Highly Enantioselective Reactions of Configurationally Labile α-Thioorganolithiums Using Chiral Bis(oxazoline)s via Two Different Enantiodetermining Steps

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Abstract: A cumene solution of α-stannyl benzyl phenyl sulfide was treated with *n*-BuLi and bis(oxazoline)-^{i}Pr at −78 °C and subsequently with benzophenone to give the product with 99% ee. We confirmed that the reaction of α-lithio benzyl phenyl sulfide proceeds through a dynamic kinetic resolution pathway. The enantioselective reactions of α-lithio benzyl 2-pyridyl sulfide gave the products with stereochemistry reverse to that obtained in the reaction of benzyl phenyl sulfide. We confirmed that this reaction proceeds through a dynamic thermodynamic resolution pathway in which the reaction with an electrophile proceeds faster than interconversion between the diastereomeric complexes.

Introduction

Asymmetric induction on the prochiral methylenes through deprotonation and subsequent reaction with electrophiles is a most basic and important asymmetric reaction. Enantioinduction would occur either in the first deprotonation step[1−3] or in a post-deprotonation step[4] which Beak has termed an asymmetric substitution pathway.[5] Reactions of the α-hetero carbanions can often be controlled so as to proceed through an asymmetric deprotonation pathway. A great number of dipole-stabilized α-alkoxy[1] and α-aminoorganolithium[2] species involving the alkyl carbamates first developed by Hoppe[1a] and co-workers have been well designed to proceed through an asymmetric deprotonation pathway giving high enantioselectivity. A certain degree of configurational stability of the carbanions may be required to attain high enantioselectivity through asymmetric deprotonation. Stereoselectivity derived from the configurational stability of the α-thio-[6] and the α-selenoorganolithium species[6d,7] has been observed only in the reactions of in situ trap with electrophiles and in the intramolecular rearrangement of allyl sulfides. The enantioselective reaction of the α-sulfenyl carbanions using tricarbonyl(η^6-arene)chromium complexes is another distinctive example proceeding through an asymmetric deprotonation process.[8] It has been, however, generally accepted that the α-sulfenyl carbanions are configurationally labile and

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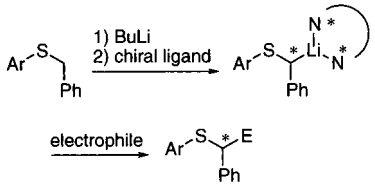
racemize rapidly even at low temperature.[6,7] This presents a contrast to the configurationally relatively stable α-oxyorganolithium compounds. Thus, the asymmetric reactions of the dipole-stabilized α-thioorganolithium compounds show moderate enantioselectivities,[9] whereas dipole-stabilized α-oxyorganolithium compounds show high enantioselectivity as mentioned above.

Highly enantioselective reaction of nondipole-stabilized α-oxyorganolithium compounds, which proceeds through a dynamic thermodynamic resolution pathway, has been recently reported.[10] A good level of enantioselectivity has been achieved in the reaction of nondipole-stabilized α-seleno carbanions through a dynamic thermodynamic resolution pathway.[11] However, there have been no reports on the highly enantioselective reaction of nondipole stabilized α-sulfenyl carbanions.[12] It is important to clarify the reaction pathways of α-sulfenyl carbanions and to develop highly enantioselective reactions. Furthermore, α-chiral sulfides have potential to be chiral templates[13] or asymmetric catalysts[14] in asymmetric reactions. By taking account of the configurationally labile nature of the α-sulfenyl carbanions that is, indeed, more labile than the α-seleno carbanions,[7a,b] a high level of asymmetric induction would be achievable in a postdeprotonation through an asymmetric substitution process controlled either by the intermediate lithium carbanion−chiral ligand complex (dynamic thermodynamic resolution) or by the complex-electrophile interaction in the transition state (dynamic kinetic resolution).[15] We verified this working assumption in the highly enantioselective reaction of the α-sulfenyl carbanion derived from benzyl phenyl sulfide with carbonyl compounds.[16] On continuing the study, we found the outstanding nature of the α-thioorganolithium compounds; their reactions proceed through either of the two distinct enantiodetermining steps, a dynamic kinetic or a dynamic thermodynamic resolution pathway, depending on the substituent attached to the sulfur. We now report, in detail, highly stereoselective asymmetric substitution reactions of the α-sulfenyl carbanions derived from benzyl phenyl sulfide and benzyl 2-pyridyl sulfide (Scheme 1) and clarify the stereochemical course of the enantioselective reactions of these anions. We analyze the reaction mechanism on the basis of the Hoffmann test[17] as well as Beak's procedure using the deficient amounts of the electrophile[2d,4b,e,h,5b] and his warm-cool procedure[4b,h,5b] together with the MO calculations.

Scheme 1



Results

Enantioselective Reactions of the Lithiated Benzyl Phenyl Sulfides. For the study of the reaction of α-lithio benzyl phenyl sulfides, we used benzyl phenyl sulfide (**1a**), α-phenylselenosulfide (**1b**), and α-tributylstannylsulfide (**1c**) as the precursors, the latter two of which were prepared from α-lithio benzyl phenyl sulfide with diphenyldiselenide and tributylstannyl chloride in THF in high yields. We chose several chiral ligands to examine (−)-sparteine (**3**), (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine (**4**),[18] and 2,2-bis{2-[(4*S*)-alkyl-1,3-dioxazolinyl]}propane (**5a**−**c**)[19,20] [bis(oxazoline)-R]. The obtained yields and the enantiomer ratios for the enantioselective reactions using these chiral ligands are shown in Table 1.

Reaction of Li-**1** with benzophenone using (−)-sparteine **3** in toluene or cumene gave the thio alcohol **2** with low enantioselectivity (entries 1 and 2). These results are noteworthy since (−)-sparteine often shows high enantioselectivity in the reactions of α-hetero carbanions.[1c−4] On the other hand, the bis(oxazoline)-^{i}Pr **5a** was found to show excellent asymmetric induction. The sulfide **1a** could be deprotonated on treatment with *n*-BuLi without addition of a chiral ligand, when the reaction was carried out in THF, giving the product **2** in high yield but with low stereoselectivity (entry 3). The reactions of **1a** with *n*-BuLi in other solvents such as hexane, ether, toluene or cumene gave **2** in low yields. The yields of **2** in the reactions using *tert*-BuLi were low in ether or hexane because **1a** precipitated out at −78 °C (entries 4 and 5). When the reaction was carried out in toluene using **5a**, good yield (77%) and high enantiomer excess (86% ee) were achieved (entry 6). The above results show the crucial noncoordinating property of the solvent to the lithium for exhibiting high enantioselectivity. In addition, **5a** and the formed complex are soluble in toluene at −78 °C. Cumene was found to be an even better solvent than toluene. The thio alcohol **2** was obtained in cumene with 97−69% ee (entries 7−9). It is well-known that the lithiated compounds can be more efficiently obtained by the Sn/Li or Se/Li exchange than by deprotonation. Lithiation of the α-seleno- and α-stannylbenzyl sulfides **1b** and **1c** could be achieved with *n*-BuLi,

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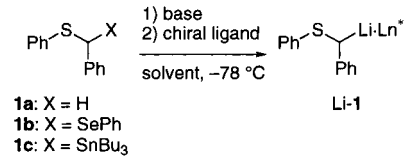
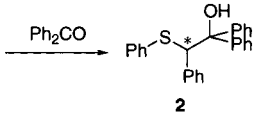
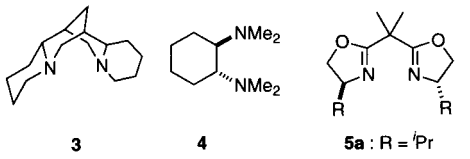
Table 1. Reactions of the Lithiated Benzyl Phenyl Sulfide **1** with Benzophenone in the Presence of Various Chiral Ligands[a]







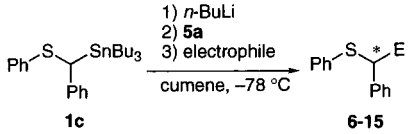
entry	substrate	chiral ligand	base	solvent	yield (%)	ee (%)[b]	config.
1	**1a**	**3**	*t*-BuLi	toluene	12	12	*R*
2	**1a**	**3**	*t*-BuLi	cumene	5	16	*R*
3	**1a**	**5a**	*n*-BuLi	THF	97	1	*S*
4	**1a**	**5a**	*t*-BuLi	Et_2O	49	57	*S*
5	**1a**	**5a**	*t*-BuLi	hexane	3	77	*S*
6	**1a**	**5a**	*t*-BuLi	toluene	77	86	*S*
7	**1a**	**5a**	*t*-BuLi	cumene	40	97	*S*
8	**1a**	**5a**[c]	*t*-BuLi	cumene	14	86	*S*
9	**1a**	**5a**	*t*-BuLi[d]	cumene	82	69	*S*
10	**1b**	**5a**	*n*-BuLi	toluene	93	93	*S*
11	**1b**	**5a**	*n*-BuLi	cumene	27	94	*S*
12	**1b**	**5a**	*t*-BuLi	toluene	79	84	*S*
13	**1b**	**5a**	*t*-BuLi	cumene	67	96	*S*
14	**1c**	**5a**	*n*-BuLi	toluene	82	85	*S*
15	**1c**	**5a**	*n*-BuLi	cumene	79	99	*S*
16	**1c**	**5a**	*n*-BuLi[d]	cumene	92	92	*S*
17	**1c**	**3**	*n*-BuLi	cumene	93	8	*R*
18	**1c**	**4**	*n*-BuLi	cumene	8	1	*S*
19	**1c**	**5b**	*n*-BuLi	cumene	60	66	*S*
20	**1c**	**5c**	*n*-BuLi	cumene	17	59	*S*

[a] The reaction was carried out using a sulfide (1.0 equiv), a base (1.2 equiv), a chiral ligand (1.25 equiv), and Ph_2CO (1.3 equiv). [b] The enantiomer excess was determined by HPLC using a Chiralcel OD-H. [c] *t*-BuLi and **5a** were mixed prior to the lithiation of **1a**. [d] BuLi (2.0 equiv) was used.

and both sulfides showed high yields and high enantioselectivities (entries 10−16). The α-stannylbenzyl sulfide **1c** in the presence of **5a** gave the product **2** with 99% ee (entry 15), although other ligands **3**, **4**, **5b** and **5c** did not afford high enantioselectivity (entries 17−20). Thus, **5a** was found to be the ligand of choice. On using excess amounts of bases, particularly when *t*-BuLi was used, enantioselectivities decreased (entries 7 vs 9 and 15 vs 16). Table 2 shows the results obtained in the reaction of Li-**1** with various electrophiles in the presence of **5a**.

The obtained enantioselectivity in the reaction with carbonyl compounds was also high (entries 1−5). In the reactions of Li-**1** with acetone and cyclohexanone, undesired deprotonation of the protons α to the carbonyl occurred at −78 °C, lowering the yields of the products together with recovery of a certain amount of benzyl phenyl sulfide. Both the enantioselectivity and the yield increased as the reaction temperature was lowered (entries 1 and 2 in parentheses). The reaction of Li-**1** with benzaldehyde, propionaldehyde or isobutyraldehyde gave a mixture of the *syn* and the *anti* isomers, and each isomer has high enantiomer excess (entries 3−5). However, the alkylation or silylation of Li-**1** gave the product **11** or **12** with moderate to low enantioselectivity. When Li-**1** was reacted with various methylating reagents having various leaving groups, the reaction proceeded with different enantioselectivity (entries 6−9). These results suggest that the reaction proceeds through an asymmetric substitution pathway for alkylation.[4e] In all reactions, the chiral ligand **5a** was quantitatively recovered without any loss of the enantiomer purity.

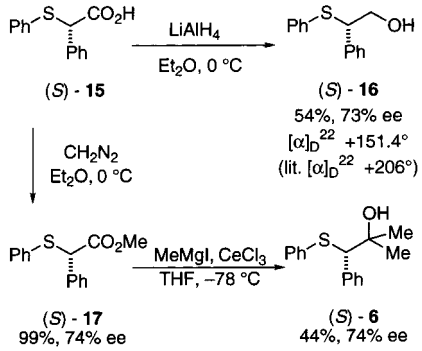
Table 2. Reactions of Li-**1** with Various Electrophiles in the Presence of the Chiral Ligand **5a**



entry	electrophile	product	yield (%)	ratio[a] *syn*:*anti*	ee (%)[b] *syn anti*
1	CH_3COCH_3	**6**	53 (71)[c]		98 (>99)[c]
2	cyclohexanone	**7**	54 (100)[c]		91 (98)[c]
3	PhCHO	**8**	100	60:40	87[d] >99[d]
4	EtCHO	**9**	51	38:62	97 96
5	^{i}PrCHO	**10**	61	38:62	94 95
6	MeI	**11**	100		64[f]
7	MeOTf	**11**	86[e]		81[f]
8	$(MeO)_3PO$	**11**	21[e]		1[f]
9	Me_2SO_4	**11**	71[e]		17[f]
10	$(CH_3)_3SiCl$	**12**	57		77[f]
11	$(CH_3)_3SiOTf$	**12**	76		77[f]
12	BuI	**13**	41		1[f]
13	CH_2=$CHCH_2Br$	**14**	25		76[f]
14	CO_2	**15**	87		74[g]

[a] The diastereomer ratio was determined by the ^{1}H NMR spectrum. [b] The enantiomer excess was determined by HPLC using a Chiralcel OD-H or a Chiralpac AD. [c] The yield and the enantiomer excess of the reaction at −95 °C are shown in parentheses. [d] The enantiomer excess was determined by HPLC after oxidation with *m*-CPBA to the sulfone. [e] Conversion yield. [f] The absolute configuration was not determined. [g] The enantiomer excess was determined after reduction with $LiAlH_4$.

Scheme 2



The absolute configurations of the products **6** and **15** were determined as follows (Scheme 2).

Reduction of the carboxylic acid **15** with $LiAlH_4$ in Et_2O at 0 °C gave the *β*-thio alcohol **16** with 73% ee determined by the HPLC analysis using a Chiralcel OD-H. The absolute stereochemistry of **16** was assigned to be (*S*) in comparison with the specific rotation reported in the literature,[21] showing the configuration of the carboxylic acid **15** to be (*S*). Esterification of (*S*)-**15** with diazomethane gave (*S*)-**17** with 74% ee. The ester

(21) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron* **1994**, *50*, 8997.

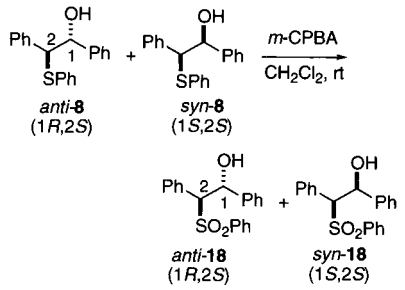


Figure 1. Absolute configurations of the major isomers of **8** and **18**.

(*S*)-**17** was treated with MeMgI in the presence of $CeCl_3$ to give the product (*S*)-**6** without racemization (44%, 74% ee),[22] which had the same stereochemistry by the HPLC analysis as that of the product predominantly obtained in the enantioselective reaction of Li-**1** using **5a**. The reaction of (*S*)-**17** with MeLi or MeMgI in place of MeMgI−$CeCl_3$ was not accomplished without partial racemization. Treatment of (*S*)-**17** with PhLi also gave the product having the same stereochemistry as that of the predominantly formed thio alcohol **2**. The relative configurations of the products obtained in the reactions with aldehydes were determined by the larger vicinal coupling constant for the *syn*-**8** (8.5 Hz) in comparison with *anti*-**8** (5.8 Hz).[23] The absolute configuration of **8** was determined by the ^{1}H NMR analysis of the (*S*)-MTPA ester of the corresponding sulfone **18** (Figure 1).[24]

The stereochemistry of the carbon α to the phenylthio group of the other products obtained in the reaction with cyclohexanone, propionaldehyde and isobutyraldehyde was tentatively assigned to be *S*. The absolute stereochemistry of the alkylation products has not yet been determined.

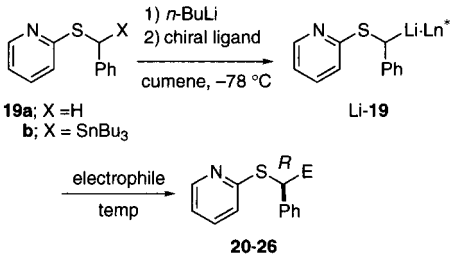
Enantioselective Reactions of Lithiated Benzyl 2-Pyridyl Sulfides. We next studied the enantioselective reaction of the α-sulfenyl carbanion Li-**19** of benzyl 2-pyridyl sulfides **19a** and **19b** (Table 3).

The reactions of **19a** using the bis(oxazoline)s **5a** and **5d** gave high yields of **20** with high stereoselectivity. The bis(oxazoline)-^{t}Bu **5d** showed higher asymmetric induction than any other chiral ligand (entries 1−6). The Sn/Li exchange reaction of **19b** also smoothly proceeded (entry 7). Notably, the enantioselectivity varies depending on the reaction temperature (entries 3, 8, 9, 10 and 11 or 6 and 12). The highest enantioselectivity (90% ee) was obtained in the reaction using **5d** at −78 °C (entry 6). The reaction of Li-**19** with acetone and cyclohexanone having acidic protons gave the products with moderate stereoselectivity (entries 13 and 14). The reaction with other electrophiles, such as PhCHO, CO_2, CH_3I, TMSCl, and TMSOTf gave the products with high stereoselectivity (entries 15−19).

The absolute configuration of the product **21** was determined as follows (Scheme 3).

The carboxylic acid **24** was reduced with $LiAlH_4$ to give the alcohol **27** with 70% ee, which was determined by the HPLC analysis. The configuration of **27** was confirmed by the derived chiral styrene oxide **28**.[25] The carboxylic acid **24** was converted to the methyl ester **29** which was treated with MeLi at 0 °C to give 18% yield of the thio alcohol (*R*)-**21** with 36% ee;[26] although partial epimerization inevitably occurred during the reaction, the stereochemistry of **21** still reflects that of **29**. The HPLC analyses using a chiral column showed that this major product (*R*)-**21** was identical with the product, shown in Table 3, entry 13. These results unequivocally indicate that the product **21** obtained in the enantioselective reaction of benzyl 2-pyridyl sulfide **19a** with acetone using **5a** has stereochemistry opposite that of the products predominantly formed in the enantioselective

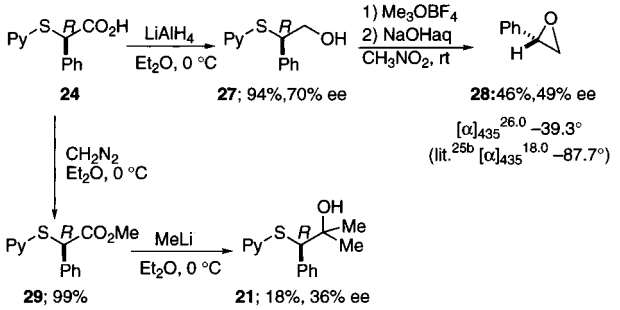
Table 3. Enantioselective Reaction of α-Lithio Benzyl 2-Pyridyl Sulfides



entry	X	ligand	electrophile	reaction temp (°C)	product	yield (%)	ee (%)
1	H	**3**	Ph_2CO	−78	**20**	79	9
2	H	**4**	Ph_2CO	−78	**20**	70	21
3	H	**5a**	Ph_2CO	−78	**20**	89	64
4	H	**5b**	Ph_2CO	−78	**20**	49	51
5	H	**5c**	Ph_2CO	−78	**20**	13	58
6	H	**5d**	Ph_2CO	−78	**20**	86	90
7	$SnBu_3$	**5a**	Ph_2CO	−78	**20**	80	64
8	H	**5a**	Ph_2CO	0	**20**	79	28
9	H	**5a**	Ph_2CO	−30	**20**	87	49
10	H	**5a**	Ph_2CO	−50	**20**	91	78
11	H	**5a**	Ph_2CO	−95	**20**	74	43
12	H	**5d**	Ph_2CO	−95	**20**	42	53
13	H	**5a**	CH_3COCH_3	−50	**21**	67	54
14	H	**5a**	cyclohexanone	−50	**22**	71	42
15	H	**5a**	PhCHO	−50	**23**	94[a]	*syn*: 79 *anti*: 81
16	H	**5a**	CO_2	−78	**24**	60	70[b]
17	H	**5d**	CH_3I	−78	**25**	72	89
18	H	**5d**	$(CH_3)_3SiCl$	−78	**26**	97	71
19	H	**5d**	$(CH_3)_3SiOTf$	−78	**26**	91	93

[a] *syn*:*anti*=37:63. [b] The enantiomer excess was determined after reduction with $LiAlH_4$.

Scheme 3



(22) (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Takada, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228. We thank Professor Tsuneo Imamoto at Chiba University for helpful suggestions.

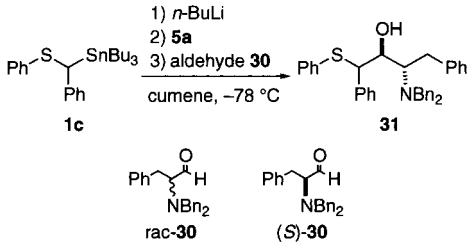
(23) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, I.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775.

(24) The stereochemistries of **18** were assigned on the basis of the upfield shift of the methoxy proton signal for the (1*R*)-isomers due to the phenyl anisotropic effect relative to that for the (1*S*) isomers. For the NMR spectral analysis of MTPA esters, see: (a) Dale, J. A.; Dull, D. L.; Mosher, H. S.; *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, S. H.; *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovek, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(25) Preparation of styrene oxide from the thio alcohol: (a) Shanklin, J. R.; Johnson, C. R.; Ollinger, J.; Coates, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3429. (b) Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B. *J. Org. Chem.* **1965**, *30*, 4091.

(26) The reaction using $CeCl_3$ did not provide the desired methylated product.

Table 4. Configurational Instability of Li-**1**



ligand	aldehyde	yield (%)	ratio
TMEDA	(*dl*)-**30**	90	58:42
TMEDA	(*S*)-**30**	88	61:39
bis(oxazoline)-^{i}Pr	(*S*)-**30**	90	80:20

reaction of **1**. The stereochemistry of the methylated product **25** was assigned to be *S* by comparison of the value of the specific rotation with the reported one.[27] The stereochemistry of the other products was tentatively assigned to be the same as that of **21**. The relative configurations of the products **23** were determined by the vicinal coupling constant as in the case of **8**.[23]

Discussion

Reaction Mechanism of α-Lithio Benzyl Phenyl Sulfide. First, we confirmed that no retroaldol reaction of the products **2** and **20** would occur during the deprotonation and the subsequent electrophilic reaction. Thus, to a cumene solution of **2** (99% ee) or **20** (49% ee) was added 1.2 equiv of *n*-BuLi and TMEDA at −78 °C. After the mixture was stirred for 1 h, benzaldehyde was added. The thio alcohols **2** and **20** were found to remain unreacted without loss of the enantiomeric purity, indicating that the stereoselective outcome in the reactions of Li-**1** and Li-**19** should be a kinetically controlled one. Although the Sn/Li exchange is known to occur with complete retention[28] of configuration at the sp^3 carbanion,[29] the reactions starting with the racemic stannyl sulfides **1c** and **19b** proceed with high enantioselectivity (Table 1, entry 15, Table 3, entry 7). This clearly shows that induction of enantioselectivity is independent of the method of generation of the organolithium species, and thus, these asymmetric lithiation-substitution reactions proceed through an asymmetric substitution pathway, involving the enantiodetermining step via either a dynamic kinetic or a dynamic thermodynamic resolution. Hoffmann and co-workers have developed a protocol for surveying the configurational stability of organolithium compounds,[17] showing that the α-lithio benzyl phenyl sulfide is configurationally labile in THF.[7a] In the present reaction, the product was obtained with no stereoselectivity in THF (Table 1, entry 3). We tried to confirm whether the lithiated **1**−ligand complex is also labile in cumene by using *dl*- and (*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylpropanals (**30**) according to their protocol (Table 4).

Provided that the complex of an organolithium and a ligand is configurationally stable, the reaction of the racemic carbanion with a chiral aldehyde should afford the product in a diastereomer ratio of 50:50. However, the reaction with the chiral aldehyde (*S*)-**30** at −78 °C gave the product **31** in a ratio of 61:39, which was experimentally identical to the ratio (58:42) obtained in the reaction of a racemic aldehyde with TMEDA. The diastereomer ratio was 80:20 when the bis(oxazoline)-^{i}Pr **5a** and the chiral aldehyde (*S*)-**30** were used. If the enantioselective reaction of **1** using **5a** proceeds through a dynamic thermodynamic resolution pathway, the reaction of **1** with (*S*)-**30** in the presence of **5a** should give the product having the de of approximately 99% as in the reaction of **1** with benzophenone in the presence of **5a**. These results show that the complex of the lithium carbanion with a ligand such as TMEDA or **5a** is configurationally labile at −78 °C. Thus, we have concluded that enantioinduction in the reaction of Li-**1** occurs through dynamic kinetic resolution, in which high enantioselectivity is derived from the difference in energy of the transition state ($\Delta\Delta G^{\ddagger}$) at the substitution step. This enantiodetermining sequence is also supported by the fact that higher enantioselectivity was obtained in the reaction at lower reaction temperature (Table 2, entries 1 and 2).[30] It is important to know the exact geometry of the α-sulfenyl carbanion, which would significantly affect the structure of the transition state. Wiberg and co-workers have recently shown by ab initio calculation (MP2/6-311++G**) that the α-sulfenyl carbanion of dimethyl sulfide is stabilized by an n-σ^*_{S-C} negative hyperconjugation.[31] Hoffmann and co-workers have elucidated the stereoselective cyclization by this hyperconjugation.[32] To understand the preferred conformation for the α-sulfenyl carbanion in our case, we performed the calculation of energies of the complexes formed from α-lithio benzyl phenyl sulfide with TMEDA as a simple model of the diamine ligand.[33] The calculations for the complexes by Gaussian 98 Becke3LYP/3-21+G*, HF/3-21+G*,[34] and MOPAC 93/PM3[35] methods showed a significantly large difference in energy between the *anti*-TMEDA-complex and *syn*-TMEDA-complex as shown in Figure 2.

These calculations indicate that the C−Li bond of the α-lithiated benzyl phenyl sulfide prefers the *anti* conformation for the S−C$_{ips}$ bond probably by an n-σ^*_{S-C} negative hyperconjugation. The plausible reaction mechanism is shown in Figure 3.

We have confirmed by performing the Hoffmann test that the (*R*)-Li complex is rapidly equilibrated with the (*S*)-Li complex (Table 4). According to the frontier orbital theory, both

(27) Oae, S.; Takeda, T.; Wakabayashi, S.; Iwasaki, F.; Yamazaki, N.; Katsube, Y. *J. Chem. Soc., Perkin Trans. 2* **1990**, 273.

(28) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. For reaction with partial inversion, see: (c) Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565.

(29) The α-lithiated benzyl phenyl sulfide is known to have an sp^3 character, Zarges, W.; Marsch, M.; Harms, K.; Koch, W.; Frenking, G.; Boche, G. *Chem. Ber.* **1991**, *124*, 543.

(30) The reaction using 0.2 equiv of cyclohexanone gave the product **7** in 13% yield, but the enantiomer excess of **7** was still 91%. This result also shows that the reactions using stoichiometric amounts of carbonyl compounds proceed through a dynamic kinetic resolution.

(31) Wiberg, K. B.; Castejon, *J. Am. Chem. Soc.* **1994**, *116*, 10497.

(32) (a) Hoffmann, R. W.; Koberstein, R.; Harms, K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 183. (b) Hoffmann, R. W.; Koberstein, R.; Remacle, B.; Krief, A. *Chem. Commun.* **1997**, 2189.

(33) The α-sulfenyl carbanion forms a dimeric complex such as the four-membered and the six-membered cyclic dimers with TMEDA, Amstutz, R.; Laube, T.; Schweiser, W. B.; Seebach. D.; Dunitz, J. D. *Helv. Chim. Acta* **1984**, *67*, 224. However, formation of these dimeric complexes seems to be difficult due to significant steric repulsion between the isopropyl groups of each bis(oxazoline). The complex of some transition metals with bis(oxazoline)s is known to show nonlinear effects, but we observed a linear relationship between the enantiomer excesses of **2** and **5a**. On the basis of these results, it would be reasonable to assume that the dimer is not formed. For the general nonlinear effect, see: (a) Guillaneux, D.; Zhao, S.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430. (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923. For the nonlinear effect using bis(oxazoline) complexes, see: (c) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027. (d) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada. E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3070. (e) Evans, D. A.; Kozlowski, M. C. Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (f) Crosignani, S.; Desimoni, G.; Faita, G.; Filippone, S.; Mortoni, A.; Righetti, P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007.

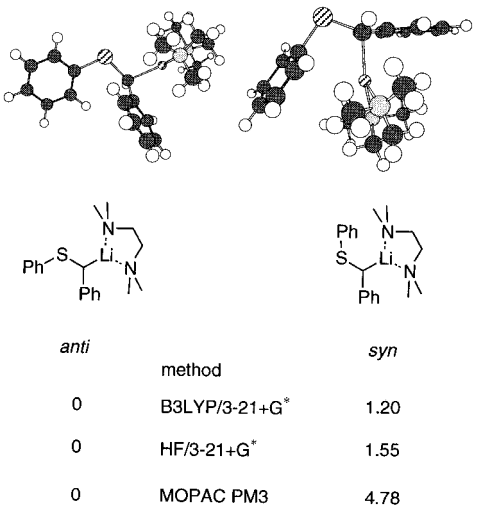


Figure 2. Geometry optimization of the lithiated **1** coordinated with TMEDA.

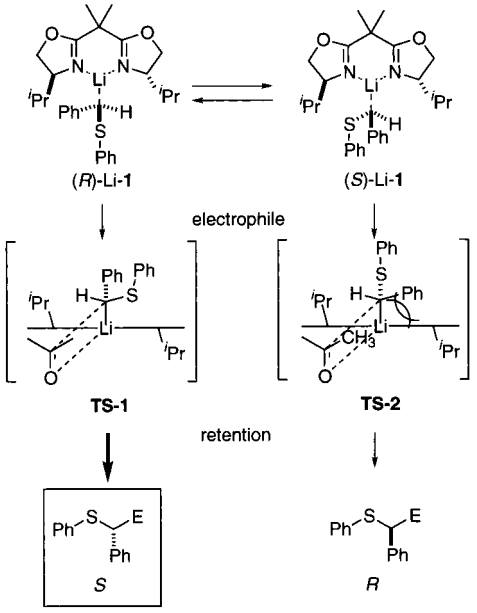


Figure 3. Reaction mechanism of α-lithio benzyl phenyl sulfide.

retention and inversion of the lithium stereochemistry are an allowed pathway in the S_E2 reaction.[36] Indeed, the stereochemical course depends on the electrophiles; the reactions with highly reactive or non-lithium coordinating electrophiles may proceed with inversion and those with less reactive or lithium coordinating electrophiles may take the retention pathway.[37] It is reasonable that the reaction of Li-**1** with the electrophiles such as the lithium-coordinating carbonyl compounds proceeds with retention. Thus, we assumed that the reaction proceeds via a four-membered cyclic transition state[38] stabilized by the negative hyperconjugation. The *S* isomer is formed via **TS-1**, which would be assumed to be much more stable than **TS-2** involving a steric interaction between the methyl and phenyl groups. The assumed energy diagram of the enantioselective reaction for Li-**1** is shown in Figure 4.

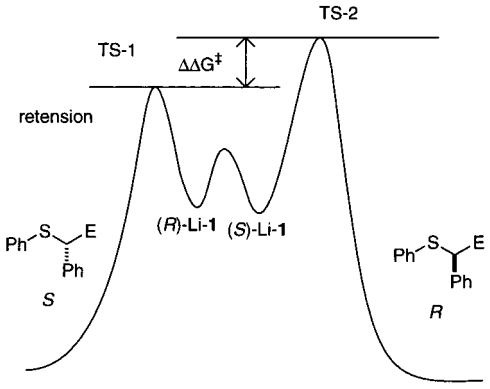


Figure 4. Assumed energy diagram of the enantioselective reaction for Li-**1** under dynamic kinetic resolution

The stereochemical outcome in the reaction of Li-**1** is noteworthy as compared with the Tomooka and Nakai results of the preferential formation of the (*R*)-isomer in the reaction of benzyl methyl ether with the bis(oxazoline).[10] They have disclosed that the reaction proceeds through a dynamic thermodynamic resolution pathway. In addition, Wiberg and coworkers[31] have shown very suggestive results that the repulsive effect of a lone pair of the α-oxy carbanion onto a lone pair of the oxygen arranges these lone pairs *anti*, that is, *syn* between the carbanion lobe and the substituent on the oxygen. We have confirmed, as described before, the *anti* configuration of the α-sulfenyl carbanion, which is completely different from that of the α-oxy carbanion.

Reaction Mechanism of α-Lithio Benzyl 2-Pyridyl Sulfide. The lithiated benzyl 2-pyridyl sulfide (Li-**19**) showed some peculiar aspects in the reactions with carbonyl compounds: (1) the (*R*)-preference of the product stereochemistry is different from the preferential formation of the (*S*)-isomer in the reaction of Li-**1**; (2) higher enantioselectivity is not always obtained in the reactions performed at lower temperature and there may be a certain temperature for the maximal enantioinduction (Table 3, entries 6−12). These features of Li-**19** may suggest the reaction pathway through dynamic thermodynamic resolution. To confirm the enantiodetermining step, we collected further information on the chemical behavior of Li-**19**. The enantioselectivity in the reaction with a deficient amount of benzophenone turned out to be different from that obtained in the reactions using stoichiometric amounts of the electrophile (Table 3, entries 3, 6, and 11, and Scheme 4). This is a notable aspect of the reaction of Li-**19** as compared with the reaction[30] of Li-**1**

(34) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998. For the Becke3LYP hybrid method, see: (b) P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.

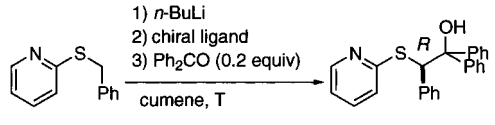
(35) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209 (b) For the lithium parameter for PM3, see: Anders, E.; Koch, R.; Freunscht, P.; *J. Comput. Chem.* **1993**, *14*, 1301.

(36) Fleming, I. *Frontier Orbital and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976.

(37) (a) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (b) Tomooka, K.; Igarashi, T.; Komine, N.; Takeshi, N. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 480.

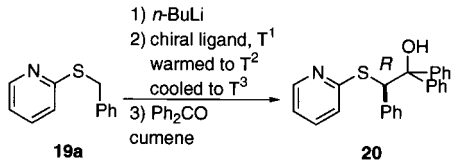
(38) The alkyllithium addition to the carbonyl group has been suggested to proceed through a four-memberd cyclic transition state. For example, see: (a) Kaufmann, E.; Schleyer, P. R. Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) Kaufmann, E.; Sieber, S.; Schleyer, P. R. *J. Am. Chem. Soc.* **1989**, *111*, 4005. (c) Ando, K.; Houk, K. N.; Busch, J.; Menassé, A.; Séquin, U. *J. Org. Chem.* **1998**, *63*, 1761. (d) Bräuer, M.; Weston, J.; Anders, E. *J. Org. Chem.* **2000**, *65*, 1193.

Scheme 4



chiral ligand		
5a	T = −78 °C,	84%, 50% ee
5a	T = −95 °C,	73%, 24% ee
5d	T = −78 °C,	91%, 52% ee

Scheme 5



chiral ligand		
5a	T^1 = −78 °C, T^2 = −50 °C, T^3 = −78 °C	77%, 70% ee
5a	$T^1 = T^2 = T^3$ = −78 °C	89%, 64% ee
5a	T^1 = −78 °C, T^2 = −50 °C, T^3 = −95 °C	46%, 76% ee
5a	$T^1 = T^2 = T^3$ = −95 °C	74%, 43% ee
5d	T^1 = −78 °C, T^2 = −78 °C, T^3 = −95 °C	90%, 88% ee
5d	$T^1 = T^2 = T^3$ = −95 °C	42%, 53% ee

which was reasonably verified to proceed through a dynamic kinetic resolution.

These results show that the diastereomeric complexes derived from Li-**19** and the bis(oxazoline) are configurationally stable at low temperature at least on the time scale of the reaction with electrophiles, and each diastereomeric complex may react with electrophiles at a different rate.[2d,4b,e,h,5b] Consequently, the reaction of Li-**19** proceeds through a dynamic thermodynamic resolution pathway. In addition, the minor diastereomeric complex can be reasonably assumed to have a lower activation energy in the reaction with an electrophile, since the enantioselectivity in the reaction with a deficient amount of the electrophile is lower than that of the reactions using stoichiometric amounts of the electrophile. We also examined Beak's excellent "warm-cool procedure"[4b,h,5b] for further confirmation of the above reaction pathway. A solution of the α-sulfenyl carbanion prepared from **19a** in the presence of **5a** at −78 °C, was warmed to −50 °C and stirred for 1 h at that temperature. The reaction mixture was divided into two parts which were subjected to separate parallel reactions, followed by recooling one reaction to −78 °C and the other to −95 °C. Each reaction mixture was stirred for 30 min and subsequently benzophenone was added. One afforded 70% ee of **20** at −78 °C and the other gave 76% ee of **20** at −95 °C (Scheme 5).

These enantiomer excess values are quite close to that obtained in the reaction performed at −50 °C (78% ee, Table 3, entry 10), but higher than those performed at −78 °C and −95 °C throughout the reaction. These results suggest that the interconversion of (*R*)-Li-**19** and (*S*)-Li-**19** is quite slow at below −78 °C, and it is necessary to warm the reaction mixture up to −50 °C to equilibrate the diastereomeric complexes. Similar results were obtained in the reaction using **5d** in which the equilibration may complete at −78 °C (90% ee, Table 3, entry 6). This evidence of the configurational stability of the carbanion unequivocally indicates that the reaction proceeds through a dynamic thermodynamic resolution pathway; that is, the reaction with an electrophile occurs before the interconversion of the diastereomeric complexes, and, therefore, the enantiomer excess of the reaction of Li-**19** reflects the ratio of the two diastereomeric complexes.[39]

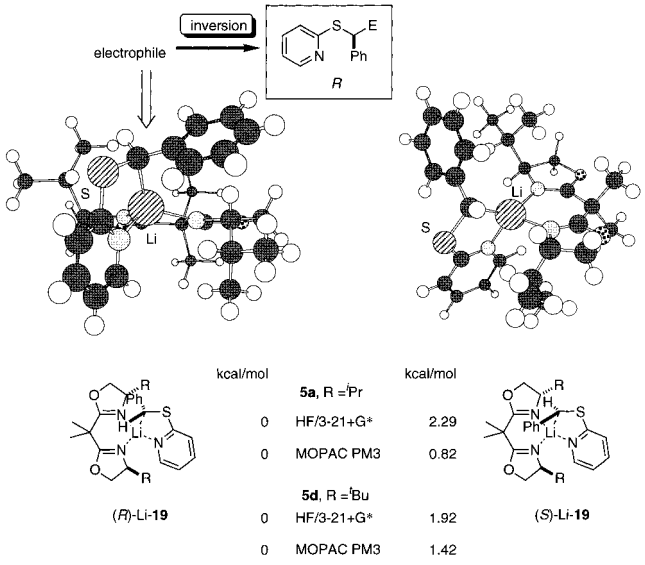


Figure 5. Geometry optimization of diastereomeric complexes of Li-**19** with **5a** and **5d**.

To gain more quantitative insight to clarify the reaction mechanism of **19**, the diastereomeric complexes with **5a** and **5d** were estimated by the MO calculation using the HF/3-21+G*, and MOPAC 93/PM3 methods. The relative energies of the optimized structures obtained by these calculations are depicted in Figure 5.

Calculations by both methods showed that the (*R*)-Li-**19** complex is more stable than the (*S*)-Li-**19** complex. The differences in energy of the (*R*)-Li-**19** and the (*S*)-Li-**19** complexes with **5a** and **5d** giving 78% ee at −50 °C and 90% ee at −78 °C correspond to 0.93 and 1.14 kcal/mol, respectively, under dynamic thermodynamic conditions, both of which are in good agreement with the calculated energy differences. In the optimized structure, the third pyridyl nitrogen in addition to the two nitrogens of the bis(oxazoline) is incorporated to the lithium ion. Since the lithium ion is fully coordinated, an electrophile can hardly approach the reaction site while coordinating to the lithium ion with retention of configuration of the carbanionic center, and thus the substitution reaction may occur with inversion of configuration.[40] The stereochemical course with inversion of configuration was also supported by the HOMO of Li-**19**−**5a** complex which obviously showed the lobe of the carbanionic center considerably expanding in the direction opposite the C−Li bond (Figure 6).

Reactions of carbanions with carbonyl compounds generally proceed with retention of stereochemistry. Indeed, the reaction of the α-sulfenyl carbanion of **1** proceeds with retention of configuration as described before. The reaction of **19** very exceptionally proceeds with inversion. Obviously, the pyridyl nitrogen plays an important role in determining the way of approach of an electrophile. The lithium ion is fully coordinated by the additional nitrogen coordination and the electrophilic carbonyl attacks the carbanion without coordination to the

(39) We also examined the configurational lability of Li-**19** using the chiral aldehyde (*S*)-**30** (the Hoffmann test). The reaction of Li-**19** with the chiral aldehyde (*S*)-**30** gave the product in a ratio of 54:46, whereas the diastereoselectivity of the reaction with the racemic aldehyde (*dl*)-**30** was 58:42. These results may support the reaction pathway.

(40) Recently, Hoppe and co-workers suggested that the S_E2 reaction on the sp^2-like hybridized carbanion proceeds with inversion of the stereochemistry. Derwing, C.; Frank, H.; Hoppe, D. *Eur. J. Org. Chem.* **1999**, 3519. The carbanionic center of the geometry-optimized structure (*R*)-Li-**19** is close to the sp^2 carbon. The sum of the three angles at the lithium-bearing carbon atom was found to be 338.8°.

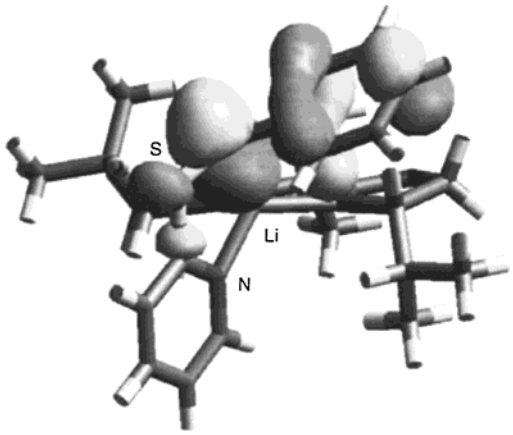


Figure 6. HOMO of the complex of the lithiated **19** with **5a**.

lithium ion. To the best of our knowledge, there is only one precedent of the S_E2 reaction with a carbonyl compound proceeding with inversion,[41] that is, the reaction of the lithium carbanion derived from *N*-pivaloyl *o*-ethylaniline which also has a nitrogen to coordinate with a lithium ion. For better understanding, the energy diagram of the enantioselective reaction of Li-**19** is shown in Figure 7.

According to the dynamic thermodynamic resolution process, the enantioselectivity should be independent of the electrophiles. The reactions with benzaldehyde, CO_2, CH_3I and TMSOTf gave the products with enantioselectivity similar to those with benzophenone (Table 3, entries 10 vs 15, 3 vs 16 and 6 vs 17 and 19). On the other hand, the reactions with acetone and cyclohexanone gave the products with slightly lower stereoselectivity (Table 3, entries 13 and 14). Deprotonation from the carbonyl compounds would occur during the reaction and reduce the yields of **21** and **22** together with the formation of the aldol product. These results show that deprotonation by (*R*)-Li-**19** would occur faster than that by (*S*)-Li-**19**.

(41) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.

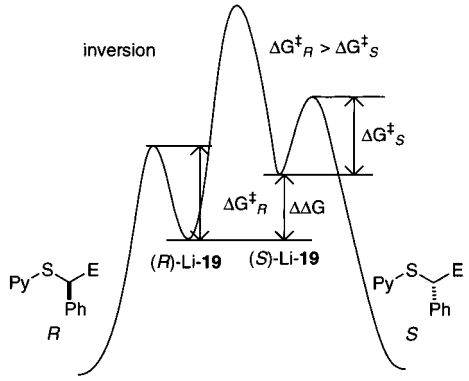


Figure 7. Assumed energy diagram of the enantioselective reaction for the Li-**19** under dynamic thermodynamic resolution

In summary, we have disclosed the first excellent enantioselective reactions of the configurationally labile α-sulfenyl carbanions by using bis(oxazoline)s as the chiral ligand. We have shown two distinct reaction pathways of the asymmetric substitution of the α-sulfenyl carbanions. Reaction of the lithiated benzyl phenyl sulfide with carbonyl compounds proceeds through a dynamic kinetic resolution pathway with retention of configuration of the carbanion center to give the (*S*)-isomer, whereas that of the lithiated benzyl pyridyl sulfide proceeds through a dynamic thermodynamic resolution pathway with inversion of configuration to give the (*R*)-isomer.

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Supporting Information Available: Spectroscopic characterization of the products **1b**,**1c**,**2**,**6**−**18**,**20**−**23**,**25**−**27**,**29** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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