

Synthesis of *P*-Stereogenic Compounds via Kinetic Deprotonation and Dynamic Thermodynamic Resolution of Phosphine Sulfides: Opposite Sense of Induction Using (–)-Sparteine

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Abstract: A systematic study of the asymmetric deprotonation of a dimethyl-substituted phosphine sulfide using organolithium bases in the presence of (–)-sparteine has been carried out. Use of *n*BuLi and (–)-sparteine in Et₂O at –78 °C gave trapped adducts in ~88:12 er via a kinetically controlled process that was successfully predicted using a computational approach at the B3LYP/6-31+G(d) level. This initial kinetic enantioselectivity could be enhanced up to 97:3 er by trapping the lithiated intermediate with a prochiral electrophile (e.g., pivaldehyde or *t*BuPCl₂). In addition, it was found that the *R_P* and *S_P* stereoisomers of the lithiated methylphosphine sulfide could interconvert at temperatures above 0 °C. Such interconversion is unprecedented and differs from the configurational instability of organolithiums that are stereogenic at a lithiated carbon atom. The major, thermodynamically preferred diastereomeric (–)-sparteine-complexed lithated phosphine sulfide was investigated by X-ray crystallography and computational methods at the B3LYP/6-31+G(d) level. Through the interconversion of the *R_P* and *S_P* stereoisomers of the lithiated methylphosphine sulfide, a novel dynamic thermodynamic resolution of a racemic lithiated phosphine sulfide has been developed. Thus, the phosphine sulfide was lithiated with *n*BuLi, and then (–)-sparteine was added. After equilibration at 0 °C for 3 h, electrophilic trapping generated an adduct in 81:19 er with the configuration opposite to that obtained under kinetic control. Thus, the methodology provides access to *P*-stereogenic compounds with the opposite sense of induction using (–)-sparteine as the ligand simply by changing the reaction conditions (kinetic or thermodynamic control).

Introduction

P-Stereogenic bisphosphine ligands such as DIPAMP,¹ BisP*,² Mini-PHOS,³ QuinoxP*,⁴ and Tangphos⁵ (Figure 1) have broad utility in transition-metal-catalyzed asymmetric processes, of which asymmetric hydrogenation is the most important.⁶ As a result, the development of new methodologies for the asymmetric synthesis of either enantiomer of such *P*-stereogenic compounds is still an important challenge. One synthetic route that has gained popularity is the lithiation–trapping reaction of phosphine boranes and sulfides mediated by org-

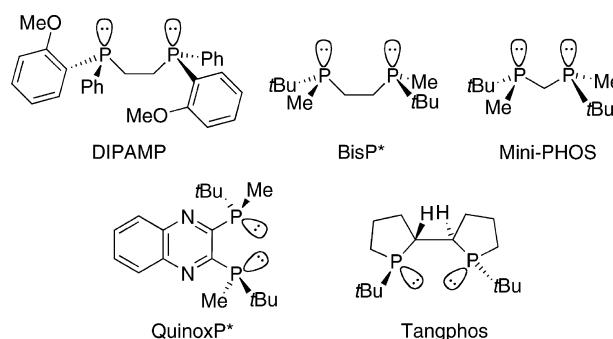


Figure 1. Examples of *P*-stereogenic bisphosphine ligands.

anolithium bases in the presence of naturally occurring (–)-sparteine. In this context, two distinct reaction manifolds have previously been identified (Scheme 1): (i) Evans-style⁷ kinetically controlled asymmetric deprotonation of dimethylphosphine boranes (or sulfides) at low temperature (–78 °C) (**1** → **2**) and (ii) Livinghouse's⁸ dynamic thermodynamic resolution of a

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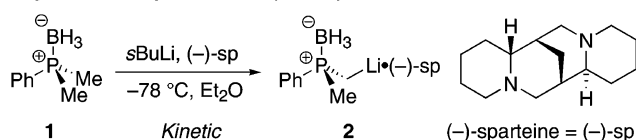
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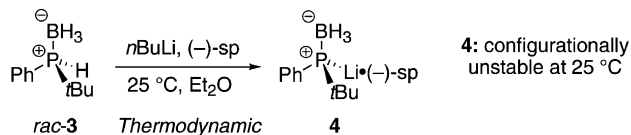
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Scheme 1

Asymmetric Deprotonation (Evans)



Dynamic Resolution (Livinghouse)

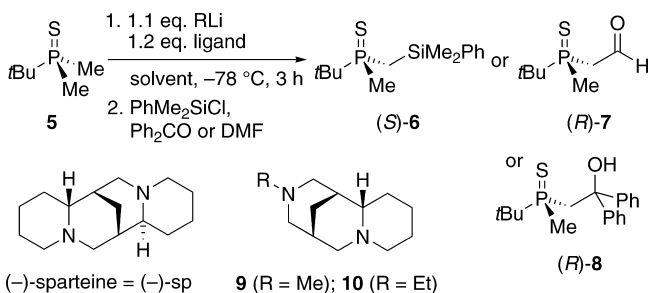


lithiated phosphane borane (lithiated at phosphorus) (**3** $\rightarrow$ **4**). Notably, high enantioselectivity was achieved in both processes using the same ligand, ($-$)-sparteine.

The Evans approach of desymmetrizing dimethyl-substituted phosphines has become one of the most useful methods for the synthesis of *P*-stereogenic bisphosphine ligands.^{2–5} Furthermore, *P*-stereogenic compounds in the opposite enantiomeric series⁹ can now be accessed using a (+)-sparteine surrogate developed in our group¹⁰ or via the regioselective lithiation of a silylphosphine sulfide.¹¹ Since Evans' seminal paper,⁷ the desymmetrization of phosphine boranes has attracted the most interest,^{2–5,9} with only isolated reports on the asymmetric lithiation–trapping of phosphine sulfides.^{5,11–13} In this paper, we report a systematic study of the factors controlling the enantioselectivity of the kinetically controlled asymmetric deprotonation of a phosphine sulfide. Notably, we highlight the opportunity for enhancement of enantioselectivity via the use of prochiral electrophiles, which is an underdeveloped strategy in asymmetric synthesis. Furthermore, a study of the effect of temperature on the lithiation process revealed that the *R_P* and *S_P* stereoisomers of the lithiated methylphosphine sulfide could interconvert at temperatures above 0 °C. This unexpected result ultimately allowed us to develop a synthetic route to *P*-stereogenic compounds via a novel dynamic thermodynamic resolution process. Thus, the two aspects of the methodology described herein provide access to *P*-stereogenic compounds with opposite sense of induction using ($-$)-sparteine as the ligand simply by changing the reaction conditions (kinetic or thermodynamic control).

Results and Discussion

Kinetically Controlled Asymmetric Deprotonation of a Phosphine Sulfide. Since some of the best *P*-stereogenic ligands (e.g., BisP*,² Mini-PHOS,³ and QuinoxP*⁴) contain *t*Bu and Me groups on the phosphorus atom, lithiation–trapping of *tert*-butyldimethylphosphine sulfide (**5**) was investigated. Lithiation of **5** was carried out using 1.1 equiv of different organolithium reagents (*s*BuLi, *n*BuLi, MeLi, and Me₃SiCH₂Li) in the presence

Table 1. Asymmetric Lithiation–Trapping of Phosphine Sulfide **5**

entry	RLi	ligand	solvent	product	yield (%) ^a	er (S/R) ^b
1	<i>n</i> BuLi	($-$)-sp	Et ₂ O	6	88	88:12
2	<i>s</i> BuLi	($-$)-sp	Et ₂ O	6	74	84:16
3	MeLi	($-$)-sp	Et ₂ O	6	17	79:21
4	Me ₃ SiCH ₂ Li	($-$)-sp	Et ₂ O	6	92	88:12
5	<i>n</i> BuLi	($-$)-sp	toluene	6	90	89:11
6	<i>n</i> BuLi	($-$)-sp	THF	6	100	55:45
7	<i>n</i> BuLi	($-$)-sp	Et ₂ O	7	18 ^c	9:91 ^{d,e}
8	<i>n</i> BuLi	($-$)-sp	Et ₂ O	8	95 ^f	13:87 ^d
9	<i>s</i> BuLi	9	Et ₂ O	6	59	26:74
10	<i>n</i> BuLi	9	Et ₂ O	6	87	14:86
11	<i>n</i> BuLi	9	toluene	6	79	19:81
12	<i>n</i> BuLi	10	Et ₂ O	6	76	21:79

^a Yield after purification by column chromatography. ^b Enantiomer ratio (er) determined by chiral-stationary-phase HPLC (CSP-HPLC). ^c Lithiation time = 10 min. ^d It should be noted that because of a Cahn–Ingold–Prelog priority change, (S)-**6**, (R)-**7**, and (R)-**8** have the same configuration and are the major enantiomers generated using ($-$)-sparteine. ^e Enantiomer ratio (er) determined by CSP-HPLC of the corresponding alcohol obtained after reduction with NaBH₄. ^f Lithiation time = 6 h.

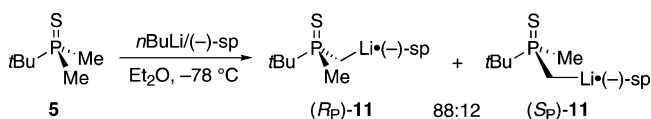
of 1.2 equiv of ($-$)-sparteine [or (+)-sparteine surrogate **9** or **10**] in Et₂O, tetrahydrofuran (THF), or toluene at -78 °C. In general, phosphine sulfide **5** was lithiated for 3 h before electrophilic quenching with PhMe₂SiCl, Ph₂CO, or *N,N*-dimethylformamide (DMF). The results of these experiments are summarized in Table 1.

Four organolithium reagents (*s*BuLi, *n*BuLi, MeLi, and Me₃SiCH₂Li) were compared in Et₂O using PhMe₂SiCl as the electrophile (entries 1–4), and the highest enantioselectivity in the formation of adduct (S)-**6** was observed with *n*BuLi (88:12 er, entry 1) and Me₃SiCH₂Li (88:12 er, entry 4). Because of the ready availability of *n*BuLi, it was selected as the optimum base. Similar enantioselectivity (89:11 er) was observed in toluene (entry 5), but as expected, poor enantioselectivity (55:45 er) was noted in THF (entry 6), presumably because a more reactive *n*BuLi/THF complex was formed in solution.¹⁴ A very short lithiation time (10 min) and trapping with DMF delivered aldehyde (R)-**7** in only 18% yield (entry 7), indicating that an extended lithiation time is required for high yield. The absolute configuration of the major enantiomer obtained from lithiation using ($-$)-sparteine was unequivocally established from the X-ray crystal structure of (R)-**8**, the product of trapping with Ph₂CO (see the Supporting Information). In this case, adduct (R)-**8** with $\geq 99:1$ er was isolated by recrystallization, and crystals of suitable quality for the X-ray structure determination were then grown. Finally, use of (+)-sparteine surrogates **9** and **10** gave the opposite sense of induction, and adduct (R)-**6** was formed in up to 86:14 er (entries 9–12).

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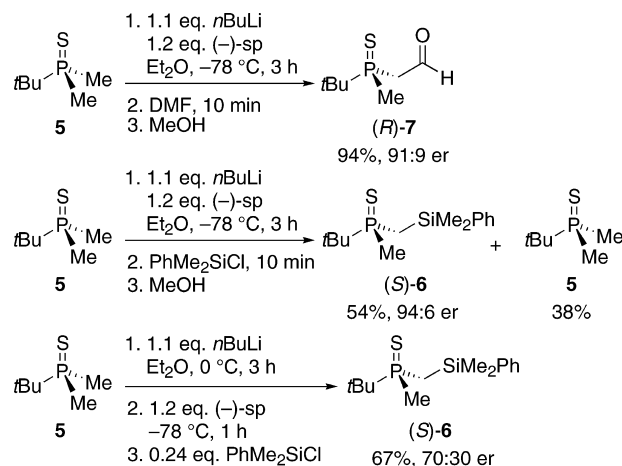
Scheme 2



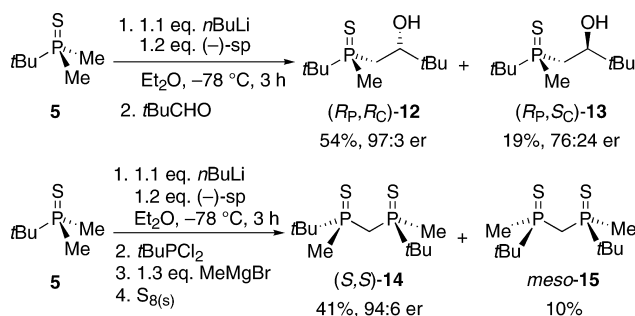
The experimental results in Table 1 indicate that asymmetric deprotonation of phosphine sulfide **5** using *n*BuLi/(–)-sparteine generates an 88:12 mixture of the (–)-sparteine-complexed diastereomeric lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11** (Scheme 2). This kinetic enantioselectivity was also predicted from a density functional theory (DFT) study of the deprotonation at the B3LYP/6-31+G(d) level. For the calculations, we explored the transition states for deprotonation of phosphine sulfide **5** using EtLi (as a model for *n*BuLi) and (–)-sparteine; 13 different diastereomeric transition states were calculated. Figure 2 depicts the most favored diastereomeric transition states to (*R_P*)-**11** and (*S_P*)-**11**. The difference in energy between *R_P*-TS and *S_P*-TS is 4 kJ mol^{–1}, which is consistent with the enantioselectivity obtained via the kinetically controlled deprotonation (for detailed information on the DFT studies, see the Supporting Information).

As part of the study of the lithiation–trapping of phosphine sulfide **5**, we were interested in comparing the efficiency of trapping of the lithiated phosphine sulfide with DMF and PhMe₂SiCl at –78 °C. Thus, phosphine sulfide **5** was lithiated using *n*BuLi/(–)-sparteine in Et₂O at –78 °C for 3 h. Next, the electrophile was added, and after 10 min at –78 °C, MeOH was added to quench any remaining lithiated intermediates. With DMF, a 94% yield of aldehyde (*R*)-**7** (91:9 er) was obtained, indicating a high rate of trapping using this electrophile. In contrast, with PhMe₂SiCl, silylphosphine sulfide (*S*)-**6** (94:6 er) was formed in only 54% yield (together with a 38% yield of recovered phosphine sulfide **5**) (Scheme 3). Clearly, PhMe₂SiCl traps the lithiated phosphine sulfide more slowly than DMF at –78 °C. Furthermore, this lower rate of trapping facilitated the formation of silylphosphine sulfide (*S*)-**6** with higher enantioselectivity (94:6 er) than when the trapping was allowed to proceed to completion (88:12 er; Table 1, entry 1). The improved enantioselectivity indicated that the major diastereomeric lithiated phosphine sulfide (*R_P*)-**11** reacts with PhMe₂SiCl at a higher rate than lithiated phosphine sulfide (*S_P*)-**11**. This was confirmed by generating a 50:50 mixture of diastereomeric lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11** (via deprotonation of phosphine sulfide with *n*BuLi and subsequent addition

Scheme 3



Scheme 4



of (–)-sparteine) and trapping with a deficiency of PhMe₂SiCl (0.24 equiv). In this way, silylphosphine sulfide (*S*)-**6** was formed with 70:30 er (67% yield based on the electrophile) (Scheme 3).

Finally, trapping of the diastereomeric lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11** obtained by *n*BuLi/(–)-sparteine-mediated asymmetric deprotonation with prochiral electrophiles was explored. With pivaldehyde, the two diastereomeric hydroxyphosphine sulfides (*R_P*,*R_C*)-**12** (54% yield, 97:3 er) and (*R_P*,*S_C*)-**13** (19% yield, 76:24 er) were isolated (Scheme 4). The configuration of hydroxyphosphine sulfide (*R_P*,*R_C*)-**12** was established by X-ray crystallography (see the Supporting Information). The difference in the ers of the two diastereomeric products can be explained by different rates of trapping of the lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11**. Fortunately, the major diastereomeric lithiated phosphine sulfide (*R_P*)-**11** traps most efficiently with pivaldehyde to give hydroxyphosphine sulfide (*R_P*,*R_C*)-**12** in higher enantioselectivity (97:3 er) than trapping with benzophenone (87:13 er; Table 1, entry 8). A similar enhancement of enantioselectivity was noticed for trapping with another prochiral electrophile, *t*BuPCl₂. In this case, trapping was followed by displacement of the remaining chloride by MeMgBr (presumably with inversion) and then treatment with sulfur. This delivered Mini-PHOS precursor (*S,S*)-**14** (41% yield, 94:6 er) and *meso*-**15** (10% yield) (Scheme 4). Thus, high enantioselectivity in the lithiation–trapping of phosphine sulfide **5** (up to 97:3 er) can be obtained using prochiral electrophiles. Such a strategy for improving the initially obtained kinetically controlled enantioselectivity may find more widespread application in organolithium/diamine-mediated lithiation–trapping reactions.

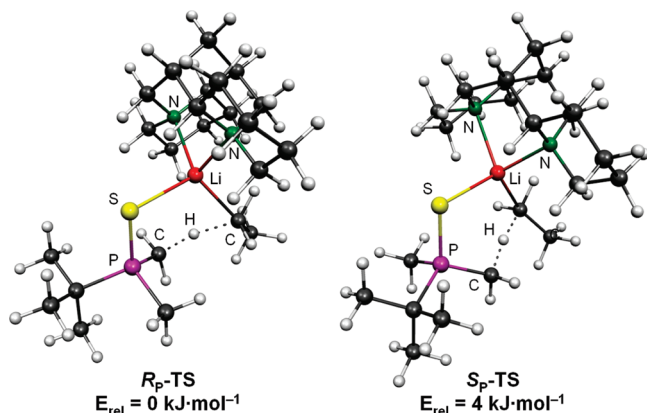


Figure 2. Most favored diastereomeric transition states for the kinetically controlled deprotonation of **5** computed at the B3LYP/6-31+G(d) level.

Table 2. Effect of Temperature on the Asymmetric Lithiation–Trapping of Phosphine Sulfide **5**

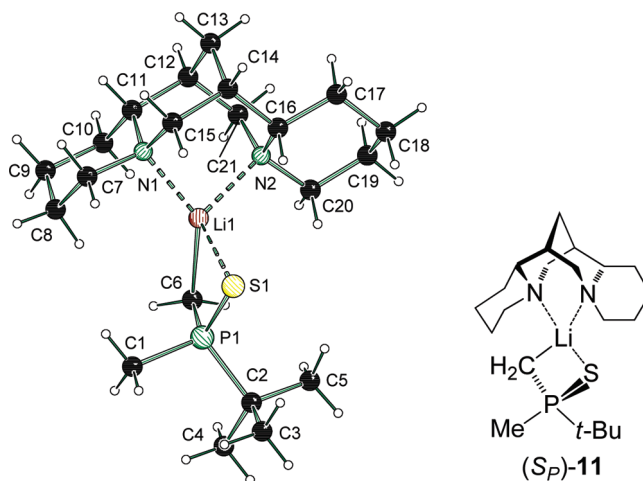
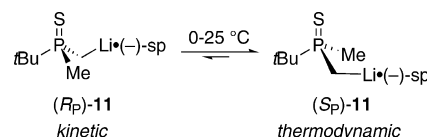
$ \begin{array}{c} \text{S} \\ \parallel \\ \text{tBu}-\text{P}-\text{Me} \\ \\ \text{Me} \\ \mathbf{5} \end{array} \xrightarrow[2. \text{PhMe}_2\text{SiCl}]{1. 1.1 \text{ eq. } n\text{BuLi}, 1.2 \text{ eq. } (-)\text{-sp}} \begin{array}{c} \text{S} \\ \parallel \\ \text{tBu}-\text{P}-\text{SiMe}_2\text{Ph} \\ \\ \text{Me} \\ (\text{S})\text{-}\mathbf{6} \end{array} $			
entry	temperature (°C)	yield (%) ^a	er (<i>S</i> / <i>R</i>) ^b
1	−90	80	91:9
2	−78	88	88:12
3	−50	88	79:21
4	0	96	39:61
5	20	86	39:61

^a Yield after purification by column chromatography. ^b Enantiomer ratio (er) determined by CSP-HPLC.

Interconversion of the *R_P* and *S_P* Stereoisomers of the Lithiated Methylphosphine Sulfide and Dynamic Thermodynamic Resolution. During the course of our studies of the kinetically controlled asymmetric deprotonation of phosphine sulfide **5** described above, we investigated the effect of temperature on the enantioselectivity using *n*BuLi/(−)-sparteine (Table 2). The enantioselectivity of the obtained silyl adduct (*S*)-**6** decreased as the temperature increased from −90 °C (91:9 er, entry 1) to −78 °C (88:12 er, entry 2) to −50 °C (79:21 er, entry 3), which is consistent with a kinetic deprotonation. However, to our surprise, a reversal of the sense of induction was observed at 0 and 20 °C: silyl adduct (*R*)-**6** (with the opposite configuration at phosphorus) was isolated in 61:39 er in both cases (entries 4 and 5).

To further investigate this unexpected deprotonation behavior of phosphine sulfide **5**, X-ray crystallography of the lithiated intermediate was attempted. Thus, phosphine sulfide **5** was lithiated using *n*BuLi and (−)-sparteine in Et₂O between −90 and −78 °C. Intermediate warming (including 6 h at 25 °C) and subsequent cooling to −78 °C produced a significant amount of crystalline lithiated phosphine sulfide **11**. It was possible to refine the structure satisfactorily (see the Supporting Information) only for an 83:17 ratio of diastereomeric lithiated phosphine sulfides (*S_P*)-**11** and (*R_P*)-**11**, in which the major configuration at phosphorus is the same as that in the major product (*R*)-**6** obtained from the 0 and 20 °C deprotonation reactions (Table 2, entries 4 and 5). The results were confirmed by repeating the crystallization experiments and structure analyses. The preference for (*S_P*)-**11** was independent of the organolithium reagent: use of *n*BuLi and *t*BuLi led to the same ratio. In the molecular structure of **11** (orthorhombic crystal system, space group *P*2₁2₁2₁), the lithium atom exhibits fourfold coordination, with two contacts to the (−)-sparteine ligand, one to the lithiated carbon atom, and one to the sulfur atom (Figure 3). Structure **11** is the first isolated α-lithiated trialkylphosphine sulfide.^{15,16}

To further confirm the uniformity of the crystals and exclude trapping with inversion of configuration, the crystals of **11** were redissolved in Et₂O and trapped with Ph₂CO to give (*S*)-**8** in

**Figure 3.** Molecular structure of the major diastereomer of lithiated phosphine sulfide (*S_P*)-**11** in the crystal. For bond lengths and angles and detailed crystallographic data, see the Supporting Information.**Scheme 5**

88:12 er. Hence, the major diastereomer (*S_P*)-**11** in the crystals (which was generated via intermediate warming to 25 °C) yielded (*S*)-**8**, in which the sense of induction is the same as that observed in the 0 and 25 °C lithiations and *opposite* that observed at −78 °C. Taken together, these results suggest that the initially formed diastereomeric lithiated phosphine sulfide/(−)-sparteine adducts (*R_P*)-**11** and (*S_P*)-**11** can interconvert at 0 °C or higher temperatures in a thermodynamic equilibration process (Scheme 5). This accounts for the formation of (*R*)-**6** in 61:39 er (Table 2, entries 4 and 5). By chance, the configuration of the major diastereomer [(*S_P*)-**11**] is the opposite of that obtained [(*R_P*)-**11**] using (−)-sparteine at −78 °C (kinetic control). This interconversion of (*R_P*)-**11** and (*S_P*)-**11** is unprecedented and totally different from the configurational instability of organolithiums that are stereogenic at a lithiated carbon atom¹⁷ or a lithiated phosphorus atom (see Scheme 1).⁸

The thermodynamic preference for lithiated phosphine sulfide (*S_P*)-**11** was predicted by a computational study of the relative energies of (*R_P*)-**11** and (*S_P*)-**11** at the B3LYP/6-31+G(d) level. Figure 4 depicts the lowest-energy structures for (*R_P*)-**11** and (*S_P*)-**11**. There is a difference in energy of 3 kJ mol^{−1} in favor of (*S_P*)-**11**, which is consistent with the 83:17 ratio of (*S_P*)-**11** and (*R_P*)-**11** observed by X-ray crystallography (for detailed information on the DFT studies, see the Supporting Information).

Next, the effect of temperature on the interconversion of lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11** was investigated. Thus, a presumed 88:12 ratio of (*R_P*)-**11** and (*S_P*)-**11** was generated by kinetic deprotonation of phosphine sulfide **5** [1.1 equiv of *n*BuLi, 1.2 equiv of (−)-sparteine, −78 °C, 3 h], and then the reaction mixture was incubated at different temperatures for 1 or 3 h before trapping with Ph₂CO at −78 °C to give adduct **8** (Table 3). After incubation at −78, −20, and −10 °C (entries 1, 3, and 5), high er (87:13) was maintained. However, at 0 °C, a reduction in er to 79:21 was obtained after 3 h at 0 °C (entry 9).

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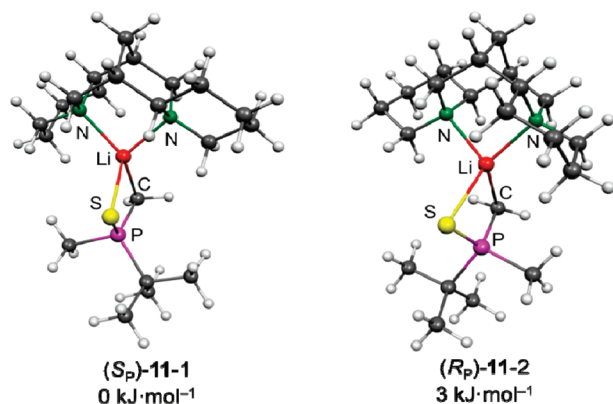


Figure 4. Optimized structures of the isomers (*S_P*)-**11** and (*R_P*)-**11** and their relative energies.

Table 3. Effect of Temperature on the Interconversion of Lithiated Phosphine Sulfides (*S_P*)-**11** and (*R_P*)-**11**

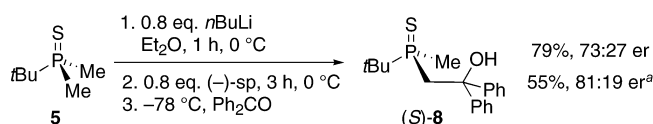
entry	temperature (°C) ^a	time (h) ^a	equiv of <i>n</i> BuLi	yield (%) ^b	er (<i>R/S</i>) ^c
1	−78	3	1.1	95	87:13
2	−78	3	0.8	76	87:13
3	−20	1	1.1	67	87:13
4	−20	1	0.8	89	67:33
5	−10	1	1.1	82	87:13
6	−10	1	0.8	93	59:41
7	0	1	1.1	83	79:21
8	0	1	0.8	60	44:56
9	0	3	1.1	87	79:21
10	0	3	0.8	62	38:62

^a Temperature/time for incubation of lithiated phosphine sulfide **11** generated using *n*BuLi/(−)-sp at −78 °C for 3 h ([**5**] = 0.07 mol dm^{−3}).
^b Yield after purification by column chromatography. ^c Enantiomer ratio (er) determined by CSP-HPLC.

A plausible mechanism for interconversion of lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11** involves nonselective proton transfer from nonlithiated phosphine sulfide **5** to the lithiated phosphine sulfide **11**.^{18,19} Such a process could occur as a result of incomplete lithiation or partial quenching of the lithiated intermediate but appears not to operate at temperatures below −20 °C. To evaluate this mechanistic conjecture further, the incubation experiments were carried out in the presence of excess **5** (obtained by lithiating **5** with only 0.8 equiv of *n*BuLi; entries 2, 4, 6, 8, and 10). At −78 °C, there was no loss of er (entry 2), but at higher temperatures, there was significant erosion of er (entries 4 and 6). Indeed, after incubation for 3 h at 0 °C, a 62% yield of adduct (*S*)-**8** in 62:38 er was obtained (entry 10). Thus, under these conditions, the initially formed 88:12 mixture of (*R_P*)-**11** and (*S_P*)-**11** was epimerized to a 62:38 mixture of (*S_P*)-**11** and (*R_P*)-**11**. The formation of (*S*)-**8** is consistent with the 0 and 25 °C lithiations of **5** (Table 2, entries 4 and 5) and the opposite of that obtained via kinetic lithiation at −78 °C (Table 1, entry 8).

(18) An intramolecular proton transfer process could also be envisaged.
 (19) An alternative mechanism involving dianion formation could also be considered. For dianion formation with phosphine boranes, see: Gessner, V. H.; Dilsky, S.; Strohmman, C. *Chem. Commun.* **2010**, 46, 4719.

Scheme 6



^a After equilibration, the precipitate was allowed to settle (no stirring), and the solvent was removed using a cannula; the remaining solid was redissolved in Et₂O and trapped with Ph₂CO.

The results in Table 3 clearly indicate that the lithiated phosphine sulfides (*R_P*)-**11** and (*S_P*)-**11** derived from **5** can interconvert above −20 °C in the presence of nonlithiated phosphine sulfide **5**. With this in mind, we reasoned that it should be possible to develop a dynamic thermodynamic resolution of a racemic lithiated phosphine sulfide at 0 °C as a means of generating nonracemic *P*-stereogenic compounds. Dynamic thermodynamic resolution of organolithium intermediates that are stereogenic at carbon was pioneered by Hoppe and Beak.^{20,21} However, there are only a few examples of crystallization-induced dynamic thermodynamic resolution of lithiated intermediates.^{8,21a–c}

In our process, phosphine sulfide **5** was lithiated in a racemic fashion using 0.8 equiv of *n*BuLi in Et₂O ([**5**] = 1.00 mol dm^{−3}) at 0 °C for 1 h. Next, (−)-sparteine (0.8 equiv) was added, and the mixture was allowed to equilibrate at 0 °C over 3 h. After the reaction mixture was cooled to −78 °C to freeze the equilibrium, Ph₂CO was added to give (*S*)-**8** in 73:27 er (79% yield) (Scheme 6). This formation of enantioenriched **8** shows that a dynamic resolution of the lithiated intermediates must have occurred. There was a noticeable degree of precipitation after the 3 h equilibration period, and better enantioselectivity was obtained when the solvent was removed (via a cannula) before trapping. Thus, after solvent removal, the remaining crystals were redissolved in Et₂O and trapped with Ph₂CO to give (*S*)-**8** in 81:19 er in a satisfactory 55% yield (Scheme 6). This result is consistent with the 83:17 ratio of (*S_P*)-**11** and (*R_P*)-**11** observed by X-ray analysis.

Conclusion

In summary, we have described the synthesis of *P*-stereogenic compounds with the opposite sense of induction using (−)-sparteine as the ligand simply by changing the reaction conditions (kinetic or thermodynamic control). Lithiation of

- (20) For reviews, see: (a) Gawley, R. E. *Top. Stereochem.* **2010**, 26, 93. (b) Coldham, I.; Sheikh, N. S. *Top. Stereochem.* **2010**, 26, 253. (c) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, 33, 715.
 (21) For examples, see: (a) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, 28, 69. (b) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2158. (c) Bou Chedid, R.; Brümmer, M.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2007**, 46, 3131. (d) Otte, R.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2005**, 44, 5492. (e) Heint, T.; Retzow, S.; Hoppe, D.; Fraenkel, G.; Chow, A. *Chem.–Eur. J.* **1999**, 5, 3464. (f) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, 118, 1575. (g) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Howard, S.; Vennall, G. P. *Angew. Chem., Int. Ed.* **2002**, 41, 3887. (h) Wang, L.; Nakamura, S.; Toru, T. *Org. Biomol. Chem.* **2004**, 2, 2168. (i) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, 128, 10943. (j) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, 119, 8209. (k) Kessar, S. T.; Singh, P.; Singh, K. N.; Venugopalan, P.; Kaur, A.; Bharatam, P. V.; Sharma, A. K. *J. Am. Chem. Soc.* **2007**, 129, 4506. (l) Coldham, I.; Raimbault, S.; Chovatia, P. T.; Patel, J. J.; Leonori, D.; Sheikh, N. S.; Whittaker, D. T. E. *Chem. Commun.* **2008**, 4174. (m) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem.–Eur. J.* **2010**, 16, 4082.

phosphine sulfide **5** using *n*BuLi and (–)-sparteine in Et₂O at –78 °C gave trapped adducts in ~88:12 er via a kinetically controlled process. Notably, this initial kinetic enantioselectivity was improved to 97:3 er by trapping of the lithiated intermediate with prochiral electrophiles (e.g., pivaldehyde or *t*BuPCl₂). In addition, we have reported for the first time that lithiated phosphine sulfides such as (*R*_P)-**11** and (*S*_P)-**11** can interconvert at temperatures above –20 °C in the presence of nonlithiated phosphine sulfide **5**. This unexpected result accounts for the fact that the configuration at phosphorus in the major diastereomeric lithiated phosphine sulfide (*S*_P)-**11** observed by X-ray crystallography is the opposite of that in the product formed from the kinetic deprotonation of **5** using *n*BuLi/(–)-sparteine (–78 °C), and these results are supported by DFT analysis. In addition, such interconversion of (*R*_P)-**11** and (*S*_P)-**11** led to the realization of a novel dynamic thermodynamic resolution of a racemic lithiated phosphine sulfide. Although the enantioselectivity is at present only moderate (81:19 er), the viability of

this novel route to *P*-stereogenic phosphine sulfides has been demonstrated. Overall, through the use of different reaction conditions with the same chiral ligand [(–)-sparteine], the methodology reported herein provides selective access to lithiated phosphine sulfide (*R*_P)-**11** (kinetic control) or (*S*_P)-**11** (thermodynamic control) and thus to *P*-stereogenic phosphines enriched in either enantiomer.

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Supporting Information Available: Full experimental procedures and data, ¹H/¹³C NMR spectra of new compounds, details of the X-ray crystal structure determinations, a summary of the calculations, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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