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Synthesis of 2,6-bis(4*R*-trialkylsiloxymethyloxazolinyl)pyridines and their use in catalytic asymmetric 1,3-dipolar cycloaddition reactions of nitrones and activated alkenes

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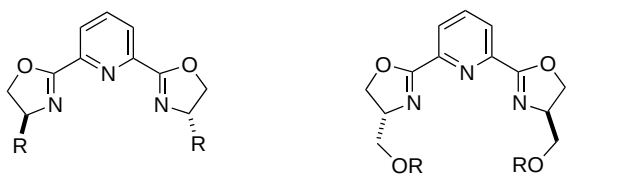
Abstract—1,3-Dipolar cycloaddition reaction of aromatic nitrones with 3-alkenoyl-2-oxazolidinones in the presence of a chiral 2,6-bis(4*R*-trialkylsiloxymethyloxazolinyl)pyridine/Ni(II) system proceeds smoothly with high enantioselectivity in up to 99% ee.

In the course of our continuous research projects on the pyridine bisoxazoline system **1**, we recently reported the synthesis of the water-soluble C_2-symmetric chiral ligand, 2,6-bis(4*R*-hydroxymethyloxazolinyl)pyridine (pybox-*hm*) **2a**.[1,2] The hydroxyl groups on oxazoline rings can be substituted for many different type of substituents such as acyl, alkyl, silyl groups, etc. via classical functional group transformations resulting in a different chiral environment in the molecules. This means that the desired chiral environment of optically active ligands for asymmetric catalytic reactions can be tuned using **2a** (Fig. 1).

In order to prove the possibility of this idea, we have chosen the 1,3-dipolar cycloaddition reaction of nitrones with alkenes, since the 1,3-dipolar cycloaddition reaction is one of the most powerful synthetic protocol for the construction of heteroatom containing frameworks and carbon–carbon bond formation via well-designed intramolecular sequences.[3] Cycloadditions of nitrones with electron-deficient alkenes in the presence of chiral Lewis acid was first reported by Jørgensen and co-workers in 1994.[4] More recently Kanemasa's and Kobayashi's research groups[5,6] found that aromatic nitrones react as a dipole in the presence of transition metal and lanthanide catalysts to give excellent enantioselectivities along with high regioselectivities.[7] Catalytic asymmetric 1,3-dipolar cycloaddition reaction between dipoles and olefinic dipolarophiles activated by chiral Lewis acids, however, is still rare compared with Diels–Alder reactions. The synthetic potential of enantioselective nitrone cycloaddition reaction should be high for the synthesis of enantiomerically pure γ-amino alcohol derivatives.[8] Here we report the catalytic asymmetric 1,3-dipolar cycloaddition reaction of nitrones with 3-alkenoyl-2-oxazolidinones catalyzed by tunable pybox/Ni(II) complexes as a new entry of Lewis acid catalysts (Scheme 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.

First of all, the classical pybox system **1** and the $Ni(ClO_4)_2{\cdot}(H_2O)_6$ complex were used as catalysts and were applied for 1,3-dipolar cycloaddition of nitrone **5a** with 3-alkenoyl-2-oxazolidinones **3** and **4**. Pybox-*t*-Bu **1b** gave 88–90% enantioselectivities along with high a *endo*/*exo* ratio (95:5). Then we started to tune up the chiral environment of pybox-*hm* **2a** by using trialkylsilyl chlorides. We examined the efficiency of this novel chiral ligand and Lewis acid system with a variety of nitrones and 3-alkenoyl-*N*-oxazolidinones. The results

Keywords: nitrone; 1,3-dipolar cycloaddition; pybox; nickel; Lewis acid; asymmetric catalyst; oxazolidinone.
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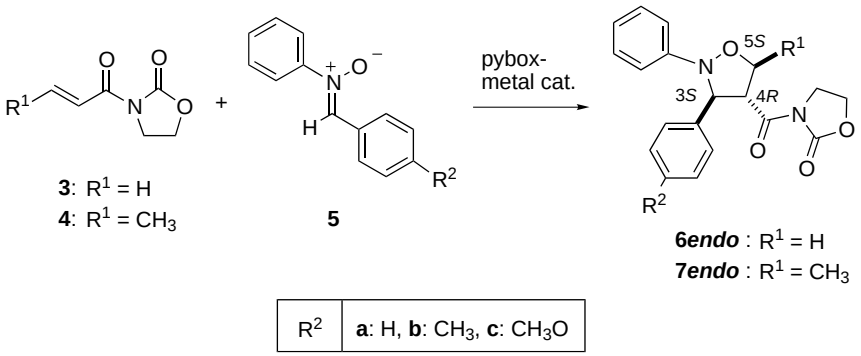

Scheme 1. Catalytic asymmetric 1,3-dipolar cycloaddition with pybox–metal catalysts.

Table 1. Catalytic asymmetric 1,3-dipolar cycloaddition of alkenoyl-2-oxazolidinones (**3** and **4**) and nitrones (**5a–c**) with pybox (**2b–d**) and $Ni(ClO_4)_2{\cdot}(H_2O)_6$[a]

Entry	Oxazolidinone	Nitrone	Pybox	*t* (h)	*T* (°C)	Product	Yield (%)	Ratio of *endo*:*exo*[b]	Ee of *endo*[c] (%)
1	**3**	**5a**	**2b**	24	0	**6a**	96	94:6	95
2	**3**	**5a**	**2b**	24	−15	**6a**	94	95:5	98
3[d]	**3**	**5a**	**2c**	4	0	**6a**	99	>99:1	>99
4	**3**	**5a**	**2d**	1.5	0	**6a**	99	97:3	>99
5	**3**	**5b**	**2b**	24	0	**6b**	93	>99:1	96
6[d]	**3**	**5b**	**2c**	4	0	**6b**	95	>99:1	>99
7	**3**	**5c**	**2b**	24	0	**6c**	94	>99:1	98
8[d]	**3**	**5c**	**2c**	4	0	**6c**	98	>99:1	>99
9	**4**	**5a**	**2c**	24	25	**7a**	95	98:2	96
10	**4**	**5b**	**2c**	24	25	**7b**	90	>99:1	96
11	**4**	**5c**	**2c**	24	25	**7c**	80	>99:1	97
12[e]	**4**	**5a**	**2d**	72	25	**7a**	99	>99:1	97
13[e]	**4**	**5b**	**2d**	72	25	**7b**	99	>99:1	95
14[e]	**4**	**5c**	**2d**	72	25	**7c**	99	99:1	94

[a] **4** (0.25 mmol), **5** (0.25 mmol), pybox **2** (0.05 mmol), $Ni(ClO_4)_2{\cdot}(H_2O)_6$ (0.05 mmol), CH_2Cl_2 (1.2 mL), rt.
[b] The ratios were determined by ^1H NMR.
[c] The ees were determined by chiral HPLC (DAICEL CHIRALCEL AD and ODH).
[d] The catalyst was prepared under MS 4 Å at 40°C for 4 h.
[e] Catalyst, 1 mol%.

are shown in Table 1. In all cases, the regio-, diastereo- (*endo*/*exo* ratio) and enantioselectivities were at excellent levels. Bulky siloxymethyl ligand **2b** (pybox-*tbdmsom*) exceedingly improved ee for the cycloaddition of **3** and **5** up to 95–98% at 25 to −15°C along with high *endo*-selectivity to 95:5 (entries 1 and 2). 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 3). *p*-Methyl and *p*-methoxy substituents on the nitrone skeleton resulted in totally higher efficiency, 93–98% yield, >99:1 of *endo* ratio, 96–99% ee by using **2b** and **2c** (entries 5–8).

Next, crotonoyl-oxazolidinone **4** was tested under the same catalytic condition with only siloxymethyl pybox **2c**. In all cases for nitrones **5a–c**, the *endo*-selectivity (>98%) and the enantioselectivity (96–97% ee) were on an excellent level (entries 9–11). It also turned out that pybox-*tipsom* **2c** can give a higher ee for each nitrone than those with pybox-*tbdmsom* **2b**. As for the catalyst loading, 1 mol% of catalyst elongated completion of the reaction to 72 h, but gave no decrease in stereoselectivity (entries 12–14). However, further decrease of the catalyst loading slightly lowered the ee by 2–5% with a longer reaction time.

In conclusion, we have found that the trialkylsiloxymethyl group, which is sufficiently bulky and widely spread around the active site to make a deeper cavity, is in tune with the size of a couple of the alkenoyl-oxazolidinones and the nitrones to control the asymmetric cycloaddition, compared to the *iso*-Pr or *tert*-Bu groups of the classical pybox. We think, in addition, that improvement of the solubility of pybox to an organic solvent is also dramatically enhanced by the silyl groups to give the total high efficiency. This system can also be applied for other Lewis acid-catalyzed reactions.

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