DOI: 10.1002/chem.200701425

Enantioselective C–C Bond Formation to Sulfonylimines through Use of the 2-Pyridinesulfonyl Group as a Novel Stereocontroller

Shuichi Nakamura,* Hiroki Nakashima, Hideki Sugimoto, Hideaki Sano, Masataka Hattori, Norio Shibata, and Takeshi Toru*[a]

Abstract: Enantioselective C–C bond formation to 2-pyridinesulfonylimines afforded products with good enantioselectivity. Dynamic induction of chirality on the sulfur by coordination of a chiral Lewis acid to the pyridine nitrogen and one of the prochiral sulfonyl oxygens induces enantioselectivity. Since the 2-pyridinesulfonyl group can easily be removed after the reaction, it acts not only as an activating group but also as an efficient stereocontroller.

Keywords: asymmetric synthesis · Grignard reactions · Mannich-type reactions · stereocontroller · Strecker-type reaction

Introduction

Optically active amines, such as chiral α-amino acids and β-amino acids, as well as chiral amines, have been used in syntheses of natural products and physiologically active compounds. The stereoselective nucleophilic addition reaction of various nucleophiles to C=N bonds is one of the most efficient methods for the preparation of chiral amines, and diastereoselective reactions of imines possessing various chiral auxiliaries have been extensively studied.[1] Enantioselective additions of nucleophiles to imines have also been developed in the reactions of *N*-aryl- or *N*-alkyl-substituted imines, diphenylphosphinoylimines, *N*-acylimines, and *N*-sulfonylimines.[2,3] There are several reports of asymmetric nucleophilic addition reactions to imines through bidentate fixation between activation groups and a chiral Lewis acid;[4] however, it is often difficult to remove the protecting group from the products in these reactions. The *N*-sulfonyl group is attractive since it enhances the imine reactivity and high crystallinity in the adducts; however, removal of the *p*-toluenesulfonyl group is often problematic.[5] We have previously reported chiral induction in radical reactions of benzimidazolyl or 2-pyridyl vinyl sulfones, for which we proposed the discriminative coordination of a chiral Lewis acid between one of the prochiral sulfonyl oxygens and the heteroaryl nitrogen as playing a key role in inducing enantioselectivity;[6] namely, this induction can be termed a chiral relay process.[7] We thus designed novel 2-pyridinesulfonylimines possessing bifunctional coordinative sulfonyl groups, which can control their conformational change by the chiral relay process. The 2-pyridinesulfonyl group has the following advantages: 1) its electron-withdrawing properties increase the reactivity of imines towards the nucleophilic addition, 2) coordination of a Lewis acid to the pyridine nitrogen and one of the prochiral sulfonyl oxygens controls the stereoselectivity as well as the stereochemistry, and 3) the 2-pyridinesulfonyl group is easily removable from the products. Carretero and co-workers have independently reported excellent enantioselective conjugate additions,[8] conjugate reductions,[9] 1,3-dipolar cycloadditions,[10] and aza-Diels–Alder reactions of 2-pyridinesulfonyl substrates,[11] and have very recently disclosed Mannich-type reactions of *N*-(2-thiophenesulfonyl)imines in the presence of their own chiral Lewis acid.[12] Shibasaki and co-workers have reported outstanding stereocontrol in direct asymmetric Mannich-type reactions in the presence of *N*-(2-thiophenesulfonyl)imines.[13] Here we report catalytic enantioselective C–C bond formation in *N*-(2-pyridinesulfonyl)imines in the presence of commercially available chiral bis(oxazoline) ligands (Figure 1).[14]

[a] Prof. S. Nakamura, H. Nakashima, Dr. H. Sugimoto, H. Sano, M. Hattori, Prof. N. Shibata, Prof. T. Toru
Department of Applied Chemistry
Graduate School of Engineering
Nagoya Institute of Technology, Gokiso, Showa-ku
Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5442
E-mail: snakamur@nitech.ac.jp
toru@nitech.ac.jp

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

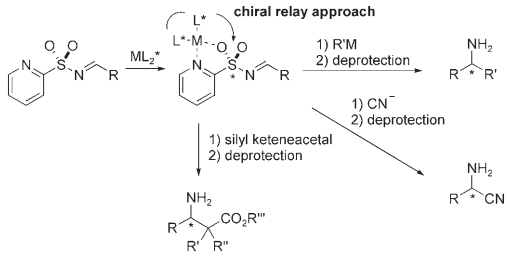
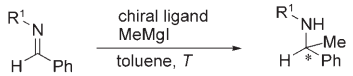


Figure 1. The 2-pyridinesulfonyl group as a new coordinative protecting and activating group and also as a stereocontroller.

Results

We first examined enantioselective reactions between sulfonylimines and Grignard reagents in the presence of various chiral ligands. Sulfonylimines and chiral ligands examined are shown in Figure 2. Although there are many reports of enantioselective reactions between imines and organolithium or organozinc reagents,[2a,15] there are no reports of enantioselective reactions involving Grignard reagents, because of their low reactivities.[16] The reactions between various sulfonylimines and CH_3MgI (2.0 equiv) in the presence of various chiral ligands (1.5 equiv) were examined, and the results are shown in Table 1. Bis(oxazoline)-Ph **A** (Figure 2) was found to be an efficient ligand for the reactions of *N*-benzylidene-2-pyridinesulfonamide (**1a**) (entries 1–5).[17] Performing the reaction at −95 °C increased enantioselectivity (entry 6). The reactions of **1a** with CH_3MgBr gave better results than those with CH_3MgI or CH_3MgCl (entries 7 and 8).

Table 1. Enantioselective additions of organometallic reagents to imines **1a–f** with MeMgI.



1a-f **2a-f**

Entry	**1**	R^1	Ligand	T [°C]	**2**	Yield [%]	*ee*[a] [%]
1	**1a**	2-$PySO_2$	**A**	−78	**2a**	75	59
2	**1a**	2-$PySO_2$	**B**	−78	**2a**	31	7
3	**1a**	2-$PySO_2$	**C**	−78	**2a**	56	40
4	**1a**	2-$PySO_2$	**D**	−78	**2a**	77	0
5	**1a**	2-$PySO_2$	**E**	−78	**2a**	90	0
6	**1a**	2-$PySO_2$	**A**	−95	**2a**	27	72
7[b]	**1a**	2-$PySO_2$	**A**	−95	**2a**	87	83 (>99)[c]
8[d]	**1a**	2-$PySO_2$	**A**	−95	**2a**	53	86
9[b]	**1b**	2-$PyCH_2$	**A**	−95	**2b**	0	–
10	**1c**	*p*-$MeOC_6H_4$	**A**	−95	**2c**	0	–
11	**1d**	*p*-$TolSO_2$	**A**	−78	**2d**	92	11
12	**1e**	$TipSO_2$	**A**	−78	**2e**	69	20
13	**1f**	8-$QnSO_2$	**A**	−78	**2f**	52	0

[a] Determined by HPLC analysis. [b] CH_3MgBr was used. [c] *ee* in parentheses is that obtained after a single recrystallization. [d] CH_3MgCl was used.

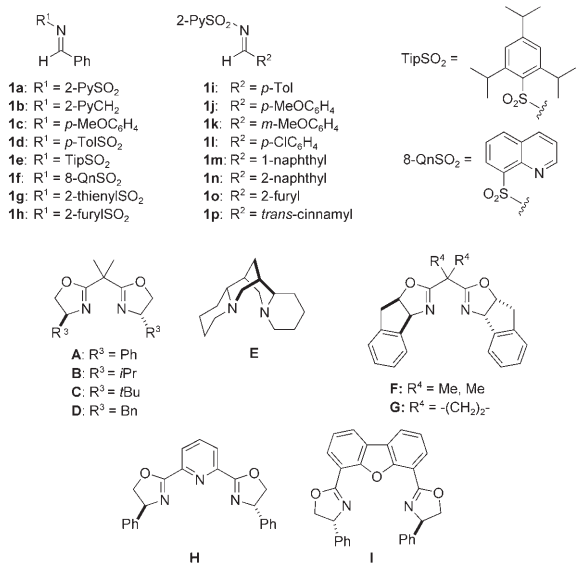
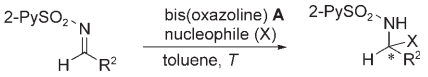


Figure 2. Structures of the sulfonylimines and chiral ligands.

A specific reaction feature of the 2-pyridinesulfonyl group in reactions with Grignard reagents is shown by the following results. The *N*-(2-pyridinemethyl)aldimine **1b** did not show enough reactivity toward CH_3MgBr because of the lack of a sulfonyl group (entry 9). In addition, *N*-benzylidene-*p*-methoxyaniline (**1c**), which is often used in enantioselective additions of organolithium reagents, was inert to the addition of CH_3MgI (entry 10). Furthermore, *N*-benzylidene-*p*-toluenesulfonamide (**1d**) and *N*-benzylidene-2,4,6-triisopropylbenzenesulfonamide (**1e**) were also not suitable choices as substrates, their reactions with CH_3MgI at −78 °C in the presence of **A** affording the products **2d** and **2e**, respectively, but with low enantioselectivities (entries 11 and 12). The reaction of *N*-benzylidene-8-quinolinesulfonamide (**1f**) afforded the racemic product **2f** (entry 13).

The reactions of various *N*-(2-pyridinesulfonyl)imines **1i–p** (R^2 = *p*-tolyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 1-naphthyl, cinnamyl, and 2-furyl) with CH_3MgBr were also examined, and it was found that the corresponding sulfonamides **2i–p** were formed in good yields and with good enantioselectivities (Table 2, entries 1–7). To the best of our knowledge, these reactions are the first highly enantioselective additions of Grignard reagents to imines.[18] The reactions of **1a** with EtMgBr, BuMgBr, and PhC≡CMgBr gave products **2q–s** in good yields, but with lower enantioselectivities than those achieved with CH_3MgBr (entries 8–11 vs. Table 1, entry 7). The reactions of **1i** with PhMgI and PhMgBr gave product **2t** in good yields and enantioselectivities (entries 12 and 13). The nucleophilic addition of Et_2Zn to sulfonylimine **1a** did not proceed with high enantioselectivity (entry 14), whereas the nucleophilic addition of MeLi preferably gave the *R* isomer (entry 15). As most of the products were crystalline, enantiomerically pure sulfonamides were easily obtainable by recrystallization. For ex-

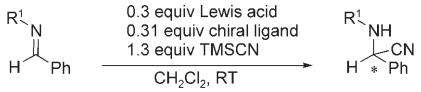
Table 2. Enantioselective additions of organometallic reagents to imines **1a** and **1i–p**.



Entry	**1**	R^2	Nucleophile	T [°C]	**2**	Yield [%]	*ee*[a] [%]
1	**1i**	*p*-Tol	CH_3MgBr	−95	**2i**	67	83
2	**1j**	*p*-$MeOC_6H_4$	CH_3MgBr	−95	**2j**	98	80 (85)[b]
3	**1k**	*m*-$MeOC_6H_4$	CH_3MgBr	−95	**2k**	74	88
4	**1l**	*p*-ClC_6H_4	CH_3MgBr	−95	**2l**	77	76
5[c]	**1m**	1-naphthyl	CH_3MgBr	−95	**2m**	74	76 (95)[b]
6[c]	**1o**	2-furyl	CH_3MgBr	−95	**2o**	38	87
7	**1p**	cinnamyl	CH_3MgBr	−95	**2p**	98	82
8	**1a**	Ph	EtMgBr	−78	**2q**	74	50
9	**1a**	Ph	BuMgBr	−95	**2r**	69	51
10	**1a**	Ph	PhC≡CMgBr	−78	**2s**	46	76
11[d]	**1a**	Ph	PhC≡CMgBr	−78	**2s**	60	78
12	**1i**	*p*-Tol	PhMgI	−95	**2t**	41	66
13	**1i**	*p*-Tol	PhMgBr	−95	**2t**	72	61
14[e]	**1a**	Ph	Et_2Zn	−78	**2q**	49	46
15	**1a**	Ph	MeLi	−78	**2a**	35	35[f]

[a] Determined by HPLC analysis. [b] *ee* in parentheses is that obtained after a single recrystallization. [c] Bis(oxazoline) **A** (2 equiv) was used. [d] Diethyl-substituted Box **A** was used. [e] Et_2Zn was added at −40 °C. [f] The *R* isomer was obtained.

Table 3. Catalytic enantioselective Strecker-type reactions with imines **1a–f** and TMSCN.



Entry	**1**	R^1	Lewis acid	Ligand	**3**	Yield [%]	*ee* [%][a]
1	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**A**	**3a**	81	75 (*R*)
2	**1b**	2-$PyCH_2$	$Mg(OTf)_2$	**A**	**3b**	0	–
3	**1c**	*p*-$MeOC_6H_4$	$Mg(OTf)_2$	**A**	**3c**	0	–
4	**1d**	*p*-$TolSO_2$	$Mg(OTf)_2$	**A**	**3d**	70	0
5	**1e**	$TipSO_2$	$Mg(OTf)_2$	**A**	**3e**	0	–
6	**1f**	8-$QnSO_2$	$Mg(OTf)_2$	**A**	**3f**	49	16
7	**1a**	2-$PySO_2$	$Mg(ClO_4)_2$	**A**	**3a**	91	49 (*R*)
8	**1a**	2-$PySO_2$	$MgBr_2OEt_2$	**A**	**3a**	92	21 (*R*)
9	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**A**	**3a**	27	71 (*R*)
10[b]	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**A**	**3a**	46	91 (*R*)
11[c]	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**A**	**3a**	10	94 (*R*)
12	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**F**	**3a**	99	80 (*S*)
13	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**G**	**3a**	71	51 (*S*)
14	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**H**	**3a**	82	13 (*R*)
15	**1a**	2-$PySO_2$	$Mg(ClO_4)_2$	**I**	**3a**	89	66 (*S*)
16[d]	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**A**	**3a**	99	72 (*R*)
17[d]	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**A**	**3a**	48	86 (*R*)
18[d,e]	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**A**	**3a**	99	75 (*R*)
19[d–f]	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**A**	**3a**	99	79 (*R*)

[a] Determined by HPLC analysis with Chiralcel OD-H, Chiralpak AD-H, or Chiralpak AS-H. [b] Lewis acid (1.0 equiv) was used with **3** (1.1 equiv). [c] MS (4 Å) were added. [d] Reaction was carried out in $ClCH_2CH_2Cl$. [e] Catalyst loading is 10 mol %. [f] Reaction was carried out at 0 °C.

ample, recrystallization of **2a** with 83 % *ee* from hexane/CH_2Cl_2 afforded enantiomerically pure (*S*)-**2a** (Table 1, entry 7).

We next examined catalytic enantioselective Strecker-type reactions of *N*-(2-pyridinesulfonyl)imines. The enantioselective Strecker-type reaction is one of the most important methods for the synthesis of optically active α-amino acid derivatives, so a variety of chiral catalysts with which to achieve high levels of asymmetric induction in the addition of cyanide to imines have been developed.[2,3,19] Although the *N*-sulfonyl group certainly increases the electrophilicity of the imino carbon center and enhances the reactivity toward the attack of a cyanide, there have been only limited reports on catalytic enantioselective Strecker-type reactions with *N*-sulfonylimines.[20,21]

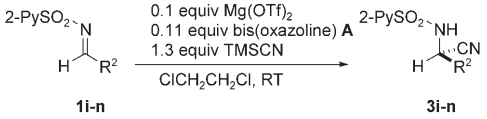
Enantioselective Strecker-type reactions were carried out in the presence of a variety of bis(oxazoline) ligands in combination with Lewis acids; the results are shown in Table 3. The reactions of *N*-aryl- and *N*-alkyl-substituted imines **1b** and **1c** with TMSCN (1.3 equiv) in the presence of catalytic amounts of $Mg(OTf)_2$ (0.3 equiv) and bis(oxazoline) **A** (0.31 equiv) as a chiral Lewis acid did not give products (entries 2 and 3). On the other hand, the reaction of sulfonylimine **1a** afforded the product **3a** with good enantioselectivity (entry 1).[22] *N*-(*p*-Toluenesulfonyl)-, *N*-(2,4,6-triisopropylbenzene)sulfonyl-, and *N*-(8-quinolinesulfonyl)imines **1d–f** did not give good results (entries 4–6). 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 **1a**, and gave **3a** in high yields but with low enantioselectivities (entries 7 and 8). When $Cu(OTf)_2$ was used as a Lewis acid, **3a** was obtained with good enantioselectivity but in low yield (entry 9).[23] Enantioselectivity was improved by the use of a stoichiometric amount of the $Cu(OTf)_2$/**A** complex or by the addition of molecular sieves (4 Å) to the reaction mixture, although the yields still remained moderate to low (entries 10 and 11).

It should be noted that **3a** obtained with the $Mg(OTf)_2$/**F** complex in high yield and with high enantioselectivity has the opposite configuration to that obtained with $Mg(OTf)_2$/Box **A** (entry 12).[24] The $Mg(ClO_4)_2$/DBFOX **I** complex also catalyzed the reaction to give good enantioselectivity (entry 15).[25] Carrying out the reaction with **1a** in dichloroethane improved the yield and enantioselectivity of **3a** (entries 16 and 17). In all these reactions, 30 mol % of the chiral catalyst was used, but it was found that the catalyst loading of the $Mg(OTf)_2$/**A** complex can be reduced to 10 mol % in dichloroethane (entry 18). Enantioselectivity was improved when the reaction was performed at 0 °C (entry 19).

The reactions of various *N*-(2-pyridinesulfonyl)imines **1i–n** with TMSCN in the presence of 10 mol % of the $Mg(OTf)_2$/**A** complex also gave the products **3i–n** in good yields and with good enantioselectivities (Table 4, entries 1–6).[26]

Catalytic enantioselective Mannich-type reactions of *N*-(2-pyridinesulfonyl)imines were also examined. β-Amino acid derivatives have established utility as building blocks for the preparation of pharmaceutical targets,[27] natural products,[28] and peptidic materials with unique structural

Table 4. Catalytic enantioselective Strecker-type reactions with imines **1a–n** and TMSCN.



1i-n **3i-n**

Entry	Imine	R^2	Product	Yield [%]	*ee* [%][a]
1[b]	**1i**	*p*-tolyl	**3i**	94	77 (*R*)
2	**1j**	*p*-$MeOC_6H_4$	**3j**	99	84 (*R*)
3[b]	**1k**	*m*-$MeOC_6H_4$	**3k**	93	78 (*R*)
4	**1l**	*p*-ClC_6H_4	**3l**	99	72 (*R*)
5	**1m**	1-naphthyl	**3m**	99	75 (*R*)
6	**1n**	2-naphthyl	**3n**	99	73 (*R*)

[a] *ee* values were determined by HPLC analysis with Chiralcel OD-H, Chiralpak AD-H, or Chiralpak AS-H. [b] Reaction was carried out at 0 °C.

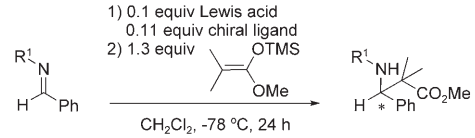
properties.[29] Although various diastereoselective approaches to Mannich-type reactions have been reported for the synthesis of β-amino acids, enantioselective additions of ester enolate equivalents to imines are one of the most important methods for the synthesis of optically active β-amino acids.[2,3,30,31] However, only a few studies on catalytic enantioselective Mannich-type reactions of *N*-sulfonylimines without other electron-withdrawing groups have been reported.[32]

Enantioselective Mannich-type reactions of various *N*-(arenesulfonyl)imines **1** in the presence of catalytic amounts of chiral Lewis acids prepared from various bis(oxazoline)s and Lewis acids were examined, and the results are shown in Table 5. The enantioselective reaction of **1a** in the presence of 30 mol % of $Mg(OTf)_2$/**A** afforded the product **4a** with low enantioselectivity, whereas the reaction in the presence of $Cu(OTf)_2$/**A** gave the product with good enantioselectivity (entries 1 and 2). However, *N*-(toluenesulfonyl)imines **1d** did not afford the product with $Cu(OTf)_2$/**A** (entry 3). The reactions in the presence of other *N*-(heteroarenesulfonyl)imines **1f–h** did not show good enantioselectivities (entries 4–6). The yield of **4a** in the reaction of **1a** was improved by use of a longer reaction time (entry 7).[33] Other chiral Lewis acids derived from CuOTf and $Zn(OTf)_2$ also afforded the product **4a** but with low enantioselectivities (entries 8 and 9). The chiral Lewis acids derived from other bis(oxazoline) ligands **C**, **F**, and **H** also catalyzed the reaction but with lower enantioselectivities than were obtained with $Cu(OTf)_2$/**A** (entries 10–13).

The reactions of various *N*-(2-pyridinesulfonyl)imines **1i–p** in the presence of $Cu(OTf)_2$/**A** were also found to give products in moderate yields but with good enantioselectivities (Table 6, entries 1–7). Enantiomerically pure sulfonamides were easily obtainable by recrystallization.

To validate the synthetic potential of this stereoselective preparation of chiral amines, we confirmed the easy removal of the 2-pyridinesulfonyl group. Removal of arenesulfonyl groups generally requires drastic reaction conditions.[5] The optically active (*S*)-**2a** and (*R*)-**4a** were desulfonylated on

Table 5. Catalytic enantioselective Mannich-type reactions with imines **1a**, **1d**, and **1f–h**.

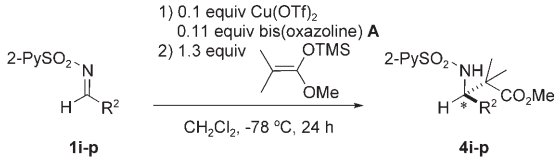


1a,d,f-h **4a,d,f-h**

Entry	**1**	R^1	Lewis acid	Ligand	**4**	Yield [%]	*ee* [%][a]
1[b]	**1a**	2-$PySO_2$	$Mg(OTf)_2$	**A**	**4a**	37	29
2	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**A**	**4a**	80	86 (>99)[c]
3	**1d**	*p*-$TolSO_2$	$Cu(OTf)_2$	**A**	**4d**	trace	–
4	**1f**	8-$QnSO_2$	$Cu(OTf)_2$	**A**	**4f**	19	1
5	**1g**	2-thienylSO_2	$Cu(OTf)_2$	**A**	**4g**	47	0
6	**1h**	2-furylSO_2	$Cu(OTf)_2$	**A**	**4h**	59	8
7[d]	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**A**	**4a**	55	86
8[b]	**1a**	2-$PySO_2$	CuOTf	**A**	**4a**	32	38
9[b]	**1a**	2-$PySO_2$	$Zn(OTf)_2$	**A**	**4a**	16	62
10[b]	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**C**	**4a**	41	2
11	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**F**	**4a**	24	71
12	**1a**	2-$PySO_2$	$Cu(OTf)_2$	**H**	**4a**	30	64
13[b]	**1a**	2-$PySO_2$	$Sc(OTf)_3$	**H**	**4a**	42	62

[a] Determined by HPLC analysis with Chiralcel OD-H or Chiralpak AD-H. [b] Catalyst loading is 30 mol %. [c] *ee* in parentheses is that obtained after a single recrystallization. [d] The reaction was performed for 72 h.

Table 6. Catalytic enantioselective Mannich-type reactions with imines **1i–p**.

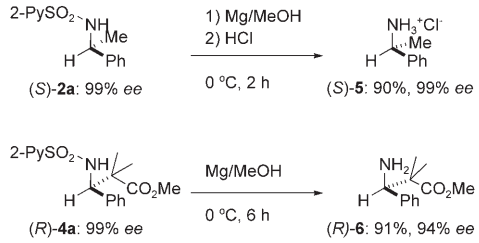


1i-p **4i-p**

Entry	Imine	R^2	Product	Yield [%]	*ee* [%][a,b]
1	**1i**	*p*-tolyl	**4i**	40	70 (95)
2[c]	**1j**	*p*-$MeOC_6H_4$	**4j**	58	83 (>99)
3[c]	**1l**	*p*-ClC_6H_4	**4l**	52	75 (90)
4[c]	**1m**	1-naphthyl	**4m**	76	73 (94)
5	**1n**	2-naphthyl	**4n**	89	63 (>99)
6	**1o**	2-furyl	**4o**	86	81 (99)
7[c]	**1p**	cinnamyl	**4p**	89	83 (>99)

[a] Determined by HPLC analysis with Chiralcel OD-H or Chiralpak AD-H. [b] *ee* in parentheses are those obtained after single recrystallizations. [c] Catalyst loading is 30 mol %.

treatment with magnesium in MeOH[34] to give the chiral



Scheme 1. Desulfonylation of (*S*)-**2a** and (*R*)-**4a**.

amine (*S*)-**5** and the chiral β-amino acid (*R*)-**6** without significant loss of optical purity (Scheme 1).

Discussion

The enantioselective nucleophilic additions of Grignard reagents and the Strecker-type reactions of *N*-(2-pyridinesulfonyl)imines **1a**, **1f**, and **1i**–**p** gave the products in good yields and with good enantioselectivities, but the reactions of *N*-(*p*-toluenesulfonyl)imine **1d** and of *N*-aryl- and *N*-alkylimines **1b** and **1c** did not afford good results. From these findings it was confirmed that the 2-pyridinesulfonyl group acts not only as an activating group but also as an efficient stereocontroller. If it is assumed that Mg^{II} forms a tetrahedral bidentate-coordinating complex with the substrate **1a**,[35,36] there are two types of coordination for the complex that may be considered. One is the *N*,*O*-type complex, in which Mg^{II} coordinates to the pyridine nitrogen and to one of the sulfonyl oxygens, while the other is the *N*,*N*-type complex, in which Mg^{II} coordinates to the imino nitrogen and to the pyridine nitrogen. In order to estimate the stabilities of these complexes, we studied MO calculations of the complexes formed between **1c** and **3** with Spartan ′06 PM3[37] and Gaussian 03[38] HF/3-21+G*. Structures were first optimized with Spartan ′06 PM3 and were then fully optimized at the HF/3-21+G* level of theory.[39,40] The relative energies of the transition state structures and the optimized structures are depicted in Figure 3. The calculation showed that the *N*,*O*-type complexes **I**, **II**, and **III** are more stable than complex **IV** depicted as one of the most stable *N*,*N*-type complexes.

In order to exert high enantioselectivity in the *N*,*O*-type complex, one of the sulfonyl oxygens should be selectively coordinated. Indeed, complex **I**, in which the *pro-S* sulfonyl oxygen is coordinated to Mg^{II}, was shown to be much more stable than the *pro-R* sulfonyl oxygen-coordinated complex **III**, because more severe steric interaction exists in the latter complex. The *pro-S* oxygen-coordinated complex **I** containing an (*E*)-imine was more stable than the (*Z*)-imine complex **II**. Nucleophiles thus approach the *Si* face of the imine in complex **I** to form products with good *ee*s. Dynamically induced chirality on the sulfur indeed plays a definitive role in induction of enantioselectivity. It can be categorized as a new type of chiral relay.[7]

The enantioselective Strecker-type reactions and Mannich-type reactions of *N*-(2-pyridinesulfonyl)imines in the presence of $Cu(OTf)_2$ as a Lewis acid gave the products with good enantioselectivities. The Cu^{II} ion would form a distorted square-planar bidentate-coordinated complex with **1a** and Box **A** (Figure 4). In the most stable complex **1a**–**A**, optimized by the Spartan ′06 PM3 method, a sulfonyl oxygen and a pyridine nitrogen coordinate to Cu^{II}. Furthermore, selective coordination between a *pro-S* sulfonyl oxygen in **1a** and Cu^{II} affords less steric interaction than in other complexes. TMSCN and silyl ketene acetal thus ap-

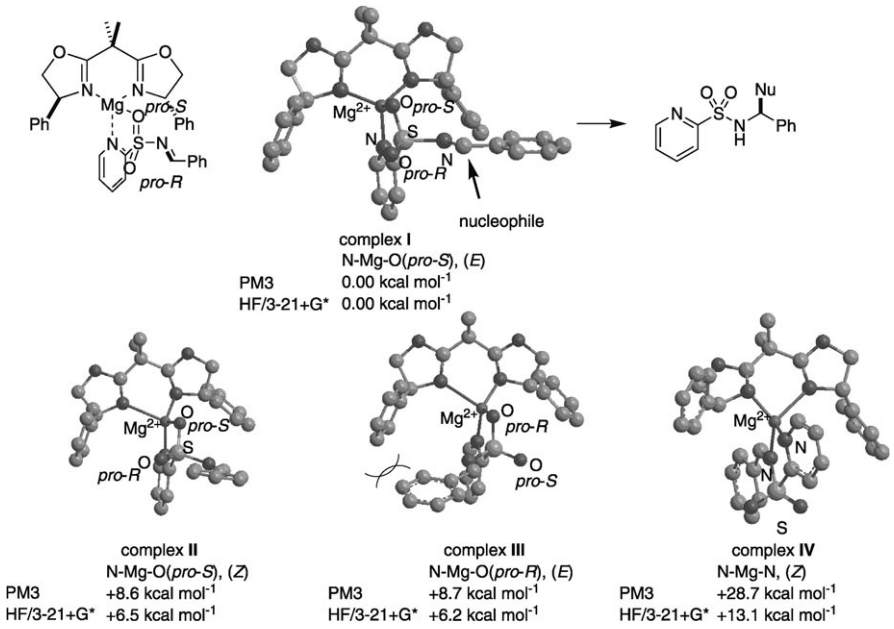


Figure 3. Geometry optimization of **1a**–**A** complexes with Spartan ′06 PM3 and Gaussian 03 HF/3-21+G*.

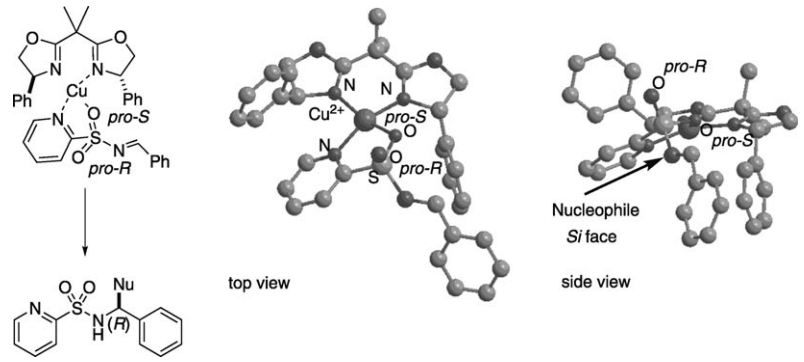


Figure 4. Proposed reaction direction in the most stable complex **1a**–**A** optimized with Spartan ′06 PM3.

proach the *Si* face of the imine, avoiding interaction with the phenyl group in bis(oxazoline)-Ph **A**, to form (*R*)-**3a** and (*R*)-**4a**.

Conclusion

We have found that the 2-pyridinesulfonyl group works not only as a good activating group for the imino group in reactions with nucleophiles, but also as a stereocontroller that shows excellent enantioselectivity through dynamically controlled chirality on the sulfur atom. The first highly enantioselective reactions between imines and Grignard reagents have been achieved in the presence of bis(oxazoline)s. Catalytic enantioselective Strecker-type reactions and Mannich-type reactions with *N*-(2-pyridinesulfonyl)imines in the presence of bis(oxazoline)s afforded chiral sulfonamides with good enantioselectivities. The MO calculations suggested that these reactions each proceed through a complex in which one of the sulfonyl oxygens is preferentially coordinated to Mg^{II} and Cu^{II}. The 2-pyridinesulfonyl group was shown to be an easily removable and efficient protective group, which has notable properties of high chiral inducibility and activation of the imino group toward the addition of nucleophiles. Further extension of work on 2-heteroarenesulfonyl groups as powerful stereocontrollers in combination with chiral ligands is now in progress.

Experimental Section

General methods and additional synthesis details are available in the Supporting Information.

Typical procedure for the preparation of *N*-benzylidene-2-pyridinesulfonamide (1a): A solution of 2-pyridinesulfonamide (501 mg, 3.17 mmol) in THF (8 mL) was added at 0 °C to a solution of benzaldehyde (0.32 mL, 3.17 mmol), triethylamine (1.32 mL, 9.50 mmol), and titanium(IV) chloride (1.46 mol L^{-1} in CH_2Cl_2, 2.25 mL, 3.17 mmol), and the mixture was stirred for 2 h. The mixture was filtered through Celite and washed with CH_2Cl_2. The combined organic solution was extracted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, and dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue that was recrystallized with hexane/ethyl acetate to afford **1a** (368 mg, 47%). R_f=0.35 (hexane/ethyl acetate 6:4); m.p. 103.8–105.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ=7.48–7.67 (m, 4H), 7.96–8.02 (m, 3H), 8.24–8.28 (m, 1H), 8.72–8.75 (m, 1H), 9.27 ppm (s, 1H); ^{13}C NMR: δ=121.8, 125.8, 127.6, 130.1, 130.7, 133.9, 136.6, 148.8, 154.2, 172.7 ppm; IR (KBr): $\tilde{\nu}$= 1599, 1572, 1314, 1171, 1114, 816 cm^{-1}; MS (70 eV): m/z (%): 246 $[M]^+$ (6), 78 (100); elemental analysis calcd (%) for $C_{12}H_{10}N_2O_2S$: C 58.52, H 4.09, N 11.37; found: C 58.36, H 4.34, N 11.28.

Typical procedure for enantioselective addition of Grignard reagents to 1a—*N*-(1-Phenylethyl)-2-pyridinesulfonamide [(*S*)-2a]: MeMgBr (1.04 mol L^{-1} in Et_2O, 0.937 mL, 0.974 mmol) was added at −95 °C to a solution of bis(oxazoline)-Ph (244 mg, 0.731 mmol) and imine **1a** (120 mg, 0.487 mmol) in toluene (10 mL), and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with HCl (1 M) and extracted with Et_2O, dried over Na_2SO_4, and concentrated under reduced pressure to leave a residue that was purified by column chromatography (silica gel 20 g, benzene/ethyl acetate 90:10) to afford (*S*)-**2a** (101 mg, 79%, 83% *ee*). Recrystallization from hexane/CH_2Cl_2 afforded (*S*)-**2a** with 99% *ee*. R_f=0.35 (hexane/ethyl acetate 6:4); m.p. 103.8–105.0 °C; $[\alpha]_D^{20}$=−42.3 (*c*=0.29, $CHCl_3$, 99% *ee*); ^{1}H NMR: δ=1.48 (d, *J*=7.0 Hz, 3H), 4.61 (dq, *J*=7.0, 8.2 Hz, 1H), 5.18 (d, *J*=8.2 Hz, 1H), 7.11–7.20 (m, 5H), 7.33–7.40 (m, 1H), 7.70–7.80 (m, 2H), 8.56–8.59 ppm (m, 1H); ^{13}C NMR: δ=23.5, 54.3, 121.9, 126.0, 126.1, 127.2, 128.1, 137.4, 141.4, 149.5, 157.4 ppm; IR (KBr): $\tilde{\nu}$=3091, 1330, 1178, 1119, 614, 541 cm^{-1}; MS (70 eV): m/z (%): 262 $[M]^+$ (4), 77 (40), 78 (28), 119 (100), 182 (15); elemental analysis calcd (%) for $C_{13}H_{14}N_2O_2S$: C 59.52, H 5.38, N 11.37; found: C 59.51, H 5.42, N 10.44; HPLC (Chiralcel OJ-H, hexane/*i*PrOH 70:30, flow rate 1.2 mL min^{-1}), t_R=11 (*S*), 33 min (*R*).

General procedure for the reactions of imines with TMSCN—2-(2-Pyridinesulfonyl)amino-2-phenylacetonitrile (3a): A solution of bis(oxazoline)-Ph (3.0 mg, 11 mol%) and $Mg(OTf)_2$ (2.6 mg, 10 mol%) in $ClCH_2CH_2Cl$ (1.0 mL) was stirred for 30 min at room temperature under nitrogen. A solution of imine **1a** (20.0 mg, 0.081 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) was added to the reaction mixture. After the reaction mixture had been stirred for 15 min at room temperature, trimethylsilyl cyanide (32 μL, 0.24 mmol) was added over a period of 5 min. The reaction mixture was stirred for 12 h until complete by TLC. Sat. aqueous Na_2CO_3 (2.0 mL) was added, and the mixture was stirred for 30 min at room temperature. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (benzene/ethyl acetate 90:10) to afford **3a** (22.1 mg, 99%, 74% *ee*) as a white solid. R_f=0.32 (benzene/ethyl acetate 8:2); m.p. 158.0–159.0 °C; $[\alpha]_D^{26}$=+35 (*c*=0.03, $CHCl_3$, 74% *ee*); ^{1}H NMR ([D$_6$]DMSO): δ=5.90 (d, *J*=8.5 Hz, 1H), 7.36–7.40 (m, 5H), 7.64–7.70 (m, 1H), 7.92–7.96 (m, 1H), 8.03–8.12 (m, 1H), 8.71 (m, 1H), 9.58 ppm (d, *J*=8.5 Hz, 1H); ^{13}C NMR ([D$_6$]DMSO): δ=47.8, 117.8, 121.6, 126.9, 127.4, 128.7, 128.9, 133.9, 149.9, 156.8 ppm; IR (KBr): $\tilde{\nu}$=3097, 1348, 1185 cm^{-1}; MS (70 eV): m/z (%): 273 $[M]^+$ (0.4), 208 (11), 130 (12), 78 (100), 77 (24); elemental analysis calcd (%) for $C_{13}H_{11}N_3O_2S$: C 57.13, H 4.06, N 15.37; found: C 57.24, H 3.99, N 15.33; HPLC (Daicel Chiralpak AS, hexane/*i*PrOH 75:25; 2.0 mL min^{-1}; t_R=18.2 (minor), t_R=27.7 min (major)).

General procedure for the Mannich-type reactions of imines—Methyl (*R*)-2,2-dimethyl-3-phenyl-3-[(2-pyridinesulfonyl)amino]propionate (4a): A solution of bis(oxazoline)-Ph (3.9 mg, 0.011 mmol, 11 mol%) and $Cu(OTf)_2$ (3.8 mg, 0.010 mmol, 10 mol%) in CH_2Cl_2 (1.0 mL) was stirred for 30 min at room temperature under nitrogen. A solution of imine **1a** (25.0 mg, 0.104 mmol) in CH_2Cl_2 (1.0 mL) was added to the reaction mixture. After the reaction mixture had been cooled to −78 °C, silylketene acetal (27 μL, 0.135 mmol) was added over a period of 5 min. The reaction mixture was stirred for 24 h until complete by TLC. Sat. aqueous NH_4Cl (10 mL) was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (5×5 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (benzene/ethyl acetate 85:15) to afford **4a** (28.9 mg, 80%, 86% *ee*) as a white solid. R_f=0.55 (benzene/ethyl acetate 7:3); m.p. 146.0–147.5 °C; $[\alpha]_D^{20}$=−26.6 (*c*=1.0, $CHCl_3$, 99% *ee*); ^{1}H NMR: δ=1.08 (s, 3H), 1.39 (s, 3H), 3.65 (s, 3H), 4.42 (d, *J*=10 Hz, 1H), 6.50 (d, *J*=10 Hz, 1H), 6.88–6.99 (m, 5H), 7.14–7.17 (m, 1H), 7.41–7.51 (m, 2H), 8.40 ppm (s, 1H); ^{13}C NMR: δ=22.5, 24.7, 47.1, 52.2, 65.0, 121.6, 125.6, 127.1, 127.4, 127.7, 136.3, 136.9, 149.2, 156.9, 175.8 ppm; IR (KBr): $\tilde{\nu}$=3167, 1734, 1289, 1582, 1337, 1180, 1131, 710 cm^{-1}; MS (70 eV): m/z (%): 348 $[M]^+$ (35), 315 (40), 256 (70), 247(100), 199 (45); elemental analysis calcd (%) for $C_{17}H_{20}N_2O_4S$: C 58.60, H 5.79, N 8.04; found: C 58.90, H 5.49, N 7.91; HPLC (Chiralpak AD-H, hexane/*i*PrOH 80:20, 1.0 mL min^{-1}): t_R = 11.3 (major), 14.8 min (minor).

(*S*)-1-Phenylethylamine hydrochloride [(*S*)-5]: A mixture of (*S*)-**2a** (20.2 mg, 0.077 mmol) and Mg powder (9.3 mg, 0.385 mmol) in MeOH (2 mL) and THF (0.5 mL) was stirred for 2 h at 0 °C. Then, diethyl ether (3 mL) and saturated aq. NH_4Cl (3 mL) were added, and the reaction mixture was stirred for 2 h at room temperature. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to leave an oil that was purified by column chromatography (CH_2Cl_2/MeOH/aq. NH_3 90:10:0.5) to afford the amine. The amine was dissolved in THF (2 mL), and HCl solution (2 N) was added to the solution. After stirring for 30 min at room temperature, the solution was concentrated under reduced pressure to give (*S*)-**5** (10.9 mg, 90%). $[\alpha]_D^{25}$=−4.5 (*c*=0.36, MeOH) [lit.[41] $[\alpha]_D^{23}$=

−4.6 ($c=4$, MeOH, 99% *ee*)]. In order to determine the enantiopurity, (*S*)-5 was treated with benzoyl chloride and triethylamine in CH_2Cl_2 at room temperature. *N*-Benzoyl-1-phenylethylamine was analyzed by HPLC: 99% *ee* [Chiralcel OD-H hexane/*i*PrOH 90:10, 1.0 mL min^{-1}: t_R = 16 min (*S*)].

Methyl (*R*)-3-amino-2,2-dimethyl-3-phenylpropionate [(*R*)-6]: A mixture of (*R*)-**4a** (200 mg, 0.574 mmol) and Mg powder (418.6 mg, 17.2 mmol) in MeOH (10 mL) was stirred for 6 h at −30 °C. Then, diethyl ether (10 mL) and saturated aq. NH_4Cl (15 mL) were added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to leave a white solid that was purified by column chromatography (benzene/ethyl acetate 90:10) to afford product (*R*)-**6** (159.2 mg, 91%). $[\alpha]_D^{20}=+30.8$ ($c=1$, 1 M HCl, 87% *ee*) [lit.[42] $[\alpha]_D^{20}=-32.4$ ($c=1$, 1 N HCl, 98% *ee*)]; ^{1}H NMR: $\delta=1.08$ (s, 3H), 1.14 (s, 3H), 1.71 (s, 2H), 3.68 (s, 3H), 4.22 (s, 1H), 7.26 ppm (s, 5H); ^{13}C NMR: $\delta=19.5$, 23.7, 47.8, 51.8, 61.9, 127.0, 127.5, 127.8, 141.5, 177.3 ppm; IR (KBr): $\tilde{\nu}=2950$, 1725, 1453, 1259, 1141, 705 cm^{-1}; MS (70 eV): m/z (%): 207 $[M]^+$ (70), 199 (60), 171 (56), 152 (100); elemental analysis calcd (%) for $C_{12}H_{17}NO_2$: C 69.54, H 8.27, N 6.76; found: C 69.65, H 8.36, N 6.85; HPLC (Chiralcel AS-H, hexane/*i*PrOH 95:5, 0.30 mL min^{-1}): t_R = 24.5 (major), 30.7 min (minor).

Acknowledgements

This work was supported by the Daiko Foundation, the Tatematsu Foundation, the Yazaki Foundation, and the Sankyo Award in Synthetic Organic Chemistry, Japan.

[1] For reviews, see: a) A. Jahansson, *Contemp. Org. Synth.* **1995**, *2*, 393–407; b) E. Enders, U. Reinhold, *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946, and references therein; c) G. Alvaro, D. Savoia, *Synlett* **2002**, 651–673; d) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407–1438.

[2] For reviews covering chiral Lewis acids, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; b) T. Vilaivan, W. Bhanthumnavin, Y. Sritana-Anant, *Curr. Org. Chem.* **2005**, *9*, 1315–1392; c) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541–2569; d) D. Ferraris, *Tetrahedron* **2007**, *63*, 9581–9597.

[3] For recent reviews covering chiral organocatalysts, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**, Chapter 5.2, pp. 97–108; b) T. Fujie, C. F. Barbas, III, *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**, Chapter 2.1, pp. 38–51.

[4] For reviews of the enantioselective reactions of acylhydrazones, see: a) S. Kobayashi, M. Sugiura, C. Ogawa, *Adv. Synth. Catal.* **2004**, *346*, 1023–1034; b) G. K. Friestad, *Eur. J. Org. Chem.* **2005**, 3157–3172; for the reactions of *N*-(2-hydroxyphenyl)imines, see: c) H. Ishitani, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 7357–7360; d) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154; e) S. Kobayashi, S. Komiyama, K. Ishitani, *Angew. Chem.* **1998**, *110*, 1026–1028; *Angew. Chem. Int. Ed.* **1998**, *37*, 979–981; f) T. Gastner, H. Ishitani, R. Akiyama, S. Kobayashi, *Angew. Chem.* **2001**, *113*, 1949–1951; *Angew. Chem. Int. Ed.* **2001**, *40*, 1896–1898.

[5] a) J. Kovacs, U. R. Ghatak, *J. Org. Chem.* **1966**, *31*, 119–121; b) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, P. Wriede, *J. Am. Chem. Soc.* **1967**, *89*, 5311–5312. Conversion of *N*-sulfonamides into *N*-alkyl-*N*-sulfonyl compounds or *N*-Boc-*N*-sulfonyl compounds prior to the cleavage is needed for removal of a tosyl group from primary amines, see: c) B. Nyasse, L. Grehn, U. Ragnarsson, *Chem. Commun.* **1997**, 1017–1018, and references therein. d) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997.

[6] a) H. Sugimoto, S. Nakamura, Y. Watanabe, T. Toru, *Tetrahedron: Asymmetry* **2003**, *14*, 3043–3045; b) H. Sugimoto, K. Kobayashi, S. Nakamura, T. Toru, *Tetrahedron Lett.* **2004**, *45*, 4213–4216; c) Y. Watanabe, N. Mase, R. Furue, T. Toru, *Tetrahedron Lett.* **2001**, *42*, 2981–2984.

[7] For a recent review on chiral relay effects, see: a) O. Corminboeuf, L. Quaranta, P. Renaud, M. Liu, C. P. Jasperse, M. P. Sibi, *Chem. Eur. J.* **2003**, *9*, 28–35; for a recent contribution, see: b) M. P. Sibi, L. M. Stanley, X. Nie, L. Venkatraman, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc.* **2007**, *129*, 395–405.

[8] a) P. Mauleón, J. C. Carretero, *Chem. Commun.* **2005**, 4961–4963; b) J. Esquivias, R. G. Arrayás, J. C. Carretero, *J. Org. Chem.* **2005**, *70*, 7451–7454.

[9] T. Llamas, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2007**, *119*, 3393–3396; *Angew. Chem. Int. Ed.* **2007**, *46*, 3329–3332.

[10] T. Llamas, R. G. Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 1795–1798.

[11] J. Esquivias, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480–1481.

[12] A. S. González, R. G. Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 2977–2980.

[13] H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588–9589.

[14] For preliminary reports, see: a) S. Nakamura, N. Sato, M. Sugimoto, T. Toru, *Tetrahedron: Asymmetry* **2004**, *15*, 1513–1516; b) H. Sugimoto, S. Nakamura, M. Hattori, S. Ozeki, N. Shibata, T. Toru, *Tetrahedron Lett.* **2005**, *46*, 8941–8944; c) S. Nakamura, H. Nakashima, H. Sugimoto, N. Shibata, T. Toru, *Tetrahedron Lett.* **2006**, *47*, 7599–7602; d) S. Nakamura, H. Sano, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Tetrahedron Lett.*, **2007**, *48*, 5565–5568.

[15] For a review, see: S. Bräse, T. Baumann, S. Dahmen, H. Voget, *Chem. Commun.* **2007**, 1881–1890.

[16] Although the reactivities of Grignard reagents towards imines are generally low, they are improved by the addition of $Sc(OTf)_3$, see: S. Saito, K. Hatanaka, H. Yamamoto, *Synlett* **2001**, 1859–1861.

[17] Treatment of **1a** with a catalytic amount (0.3 equiv) of bis(oxazoline) **A** and MeMgBr gave **2a** with 29% *ee*.

[18] There are some examples of enantioselective reactions of nitrones with Grignard reagents: a) Y. Ukaji, T. Hatanaka, A. Ahmed, K. Inomata, *Chem. Lett.* **1993**, 1313–1316; b) F. L. Merchan, P. Merino, I. Rojo, T. Tejero, A. Dondoni, *Tetrahedron: Asymmetry* **1996**, *7*, 667–670.

[19] For reviews, see: a) L. Yet, *Angew. Chem.* **2001**, *113*, 900–902; *Angew. Chem. Int. Ed.* **2001**, *40*, 875–877; b) H. Gröger, *Chem. Rev.* **2003**, *103*, 2795–2827. For a recent report on catalytic enantioselective Strecker-type reactions in the presence of chiral Lewis acids, see: c) S. Masumoto, H. Usuda, M. Suzuki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5634–5635; d) J. Blacker, L. A. Clutterbuck, M. R. Crampton, C. Grosjean, M. North, *Tetrahedron: Asymmetry* **2006**, *17*, 1449–1456. For recent reports on catalytic enantioselective Strecker-type reactions in the presence of chiral organocatalysts, see: e) X. Huang, J. Huang, Y. Wen, X. Feng, *Adv. Synth. Catal.* **2006**, *348*, 2579–2584; f) R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Perrersen, A. Ricci, *J. Org. Chem.* **2006**, *71*, 9869–9872; g) J. Huang, X. Liu, Y. Wen, B. Qin, X. Feng, *J. Org. Chem.* **2007**, *72*, 204–208; h) M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, *349*, 759–764; i) S. C. Pan, B. List, *Org. Lett.* **2007**, *9*, 1149–1151; j) S. C. Pan, P. J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 618–620; *Angew. Chem. Int. Ed.* **2007**, *46*, 612–614.

[20] Catalytic enantioselective Strecker-type reactions of *N*-(trimethylphenylsulfonyl)imines derived from aliphatic aldehydes by use of chiral quaternary ammonium salts afford the products with high *ee*s, although this catalytic system cannot be applied to the reactions of aromatic aldimines, see: a) T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548–2549; b) T. Ooi, Y. Uematsu, J. Fujimoto, K. Fukumoto, K. Maruoka, *Tetrahedron Lett.* **2007**, *48*, 1337–1340.

[21] For achiral Strecker-type reactions with *N*-tosylimines, see: a) B. A. B. Prasad, A. Bisai, V. K. Singh, *Tetrahedron Lett.* **2004**, *45*, 9565–9567; b) E. Takahashi, H. Fujisawa, T. Yanai, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 318–319.

[22] We also examined the reaction with Bu_3SnCN, TMSCN, TBDPSCN, and KCN as a cyanation reagent, obtaining the product **3a** in low yield.
[23] Various chiral Lewis acids such as $Zn(OTf)_2$/**A**, $Sc(OTf)_3$/**A**, $Yb(OTf)_3$/**A**, $Ni(ClO_4)_2 \cdot 6H_2O$/**A**, $FeCl_3$/**A**, $Sn(OTf)_2$/**A**, $Cu(OTf)_2$/BINAP, AgOTf/BINAP, Me_3Al/BINOL, $ZrCl_4$/BINOL, $AlCl_3$/**H**, and chiral salen/AlCl complexes afforded the product **3a** either in low yields or with low enantioselectivities.
[24] Similar observations of the reversal of stereochemistry have been reported, see: a) M. P. Sibi, J. Ji, *J. Org. Chem.* **1997**, *62*, 3800–3801; b) M. P. Sibi, H. Matsunaga, *Tetrahedron Lett.* **2004**, *45*, 5925–5929.
[25] The $Mg(OTf)_2$ and DBFOX reaction did not afford the product **3a**.
[26] The $Mg(OTf)_2$/ligand **F** catalyst can be used most efficiently for the reactions of **1a**, but the Stecker-type reactions with other sulfonylimines **1i–n** and this catalyst afford the product in low yield and with low enantioselectivity.
[27] *Enantioselective Synthesis of β-Amino Acids* (Eds.: E. Juaristi, V. A. Soloshonok), Wiley-VCH, New York, **2005**.
[28] E. F. Kleinmann, in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, Chapter 4.1.
[29] a) T. Hintermann, D. Seebach, *Chimia* **1997**, *50*, 244–247; b) D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015–2022; c) U. Koert, *Angew. Chem.* **1997**, *109*, 1922–1923; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1836–1837; d) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180.
[30] For reviews on the asymmetric Mannich reaction, see: a) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102–112; b) M. Ueno, S. Kobayashi, in *Enantioselective Synthesis of β-Amino Acids* (Eds.: E. Juaristi, V. A. Soloshonok), Wiley-VCH, New York, **2005**, Chapter 6.
[31] For recent reports on the catalytic asymmetric Mannich reaction in the synthesis of β-amino acid derivatives, see: a) N. S. Josephsohn, E. L. Carswell, M. L. Snapper, A. H. Hoveyda, *Org. Lett.* **2005**, *7*, 2711–2713; b) M. Sugiura, S. Kobayashi, *Angew. Chem.* **2005**, *117*, 5306–5317; *Angew. Chem. Int. Ed.* **2005**, *44*, 5176–5186; c) S. Kobayashi, K. Arai, H. Shimizu, Y. Ihori, H. Ishitani, Y. Yamashita, *Angew. Chem.* **2005**, *117*, 771–774; *Angew. Chem. Int. Ed.* **2005**, *44*, 761–764; reaction with β-ketoesters, see: d) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257; e) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549–1553; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525–1529; for recent reports covering organocatalysts: f) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; g) F. Fini, L. Bernardi, R. P. Herrera, D. Pettersen, A. Ricci, V. Sgarzani, *Adv. Synth. Catal.* **2006**, *348*, 2043–2046; h) J. Song, H. Shih, L. Deng, *Org. Lett.* **2007**, *9*, 603–607; i) Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 500–501; j) A. Sigh, R. A. Yoder, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2007**, *129*, 3466–3467; k) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764.
[32] For enantioselective Mannich-type reactions of highly electronically activated α-tosylimino esters, see: a) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10–19; b) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549; c) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury, III, L. Ryzhkov, A. E. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67–77; d) M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367; for enantioselective reactions of simple α-sulfonylimines, see: e) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583–2591; f) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4439–4442; *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368, see also ref. [5d].
[33] High enantioselectivity was not shown in reactions in other solvents or with various other copper(II) salts.
[34] a) C. Goulaouic-Dubois, A. Guggisberg, M. Hesse, *J. Org. Chem.* **1995**, *60*, 5969–5972; b) C. S. Pak, D. S. Lim, *Synth. Commun.* **2001**, *31*, 2209–2214.
[35] The tetrahedral Mg^{II} complex has been proposed, see: a) E. J. Corey, K. Ishihara, *Tetrahedron Lett.* **1992**, *33*, 6807–6810; b) M. P. Sibi, J. B. Sausker, *J. Am. Chem. Soc.* **2002**, *124*, 984–991. The octahedral structure has been also proposed: c) M. P. Sibi, G. Petrovic, J. Zimmerman, *J. Am. Chem. Soc.* **2005**, *127*, 2390–2391; d) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 5483–5488.
[36] Another plausible reaction mechanism through a seven-membered transition state in which the pyridine nitrogen is coordinated to magnesium may be considered, but it is ruled out because the transition state would form the *R* isomer preferentially.
[37] Spartan '06 PM3, Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. DiStasio, Jr., R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock, III, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, III, J. Kong, A. I. Krylov, P. M. W. Gill, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172–3191.
[38] *Gaussian 03*, *Revision C.02*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
[39] All optimized structures were confirmed to have no negative frequency by frequency calculations. All transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of newly created C–C bonds. The transition states reported were shown to belong to the studied reaction through the intrinsic reaction coordinate (IRC).
[40] The calculation of the octahedral Mg^{II} complex did not result in convergence.
[41] M.-V. Rangaishenvi, B. Singaram, H.-C. Brown, *J. Org. Chem.* **1991**, *56*, 3286–3294.
[42] H. Kunz, D. Schanzenbach, *Angew. Chem.* **1989**, *101*, 1063–1065; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1042–1043.

Received: September 11, 2007
Published online: December 14, 2007

