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Enantioselective Mannich-type reaction of sulfonylimines having 2-pyridylsulfonyl group as a novel stereocontroller

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Abstract—A catalytic enantioselective Mannich-type reaction of *N*-(2-pyridylsulfonyl)imines in the presence of chiral bis(oxazoline)s afforded the products with high enantioselectivity. Asymmetric induction was supposed to be efficiently controlled by a new chiral center on the sulfur dynamically induced through the discriminative coordination of a chiral Lewis acid to one of the sulfonyl oxygens.

β-Amino acid derivatives have proven utility as building blocks for the preparation of pharmaceutical targets,[1] natural products,[2] and peptidic materials with unique structural properties.[3] The enantioselective Mannich-type reaction, addition of ester enolate equivalents to imines, is one of the most important methods for the synthesis of optically active β-amino acids,[4] although various diastereoselective approaches to Mannich-type reactions have been reported for the synthesis of β-amino acids. Recently, catalytic enantioselective reactions have been developed,[4,5] however, only a few studies have been reported on the catalytic enantioselective Mannich-type reaction of non-activated *N*-sulfonylimines.[6] Although the *N*-sulfonyl group is one of the well studied imino protecting group because it certainly enhances the reactivity of the imino group, deprotection of the *p*-tolylsulfonyl group has some problem under mild conditions. We reported chiral induction in radical reactions of benzimidazolyl or 2-pyridyl vinyl sulfones, where we first proposed the discriminative coordination of a chiral Lewis acid between one of the prochiral sulfonyl oxygens and the heteroaryl nitrogen playing a key role in inducing enantioselectivity.[7] Namely, a new chiral sulfur center is dynamically induced by a chiral relay process[8] in these reactions. We have proven this type of new chiral induction in enantioselective Grignard and Strecker reactions of *N*-(2-pyridyl)sulfonylimines, showing the 2-pyridylsulfonyl group as a new type of the activating group of the imino group and a stereocontroller.[9] Carretero and co-workers have reported excellent enantioselective conjugate addition,[10] conjugate reduction,[11] 1,3-dipolar cycloaddition[12] and aza Diels–Alder reaction of 2-pyridylsulfonyl substrates[13] and, very recently, they disclosed the Mannich-type reaction of *N*-(2-thienyl)sulfonylimines using a chiral Lewis acid developed by them.[14] Herein we report a catalytic enantioselective Mannich-type reaction of *N*-(2-pyridylsulfonyl)imines using commercially available bis(oxazoline) ligands (Fig. 1).

We examined the enantioselective Mannich-type reaction of various arylsulfonylimines **1a**–**f** using a catalytic amount (10 mol %) of chiral Lewis acids prepared from various bis(oxazoline)s and Lewis acids. The results are shown in Table 1. The reaction of *N*-tosylimines **1a** with $Cu(OTf)_2$/Box-Ph **3** did not give the product, whereas *N*-(2-pyridylsulfonyl)imines **1b** afforded product **2b** with good enantioselectivity (entries 1 and 2). It is noteworthy that only *N*-(2-pyridyl)sulfonylimine **1b** showed good enantioselectivity among *N*-(heteroaryl)sulfonylimines **1b**–**f** (entries 3–6). Other chiral Lewis acids derived from CuOTf, $Mg(OTf)_2$, and $Zn(OTf)_2$ with **3** afforded product **2b** with lower enantioselectivity than $Cu(OTf)_2$/**3** (entries 7–9).[15] The chiral Lewis acid derived from other Box ligands such as Box-*t*-Bu **4**, indaBox **5**, and PyBox **6** also catalyzed the reaction

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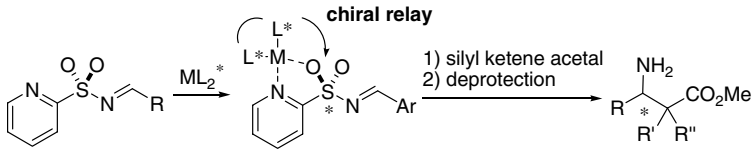
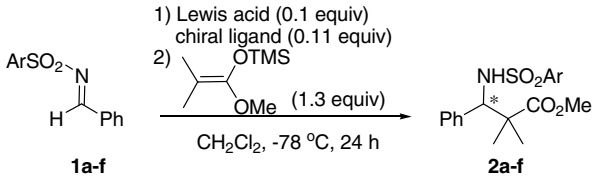
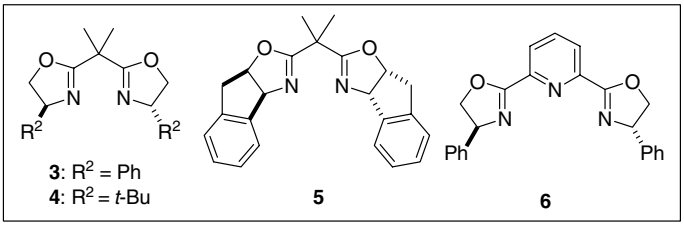


Figure 1. Enantioselective Mannich-type reaction using 2-pyridylsulfonyl group as a stereocontroller.

Table 1. Enantioselective Mannich-type reaction of imines **1a**–**f** in the presence of various chiral Lewis acids (0.1 equiv)





Entry	Imine	Ar	Lewis acid	Ligand	Product	Yield (%)	ee[a,b] (%)	Absolute configuration
1	**1a**	*p*-Tolyl	$Cu(OTf)_2$	**3**	**2a**	Trace	—	
2	**1b**	2-Pyridyl	$Cu(OTf)_2$	**3**	**2b**	80	86 (>99)	(*R*)
3	**1c**	8-Quinolyl	$Cu(OTf)_2$	**3**	**2c**	19	1	
4	**1d**	2-Thienyl	$Cu(OTf)_2$	**3**	**2d**	47	0	
5	**1e**	2-Furyl	$Cu(OTf)_2$	**3**	**2e**	59	8	
6	**1f**	5-Me-2-pyridyl	$Cu(OTf)_2$	**3**	**2f**	52	30	
7[c]	**1b**	2-Pyridyl	Cu(OTf)	**3**	**2b**	32	38	(*R*)
8[c]	**1b**	2-Pyridyl	$Mg(OTf)_2$	**3**	**2b**	37	29	(*R*)
9[c]	**1b**	2-Pyridyl	$Zn(OTf)_2$	**3**	**2b**	16	62	(*R*)
10[c]	**1b**	2-Pyridyl	$Cu(OTf)_2$	**4**	**2b**	41	2	(*R*)
11	**1b**	2-Pyridyl	$Cu(OTf)_2$	**5**	**2b**	24	71	(*R*)
12	**1b**	2-Pyridyl	$Cu(OTf)_2$	**6**	**2b**	30	64	(*R*)
13[c]	**1b**	2-Pyridyl	$Sc(OTf)_3$	**6**	**2b**	42	62	(*R*)

[a] ee Was determined by the HPLC analysis using Chiralcel OD-H or Chiralpak AD-H.
[b] ee Obtained after single recrystallization from acetone is shown in parenthesis.
[c] Catalyst loading is 30 mol %.

but with lower enantioselectivity than that with $Cu(OTf)_2$/**3** (entries 10–13).

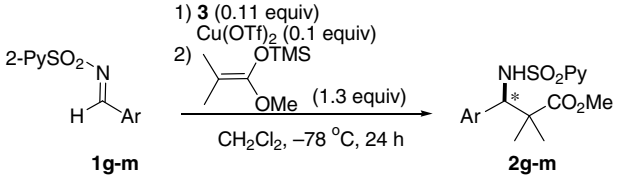
The reaction of various *N*-(2-pyridylsulfonyl)imines **1g**–**m** using $Cu(OTf)_2$/**3** gave products in moderate yield with good enantioselectivity **2g**–**m** (Table 2, entries 1–7).[16] Furthermore, enantiomerically pure sulfonamides were easily obtainable by recrystallization. Thus, single recrystallization of sulfonamides **2b,g**–**m** from acetone afforded almost enantiomerically pure (*R*)-**2b,g**–**m**.

To realize the synthetic potential of this stereoselective preparation of chiral β-amino acids, we confirmed the easy removal of the 2-pyridylsulfonyl group. Although removal of arylsulfonyl groups generally needs drastic reaction conditions, the 2-pyridylsulfonyl group could be removed from the optically active (*R*)-**2b** on treatment with magnesium in MeOH at 0 °C[17] and the chiral amine (*R*)-**7** was found to be formed without significant loss of optical purity (Scheme 1). The absolute configuration was determined by comparing the specific rotation of **7** with that of the literature data.[18]

The enantioselective Mannich-type reaction of *N*-(2-pyridylsulfonyl)imines **1b**,**g**–**m** gave the products in moderate yield with good enantioselectivity, whereas the reaction of *N*-(*p*-tolylsulfonyl)imine **1a** did not afford the products. These results show that the 2-pyridylsulfonyl group acts not only as an efficient stereocontroller but also as an activating group. The Cu(II) Lewis acid would form a distorted square-planar bidentate-coordinating complex[19] with **1b** and **3**. We assumed, by model study, the most stable complex would be the one shown in Figure 2, where one of the sulfonyl oxygens, a *pro*-*R* sulfonyl oxygen, is preferably coordinated to Cu(II) together with two Box nitrogens and one pyridyl nitrogen; the complex coordinated to a pro-*S* sulfonyl oxygen apparently has a strong interaction between the phenyl groups. The chiral relay on the sulfur thus formed allows the silyl ketene acetal to approach the *Si*-face of the imine, avoiding the interaction with the phenyl group in Box-Ph **3**, and (*R*)-**2** is preferably formed.

In conclusion, the enantioselective Mannich-type reaction of *N*-(2-pyridylsulfonyl)imines in the presence of

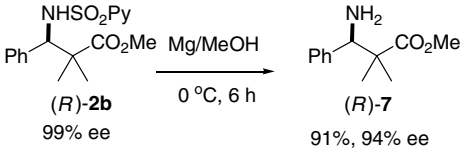
Table 2. Enantioselective Mannich-type reaction of various imines **1g–m** in the presence of **3**/$Cu(OTf)_2$ (0.1 equiv)



1g-m **2g-m**

Entry	Imine	Ar	Product	Yield (%)	ee[a,b] (%)
1	**1g**	*p*-Tolyl	**2g**	40	70 (95)[c]
2[d]	**1h**	*p*-ClC_6H_4	**2h**	52	75 (90)
3[d]	**1i**	*p*-$MeOC_6H_4$	**2i**	58	83 (>99)
4[d]	**1j**	1-Naphthyl	**2j**	76	73 (94)
5	**1k**	2-Naphthyl	**2k**	97	67 (>99)
6	**1l**	2-Furyl	**2l**	86	81 (99)
7[d]	**1m**	*trans*-Cinnamyl	**2m**	89	83 (>99)

[a] ee Was determined by the HPLC analysis using Chiralcel OD-H or Chiralpak AD-H.
[b] ee Obtained after single recrystallization from acetone is shown in parenthesis.
[c] The absolute configuration of the product is determined to be *R*.
[d] Catalyst loading is 30 mol %.



(*R*)-**2b** 99% ee (*R*)-**7** 91%, 94% ee

Scheme 1.

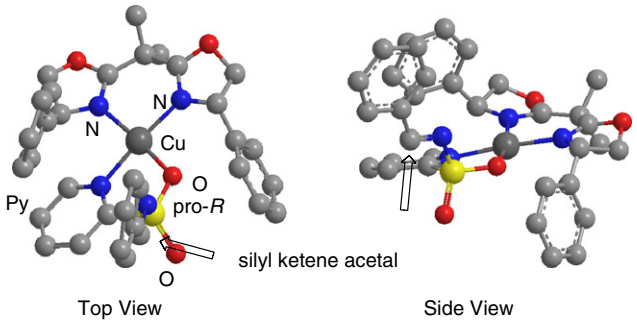


Figure 2. Presumed reaction model of **1b**-$Cu(OTf)_2$/**3**.

bis(oxazoline)s afforded chiral sulfonamides with good enantioselectivity. The 2-pyridylsulfonyl group works not only as an activating group of the imino group in the reaction with the silyl ketene acetal but also as a stereocontroller which shows excellent enantioselectivity through dynamically controlled chirality on the sulfur atom.

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