.73 (dd, $J=6.3$ and 7.9 Hz, 1H; C*H*OH), 7.19–7.44 ppm (m, 5H; aromatics); ^{13}C NMR (67.8 MHz, $CDCl_3$) $\delta=45.90$, 69.94, 70.61, 128.05 (two signals), 128.13, 129.00 (two signals), 134.90, 176.51 ppm; IR (KBr): $\tilde{\nu}=3440$, 1765, 1189 cm^{-1}; elemental analysis: calcd (%) for $C_{10}H_{10}O_3$: C 67.41, H 5.66; found: C 67.45, H 5.72; MS (EI, relative intensity): 178 (61), 121 (30), 104 (100), 91 (59), 78 (27); HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}O_3$: 178.0630 ($[M]^+$); found: 178.0622; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 1.0 mL min^{-1}; detection, 254 nm light; t_R of (*R*)-*cis*-**4**, 7.2 min; t_R of (*S*)-*cis*-**4**, 6.0 min. The absolute configuration was estimated by ^1H NMR analysis after conversion into the corresponding (*R*)- and (*S*)-MTPA esters (see the Supporting Information).[24]

(3*S*,4*S*)-Dihydro-4-phenyl-3-propylaminocarbonyloxy-2(3*H*)-furanone [(*S*)-*cis*-**5**] (Table 5): 45% yield. M.p. 118 °C; $[\alpha]_D^{20}$ +135 ($c=0.20$, $CHCl_3$), 96% *ee*. The carbamate *cis*-**5** existed as an 87:13 mixture of conformational isomers in $CDCl_3$ at ambient temperature: ^1H NMR (270 MHz, $CDCl_3$) $\delta=0.52$–0.74 (m, 0.4H; $CH_3CH_2CH_2$ (minor isomer)), 0.83 (t, $J=7.3$ Hz, 2.6H; $CH_3CH_2CH_2$ (major isomer)), 0.98–1.30 (m, 0.3H; $CH_3CH_2CH_2$ (minor isomer)), 1.42 (sext, $J=7.3$ Hz, 1.7H; $CH_3CH_2CH_2$ (major isomer)), 2.59–2.82 (m, 0.3H; $CH_3CH_2CH_2$ (minor isomer)), 2.95–3.17 (m, 1.7H; $CH_3CH_2CH_2$ (major isomer)), 4.00–4.13 (m, 1H; CHOCO), 4.57–4.78 (m, 3H; CH_2O and PhC*H*), 5.60 (d, $J=8.2$ Hz, 0.9H; NH (major isomer)), 5.63–5.73 (m, 0.1H; NH (minor isomer)), 7.10 ppm (m, 5H; aromatics); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=11.0$, 22.8, 42.7, 44.5, 70.5, 70.9, 127.7 (two signals), 127.8, 128.8 (two signals), 135.6, 154.4, 172.7 ppm; IR (KBr): $\tilde{\nu}=3342$, 1776, 1705, 1548 cm^{-1}; elemental analysis: calcd (%) for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32; found: C 63.88, H 6.55, N 5.31; MS (EI, relative intensity): 263 (8), 234 (13), 178 (9), 161 (13), 133 (10), 117 (9), 104 (100), 92 (16), 77 (11); HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_4$: 263.1157 ($[M]^+$); found: 263.1160; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 1.0 mL min^{-1}; detection, 254 nm light; t_R of (*R*)-*cis*-**5**, 6.7 min; t_R of (*S*)-*cis*-**5**, 7.6 min.

(3*R*,4*S*)-Dihydro-3-hydroxy-4-phenyl-2(3*H*)-furanone [(*R*)-*trans*-**4**] (Table 5): Isolation: TLC (eluent, 1:1 ethyl acetate/hexane), 43% yield. M.p. 83–84 °C; $[\alpha]_D^{19}$ +17 ($c=0.30$, $CHCl_3$), 32% *ee*; ^1H NMR (270 MHz, $CDCl_3$) $\delta=3.05$ (d, $J=3.3$ Hz, 1H; OH), 3.61–3.83 (m, 1H; PhC*H*), 4.16–4.83 (m, 1H; OC*H*H), 4.58 (dd, $J=3.3$ and 10.9 Hz, 1H; C*H*OH), 4.67 (t, $J=8.6$ Hz, 1H; OCH*H*), 7.18–7.54 ppm (m, 5H; aromatics); ^{13}C NMR (67.8 MHz, $CDCl_3$) $\delta=48.73$, 69.42, 72.85, 127.11 (two signals), 128.02, 129.07 (two signals), 135.82, 176.95 ppm; IR (KBr): $\tilde{\nu}=3381$, 1763 cm^{-1}; elemental analysis: calcd (%) for $C_{10}H_{10}O_3$: C 67.41, H 5.66; found: C 67.22, H 5.67; MS (EI, relative intensity): 178 (97), 134 (21), 121 (22), 104 (100), 91 (88), 78 (42); HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}O_3$: 178.0630 ($[M]^+$); found: 178.0633; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 1.0 mL min^{-1}; detection, 254 nm light; t_R of (*R*)-*trans*-**4**, 8.1 min; t_R of (*S*)-*trans*-**4**, 9.5 min. The absolute configuration was determined after conversion into (*S*)-*cis*-**4** (see the Supporting Information).

(3*S*,4*R*)-Dihydro-4-phenyl-3-propylaminocarbonyloxy-2(3*H*)-furanone [(*S*)-*trans*-**5**] (Table 5): 45% yield. M.p. 75–76 °C; $[\alpha]_D^{20}$ −17 ($c=0.10$, $CHCl_3$), 37% *ee*; ^1H NMR (270 MHz, $CDCl_3$) $\delta=0.90$ (t, $J=7.3$ Hz, 3H; $CH_3CH_2CH_2$), 1.51 (sext, $J=7.3$ Hz, 2H; $CH_3CH_2CH_2$), 3.15 (m, 2H; $CH_3CH_2CH_2$), 3.87 (dd, $J=8.5$ and 10.7 Hz, 1H; PhC*H*), 4.19–4.28 (m, 1H; OC*H*H), 4.67 (t, $J=8.6$ Hz, 1H; OCH*H*), 4.92 (br s, 1H; CHOCO), 5.72 (d, $J=10.9$ Hz, 1H; NH), 7.24–7.47 ppm (m, 5H; aromatics): ^{13}C NMR (67.8 MHz, $CDCl_3$) $\delta=11.05$, 22.83, 42.91, 46.77, 69.69, 72.50, 127.09 (two signals), 128.14, 129.11 (two signals), 135.09, 154.58, 172.63 ppm; IR (KBr): $\tilde{\nu}=3363$, 3064, 3033, 2966, 2934, 2876, 1793, 1730, 1530, 1148 cm^{-1}; elemental analysis: calcd (%) for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32; found: C 63.61, H 6.57, N 5.02; MS (EI, relative intensity): 264 ($[M+H]^+$, 1), 233 (14), 190 (12), 161 (100), 131 (67), 120 (7), 104 (35), 91 (20), 77 (12); HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}NO_4$: 264.1236 ($[M+H]^+$); found: 264.1228; HPLC: column, AD-H; eluent, 10:90 2-propanol/hexane; flow rate, 1.0 mL min^{-1}; detection, 254 nm light) t_R of (*R*)-*trans*-**5**, 19.2 min; t_R of (*S*)-*trans*-**5**, 13.2 min.

Acknowledgements

This work was financially supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS; No. 18350046), by the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science) of the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the Akiyama Foundation.

[1] *Lewis Acids in Organic Synthesis*, *Vols. 1 and 2* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**.

[2] For pioneering works on asymmetric reactions with box-metal catalysts, see: a) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726–728; b) E. J. Corey, N. Imai, H.-Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728–729.

[3] For recent reviews, see: a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605–613; c) D. A. Evans, T. Rovis, J. S. Johnson, *Pure Appl. Chem.* **1999**, *71*, 1407–1415; d) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; e) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202; f) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.

[4] K. Matsumoto, M. Mitsuda, N. Ushijima, Y. Demizu, O. Onomura, Y. Matsumura, *Tetrahedron Lett.* **2006**, *47*, 8453–8456.

[5] J. Otera, K. Sakamoto, T. Tsukamoto, A. Orita, *Tetrahedron Lett.* **1998**, *39*, 3201–3204.

[6] For selected reviews, see: a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330; b) C. J. Sih, S.-H. Wu, *Top. Stereochem.* **1989**, *19*, 63–125.

[7] a) S. El-Baba, J.-C. Poulin, H. B. Kagan, *Tetrahedron* **1984**, *40*, 4275–4284; b) H. B. Kagan, *Croat. Chem. Acta* **1996**, *69*, 669–680; c) H. B. Kagan, *Tetrahedron* **2001**, *57*, 2449–2468.

[8] For resolution of (±)-**1 a** by chemical methods, see: a) E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, K. Folkers, *J. Am. Chem. Soc.* **1940**, *62*, 1785–1790; b) F. Kagan, R. V. Heinzelman,

D. I. Weisblat, W. Greiner, *J. Am. Chem. Soc.* **1957**, *79*, 3545–3549; c) K. Fuji, M. Node, M. Murata, S. Terada, K. Hashimoto, *Tetrahedron Lett.* **1986**, *27*, 5381–5382.

[9] For resolution of (±)-**1a** by enzymatic methods, see: a) H. S. Bevinakatti, A. A. Banerji, R. V. Newadkar, *J. Org. Chem.* **1989**, *54*, 2453–2455; b) M. Baumann, B. H. Hauer, U. T. Bornscheuer, *Tetrahedron: Asymmetry* **2000**, *11*, 4781–4790.

[10] E. J. J. Grabowski in *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis* (Ed.: L. A. Paquette), Wiley, New York, **2003**, pp. 466–468, and references cited therein.

[11] a) R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, R. O. Roblin, Jr., *J. Am. Chem. Soc.* **1947**, *69*, 1393–1401; b) T. E. King, C. J. Stewart, V. H. Cheldelin, *J. Am. Chem. Soc.* **1953**, *75*, 1290–1292; c) R. Neidlein, P. Greulich, *Helv. Chim. Acta* **1992**, *75*, 2545–2552; d) R. Schmid, M. Scalone in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1439–1449.

[12] a) R. E. Dolle, K. C. Nicolau, *J. Am. Chem. Soc.* **1985**, *107*, 1691–1694; b) G. C. Fischer, R. H. Turakhia, C. J. Morrow, *J. Org. Chem.* **1985**, *50*, 2011–2019; c) P. Lavallée, R. Ruel, L. Grenier, M. Bissonnette, *Tetrahedron Lett.* **1986**, *27*, 679–682; d) H. Sone, K. Suenaga, Y. Bessho, T. Kondo, H. Kigoshi, K. Yamada, *Chem. Lett.* **1998**, 85–86.

[13] For recent works, see: a) M. M. Hansen, C. F. Bertsch, A. R. Harkness, B. E. Huff, D. R. Hutchison, V. V. Khau, M. E. LeTourneau, M. J. Martinelli, J. W. Misner, B. C. Peterson, J. A. Rieck, K. A. Sullivan, I. G. Wright, *J. Org. Chem.* **1998**, *63*, 775–785; b) H. M. L. Davies, G. Ahmed, R. L. Calvo, M. R. Churchill, D. G. Churchill, *J. Org. Chem.* **1998**, *63*, 2641–2645; c) J. A. O'Meara, N. Gardee, M. Jung, R. N. Ben, T. Durst, *J. Org. Chem.* **1998**, *63*, 3117–3119.

[14] D. A. Evans, G. S. Peterson, J. S. Johnson, D. M. Barnes, K. R. Campos, K. A. Woerpel, *J. Org. Chem.* **1998**, *63*, 4541–4544.

[15] Compounds (*S*,*S*)-**3a** and (*S*,*S*)-**3b** show opposite senses of enantioselection from each other in aldol addition of enolsilane to (benzyloxy)acetaldehyde; see: D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669–685.

[16] D. A. Evans, J. A. Murray, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem.* **1995**, *107*, 864–867; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800.

[17] For bis(oxazolinyl)pyridine ligands, see: H. Nishiyama, M. Kondo, T. Nakamura, K. Itoh, *Organometallics* **1991**, *10*, 500–508.

[18] Gaussian 03 (Revision B.04), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**.

[19] The distorted square-planar structures of (*R*/*S*,*S*)-**7** and (*S*/*S*,*S*)-**7** agree well with the X-ray crystal structures of [Cu{(*S*,*S*)-*t*Bu-box}-$(H_2O)_2$]$(SbF_6)_2$, [Cu{(*S*,*S*)-*t*Bu-box}{PhCH=C$(CO_2Me)_2$}]$(SbF_6)_2$, and [Cu{(*S*,*S*)-*t*Bu-box}$(HCOCH_2COCO_2Et)$](OTf)$_2$; for the structure of [Cu{(*S*,*S*)-*t*Bu-box}$(H_2O)_2$]$(SbF_6)_2$, see: a) D. A. Evans, J. S. Johonson, C. S. Burgey, K. R. Campos, *Tetrahedron Lett.* **1999**, *40*, 2879–2882; see also reference [14]; for the structure of [Cu{(*S*,*S*)-*t*Bu-box}-{PhCH=C$(CO_2Me)_2$}]$(SbF_6)_2$, see: b) D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142; for the structure of [Cu{(*S*,*S*)-*t*Bu-box}$(HCOCH_2COCO_2Et)$](OTf)$_2$, see: c) H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 4487–4497.

[20] S. D. Evans, R. P. Houghton, *J. Mol. Catal. A* **2000**, *164*, 157–164.

[21] S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, A.-M. Faucher, J. P. Edwards, *J. Org. Chem.* **1995**, *60*, 4884–4892.

[22] M. E. Duggan, J. S. Imagire, *Synthesis* **1989**, 131–132.

[23] D. A. Evans, J. Wu, C. E. Masse, D. W. C. MacMillan, *Org. Lett.* **2002**, *4*, 3379–3382.

[24] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

[25] B. A. Shinkre, A. Rakeeb, A. S. Deshmukh, *Tetrahedron: Asymmetry* **2004**, *15*, 1081–1084.

[26] D. Schinzer, A. Bauer, J. Schieber, *Chem. Eur. J.* **1999**, *5*, 2492–2500.

[27] T. Konno, H. Meguro, K. Tuzimura, *Tetrahedron Lett.* **1975**, *16*, 1305–1308.

[28] Conversion of **2f** into **1f** was made by reaction with trichlorosilane according to the method described in the literature; see: W. H. Pirkle, J. R. Hauske, *J. Org. Chem.* **1977**, *42*, 2781–2782.

Received: December 25, 2007
Published online: May 6, 2008

