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Regioselective Lithiation of Silyl Phosphine Sulfides: Asymmetric Synthesis of *P*-Stereogenic Compounds

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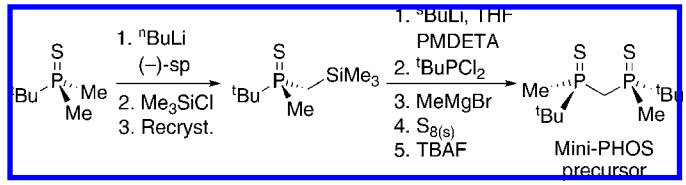
ABSTRACT



Starting from a trimethylsilyl-substituted phosphine sulfide of 99:1 er (generated by *n*-BuLi/(−)-sparteine-mediated asymmetric lithiation of a dimethylphosphine sulfide), a two-step process of regioselective lithiation-trapping and silyl group removal has been used to prepare a range of *P*-stereogenic compounds, including precursors to diphosphine ligands (e.g., Mini-PHOS). This two-step protocol delivers products with the opposite configuration to that obtained by direct asymmetric lithiation−trapping of a dimethylphosphine sulfide using *n*-BuLi/(−)-sparteine.

P-Stereogenic phosphines constitute one class of chiral phosphines that have been utilized as ligands in a broad range of transition-metal-catalyzed asymmetric hydrogenation processes.[1] Of the methods available for the synthesis of *P*-stereogenic compounds,[2] one of the most successful involves the asymmetric lithiation-trapping of phosphine boranes or sulfides using an organolithium reagent/(−)-sparteine chiral base complex.[3] Such an approach has been used in the synthesis of *P*-stereogenic phosphine and diphosphine ligands, and representative examples include BisP*,[4] Mini-PHOS,[4b,5] and *P*,*N*-ligands[6] (Figure 1). The opposite configuration of the ligands depicted in Figure 1 can be accessed by employing the (+)-sparteine surrogates

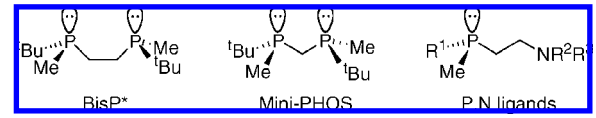


Figure 1. *P*-Stereogenic mono- and diphosphine ligands.

(developed in our laboratory[7]), as first demonstrated by Kann and co-workers[8] and later by ourselves.[9] However, to obviate the need for synthesis of the (+)-sparteine surrogates, we

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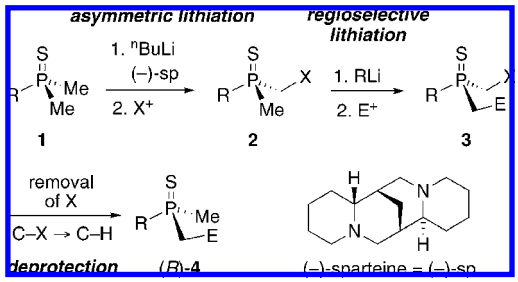
have now developed an alternative approach to *P*-stereogenic compounds with the configuration opposite to those shown in Figure 1. Herein, we present our results.

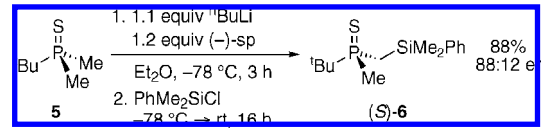
Our proposed strategy for the asymmetric synthesis of *P*-stereogenic compounds from dimethylphosphine sulfides **1** is outlined in Scheme 1 and comprises three key steps: (i) *n*-BuLi/(−)-sparteine-mediated asymmetric lithiation-trapping of phosphine sulfide **1** → **2** in which a suitable functional group (X) would be introduced; (ii) regioselective, kinetically controlled lithiation α to phosphorus on the less sterically encumbered methyl group and subsequent electrophilic trapping to give **3**, and (iii) removal of the functional group X in which the C−X bond is transformed into a C−H bond to produce substituted phosphine sulfide (*R*)-**4**.[10] In contrast, direct asymmetric lithiation-trapping of phosphine sulfide **1** using *n*-BuLi/(−)-sparteine would deliver (*S*)-**4** (the configuration present in the ligands in Figure 1). For our strategy to be successful, the functional group X needed to be easy to introduce/remove and had to be compatible with the rather harsh lithiation-trapping conditions (**2** → **3**) typically employed. With this in mind, we selected trialkylsilyl substituents (X = SiR_3) for our investigation. A related strategy with phosphine boranes in which X = OH (via dianion chemistry) has been used by Imamoto to prepare *ent*-BisP*, although a two-step method for converting CH_2OH into CH_3 was employed.[11]

Scheme 1. Strategy for the Asymmetric Synthesis of Substituted Phosphine Sulfides (*R*)-**4**



To start with, $PhMe_2Si$-substituted phosphine sulfide (*S*)-**6** was prepared using our previously reported procedure.[12] Thus, treatment of phosphine sulfide **5** with *n*-BuLi/(−)-sparteine in Et_2O at −78 °C and subsequent reaction with $PhMe_2SiCl$ delivered silyl phosphine sulfide (*S*)-**6** in 88% yield (88:12 er by CSP-HPLC) (Scheme 2). Next, a wide range of conditions was examined to explore the regioselectivity of the lithiation of phosphine sulfide (*S*)-**6** (Tables 1 and 2). Our plan was to trap the lithiated intermediate(s) derived from (*S*)-**6** with $PhMe_2SiCl$ as this would generate achiral bis-silyl phosphine sulfide **7** or chiral bis-silyl phosphine sulfide (*S*)-**8**, which could be distinguished by ^1H NMR spectroscopy. Ultimately, we hoped to optimize conditions for regioselective lithiation at the unsubstituted methyl group, thus allowing access to achiral bis-silyl phosphine sulfide **7** selectively.

Scheme 2. Synthesis of Silyl Phosphine Sulfide (*S*)-**6**



Lithiation of silyl phosphine sulfide (*S*)-**6** using *n*-BuLi in Et_2O at −78 °C for 3 h and subsequent electrophilic trapping gave adduct (*S*)-**8** exclusively (68% yield) (Table 1, entry 1). This clearly indicated preferential lithiation α to the silyl substituent, which was opposite to that required for our purposes (see Scheme 1). However, on switching to the more sterically hindered base *s*-BuLi, lithiation-trapping gave a 50:50 mixture of **7** and (*S*)-**8** from which we isolated a 50% yield of adduct **7** (entry 2). A similar outcome was obtained using *n*-BuLi and *s*-BuLi in THF (entries 3 and 4). With a view to increasing the amount of lithiation at the methyl group in (*S*)-**6**, we investigated the effect of diamines (TMEDA **9** and bispidines **10** and **11**) and a triamine (PMDETA **12**) (entries 5−13). Use of *n*-BuLi/TMEDA in Et_2O and *s*-BuLi/bispidine **10** in Et_2O or THF all gave (*S*)-**8** only, although the isolated yields were ≤44% (entries 5, 8 and 9). In contrast, use of *s*-BuLi/TMEDA **9** or PMDETA **12** in Et_2O or THF and subsequent trapping generated the highest proportions of adduct **7** (regioselectivity ranging from 70:30−80:20), entries 6, 7, 12, and 13). The highest overall yields of **7** and (*S*)-**8** were obtained in THF, and from these regioselective lithiations it was possible to isolate 67−69% yields of adduct **7** (entries 7 and 13). The highest level of regioselectivity in the desired sense (i.e., to give **7**) was obtained using *s*-BuLi/PMDETA **12**. We speculate that this is due to the increased steric hindrance and basicity of the *s*-BuLi/PMDETA reagent, which leads to preferential lithiation at the methyl group in a kinetically controlled event (at −78 °C).

Finally, we explored the use of different equivalents of *s*-BuLi/PMDETA **12** and different lithiation times (Table 2). Interestingly, use of *s*-BuLi/PMDETA **12** in THF and increasing the lithiation time to 6.5 h led to poor regioselectivity: a 60:40 mixture of **7** and (*S*)-**8** was obtained (Table 2, entry 1). The usual 3 h lithiation time generated a 75:25 mixture of **7** and (*S*)-**8** under comparable conditions (entry 2). To explain this, we suggest that preferential lithiation at the methyl group occurs but during the extended lithiation time, equilibration of the carbanion to the thermodynamically preferred position (α to phosphorus *and* silicon) occurs. As a result, we focused our attention on shorter lithiation times (entries 3 and 4), and the best compromise between yield and regioselectivity was observed using 1.5 equiv of *s*-BuLi/

(10) We have assigned phosphine sulfide **4** in Scheme 1 with (*R*)-configuration. This assumes that the CH_2E substituent is of higher priority in the Cahn−Ingold−Prelog rules than the R and CH_3 groups.

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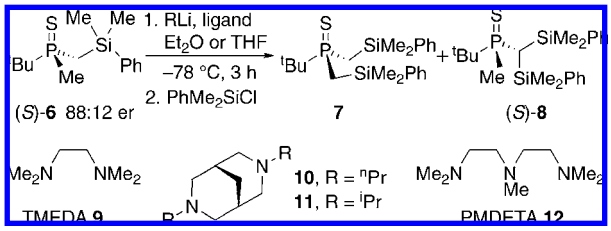
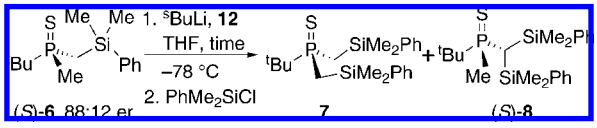
Table 1. Optimization of the Regioselective Lithiation of Silyl Phosphine Sulfide (*S*)-**6**: Effect of Base, Solvent, and Ligand



entry	base[a]	solvent	ligand	**7**/(*S*)-**8**[b]	yield of **7**[c] (%)	yield of (*S*)-**8**[c] (%)
1	*n*-BuLi	Et_2O		0:100	0	68
2	*s*-BuLi	Et_2O		50:50	50	32
3	*n*-BuLi	THF		0:100	0	60
4	*s*-BuLi	THF		60:40	37	15
5	*n*-BuLi	Et_2O	**9**[d]	0:100	0	44
6	*s*-BuLi	Et_2O	**9**[d]	80:20	50	8
7	*s*-BuLi	THF	**9**[e]	70:30	67	19
8	*s*-BuLi	Et_2O	**10**[d]	0:100	0	9
9	*s*-BuLi	THF	**10**[d]	0:100	0	40
10	*s*-BuLi	Et_2O	**11**[d]	*f*	0	0
11	*s*-BuLi	THF	**11**[d]	40:60	26	27
12	*s*-BuLi	Et_2O	**12**[g]	75:25	60	19
13	*s*-BuLi	THF	**12**[h]	75:25	69	15

[a] Reaction conditions: 1.1 equiv of RLi, 1.2 equiv of ligand (if used). [b] Ratio determined by ^{1}H NMR spectroscopy of the crude product. [c] Yield after purification by column chromatography. [d] 1.0 equiv of RLi/ligand. [e] 1.2 equiv of *s*-BuLi/**9**, 1.5 h lithiation time. [f] H NMR spectrum of crude product indicated starting material only. [g] 1.1 equiv of *s*-BuLi/**12**. [h] 1.2 equiv of *s*-BuLi/**12**.

Table 2. Optimization of the Regioselective Lithiation of Silyl Phosphine Sulfide (*S*)-**6**: Effect of Lithiation Time



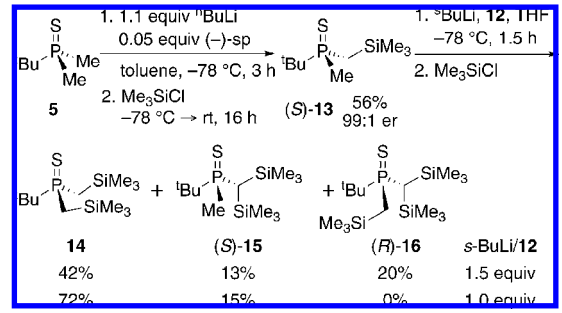
entry	*s*-BuLi[a] (equiv)	time (h)	**7**/(*S*)-**8**[b]	yield of **7**[c] (%)	yield of (*S*)-**8**[c] (%)
1	1.2	6.5	60:40	44	43
2	1.1	3	75:25	60	19
3	1.5	1.5	85:15	72	14
4	1.1[d]	0.5	80:20	60	9

[a] *s*-BuLi/ligand (equiv). [b] Ratio determined by ^{1}H NMR spectroscopy of the crude product. [c] Yield after purification by column chromatography. [d] 1.1 equiv of *s*-BuLi/1.2 equiv **12**.

PMDETA **12** in THF at −78 °C for 1.5 h. In this way, a 72% yield of adduct **7** was isolated (entry 3).

Although we had now identified optimum conditions for the required regioselective lithiation of silyl phosphine sulfide (*S*)-**6**, limitations to our proposed methodology remained: (*S*)-**6** was produced in only 88:12 er by a lithiation using stoichiometric amounts of (−)-sparteine. Although improvement of the er of (*S*)-**6** via recrystallization was not available to us ((*S*)-**6** is not crystalline), the corresponding trimethylsilyl derivative, (*S*)-**13**, is crystalline and appeared suitable for our purposes. Thus, silyl phosphine sulfide (*S*)-**13** was produced using our previously reported *catalytic* asymmetric deprotonation protocol[12] (1.1 equiv of *n*-BuLi, 0.05 equiv (−)-sparteine in toluene). Recrystallization of the crude product delivered a 56% yield of (*S*)-**13** of 99:1 er (by CSP-HPLC) (Scheme 3).

Scheme 3. Synthesis and Regioselective Lithiation of Silyl Phosphine Sulfide (*S*)-**13**

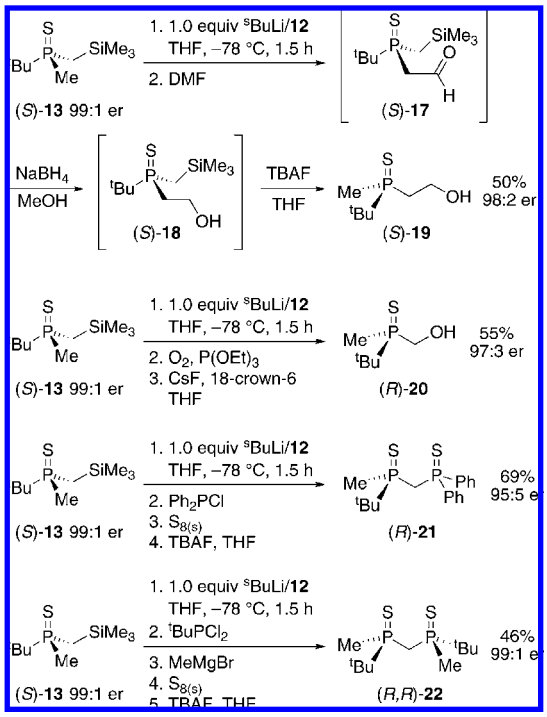


Regioselective lithiation-trapping (with Me_3SiCl) of (*S*)-**13** using the lithiation conditions optimized above for (*S*)-**6** (1.5 equiv *s*-BuLi/PMDETA **12** in THF at −78 °C for 1.5 h) was rather disappointing as only a 42% yield of adduct **14** was obtained (Scheme 3). Surprisingly, we obtained a 20% yield of (*R*)-**16** in which two new trimethylsilyl groups had been incorporated. In this case, use of excess *s*-BuLi has a detrimental effect on the lithation. We suspect that the initially formed carbanions trap to give **14** and (*S*)-**15** and these intermediates are then deprotonated by the excess *s*-BuLi (which presumably reacts slowly with Me_3SiCl at −78 °C). Subsequent trapping then gives (*R*)-**16**. To circumvent this problem, the amount of *s*-BuLi/PMDETA **12** used was reduced to 1.0 equiv resulting in a 72% yield of adduct **14** (with no formation of (*R*)-**16**) (Scheme 3).

Finally, it was necessary to demonstrate that silyl phosphine sulfide (*S*)-**13** of 99:1 er could be used to access chiral phosphines with the configuration opposite to that obtained by direct lithiation-trapping with organolithium reagents and (−)-sparteine. Thus, (*S*)-**13** was subjected to regioselective lithiation and trapped with DMF to generate aldehyde (*S*)-**17**. Crude aldehyde (*S*)-**17** was reduced ($NaBH_4$) and then desilylated (TBAF) to give a 50% yield (after chromatography) of hydroxy phosphine sulfide (*S*)-**19** (98:2 er) over three steps (Scheme 4). As anticipated, the adduct generated in this way had the configuration opposite to that obtained from **5** by direct lithiation (*n*-BuLi/(−)-sparteine)-DMF trapping-reduction (as shown by CSP-HPLC, see the Supporting Information).[13] The phosphine borane corresponding to **19** (P-BH_3 in place of P═S) has been used by Kann to prepare *P*,*N*-ligands[6] (Figure 1). In a similar way, lithiation−

(13) The sense of induction obtained by direct lithiation of phosphine sulfide **5** using *n*-BuLi/(−)-sparteine is known (see ref 11).

Scheme 4. Synthesis of *P*-Stereogenic Mono- and Diphosphine Sulfides



oxygenation of (*S*)-**13**, and then desilylation (using CsF and 18-crown-6) gave hydroxy phosphine sulfide (*R*)-**20** (55% yield, 97:3 er) (Scheme 4). Imamoto has used the phosphine borane corresponding to **20** to prepare QuinoxP*.[14]

Next, we prepared two diphosphine sulfides (*R*)-**21** (a protected analogue of trichickenfootphos[15]) and (*R*,*R*)-**22** (a protected form of MiniPHOS[5]) (Scheme 4). Lithiation of (*S*)-**13** was followed by reaction with Ph_2PCl; subsequent treatment with sulfur and then TBAF delivered a 69% yield of (*R*)-**21** (95:5 er) over the three steps. A similar sequence but trapping with *t*-$BuPCl_2$ and then reaction with MeMgBr gave (*R*,*R*)-**22** (99:1 er) in 46% yield. In the synthesis of (*R*,*R*)-**22**, high stereoselectivity in the creation of the second stereocenter at phosphorus (formed in the trapping with *t*-$BuPCl_2$) was observed: none of the *meso* diastereomer was produced. This contrasts with the ∼1:1 diastereoselectivity observed for the trapping of lithiated *tert*-butyldimethylphosphine borane in Imamoto's synthesis of MiniPHOS.[5] We believe that this stereocontrol is due to the phosphine sulfide and not due to the silyl substituent since lithiation of **5** using *n*-BuLi/(−)-sparteine and subsequent reaction with *t*-$BuPCl_2$, MeMgBr, and then sulfur delivered a ∼3:1 mixture of (*S*,*S*)-**22** and its *meso* diastereomer.

In summary, the successful implementation of a new strategy for accessing *P*-stereogenic compounds with the opposite configuration to that obtained by direct lithiation-trapping using organolithium reagents and (−)-sparteine is described. A study on the factors controlling the regioselectivity of lithiation of silyl phosphine sulfides is also reported. We believe that both these aspects will prove useful to those involved in the synthesis of *P*-stereogenic phosphine ligands via lithiation processes.

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Supporting Information Available: Full experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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