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Enantioselective Cu-Catalyzed 1,4-Addition of Me_3Al to a 4,4-Disubstituted Cyclohexa-2,5-dienone

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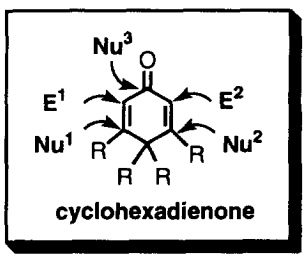
Abstract: A series of chiral enantiomerically pure 2-aryloxazolines was synthesized. (4*S*)-2-(2',6'-dimethoxyphenyl)-4-isopropyloxazoline proved to be an efficient chiral ligand for the Cu-catalyzed conjugate addition of Me_3Al to cyclohexadienone, and by using 20mol% of this ligand, 1,4-adduct was obtained in 68% ee. In addition, TBDMSOTf is crucial for the asymmetric conjugate addition to proceed with good chemical yield and high ee.

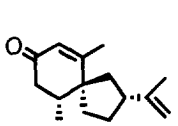
INTRODUCTION

Recently, considerable attention has been given to cyclohexa-2,5-dienones as versatile chiral synthons because of their multi-functionality.[1] Although several efficient methods have been developed to introduce chirality into achiral cyclohexa-2,5-dienones, most of these involve the temporary conversion of cyclohexa-2,5-dienones to chiral tricycloadducts by diastereoselective Diels-Alder cycloaddition with chiral cyclopentadiene,[1a] and lipase-mediated or Rh(I)(chiral BINAP)-catalyzed asymmetrization of meso-tricycloadduct.[1b,1c] There are few methods directly introducing chirality into achiral cyclohexa-2,5-dienones. To the best of our knowledge, only one example of direct chiral induction by Sharpless epoxidation has been reported (80% ee).[1d] This stimulated us to investigate other methods for differentiating both the enantiotopic face and group (C=C double bond) of achiral cyclohexa-2,5-dienone. In addition, the resulting 2-cyclohexenones containing chirality at the C5-position are versatile optically active intermediates for biologically active natural products such as solavetivone[2] and cyclointeinone.[3] From these points of view, it would be useful to develop a convenient method for synthesizing chiral 5-substituted-2-cyclohexenones. Accordingly, we undertook study on the catalytic asymmetric conjugate addition of alkylcopper reagents to **1**.

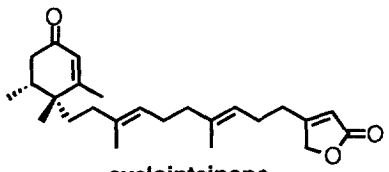
Thus far, both the stoichiometric and catalytic asymmetric conjugate additions of organocuprates to enones, which is currently a topic of interest in asymmetric organic synthesis, have been studied and quite high enantioselectivities have been realized.[4,5] However, there has been no reported examination of the asymmetric Cu-catalyzed conjugate addition of organometals to cyclohexa-2,5-dienones. These asymmetric conjugate



cyclohexadienone



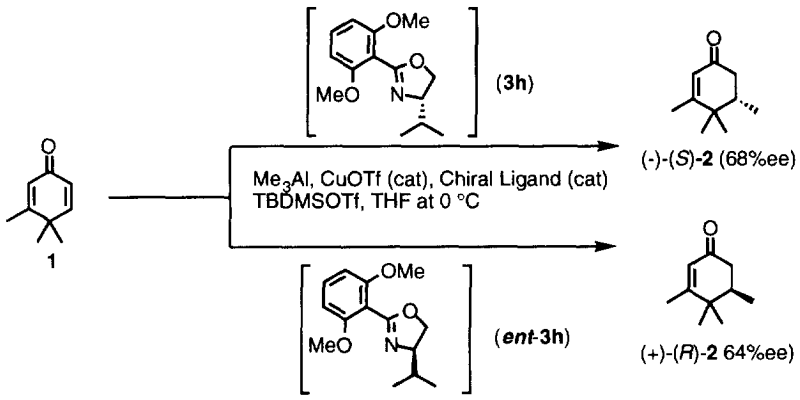
(-)-solavetivone



cyclointeinone

additions are divided into two classes depending on the type of organocopper reagent employed: *i.e.*, chirally modified heterocuprates with chiral auxiliaries[4] and achiral cuprates coordinated by external chiral ligands.[5] Although we investigated both types of reactions which had been successfully applied to enone-systems, only unsatisfactory results (low chemical yield and poor enantioselectivity) were obtained due to the poor reactivity and steric hindrance of the substrate **1**.

On the other hand, Kabbara and Westermann reported the novel Cu-catalyzed conjugate addition of trialkylaluminum (R_3Al) to steric hindered enones and cross-conjugated dienones (steroids) in the presence of silylating reagents.[6] Although the mechanistic details of the R_3Al-mediated conjugate addition have not been identified, we were intrigued by its high reactivity and examined its possibilities in asymmetric conjugate addition. Our initial effort was directed toward the search for efficient chiral ligand which can combine or coordinate to presumed active species (RCu). We evaluated a variety of chiral oxazolines **3-5**, successfully used in enantioselective Pd-catalyzed allylic alkylation,[7] and some other types of ligands **6-11** (Fig.1).



Scheme 1.

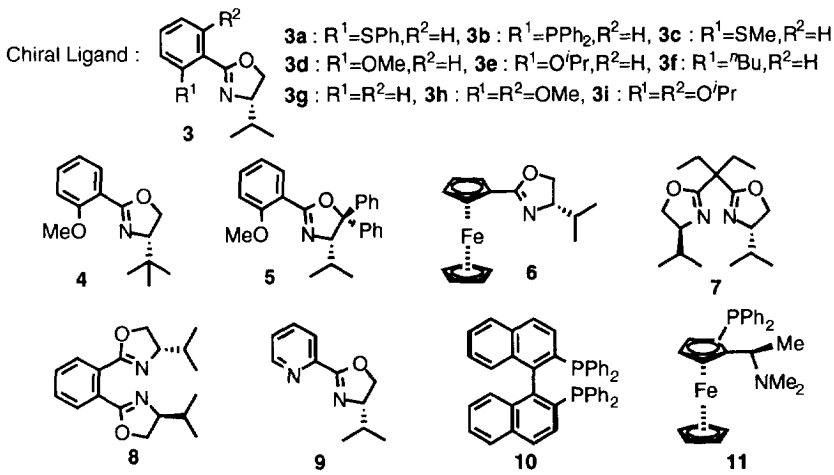


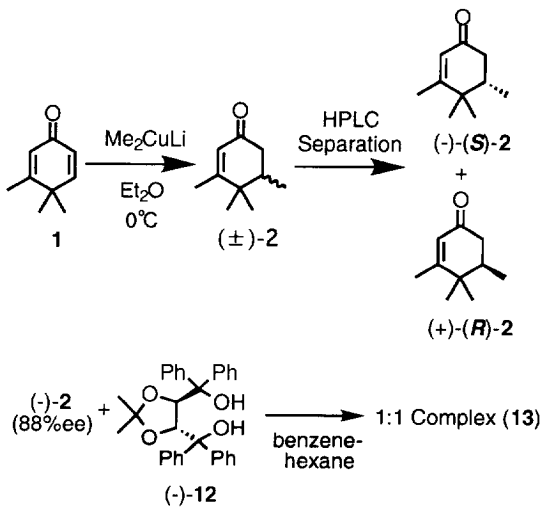
Fig. 1. Chiral ligands **3-11** using in the enantioselective Cu-catalyzed 1,4-addition of Me_3Al to cyclohexadienone **1**

Furthermore, we investigated the reaction conditions concerning additives, reaction temperature and solvent to optimize both the chemical yield and ee. Consequently, an optically active 1,4-adduct (-)-**2** was obtained in 68% ee by using a catalytic amount of a new ligand **3h** in the presence of 120 mol% of *tert*-butyldimethylsilyl triflate (TBDMSOTf) (Scheme 1). We describe here the effect of the aromatic substituents (R^1 and R^2) of **3a-i** and the role of trialkylsilyl triflate in achieving the enantioselectivity of asymmetric Cu-catalyzed conjugate addition to **1**.[8]

RESULTS AND DISCUSSION

Preparation of (+)-(R)- and (-)-(S)-3,4,4,5-tetramethyl-2-cyclohexenone 2 and determination of their absolute configurations

The chiral authentic samples of both (+)-(*R*)-**2** and (-)-(*S*)-**2** were obtained by 1,4 addition of Me_2CuLi to 3,4,4-trimethylcyclohexa-2,5-dienone **1**[9] in Et_2O and sequential HPLC separation by Daicel CHIRALPAK AS. The absolute configuration of (-)-**2** was determined to be 5*S* by a single X-ray crystallographic analysis of a 1:1 complex of (-)-*trans*-α,α-(2,2-dimethyl-1,3-oxolane-4,5-diyl)bis(diphenylmethanol) **12** and (-)-**2** according to Toda's method[10] (Scheme 2, Fig. 2).



Scheme 2. Preparation of (*S*)-**2**, (*R*)-**2** and 1:1 complex **13**

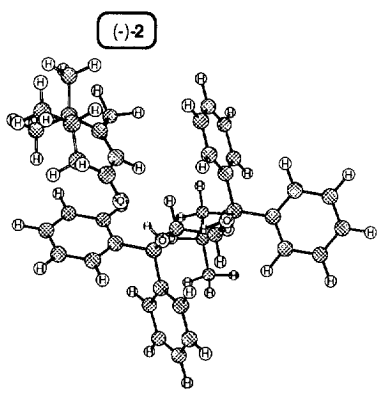
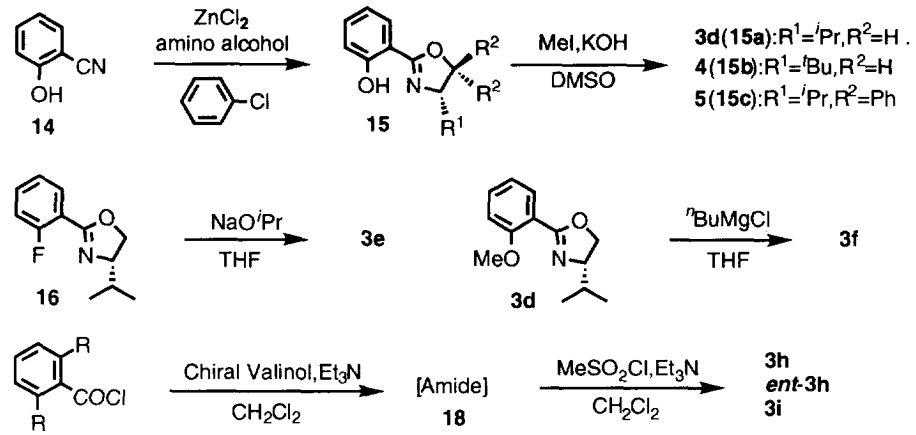


Fig. 2. X-ray structure of **13** drawn by Chem 3D

Synthesis of chiral 2-(2'- or 2',6'-substituted-phenyl)oxazolines

The syntheses of various chiral 2-(2'- and 2',6'-substituted-phenyl)oxazolines are shown in Scheme 3. 2-(2'-Methoxyphenyl)oxazolines **3d**, **4** and **5** were prepared according to the method of Balm.[11] The $ZnCl_2$-catalyzed condensation of 2-hydroxybenzonitrile **14** with appropriate chiral amino alcohols afforded the corresponding oxazolines **15**, of which the phenolic hydroxy groups[12] were methylated with methyl iodide and KOH to give **3d**, **4** and **5** in 36-94% yields. The 2-(2'-isopropoxyphenyl)oxazoline **3e** and 2-(2'-butylphenyl)oxazoline **3f** were prepared from 2-(2'-fluorophenyl)oxazoline **16**[13] and **3d** by treatment with sodium isopropoxide and butylmagnesium chloride,[14] respectively. The 2-(2',6'-dialkoxyphenyl)oxazolines **3h**, ***ent*-3h**, **3i** were prepared from appropriate acid chlorides **17a-b** *via* the corresponding amides **18** according to the modified method of Denmark.[15] Exposure of **18** to the mesylation with MsCl and Et_3N at room temperature promoted the cyclization of the mesylates into a oxazoline ring in one pot to give the desired oxazolines **3h**, ***ent*-3h** and **3i** in good yields. In this way, starting from commercially available amino alcohols, differently



Scheme 3. Synthesis of Chiral 2-(2'- and 2',6'-Substituted-phenyl)oxazolines

substituted ligands were readily accessible in enantiomerically pure form. Finally, the other known chiral ligands **3a**,[7b] **3b**,[13] **3c**,[13] **3g**,[13] **6**,[16] **7**,[15] **8**[11] and **9**[11] were prepared as previously reported, and (+)-(*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(+)-(*R*)-BINAP] **10** and (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl] ethylamine [(*S*)-(*R*)-PPFA] **11** were purchased from Kanto Chemicals.

Asymmetrization of **1** *by the Cu-catalyzed conjugate addition of* R_3Al

We first investigated the asymmetric Cu-catalyzed conjugate addition of R_3Al in the presence of 20 mol% of phenylthio- or diphenylphosphino-oxazolines **3a** and **3b**, which had been successfully used in the enantioselective Pd-catalyzed allylic alkylation as bidentate ligands (Table 1). The reactions were carried out with Me_3Al (110 mol%), copper(I) bromide (1 mol%), and **3a** or **3b** (20 mol%) in the presence of various additives. Contrary to zinc chloride and lithium bromide which inhibited the reaction, 120 mol% of trimethylsilyl chloride (TMSCl) effectively promoted the reaction rate. However, Me_2AlCl, which should be produced in the course of the reaction if TMSCl is used as the additive, decreased the ee of the conjugate addition (entries 1-6). Therefore, we employed trimethylsilyl triflate (TMSOTf), possessing higher Lewis acidity and no halogen atom, as a counter anion instead of TMSCl. In practice, TMSOTf had a beneficial effect on enantioselectivity and gave (-)-(*S*)-**2** in 14-48% ee, depending on the reaction temperature (entries 7-9). In addition, the enantioselectivity further increased to 63% ee when the reaction was carried out at 0℃ in the presence of TBDMSOTf (entry 11). While increasing the amount of TBDMSOTf (200 mol%) had no effect on the ee (entry 12), an increased amount of Me_3Al (200 mol%) improved both the chemical yield and ee of (-)-(*S*)-**2** (entry 10). Moreover, an increased amount of CuBr (5 mol%) improved only the chemical yield with a negligible loss of ee (entry 13), and changing Cu(I) salt from CuBr to CuOTf significantly affected the chemical yield but not enantioselectivity (entry 14). The ee was dramatically decreased when the ratio of lignd/CuOTf was reduced to less than 4/1 (entries 14-17). Unfortunately, the asymmetric conjugate addition of Et_3Al to **1** gave the corresponding ethyl adduct only with poor enantioselectivity even under the optimized conditions (entry 18).

Enantioselective 1,4-addition of Me_3Al *to* **1** *with TBDMSOTf in the presence of various oxazolines*

Since asymmetrization of **1** by the Cu-catalyzed conjugate addition with the chiral oxazoline **3a** was revealed to be possible, we further examined the efficiency of other chiral ligands (**3c-i** and **ent-3h**) to clarify the mechanism of this asymmetric conjugate addition as well as to increase both the chemical yield and ee (Table 2). As switching the thiophenyl group of **3a** to a thiomethyl group had no effect on enantioselectivity (**3c**: entry 1),

Table 1. Optimization of Cu-Catalyzed Asymmetric Conjugate Addition of R_3Al to Cyclohexadienone **1** in the Presence of the Chiral Oxazolines **3a** or **3b**: Effects of the Additive, Temperature, and Copper Salt[a]

Entry	Ligand	R_3Al (R)	CuX	Additive	R_3Al/CuX/ Ligand/Additive	Temp. ℃	Time hr	Yield[b] %	ee[c] %
1	**3a**	Me	CuBr	none	1.1/0.01/0.2/0.0	rt	23	11	5
2	**3a**			$ZnCl_2$	1.1/0.01/0.2/1.2	rt	24	(no reaction)	
3	**3a**			LiBr	1.1/0.01/0.2/1.2	rt	24	(no reaction)	
4	**3a**			Me_2AlCl	1.1/0.01/0.2/1.2	rt	22	15	0
5	**3a**			TMSCl	1.1/0.01/0.2/1.2	rt	5	39	8
6	**3b**			TMSCl	1.1/0.01/0.2/1.2	rt	22	28	0
7	**3a**			TMSOTf	1.1/0.01/0.2/0.0	rt	2	37	37
8	**3a**			TMSOTf	1.1/0.01/0.2/1.2	0	5	28	48
9	**3a**			TMSOTf	1.1/0.01/0.2/1.2	-20	5	61	14
10	**3a**			TMSOTf	2.0/0.01/0.2/1.2	0	2	46	56
11	**3a**			TBDMSOTf	2.0/0.01/0.2/1.2	0	2	35	63
12	**3a**			TBDMSOTf	2.0/0.01/0.2/2.0	0	3	28	52
13	**3a**			TBDMSOTf	2.0/0.05/0.2/1.2	0	1.5	59	54
14	**3a**		CuOTf[d]	TBDMSOTf	2.0/0.01/0.2/1.2	0	2	53	63
15	**3a**			TBDMSOTf	2.0/0.05/0.2/1.2	0	2	66	59
16	**3a**			TBDMSOTf	2.0/0.05/0.1/1.2	0	2	42	42
17	**3a**			TBDMSOTf	2.0/0.05/0.05/1.2	0	2	46	8
18	**3a**	Et		TBDMSOTf	2.0/0.05/0.2/1.2	0	2	24	17

[a] All reactions were carried out in dry THF. [b] Isolated yield. [c] Determined by HPLC analysis [Daicel CHIRALPAK AS, hexane/2-propanol=7/3, 0.5 ml/min at 35 ℃, (+)-(*R*)-**2** 43.0 min, (-)-(*S*)-**2** 56.2 min]. [d] Cu(I)·1/2C_6H_6 complex was used.

we next investigated the effect of the aromatic substituents of the ligands **3d-f** to identify the role of the sulfur atom by changing the coordination ability of the chiral ligand. By using 2-(2'-methoxyphenyl)oxazoline **3d**, the chemical yield remarkably increased while optical yield decreased (entry 2). However, the optical yield was restored by use of 2-(2'-isopropoxyphenyl)oxazoline **3e**, a more sterically hindered ligand, without any loss ofthe reactivity (entry 3). We presumed that this augmentation of reactivity in the conjugate addition was attributable to the electric factor of the 2'-alkoxy groups. Interestingly, similar chiral induction was observed with 2-(2'-butylphenyl)oxazoline **3f** but not 2-phenyloxazoline **3g** which possesses no substituent on the aromatic ring (entries 4 and 5). In general, 2-(2'-heteroatom-substituted-phenyl)oxazolines are considered to coordinate to transition metals (Pd, Ni, Cu, *etc.*) as bidentate ligands.[7] However, considering that the alkoxy- and alkyl-substituted chiral ligands **3d-f** showed a similar ee, **3a-e** seem to work as monodentate ligands. That is, the substituent (R^1) in these ligands may not participate in coordination to the copper(I) atom, but may provide conformational restriction of the transition state *via* steric factors. Expecting a more restricted transition assembly, we performed the reaction with new chiral ligands, 2-(2',6'-disubstituted-phenyl)oxazolines **3h-i**. The reaction with **3h** gave (-)-(*S*)-**2** in 88% yield with a maximum ee of 68% (entry 6), while use of **3i**, a more

Table 2. Asymmetric Conjugate Addition of Me_3Al to **1** with Various Chiral Oxazoline Ligands[a]

Entry	Ligand	Solvent	Time / hr	Yield[b] / %	ee / %[c]
1	**3c** (R^1=SMe, R^2=H)	THF	1	39	63
2	**3d** (R^1=OMe, R^2=H)	THF	0.5	88	45
3	**3e** (R^1=O^{i}Pr, R^2=H)	THF	0.5	70	59
4	**3f** (R^1=^{n}Bu, R^2=H)	THF	2	48	46
5	**3g** (R^1=R^2=H)	THF	1	61	0
6	**3h** (R^1=R^2=OMe)	THF	1	88	68
7		AcOEt	0.5	57	51
8		Et_2O	0.5	48	29
9	***ent*-3h** (R^1=R^2=OMe)	THF	0.5	79	64
10	**3i** (R^1=R^2=O^{i}Pr)	THF	4	62	63

[a] Me_3Al/CuOTf·1/2C_6H_6/ligand/TBDMSOTf/**1** = 2.0/0.05/0.2/1.2/1.0 at 0℃. [b] Isolated yield. [c] Determined by HPLC analysis [Daicel CHIRALPAK AS].

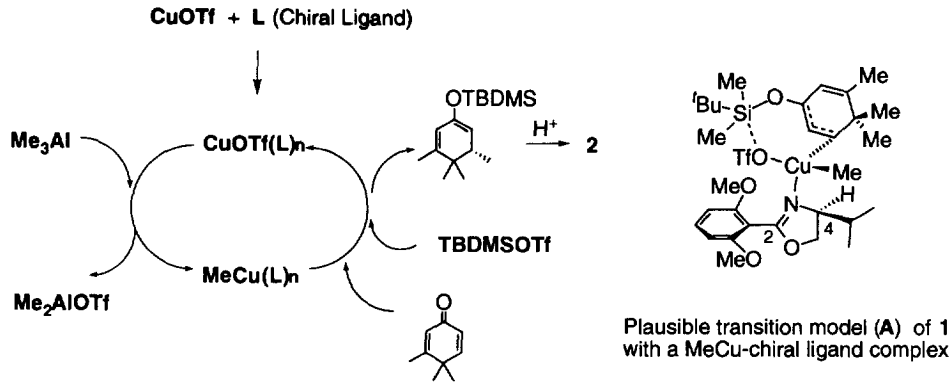


Fig. 3. Mechanism for Cu-Catalyzed 1,4-Addition of Me_3Al in the Presence of TBDMSOTf

sterically hindered ligand, gave no improvement (entry 10). With regard to the reaction solvent, enantioselectivities decreased in the sequence: THF > AcOEt > Et_2O (entries 6-8). Whereas (-)-(*S*)-**2** was always obtained as the major product when (4*S*)-isopropyloxazolines were used as a chiral ligand, the reaction with ***ent*-3h** gave (+)-(*R*)-**2** with a compatible ee value but a reverse sense (entry 9). This result strongly indicates that the induction of chirality in the asymmetric conjugate addition originates from the C4-chirality of the oxazoline ligands.

The postulated reaction mechanism of the asymmetric conjugate addition

We have clarified the following facts in our investigation.

a) The oxazoline ring plays a crucial role in the coordination to copper catalysis.
b) The chiral induction of the asymmetric conjugate addition to **1** originates from the chirality of the alkyl-substituted C4-position of the oxazoline ring.
c) Use of TBDMSOTf as an additive gives the best ee value (up to 68% ee).
d) ortho-Substituents of the aromatic ring in 2-aryloxazoline ligand are crucial for good ee.

The transition state model in Fig. 3 may explain the enantiofacial differentiation in the present asymmetric conjugate addition.[17] At first, $MeCu(L)_n$ would be formed by addition of Me_3Al to a mixture of CuOTf and the ligand (L). Then, dienone **1** coordinates to this complex reversibly to generate a non-reactive $MeCu(dienone)(L)_{n-1}$ complex, which gives no 1,4-addition adduct at 0℃ without TBDMSOTf. From the steric consideration by model study, **1** may predominantly approach from the upper-right face of the $MeCu(L)_n$ (model **A**) due to steric hindrance of the C4-isopropyl group and the C2-aryl ring of the ligand. Therefore, by adding TBDMSOTf to the reaction mixture, the activated dienone and copper π-complex (**A**) would be formed as major products, and then the TBDMS enol ether of (-)-(*S*)-**2** is obtained predominantly together with the regeneration of $CuOTf(L)_n$. Although interaction of the triflate anion with the copper atom may help to make the transition state more rigid, effect of the trialkylsilyl groups on ee is not clear from the experimental results.

Other Chiral Ligands

The results with other types of chiral ligands are shown in Table 3. As regards the effect of the C4-substituent of the oxazoline ring, the ee value increased a little by replacing the isopropyl group with a *tert*-butyl group **4** (entries 1,2). Although the use of other ligands **5-11** gave no improved results (entries 3-8), an interesting result was demonstrated in the cases of ligands **6-9**, where the senses of chirality induced in the conjugate addition were reversed notwithstanding that all of these chiral ligands had been derived from the same amino alcohol (entries 3-6).

Table 3. Asymmetric Conjugate Addition of Me_3Al to Cyclohexadienone **1** with Various Chiral Ligands **4-11**[a]

Entry	Ligand	Time / hr	Yield[b] / %	*S/R* (ee / %)[c]
1	**4**	4	49	75/25 (50)
2	**5**	3.5	20	68/32 (36)
3	**6**	1	50	45/55 (11)
4	**7**	2	46	46/54 (8)
5	**8**	1	13	67/33 (33)
6	**9**	1	33	44/56 (12)
7	**10**		(no reaction)	
8	**11**		(no reaction)	

[a] $Me_3Al/CuOTf \cdot 1/2C_6H_6$/ligand/TBDMSOTf/**1** = 2.0/0.05/0.2/1.2/1.0 in THF at 0℃. [b] Isolated yield. [c] Determined by HPLC analysis [Daicel CHIRALPAK AS, hexane/2-propanol=7/3, 0.5 ml/min at 35℃.

CONCLUSION

In summary, we have achieved the first Cu-catalyzed asymmetric conjugate addition of trialkylaluminum to 3,4,4-trimethylcyclohexa-2,5-dienone in the presence of 2-aryloxazoline as a catalytic chiral ligand and TBDMSOTf as an additive. We have clarified here the effect of the aryl substituents of the chiral oxazolines and the role of TBDMSOTf in achieving the enantioselectivity in our asymmetric conjugate addition reaction. Although the ee's are still unsatisfactory (up to 68% ee), the mild conditions, ease of preparation and stability of the chiral ligand are all very encouraging. Also, this process is superior in that it is free of ecological hazards due to the use of catalytic amounts of transition metals and the avoidance of additives such as HMPA or TMEDA. Further examination of the use of new catalysis and mechanistic studies are underway in our laboratory to achieve a much higher ee. In addition, we have succeeded in applying this asymmetric conjugate addition to the total synthesis of (-)-solavetivone.[18]

Acknowledgments. We are grateful to Dr. T. Date and Mr. K. Okamura (Analytical Research Laboratory, Tanabe Seiyaku Co., Ltd.) for a measurement of CD spectra of (+)-(*R*)-**2** and (-)-(*S*)-**2**.

EXPERIMENTAL

General: Melting points are uncorrected. IR spectra were obtained using a Horiba FT-210 and Shimadzu IR-420 spectrometer. ^{1}H-NMR spectra were obtained using a JEOL JNM-GX-500 (500MHz), Varian VXR-200 (200MHz) and Bruker AC-200 (200MHz) spectrometer. ^{13}C-NMR spectra were obtained using a JEOL JNM EX-270 (67.8MHz) and Bruker AC-200 (50.3MHz) spectrometer. Optical rotations were measured with a JASCO DIP-360 polarimeter. Mass spectra (MS) were measured with a Shimadzu GCMS-QP-1000 and HITACHI M-2000A spectrometer. High resolution mass spectra (HI-MS) were measured with a JEOL JMS-D300 spectrometer. HPLC analysis of **2** was carried out on a Shimadzu LC-6A with a Shimadzu SPD-6A UV detector (set at 254 nm) equipped with a Daicel CHIRALPAK AS (4.6×250 mm). Each enantiomers of **2** was separated by TOSOH CCPP-M HPLC system equipped with a Daicel CHIRALPAK AS. X-ray crystallographic analysis was performed using a RIGAKU AFC-5R diffractometer. Circular dichroism spectra (CD) were obtained using a JASCO J-720W spectropolarimeter. (*S*)-(+)-, (*R*)-(-)-2-Amino-3-methyl-1-butanol, and (*S*)-(+)-2-amino-3,3-dimethyl-1-butanol were purchased from Aldrich. (*S*)-(+)-2-amino-3-methyl-1,1-diphenyl-1-butanol was prepared from L-Val-OMe·HCl according to the literature.[19] 2,6-Dimethoxybenzoyl chloride was purchased from Aldrich. 2,6-Di-isopropoxybenzoyl chloride was prepared from 2,6-dihydroxybenzoic acid according to the literature.[20] Column chromatography was carried out using Merck Kieselgel 60. All dry solvents were obtained from Kanto Chemicals.

(±)-3,4,4,5-Tetramethylcyclohexa-2-en-1-one [(±)-2]. To a suspension of copper(I) iodide (380 mg, 2.0 mmol) in dry Et_2O (2 ml) was added dropwise a 1.6 M Et_2O solution of methyllithium (2.9 ml, 4.0 mmol) at

0℃ under a nitrogen atmosphere. After being stirred at 0℃ for 20 min, 3,4,4-trimethylcyclohexa-2,5-dien-1-one **1** (136 mg, 1.0 mmol) was added at 0℃ to the mixture and the stirring was continued for additional 10 min. The mixture was quenched with a saturated aqueous NH_4Cl solution at 0℃, and then allowed to warm to room temperature. After the resulting mixture was filtered through a pad of Celite and solid residue was washed with Et_2O, the collected extracts were washed with a saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$ and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 5/1) to give the enone (±)-**2** (131 mg, 86%) as a colorless oil. IR (film): 1671 (C=O), 1620 (C=C) cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$): δ 1.00 (d, 3H, *J* = 6.8 Hz, C5-Me), 1.04 and 1.17 (s, 3H x 2, C4-Me), 1.93 (s, 3H, C3-Me), 2.01-2.06 (m, 1H, C5), 2.24 (dd, 1H, *J* = 17.1 and 11.1 Hz, C6), 2.40 (dd, 1H, *J* = 17.1 and 4.3 Hz, C6), 5.79 (s, 1H, C2). ^{13}C-NMR (67.8 MHz, $CDCl_3$): δ 16.0 and 20.0 (C4-Me x 2), 20.4 (C3-Me), 25.0 (C5-Me), 38.7 (C4), 39.2 (C5), 42.4 (C6), 126.3 (C2), 169.3 (C3), 199.1 (C1). MS: 153 (10, M^++1), 152 (24, M^+), 110 (100), 95 (67), 83 (67), 67 (53), 41 (83). HI-MS: calcd for $C_{10}H_{16}O$: 152.1199, found: 152.1198.

***(+)-(R)- and (-)-(S)-3,4,4,5-Tetramethylcyclohexa-2-en-1-one* 2.** (±)-**2** (100 mg) was purified by HPLC to give 39 mg (39%) of (+)-(*R*)-**2** and 42 mg (42%) of (-)-(*S*)-**2**. [HPLC separation conditions: Daicel CHIRALPAK AS, hexane/2-propanol = 5/5, flow rate 0.8 ml/min, column temperature 35℃, t_R[(+)-(*R*)-**2**] = 11.4 min, t_R[(-)-(*S*)-**2**] = 13.9 min]. (+)-(*R*)-**2**: a colorless oil. $[\alpha]_D^{26}$ +102 (c = 0.53, $CHCl_3$)(>99% ee by HPLC). CD (3 mM in MeOH); Δε = +0.32 (328 nm, n→π* cotton effect). (-)-(*S*)-**2**: a colorless oil. $[\alpha]_D^{24}$ -92.0 (c = 0.57, $CHCl_3$)(88% ee by HPLC). CD (3 mM in MeOH); Δε = −0.28 (328 nm, n→π * cotton effect).

1:1 Complex of (-)-(S)-3,4,4,5-tetramethylcyclohexa-2-enone 2 and (-)-trans-α,α'-(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) 12 (13). To (-)-**12** (35 mg, 0.074 mmol) in benzene (2 ml) was added (-)-(*S*)-**2** (11 mg, 0.074 mmol) in hexane (2 ml). The mixture was kept at room temperature for 24 h to give 36 mg (78%) of **13** as colorless prisms. mp 143-144℃ (benzene/hexane). $[\alpha]_D^{18}$ -60.8 (c = 0.13, $CHCl_3$)(>96% ee by HPLC). IR (KBr): 3265 (OH), 1639 (C=O) cm^{-1}; ^{1}H-NMR (200MHz, $CDCl_3$): δ 0.99 (d, 3H, *J* = 6.8 Hz, C5-Me), 1.04 (s, 3H x 3, C4-Me and oxolane-Me x 2), 1.17 (s, 3H, C4-Me), 1.93 (d, 3H, *J* = 1.2 Hz, C3-Me), 1.95-2.10 (m, 1H, C5), 2.19 (dd, 1H, *J* = 16.8 and 10.6 Hz, C6), 2.41 (dd, 1H, *J* = 16.8 and 4.7 Hz, C6), 3.88 (br-s, 2H, OH x 2), 4.60 (s, 2H, oxolane-CH x 2), 5.80 (s, 1H, C2), 7.23-7.38 (m, 16H, ArH), 7.51-7.55 (m, 4H, ArH). *Anal.* Calcd. for $C_{41}H_{46}O_5 \cdot 1/10H_2O$: C; 79.35, H; 7.50. Found: C; 79.12, H; 7.24.

X-Ray crystallographic analysis of 13. Crystal data for **13**: $C_{41}H_{46}O_5$, M.W. = 618.78, a = 10.204(1), b = 35.041(1), c = 9.673(1), U = 3458.5(5)A^3, space group: $P2_12_12_1$, Z = 4. The crystal structure was solved by the direct method using SHELXS-86[21] program. Full matrix least-squares refinement of positional and thermal parameters led to the final convergence with R = 0.036 (Rw = 0.075) using SHELXL-93.[22] The absolute configuration (5*S*) of (-)-**2** was determined from the known absolute configuration of (-)-**12**. Atomic co-ordinates and temperature factors, bond distances and angles have been deposited at the Cambridge Crystallographic Data centre.

Synthesis of mono-alkoxyphenyloxazolines 3d, 4 and 5. General procedure:

(4S)-2-(2'-Methoxyphenyl)-4-isopropyloxazoline (3d). The mixture of 2-hydroxybenzonitrile **14** (1.19 g, 10.0 mmol), (*S*)-(+)-2-amino-3-methyl-1-butanol (1.7 ml, 15.0 mmol), $ZnCl_2$ (0.21 g, 1.0 mmol), and chlorobenzene (12 ml) was refluxed for 20 h. After removal of the solvent *in vacuo*, the residue was purified by SiO_2 column chromatography (hexane/AcOEt = 9/1) to give (4*S*)-2-(2'-hydroxyphenyl)-4-isopropyloxazoline **15a** (1.96 g, 96%) as a colorless oil. To a suspension of a powdered KOH (274 mg, 4.9 mmol) and **15a** (250 mg, 1.2 mmol) in DMSO (1 ml) was added methyl iodide (0.15 ml, 2.4 mmol) at room temperature. After being stirred for 20 min at room temperature, the mixture was poured into ice water and extracted with AcOEt. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and a saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 2/1) to give **3d** (261 mg, 98%) as a pale yellow viscous oil. $[\alpha]_D^{24}$ -50.8 (c = 0.90, EtOH). IR (film): 1650 (C=N) cm^{-1}. ^{1}H-NMR (200MHz, $CDCl_3$): δ 0.94 and 1.04 (d, 3H x 2, *J* = 6.8 Hz, ^{i}Pr-Me), 1.94 (sept, 1H, *J* = 6.8 Hz, ^{i}Pr-CH), 3.90 (s, 3H, OMe), 4.13-4.22 (m, 2H, C4 and C5), 4.32-4.46 (m, 1H, C5), 6.93-7.01 (m, 2H, ArH), 7.37-7.46 (m, 1H, ArH), 7.73 (dd, 1H, *J* = 8.0 and 1.9 Hz, ArH).

^{13}C-NMR (50.3MHz, $CDCl_3$): δ 18.0 and 18.9 (Me x 2), 32.7 (^{i}Pr-CH), 56.1 (OMe), 69.6 (C5), 72.7 (C4), 111.9 (C3'), 117.6 (C1'), 120.3 (C5'), 131.3 (C6'), 132.0 (C4'), 158.4 (C2'), 162.2 (C2). MS: 220 (7, M^++1), 219 (15, M^+), 206 (35), 176 (72), 148 (15), 135 (100), 121 (14). *Anal.* Calcd for $C_{13}H_{17}NO_2$•1/10H_2O: C; 70.63, H; 7.84, N; 6.34. Found: C; 70.60, H; 7.94, N; 6.34.

(4S)-2-(2'-Methoxyphenyl)-4-tert-butyloxazoline (4). **4** was prepared from **14** (775 mg, 6.5 mmol) and (*S*)-(+)-2-amino-3,3-dimethyl-1-butanol (762 mg, 6.5 mmol) *via* **15b** by the same procedure described for **3d**. The obtained residue was purified by SiO_2 column chromatography (hexane/AcOEt = 4/1) to give **4** (1.01 g, 67%) as colorless prisms. mp 41-42℃ (hexane). $[\alpha]_D^{24}$ -18.8 (c = 0.25, EtOH). IR (film): 1653 (C=N) cm^{-1}. ^{1}H-NMR (200MHz, $CDCl_3$): δ 0.95 (s, 9H, ^{t}Bu), 3.79 (s, 3H, OMe), 3.92-4.32 (m, 3H, C4 and C5), 6.85-6.95 (m, 2H, ArH), 7.29-7.37 (m, 1H, ArH), 7.68-7.73 (m, 1H, ArH),. ^{13}C-NMR (50.3MHz, $CDCl_3$): δ 25.8 (^{t}Bu-Me x 3), 33.9 (^{t}Bu), 55.9 (OMe), 68.3 (C5), 76.3 (C4), 111.9 (C3'), 118.0 (C1'), 120.2 (C5'), 131.2 (C6'), 131.9 (C4'), 158.4 (C2'), 162.3 (C2). MS: 234 (3, M^++1), 233 (5, M^+), 176 (100), 148 (20), 121 (20). *Anal.* Calcd for $C_{14}H_{19}NO_2$: C; 72.07, H; 8.21, N; 6.00. Found: C; 71.98, H; 8.06, N; 5.96.

(4S)-2-(2'-Methoxyphenyl)-4-isopropyl-5,5-diphenyloxazoline (5). **5** was prepared from **14** (306 mg, 2.6 mmol) and (*S*)-(+)-2-amino-3-methyl-1,1-diphenyl-1-butanol (655 mg, 2.6 mmol) *via* **15c** by the same procedure described for **3d**. The obtained residue was purified by SiO_2 column chromatography (hexane/AcOEt = 5/1) to give **5** (280 mg, 36%) as a pale yellow viscous oil. $[\alpha]_D^{25}$ −300 (c = 1.37, $CHCl_3$). IR (KBr): 1656 (C=N) cm^{-1}; ^{1}H-NMR (200MHz, $CDCl_3$): δ 0.67 and 1.04 (d, 3H x 2, *J* = 6.8 Hz, ^{i}Pr-Me), 1.62-1.87 (m, 1H, ^{i}Pr-CH), 3.90 (s, 3H, OMe), 4.81 (d, 1H, *J* = 4.4 Hz, C4), 6.96-7.06 (m, 2H, ArH), 7.24-7.48 (m, 9H, ArH), 7.57-7.62 (m, 2H, ArH), 7.77-7.82 (m, 1H, ArH). ^{13}C-NMR (67.8MHz, $CDCl_3$): δ 17.0 and 22.0 (Me x 2), 30.4 (^{i}Pr-CH), 56.1 (OMe), 80.1 (C4), 92.4 (C5), 112.4 (C3'), 118.6 (C1'), 120.4 (C5'), 126.5, 127.0, 127.2, 127.5, 127.6, 128.1, 131.3, 131.9, 141.2, 146.1 (Ar-C), 158.9 (C2'), 160.7 (C2). MS: 371 (M^+, 0.2), 356 (0.1), 189 (10), 174 (20), 119 (22). *Anal.* Calcd for $C_{25}H_{25}NO_2$: C; 80.83, H; 6.78, N; 3.77. Found: C; 80.70, H; 6.79, N; 3.77.

(4S)-2-(2'-Isopropoxyphenyl)-4-isopropyloxazoline (3e). To a suspension of 62.5% NaH in mineral oil (200 mg, 5.2 mmol) in THF (9 ml) was added dropwise 2-propanol (0.4 ml, 5.2 mmol) at 0℃ and the resulting mixture was refluxed for 30 min under a nitrogen atmosphere. After the solution was cooled to room temperature, a solution of (4*S*)-2-(2'-fluorophenyl)-4-isopropyloxazoline **16** (360 mg, 1.7 mmol) in THF (1 ml) was added to the mixture, and the whole was refluxed for 30 min. The cooled mixture was quenched with water and extracted with AcOEt. The organic phase was washed with a saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/Et_2O = 9/1) to give **3e** (223 mg, 52%) as a pale yellow viscous oil. $[\alpha]_D^{26}$ -75.7 (c = 0.22, EtOH). IR (film): 1651 (C=N) cm^{-1}. ^{1}H-NMR (200MHz, $CDCl_3$): δ 0.96 and 1.02 (d, 3H x 2, *J* = 6.7 Hz, ^{i}Pr-Me), 1.32 and 1.33 (d, 3H x 2, *J* = 6.1 Hz, O^{i}Pr-Me), 1.85 (m, 1H, ^{i}Pr-CH), 4.03-4.16 (m, 2H, C4 and C5), 4.29-4.41 (m, 1H, C5), 4.52 (sept, 1H, *J* = 6.1 Hz, O^{i}Pr-CH), 6.89-7.06 (m, 2H, ArH), 7.28-7.37 (m, 1H, ArH), 7.65 (dd, 1H, *J* = 8.1 and 2.0 Hz, ArH),. ^{13}C-NMR (50.3MHz, $CDCl_3$): δ 18.3 and 18.7 (Me x 2), 22.2 (O^{i}Pr-Me x 2), 32.8 (^{i}Pr-CH), 69.9 (C5), 72.1 (O^{i}Pr-CH), 72.6 (C4), 116.0 (C3'), 120.0 (C1'), 120.6 (C5'), 131.2 (C6'), 131.6 (C4'), 157.0 (C2'), 163.0 (C2). MS: 248 (24, M^++1), 232 (63), 218 (33), 204 (100), 189 (30), 162 (76), 146 (218), 134 (38), 121 (24), 107 (26). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C; 72.84, H; 8.56, N; 5.66. Found: C; 72.69, H; 8.64, N; 5.84.

(4S)- 2-(2'-"Butylphenyl)-4-isopropoxyoxazoline (3f). To a solution of **3d** (220 mg, 1.0 mmol) in THF (10 ml) was added dropwise 2.0 M THF solution of "butylmagnesium chloride (0.60 ml, 1.2 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 21 h, the solution was quenched with a saturated aqueous NH_4Cl solution at 0℃ and extracted with AcOEt. The organic phase was washed with a saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and then concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt = 95/5) to give **3f** (170 mg, 69%) as colorless viscous oil. $[\alpha]_D^{27}$ -66.3 (c = 0.18, EtOH). IR (film): 1647 (C=N) cm^{-1}. ^{1}H-NMR (200MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.1 Hz, $CH_2CH_2CH_2\underline{CH_3}$), 0.96 and 1.04 (d, 3H x 2, *J* = 6.7 Hz, ^{i}Pr-Me), 1.26-1.65 (m, 4H, *J* = 7.1 Hz, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 1.72-1.92 (m, 1H, ^{i}Pr-CH), 2.83-3.09 (m, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_2CH_2CH_3$), 4.01-4.15

(m, 2H, C4 and C5), 4.28-4.42 (m, 1H, C5), 7.14-7.36 (m, 3H, ArH), 7.70-7.74 (m, 1H, ArH),. ^{13}C-NMR (50.3MHz, $CDCl_3$): δ 14.0 ($CH_2CH_2CH_2\underline{C}H_3$), 18.5 and 18.9 (^{i}Pr-Me x 2), 22.8 ($CH_2CH_2\underline{C}H_2CH_3$) 33.1 (^{i}Pr-CH), 33.9 ($CH_2\underline{C}H_2CH_2CH_3$), 34.1 ($\underline{C}H_2CH_2CH_2CH_3$), 69.7 (C5), 73.2 (C4), 125.5 (C5'), 127.4 (C1'), 130.1 (C3'), 130.3 (C4'+C6'), 143.5 (C2'), 163.9 (C2). MS: 246 (7, M^++1), 245 (38, M^+), 216 (100), 202 (41), 131 (16). *Anal.* Calcd for $C_{16}H_{23}NO_2$: C; 78.32, H; 9.45, N; 5.71. Found: C; 78.43, H; 9.44, N; 5.89.

Synthesis of dialkoxyphenyloxazolines 3h, ent-3h, and 3i. General procedure:

(4S)- 2-(2',6'-Dimethoxyphenyl)-4-isopropyloxazoline (3h). **3h** and **18a** were prepared according to the Denmark's procedure. To a mixture of 2,6-dimethoxybenzoylchloride **17a** (895 mg, 4.5 mmol), Et_3N (0.93 ml, 6.7 mmol) and CH_2Cl_2 (5 ml) was added a solution of (*S*)-(+)-2-amino-3-methyl-1-butanol (460 mg, 4.5 mmol) in CH_2Cl_2 (2 ml) at 0℃. After being stirred at room temperature for 12 h, the mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with a saturated aqueous NaCl solution, dried with anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1/5) to give **18a** (614 mg, 51%). To a solution of the amide **18a** (614 mg, 2.0 mmol) in CH_2Cl_2 (5 ml) were added Et_3N (0.77 ml, 5.5 mmol) and methanesulfonyl chloride (0.21 ml, 2.8 mmol) at 0℃. After being stirred at room temperature for 12 h, the mixture was quenched with a saturated aqueous NH_4Cl solution and the CH_2Cl_2 layer was separated. The water layer was extracted with CH_2Cl_2. The combined extracts were washed with a saturated aqueous NaCl solution, dried with anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 2/1) to give **3h** (551 mg, 96%) as a pale yellow viscous oil. $[\alpha]_D^{24}$ -50.7 (c = 1.21, $CHCl_3$). IR (KBr): 1674 (C=N) cm^{-1}. ^{1}H-NMR (200MHz, $CDCl_3$): δ 1.00 and 1.03 (d, 3H x 2, *J* = 6.8 Hz, ^{i}Pr-Me), 1.81-2.01 (m, 1H, ^{i}Pr-CH), 3.81 (s, 6H, OMe x 2), 4.10-4.27 (m, 2H, C4 and C5), 4.33-4.44 (m, 1H, C5), 6.55 (d, 2H, *J* = 8.4 Hz, C3' and C6'), 7.29 (t, 1H, *J* = 8.4 Hz, C4'). ^{13}C-NMR (67.8MHz, $CDCl_3$): δ 17.8 and 18.4 (Me x 2), 32.2 (^{i}Pr-CH), 55.9 (OMe x 2), 69.5 (C5), 72.5 (C4), 103.7 (C3' and C5'), 107.9 (C1'), 131.2 (C4'), 158.7 (C2' and C6'), 159.8 (C2). MS: 249 (25, M^+), 206 (100), 178 (67), 165 (15), 163 (14). *Anal.* Calcd for $C_{14}H_{19}NO_2 \cdot 1/10H_2O$: C; 66.96, H; 7.71, N; 5.58. Found: C; 66.77, H; 7.64, N; 5.50.

(4R)-2-(2',6'-Dimethoxyphenyl)-4-isopropyloxazoline ent-(3h). **ent-3h** was prepared from 2,6-dimethoxybenzoylchloride **17a** (700 mg, 3.5 mmol) and (*R*)-(-)-2-amino-3-methyl-1-butanol (360 mg, 3.5 mmol) *via* **18b** by the same procedure described above. a pale yellow viscous oil. $[\alpha]_D^{24}$ +49.0 (c = 1.10, $CHCl_3$).

(4S)-2-(2',6'-Diisopropoxyphenyl)-4-isopropyloxazoline (3i). **3i** was prepared from 2,6-diisopropoxybenzoylchloride **17b** (400 mg, 1.6 mmol) and (*S*)-(+)-2-amino-3-methyl-1-butanol (160 mg, 1.6 mmol) *via* **18c** by the same procedure described for **3h**. The residue obtained was purified by SiO_2 column chromatography (hexane/AcOEt = 5/1) to give **3i** (371 mg, 76%) as a pale yellow viscous oil. $[\alpha]_D^{25}$ -54.6 (c = 1.28, $CHCl_3$). IR (KBr): 1672 (C=N) cm^{-1}. ^{1}H-NMR (200MHz, $CDCl_3$): δ 1.00 and 1.03 (d, 3H x 2, *J* = 6.8 Hz, ^{i}Pr-Me), 1.30 (d, 6H, *J* = 6.0 Hz, O^{i}Pr-Me), 1.82-2.02 (m, 1H, ^{i}Pr-CH), 4.07-4.21 (m, 2H, C4 and C5), 4.26-4.41 (m, 1H, C5), 4.51 (sept, 2H, *J* = 6.0 Hz, O^{i}Pr-CH), 6.60 (d, 2H, *J* = 8.4 Hz, C3' and C6'), 7.20 (t, 1H, *J* = 8.4 Hz, C4'). ^{13}C-NMR (67.8MHz, $CDCl_3$): δ 18.2 and 18.6 (^{i}Pr-Me x 2), 22.1 (O^{i}Pr-Me x 2), 32.3 (^{i}Pr-CH), 69.4 (C5), 71.2 (O^{i}Pr-CH), 72.5 (C4), 106.4 (C3' and C5'), 111.2 (C1'), 130.6 (C4'), 155.6 (C2' and C6'), 160.1 (C2). MS: 305 (5, M^+), 290 (91), 262 (35), 247 (60), 221 (33), 204 (47), 178 (100), 163 (98), 150 (44), 135 (46), 121 (10). *Anal.* Calcd for $C_{18}H_{27}NO_2 \cdot 1/10H_2O$: C; 70.37, H; 8.92, N; 4.56. Found: C; 70.38, H; 8.74, N; 4.53.

Cu-catalyzed 1,4-addition. Typical procedure (Table 2, entry 6) is as follows: A solution of CuOTf•1/2C_6H_6 complex (1.9 mg, 7.5 μmol) and **3h** (7.5 mg, 0.030 mmol) in THF (2 ml) was stirred at room temperature for 30 min. After a solution of **1** (20.4 mg, 0.15 mmol) in THF (1 ml) was added to the mixture, 1.0 M solution of Me_3Al in hexane (0.30 ml, 0.30 mmol) and TBDMSOTf (0.04 ml, 0.18 mmol) were successively added to the reaction mixture at 0℃ and the whole was stirred at the same temperature for 1 h. Then the mixture was quenched with 5% HCl aqueous solution at 0℃ and extracted with AcOEt. The extract was washed with a saturated aqueous NaCl solution, dried with anhydrous $MgSO_4$, and then concentrated *in*

vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 9/1) to give **2** (20.0 mg, 88% isolated yield) as a colorless oil. The ee was determined to be 68% by chiral HPLC analysis (Daicel CHIRALPAK AS, hexane/2-propanol = 7/3, flow rate 0.5 ml/min, column temperature 35℃, retention time: (+)-**2** = 43.0 min, (-)-**2** = 56.2 min).

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