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Highly diastereo- and enantioselective reactions of enecarbamates with an aldehyde

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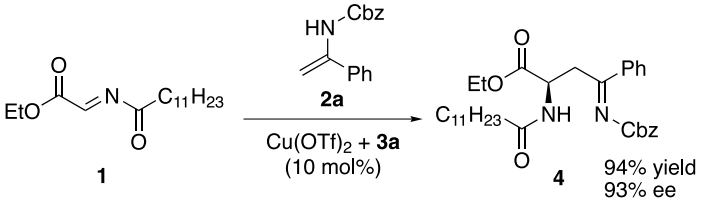
Abstract—Catalytic asymmetric addition reactions of enecarbamates with ethyl glyoxylate have been developed using $CuClO_4 \cdot 4CH_3CN$ and a diimine ligand as the catalyst. Highly diastereo- and enantioselective addition reactions of α-mono-substituted enecarbamates have been also achieved. These reactions afforded the corresponding adducts with high selectivity; that is, *syn* adducts from *Z*-enecarbamates and *anti* adducts from *E*-enecarbamates. The proposed reaction mechanism is an aza-ene type pathway, where the proton of an enecarbamate's N–H group plays an important role, not only for accelerating the reaction but also for providing a transition state suitable for the highly selective chiral induction.

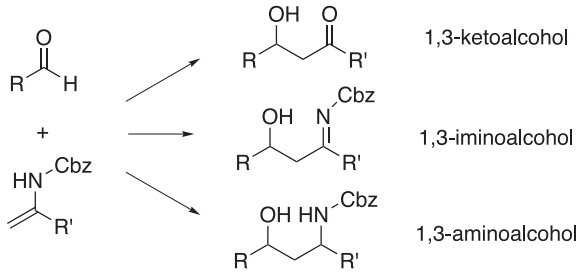
1. Introduction

Enamides and enecarbamates are potentially useful nucleophiles, which bear amide and carbamate moieties after undergoing nucleophilic additions. While enamides are readily prepared,[1] are easy to handle, and can be stored at room temperature, their use in organic synthesis is limited.[2] Recently, we have reported the first catalytic enantioselective addition of enamides and enecarbamates to imines, which afforded imine **4** in high yield with high selectivity (Scheme 1).[3] A C_2-symmetric copper catalyst prepared from $Cu(OTf)_2$ and diamine ligand **3a**, derived from 1,2-diphenyl ethylenediamine, catalyzed the reaction efficiently.[4] Imine **4** is a versatile compound, which can be converted into 1,3-diamides, 5-membered lactams, 3-keto 1-amides, etc. The use of aldehydes instead of imines as substrates for this reaction might lead to 1,3-ketoalcohols, 1,3-iminoalcohols, and 1,3-aminoalcohols, etc.



Scheme 1.

The objective of this research effort is to investigate the reactions of enamides with aldehydes.[5] The reaction of ethyl glyoxylate with enecarbamates would lead to products which have α-hydroxy γ-imino ester functionalities (Scheme 2). In the absence of a Lewis-acid catalyst, the reaction of ethyl glyoxylate (1.2 equiv.) with enecarbamate **2a** (1.0 equiv.) proceeded at 0 °C for 1.5 h to give **6a**, which was hydrolized to **7a** by treatment with HBr aq. (13% yield,



Scheme 2.

Keywords: Enamide; Enecarbamate; Asymmetric catalysis; Aza-ene reaction; Copper; N ligands.
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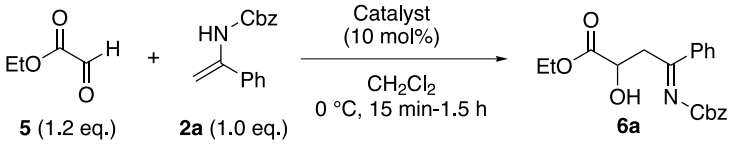
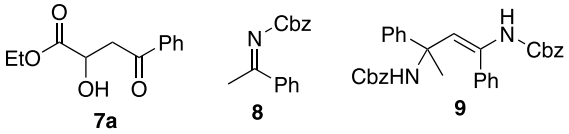
Table 1. Reaction of enecarbamate **2a** with ethyl glyoxylate (**5**). Initial results



5 (1.2 eq.) **2a** (1.0 eq.) **6a**

Entry	Catalyst	Yield (%)[a]	ee (%)
1	None	13	—
2	$Cu(OTf)_2$	18	—
3	$CuClO_4 \cdot 4CH_3CN$	67	—
4	$Sc(OTf)_3$	40	—
5	$Yb(OTf)_3$	59	—
6[b]	$Cu(OTf)_2$ + **3a**	93	55



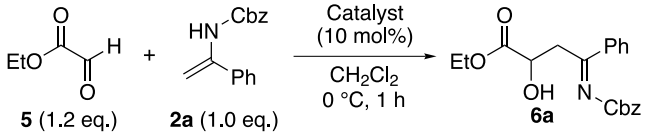
7a **8** **9**

[a] Yield of **7a** following an acidic work-up.
[b] 15 min.

entry 1 in Table 1). Use of copper (II) triflate as a catalyst (10 mol%) resulted in the formation of **8** and **9**, which indicated that an equilibrium between **2a** and **8** existed under Lewis acidic conditions and caused a self-coupling reaction between **2a** and **8** to form **9** (ca. 30% yield, entry 2 in Table 1). A similar phenomenon was observed when other Lewis acids such as $CuClO_4 \cdot 4CH_3CN$, $Sc(OTf)_3$, and $Yb(OTf)_3$ were employed as catalysts (entries 2–5 in Table 1). It is noted that a complex derived from $Cu(OTf)_2$ and diamine ligand **3a** did not accelerate the formation of **8** from **2a** at all, and that **7a** was isolated in high yield with modest enantioselectivity (93% yield, 55% ee, entry 6 in Table 1). This result would be attributed to lower Lewis acidity of the copper coordinated to diamine ligand **3a**.

These results prompted us to screen various metals in the presence of a range of diamine ligands, and the results are summarized in Table 2. The use of $Sc(OTf)_3$, $CoCl_2$, or $Zn(OTf)_2$ was found to accelerate the reaction of enecarbamates with ethyl glyoxylate selectively (58–86% yields), and in these cases the enecarbamate self-coupling

Table 2. Reaction of enecarbamate **2a** with **5** using various catalysts



5 (1.2 eq.) **2a** (1.0 eq.) **6a**

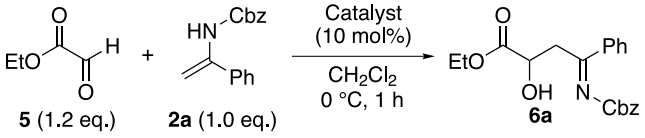
Entry	Metal	Ligand	Yield (%)	ee (%)
1	$Cu(OTf)_2$	**3a**	93	55
2	$CuClO_4 \cdot 4CH_3CN$	**3a**	90	35
3	$LiClO_4$	**3d**	21	0
4	NaOTf	**3d**	Trace	—
5	$Mg(OTf)_2$	**3b**	5	38
6	$Sc(OTf)_3$	**3d**	58	28
7	$Sc(OTf)_3$	**3h**	60	1
8	$FeCl_2$	**3d**	38	2
9	$CoCl_2$	**3d**	77	2
10	$CoCl_2$	**3h**	73	1
11	$Zn(OTf)_2$	**3a**	86	39
12	$Zn(OTf)_2$	**3i**	62	16
13	$AgSbF_6$	**3i**	14	18
14	AgOTf	**3i**	31	35
15	$Sn(OTf)_2$	**3d**	44	8
16	$La(OTf)_3$	**3d**	70	0
17	$Ce(OTf)_3$	**3d**	68	0
18	$Pr(OTf)_3$	**3d**	61	0
19	$Nd(OTf)_3$	**3d**	74	2
20	$Sm(OTf)_3$	**3d**	72	0
21	$Sm(OTf)_3$	**3i**	65	2
22	$Sm(OTf)_3$	**3h**	88	0
23	$Ho(OTf)_3$	**3d**	66	0
24	$Yb(OTf)_3$	**3b**	40	2
25	$Lu(OTf)_3$	**3d**	53	6

compound **9** was not observed. Ag (I) and Sn (II) salts were less active catalysts for this reaction. When various lanthanide salts were employed as catalysts (entries 16–25 in Table 2) in the presence of diamine ligand (commonly **3d**), the desired adducts were formed in moderate to high yields (40–88% yields), albeit enantioselectivities were negligible (<6% ee).

The copper complexes showed the best catalytic activity in this reaction, which led to the selection of Cu (I) and (II) in the parallel screening of ligand types. Diamine ligands **3a–f** derived from diphenyl ethylenediamine, box-type ligands **3g** and **3h**, diimine ligands **3i–3t** derived from cyclohexyl diamine, and diamine ligands **3v–3x** derived from cyclohexyl diamine were all used in conjunction with the Cu (I) and Cu (II). Among Cu (II) complexes (Table 3), a complex prepared from $Cu(OTf)_2$ and box ligand **3h** gave the highest enantioselectivity (73% ee).[6]

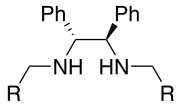
Preliminary tests using $CuClO_4 \cdot 4CH_3CN$ as a Lewis acid revealed that a catalyst derived from Cu (I) and diimine ligand **3i** exhibited good facial discrimination (entry 2 in Table 4, 93% ee).[7] Alternate counter anions $^{-}PF_6$ and ^{-}OTf gave adducts with lower selectivities (82% ee and 78% ee, respectively, entries 3 and 4 in Table 4). When 1-naphthyl and 2-naphthyl-substituted ligands **3j** and **3k** were examined (entries 5 and 6 in Table 4), moderate enantioselectivities were observed (73% ee and 68% ee,

Table 3. Reactions of enecarbamate **2a** with **5** using various copper(II) catalysts

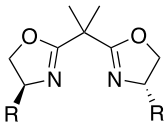


5 (1.2 eq.) **2a** (1.0 eq.) **6a**

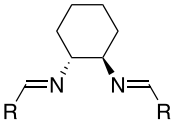
Entry	Metal	Ligand	Yield (%)	ee (%)[a]
1	$Cu(OTf)_2$	**3a**	93	55
2[b]	$Cu(OTf)_2$	**3a**	91	54
3[c]	$Cu(OTf)_2$	**3a**	89	58
4	$Cu(OTf)_2$	**3b**	74	59
5[d]	$Cu(OTf)_2$	**3b**	44	47
6	$Cu(OTf)_2$	**3c**	58	57
7	$Cu(OTf)_2$	**3d**	96	46
8	$Cu(OTf)_2$	**3e**	97	37
9	$Cu(OTf)_2$	**3f**	94	31
10	$Cu(OTf)_2$	**3g**	85	31[a]
11[c]	$Cu(OTf)_2$	**3g**	91	31[a]
12	$Cu(OTf)_2$	**3h**	70	73[a]
13	$Cu(OTf)_2$	**3i**	65	70
14	$Cu(OTf)_2$	**3j**	66	28
15	$Cu(OTf)_2$	**3k**	71	52
16	$Cu(OTf)_2$	**3l**	68	17
17	$Cu(OTf)_2$	**3v**	89	51
18	$Cu(OTf)_2$	**3w**	91	50
19	$Cu(OTf)_2$	**3x**	Quant	62
20	$CuCl_2$	**3a**	47	17
21	$CuCl_2$	**3b**	55	26
22	$CuCl_2$	**3i**	50	19[a]
23	$Cu(SbF_6)_2$	**3b**	77	44



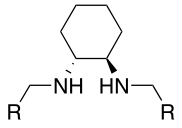
3a: R = 1-nap
3b: R = (3,5-(^{t}Bu)$_2$)-Ph
3c: R = ^{t}Bu
3d: R = Ph
3e: R = (*o*-F)-Ph
3f: R = (*o*-OMe)-Ph



3g: R = Ph
3h: R = ^{t}Bu



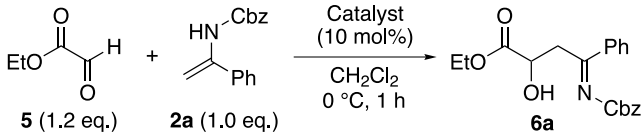
3i: R = Ph
3j: R = 1-nap
3k: R = 2-nap
3l: R = (3,5-di^{t}Bu)-C_6H_3
3m: R = *o*-Tol
3n: R = *m*-Tol
3o: R = *p*-Tol
3p: R = *p*-Et-C_6H_4
3q: R = *p*-^{i}Pr-C_6H_4
3r: R = *p*-F-C_6H_4
3s: R = *p*-Cl-C_6H_4
3t: R = *p*-Br-C_6H_4



3v: R = Ph
3w: R = 2-nap
3x: R = (3,5-(^{t}Bu)$_2$)-Ph

[a] The absolute configuration is *R* except in entries 10–12 and 22 (*S*).
[b] Catalyst (30 mol%) was used.
[c] −20 °C.
[d] −78 °C.

Table 4. Reactions of enecarbamate **2a** with **5** using various copper(I) catalysts



5 (1.2 eq.) **2a** (1.0 eq.) **6a**

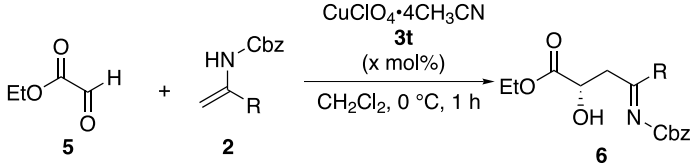
Entry	Metal	Ligand	Yield (%)	ee (%)[a]
1	$CuClO_4 \cdot 4CH_3CN$	**3a**	90	35[a]
2	$CuClO_4 \cdot 4CH_3CN$	**3i**	94	93
3	$CuPF_6 \cdot 4CH_3CN$	**3i**	94	82
4	$CuOTf \cdot 0.5C_6H_5CH_3$	**3i**	66	78
5	$CuClO_4 \cdot 4CH_3CN$	**3j**	92	73
6	$CuClO_4 \cdot 4CH_3CN$	**3k**	52	68
7[b]	$CuClO_4 \cdot 4CH_3CN$	**3i**	48	91
8[c]	$CuClO_4 \cdot 4CH_3CN$	**3i**	97	93
9[d]	$CuClO_4 \cdot 4CH_3CN$	**3i**	Quant	94
10[d]	$CuClO_4 \cdot 4CH_3CN$	**3m**	97	81
11[d]	$CuClO_4 \cdot 4CH_3CN$	**3n**	Quant	86
12[d]	$CuClO_4 \cdot 4CH_3CN$	**3o**	98	95
13[d,e]	$CuClO_4 \cdot 4CH_3CN$	**3o**	20	17
14[d,f]	$CuClO_4 \cdot 4CH_3CN$	**3o**	Trace	—
15[d]	$CuClO_4 \cdot 4CH_3CN$	**3p**	87	94
16[d]	$CuClO_4 \cdot 4CH_3CN$	**3q**	93	94
17[d]	$CuClO_4 \cdot 4CH_3CN$	**3r**	97	96
18[d]	$CuClO_4 \cdot 4CH_3CN$	**3s**	93	96.5
19[d]	$CuClO_4 \cdot 4CH_3CN$	**3t**	93	97.0

[a] The absolute configuration is *S* except in entry 1 (*R*).
[b] −78 °C.
[c] Ethyl glyoxylate (1.5 equiv.) was used.
[d] Ethyl glyoxylate (2.0 equiv.) was used.
[e] Toluene was used as a solvent.
[f] Acetonitrile was used as a solvent.

respectively). The reaction catalyzed by a copper complex derived from $CuClO_4 \cdot 4CH_3CN$ and ligand **3i** proceeded at −78 °C to give a lower yield (48% yield, entry 7 in Table 4). Use of excess amounts of ethyl glyoxylate (1.5 and 2.0 equiv.) gave higher yields, 91% and quantitative yields, respectively (entries 8 and 9 in Table 4). Ligands bearing *para*-substituents on the phenyl arms led to higher enantiomeric excesses in the Cu (I)-catalyzed reaction (compare entry 12 with entries 2, 10 and 11 in Table 4). Finally, the Cu (I) complex of *para*-bromo ligand **3t** was found to give the highest stereoselectivity (97% ee, entry 19 in Table 4). The ligand **3t** gave rise to the best stereoselectivity in catalysis, presumably due to a strong steric contribution from the *para* substituent of the ancilary phenyl groups about the C_2 environment of the catalysts. Solvents other than dichloromethane were tested (toluene and acetonitrile, entries 13 and 14 in Table 4, respectively), but the catalytic activity of the resultant Cu (I) complexes was decreased significantly.

The optimal ligand, metal source, and solvent (**3t**, $CuClO_4 \cdot 4CH_3CN$ and CH_2Cl_2, respectively) were, therefore, employed in experiments where the loadings of both metal and ligand were reduced (entries 1–4 in Table 5). Only 1 mol% of the catalyst ($CuClO_4 \cdot 4CH_3CN$ 1 mol%, ligand **3t** 1.1 mol%) afforded **7a** in good yield with a slightly reduced enantiomeric excess (90% yield, 94% ee, entry 4 in Table 5). Other enecarbamates (**2b–e**) derived from

Table 5. Catalytic asymmetric reactions of various enecarbamates **2** with **5**



5 **2** **6**

Entry	**2**	*x* (mol%)	Yield (%)	ee (%)
1	**2a** (R=Ph)	10	93	97
2	**2a**	5	94	96
3	**2a**	2	96	95
4	**2a**	1	90	94
5	**2b** (R=PMP)	10	94	93
6	**2c** (R=PCP)	10	97	97
7	**2d** (R=PMeP)	10	Quant	96
8	**2e** (R=2-Nap)	10	91	96

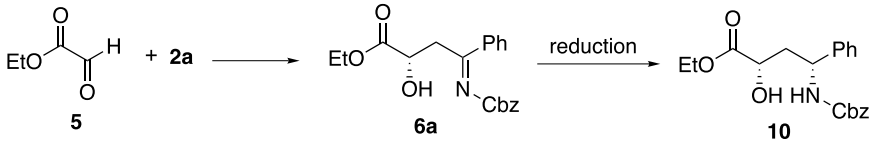
Cbz, benzyloxycarbonyl; PMP, *p*-methoxyphenyl; PCP, *p*-chlorophenyl; PMeP, *p*-methylphenyl; 2-Nap, 2-naphthyl.

aromatic ketones also reacted with ethyl glyoxylate to provide the corresponding adducts **7b–e** in high yields (91% to quant.) with high enantioselectivities (93–97% ee). It is noteworthy that all reactions were complete within only 1 h at 0 °C.

The Cu (I)-catalyzed protocol was able to furnish the potentially useful β-iminoalcohols in high ee, and subsequent reduction was then performed in order to demonstrate the utility of this enecarbamate process. Whilst the diastereoselective reduction of 1,3-ketoalcohols is well known,[8] there are relatively few reports concerning the diastereoselective reduction of 1,3-iminoalcohols.[9] Attempts for the selective reduction of **6a** are summarized in Table 6 (**6a** was prepared freshly as per entry 1 in Table 5). It has been previously reported that chelation of 1,3-ketoalcohols is often crucial for stereoselective reduction. Considering that β-iminoalcohols might coordinate in an analogous fashion, similar protocols were adopted. The use of $Zn(BH_4)_2$[8b] as a reducing agent resulted in around 60% yield with modest *syn*-selectivities. Reduction of **6a** did not proceed at −78 °C when $LiAlH(O^tBu)_3$[8g] was employed as a reductant, (**6a** was completely recovered). Sodium borohydride in the presence of $ZnCl_2$[10] at −78 °C gave benzylalcohol mainly, and only a trace amount of the desired product was observed (entry 5 in Table 6). Although benzylalcohol is assumed to be derived from the Cbz group attached to the nitrogen, the precise mechanism for the formation of benzylalcohol remains unclear. Additionally, K-selectride also formed a considerable amount of benzylalcohol even at −78 °C (entries 8–10 in Table 6), while L-selectride afforded the desired product in moderate yield (ca. 59% yield) with modest *anti*-selectivity (*syn*/*anti*=22/78, entry 11 in Table 6). Satisfactory selectivity was observed (*syn*/*anti*=94/6) when $NaBH_4$ was used in the presence of $Et_2B(OMe)$ which is known to aid chelation of 1,3-ketoalcohols in a THF/MeOH mixtures,[8d] and a slightly modified procedure was used (entry 13 in Table 6). Optimization studies showed that a threefold excess of reductants at −78 °C over 2 h afforded **10** in 65% yield with high *anti*-selectivity (94/6, entry 18 in Table 6). The relative configuration of **10** was assigned on the basis of NMR NOE experiments performed in the cyclic derivative **12** (Scheme 3).

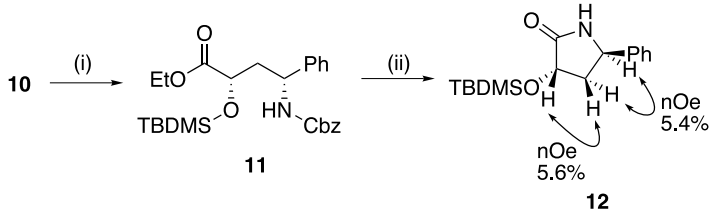
Diastereoselection in addition reactions of α-mono-substituted

Table 6. Selective reduction of **6a** into **10**

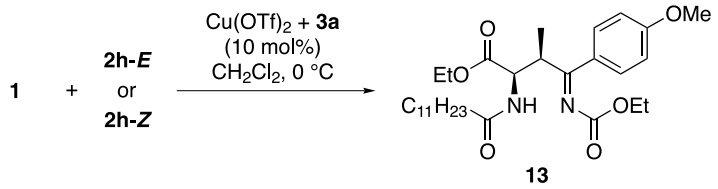


Entry	Reagent (equiv.)	Additive (equiv.)	Solvent	Temperature	Time (h)	Yield (%)[a]	*syn*/*anti*
1	$Zn(BH_4)_2$ (1.0)	—	Et_2O	−78	1	<65	71/29
2	$Zn(BH_4)_2$ (1.0)	—	Et_2O	−78	3	<66	78/22
3	$Zn(BH_4)_2$ (1.0)	MS4A[b]	Et_2O	−78	3	<75	78/22
4	$Zn(BH_4)_2$ (1.0)	—	Toluene–Et_2O[c]	−78	1	<75	75/25
5	$NaBH_4$ (2.0)	$ZnCl_2$ (1.5)	MeOH	−78	5.5	Trace	—
6	$LiAlH(O^tBu)_3$ (5.0)	—	Et_2O	−78	20	Trace	—
7	$LiAlH(O^tBu)_3$ (5.0)	LiL (5.0)	Et_2O	−78	20	Trace	—
8	K-Selectride (2.2)	—	THF	−20	1.2	0	—
9	K-Selectride (2.2)	—	THF	−45	4	0	—
10	K-Selectride (2.2)	—	THF	−78	4	0	—
11	L-Selectride (2.2)	—	THF	−20	16.5	<59	22/78
12	9-BBN (3.0)	—	THF	−20	16.5	Trace	—
13	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (1.1)	THF–MeOH[d]	−78	3	<60	94/6
14	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (1.1)	THF–MeOH[d]	−45	3	<68	91/9
15	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (2.2)	THF–MeOH[d]	−78	5.5	55	91/9
16	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (2.2)	THF–MeOH[d]	−45	5.5	69	88/12
17	$NaBH_4$ (2.2)	$Et_2B(OMe)$ (2.2)	THF–MeOH[e]	−78	2	<37	ND[f]
18	$NaBH_4$ (3.0)	$Et_2B(OMe)$ (3.0)	THF–MeOH[d]	−78	2	65	94/6

[a] The yields from **2**. A small amount of unknown compounds was contained except in entries 15, 16, and 18.
[b] 10 mg/0.1 mmol.
[c] Toluene/Et_2O=1/1.
[d] THF/MeOH=4/1.
[e] THF/MeOH=3/2.
[f] Not determined.



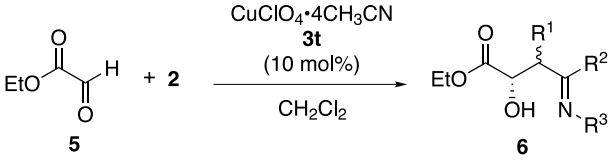
Scheme 3. (i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 92% (ii) Pd/C, H_2, AcOH, AcOEt, quant



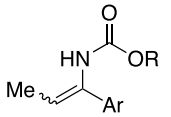
Scheme 4. **2h**–***E***: 77% y, *syn*/*anti*=86/14, 94% ee (*syn*) **2h**–**Z**: 63% y, *syn*/*anti*=68/32, 32% ee (*syn*)

enecarbamates with carbonyls is of great interest not only from a synthetic point of view but also from a mechanistic aspect. In our recent report *syn*-adducts were obtained from both (*E*)- and (*Z*)-enecarbamates **2h** and imine **1** catalyzed by a complex derived from Cu (II) and diamine ligand **3a** (Scheme 4).[3] Unlike their silicon enolate analogues, both geometric isomers of **2h** are stable on silica gel and separable by a standard chromatography technique. The α-substituted enecarbamate **2f** reacted with ethyl glyoxylate smoothly in the presence of $CuClO_4 \cdot 4CH_3CN$ and diimine ligand **3t** to afford **6f** in good yield (entries 1 and 4 in Table 7). It is noted that *anti*- and *syn*-adducts were obtained from the *E*- and *Z*-enecarbamates, respectively. The diastereoselectivities were excellent (*syn*/*anti*=1/99 and 98/2, respectively) and the enantiomeric excess of the major diastereomer was 98% ee in both cases. The same tendency on selectivity was observed for enecarbamates derived from *para*-substituted propiophenone (entries 7–12 in Table 7). The enecarbamates having an ethyl group at the α-position also gave similar diastereo- and enantioselectivities (entries 13 and 14 in Table 7). This reaction could be applied to aliphatic ketone-derived enecarbamates (entries 15–17 in Table 7). The reaction of enecarbamate **2l** derived from cyclohexanone afforded the desired product **6l** in good yield (85% yield) with slightly lower diastereoselectivity (*syn*/*anti*=16/84). Although prolonged reaction time (6–46 h) and lower temperature (−20 °C) were sometimes necessary, decrease of the catalyst loading

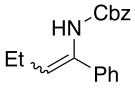
Table 7. Reactions of enecarbamates derived from α-substituted ketones



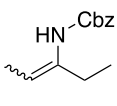
Entry	2	Product	Yield (%)[a]	*syn*/*anti*[b]	Ee (%)[c]
1	**2f***E*	**7f**	83	1/99	98
2[d]	**2f***E*[e]	**7f**	93	1/99	97
3[d]	**2f***E*[f]	**7f**	95	1/99	98
4	**2f***Z*	**7f**	82	98/2	98
5	**2f***Z*[e]	**7f**	93	98/2	98
6	**2f***Z*[f]	**7f**	96	98/2	98
7	**2g***E*	**7g**	96	2/98	98
8	**2g***Z*	**7g**	97	98/2	98
9	**2h***E*	**7g**	82	3/97	96
10	**2h***Z*	**7g**	96	99/1	98
11	**2i***E*	**7i**	85	2/98	98
12	**2i***Z*	**7i**	79	99/1	98
13	**2j***E*[g]	**7j**	58	1/99	98
14	**2j***Z*	**7j**	92	99/1	98
15[d]	**2k***E*	**7k**	83	3/97[h]	97
16[d]	**2k***Z*	**7k**	89	92/8[h]	98
17	**2l**	**7l**	85	16/84[h]	94



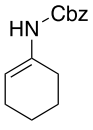
2f: Ar = Ph, R = Bn
2g: Ar = PMP, R = Bn
2h: Ar = PMP, R = Et
2i: Ar = PCP, R = Bn



2j

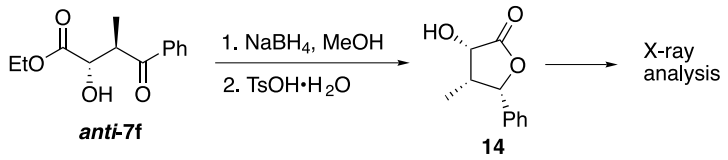


2k



2l

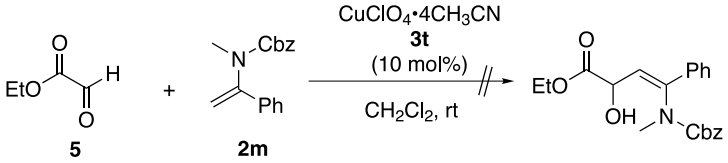
[a] Isolated yield of ketone product.
[b] Determined by HPLC.
[c] Ee of the major diastereomer, determined by HPLC.
[d] −20 °C.
[e] 1 mol% of catalyst was used.
[f] 0.1 mol% of catalyst was used.
[g] **5** (1.0 equiv.) and **2** (2.0 equiv.) were used.
[h] Determined by NMR analysis.



Scheme 5.

gave slightly better yields as shown in entries 1–6 of Table 7. Thus, the (*E*)- and (*Z*)-enecarbamates **2f** reacted with ethyl glyoxylate in the presence of only 0.1 mol% of the catalyst to afford the corresponding adducts in excellent yield (95 and 96%, respectively) with high diastereoselectivity (*syn*/*anti*=1/99 and 98/2, respectively) and enantioselelctivity (98% ee in both cases). The relative configuration of adduct **7f** was determined by the X-ray crystal structure analysis of **14**, which was synthesized from **7f** by reduction and subsequent cyclization in one pot (Scheme 5). The relative configuration of other adducts, general formula **7**, was determined by an analogy of the ^{1}H NMR spectrum of **7f**.

In a bid to elucidate the reaction mechanism, enecarbamate **2m**, which has a tertiary amide moiety, was used to assess the role of the proton attached to the nitrogen. It was interesting to find that no reaction occurred in the presence of 10 mol% of the catalyst even at room temperature (Scheme 6). That the reaction proceeded stereospecifically when α-substituted enecarbamates bear N–H functionalities suggests a concerted aza-ene type reaction mechanism;[11] that is, a hydrogen atom attached to the nitrogen of enecarbamates would accelerate the reaction rate considerably through an intramolecular hydrogen transfer pathway. Two possible modes of a nucleophilic attack exist; an open transition state model or a concerted 6-membered ring fashion. Possible open transition states are shown in Figure 1; *E*-enecarbamates are used in TS-1 and TS-2, while *Z*-enecarbamates are used in TS-3 and TS-4. The steric interaction between the methyl group at the α-position of an enecarbamate and the copper complex is believed to be large, TS-2 would be favorable over TS-1. Similarly, since TS-3 would predominate over TS-4, *syn*-adducts are obtained in both cases. This contradicts the experimental results (*syn*-products from *Z*-enecarbamates, *anti*-products from *E*-enecarbamates). Possible concerted cyclic transition states are shown in Figure 2; TS-5 and TS-7 are derived from *Z*-enecarbamates, TS-6 and TS-8 are derived from *E*-enecarmates. In TS-7 and TS-8, since the steric interaction between the R group of enecarbamates and ethyl glyoxylate would be large, TS-5 and TS-6 are believed to predominate over TS-7 and TS-8, respectively. This explains the observed stereoselectivity and the role of the



Scheme 6.

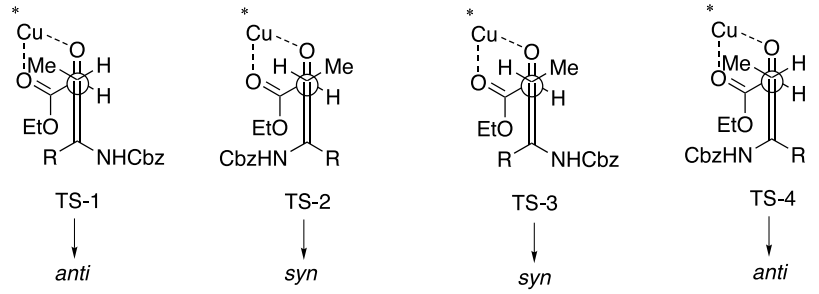


Figure 1. Possible acyclic transition state models.

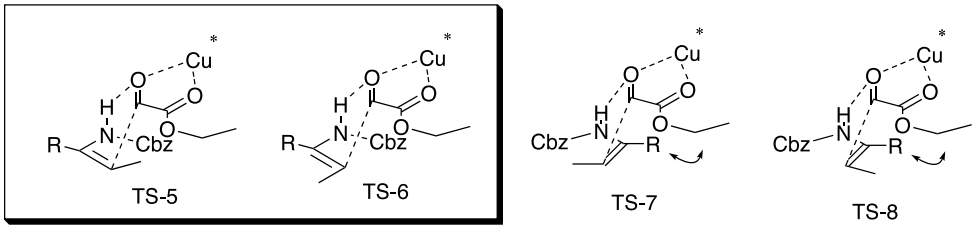


Figure 2. Possible cyclic transition state models.

N–H proton of enecarbamates. Attempts to crystallize model systems for X-ray diffraction are now under way.

In conclusion, catalytic asymmetric addition reactions of enecarbamates with ethyl glyoxylate have been developed using $CuClO_4 \cdot 4CH_3CN$ and diimine ligand **3t** as a catalyst. The products were 1,3-iminoalcohols, which were converted to the corresponding 1,3-amidealcohols diastereoselectively, employing $NaBH_4$ and $Et_2B(OMe)$ in the reduction. We have also developed highly diastereo- and enantioselective addition reactions of α-mono-substituted enecarbamates. These reactions afforded the corresponding adducts with high selectivity; that is, *syn* adducts from *Z*-enecarbamates and *anti* adducts from *E*-enecarbamates. The reaction proceeded smoothly in the presence of only 0.1 mol% of the catalyst to afford 1,3-iminoalcohols in high yields with high diastereo- and enantioselectivities. Aromatic ketone-derived enecarbamates as well as those derived from aliphatic and cyclic ketones were also found to be good substrates. The proposed reaction mechanism is an aza-ene type pathway, where the proton of an enecarbamate's N–H group plays an important role, not only accelerating the reaction but also providing a transition state suitable for the highly selective chiral induction.

2. Experimental

2.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta=0$) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta=77.0$) for ^{13}C NMR. IR spectra were measured with a JASCO FT/IR-610. Optical rotations were measured with a JASCO P-1010 polarimeter. High-performance liquid chromatography was carried out using following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. Gas chromatography and mass spectrometry analysis were carried out using the following apparatuses; SHIMADZU GC-17A, SHIMADZU GCMS-QP5050A. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. All reactions were carried out under argon atmosphere in dried glassware. All solvents were dried and distilled by standard procedures. Enecarbamates **2a–j** were prepared according to the method reported by Kagan et al.[1a] Enecarbamates **2k** and **2l** were prepared by using a modified procedure reported by Machida et al.[1b,12] Enecarbamate **2m** was prepared from **2a**. Diamine ligands **3a–f** were prepared according to the reported method.[4b] Diimine ligands **3i–t** were prepared from commercially available (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate according to the reported method.[13] Diamine ligands **3v–x** were prepared by reduction of **3i**, **3k**, and **3l**, respectively using $NaBH_4$ in MeOH.

3. Enecarbamates

3.1. Analytical data for enecarbamates 2a–j

3.1.1. (1-Phenyl-vinyl)-carbamic acid benzyl ester (2a). Mp 69.4–69.5 °C; ^1H NMR ($CDCl_3$) $\delta=4.96$ (s, 1H), 5.16 (s, 2H), 5.63 (s, 1H), 6.33 (s, 1H), 7.25–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) $\delta=67.0$, 99.6, 126.0, 128.3, 128.5, 128.6, 128.7, 136.0, 138.1, 140.5, 153.7; IR (neat) 3310, 3060, 3033, 1739, 1701, 1634, 1523, 1452, 1227, 1125, 1063, 857, 772, 740, 696, 596 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{16}H_{15}NO_2$ $[M]^+$, 253.1103. Found 253.1093. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.77; H, 6.16; N, 5.52.

3.1.2. [1-(4-Methoxy-phenyl)-vinyl]-carbamic acid benzyl ester (2b). Mp 54.7–54.8 °C; ^1H NMR ($CDCl_3$) $\delta=3.81$ (s, 3H), 4.89 (d, 1H, $J=1.0$ Hz), 5.18 (s, 2H), 5.54 (s, 1H), 6.26 (s, 1H), 6.85–6.90 (m, 2H), 7.30–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) $\delta=55.3$, 66.9, 98.4, 113.9, 127.2, 128.3, 128.5, 130.6, 136.0, 140.1, 153.7, 160.0; IR (neat) 3330, 1736, 1632, 1608, 1509, 1456, 1219, 1179, 1126, 1063, 1030, 834, 742, 698 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{17}H_{17}NO_3$ $[M]^+$, 283.1208. Found 283.1208. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.09; N, 4.91.

3.1.3. [1-(4-Chloro-phenyl)-vinyl]-carbamic acid benzyl ester (2c). Mp 79.0–79.1 °C; ^1H NMR ($CDCl_3$) $\delta=4.96$ (s, 1H), 5.17 (s, 2H), 5.59 (s, 1H), 6.25 (s, 1H), 7.28–7.43 (m, 9H); ^{13}C NMR ($CDCl_3$) $\delta=67.1$, 100.6, 127.3, 128.3, 128.4, 128.6, 128.8, 134.6, 135.8, 136.5, 139.7, 153.6; IR (neat) 3299, 1699, 1532, 1239, 1059, 838, 741, 696 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{16}H_{14}ClNO_2$ $[M]^+$, 287.0713. Found 287.0708. Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.53; H, 5.02; N, 4.91.

3.1.4. (1-*p*-Tolyl-vinyl)-carbamic acid benzyl ester (2d). Mp 52.3–53 °C; ^1H NMR ($CDCl_3$) $\delta=2.34$ (s, 3H), 4.93 (s, 1H), 5.16 (s, 2H), 5.58 (s, 1H), 6.30 (s, 1H), 7.14 (apparent d, 2H, $J=7.8$ Hz), 7.25–7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) $\delta=21.1$, 66.9, 98.8, 125.8, 128.3, 128.5, 129.3, 135.3, 136.0, 138.7, 140.4, 153.7; IR (neat) 3398, 3327, 3032, 1736, 1361, 1508, 1454, 1383, 1321, 1219, 1124, 1063, 955, 852, 825, 735 cm^{-1}; LRMS (FAB) $m/z=268$ ($M+H^+$); Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.20; H, 6.48; N, 5.21.

3.1.5. (1-Naphthalen-2-yl-vinyl)-carbamic acid benzyl ester (2e). Mp 100.3–101.5 °C; ^1H NMR ($CDCl_3$) $\delta=5.11$ (s, 1H), 5.19 (s, 2H), 5.72 (s, 1H), 6.45 (s, 1H), 7.30–7.60 (m, 8H), 7.76–7.86 (m, 4H); ^{13}C NMR ($CDCl_3$) $\delta=67.1$, 100.4, 124.0, 124.7, 126.5, 127.6, 128.2, 128.3, 128.4, 128.6, 133.1, 133.3, 135.3, 135.9, 140.5, 153.8; IR (neat) 3282, 3046, 1701, 1622, 1527, 1226, 1106, 1064, 968, 884, 827, 694, 583 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{20}H_{17}NO_2$ $[M]^+$, 303.1259. Found 303.1251. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.49; H, 5.82; N, 4.64.

3.1.6. (*Z*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (2f*Z*). Mp 73.5–74.0 °C; ^1H NMR ($CDCl_3$) $\delta=1.79$

(d, 3H, $J=6.8$ Hz), 5.13 (s, 2H), 5.79 (q, 1H, $J=6.8$ Hz), (6.00 (brs, 1 H), 7.00–7.62 (m, 10 H); ^{13}C NMR (C_6D_6) $\delta=$ 13.5, 67.0, 119.5, 126.0, 127.7, 128.5, 128.5, 135.0, 137.1, 139.2; IR (neat) 3385, 3296, 3032, 2941, 1701, 1498, 1452, 1399, 1329, 1225, 1089, 1018, 916, 824, 760, 695 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1339.

3.1.7. (*E*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (2f*E*). Mp 63.9–64.0 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.70$ (d, 3H, $J=7.3$ Hz), 5.11 (s, 2H), 5.90–6.25 (br, 2H), 7.20–7.50 (m, 10H); ^{13}C NMR (C_6D_6) $\delta=13.7$, 66.7, 112.0, 128.0, 128.1, 128.5, 128.5, 128.6, 129.1, 134.6, 137.0, 137.2, 153.9; IR (neat) 3398, 3316, 3032, 2938, 1713, 1516, 1449, 1393, 1328, 1213, 1137, 1033, 922, 835, 771, 739, 699, 587 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1347.

3.1.8. (*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (2g*Z*). Mp 110–110.5 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.77$ (d, 3H, $J=6.9$ Hz), 3.80 (s, 3H), 5.14 (s, 2H), 5.68 (q, 1H, $J=6.9$ Hz), 5.96 (brs, 1H), 6.84 (apparent d, 2H, $J=8.8$ Hz), 7.32 (m, 7H); ^{13}C NMR (C_6D_6) $\delta=13.5$, 54.8, 66.9, 114.0, 117.6, 127.2, 128.5, 131.8, 134.6, 137.2, 154.1, 159.8; IR (neat) 3305, 3039, 2945, 2843, 1709, 1611, 1509, 1452, 1400, 1334, 1294, 1247, 1176, 1089, 1029, 820, 742, 699, 590 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1435.

3.1.9. (*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (2g*E*). Mp 66.0–66.5 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.69$ (d, 3H, $J=7.1$ Hz), 3.82 (s, 3H), 5.11 (s, 2H), 5.80–6.15 (m, 2H), 6.85–6.95 (m, 2H), 7.20–7.50 (m, 7H); ^{13}C NMR (C_6D_6) $\delta=13.8$, 54.7, 66.6, 111.1, 114.0, 128.1, 128.5, 128.6, 129.5, 130.3, 134.4, 137.1, 153.9, 159.7; IR (neat) 3323, 3033, 2941, 2843, 1719, 1609, 1509, 1296, 1247, 1177, 1135, 1027, 840, 739, 697 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1452.

3.1.10. (*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (2h*Z*). Mp 57.1–57.2 °C; ^{1}H NMR ($CDCl_3$) $\delta=1.25$ (brs, 3H), 1.75 (d, 3H, $J=7.1$ Hz), 3.78 (s, 3H), 4.13 (q, 2H, $J=7.1$ Hz), 5.66 (q, 1H, $J=7.1$ Hz), 5.88 (brs, 1H), 6.80–6.85 (m, 2H), 7.28–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta=13.4$, 14.5, 55.2, 61.2, 113.6, 117.4, 126.7, 131.1, 133.9, 159.2; IR (neat) 3301, 2979, 1703, 1609, 1510, 1376, 1329, 1245, 1178, 1099, 1037, 824, 774, 594, 448 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1204. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.21; H, 7.32; N, 5.95.

3.1.11. (*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (2h*E*). ^{1}H NMR ($CDCl_3$) $\delta=1.11$ (t, 3H, $J=7.1$ Hz), 1.57 (d, 3H, $J=7.3$ Hz), 3.70 (s, 3H), 4.01 (q, 2H, $J=7.1$ Hz), 5.70–5.95 (m, 2H), 6.73–6.80 (m, 2H), 7.10–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta=13.7$, 14.5, 55.2, 60.8, 111.6, 113.6, 129.1, 129.9, 133.7, 154.3, 159.1; IR (neat) 3319, 2980, 1715, 1608, 1511, 1382, 1293, 1247, 1175, 1138, 1037, 836, 614, 499 cm^{-1}; HRMS (EI). Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1201.

3.1.12. (*Z*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (2i*Z*). Mp 95.2–95.3 °C; ^{1}H NMR (C_6D_6) $\delta=1.48$ (br, 3H), 5.02 (brs, 2H), 5.20–5.90 (br, 2H), 6.60–7.40 (m, 9H); ^{13}C NMR (C_6D_6) $\delta=13.4$, 67.1, 119.8, 127.2, 128.3, 128.6, 133.4, 134.0, 136.9, 137.7, 153.8; IR (neat) 3292, 3033, 2947, 1706, 1589, 1494k 1398, 1327, 1299, 1094, 1016, 819, 741, 697 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0936.

3.1.13. (*E*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (2i*E*). Mp 71.2–71.3 °C; ^{1}H NMR (C_6D_6) $\delta=1.44$ (d, 3H, $J=7.4$ Hz), 5.02 (s, 2H), 5.47 (brs, 1H), 6.12 (brs, 1H), 6.70–6.80 (m, 2H), 6.95–7.25 (m, 7H); ^{13}C NMR (C_6D_6) $\delta=13.5$, 66.8, 128.6, 128.6, 128.7, 130.4, 133.5, 133.8, 135.4, 136.9, 153.7; IR (neat) 3398, 3309, 3033, 2941, 1708, 1595, 1517, 1497, 1458, 1393, 1327, 1219, 1138, 1093, 1034, 836, 740, 701 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0943.

3.1.14. (*Z*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (2j*Z*). Mp 60.3–60.8 °C; ^{1}H NMR (C_6D_6) $\delta=0.89$ (t, 3H, $J=7.1$ Hz), 2.03 (br, 2H), 5.04 (s, 2H), 5.30–5.55 (m, 2H), 7.00–7.25 (m, 8H), 7.28–7.36 (m, 2H); ^{13}C NMR (C_6D_6) $\delta=13.6$, 21.6, 67.0, 126.1, 126.8, 127.4, 128.1, 128.5, 128.6, 133.5, 137.1, 139.2; IR (neat) 3294, 3033, 2961, 2876, 1705, 1498, 1458, 1400, 1334, 1223, 1092, 1026, 753, 691 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1495.

3.1.15. (*E*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (2j*E*). ^{1}H NMR (C_6D_6) $\delta=0.87$ (t, 3H, $J=7.4$ Hz), 1.99 (quint, 3H, $J=7.4$ Hz), 5.01 (s, 2H), 5.56 (brs, 1H), 6.26 (brs, 1H), 6.95–7.25 (m, 10H); ^{13}C NMR (C_6D_6) $\delta=$ 15.1, 21.0, 66.6, 118.8, 126.4, 126.9, 128.2, 128.5, 128.6, 128.6, 129.0, 133.6, 137.1, 137.5, 153.6; IR (neat) 3398, 3319, 3032, 2962, 2876, 1723, 1514, 1454, 1367, 1327, 1219, 1134, 1039, 984, 922, 857, 743, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1481.

3.2. Preparation and analytical data for enecarbamates 2k and 2l

3.2.1. Enecarbamate 2k*E* and 2k*Z*. To a solution of NaN_3 (1.675 g, 25.8 mmol) in H_2O (12 mL) was added a solution of **15**[14] (2.85 g, 21.47 mmol) in THF (7 mL) dropwise at 0 °C. The mixture was vigorously stirred overnight and Et_2O was added. After separation of the phases, the organic layer was washed with a saturated Na_2CO_3 aqueous solution and brine sequentially. Et_2O was evaporated under reduced pressure of 300 mm Hg (Caution!) to give the crude adduct **16** in THF. This solution was added to boiling THF (10 mL) at 80 °C very slowly for over 1.5 h. After completion of the addition, the mixture was stirred at 80 °C until evolution of N_2 gas stopped (for about 2 h). The mixture was allowed to cool to room temperature (rt), and THF was evaporated at 100 mm Hg. The residue was distilled 2 times (65 °C, 100 mm Hg) to give pure **17** (1.113 g, 47% yield). Benzyl alcohol was added to **17** (1.113 g, 10.0 mmol) at −78 °C. The freezed reaction mixture was allowed to warm to rt for over 6 h, and was stirred until **17** was not detected in NMR

analysis (about over 3 days). The mixture was chromatogaphed on silica gel to afford geometric isomer **2k***Z* as a white solid (1.86 g, 85% yield). To a solution of **2k***Z* (237 mg, 1.079 mmol) in THF (12 mL) was added KO^{t}Bu (145.5 mg, 1.29 mmol) at rt. The reaction mixture was kept stirred for 14 h. The reaction was quenched by addition of a saturated NH_4Cl aqueous solution at rt, and the product was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel to afford almost 1:1 geometric mixture **2k** (184 mg, 78% yield). The mixture was separated by careful thin layer chromatography on silica gel (eluent: toluene/Et_2O=10/1) to afford geometric isomer **2k***E* (Scheme 7).

3.2.2. Enecarbamate 2l. According to the procedure mentioned above, **2l** was obtained. The boiling point of the corresponding isocyanate was 78 °C/40 mm Hg.

3.2.3. (*Z*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (2k*Z*). Mp 33.0–33.5 °C; ^{1}H NMR (C_6D_6) δ=0.79 (t, 3H, J=7.5 Hz), 1.45 (d, 3H, J=7.0 Hz), 1.95 (q, 2H, J=7.5 Hz), 5.04 (s, 2H), 5.38 (brs, 1H), 5.72 (q, 1H, J=7.0 Hz), 7.00–7.30 (m, 5H); ^{13}C NMR (C_6D_6) δ=11.9, 12.4, 22.7, 66.5, 128.2, 128.6, 128.6, 136.2, 137.3; IR (neat) 3322, 3064, 3033, 2969, 2935, 2877, 1706, 1523, 1455, 1380, 1351, 1307, 1234, 1097, 1029, 998, 831, 738 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1347.

3.2.4. (*E*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (2k*E*). Mp 53.0–54.0 °C; ^{1}H NMR (C_6D_6) δ=0.95 (t, 3H, J=7.5 Hz), 1.28 (d, 3H, J=6.8 Hz), 2.34 (brq, 2H, J=7.5 Hz), 4.70 (q, 1H, J=6.8 Hz), 5.05 (s, 2H), 5.50 (brs, 1H), 7.00–7.26 (m, 5H); ^{13}C NMR (C_6D_6) δ=11.7, 12.6, 27.9, 66.7, 110.5, 128.2, 128.5, 128.6, 137.2, 137.3; IR (neat) 3305, 2967, 2751, 1693, 1515, 1450, 1321, 1257, 1108, 966, 848, 738, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1348.

3.2.5. Cyclohex-1-enyl-carbamic acid benzyl ester (2l). Mp 49.0–50.0 °C; ^{1}H NMR (C_6D_6) δ=1.26–1.45 (m, 4H), 1.70–1.80 (m, 2H), 1.86–1.98 (m, 2H), 5.03 (s, 2H), 5.31 (brs, 1H), 6.01 (brs, 1H), 7.00–7.25 (m, 5H); ^{13}C NMR (C_6D_6) δ=22.4, 22.8, 24.1, 27.7, 66.4, 109.3, 128.2, 128.6, 128.6, 132.3, 137.3, 153.2; IR (neat) 3322, 3058, 3033, 2931, 2838, 1706, 1538, 1452, 1380, 1348, 1305, 1232, 1062, 1037, 917, 840, 804, 736, 696 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$, 232.1338. Found 232.1342.

3.3. Preparation and analytical data for enecarbamte 2m

NaH (60%, 94.7 mg, 2.37 mmol) freshly washed with pentane was added to a flask, followed by addition of DMF (2.0 mL). The suspension was cooled to 0 °C, and **2a** (300 mg, 1.18 mmol) in DMF (3.0 mL) was added. The mixture was stirred for 30 min at rt, and then cooled to 0 °C. MeI (0.30 mL, 4.74 mmol) was added and the reaction mixture was stirred overnight at rt until the starting material disappeared. The reaction was quenched by addition of saturated aqueous NH_4Cl, and the aqueous layer was extracted with AcOEt. The organic layer was washed with water twice and brine, and then dried over $MgSO_4$. The solvents were evaporated and the residue was purified by chromatography on silica gel to afford **2m** (307.8 mg, 97% yield).

3.3.1. Methyl-(1-phenyl-vinyl)-carbamic acid benzyl ester (2m). Mp 34.0–35.0 °C; ^{1}H NMR ($CDCl_3$) δ=3.21 (s, 3H), 5.04 (s, 2H), 5.16 (s, 1H), 5.46 (s, 1H), 6.80–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ=37.6, 67.2, 110.0, 125.5, 127.5, 127.6, 128.2, 128.3, 128.5, 136.3, 137.2, 148.1, 155.5; IR (neat) 3032, 2954, 2888, 1703, 1626, 1446, 1389, 1337, 1203, 1146, 1027, 955, 902, 777, 696 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1349.

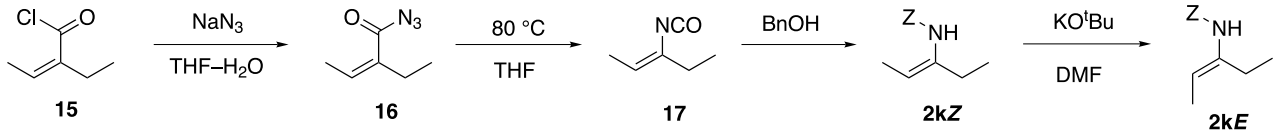
4. Typical procedure for distillation of ethyl glyoxylate

Ethyl glyoxylate was purchased from Tokyo Kasei Kogyo (TCI) as a polymer form in toluene. The ethyl glyoxylate toluene solution (30 g) was added to the flame dried flask. Toluene was evaporated completely under vacuum (<1 mm Hg) at rt, and P_2O_5 (ca. 300 mg) was added to the polymeric ethyl glyoxylate. The mixture was distilled to give almost-toluene-free monomeric ethyl glyoxylate as a slightly yellow liquid (150 mm Hg, 80 °C). Monomeric ethyl glyoxylate easily polymerizes within 30 min to give viscous liquid. Therefore, distilled ethyl glyoxylate should be used immediately after purification.

5. Addition reactions of enecarbamates to ethyl glyoxylate

5.1. Typical procedure for addition reactions of enecarbamates to ethyl glyoxylate using a chiral copper catalyst prepared from $CuClO_4\cdot 4CH_3CN$ and chiral diimine ligand 3t

Ligand **3t** (9.9 mg, 0.022 mmol) in CH_2Cl_2 (1.5 mL) was added to the $CuClO_4\cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) flask under argon The yellow solution was stirred for over 12 h, and cooled to 0 °C. Freshly distilled ethyl glyoxylate (100 μL, 0.40 mmol) in CH_2Cl_2 (0.8 mL) was added to the mixture, and then enecarbamate **2** (0.20 mmol) in CH_2Cl_2 (0.8 mL) was added in one portion. The reaction mixture was stirred at 0 °C, and was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was allowed to warm to rt, and was extracted with CH_2Cl_2. The



Scheme 7.

organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was dissolved in EtOH (3.0 mL), and a 48% HBr aqueous solution (0.3 mL) was added to the solution. The mixture was stirred at rt for 1.5 min, and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C. The reaction mixture was allowed to warm to rt. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvents were evaporated, the crude product was purified by chromatography on silica gel to afford the desired compound **7**.

5.2. Analytical data for 7

5.2.1. (2*S*)-2-Hydroxy-4-oxo-4-phenyl-butyric acid ethyl ester (7a). ^{1}H NMR ($CDCl_3$) δ=1.27 (t, 3H, J=7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H, J=6.1, 17.6 Hz), 3.52 (dd, 1H, J=3.9, 17.6 Hz), 4.25 (q, 2H, J=7.1 Hz), 4.61–4.67 (m, 1H), 7.44–7.50 (m, 2H), 7.54–7.60 (m, 1H), 7.92–7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=14.0, 42.1, 61.8, 67.1, 128.1, 128.6, 133.5, 136.4, 173.7, 197.5. IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582, 499 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{12}H_{15}O_4$ $[M+H]^+$, 223.0970. Found 223.0972; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=19.9 min (*S*), t_R=22.2 min (*R*).

5.2.2. (2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester (7b). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 3.41 (dd, 1H, J=5.9, 17.4 Hz), 3.48 (dd, 1H, J=4.0, 17.4 Hz), 3.48 (brd, 1H, J=6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H, J=7.1 Hz), 4.60–4.70 (m, 1H), 6.91–6.97 (m, 2H), 7.90–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1. IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1465, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_5$ $[M+H]^+$, 253.1076. Found 253.1097; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.4 mL/min: t_R=43.1 min (*S*), t_R=45.7 min (*R*).

5.2.3. (2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyric acid ethyl ester (7c). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 3.42 (dd, 1H, J=6.1, 17.3 Hz), 3.49 (dd, 1H, J=3.9, 17.3 Hz), 3.41–3.47 (brd, 1H), 4.26 (q, 2H, J=7.1 Hz), 4.62–4.70 (m, 1H), 7.42–7.48 (m, 2H), 7.86–7.93 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3. IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{12}H_{14}ClO_4$ $[M+H]^+$, 257.0580. Found 257.0584; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=24.2 min (*S*), t_R=26.5 min (*R*).

5.2.4. (2*S*)-2-Hydroxy-4-oxo-4-*p*-tolyl-butyric acid ethyl ester (7d). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H, J=5.9, 17.4 Hz), 3.51 (dd, 1H, J=4.0, 17.4 Hz), 3.45–3.55 (brs, 1H), 4.26 (q, 2H, J=7.1 Hz), 4.66 (dt, 1H, J=4.2, 5.5 Hz), 7.26 (apparent d, 2H, J=8.0 Hz), 7.85 (apparent d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ=14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3, 133.9, 144.4, 173.7, 197.1. IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1120; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.3 mL/min: t_R=36.1 min (*S*), t_R=38.2 min (*R*).

5.2.5. (2*S*)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester (7e). ^{1}H NMR ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 3.52 (d, 1H, J=5.9 Hz), 3.59 (dd, 1H, J=6.1, 17.3 Hz), 3.66 (dd, 1H, J=3.9, 17.3 Hz), 4.28 (q, 2H, J=7.1 Hz), 4.73 (dt, 1H, J=4.2, 5.4 Hz), 7.50–7.65 (m, 2H), 7.82–8.20 (m, 4H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5. IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$, 273.1127. Found 273.1125; HPLC, Daicel Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=27.0 min (*S*), t_R=30.4 min (*R*).

5.2.6. (2*S*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (7f, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.26 (t, 3H, J=7.0 Hz), 1.29 (d, 3H, J=7.0 Hz), 3.28 (br, 1H), 3.93 (dq, 1H, J=4.2, 7.0 Hz), 4.25 (q, 2H, J=7.0 Hz), 4.58 (d, 1H, J=4.2 Hz), 7.40–7.65 (m, 3H), 7.90–8.05 (m, 2H); *anti* ($CDCl_3$) δ=1.20 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=7.3 Hz), 3.61 (d, 1H, J=8.3 Hz), 3.98 (dq, 1H, J=4.6, 7.1 Hz), 4.10–4.25 (m, 2H), 4.39 (dd, 1H, J=4.6, 8.3 Hz), 7.40–7.65 (m, 3H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.1, 14.0, 44.3, 61.9, 71.6, 128.4, 128.7, 133.3, 135.7, 173.1, 201.6; *anti* ($CDCl_3$) δ=14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) *syn* 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369, 1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708; *anti* 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1118; HPLC, Daicel Chiralcel AS+ADH+AD, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=46.7 min (2*S*,3*S*), t_R=50.6 min (2*R*,3*R*), t_R=54.3 min (2*S*,3*R*), t_R=61.9 min (2*R*,3*S*).

5.2.7. (2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (7g, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.28 (t, 3H, J=7.1 Hz), 1.29 (d, 3H, J=7.1 Hz), 3.35 (br, 1H), 3.84–3.96 (m, 4H), 4.27 (q, 2H, J=7.1 Hz), 4.58 (t, 1H, J=4.2 Hz), 6.96 (apparent d, 2H, J=9.0 Hz), 7.30–7.45 (m, 5H), 7.95 (apparent d, 2H, J=8.8 Hz); *anti* ($CDCl_3$) δ=1.19 (t, 3H, J=7.1 Hz), 1.36 (d, 3H, J=7.3 Hz), 3.75 (d, 1H, J=9.3 Hz), 3.88 (s, 3H), 3.94 (dq, 1H, J=4.6, 7.3 Hz), 4.15 (apparent dq, 2H, J=3.2, 7.1 Hz), 4.36 (dd, 1H, J=4.6, 9.3 Hz), 6.92–6.99 (m, 2H), 7.90–7.97 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; *anti* ($CDCl_3$) δ=14.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) *syn* 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604; *anti* 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{14}H_{19}O_5$ $[M+H]^+$, 267.1232. Found 267.1232; HPLC, Daicel

Chiralcel ADH, hexane/^{i}PrOH=4/1, flow rate=0.2 mL/min: t_R=60.5 min (2*R*,3*R*), t_R=65.4 min (2*S*,2*S*), t_R=75.2 min (2*R*,3*S*), t_R=78.9 min (2*S*,3*R*).

5.2.8. (2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester (7i, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.26 (t, 3H, *J*=7.0 Hz), 1.28 (d, 3H, *J*=7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H, *J*=4.4, 7.0 Hz), 4.25 (q, 2H, *J*=7.0 Hz), 4.55 (d, 1H, *J*=4.4 Hz), 7.40–7.55 (m, 2H), 7.84–7.97 (m, 2H); *anti* ($CDCl_3$) δ=1.21 (t, 3H, *J*=7.1 Hz), 1.34 (d, 3H, *J*=7.1 Hz), 3.53 (d, 1H, *J*=8.2 Hz), 3.91 (dq, 1H, *J*=5.0, 7.1 Hz), 4.08–4.24 (m, 2H), 4.38 (dd, 1H, *J*=5.0, 8.2 Hz), 7.42–7.52 (m, 2H), 7.80–7.95 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; *anti* ($CDCl_3$) δ=13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) *syn* 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478; *anti* 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402, 1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$, 271.0737. Found 271.0745; HPLC, Daicel Chiralcel AS, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=15.1 min (2*S*,3*S*), t_R=16.6 min (2*S*,3*R*), t_R=21.4 min (2*R*,3*S*), t_R=23.9 min (2*R*,3*R*).

5.2.9. (2*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester (7j, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=0.93 (t, 3H, *J*=7.5 Hz), 1.19 (t, 3H, *J*=7.1 Hz), 1.70–2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J*=5.3, 8.3 Hz), 4.19 (q, 2H, *J*=7.1 Hz), 4.51 (d, 1H, *J*=5.3 Hz), 7.42–7.54 (m, 2H), 7.54–7.62 (m, 1H), 7.90–8.02 (m, 2H); *anti* ($CDCl_3$) δ=1.04 (t, 3H, *J*=7.6 Hz), 1.15 (t, 3H, *J*=7.1 Hz), 1.80–1.95 (m, 2H), 3.70 (d, 1H, *J*=9.5 Hz), 3.83 (dt, 1H, *J*=4.2, 7.1 Hz), 4.09 (q, 2H, *J*=7.1 Hz), 4.43 (dd, 1H, *J*=4.2, 9.5 Hz), 7.46–7.52 (m, 2H), 7.56–7.63 (m, 1H), 7.88–7.95 (m, 2H); ^{13}C NMR *syn* ($CDCl_3$) δ=12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; *anti* ($CDCl_3$) δ=12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) *syn* 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701; *anti* 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1283. Found 251.1277; HPLC, Daicel Chiralcel AS, hexane/^{i}PrOH=4/1, flow rate=0.5 mL/min: t_R=13.7 min (2*S*,3*S*), t_R=15.3 min (2*S*,3*R*), t_R=17.6 min (2*R*,3*R*), t_R=23.1 min (2*R*,3*S*).

5.2.10. (2*S*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester (7k, *syn/anti* mixture). ^{1}H NMR *syn* (C_6D_6) δ=0.89 (t, 3H, *J*=7.1 Hz), 0.99 (d, 3H, *J*=7.2 Hz), 1.97–2.08 (m, 2H), 2.70 (dq, 1H, *J*=4.9, 7.2 Hz), 3.39 (d, 1H, *J*=6.7 Hz), 3.80–4.00 (m, 2H), 4.11 (dd, 1H, *J*=4.9, 6.7 Hz); *anti* (C_6D_6) δ=0.87 (t, 3H, *J*=7.1 Hz), 0.93 (t, 3H, *J*=7.3 Hz), 1.02 (d, 3H, *J*=7.2 Hz), 1.95–2.22 (m, 2H), 2.65 (dq, 1H, *J*=4.4, 7.2 Hz), 3.05–3.23 (m, 1H), 3.80–4.00 (m, 2H), 4.38–4.47 (m, 1H); ^{13}C NMR *syn* ($CDCl_3$) δ=7.58, 12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; *anti* (C_6D_6) δ=7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) *syn* 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748; *anti* 3488, 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800, 752 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_9H_{17}O_4$ $[M+H]^+$, 189.1127. Found 189.1120.

5.2.11. (1*S*)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester (7l, *syn/anti* mixture). ^{1}H NMR *anti* ((1*S*,1′*R*), tentatively assignment) (C_6D_6) δ=0.95 (t, 3H, *J*=7.1 Hz), 0.94–1.20 (m, 2H), 1.30–1.42 (m, 2H), 1.56–1.84 (m, 3H), 2.02–2.12 (m, 1H), 2.60–2.70 (m, 1H), 3.35 (d, 1H, *J*=7.2 Hz), 3.84 (dd, 1H, *J*=3.2, 7.2 Hz), 4.02 (dq, 2H, *J*=1.9, 7.1 Hz); distingishable *syn* peaks δ=0.88 (t, 3H, *J*=7.1 Hz), 2.12–2.21 (m, 1H), 2.48–2.57 (m,1H), 2.94 (d, 1H, *J*=5.0 Hz), 4.60 (dd, 1H, *J*=3.2, 5.0 Hz); ^{13}C NMR *anti* ($CDCl_3$) δ=14.1, 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2; distinguishable *syn* peaks δ=14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4; HRMS (FAB). Exact mass calcd for $C_{10}H_{17}O_4$ $[M+H]^+$, 201.1127. Found 201.1127.

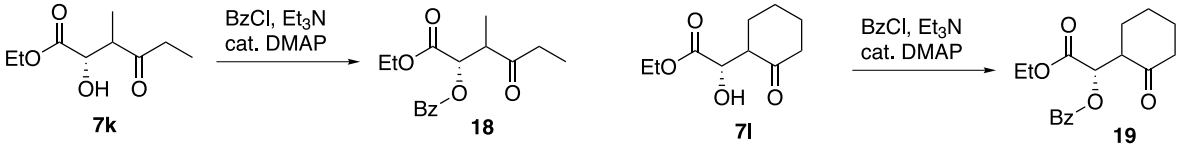
6. Determination of the ee's of 7k and 7l

In order to determine the ee's of **7k** and **7l** whose ee's could not be determined by HPLC analysis as their UV absorbance were very weak, they were converted to **18** and **19**, respectively (Scheme 8).

6.1. Synthesis of 18

To a solution of **7k** (17.9 mg, 0.095 mmol) in CH_2Cl_2 (0.4 mL) was added a solution of Et_3N (19.9 μL, 0.143 mmol) in CH_2Cl_2 (0.3 mL) followed by a solution of BzCl (16.6 μL, 0.143 mmol) in CH_2Cl_2 (0.3 mL) and DMAP (catalytic amount) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C, and water was added, followed by addition of a 1N HCl aqueous solution. The reaction mixture was extracted with Et_2O, and the organic phase was washed with a saturated $NaHCO_3$ aqueous solution and brine, and dried over anhydrous $MgSO_4$. After evaporation of solvents, the crude adduct was purified by chromatography on silica gel to afford **18** (22.2 mg, 80% yield). **19** was also synthesized by using the same method mentioned above (74% yield).

6.1.1. (1*S*)-Benzoic acid 1-ethoxycarbonyl-2-methyl-3-oxo-pentyl ester (18, *syn/anti* mixture). ^{1}H NMR *syn* ($CDCl_3$) δ=1.09 (t, 3H, *J*=7.1 Hz), 1.23 (t, 3H, *J*=7.1 Hz),



Scheme 8.

1.25 (t, 3H, J=7.1 Hz), 2.59 (q, 2H, J=7.1 Hz), 3.23 (quint, 1H, J=7.1 Hz), 4.22 (q, 1H, J=7.1 Hz), 4.22 (q, 1H, J=7.1 Hz), 5.39 (d, 1H, J=7.1 Hz), 7.35–7.50 (m, 2H), 7.50–7.60 (m, 1H), 7.92–8.04 (m, 2H); *anti* δ=1.05 (t, 3H, J=7.3 Hz), 1.24 (t, 3H, J=7.1 Hz), 1.26 (t, 3H, J=7.1 Hz), 2.57 (q, 2H, J=7.3 Hz), 3.21 (dq, 1H, J=5.1, 7.1 Hz), 4.21 (q, 2H, J=7.1 Hz), 5.69 (d, 1H, J=5.1 Hz), 7.42 (apparent t, 2H, J=7.5 Hz), 7.50–7.60 (m, 1H), 7.95–8.05 (m, 2H); ^{13}C NMR *anti* ($CDCl_3$) δ=7.7, 11.6, 14.1, 34.1, 47.1, 61.8, 72.6, 128.4, 129.2, 129.8, 133.4, 165.6, 168.9, 209.6; distinguishable *syn* peaks δ=12.6, 35.0, 61.6, 73.9, 129.1, 129.9, 130.2, 133.7, 209.7; IR (neat) 2981, 2940, 1725, 1602, 1454, 1375, 1348, 1280, 1211, 1103, 1070, 1027, 977, 713 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{21}O_5$ $[M+H]^+$, 293.1389. Found 293.1380; HPLC, Daicel Chiralcel ADH+ADH, hexane/^{i}PrOH=19/1, flow rate=0.5 mL/min: t_R=42.7 min (1*R*,2*R*), t_R=51.3 min (1*S*,2*S*), t_R=54.7 min (1*S*,2*R*), t_R=56.8 min (1*R*,2*S*).

6.1.2. (1*S*)-Benzoic acid ethoxycarbonyl-(2-oxo-cyclohexyl)-methyl ester (19, *syn/anti* mixture). ^{1}H NMR *anti* ((1*S*,1′*R*) tentatively assignment) ($CDCl_3$) δ=1.26 (t, 3H, J=7.1 Hz), 1.60–1.85 (m, 3H), 1.85–2.20 (m, 3H), 2.25–2.60 (m, 2H), 3.14–3.30 (m, 1H), 4.23 (q, 2H, J=7.1 Hz), 5.51 (d, 1H, J=4.8 Hz), 7.40–7.50 (m, 2H), 7.52–7.61 (m, 1H), 7.98–8.14 (m, 2H); distinguishable *syn* peaks δ=1.27 (t, 3H, J=7.0 Hz), 2.96–3.10 (m, 1H), 4.23 (q, 2H, J=7.0 Hz), 5.86 (d, 1H, J=3.3 Hz); ^{13}C NMR *anti* ($CDCl_3$) δ=14.0, 24.6, 26.8, 29.5, 41.8, 51.7, 61.5, 70.9, 128.4, 129.4, 129.9, 133.3, 165.9, 169.2, 207.5; *syn* δ=14.1, 26.7, 27.8, 41.7, 51.6, 61.6, 70.1, 128.3, 129.6, 129.8, 133.2, 165.5, 169.6, 207.3; HRMS (FAB). Exact mass calcd for $C_{17}H_{21}O_5$ $[M+H]^+$, 305.1389. Found 305.1382; HPLC, Daicel Chiralcel ADH+AS, hexane/^{i}PrOH=9/1, flow rate=0.9 mL/min: t_R=25.2 min (1*S*,1′*R*), t_R=27.4 min (*syn*, the absolute configuration was not determined.), t_R=29.9 min (1*R*,1′*S*), t_R=36.6 min (*syn*).

7. Reduction of 6a

7.1. Procedure for the synthesis of 10

Ligand **3t** (9.9 mg, 0.022 mmol) in CH_2Cl_2 (1.5 mL) was added to the $CuClO_4 \cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) flask under argon The yellow solution was stirred for over 8 h, and cooled to 0 °C. Freshly distilled ethyl glyoxylate (100 μL, 0.40 mmol) in CH_2Cl_2 (0.8 mL) was added to the mixture, and then enecarbamate **2a** (50.7 mg, 0.20 mmol) in CH_2Cl_2 (0.8 mL) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was allowed to warm to rt, and was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and then the residue was dried with benzene azeotropy three times and then under vacuum. THF (2.0 mL) and MeOH (0.5 mL) were added to the residue, and then the solution was cooled to −78 °C. Diethyl methoxyborane (79 μL, 0.6 mmol) was added, and the mixture was stirred for 15 min. To the mixture was added $NaBH_4$ (22.7 mg, 0.6 mmol) in one portion. The mixture was stirred for 2 h at −78 °C. The reaction was quenched by addition of AcOH (0.3 mL) and was allowed to warm to rt. The mixture was alkalized at 0 °C by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O twice. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvents were evaporated, the crude product was purified by chromatography on silica gel to afford the desired compound **10** (46.5 mg, 65% yield in two steps, *syn/anti*=94/6).

7.1.1. 4-Benzyloxycarbonylamino-2-hydroxy-4-phenyl-butyric acid ethyl ester: (10, *syn/anti*=94/6). ^{1}H NMR ($CDCl_3$) δ=1.23 (t, 3H x 19/20, J=7.1 Hz), 1.25 (t, 3H x 1/20, J=7.0 Hz), 1.95–2.40 (m, 2H), 3.33 (brs, 1H x 19/20), 3.51 (brs, 1H x 1/20), 4.00–4.40 (m, 3H), 4.85–5.20 (m, 3H), 5.52 (d, 1H x 19/20, J=7.3 Hz), 5.96 (d, 1H x 1/20, J=8.2 Hz), 7.00–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) *syn*: δ=14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; *anti*: (distinguishable peak) 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3; LRMS (FAB) m/z=358 $[M+H]^+$

7.2. Determination of relative configuration of compound 10

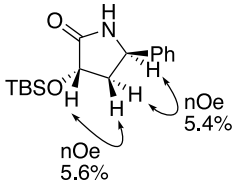
7.2.1. Synthesis of 11. To a solution of **10** (31.3 mg, 0.088 mmol) in CH_2Cl_2 (0.6 mL) was added 2,6-lutidine (12.0 mg, 0.114 mmol) in CH_2Cl_2 (0.2 mL) and TBDMSOTf (27.8 mg, 0.105 mmol) in CH_2Cl_2 (0.2 mL) successively at 0 °C. The reaction mixture was allowed to warm to rt, and was stirred for 10 h. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was purified on silica gel column chromatography to give **11** (37.9 mg, 92% yield).

7.2.2. 4-Benzyloxycarbonylamino-2-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-butyric acid ethyl ester (11, diastereomer mixture). ^{1}H NMR ($CDCl_3$) δ=*syn*: −0.03 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.15–1.27 (m, 3H), 2.00–2.35 (m, 2H), 3.90–4.30 (m, 3H), 4.80–5.15 (m, 3H), 5.50 (brs, 1H), 7.15–7.40 (m, 10 H); *anti*: (distinguishable peak) δ=−0.02 (s, 3H), 0.03 (s, 3H), 5.62 (brd, 1H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$) *syn*: δ=−5.4, −5.0, 14.0, 18.1, 25.7, 41.0, 52.9, 61.0, 66.6, 70.3, 126.4, 127.4, 128.0, 128.1, 128.4, 128.6, 136.4, 141.8, 155.3, 173.2; *anti*: (distinguishable peak) −5.0, 14.1, 41.8, 52.3, 69.8, 126.0, 127.3, 128.6, 142.2, 155.6, 173.1; IR (neat) 3343, 2940, 1720, 1518, 1254, 1131, 1038, 839, 781, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{26}H_{38}NO_5Si$ $[M+H]^+$, 472.2519. Found 472.2508.

7.2.3. Synthesis of 12. To a solution of **11** (21.4 mg, 0.0454 mmol) in AcOEt (2.0 mL) was added AcOH (16.8 mg, 0.0.272 mmol) and 5% wet Pd/C (9.7 mg, 10 mol%) at rt. After replacement of argon by hydrogen, the mixture was stirred at rt until the starting material completely disappeared (11 h). Pd/C was filtered off and saturated aqueous $NaHCO_3$ was added to the filtrate. The mixture was extracted with AcOEt, and then the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was purified on silica gel column chromatography to give **12**

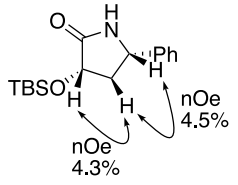
(13.4 mg, quantitative yield). Diastereomers **12** were separated by silica gel column chromatography.

7.2.4. (3*S*,5*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-major). ^{1}H NMR ($CDCl_3$) δ= 0.14 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 2.21 (ddd, 1H, J=5.1, 7.1, 13.2 Hz), 2.46 (ddd, 1H, J=5.1, 7.5, 13.2 Hz), 4.38 (dd, 1H, J=5.1, 7.1 Hz), 4.83 (dd, 1H, J=5.0, 7.5 Hz), 6.02 (brs, 1H), 7.20–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=−5.1, −4.5, 18.3, 25.8, 41.5, 55.1, 69.9, 125.5, 127.9, 129.0, 142.1, 176.3; IR (neat) 3226, 2927, 2892, 2855, 1715, 1496, 1471, 1331, 1253, 1151, 1091, 1028, 963, 880, 839, 780, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1733 (Scheme 9).



Scheme 9.

7.2.5. (3*S*,5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-minor). ^{1}H NMR ($CDCl_3$) δ= 0.15 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 1.94 (dt, 1H, J=9.2, 12.6 Hz), 2.75–2.87 (m, 1H), 4.42 (dd, 1H, J=7.9, 9.2 Hz), 4.53 (dd, 1H, J=6.2, 8.6 Hz), 5.76 (brs, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=−5.1, −4.5, 18.3, 25.8, 42.0, 53.9, 70.8, 126.1, 128.1, 128.9, 176.0; IR (neat) 3220, 2936, 2858, 2359, 1717, 1463, 1330, 1247, 1151, 882, 838, 781, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1736 (Scheme 10).



Scheme 10.

8. Determination of the absolute and relative configuration of 7f

8.1. Determination of the relative configuration of 7f

To a solution of *anti*-**7f** (45.6 mg, 0.193 mmol) in MeOH (1.0 mL) was added $NaBH_4$ (14.6 mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred for 10 min, and the reaction was quenched by addition of acetone. The mixture was kept stirred for 5 min, and then saturated NH_4Cl aqueous solution was added. The mixture was extracted with CH_2Cl_2 three times, and the extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a crude keto alcohol. To a solution of the crude product in CH_2Cl_2 (1 mL) was added $TsOH\cdot H_2O$, and the reaction mixture was stirred for 13.5 h at rt. The reaction was quenched by addition of a saturated $NaHCO_3$ aqueous solution, and was extracted with CH_2Cl_2 three times. The extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a residue, followed by purification on silica gel chromatography to afford **14** as a diastereomer mixture (19.8 mg, 53% yield, **14**/*epi*-**14**=55/45). **14** was recrystallized from CH_2Cl_2/hexane to give single crystals which were suitable for X-ray structure analysis. From *syn*-**7f**, **20** was obtained as a diastereomer mixture (84% yield, **20**/*epi*-**20**=86/14) according to the same procedure as mentioned above. The relative stereochemisty of **20** was determined by NOE analysis. Lactones **14** and **20** were used for determination of the absolute configuration as follows.

8.1.1. (3*S*,4*R*,5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (14). Mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ=0.65 (d, 3H, J=7.3 Hz), 2.75 (brs, 1H), 2.98–3.08 (m, 1H), 4.79 (d, 1H, J=6.8 Hz), 5.57 (d, 1H, J= 4.6 Hz), 7.25–7.30 (m, 2H), 7.30–7.38 (m, 1H), 7.38–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=7.4, 41.1, 72.1, 80.2, 125.2, 128.2, 128.6, 135.1, 177.0; IR (neat) 3443, 2963, 1758, 1452, 1414, 1294, 1194, 1148, 1051, 956, 754, 701, 622, 478 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.

8.1.2. (3*S*,4*R*,5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (*epi*-14). ^{1}H NMR ($CDCl_3$) δ=1.22 (d, 3H, J=7.1 Hz), 2.62 (tq, 1H, J=5.1, 6.8 Hz), 2.86 (brs, 1H), 4.47 (d, 1H, J=6.8 Hz), 5.26 (d, 1H, J=5.1 Hz), 7.20–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=10.8, 43.2, 69.7, 85.8, 125.3, 128.6, 128.8, 137.7, 176.9; IR (neat) 3430, 3039, 2924, 2857, 1772, 1455, 1275, 1202, 1143, 1093, 986, 889, 805, 742, 702 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0864.

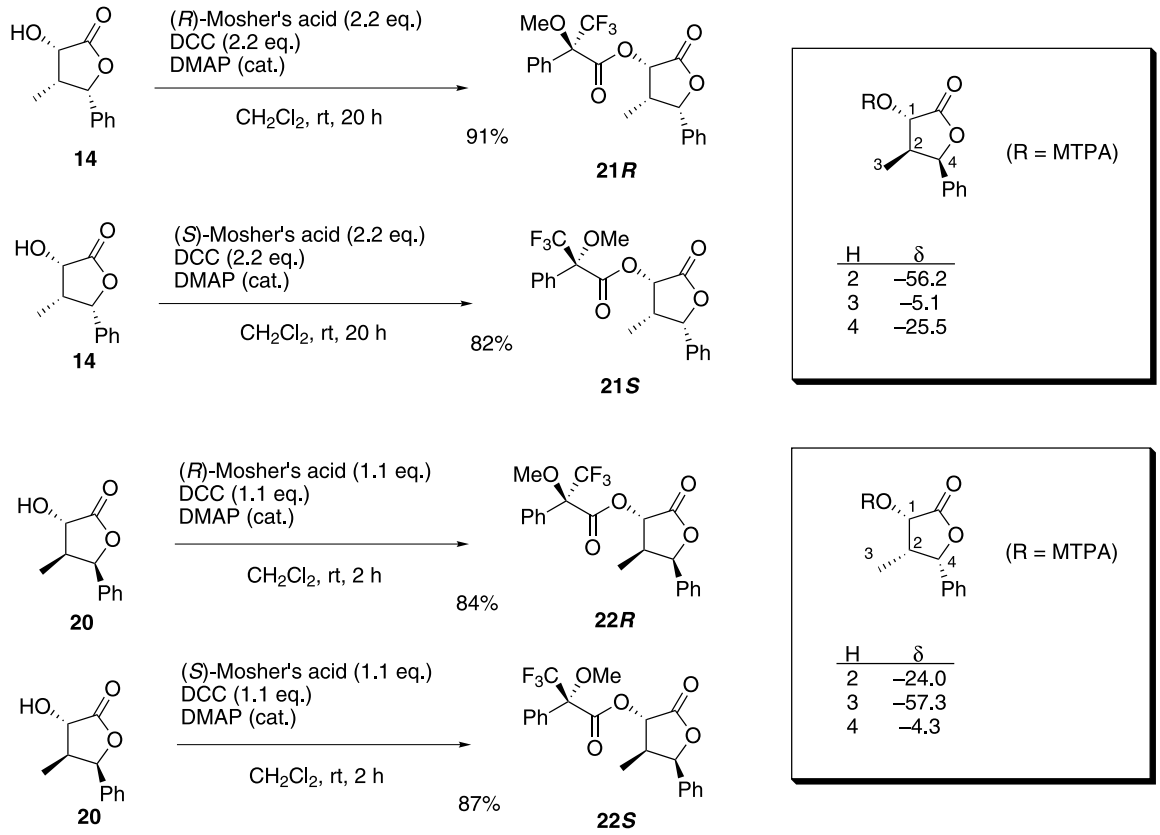
8.1.3. (3*S*,4*S*,5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (20). ^{1}H NMR ($CDCl_3$) δ=0.87 (d, 3H, J=7.0 Hz), 2.70–2.92 (m, 1H), 3.18 (brs, 1H), 4.24 (d, 1H, J=9.9 Hz), 5.63 (d, 1H, J=8.1 Hz), 7.05–7.18 (m, 2H), 7.30–7.45 (m, 3H); ^{13}C NMR ($CDCl_3$) δ=13.3, 42.1, 72.2, 82.4, 125.7, 128.5, 128.6, 135.5, 177.5; IR (neat) 3362, 2970, 1776, 1455, 1334, 1184, 1145, 1096, 991, 897, 755, 701, 464 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.

8.1.4. (3*S*,4*S*,5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (*epi*-20). ^{1}H NMR ($CDCl_3$) δ=1.24 (d, 3H, J=6.4 Hz), 2.41 (tq, 1H, J=6.4, 10.6 Hz), 3.24 (brs, 1H), 4.25 (d, 1H, J=11.0 Hz), 4.87 (d, 1H, J=10.1 Hz), 7.30–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=13.3, 47.5, 74.7, 84.1, 126.5, 128.8, 129.2, 136.2, 176.8; IR (neat) 3319, 2967, 2921, 1776, 1459, 1318, 1237, 1152, 1110, 981, 765, 700, 540 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0857.

8.2. Determination of the absolute configuration of 7f

Lactones **14** and **20** were converted into **21** and **22** respectively, by using a standard method as shown below (Scheme 11).

$\Delta\delta$ ($\delta_S-\delta_R$) in the ^{1}H NMR analysis showed minus values for all H2, H3, and H4. As expected from an analogy of **7a**, the absolute configuration of C3 was determined to be *S*.[15]



Scheme 11.

From the knowledge of the absolute stereochemistry of **14** and **20**, the absolute configurations of both *anti*-**7f** and *syn*-**7f** were determined.

8.2.1. (3*S*,4*S*,5*S*,2′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (21*R*). ^{1}H NMR ($CDCl_3$) δ=0.66 (d, 3H, J=7.1 Hz), 3.10–3.26 (m, 1H), 3.54 (d, 3H, J=0.9 Hz), 5.67 (d, 1H, J=4.8 Hz), 6.04 (d, 1H, J=7.1 Hz), 7.20–7.30 (m, 2H), 7.30–7.50 (m, 6H), 7.55–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=8.4, 39.3, 55.5, 73.3, 80.1, 125.2, 127.8, 128.5, 128.5, 128.7, 129.9, 131.0, 134.4, 165.7, 170.4; IR (neat) 3063, 3033, 2987, 2947, 2850, 1802, 1754, 1504, 1455, 1364, 1245, 1179, 1111, 1089, 1057, 975, 698 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1277.

8.2.2. (3*S*,4*S*,5*S*,2′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (21*S*). ^{1}H NMR ($CDCl_3$) δ=0.47 (d, 3H, J=7.1 Hz), 3.00–3.20 (m, 1H), 3.66 (d, 3H, J=0.9 Hz), 5.66 (d, 1H, J=5.0 Hz), 6.07 (d, 1H, J=7.1 Hz), 7.20–7.30 (m, 2H), 7.30–7.50 (m, 6H), 7.60–7.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=8.1, 39.4, 55.8, 73.0, 80.2, 125.2, 127.3, 128.5, 128.5, 128.7, 129.9, 131.6, 134.4, 165.7, 170.8; IR (neat) 3065, 2941, 2857, 1802, 1755, 1497, 1455, 1393, 1367, 1243, 1178, 1125, 1058, 977, 705 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1277.

8.2.3. (3*S*,4*R*,5*R*,2′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (22*R*). ^{1}H NMR (C_6D_6) δ=0.30 (d, 3H, J=7.0 Hz), 2.38–2.50 (m, 1H), 3.46 (d, 3H, J=0.9 Hz), 4.91 (d, 1H, J=8.6 Hz), 5.37 (d, 1H, J=11 Hz), 6.65–6.73 (m, 2H), 6.96–7.05 (m, 3H), 7.08–7.12 (m, 1H), 7.18–7.24 (m, 2H), 7.91 (apparent d, 2H, J=7.9 Hz); ^{13}C NMR (C_6D_6) δ=12.7, 39.0, 55.4, 74.2, 81.6, 125.9, 128.6, 128.7, 128.8, 130.0, 132.1, 135.3, 166.0, 170.6; IR (neat) 3033, 2974, 2945, 2850, 1800, 1757, 1497, 1453, 1340, 1243, 1170, 1116, 1056, 998, 909, 757, 699 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1245.

8.2.4. (3*S*,4*R*,5*R*,2′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (22*S*). ^{1}H NMR (C_6D_6) δ=0.28 (d, 3H, J=6.9 Hz), 2.15–2.35 (m, 1H), 3.65 (d, 3H, J=0.7 Hz), 4.83 (d, 1H, J=8.2 Hz), 5.61 (d, 1H, J=10.6 Hz), 6.64–6.72 (m, 2H), 6.90–7.05 (m, 3H), 7.05–7.25 (m, 3H), 7.80–7.90 (m, 2H); ^{13}C NMR (C_6D_6) δ=12.5, 39.4, 55.7, 73.6, 81.8, 122.2, 125.9, 127.9, 128.6, 128.8, 128.8, 130.0, 132.6, 135.2, 166.3, 171.2; IR (neat) 3065, 3033, 2945, 2851, 1800, 1759, 1496, 1454, 1342, 1273, 1247, 1172, 1123, 1081, 1057, 994, 903, 795, 763, 723 cm^{-1}; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1282.

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