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Enantioselective Strecker-type reaction to sulfonylimines having a 2-pyridylsulfonyl group as a novel stereocontroller

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

The enantioselective Strecker-type reaction is one of the most important methods for the synthesis of optically active α-amino acids. Therefore, a variety of chiral catalysts have been developed to achieve a high level of asymmetric induction in the addition of a cyanide to imines.[1] Although the *N*-sulfonyl group certainly activates the electrophilicity of the imino carbon center, there was no report on the catalytic enantioselective Strecker-type reaction to *N*-sulfonylimines except for a paper, which appeared very recently.[2,3] Since *N*-sulfonylimines would be conformationally flexible, it is necessary to control the conformational change for achieving a high enantioselectivity. We recently proposed a 2-pyridylsulfonyl group as a new type of activating group of the imino group.[4,5] In the 2-pyridylsulfonyl group, there are three possible coordinative sites, a pyridyl nitrogen in the 2-pyridyl group and two sulfonyl oxygens. If the coordinative position of Lewis acids to these heteroatoms can be controlled, the 2-pyridylsulfonyl group becomes a powerful stereocontroller.[6] Herein we report a catalytic enantioselective Strecker-type reaction of *N*-(2-pyridylsulfonyl)imines (Fig. 1).

The enantioselective Strecker-type reaction was carried out using a variety of C_2-symmetric bis(oxazoline) ligands in combination with Lewis acids. The results are shown in Table 1. Since the reaction of *N*-aryl- and *N*-alkyl-substituted imines **1a**–**c** did not give the products (entries 1–3), various *N*-(arylsulfonyl)imines **1d**–**g** were examined by treating them with TMSCN (1.3 equiv)[7] in the presence of a catalytic amount of $Mg(OTf)_2$ (0.3 equiv) and bis(oxazoline) **3** (0.31 equiv) as a chiral Lewis acid. *N*-(Tolylsulfonyl)- and *N*-[(2,4,6-triisopropylphenyl)sulfonyl]imine **1d**,**e** did not give good results whereas the reaction of *N*-(2-pyridylsulfonyl)imine **1f** gave **2f** in good yield with a good enantioselectivity (entries 4–6). Unfortunately, *N*-(quinolylsulfonyl)imine **1g** did not give the product although the starting **1g** disappeared during the reaction (entry 7). The chiral Lewis acids derived from other magnesium salts such as $Mg(ClO_4)_2$ and $MgBr_2{\cdot}OEt_2$ were also examined in the reaction of **1f** to give **2f** in high yield but with a low enantioselectivity (entries 8 and 9). When $Cu(OTf)_2$ or $Cu(SbF_6)_2$ was used as a Lewis acid, **2f** was obtained with a good enantioselectivity but in a low yield (entries 10 and 11).[8] Enantioselectivity was improved by the use of a stoichiometric amount of the $Cu(OTf)_2$-bis(oxazoline) **3** complex or by the addition of molecular sieves 4 Å to the reaction mixture, although the yield still remained moderate to low (entries 12 and 13). Strangely enough, $Mg(OTf)_2$ in the presence of bis(oxazoline)s **4** and **5** did not activate the reaction of **1f** with TMSCN (entries 14 and 15). It should be noted that **2f** obtained with the $Mg(OTf)_2$-bis(oxazoline) **6** complex in high yield and a high enantioselectivity has the configuration opposite that obtained with the bis(oxazoline) **3** (entry 16).[9] The $Mg(ClO_4)_2$-DBFOX **9** complex also catalyzed the reaction to give

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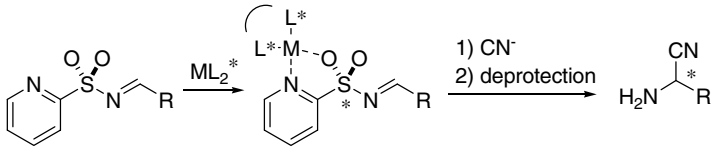
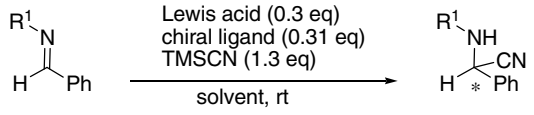


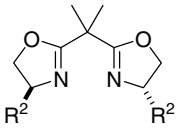
Figure 1. 2-Pyridylsulfonyl group as a new coordinative activating group as well as a stereocontroller.

Table 1. Enantioselective Strecker-type reaction in the presence of a Lewis acid (0.3 equiv) and a chiral ligand (0.31 equiv) to imines **1a–g**

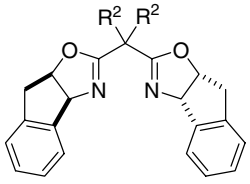


1a-g **2a-g**

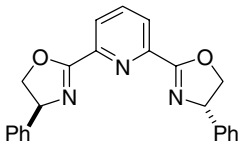
1a: R^1 = phenyl
1b: R^1 = *p*-methoxyphenyl
1c: R^1 = 2-pyridylmethyl
1d: R^1 = *p*-tolylsulfonyl
1e: R^1 =(2,4,6-triisopropylphenyl)sulfonyl
1f: R^1 = 2-pyridylsulfonyl
1g: R^1 = 8-quinolylsulfonyl



3: R^2 = Ph
4: R^2 = *i*Pr
5: R^2 = *t*-Bu



6: R^2 = Me, Me
7: R^2 = -$(CH_2)_2$-



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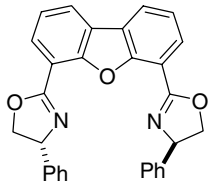

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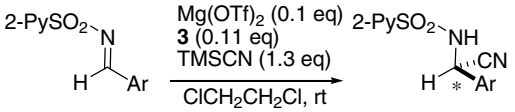
Entry	Imine	Lewis acid	Ligand	Solvent	Product	Yield (%)	ee (%)[a]
1	**1a**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2a**	0	—
2	**1b**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2b**	0	—
3	**1c**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2c**	0	—
4	**1d**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2d**	70	0
5	**1e**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2e**	0	—
6	**1f**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2f**	81	75 (*R*)
7	**1g**	$Mg(OTf)_2$	**3**	CH_2Cl_2	**2g**	Decomp.	—
8	**1f**	$Mg(ClO_4)_2$	**3**	CH_2Cl_2	**2f**	91	49 (*R*)
9	**1f**	$MgBr_2{\cdot}OEt_2$	**3**	CH_2Cl_2	**2f**	92	21 (*R*)
10	**1f**	$Cu(OTf)_2$	**3**	CH_2Cl_2	**2f**	27	71 (*R*)
11	**1f**	$Cu(SbF_6)_2$	**3**	CH_2Cl_2	**2f**	28	73 (*R*)
12[b]	**1f**	$Cu(OTf)_2$	**3**	CH_2Cl_2	**2f**	46	91 (*R*)
13[c]	**1f**	$Cu(OTf)_2$	**3**	CH_2Cl_2	**2f**	10	94 (*R*)
14	**1f**	$Mg(OTf)_2$	**4**	CH_2Cl_2	**2f**	Trace	—
15	**1f**	$Mg(OTf)_2$	**5**	CH_2Cl_2	**2f**	Trace	—
16	**1f**	$Mg(OTf)_2$	**6**	CH_2Cl_2	**2f**	99	80 (*S*)
17	**1f**	$Mg(OTf)_2$	**7**	CH_2Cl_2	**2f**	86	9 (*R*)
18	**1f**	$Mg(OTf)_2$	**8**	CH_2Cl_2	**2f**	82	13 (*R*)
19	**1f**	$Mg(ClO_4)_2$	**9**	CH_2Cl_2	**2f**	89	66 (*S*)
20	**1f**	$Mg(OTf)_2$	**3**	$ClCH_2CH_2Cl$	**2f**	99	72 (*R*)
21	**1f**	$Cu(OTf)_2$	**3**	$ClCH_2CH_2Cl$	**2f**	48	86 (*R*)
22[d]	**1f**	$Mg(OTf)_2$	**3**	$ClCH_2CH_2Cl$	**2f**	99	75 (*R*)

[a] Ee was determined by the HPLC analysis using Chiralcel OD-H or Chiralpak AD-H.
[b] Lewis acid (1.0 equiv) was used with **3** (1.1 equiv).
[c] MS4A was added.
[d] Catalyst loading is 10 mol %.

a good enantioselectivity (entry 19).[10] The reaction of **1f** in dichloroethane improved the yield and enantioselectivity of **2f** (entries 20 and 21). In all these reactions, 30 mol % of the chiral catalyst was used, but it was found that the catalytic loading of $Mg(OTf)_2$-bis(oxazoline) **3** complex can be reduced to 10 mol % in dichloroethane (entry 22). The reaction of various *N*-(2-pyridylsulfonyl)imines **1h–l** with TMSCN in the

Table 2. Enantioselective Strecker-type reaction to various *N*-(2-pyridylsulfonyl)imines **1f**,**h**–**l** in the presence of $Mg(OTf)_2$ (0.1 equiv) and bis(oxazoline) **3** (0.11 equiv)



1f,h-l **2f,h-l**

1h: Ar = 4-methylphenyl
1i: Ar = 4-chlorophenyl
1j: Ar = 4-methoxyphenyl
1k: Ar = 1-naphthyl
1l: Ar = 2-naphthyl

Entry	Imine	Product	Yield (%)	ee[a] (%)
1	**1f**	**2f**	99	75
2	**1h**	**2h**	99	72
3	**1i**	**2i**	99	72
4	**1j**	**2j**	99	84
5	**1k**	**2k**	99	75
6	**1l**	**2l**	99	73

[a] Ee was determined by the HPLC analysis using chiral column.

presence of 10 mol % of the $Mg(OTf)_2$-bis(oxazoline) **3** complex was also found to give products **2h**–**l** in a good yield with a good enantioselectivity as shown in Table 2.

The enantioselective Strecker-type reaction of *N*-(2-pyridylsulfonyl)imines **1f**,**h**–**l** gave the products in good yield with a good enantioselectivity, although the reaction of (*p*-tolylsulfonyl)imine **1d** gave the racemic product **2d** and the reaction of *N*-aryl- and *N*-alkylimines **1a**–**c** did not afford the products.[11] These results show that the 2-pyridylsulfonyl group acts not only as an activating group but also as an efficient stereocontroller. Provided that the Mg(II) ion forms a tetrahedral bidentate-coordinating complex with **1f**, there are two types of coordination for the complexes to be considered.[12] One is the *N*,*O*-type complex, in which Mg(II) coordinates to the pyridyl nitrogen and one of the sulfonyl oxygens and the other is the *N*,*N*-type complex, in which Mg(II) coordinates to the imino nitrogen and the pyridyl nitrogen. In order to estimate the stability of these complexes, we studied the MO calculation of the complexes between **1f** and **3** by Gaussian 03[13] HF/3-21+G* (Fig. 2). The calculation showed that complexes **A**, **B**, and **C** depicted for the stable *N*,*O*-type complex is more stable than the *N*,*N*-type complex (complex **D**). In order to exert a high enantioselectivity in the *N*,*O*-type complex, one of the sulfonyl oxygens should be selectively coordinated. Indeed, complex **A** in which the *pro-S* sulfonyl oxygen is coordinated to Mg(II) was shown to be much a more stable than the *pro-R* sulfonyl oxygen-coordinated complex **C**, because more severe steric interaction exists in the latter complex. The *pro-S* oxygen-coordinated complex **A** having an (*E*)-imine was more stable than complex **B** having a (*Z*)-imine by 6.5 kcal/mol. Thus, TMSCN approaches the *Si*-face of the imine in complex **A** to form (*R*)-**2f**.[14] Dynamically induced chirality on the sulfur indeed plays a definitive role in the induction of enantioselectivity.

In conclusion, the enantioselective Strecker-type reaction to *N*-(2-pyridylsulfonyl)imines in the presence of bis(oxazoline)s afforded chiral sulfonamides with a good enantioselectivity. We found that the 2-pyridylsulfonyl group works not only as a good activating group of the imino group in the reaction with TMSCN but also

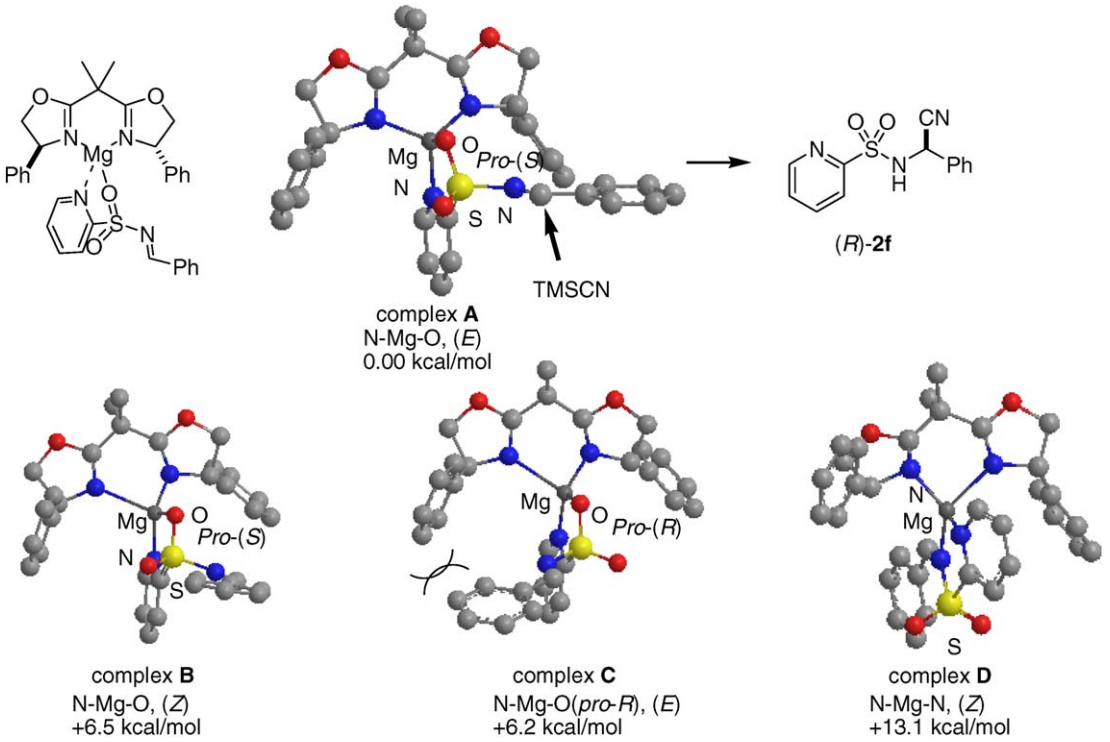


Figure 2. Geometry optimization of **1f**–**3** complexes by Gaussian 03 HF/3-21+G*.

as a stereocontroller, which shows an excellent enantioselectivity through dynamically controlled chirality on the sulfur atom. A further extension of 2-heteroarylsulfonyl groups as a powerful stereocontroller in combination with chiral ligands is now in progress.

Acknowledgement

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References and notes

1. For reviews, see: (a) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875; (b) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795; (c) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315; For recent report on the catalytic enantioselective Strecker-type reaction, see: Blacker, J.; Clutterbuck, L. A.; Crampton, M. R.; Grosjean, C.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1449.
2. Recently, the catalytic enantioselective Strecker-type reaction of *N*-(trimethylphenylsulfonyl)imines using chiral quaternary ammonium salts has been reported. The reaction of *N*-sulfonylimines derived from aliphatic aldehydes affords the products with high ee; however, this catalytic system cannot be applied to the reaction of aromatic aldimines, see: Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548.
3. The achiral Strecker-type reaction to *N*-tosylimines has been reported, see: (a) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 9565; (b) Takahashi, E.; Fujisawa, H.; Yanai, T.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 318.
4. Sugimoto, H.; Nakamura, S.; Hattori, M.; Ozeki, S.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2005**, *46*, 8941.
5. The 2-pyridylsulfonyl group has been used in some asymmetric inductions, see: (a) Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109; (b) Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 7451; (c) Arrayás, R. G.; Cbrera, S.; Carretero, J. C. J. *Synthesis* **2006**, 1205; (d) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 1795; (e) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961.
6. We have reported the highly enantioselective radical addition to vinylsulfones, in which a chiral Lewis acid selectively coordinates with one of the enantiotopic sulfonyl oxygens and nitrogen in the heteroarylsulfonyl group, see: (a) Sugimoto, H.; Nakamura, S.; Watanabe, Y.; Toru, T. *Tetrahedron: Asymmetry* **2003**, *14*, 3045; (b) Sugimoto, H.; Kobayashi, K.; Nakamura, S.; Toru, T. *Tetrahedron Lett.* **2004**, *45*, 4213; (c) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981.
7. We also examined the reaction using Bu_3SnCN and KCN as a cyanation reagent, which gave product **2f** in a low yield.
8. Various chiral Lewis acids such as $Zn(OTf)_2$-**3**, $Sc(OTf)_3$-**3**, $Yb(OTf)_3$-**3**, $Ni(ClO_4)_2{\cdot}6H_2O$-**3**, $FeCl_3$-**3**, $Sn(OTf)_2$-**3**, $Cu(OTf)_2$-BINAP, AgOTf-BINAP, Me_3Al-BINOL, $ZrCl_4$-BINOL, $AlCl_3$-PyBOX, and chiral salen-AlCl complexes, afforded product **2f** either in low yields or with a low enantioselectivity.
9. Similar aspects for the reversal of stereochemistry have been reported, see: (a) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800; (b) Sibi, M. P.; Matsunaga, H. *Tetrahedron Lett.* **2004**, *45*, 5925.
10. The $Mg(OTf)_2$ and DBFOX reaction did not afford product **2f**.
11. Unfortunately aliphatic 2-pyridylsulfonylimines could not be obtained from aliphatic aldehydes under various reaction conditions.
12. We have already reported a similar reaction mechanism in the alkylation of *N*-(2-pyridylsulfonyl)imines by the MOPAC 93/PM3 method, see Ref. 4.
13. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
14. The origin of the reversed stereochemistry obtained with bis(oxazoline) **6** is unclear. A possible explanation may be derived from the fact that the coordinating geometry of Mg(II) is changed from that with **3**; For the tetrahedral Mg(II) complex, see: (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; (b) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984; An octahedral Mg(II) complex has also been proposed: (c) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390; (d) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483.