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Synthesis of novel chiral bis(2-oxazolinyl)xanthene (xabox) ligands and their evaluation in catalytic asymmetric 1,3-dipolar cycloaddition reactions of nitrones with 3-crotonoyl-2-oxazolidinone

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Abstract—Chiral 4,5-bis(2-oxazolinyl)-(2,7-di-*tert*-butyl-9,9-dimethyl)-9*H*-xanthenes (xabox) were synthesized and the chiral environments were evaluated in catalytic asymmetric 1,3-dipolar cycloaddition reactions of nitrones resulting in good to excellent enantioselectivities. 1,3-Dipolar cycloaddition reactions of nitrones with 3-crotonoyl-2-oxazolidinone in the presence of a bis(2-oxazolinyl)xanthene (**4c**; xabox-Bn) and Mn(II) or Mg(II) complex as a chiral Lewis acid catalyst proceeded smoothly to give the corresponding cycloadducts ranging from 96:4 to >99:1 of *endo*:*exo* ratio and ranging from 91% to 98% ee for the *endo* adduct.

In order to develop a powerful synthetic alternative methodology to enzymatic synthesis, much attention has been paid to the design and synthesis of chiral ligands of optically active organic molecules.[1] Bis- and tridentate oxazoline-derived C_2-symmetry chiral ligands have played an important role in the field of asymmetric induction since these are easily accessible from amino alcohols and carboxylic acids.[2,3] During the course of our studies on the design of oxazoline-derived chiral ligands, we became interested in a C_2-symmetric helical chiral ligand based on the C_2-symmetry to increase the rigidity of the chiral environment.[4] Here, a series of new tridentate oxazoline-derived chiral ligands having a xanthene backbone was synthesized, and the chiral environment after the complexation with metals may be constructed as a helical structure. These new ligands were investigated and evaluated in catalytic asymmetric 1,3-dipolar cycloaddition (D.C.) reactions of nitrones with 3-crotonoyl-2-oxazolidinone.[5,6]

The oxazoline-derived xanthene ligands were synthesized from the corresponding carboxylic acid in four steps to give 70–80% yields (Scheme 1). The reaction of xanthene-2,6-dicarboxylic acid chloride with amino alcohols **2** under basic conditions afforded the corresponding dihydroxyl amides **3a–c** in 71–85% yields. The crude reaction products **3** can be used for the next step without any purification. The dihydroxyl amides **3** were easily converted to chiral bis(2-oxazolinyl)xanthenes (xabox) via mesylation of **3** followed by oxazoline ring formation reactions in a one-pot procedure in high yields.

The chiral environment of these new xabox ligands was evaluated in nitrone 1,3-D.C. reaction by comparing with our previous reaction in which pybox/Ni(II) complexes were employed.[7] Initially, we have chosen Ni(II) as a central metal and briefly examined the chiral shielding substituent effect on the oxazoline rings. It was found that xabox-Bn **4c** was the best ligand for the nitrone 1,3-D.C. reaction (Scheme 2). Therefore, we used xabox-Bn **4c** for further optimization and the results are summarized in Table 1. The metal profile showed that the combination of xabox-Bn **4c** and Mn(II) and Mg(II) gave the highest enantioselectivities (entries 1–3 and 6).[8] These results indicate that the

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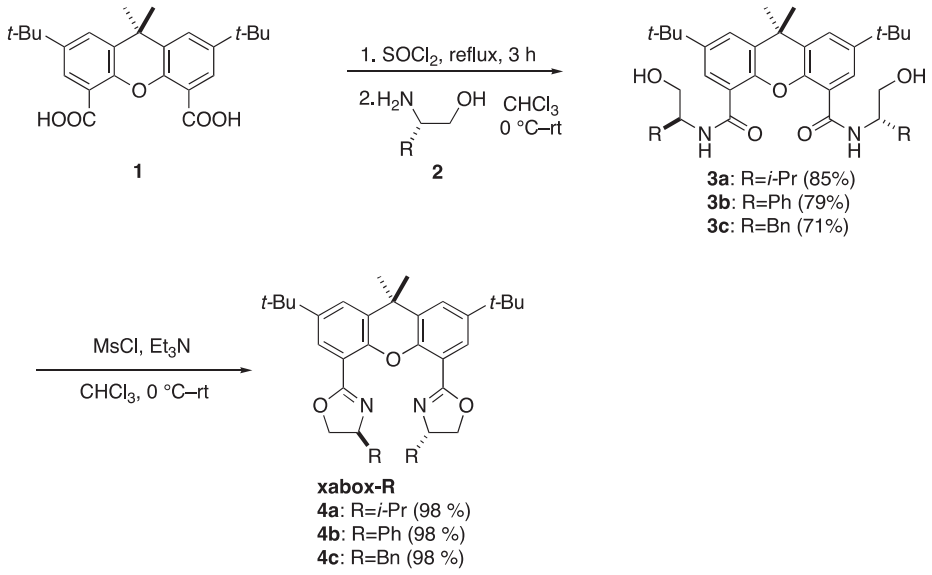
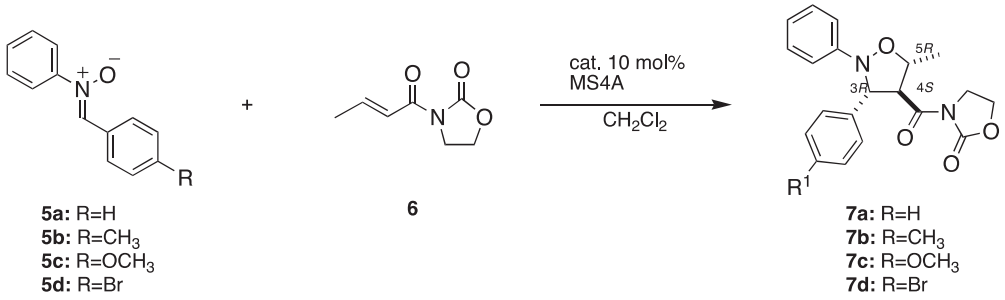


Scheme 1. Synthesis of chiral 4,6-bis(2-oxazolinyl)xanthene (xabox) ligands.



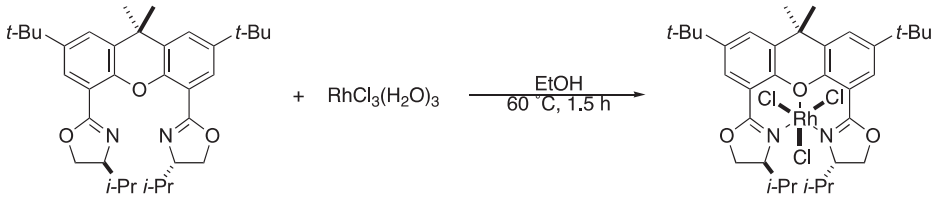
Scheme 2. Catalytic asymmetric 1,3-D.C. reaction of nitrones **5** and **6** with (*S*,*S*)-xabox-Bn/metal catalysts.

Table 1. (*S*,*S*)-xabox-Bn and Mn(II) and Mg(II) catalyzed 1,3-D.C. reaction of nitrones **5** and crotonoyl-oxazolidinone **6**[a]

Entry	Metal	Nitrone	Product	Temp. (°C)	Time (h)	Yield[b] (%)	*endo*:*exo*[c]	*endo* ee[d] (%)
1	$Cu(OTf)_2$	**5a**	**7a**	25	24	55	86:14	77
2	$Ni(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	25	21	87	85:15	80
3	$Mn(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	25	21	85	92:8	93
4	$Mn(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	10	48	85	96:4	95
5	$Mn(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	0	72	78	96:4	93
6	$Mg(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	25	12	96	>99:1	85
7	$Mg(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	10	24	88	99:1	92
8	$Mg(ClO_4)_2\cdot(H_2O)_6$	**5a**	**7a**	0	48	85	>99:1	92
9	$Mn(ClO_4)_2\cdot(H_2O)_6$	**5b**	**7b**	25	12	90	96:4	94
10	$Mn(ClO_4)_2\cdot(H_2O)_6$	**5c**	**7c**	25	12	95	97:3	95
11	$Mn(ClO_4)_2\cdot(H_2O)_6$	**5d**	**7d**	25	24	81	98:2	91

[a] **5a** (0.25 mmol), **6** (0.25 mmol), (*S*,*S*)-xabox-Bn **4c** (0.025 mmol), metal-perchlorate (0.025 mmol), MS 4A (250 mg), dichloromethane (1.5 mL). The catalyst was prepared under MS 4A at 40 °C for 4 h.
[b] Isolated yield.
[c] The ratios were determined by ^1H NMR (300 MHz).
[d] The ees were determined by chiral HPLC analysis (Daicel Chiralpak AD).

xabox ligand system seems to need a smaller ionic diameter for the central metals to coordinate in the cavity of the chiral environment compared to the pybox system. Temperature effects were also examined for both metals (entries 4, 6, 7, and 8). The nitrone 1,3-D.C. reactions proceeded smoothly at 0–25 °C in the presence of 10 mol% of **4c** and metals to afford the cycloadducts in high yields as well as high stereoselectivities, though the reaction time was prolonged. Encouraged by the marked results for both the diastereo- and enantio-



Scheme 3. Complexation of xabox-*i*-Pr **3a** and $RhCl_3(H_2O)_3$.

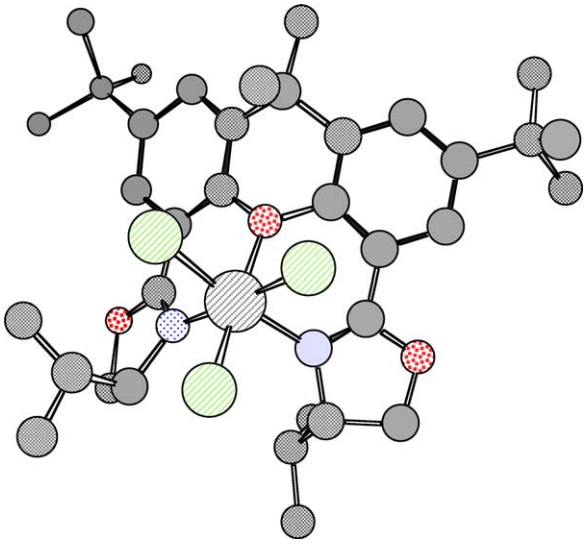


Figure 1. Crystal structure of complex **8**.

selectivities, we then examined the optimized catalytic conditions for catalytic asymmetric 1,3-D.C. reaction of various nitrones with 3-alkenoyl oxazolidinones (entries 9–11). The cycloadducts were obtained with excellent stereoselectivities for all of the nitrones.[9]

Furthermore, we examined the complexation of various xabox ligands with several transition metals to investigate the coordination type of the complexes and the mechanism. Among them, $RhCl_3$ and xabox-*i*-Pr **4a** underwent smooth complexation whose structures were determined by X-ray analysis as a facial type complexation (Scheme 3 and Fig. 1).[10] However, it was surprising that the complexation of Kanemasa's DBFOX and $RhCl_3$ or $Ru[(p\text{-cymene})Cl_2]_2$ failed to give complex mixtures. The different topology of the ligand may have given different stability to both ligands. We now believe that the interaction between the xabox/metal complex and the substrates might include a facial coordination intermediate in the nitrone 1,3-D.C. reactions with 3-alkenoyl-2-oxazolidinone even though different metals are used.

In conclusion, various xabox ligands having a xanthene backbone were synthesized and were applied to catalytic asymmetric 1,3-D.C. reactions of nitrones with 3-alkenoyl oxazolidinone resulting in good to excellent stereoselectivities. Chiral xabox ligands can be used for other catalytic asymmetric reactions as a new chiral inducer. X-ray analysis of the complex shows a facial coordination of the xabox ligand to the metal, which may give information on the mechanism of the 1,3-D.C. reaction for the transition state.

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9. General procedure is as follows: catalysts were prepared by heating xabox-Bn **3c** with $Mn(II)(ClO_4)_2{\cdot}(H_2O)_6$ or $Mg(II)(ClO_4)_2{\cdot}(H_2O)_6$ at 40 °C for 4 h in CH_2Cl_2 in the presence of MS 4A. After the complexation, the MS was filtered off to give a pale blue solution which was again filtered via membrane filter. The catalyst solution was added to pre-activated MS 4A at room temperature followed by addition of 3-crotonoyl-2-oxazolidinone **6** and nitrone. The resulting suspension was stirred at 25 °C and the reaction was monitored by TLC. At the end of the reaction, the reaction product was directly purified by flash column chromatography on silica gel to give the desired 1,3-D.C. product.
10. X-ray analysis: a single crystal ($0.15 \times 0.2 \times 0.6$ mm) was obtained by recrystallization from $CHCl_3$–ether–hexane. Selected bond lengths and angle: 2.129 Å, Rh–O; 2.05 Å, Rh–N1; 2.07 Å, Rh–N2; 2.330 Å, Rh–Cl1; 2.331 Å, Rh–Cl2; 2.270 Å, Rh–Cl3; 93.8°, N1–Rh–N2; 86.9°, N1–Rh–O; 83.7°, N2–Rh–O; 89.1°, N1–Rh–Cl1; 178.2°, N1–Rh–Cl2; 91.6°, N1–Rh–Cl3; 173.7°, N2–Rh–Cl1; 86.8°, N2–Rh–Cl2; 92.1°, N2–Rh–Cl3; 90.8°, O–Rh–Cl1; 91.5°, O–Rh–Cl2; 175.5°, O–Rh–Cl3.
Crystal data: $C_{39}H_{48}N_2O_3Cl_6Rh$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 16.735(2)$ Å, $b = 27.482(6)$ Å, $c = 9.067(2)$ Å, $V = 4169(1)$ Å^3, $\rho_{calcd} = 1.447\ g\,cm^{-1}$, $Z = 4$, $\mu = 8.31\ cm^{-1}$. The crystal contains a 1:1 mole ratio of **8** and $CHCl_3$: the solvent molecules in the crystal were omitted in Figure 1. The intensity data ($28.99 < \vartheta < 29.88°$) were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å), and the structure was solved by Patterson methods (DIRDIF92, PATTY). The final cycle of refinement was based on 2686 observed reflections ($I > 3.00\sigma(I)$) and 433 variable parameters and converged with $R = 5.6\%$ and $R_w = 6.1\%$. Crystallographic data for **8** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-199961. Copies of the data can be obtained, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223336033 or e-mail: deposit@ccdc.cam.ac.uk].