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A highly enantioselective 1,3-dipolar cycloaddition reaction in alcoholic media: Ni(II)-pybox-*tipsom* catalyst

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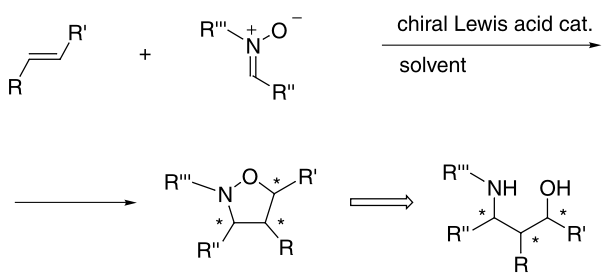
Abstract—From the viewpoint of environmentally friendly reaction conditions, catalytic asymmetric nitrone 1,3-dipolar cycloaddition (DC) reactions in protic media have been investigated. DC reaction of nitrones with alkenoyl oxazolidinone and pyrrolidinone derivatives in *t*-BuOH in the presence of sterically tuned bis(oxazolinyl)pyridine (pybox-*tipsom* **1d**) and Ni(II) complex as a chiral Lewis acid catalyst proceeded smoothly to give the corresponding cycloadducts ranging from 90:10 to >99:1 of *endo*/*exo* ratio and ranging from 90 to 98% ee for the *endo* adduct. The use of sterically hindered alcohols such as *t*-BuOH and *s*-BuOH as a non-halogenated solvent was shown to effect rate acceleration for the DC reaction compare to CH_2Cl_2 at the same temperature. Furthermore, no solvolysis products of nitrones and cycloadducts were observed in these protic media despite the possible formation of Brønsted acid. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

1,3-Dipolar cycloaddition (DC) reactions of nitrones have been applied to the total synthesis of complicated natural products related to 1,3-amino alcohol derivatives (Scheme 1).[1] Remarkable results have been achieved in the past decade, especially in the field of catalytic asymmetric 1,3-DC reactions since Jørgensen[2a] and Sheeren[2b] independently reported their first examples in 1994, followed by the Kanemasa,[3a] Kobayashi[3b] and Furukawa[3c] research groups. After that, catalytic asymmetric 1,3-DC has been intensively studied for optically active organic finechemical synthesis on the basis of molecular design of chiral Lewis acid catalysts.[4] Most of the catalytic asymmetric 1,3-DC reactions can, however, be carried out in a halogenated media such as CH_2Cl_2 and 1,2-dichloroethane because of the solubility of the catalysts, thus preventing the hydrolysis of nitrones. The use of protic media such as alcohols and water has not been studied for catalytic asymmetric 1,3-DC reactions so far. Recently, we reported highly enantioselective 1,3-DC reactions of nitrones with alkenoyl oxazolidinones catalyzed by chiral 2,6-bis(oxazolinyl)-pyridine (pybox) and Ni(II) complexes.[5] Previous work has shown efficient tuning of the chiral environment of pybox-*hm* (**1a**)[6] by using trialkyl silyl groups well-known as protecting groups of alcohols (Fig. 1). Then, as a result of applying them in the catalytic asymmetric 1,3-DC in hindered alcohols, excellent chiral control along with regioselectivities and acceleration of the reaction rate were successfully achieved.



Scheme 1.

pybox ligands:
1a: R = H (pybox-*hm*)
1b: R = Si*t*-BuMe_2 (pybox-*tbdmsom*)
1c: R = Si*t*-BuPh_2 (pybox-*tbdpsom*)
1d: R = Si(*i*-Pr)$_3$ (pybox-*tipsom*)

1e: R = pybox-*i*-Pr

Figure 1.

Keywords: 1,3-dipolar cycloaddition; molecular catalyst; nickel; nitrogen ligand; nitrogen heterocycle; nitrone.

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2. Results and discussion

2.1. Synthesis of Ni-pybox catalyst

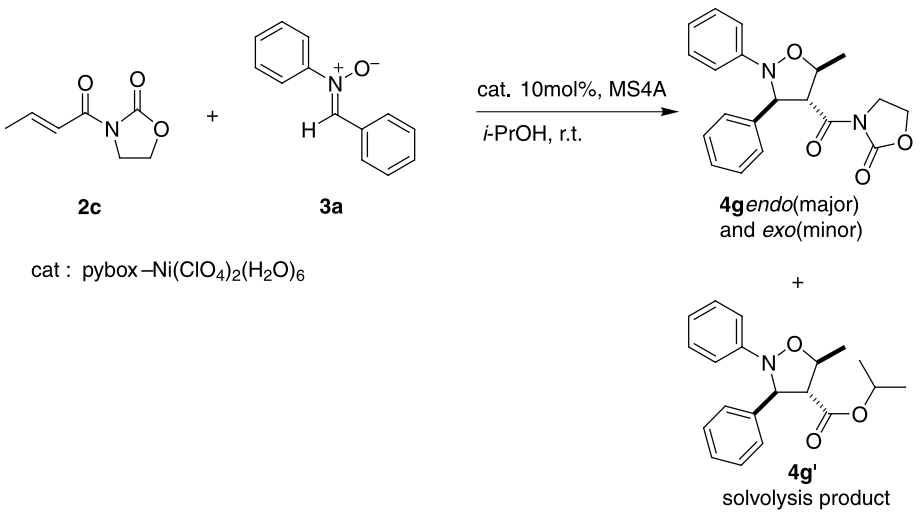
Catalysts were prepared by heating pybox ligands (**1b**–**e**) with $Ni(II)(ClO_4)_2(H_2O)_6$ at 40°C for 4 h in CH_2Cl_2 in the presence of MS 4A.[7] In the use of pybox-*i*-Pr **1e**, Ni(II) should be used in more than 2 equiv. to the ligand to avoid homo- and/or hetero chiral dimerization reaction between the pybox ligand and Ni(II) which was confirmed as positive chiral amplification in our previous studies.[5b] After the complexation, which usually required 2–4 h, the MS was filtered off to give a pale blue solution which was again filtered off via a membrane filter. This process is important to get high stereoselectivity because the 1,3-DC reaction can be activated by $Ni(II)(ClO_4)_2(H_2O)_6$ particles as a Lewis acid to give a racemic cycloadduct. The catalyst solution was added to pre-activated MS 4A at room temperature. Then, the solvent was removed under reduced pressure followed by addition of various alcohols. The suspension was used as a catalyst for nitrone 1,3-DC reactions.

2.2. Effect of pybox ligands

First of all, we chose *i*-PrOH as a non-halogenated protic solvent, and chiral pybox ligands, **1b**–**d** and pybox-*i*-Pr **1e**[8a] were evaluated for the nitrone 1,3-DC reaction of **2c** and **3a** (Scheme 2). The results are summarized in Table 1. Pybox-*i*-Pr **1e** with Ni(II) complex showed low enantioselectivitiy in *i*-PrOH but high *endo*/*exo* ratio (entry 1). On the other hand, a series of chiral pybox ligands (**1b**–**d**) bearing with trialkylsilyl groups on their oxazoline rings showed high enantioselectivities up to 90% ee and good *endo*/*exo* ratios in moderate yields. Thus, pybox-*tipsom* **1d** was used as a chiral ligand for further optimization of the nitrone 1,3-DC reaction. The catalyst in this protic medium seems to be stabilized by the ether groups on the ligands. Since hydrolysis products were obtained in *i*-PrOH, more hindered alcohols such as *s*-BuOH and *t*-BuOH were examined for the nitrone 1,3-DC reaction.

2.3. Temperature and solvent profiles

Temperature and solvent profiles in various alcoholic media are summarized in Table 2. The cycloadduct was obtained in low yields in *i*-PrOH at 30°C (entry 1). The solvolysis product, isopropylester **4g′** of the cycloadduct, was isolated in 7% yield, which suggested formation of an oxazolidinone fragment that may coordinate to the central metal resulting in deactivation of the catalyst for the 1,3-DC reaction. In *s*-BuOH, no solvolysis product was observed, and the yield of cycloadduct increased to 50% (entry 2). On the other hand, as shown in Table 2, *t*-BuOH markedly improved the enantioselectivity of the nitrone 1,3-DC reaction at 30°C up



Scheme 2. Catalytic asymmetric nitrone 1,3-dipolar cycloaddition in *i*-PrOH.

Table 1. Effect of ligands for catalytic asymmetric nitrone DC reactions in *i*-PrOH

Entry	Pybox	Time (h)	Cycloadduct			Solvolysis product	
			Yield[a] (%)	*endo*/*exo*[b]	*endo* ee[c] (%)	Yield[a] (%)	*endo* ee[b] (%)
1	**1e**[d]	24	68	99:1	35[e]	6	33[e]
2	**1b**	72	45	86:14	70	6	70
3	**1c**	24	26	93:7	83	6	82
4	**1d**	48	21	89:11	90	4	86

2c (0.25 mol), **3a** (0.25 mol), pybox (0.025 mol), $Ni(ClO_4)_2(H_2O)_6$ (0.025 mol), MS 4A 250 mg, *i*-PrOH (1.5 mL).
[a] Isolated yields.
[b] The ratios were determined by ^1H NMR (300 MHz).
[c] The ees were determined by chiral HPLC analysis.
[d] Ref. 8a.
[e] (3*R*,4*S*,5*R*).

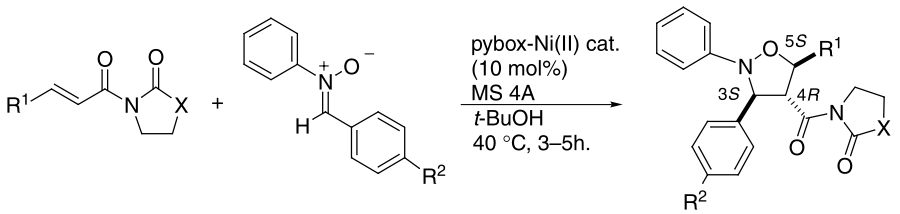
Table 2. Temperature and solvent profiles for catalytic asymmetric nitrone DC reactions in alcoholic media

Entry	Solvent (ROH)	Temperature (°C)	Time (h)	Cycloadduct			Solvolysis product	
				Yield[a] (%)	*endo*/*exo*[b]	*endo* ee[c] (%)	Yield[a] (%)	*endo* ee[c] (%)
1	*i*-PrOH	30	24	23	74:26	86	7	75
2	*s*-BuOH	30	24	50	83:17	86	–	–
3	*t*-BuOH	30	24	85	>99:1	95	–	–
4	CH_2Cl_2	40	5	58	>99:1	96	–	–
5	*t*-BuOH	40	5	89	>99:1	93	–	–
6	*t*-BuOH	50	3	85	98:2	92	–	–
7[d]	*t*-BuOH	40	60	88	98:2	87	–	–

2c (0.25 mmol), **3a** (0.25 mmol), pybox-*tipsom* **1d** (0.025 mmol), $Ni(ClO_4)_2(H_2O)_6$ (0.025 mmol), MS 4A (250 mg), solvent (1.5 mL).
[a] Isolated yields.
[b] The ratios were determined by ^1H NMR (300 MHz).
[c] The ees were determined by chiral HPLC analysis.
[d] 1 mol%.

to 95% ee and >99:1 of *endo*/*exo* selectivity (entry 3). As previously demonstrated, CH_2Cl_2 was an excellent solvent for catalytic asymmetric nitrone 1,3-DC reactions;[4] nevertheless, we have found that the catalytic asymmetric nitrone 1,3-DC reactions proceeded much faster than those in CH_2Cl_2 at the same temperature (entries 4 and 5). When the reaction temperature was increased to 50°C, the rate of the 1,3-DC reaction was also increased (entry 6). However, in the use of metal perchlorate, the reaction temperature should not be increased so high so as not to adversely affect the stability of perchlorate compounds. The reaction temperature in *t*-BuOH should be over 30°C to prevent from the solvent freezing. The catalyst loading (1 mol%) gave good stereoselectivities except the reaction time (entry 7). Under these reaction conditions, molecular sieves were still necessary.

Encouraged by the marked rate acceleration in *t*-BuOH without any solvolysis products, we then examined the optimized catalytic condition for catalytic asymmetric 1,3-DC reaction of various nitrones with both 3-alkenoyl oxazolidinones and 3-alkenoyl pyrrolidinones.[8] The results are summarized in Table 3. 3-Acryloyl and crotonoyl oxazolidinones were reacted with nitrones in high yields



2a: R^1 = H, X = O
2b: R^1 = H, X = CH_2
2c: R^1 = CH_3, X = O
2d: R^1 = CH_3, X = CH_2

3a: R^2 = H
3b: R^2 = CH_3
3c: R^2 = CH_3O

4a-l (*endo*)

Scheme 3. Catalytic asymmetric nitrone 1,3-dipolar cycloaddition in *t*-BuOH.

Table 3. Catalytic asymmetric nitrone DC reactions in *t*-BuOH

Entry	Dipolalophile	Nitrone	Time (h)	Product	Yield[a] (%)	*endo*/*exo*[b]	*endo* ee[c] (%)
1	**2a**	**3a**	4.0	**4a**	97	91:9	93
2	**2a**	**3b**	4.0	**4b**	95	92:8	95
3	**2a**	**3c**	4.0	**4c**	94	90:10	93
4	**2b**	**3a**	4.0	**4d**	94	97:3	98
5	**2b**	**3b**	3.0	**4e**	96	>99:1	97
6	**2b**	**3c**	3.5	**4f**	85	>99:1	96
7	**2c**	**3a**	5.0	**4g**	89	>99:1	93
8	**2c**	**3b**	5.0	**4h**	87	>99:1	90
9	**2c**	**3c**	5.0	**4i**	86	>99:1	90
10	**2d**	**3a**	3.0	**4j**	80	>99:1	95
11[d]	**2d**	**3a**	5.0	**4j**	60	>99:1	93
12	**2d**	**3b**	3.0	**4k**	79	>99:1	96
13	**2d**	**3c**	3.0	**4l**	81	>99:1	95

2 (0.25 mmol), **3** (0.25 mmol), pybox-*tipsom* **1d** (0.025 mmol), $Ni(ClO_4)_2(H_2O)_6$ (0.025 mmol), MS 4A (250 mg), *t*-BuOH (1.5 mL).
[a] Isolated yields.
[b] The ratios were determined by ^1H NMR (300 MHz).
[c] The ees were determined by chiral HPLC analysis.
[d] 5 mol%.

with good level of enantioselectivities except *endo*/*exo* ratios (entries 1–3, 7–9). The stereoselectivies were almost the same as those at 30°C. On the other hand, 3-acryloyl pyrrolidinone as an achiral template gave excellent level of enantioselectivities along with almost perfect *endo*/*exo* selectivities (entries 4–6). This phenomenon was also found in the reactions of 3-crotonoyl pyrrolidinones (entries 10–13). The use of pyrrolidinone was found to be a useful template for the nitrone 1,3-DC reaction. Presumably, the steric and electronic effects of pyrrolidinone compared to the oxazolidinone template can help the rate acceleration and high enantioselectivity in the environment of pybox-*tipsom*/Ni(II) complex. As shown in Table 3, the use of sterically hindered alcohols such as *t*-BuOH and *s*-BuOH as a non-halogenated solvent was shown to effect rate acceleration for the 1,3-DC reaction compared to CH_2Cl_2 at the same temperature (entry 7). Furthermore, no solvolysis nitrones and cycloadducts were observed in these protic media.

3. Conclusion

Various trialkylsiloxymethyl pybox ligands synthesized from pybox-*hm* **1a** were applied to catalytic asymmetric 1,3-DC reactions of nitrones with 3-alkenoyl oxazolidinones and pyrrolidinones in protic solvents. Pybox-*tipsom* **1d** sterically tuned by the trialkylsilyl groups was attained to afford highly stereocontrolled cycloadducts in both enantioselectivities and diastereoselectivities in *t*-BuOH. Upon consideration of the recent social demands for environmentally friendly media, we would like to state that this steric tuning based on pybox-*hm* **1a** can enhance the potentiality of pybox for asymmetric catalysis.

4. Experimental

4.1. General methods

All reactions were carried out under nitrogen atmosphere. Common solvents were purified before use. THF (anhydrous), Et_2O (anhydrous), *t*-BuOH, *i*-PrOH (anhydrous) and CH_2Cl_2 (anhydrous) are commercially available from Kanto Chemical Co. Ltd, 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 Yanaco MP-J3 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-*hm* **1a**,[6] pybox-*tbdmsom* **1b**,[5a,b] pybox-*tbdpsom* **1c**,[5a,b] pybox-*tipsom* **1d**[5a,b] and pybox-*i*-Pr **1e**[8a] were synthesized according to the literature. Starting materials, dipolarophiles, 3-alkenoyl oxazolidinones **2a**, **2c**, and 3-alkenoyl pyroridones **2b** and **2d** were synthesized according to the literature.[9] Starting materials, nitrones **3a–c** were synthesized according to the literature.[10] The absolute stereochemistry of 1,3-DC adducts **4a–l** was determined by chiral HPLC (Scheme 3).[5b]

4.1.1. Typical procedure for 1,3-dipolar cycloaddition reaction of 3a with acryloyl oxazolidinone 2a catalyzed by pybox-*tipsom*/Ni(II) complex (Table 3, entry 1). A mixture of $Ni(ClO_4)_2(H_2O)_6$ (18.5 mg, 0.05 mmol) and pybox-*tipsom* **1d** (14.7 mg, 0.025 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) and the solvent was removed under reduced pressure. To this was added *t*-BuOH (1.5 mL), oxazolidinone **2a** (35.3 mg, 0.25 mmol) and nitrone **3a** (49.3 mg, 0.25 mmol) at 30°C. The resulting pale yellow suspension was heated to 40°C for 4.0 h. Then after cooling the reaction mixture, the solvent was removed under reduced pressure, and the product was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to afford *(+)-(3S,4R)-3-p-methylphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2-phenylisoxazolidine* **4a** (81.7 mg) in 97% yield; 91:9 (*endo*/*exo* ratio), 93% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1:5 (1 mL min^{-1}), (3*S*,4*R*,) isomer t_{major}=26.8 min, (3*R*,4*S*) isomer t_{minor}=22.8 min, $[\alpha]_D^{19}$=+27.0° (*c*=1.00, $CHCl_3$).

4.1.2. (+)-(3*S*,4*R*)-3-*p*-Methylphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2-phenylisoxazolidine 4b. Table 3, entry 2; 95% yield; 92:8 (*endo*/*exo* ratio), 95% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1:9 (1 mL min^{-1}), (3*S*,4*R*,) isomer t_{major}=108.6 min, (3*R*,4*S*) isomer t_{minor}=120.4 min, $[\alpha]_D^{25}$=+13.3° (*c*=1.00, $CHCl_3$).

4.1.3. (+)-(3*S*,4*R*)-3-*p*-Methoxylphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2-phenylisoxazolidine 4c. Table 3, entry 3; 94% yield; 90:10 (*endo*/*exo* ratio), 93% 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}=99.0 min, (3*R*,4*S*) isomer t_{minor}=89.7 min, $[\alpha]_D^{25}$=+13.5° (*c*=1.00, $CHCl_3$).

4.1.4. Typical procedure for nitrone 1,3-dipolar cycloaddition reaction with acryloyl pyrrolidinone catalyzed by pybox-*tipsom*/Ni(II) complex (Table 3, entry 4). A mixture of $Ni(ClO_4)_2(H_2O)_6$ (18.5 mg, 0.05 mmol) and pybox-*tipsom* **1d** (14.7 mg, 0.025 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) and the solvent was removed under reduced pressure. To this was added *t*-BuOH (1.5 mL), pyrrolidinone **2b** (35.3 mg, 0.25 mmol) and nitrone **3a** (49.3 mg, 0.25 mmol) at 30°C. The resulting pale yellow suspension was heated to 40°C for 4.0 h. Then after cooling the reaction mixture, the solvent

was removed under reduced pressure, and the product was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to afford *(+)-(3S,4R)-3-phenyl-4-(2-oxo-pyrrolidine-1-carbonyl)-2-phenylisoxazolidine* **4d** (78.9 mg) in 94% yield; 97:3 (*endo*/*exo* ratio), 98% ee determined by HPLC analysis (Chiralcel AS, 2-propanol/hexane 1:6 (0.5 mL min^{-1}), (3*S*,4*R*,) isomer t_{major}=27.3 min, (3*R*,4*S*) isomer t_{minor}=31.8 min, $[\alpha]_D^{24}$=+32.8° (*c*=1.00, $CHCl_3$). White solid (mp 91.0–92.0°C). IR (NaCl): 2991, 1728, 1694, 1596, 1490, 1364, 1265, 1193, 1055, 1028, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.98–2.08 (2H, m, CH_2), 2.54–2.59 (2H, m, CH_2), 3.70–3.83 (2H, m), 4.07 (1H, dd, *J*=8.24, 5.63 Hz), 4.89 (1H, dt, *J*=8.24, 5.63 Hz), 5.28 (1H, d, *J*=5.63 Hz), 6.91–7.00 (3H, m), 7.17–7.40 (5H, m), 7.55–7.55 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.15, 33.45, 45.83, 60.42, 69.71, 70.44, 115.67, 122.18, 127.06, 127.66, 128.62, 128.81, 141.25, 150.42, 170.70, 175.31. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33, Found: C, 71.32; H, 6.08; N, 8.37.

4.1.5. (+)-(3*S*,4*R*)-3-*p*-Methylphenyl-4-(2-oxo-pyrrolidine-1-carbonyl)-2-phenylisoxazolidine 4e. Table 3, entry 5; 96% yield; >99:1 (*endo*/*exo* ratio), 97% ee determined by HPLC analysis (Chiralcel AS, 2-propanol/hexane 1:6 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=24.8 min, (3*R*,4*S*,5*R*) isomer t_{minor}=29.2 min, $[\alpha]_D^{21}$=+17.0° (*c*=1.00, $CHCl_3$). White solid (mp 32.0–33.0°C). IR (NaCl): 2925, 1738, 1689, 1597, 1489, 1362, 1259, 1191, 1022, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.97–2.07 (2H, m, CH_2), 2.34 (3H, s), 2.54–2.60 (2H, m, CH_2), 3.72–3.85 (2H, m), 4.06 (1H, dd, *J*=8.52, 5.49 Hz), 4.47 (1H, dt, *J*=8.24, 5.49 Hz), 4.63 (1H, t, *J*=8.24 Hz), 5.22 (1H, d, *J*=5.77 Hz), 6.90–7.00 (3H, m), 7.15–7.22 (4H, m), 7.40 (2H, d, *J*=7.97 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.16, 21.10, 33.48, 45.82, 60.41, 69.69, 70.35, 115.77, 122.17, 127.03, 128.59, 129.49, 137.37, 138.18, 150.49, 170.79, 175.30. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99, Found: C, 72.09; H, 6.44; N, 7.95.

4.1.6. (+)-(3*S*,4*R*)-3-*p*-Methoxylphenyl-4-(2-oxo-pyrrolidine-1-carbonyl)-2-phenylisoxazolidine 4f. Table 3, entry 6; 85% yield; >99:1 (*endo*/*exo* ratio), 96% ee determined by HPLC analysis (Chiralcel OD, 2-propanol/hexane 1:6 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=47.2 min, (3*R*,4*S*,5*R*) isomer t_{minor}=75.9 min, $[\alpha]_D^{20}$=+9.9° (*c*=1.00, $CHCl_3$). White solid (mp 34.0–35.0°C). IR (NaCl): 2930, 1739, 1689, 1597, 1512, 1489, 1363, 1251, 1177, 1031, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.97–2.07 (2H, m, CH_2), 2.34 (3H, s), 2.54–2.59 (2H, m, CH_2), 3.71–3.85 (2H, m), 3.80 (3H, s), 4.07 (1H, dd, *J*=8.24, 5.49 Hz), 4.47 (1H, dt, *J*=8.24, 5.50 Hz), 4.63 (1H, t, *J*=8.52 Hz), 5.18 (1H, d, *J*=5.77 Hz), 6.87–7.00 (5H, m), 7.17–7.23 (2H, m), 7.43 (2H, d, *J*=8.51 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.15, 33.48, 45.81, 55.25, 60.27, 69.65, 70.22, 114.17, 115.93, 122.27, 128.32, 128.57, 133.02, 150.41, 159.12, 170.84, 175.32. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65, Found: C, 68.66; H, 6.23; N, 7.48.

4.1.7. Typical procedure for 1,3-dipolar cycloaddition reaction of 3a with crotonoyl oxazolidinone 2c catalyzed by pybox-*tipsom*/Ni(II) complex (Table 3, entry 7). A mixture of $Ni(ClO_4)_2(H_2O)_6$ (18.5 mg, 0.05 mmol) and pybox-*tipsom* **1d** (14.7 mg, 0.025 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) and the solvent was removed under reduced pressure. To this was added *t*-BuOH (1.5 mL), oxazolidinone **2c** (38.8 mg, 0.25 mmol) and nitrone **3a** (52.8 mg, 0.25 mmol) at 30°C. The resulting pale yellow suspension was heated to 40°C for 5.0 h. Then after cooling the reaction mixture, the solvent was removed under reduced pressure, and the product was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to afford *(−)-(3S,4R,5S)-5-methyl-3-phenyl-4-(2-oxo-oxazolidine-3-carbonyl)-2-phenylisoxazolidine* **4g** (80.0 mg) in 89% yield; >99:1 (*endo*/*exo* ratio), 93% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1:5 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=27.8 min, (3*R*,4*S*,5*R*) isomer t_{minor}=41.0 min, $[\alpha]_D^{20}$=−13.3° (*c*=1.00, $CHCl_3$).

4.1.8. (−)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-methylphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2-phenylisoxazolidine 4h. Table 3, entry 8; 87% yield; >99:1 (*endo*/*exo* ratio), 90% ee determined by HPLC analysis (Chiralcel OD-H, 2-propanol/hexane 1:2 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=31.4 min, (3*R*,4*S*,5*R*) isomer t_{minor}=21.6 min, $[\alpha]_D^{25}$=−23.7° (*c*=1.00, $CHCl_3$).

4.1.9. (−)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-methoxylphenyl-4-(2-oxo-1,3-oxazolidine-3-carbonyl)-2-phenylisoxazolidine 4i. Table 3, entry 9; 86% yield; >99:1 (*endo*/*exo* ratio), 90% ee determined by HPLC analysis (Chiralcel ODH, 2-propanol/hexane 1:2 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=44.8 min, (3*R*,4*S*,5*R*) isomer t_{minor}=33.3 min, $[\alpha]_D^{25}$=−23.5° (*c*=1.00, $CHCl_3$).

4.1.10. Typical procedure for 1,3-dipolar cycloaddition reaction of 3a with acryloyl pyrrolidinone 2d 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-*tipsom* **1d** (14.7 mg, 0.025 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) and the solvent was removed under reduced pressure. To this was added *t*-BuOH (1.5 mL), pyrrolidinone **2d** (34.7 mg, 0.25 mmol) and nitrone **3a** (56.8 mg, 0.25 mmol) at 30°C. The resulting pale yellow suspension was heated to 40°C for 4.0 h. Then after cooling the reaction mixture, the solvent was removed under reduced pressure, and the product was directly purified by flash column chromatography on silica gel (CH_2Cl_2) to afford *(−)-(3S,4R,5S)-5-Methyl-3-phenyl-4-(2-oxo-pyrrolidine-1-carbonyl)-2-phenylisoxazolidine* **4j** (77.4 mg) in 80% yield; >99:1 (*endo*/*exo* ratio), 95% ee determined by HPLC analysis (Chiralcel OD, 2-propanol/hexane 1:5 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=25.1 min, (3*R*,4*S*,5*R*) isomer t_{minor}=20.4 min, $[\alpha]_D^{20}$=−35.1° (*c*=1.00, $CHCl_3$). White solid (mp 116.0–117.0°C). IR (KBr): 3005, 1742, 1683, 1595, 1489, 1454, 1387, 1354, 1289, 1250, 1188, 1138, 1086, 1027, 876, 814, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (3H, d, *J*=6.05 Hz, CH_3), 1.90–2.05,2.34 (2H, m, CH_2), 2.40–2.59 (2H, m, CH_2), 3.80 (2H, t, *J*=7.41 Hz), 4.45 (1H, dq, *J*=7.42,

6.04 Hz), 4.84 (1H, t, J=7.42 Hz), 5.17 (1H, d, J=6.87 Hz), 6.88–7.00 (3H, m), 7.18–7.41 (5H, m), 7.44–7.51 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.05, 33.70, 46.21, 63.77, 63.79, 74.50, 79.63, 114.66, 121.67, 126.73, 127.78, 128.85, 128.90, 141.26, 151.76, 171.51, 175.02. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.97; H, 6.31; N, 7.93, Found: C, 71.98; H, 6.33; N, 7.99.

4.1.11. (−)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-methylphenyl-4-(2-oxo-pyrrolidine-1-carbonyl)-2-phenylisoxazolidine 4k. Table 3, entry 12; 79% yield; >99:1 (*endo*/*exo* ratio), 96% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1:5 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=35.1 min, (3*R*,4*S*,5*R*) isomer t_{minor}=18.7 min, $[\alpha]_D^{20}$=−46.7° (c=1.00, $CHCl_3$). White solid (mp 126.0–127.0°C). IR (NaCl): 3005, 2933, 1742, 1685, 1596, 1512, 1488, 1390, 1350, 1291, 1251, 1227, 1186, 1028, 817, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (3H, d, J=6.04 Hz, CH_3), 1.94–2.43 (2H, m), 2.34 (3H, s, CH_3), 2.43–2.62 (2H, m, CH_2), 3.71–3.82 (2H, m), 4.47 (1H, ddd, J=12.36, 7.69, 6.43 Hz), 4.82 (1H, t, J=7.69 Hz), 5.13 (1H, d, J=6.87 Hz), 6.88–7.00 (5H, m), 7.14–7.24 (3H, m), 7.36 (2H, d, J=7.97 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.95, 17.74, 21.13, 33.63, 46.10, 63.70, 74.23, 79.45, 114.60, 121.50, 126.57, 128.72, 129.47, 137.29, 138.12, 151.75, 171.49, 174.91. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69, Found: C, 72.54; H, 6.61; N, 7.78.

4.1.12. (−)-(3*S*,4*R*,5*S*)-5-Methyl-3-*p*-methoxyphenyl-4-(2-oxo-pyrrolidine-1-carbonyl)-2-phenylisoxazolidine 4l. Table 3, entry 13; 81% yield; >99:1 (*endo*/*exo* ratio), 95% ee determined by HPLC analysis (Chiralcel AD, 2-propanol/hexane 1:3 (0.5 mL min^{-1}), (3*S*,4*R*,5*S*) isomer t_{major}=21.4 min, (3*R*,4*S*,5*R*) isomer t_{minor}=37.4 min, $[\alpha]_D^{26}$=−42.1° (c=1.00, $CHCl_3$). White solid (mp 101.0–102.0°C). IR (NaCl): 3004, 2953, 2933, 1743, 1681, 1607, 1512, 1487, 1458, 1389, 1352, 1289, 1250, 1228, 1186, 1137, 1029, 837, 771, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (3H, d, J=6.30 Hz, CH_3), 1.93–2.04 (2H, m, CH_2), 2.44–2.62 (2H, m, CH_2), 3.76–3.80 (1H, m), 3.80 (3H, s), 4.45 (1H, dq, J=7.40, 6.00 Hz), 4.83 (1H, t, J=7.40 Hz), 5.10 (1H, d, J=7.10 Hz), 6.86–7.00 (5H, m), 7.18–7.25 (2H, m), 7.38 (2H, d, J=8.52 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.95, 17.75, 33.65, 46.12, 55.25, 63.64, 74.14, 79.39, 114.15, 114.72, 121.60, 127.90, 128.72, 133.02, 150.73, 159.10, 171.84, 174.94. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36, Found: C, 69.41; H, 6.39; N, 7.32.

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References

1. (a) Ihara, M.; Tokunaga, Y.; Taniguchi, N.; Fukumoto, K. *J. Org. Chem.* **1991**, *56*, 5281. (b) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. For reviews, see: (c) Gothelf, K. V.; Jørgensen, K. A. *Acta Chem. Scand.* **1996**, *50*, 652. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (e) In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley–VCH: Weinheim, 2001.
2. (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Seerden, J.-P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419.
3. (a) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (c) Hori, K.; Komada, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *63*, 5017.
4. (a) Seerden, J.-P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441. (b) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346. (c) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (d) Hori, K.; Komada, H.; Ohta, T.; Furukawa, I. *Tetrahedron Lett.* **1996**, *37*, 5497. (e) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039. (f) Jensen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *Helv. Chem. Acta* **1997**, *80*, 2039. (g) Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett.* **1997**, *38*, 7923. (h) Meske, M. J. *Prakt. Chem.* **1997**, *339*, 426. (i) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (j) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483. (k) Simonen, K. B.; Jørgensen, K. A.; Hu, Q.-S.; Pu, L. *J. Chem. Soc., Chem. Commun.* **1999**, 811. (l) Crosignani, S.; Desimoni, G. G.; Faita, G.; Fillippone, S.; Mortoni, A.; Righetti, P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007. (m) Ellis, W. W.; Gavrilova, A.; Liable-Sands, L.; Rheingold, A. L.; Bosnich, B. *Organometallics* **1999**, *18*, 332. (n) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **2001**, *1999*, 40. (o) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213. (p) Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845. (q) Seebach, D.; Heckel, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 163. (r) Jensen, K. B.; Roberson, M.; Jorgensen, K. A. *J. Org. Chem.* **2000**, *65*, 9080. (s) Tanaka, J.; Kanemasa, S. *Tetrahedron* **2001**, *57*, 899. (t) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y.; Labande, A. H.; Johnstone, C. *Chemistry* **2001**, *7*, 4465. (u) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923. (v) Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 657. (w) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572. (x) Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227. (y) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, *124*, 2888.
5. (a) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715. (b) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227.
6. Iwasa, S.; Nakamura, H.; Nishiyama, H. *Heterocycles* **2000**, *52*, 939.
7. Ni(II)$(ClO_4)_2(H_2O)_6$ was first used by Kanemasa et al. as a chiral metal center for nitrone 1,3-DC reaction. See Ref. 3a.
8. 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) Yao, S.; Johannsen, M.;

Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8598. (f) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454. (g) 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 $Ni(II)(ClO_4)_2(H_2O)_6$. (h) 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. (i) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (j) 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. (k) Aspinall, H. C.; Greeves, N.; Smith, P. S. *Tetrahedron Lett.* **1999**, *40*, 1763. (l) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001. (m) Iwasa, S.; Takezawa, F.; Tsuchiya, Y.; Nishiyama, H. *Chem. Commun.* **2001**, 59. For reviews, see: (n) Nishiyama, H. *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI: New York, 1997; Vol. 2, p 153. (o) Nishiyama, H. *Enantiomer* **1999**, *4*, 569.

9. Shibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181.
10. (a) Murahashi, S.-I.; Shioda, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265. (b) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 30.