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Chiral bis(trialkylsiloxymethyloxazolinyl)pyridine ligands. Highly enantioselective 1,3-dipolar cycloaddition reactions

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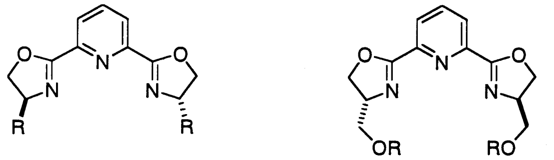
Abstract—A series of trialkylsilyl groups containing ligands have been prepared from C_2 symmetric 2,6-bis(oxazolinyl)pyridine (pybox-*hm*) (**2a**) bearing a hydroxymethyl group on the oxazoline ring. 1, 3-Dipolar cycloaddition reaction of nitrones and oxazolidinone derivatives in the presence of sterically tuned bis(oxazolinyl)pyridine (pybox-*tbdmsom* **2b**, -*tipsom* **2c** and -*tbdpsom* **2d**) and Ni(II) complexes as a Lewis acid catalyst proceeded smoothly to give the corresponding cycloadducts in 97:3 to >99:1 of *endo*/*exo* ratio and 97 to >99% ee for the *endo* adduct. Steric tuning of the chiral environment of pybox ligands was simply achieved by using silyl protecting groups of the hydroxyl groups. The solubility of the new pybox series **2b–d** in organic solvent is dramatically increased; hence, the efficiency of these catalysts enhanced the rate of nitrone 1,3-dipolar cycloaddition. Furthermore, these ligands can make a single-coordinated Ni(pybox) as a catalyst, since clear linear effect between the enantiopurity of the ligand **2c** and product **6a** was observed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The chiral environment formed by a metal and a ligand in the design of a molecular catalyst seems to be a decisive factor in order to achieve advanced chiral control.[1] Although excellent asymmetric catalyst systems have been reported, minute steric tuning of the chiral environment is still limited. Assuming that there is a basic molecule for the tuning of the chiral environment, more advanced chiral control can be attained. A series of trialkyl silyl groups well known as protecting groups of alcohols facilitates the steric tuning of the chiral environment of pybox-*hm* (**2a**), which has been developed by us as a new chiral ligand. Then, as a result of applying it in the catalytic asymmetric 1,3-dipolar cycloaddition reaction (CADC), excellent chiral control, acceleration of the reaction rate, and linear effect between the optical purity of the ligand and the product were successfully achieved (Fig. 1).



1a: R = *i*-Pr (pybox-*i*-Pr)
1b: R = *t*-Bu (pybox-*t*-Bu)

2a; R = H (pybox-*hm*)
2b; R = Si*t*-BuMe$_2$ (pybox-*tbdmsom*)
2c; R = Si(*i*-Pr)$_3$ (pybox-*tipsom*)
2d; R = Si*t*-BuPh$_2$ (pybox-*tbdpsom*)

Figure 1.

2. Results and discussion

Catalytic asymmetric 1,3-dipolar cycloaddition (CADC) has been intensively studied,[2] because of its high potentiality for organic fine chemical synthesis, on the basis of molecular design of chiral Lewis acid catalysts including complexes of Mg,[3] Ti,[4] Ni,[5] Pd,[6] Yb,[7] etc.[8] (Fig. 2).[2] During our continuous research on asymmetric catalysis with chiral bis(boxazolinyl)pyridine (pybox, **1**), we have been intrigued by the challenges of CADC methodology.[9] An initial attempt, reported in 1997 by Jørgensen, with a pybox-*ip* (**1a**) complex of ytterbium triflate resulted in 67 and 73% ee for the cycloaddition of crotonoyl-oxazolidinone **4**[10] and nitrones **5a** and **5b**,[11] respectively (Scheme 1).[7] As Kanemasa later developed chiral dibenzofurandiyl-bis(oxazoline) (DBFOX) for highly efficient asymmetric Diels–Alder reaction as well as CADC in a combination of the Ni(ClO$_4$)$_2$ aqua complex,[5,12] we attempted the reaction between **4** and **5a** with a combination of pybox-*ip* **1a** and nickel perchlorate as a catalyst to eventually obtain 66% ee with high *endo*-selectivity (Table 1, entry 5). Pybox-*ip* **1a** complexes with cobalt(II), manganese(II) and iron(II) perchlorates (20 mol%) gave 63% ee (*endo*/*exo*=96:4, 62% yield), 71% ee (*endo*/*exo*=96:4, 77% yield), and 24% ee (*endo*/*exo*=52:48, 60% yield), respectively. When isopropyl groups of pybox were replaced to bulky *tert*-butyl

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Keywords: cycloaddition; molecular catalyst; nitrogen ligand; nickel; nitrogen heterocycle.

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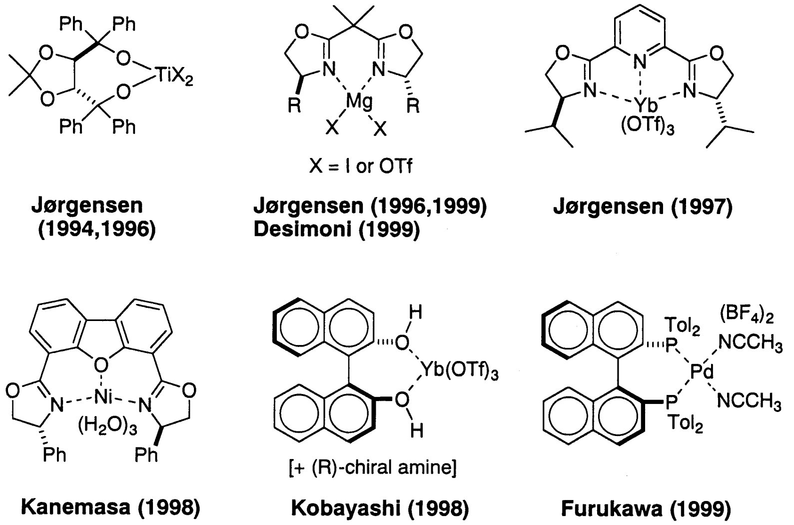
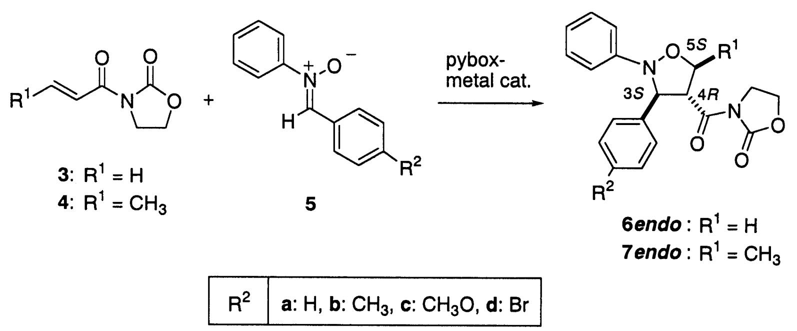


Figure 2.



Scheme 1. Catalytic asymmetric 1,3-dipolar cycloaddition with pybox-metal catalysts.

Table 1. Catalytic asymmetric 1,3-dipolar cycloaddition of oxazolidinones (**3** and **4**) and nitrones (**5a** and **5b**) with pybox (**1**) and $Ni(ClO_4)_2(H_2O)_6$

Entry	Oxazolidinone	Nitrone	Pybox	Product (3*R*,4*S*,5*R*)	Yield (%)	Ratio of *endo*/*exo*[a]	Ee of *endo*[b] (%)
1[c]	**3**	**5a**	**1b**	**6a**	97	98:2	90
2[c]	**3**	**5b**	**1b**	**6b**	99	96:4	86
3	**4**	**5a**	**1b**	**7a**	98	97:3	86
4	**4**	**5b**	**1b**	**7b**	99	99:1	82
5	**4**	**5a**	**1a**	**7a**	89	97:3	66
	4[d]	**5a**	**1a**	**7a**	37	93:7	67
	4[d]	**5b**	**1a**	**7b**	54	96:4	73

3 (or **4**)(0.25 mmol), **5** (0.25 mmol), pybox (0.05 mmol), $Ni(ClO_4)_2(H_2O)_6$ (0.05 mmol), CH_2Cl_2 (1.2 mL), 72 h, rt. The catalyst was prepared under MS 4A at 40°C.

[a] The ratios were determined by ^1H NMR.

[b] The ees were determined by chiral HPLC (DAICEL CHIRALCEL AD).

[c] At 0°C.

[d] With $Yb(OTf)_3$ (10 mol%), see Ref. 7a by Jørgensen.

groups, the enantioselectivity markedly increased to 82–86% ee for nitrone **5a** and **5b** (entry 3 and 4). Acryloyl-oxazolidinone **3** was also cyclized to **5** in 86–90% ee (3*R*,4*S*) (entry 1 and 2), which are comparably high levels of asymmetric induction to 86–88% so far reported by Desimoni[3] and Kobayashi.[7b,d] Thus, we learned that the bulky circumstance of the ligand pybox can provide higher enantioselectivity with sufficient *endo*-selectivity 99%; several substituents such as Ph or *n*-Bu of pybox were examined and found not to give higher sufficient stereo-selectivity.[13]

As we recently developed 2,6-bis(4*R*-hydroxymethyl-oxazolinyl)pyridine (pybox-*hm*) **2a** as a hydrophilic ligand in aqueous or protic media,[14,15] we intended conversion of the hydroxylmethyl groups on the oxazoline rings into the corresponding ethers bearing substituents such as Si(*tert*-Bu)Me_2 (TBDMS), Si(*iso*-Pr)$_3$ (TIPS), Si(*tert*-Bu)Ph_2

Table 2. Catalytic asymmetric 1,3-dipolar cycloaddition of acryloyl-oxazolidinone **3** and nitrones (**5a–c**) with pybox (**2b–d**) and $Ni(ClO_4)_2(H_2O)_6$

Entry	Nitrone	Pybox	*t* (h)	*T* (°C)	Product (3*S*,4*R*,5*S*)	Yield (%)	Ratio of *endo*/*exo*[a]	Ee of *endo*[b] (%)
1[c]	**5a**	**2a**	24	25	**6a**	0	–	–
2	**5a**	**2b**	24	25	**6a**	83	93:7	93
3	**5a**	**2b**	24	0	**6a**	96	94:6	95
4	**5a**	**2b**	24	−15	**6a**	94	95:5	98
5[d]	**5a**	**2c**	4	0	**6a**	99	>99:1	>99
6	**5a**	**2d**	1.5	0	**6a**	99	97:3	>99
7	**5b**	**2b**	24	0	**6b**	93	>99:1	96
8[d]	**5b**	**2c**	4	0	**6b**	95	>99:1	>99
9	**5c**	**2b**	24	0	**6c**	94	>99:1	98
10[d]	**5c**	**2c**	4	0	**6c**	98	>99:1	>99

3 (0.25 mmol), **5**(0.25 mmol), pybox (0.05 mmol), $Ni(ClO_4)_2(H_2O)_6$ (0.05 mmol), CH_2Cl_2 (1.2 mL).

[a] The ratios were determined by ^1H NMR.

[b] The ees were determined by chiral HPLC (DAICEL CHIRALCEL AD).

[c] Solvent: *i*-PrOH/CH_2Cl_2/H_2O=3/3/1 v/v.

[d] The catalyst was prepared under MS 4A at 40°C for 4 h.

(TBDPS): **2b–d**.[16] Steric tuning of pybox obtained by a simple etherification method was expected to provide high efficiency for CADC.

Now, we subjected the sterically tuned-up pybox **2b–d** to CADC of acryloyl-oxazolidinone **3** and nitrone **5a** in a combination of nickel perchlorate (20 mol%), along Kanemasa's procedure of the DBFOX-Ni aqua catalyst.[5,12] Hydroxymethyl pybox **2a** itself is not effective ligand, because of low solubility, even in a protic media such as *i*-PrOH/H_2O/CH_2Cl_2 (Table 2, entry 1). Bulky siloxymethyl ligand **2b** (pybox-*tbdmsom*) markedly improved ee up to 93–98% at 25 to −15°C along with high *endo*-selectivity to 95:5 (entries 2–4). Triisopropylsiloxymethyl ligand **2c** (pybox-*tipsom*) exhibited reaction-rate acceleration, at 0°C for 4 h, to give complete chemical yield and *endo*-selectivity with >99% ee (entry 5). Furthermore, the use of pybox-*tbdpsom* **2d** gave the highest enantioselectivity (>99% ee) within 1.5 h (entry 6), while *p*-methyl and *p*-methoxy substituents on the nitrone skeleton resulted in totally higher efficiency, 93–98% yield, >99:1 of *endo* ratio, and 96–99% ee by using **2b** and **2c** (entries 7–10).

Next, crotonoyl-oxazolidinone **4** was tested under the same catalytic conditions with siloxymethyl pybox-*tbdmsom* **2b**, -*tipsom* **2c** and -*tbdpsom* **2d** (Table 3). In all cases for nitrones **5a–d**, the *endo*-selectivity (>99%) and the enantioselectivity (92–98% ee) were at an excellent level. It is also turned out that **2c** can give higher ee for each nitrone than those with **2b**. As for the catalyst loading, 4 mol% of the catalyst prolonged completion of the reaction from 24 to 48 h, but there was no decrease of the stereoselectivity (entry 3). Using **2d** as a ligand, even 1 mol% of catalyst loading, the CADC could be carried out completely (entries 10–13). However, further decrease of the catalyst loading slightly lowered the ee by 2–5% with longer reaction time.

Incidentally, the phenomenon of asymmetric amplification was observed for the Diels–Alder reaction in a chiral Ni(DBFOX) system containing hetero- and homo-chiral $Ni(DBFOX)_2$.[12] Therefore, we checked the relation of optical purity of pybox-*ip* **1a** and pybox-*tipsom* **2c** to the enantioselectivity of the product **6endo** to observe weak positive amplification for **1a** but complete linear relation

Table 3. Catalytic asymmetric 1,3-dipolar cycloaddition of acryloyl-oxazolidinone **4** and nitrones (**5a–d**) with pybox (**2b–d**) and $Ni(ClO_4)_2(H_2O)_6$

Entry	Nitrone	Pybox	*t* (h)	Product (3*S*,4*R*,5*S*)	Yield (%)	Ratio of *endo*/*exo*[a]	Ee of *endo*[b] (%)
1	**5a**	**2b**	24	**7a**	60	>99:1	95
2	**5a**	**2c**	24	**7a**	95	98:2	96
3[c]	**5a**	**2c**	48	**7a**	91	>99:1	97
4[d,e]	**5b**	**2b**	72	**7b**	56	98:2	93
5	**5b**	**2c**	24	**7b**	90	>99:1	96
6[d]	**5c**	**2b**	72	**7c**	71	>99:1	92
7	**5c**	**2c**	24	**7c**	80	>99:1	97
8[d]	**5d**	**2b**	72	**7d**	77	>99:1	94
9	**5d**	**2c**	24	**7d**	72	>99:1	98
10[f]	**5a**	**2d**	72	**7a**	99	>99:1	97
11[f]	**5b**	**2d**	72	**7b**	99	>99:1	95
12[f]	**5c**	**2d**	72	**7c**	99	99:1	94
13[f]	**5d**	**2d**	72	**7d**	38	>99:1	95

4 (0.25 mmol), **5**(0.25 mmol), pybox **2**(0.05 mmol), $Ni(ClO_4)_2(H_2O)_6$ (0.05 mmol), CH_2Cl_2 (1.2 mL), rt. The catalyst was prepared under MS 4A at 40°C for 4 h.

[a] The ratios were determined by ^1H NMR.

[b] The ees were determined by chiral HPLC (DAICEL CHIRALCEL AD for entry 1–3 and ODH for entry 4–9.

[c] Catalyst, 4 mol%.

[d] No treatment with MS 4A.

[e] At 0°C.

[f] Catalyst, 1 mol%.

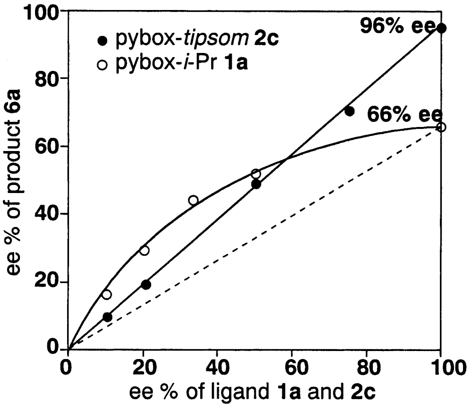


Figure 3. Linear and non-linear correlation between ee of ligand **1a** and **2c** and product **6a**.

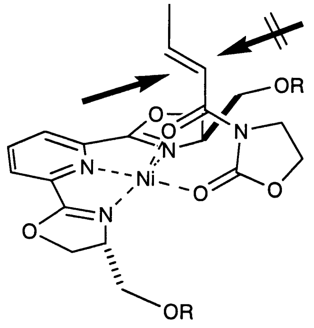


Figure 4.

for **2c** (Fig. 3). There is no doubt that bulky pybox-*tipsom* can make only a singly-coordinated Ni(pybox-*tipsom*) species, not a mixture of doubly-coordinated homochiral and heterochiral Ni(pybox-*tipsom*)$_2$ species at the reaction temperature.

We have found that the trialkylsiloxymethyl groups, which are sufficiently bulky and widespread around the active site to make a deeper cavity, are in tune with the size of a couple of the alkenoyl-oxazolidinones and the nitrones to control the asymmetric cycloaddition, comparing to *i*-Pr or *t*-Bu groups of the classical pybox. Bulky trialkylsilyl groups can block the only one side (*Si*(α), *Si*(β)-face) of the corresponding olefin moiety of the crotonoyl-oxazolidinone, probably inhibiting rotation of the olefin parts (Fig. 4). We think, in addition, that improvement of the solubility of pybox to organic solvents is also dramatically enhanced by the silyl groups to give the totally high efficiency.

3. Conclusion

Various trialkylsiloxymethyl pybox ligands were synthesized from pybox-*hm* **2a**. These ligands were applied to catalytic asymmetric 1,3-dipolar cycloaddition of nitrones with 3-alkenoyl oxazolidinones. Steric tuning by the trialykylsilyl groups was attained to afford highly stereocontrolled cycloadducts in both enantioselectivities and diastereoselectivities. Upon consideration of the recent popular application of pybox as a chiral ligand,[5] we can state that this steric tuning based on pybox-*hm* **2a** can enhance the potentiality of pybox for asymmetric catalysis, as well as electronic tuning reported before by us.[17]

4. Experimental

4.1. General methods

All reactions were carried out under a nitrogen atmosphere. Common solvents were purified before use. THF (anhydrous), Et_2O (anhydrous) and CH_2Cl_2 (anhydrous) are commercially available from Kanto Chemical, and were used without further purification. All reagents were reagent grade and purified when necessary. Reactions were monitored by TLC using 250 μm Merck (Art. 5715) precoated silica gel. Flash column chromatography was performed over Merck (Art. 7734) silica gel. Melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-300 spectrometer. ^1H NMR chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane and splitting patterns are designated as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Coupling constants are given in Hz. IR spectra were recorded with JASCO FT/IR-230 spectrometer and are reported in reciprocal centimeter (cm^{-1}). Elemental analyses were performed with Yanagimoto MT-3 CHN corder. Optical rotations were measured on JASCO DIP-140 polarimeter at the sodium D line (1 mL sample cell).

Chiral ligands, pybox-*tbdmsom* **2b**[14] and its enantiomer were synthesized according to the literature. Starting materials nitrones **5a–d**[11] and 3-alkenoyl oxazolidinones **3** and **4**[10] were synthesized according to the literature. The absolute stereochemistry of 1,3-DC adducts **6a–c**, **7a–d**[4c] was determined by chiral HPLC.

4.1.1. Pybox-*tipsom* 2c. To a white solid of pybox-*hm* **2a** (144.5 mg, 0.52 mmol) in CH_2Cl_2 (2.0 mL) was added imidazole (200.0 mg, 2.93 mmol) and triisopropylsilyl chloride (380 μL, 1.78 mmol) at room temperature. The resulting mixture was stirred for 17 h. The white suspention was directly purified by flash column chromatography on silica gel (hexane/EtOAc/Et_3N=10:20:5 v/v) to afford pybox-*tipsom* **2c** (247.6 mg) in 81% yield. White solid (mp 69.0–69.5°C). $[\alpha]_D^{23}=+66.8°$ (c=1.00, CH_2Cl_2). IR (NaCl): 2942, 2865, 1641, 1575, 1464, 1382, 1254, 1134, 1115, 1069, 1019, 883, 682 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.00–1.14 (42H, m), 3.70 (2H, dd, J=9.9, 6.9 Hz), 4.60 (2H, dd, J=9.9, 3.9 Hz), 4.43–4.62 (6H, m), 7.86 (1H, dd, J=8.0 Hz), 8.15 (2H, d, J=8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.85, 17.90, 65.38, 68.51, 71.34, 125.70, 137.21, 146.79, 163.57. Anal. calcd for $C_{31}H_{55}N_3O_4Si_2$: C, 63.11; H, 9.40; N, 7.12. Found: C, 63.03; H, 9.38; N, 7.04.

4.1.2. Pybox-*tbdpsom* 2d. To a white solid of pybox-*hm* **2a** (55.5 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) was added imidazole (74.1 mg, 1.08 mmol) and *t*-butyldiphenylsilyl chloride (120 μL, 0.47 mmol) at room temperature. The resulting mixture was stirred for 6 h. The white suspension was directly purified by flash column chromatography on silica gel (hexane/EtOAc/Et_3N=20:4:1 v/v/v) to afford pybox-*tbdpsom* **2d** (95.5 mg) in 64% yield. White solid (mp 129.0–129.5°C). $[\alpha]_D^{25}=+117.0°$ (c=1.00, CH_2Cl_2). IR(NaCl): ν=3070, 3049, 2957, 2931, 2896, 2858, 1643, 1576, 1469, 1428, 1383, 1112, 1077, 824, 741, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (2H, dd, J=10.17, 6.46 Hz), 3.95 (2H, dd, J=10.17, 3.58 Hz), 4.45–4.65 (6H, m), 7.32–7.45 (12H, m), 7.65 (8H, bd d), 7.83 (1H, t, J=7.97 Hz), 8.13 (2H, d, J=7.97 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 19.27, 26.75, 65.61, 68.29, 71.18, 125.74, 127.68, 127.72, 129.69, 129.74, 133.20, 133.36, 135.54, 135.54, 135.59, 137.16, 146.79, 163.62. Anal. calcd for $C_{45}H_{51}N_3O_4Si_2$: C, 71.67; H, 6.82; N, 5.57. Found: C, 72.09; H, 6.91; N, 5.62.

4.2. Typical procedure for nitrone 1,3-dipolar cycloaddition reaction with acryloyl oxazolidinone catalyzed by pybox-*tipsom*/Ni(II) complex (Table 2, entry 5)

A mixture of $Ni(ClO_4)_2(H_2O)_6$ (18.5 mg, 0.05 mmol) and pybox-*tipsom* **2c** (25.5 mg, 0.05 mmol) in CH_2Cl_2 (1.2 mL) was refluxed for 4 h under N_2 atmosphere. After cooling the flask to room temperature, the pale blue suspension was filtered off via a membrane filter. The filtrate was added to activated MS 4A (250 mg). To this was added CH_2Cl_2 (0.7 mL), oxazolidinone **3** (35.3 mg, 0.25 mmol) and nitrone **5c** (56.8 mg, 0.25 mmol) at 0°C. The resulting pale yellow suspension was stirred for 24 h at 0°C. Then the mixture was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to afford **6a** (88.0 mg) in 99% yield. >99:1 (*endo*/*exo* ratio). >99% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1/9 (1 mL min^{-1}), (3*S*,4*R*,) isomer t_{major}=113.7 min, (3*R*,4*S*) isomer t_{minor}=102.7 min. $[\alpha]_D^{20}=+14.0°$ (c=1.00, $CHCl_3$). White solid (mp 94.5–95.0°C).

4.2.1. (+)-(3*S*,4*R*)-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2,3-diphenylisoxazolidinone 6a. Table 2, entry 6; 99% yield. 97:3 (*endo*/*exo* ratio). >99% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1/5 (1 mL min^{-1}), (3*S*,4*R*) isomer 30.0 min, (3*R*,4*S*) isomer 25.3 min. $[\alpha]_D^{21}=+31.1°$ (c=1.00, $CHCl_3$). White solid (mp 108.0–108.5°C).

4.2.2. (−)-(3*S*,4*R*)-3-*p*-Methylphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2,3-diphenylisoxazolidinone 6b. Table 2, entry 8; 95% yield. >99:1 (*endo*/*exo* ratio). >99% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1/9 (1 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=27.4 min, (3*R*,4*S*,5*R*) isomer t_{minor}=42.0 min. $[\alpha]_D^{22}=+13.1°$ (c=1.00, $CHCl_3$). White solid (mp 133.5–134.5°C).

4.3. Typical procedure for nitrone 1,3-dipolar cycloaddition reaction with crotonoyl oxazolidinone catalyzed by pybox-*tipsom*/Ni(II) complex (Table 3, entry 10)

A mixture of $Ni(ClO_4)_2(H_2O)_6$ (18.5 mg, 0.05 mmol) and pybox-*tbdpsom* **2c** (25.5 mg, 0.05 mmol) in CH_2Cl_2 (1.2 mL) was refluxed for 4 h under N_2 atmosphere. After cooling the flask to room temperature, the pale blue suspension was filtered off via a membrane filter. The filtrate was added to activated MS 4A (250 mg). To this was added CH_2Cl_2 (0.7 mL), oxazolidinone **4** (35.3 mg, 0.25 mmol) and nitrone **5a** (56.8 mg, 0.25 mmol) at 0°C. The resulting pale yellow suspension was stirred for 24 h at 0°C. Then the mixture was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to afford cycloadduct (−)-(3*S*,4*R*,5*S*)-5-methyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2,3-diphenylisoxazolidinone **7a** 99% yield. >99:1 (*endo*/*exo* ratio). 97% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1/9 (1 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=27.4 min, (3*R*,4*S*,5*R*) isomer t_{minor}=42.0 min. $[\alpha]_D^{30}=-22.5°$ (c=1.00, $CHCl_3$). White solid (mp 130.0–131.0°C).

4.3.1. (−)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-methyphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2,3-diphenylisoxazolidinone 7b. Table 3, entry 11, 1 mol% catalyst; 99% yield. >99:1 (*endo*/*exo* ratio). 95% ee determined by HPLC analysis (Chiralcel OD-H, 2-propanol/hexane 1/5 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=44.0 min, (3*R*,4*S*,5*R*) isomer t_{minor}=30.3 min. White solid (mp 42.5–43.5°C). $[\alpha]_D^{31}=-25.1°$ (c=1.00, $CHCl_3$).

4.3.2. (+)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-methoxyphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2,3-diphenylisoxazolidinone 7c. Table 3, entry 12, 1 mol% catalyst; 99% yield. 99:1 (*endo*/*exo* ratio). 94% ee determined by HPLC analysis (Chiralcel OD-H, 2-propanol/hexane 1/2 (1 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=32.0 min, (3*R*,4*S*,5*R*) isomer t_{minor}=24.7 min. White solid (mp 121.0–122.0°C). $[\alpha]_D^{31}=-22.1°$ (c=1, $CHCl_3$).

4.3.3. (−)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-bromophenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2,3-diphenylisoxazolidinone 7d. Table 3, entry 13, 1 mol% catalyst; 38% yield. >99:1 (*endo*/*exo* ratio). 95% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1/3 (1 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=14.5 min, (3*R*,4*S*,5*R*) isomer t_{minor}=20.1 min. $[\alpha]_D^{22}=-19.6°$ (c=1, $CHCl_3$). White solid (mp 61.0–62.0°C). IR (NaCl): 2982, 2925, 1780, 1695, 1596, 1486, 1387, 1250, 1219, 1106, 1039, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (3H, d, J=6.32 Hz, CH_3), 3.97–4.03 (2H, m, H-4′), 4.36–4.41 (2H, m, H-5′), 4.45 (1H, dq, J=7.42, 6.32 Hz, H-5), 4.76 (1H, dd, J=7.42, 6.59 Hz, H-4), 5.15 (1H, d, J=6.59 Hz, H-3), 6.92–6.97 (3H, m, Ph–H), 7.21–7.27 (2H, m, Ph–H), 7.34–7.38 (2H, m, Ph–H), 7.47–7.51 (2H, m, Ph–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.71, 42.95, 61.89, 62.37, 73.68, 79.61, 114.58, 121.73, 121.93, 128.35, 128.86, 132.04, 139.93, 151.14, 152.78, 170.46. Anal. calcd for $C_{20}H_{19}BrN_2O_4$ ($0.5CH_2Cl_2$): C, 51.97; H, 4.26; N, 5.91, Found: C, 52.31; H, 4.43; N, 5.64.

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References

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1993. (b) Beller, M., Bolm, C., Eds.;

Transition Metals for Organic Synthesis, Wiley-VCH: Weinheim, 1998; Vol. 1,2.

2. For reviews, see (a) Gothelf, K. V.; Jørgensen, K. A. *Acta. Chem. Scand.* **1996**, *50*, 652. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
3. (a) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346. (b) Crosignani, S.; Desimoni, G. G.; Faita, G.; Fillippone, S.; Mortoni, A.; Righetti, P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007.
4. (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (c) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chem. Acta* **1997**, *80*, 2039. (d) Ellis, W. W.; Gavrilova, A.; Liable-Sands, L.; Rheingold, A. L.; Bosnich, B. *Organometallics* **1999**, *18*, 332. (e) Seebach, D.; Heckel, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 163.
5. Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.
6. Hori, K.; Komada, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *63*, 5017.
7. (a) Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (c) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001. (d) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213.
8. Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845.
9. For pybox, see (a) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (b) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1991**, *10*, 500. (c) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223. (d) Nishiyama, H.; Itoh, K.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1247. (e) Nishiyama, H. *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI: New York, 1997; Vol. 2, pp 153–188. (f) Nishiyama, H. *Enantiomer* **1999**, *4*, 569 and references therein.
10. Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 30.
11. Murahashi, S.-I.; Shioda, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265.
12. (a) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454. (b) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074. Kanemasa comparatively applied pybox as a chiral ligand to asymmetric Diels–Alder reaction with $Ni(ClO_4)_2(H_2O)_6$.
13. Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715.
14. Iwasa, S.; Nakamura, H.; Nishiyama, H. *Heterocycles* **2000**, *52*, 939.
15. Iwasa, S.; Takezawa, F.; Tsuchiya, Y.; Nishiyama, H. *Chem. Commun.* **2001**, 59.
16. Pybox recently reported by other chemists, see (a) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8598. (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connel, B. N.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (c) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (d) Evans, D. A.; Barnes, D. M.; Johnson, J.; Lectka, S.; Matt, T. P. V.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582. (e) Aspinall, H. C.; Greeves, N.; Smith, P. S. *Tetrahedron Lett.* **1999**, *40*, 1763. (f) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.
17. (a) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306. (b) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487.