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Asymmetric desymmetrization of organophosphorus compounds with organolithium-sparteine chiral bases

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1. INTRODUCTION

Chiral organophosphorus compounds, especially chiral tertiary phosphines, play a very important role in organic synthesis. The major use for them is as chiral ligands in homogenous transition metal catalysis, most notably asymmetric hydrogenation of alkenes and ketones which was the first stereoselective metal-catalyzed reaction to be developed along with the first chiral phosphine ligands during 1970's and 1980's [1–5]. Other stereoselective reactions commonly carried out using metal-chiral phosphine complexes conjugate addition [6–8], allylic substitution [9, 10], addition to ketones [11].

Although the first phosphines to be used in catalytic stereoselective reactions were P-chiral, nowadays the majority of commonly used phosphine ligands are based on C-chiral backbones due to ready availability of chiral scaffolds from natural compounds. Protocols for obtaining enantiopure P-chiral compounds almost always call for enantiomer resolution via diastereomeric crystallization of salts or molecular complexes of chiral organophosphorus compounds or installation of chiral auxiliary group(s) at the phosphorus. Meisenheimer was the first one to

resolve racemic tertiary phosphine oxides using (+)-bromocamphorsulfonic and (+)-camphorsulfonic acids as the resolving agents [12, 13]. Resolution of diastereomeric molecular complexes is the oldest approach used to obtain enantiopure organophosphorus compounds, however, it is still in common use and the most popular resolving agents are tartaric acid derivatives DBTA (dibenzoyltartartic acid) [14] and TADDOL (α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol) [15–18] and chiral diols (e.g. BINOL [19]).

Another approach is the formation of menthyl phosphinate from the corresponding phosphoryl chloride and (–)-menthol, two epimers formed can be separated through fractional crystallization and a single diastereomer can be transformed into enantiopure tertiary phosphine oxide through nucleophilic substitution at phosphorus with organometallic reagents [20–24] or reduction with lithium in ammonia, alkali naphthalenides or LDBB (lithium 4,4'-di-*tert*-butylbiphenylide) followed by electrophilic substitution with alkyl halides [25, 26]. Aside from menthol ephedrine is another derivatizing agent that allows for the synthesis of enantiopure tertiary phosphine derivatives through the formation of P-chiral oxazaphospholidines and double nucleophilic substitution at phosphorus [27, 28].

The methods relying on the resolution of molecular complexes or fractional crystallization of diastereomers, despite being very general, possess a major drawback which is partial loss of the compound being resolved as the "undesired". Thus from the atom economy perspective in cases where a single enantiomer is required, methods allowing for stereoselective formation of the desired enantiomer are desirable.

These include enantioselective catalytic reactions using metal catalysts or organocatalysts and transformations using stoichiometric chiral reagents. This review is focused on asymmetric desymmetrization of heteroleptic phosphine derivatives using asymmetric deprotonation and dynamic resolution with chiral organolithium-sparteine complexes.

2. ASYMMETRIC DESYMMETRIZATION WITH ORGANOLITHIUM/SPARTEINE IN ORGANOPHOSPHORUS CHEMISTRY

(–)-Sparteine is a lupidine alkaloid occurring in certain papilionaceous plants from which it is extracted. Chemically it is a diamine with a tetracyclic structure possessing four chiral centers. It acts as a bidentate chiral ligand for metal cations and its lithium complexes found wide application in organic synthesis, including deprotonation of P-H and C-H groups in organophosphorus compounds.

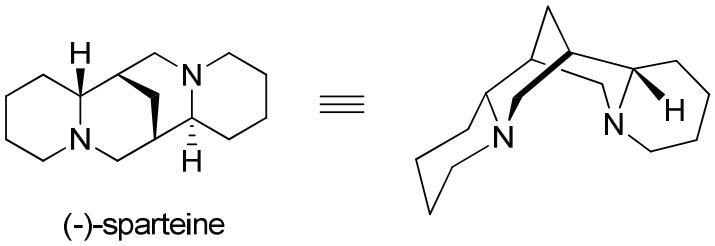
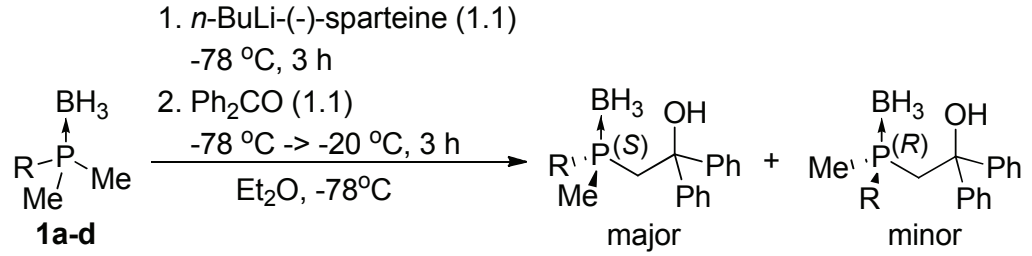
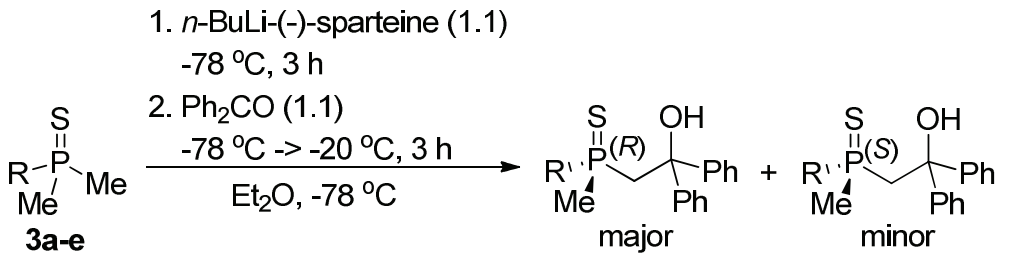


Fig. 1. (–)-Sparteine

The first report on stereoselective α-lithiation of a dimethylphosphine derivative appeared in 1989. White et al. used *n*-butyllithium-(–)-sparteine complex in hexane to deprotonate dimethylphenylphosphine oxide, quenching the reaction with ethyl iodide gave chiral ethyl(phenyl)propylphosphine oxide albeit of very low optical purity [29]. In 1995 the group of Evans published an effective method for asymmetric deprotonation of aryldimethylphosphine-boranes and sulfides at low temperature of –78 to –30°C in diethyl ether using *s*- or *n*-butyllithium complex with sparteine [30]. The resulting chiral α-lithiated compounds were reacted with benzophenone or copper(II) pivalate to give β-hydroxyalkylphosphine analogues **2a-d** and **4a-e** (Scheme 1) and 1,2-bis(aryl(methyl)phosphino)ethane derivatives **5a-d** (Scheme 2) respectively in high yields and with 60-87% ee.

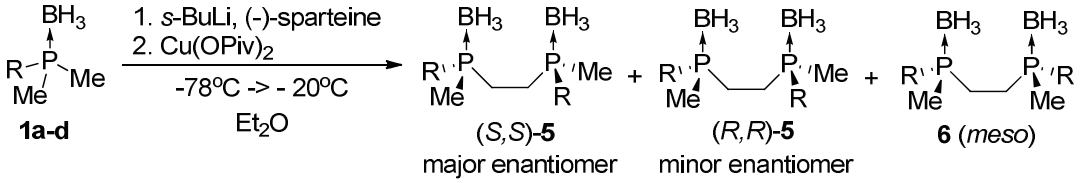


	R	yield (%)	ee (%)
2a	Ph	88	79
2b	*o*-Tol	81	83
2c	*o*-An	84	87
2d	1-Np	86	82



	R	yield (%)	ee (%)
4a	Ph	94	78
4b	*o*-Tol	79	79
4c	*o*-An	83	76
4d	1-Np	80	60
4e	*t*-BuO	80	81

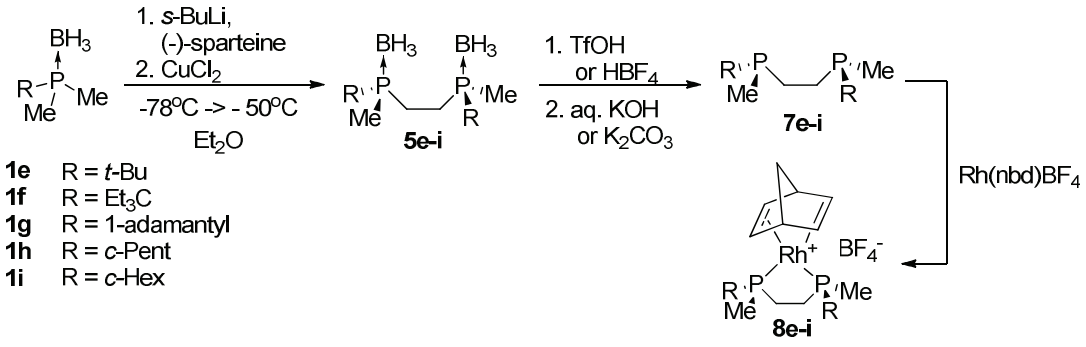
Scheme 1.



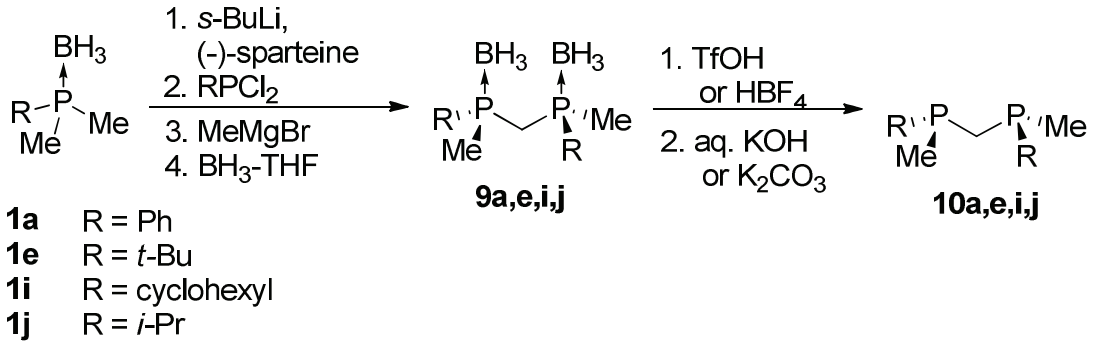
	R	yield (%)	5 : 6	ee of **5** (%)
5a	Ph	72	79:21	98
5b	*o*-Tol	67	88:12	99
5c	*o*-An	69	85:15	99
5d	1-Np	68	85:15	96

Scheme 2.

Using the same methodology Imamoto et al. obtained a series of diphosphine-diboranes **5e-i** through desymmetrization of *tert*-alkyl- and cycloalkyldimethylphosphine-boranes (Scheme 3). [31] The reactions showed very high stereoselectivity for *tert*-alkylphosphine-boranes **1e-g** and moderate stereoselectivity for cycloalkyl analogues **1h-i**, however enantiopure compounds were obtained after recrystallization. Similar alkyl- and phenyldimethylphosphine-boranes were also used by Imamoto et al. to obtain MiniPHOS analogues **10** (Scheme 4). [32-33] Both groups of ligands were used to synthesize Rh complexes, which were tested in asymmetric hydrogenation of α-(acylamino)acrylic acid and dehydroaminoacid derivatives, and asymmetric hydrosilylation of ketones, as well as Cu complexes which were tested in asymmetric conjugate addition of Et_2Zn to cyclic enones.



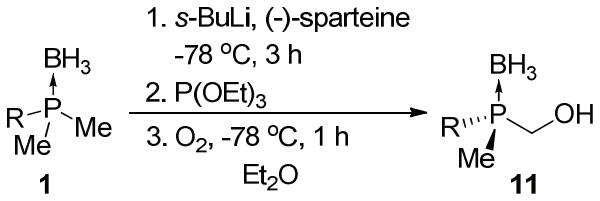
Scheme 3.



Scheme 4.

Among other electrophiles molecular oxygen can be used to effect hydroxylation of stereoselectively deprotonated dimethyl-

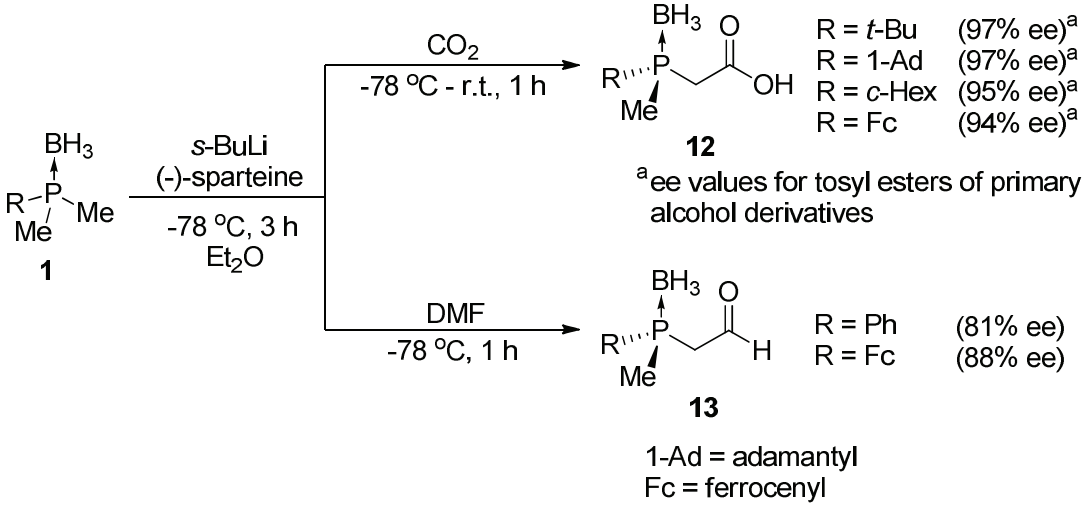
phosphine-boranes **1**, α-hydroxymethylphosphine-boranes **11** can be transformed into chiral secondary phosphine-boranes via deformylation or oxidation-decarboxylation. [34]



R	yield (%)	ee (%)
1-adamantyl	74	93
tert-butyl	73	91
cyclohexyl	70	75
phenyl	67	81

Scheme 5.

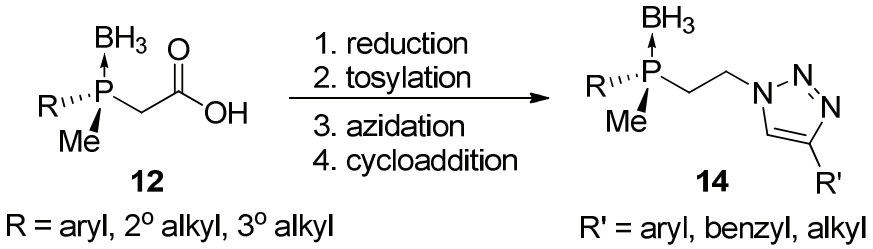
The group of Kann showed that enantioenriched α-lithiated dimethylphosphine-boranes also react efficiently with CO_2 [35] and DMF [36] affording α-carboxylated (**12**) and α-formylated (**13**) derivatives respectively (Scheme 6). These are particularly useful considering the vast amount of available transformations of carboxylic acids and aldehydes.



Scheme 6.

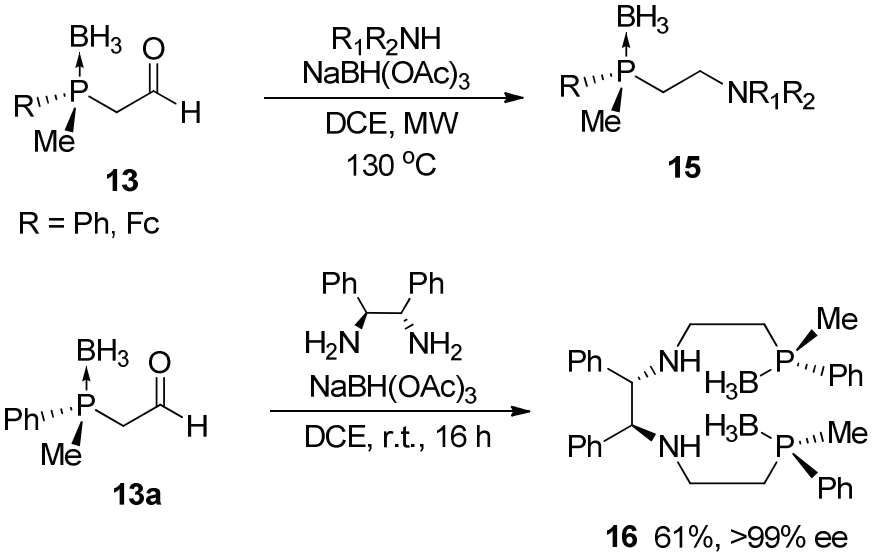
Carboxylic acids **12** have been subsequently used to synthesize ChiraClick ligands in a series of 4 steps starting with reduction to primary alcohols using $BH_3{\cdot}SMe_2$ followed by tosylation with tosyl chloride in the presence of pyridine, nucleophilic substitution of the tosyl group by sodium azide afforded β-azidoethylphosphine-boranes

which were then reacted with terminal alkynes in copper-catalyzed cycloaddition (Scheme 7) [35].



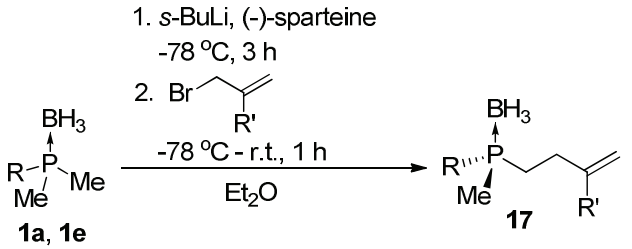
Scheme 7.

Aldehydes **13** have been subjected to microwave-assisted reductive amination which led to aminophosphine ligand precursors **15**. Using this approach tetradentate ligand precursors have also been obtained, one example being 1,2-diphenylethane-1,2-diamine derivative **16** (Scheme 8) [36].

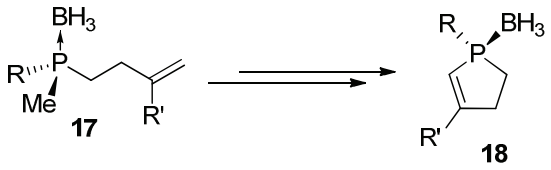


Scheme 8.

O'Brien et al. carried out asymmetric desymmetrization of phosphine-boranes **1a** and **1e** using allyl bromides and the products **17** were successfully transformed into chiral 2-phospholene-boranes **18** in several steps using olefin metathesis as the final reaction (Scheme 9) [37].

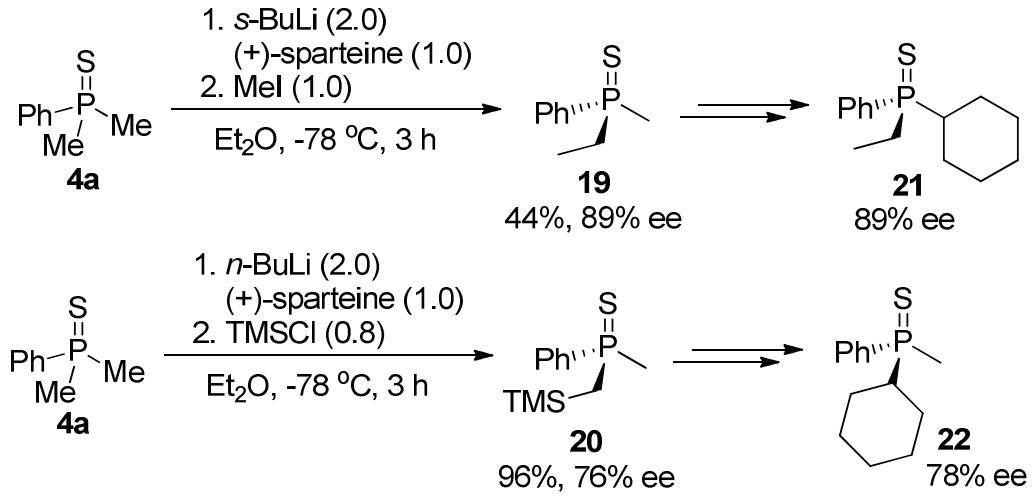


R	R'	yield (%)	ee (%)
Ph	Me	73	78
Ph	H	57	76
t-Bu	Me	57	92
t-Bu	H	58	86



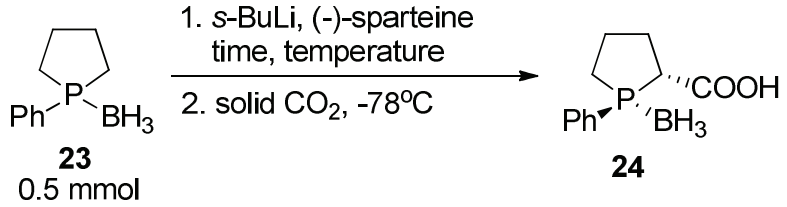
Scheme 9.

More recently the group of Stankevič used asymmetric lithiation of dimethylphenylphosphine sulfide with MeI and TMSCl as quenching electrophiles to synthesize enantioenriched products which after haloalkylation and intramolecular cyclization led to the formation of enantioenriched ethyl- and methyl(cyclohexylphenyl) phosphine sulfides **21** and **22** with ee of 89% and 78% respectively (Scheme 10). Interestingly, α-lithiated dimethylphenylphosphine sulfide complexed with sparteine did not react with 1-bromo-6-chlorohexane at –78°C and reacted very sluggishly even at room temperature which suggests complexation with sparteine impedes reaction with less reactive alkyl halides. [38]



Scheme 10.

Aside from desymmetrization of methyl groups in dimethylphosphine-boranes and sulfides, butyllithium-sparteine complexes have also been used to stereoselectively deprotonate methylene groups in *P*-heterocyclic compounds. Kobayashi et al. carried out carboxylation of lithiated phenylphospholane-borane **23** and phenylphosphorinane-borane **25** with solid CO_2. [39] The reaction was tested under different conditions and with different amount of chiral base. In all cases mixtures of both diastereomers were formed with *trans* isomer being the major product. For phenylphospholane-borane **23** an interesting trend in both diastereoselectivity and enantioselectivity was observed (Scheme 11, Table 1).



23
0.5 mmol

24

Scheme 11.

Table 1.

entry	*s*-BuLi/(–)-sparteine (eq.)	conditions	yield (%)	*trans/cis*	*trans* ee (%)
1	1.0 / 1.0	–78°C, 3 h	24	3.0	83
2	1.5 / 1.5	–78°C, 3 h	62	2.2	32
3	1.5 / 1.5	0°C, 2 h	76	1.5	34
4	1.5 / 1.5	0°C, 3 h	59	1.5	55
5	1.5 / 1.5	0°C, 4 h	48	1.6	85
6	1.5 / 1.5	0°C, 6 h	45	1.5	87
7	1.5 / 1.5	25°C, 2 h	41	2.0	92
8[a]	1.2 / 1.2	0°C, 4 h	52	3.1	75
9[b]	1.0 / 1.0	25°C, 8 h	55	4.0	92

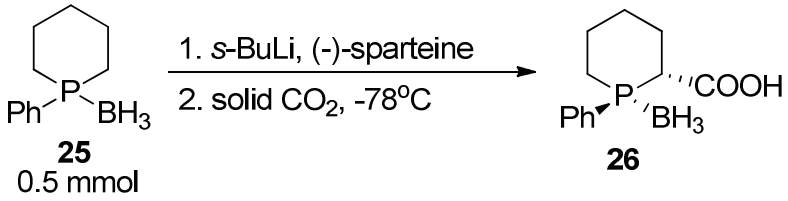
[a] 5 mmol scale

[b] 25 mmol scale

Excess of chiral base always led to lower overall stereoselectivity. When the reaction was carried out at –78°C high ee

and de were obtained with 1.0 eq. of *s*-BuLi/(−)-sparteine, but the yield was low. Surprisingly, the highest enantiopurity for the *trans* isomer was obtained when the reaction was carried out at room temperature and experiments carried out at 0°C showed that longer reaction times were also associated with higher enantioselectivity while excess base gave the product with somewhat lower ee.

The reaction of phenylphosphorinane-borane **25** was only tested at −78°C, diastereoselectivity was much higher compared to lower homologue and the *trans* isomer had 90% ee (Scheme 12, Table 2).



Scheme 12.

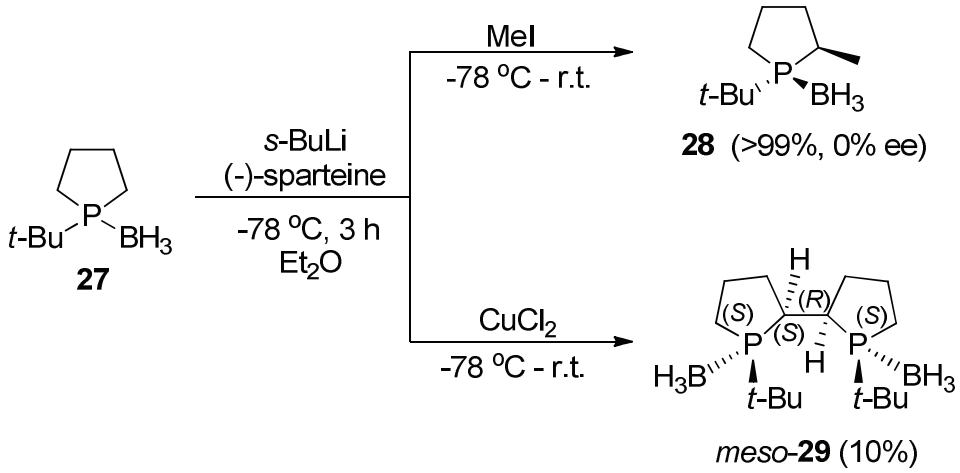
Table 2.

entry	*s*-BuLi/(−)-sparteine (eq.)	conditions	yield (%)	*trans/cis*	*trans* ee (%)
1	1.0 / 1.0	−78°C, 3 h	40	18	90
2	3.0 / 1.5	−78°C, 3 h	64	14	81
3	1.5 / 1.5	−78°C, 1 h	65	7.1	80
4	1.5 / 1.5	−78°C, 3 h	57	36	83
5	1.5 / 1.5	−78°C, 6 h	36	8.1	89
6[a]	1.2 / 1.2	−78°C, 3 h	79	7.4	76

[a] 5 mmol scale

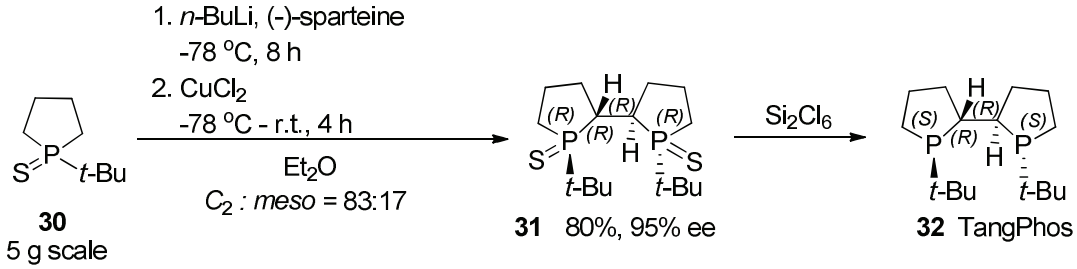
Ohashi and Imamoto attempted stereoselective deprotonation of *tert*-butylphospholane-borane **27** combined with methylation and copper-mediated homocoupling (Scheme 13). [40] Interestingly, they found out that in case of methylated derivative **28** a single diastereomer was formed with a very high yield, however the product was racemic. This may indicate that lithiation takes place in a diastereoselective but not enantioselective manner. In case of homocoupling only non-chiral *meso*-isomer **29** was obtained with a

low yield of 10%. The authors argue that the *meso* isomer is formed rather than racemic product due to steric repulsion between *tert*-butyl groups. Both compounds **28** and **29** were obtained in crystalline form and analyzed crystalographically.



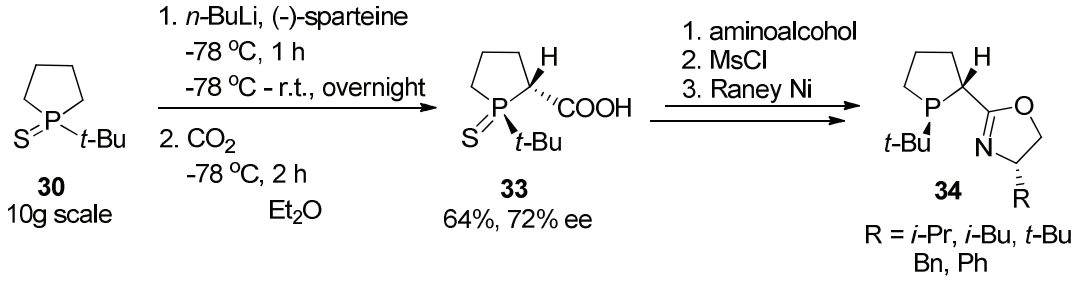
Scheme 13.

The synthesis of TangPhos is another example of the application of asymmetric deprotonation in the synthesis of phosphine ligands [41]. Tang and Zhang stereoselectively transformed *tert*-butylphospholane sulfide **30** into the diphospholane derivative **31** via copper-mediated homocoupling (Scheme 14). The product after purification via chromatography and recrystallization was reduced to TangPhos (**32**) using hexachlorodisilane. The rhodium complex with TangPhos gave very good results in asymmetric hydrogenation of dehydroaminoacids and α-arylenamides, the majority of products were obtained with >99% ee.



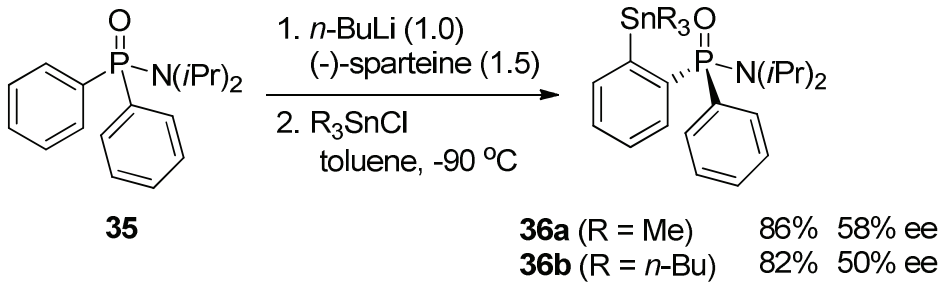
Scheme 14.

The group of Tang also used *tert*-butylphospholane sulfide **30** in stereoselective carboxylation obtaining carboxylic acid **33**. The enantioselectivity of the reaction was moderate but double recrystallization from ethanol provided the enantiopure product. It was then used in the synthesis of mixed phospholane-oxazoline *P,N*-ligand **34** (Scheme 15) [42] .



Scheme 15.

Ortiz et al. published a paper on stereoselective desymmetrization of *N,N*-diisopropyl-*P,P*-diphenylphosphinic amide **35** via directed *ortho*-lithiation. [43] The reactions were carried out in toluene at –90°C using *n*-butyllithium/(–)-sparteine complex as the chiral base and intermediate organolithium reagents were quenched with tin reagents to give ortho-substituted products **36a** and **36b** with high yield but only moderate ee (Scheme 16).

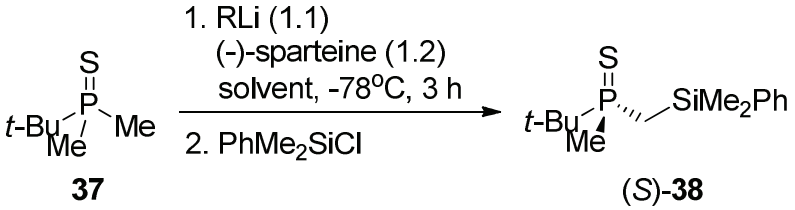


Scheme 16.

Although not crucial in asymmetric deprotonation of dimethylphosphine derivatives, preformation of the chiral base was necessary in this case to obtain stereoselective reaction, thus ortho-lithiation is more rapid than *n*-butylllithium complexation by (–)-sparteine. No difference in enantioselectivity was observed between experiments with lithiation carried out for 1 and 12 h, also, carrying

out the reaction with tin reagent at –35°C had very little effect on the ee value which suggests that diastereomeric intermediate complexes of *ortho*-lithiated substrate with sparteine do not interconvert at this temperature.

In 2010 O'Brien et al. published an important publication dealing with the stereoinduction mechanism in the reactions of dimethylphosphine sulfide with organolithium-sparteine complexes as well as stereochemical stability of α-lithiated intermediates. [44] Experiments using different organolithium compounds with (–)-sparteine carried out by the group gave deeper understanding of the factors influencing the yield and stereoselectivity of asymmetric deprotonation/silylation of *tert*-butyldimethylphosphine sulfide **37** (Scheme 17, Table 3). In accordance with the findings of Evans et al. the use of *n*-BuLi provided the product with higher ee than *s*-BuLi, while MeLi caused further decrease in stereoselectivity and the yield was low. Interestingly, more sterically hindered and weaker base $TMSCH_2Li$ gave a similar result to *n*-BuLi. Also, the reaction was stereoselective in diethyl ether or toluene, but not in THF.



37 (*S*)-**38**

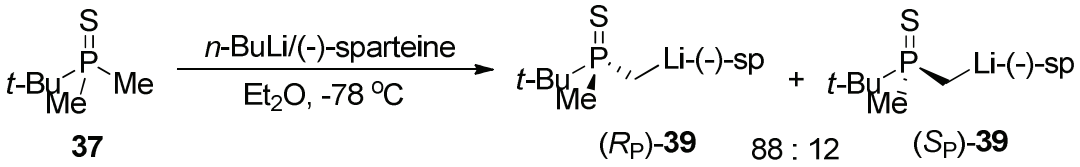
Scheme 17.

Table 3.

entry	RLi	solvent	yield (%)	ee (%)
1	*n*-BuLi	Et_2O	88	76
2	*s*-BuLi	Et_2O	74	68
3	MeLi	Et_2O	17	58
4	$TMSCH_2Li$	Et_2O	92	76
5	*n*-BuLi	toluene	90	78
6	*n*-BuLi	THF	100	10

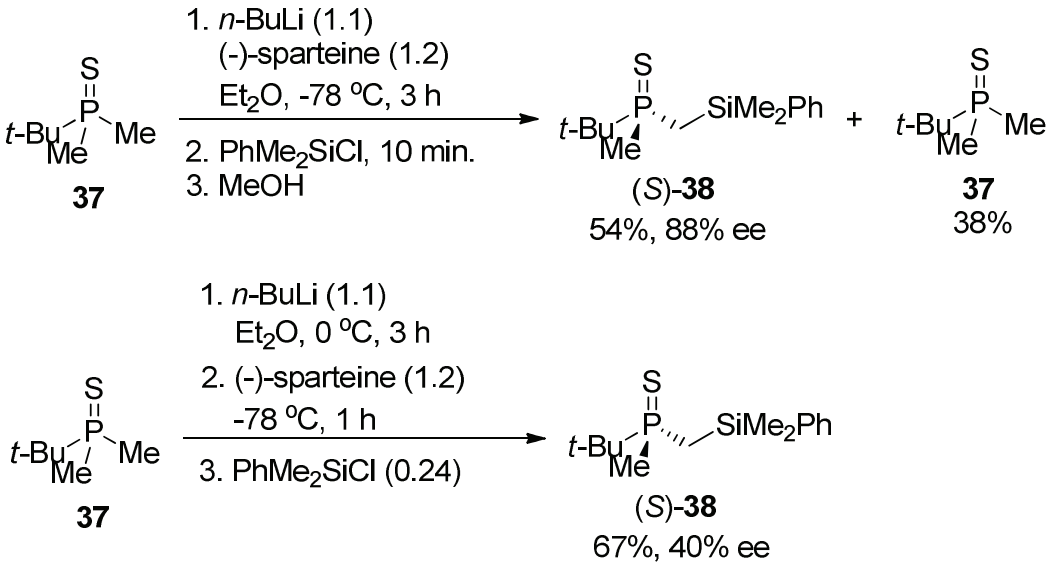
The authors established based on experimental and computation results that deprotonation of phosphine sulfide **37** with the *n*-BuLi/(–)sparteine complex in diethyl ether at –78°C leads to a mixture of two diastereomeric complexes (R_P)-**39** and (S_P)-**39** in a ratio of 88:12 (Scheme 18). The energy difference for transition states leading to

the formation of the two isomers with R_P and S_P configurations was calculated to be 4 kJ/mol.



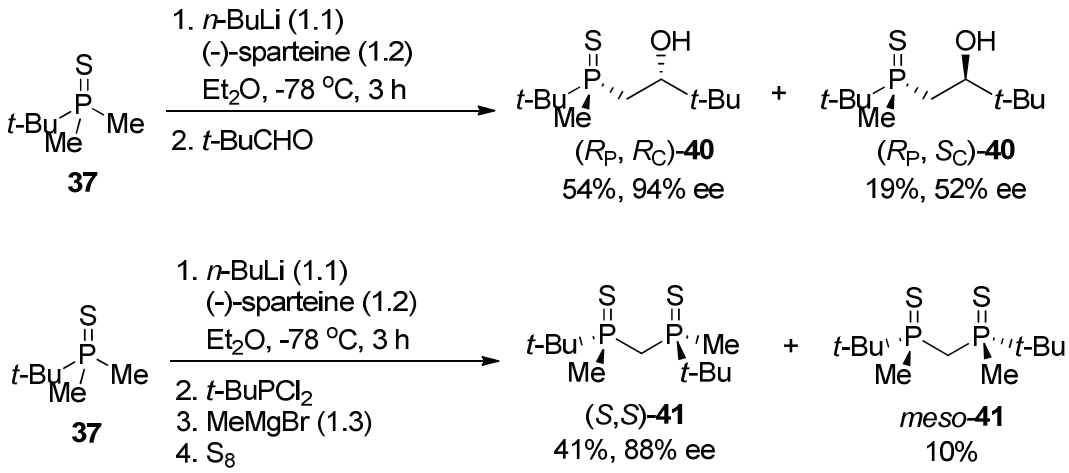
Scheme 18.

Moreover, the enantiomeric excess of the silylated product was 88%, thus the major isomer reacts faster with $Me_2PhSiCl$ than the minor one. This was confirmed with the control reaction using a deficiency of the electrophile and equimolar amounts of (R_P)-**39** and (S_P)-**39** complexes formed through non-stereoselective deprotonation with *n*-BuLi at 0°C and subsequent complexation of α-lithiated phosphine sulfide with (−)-sparteine at –78°C, temperature at which (R_P)-**39** and (S_P)-**39** do not interconvert (Scheme 19).



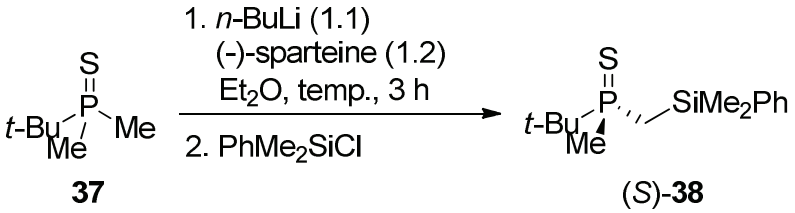
Scheme 19.

Another finding was that the reactions of enantiomerically enriched α-lithiated intermediates with prochiral reagents such as pivaldehyde and *tert*-butyldichlorophosphine lead to products with even higher enantiomeric excess (Scheme 20).



Scheme 20.

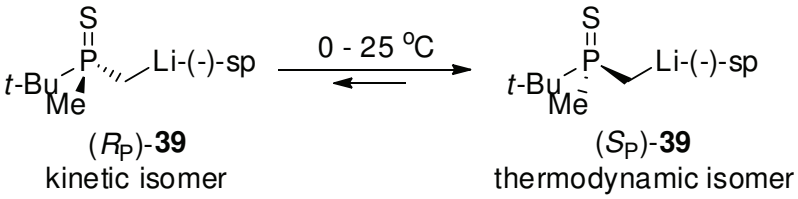
Research on the influence of the lithiation temperature on deprotonation/silylation stereoselectivity showed that low temperature is crucial for high enantioselectivity and the best result was obtained when the reaction was carried out at –90°C (Scheme 21). Interestingly, after lithiation at 0°C or 20°C the obtained product **38** had an opposite configuration at the phosphorus atom compared to experiments at –50°C and below. The same enantiomer was obtained when the reaction mixture, after lithiation at –78°C, was warmed to 25°C.



entry	temp. (°C)	yield (%)	er (*S*/*R*)
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

Scheme 21.

The finding suggests that at sufficiently high temperature diastereomeric complexes (R_P)-**39** and (S_P)-**39** interconvert in thermodynamic equilibration process (Scheme 22). The thermodynamic isomer (S_P)-**39** was characterized with X-ray crystallography and the crystal structure revealed tetracoordinated lithium atom in which, aside from the C-Li bond and the coordinating bonds from sparteine, the thiophosphoryl group acts as a ligand as well (Fig. 2).



Scheme 22.

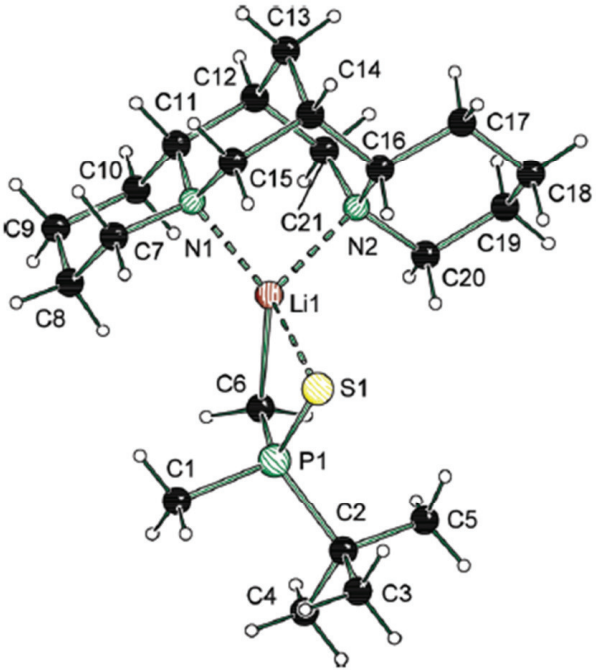
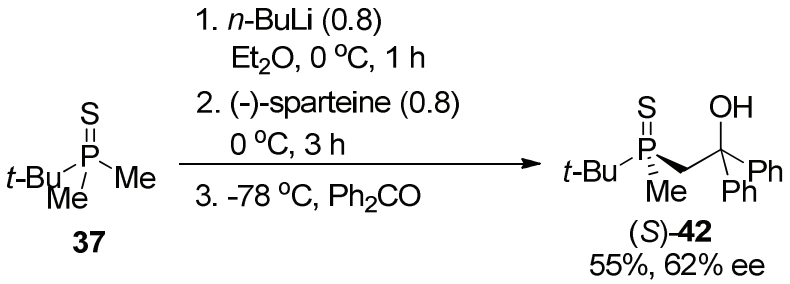


Fig. 2. Molecular structure of major diastereomer (S_P)-39 in the crystal.

After optimization of the conditions for dynamic thermodynamic resolution of lithiated *tert*-butyldimethylphosphine sulfide the product with the opposite configuration at the phosphorus atom compared to the reaction under kinetic control was obtained with moderate enantioselectivity (Scheme 23).



Scheme 23.

Although out of the scope of this review, worth mentioning is asymmetric alkylation of racemic secondary phosphine-boranes with methyl iodide and benzylic halides based on dynamic resolution using *n*-BuLi/(–)-sparteine complex carried out earlier with success by Wolfe and Livinghouse [45].

2.1. Sparteine surrogate

BuLi/(–)-sparteine complexes have found wide application in stereoselective synthesis of not only organophosphorus compounds but also an array of many other classes of compounds. However, at the peak time of (–)-sparteine's popularity among researchers working in the field of asymmetric synthesis (+)-sparteine was much less available and more expensive as it is prepared semi-synthetically through a tedious process from lupanine [46], thus a great effort has been put into finding diamines that would be complementary or could even substitute for (–)-sparteine. More recently periodic lack of commercial availability of (–)-sparteine has also been a recurring problem and its price has increased considerably. [57–59]. As of February 2020 both enantiomers are available from Sigma-Aldrich and (–)-sparteine costs more than (+)-sparteine (prices of analytical grade reagents are 596 PLN/100 mg and 498 PLN/1 g respectively). [60]

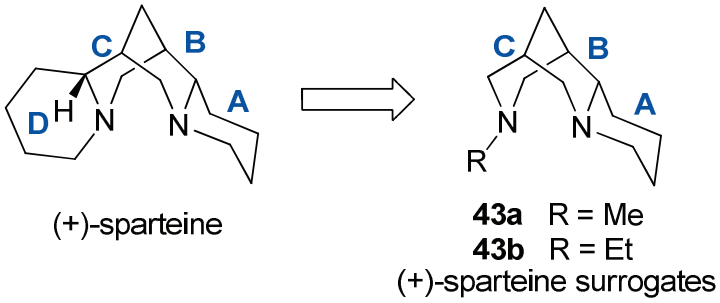
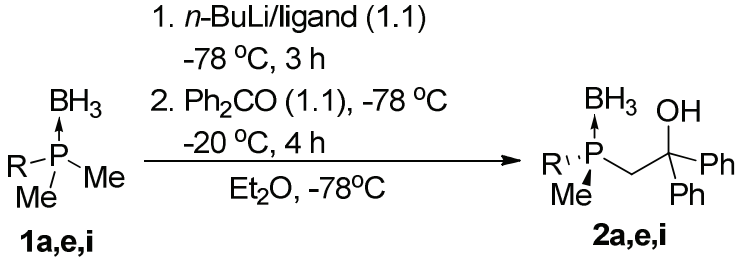


Fig. 3. D-ring removal from (+)-sparteine.

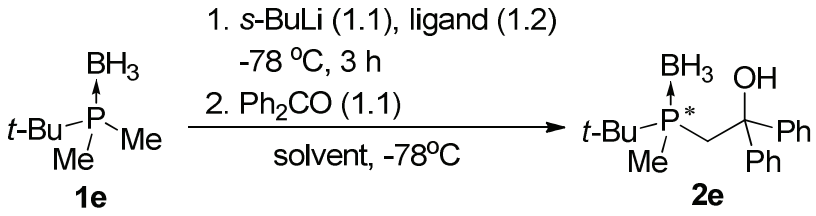
The first diamine which was used with success as (+)-sparteine surrogate in asymmetric deprotonation of N-Boc-pyrrolidine was **43a** devoid of the D ring (Fig. 2). [47] In 2004 the Kann group tested several analogues of **43a** for asymmetric deprotonation of aryl- and alkyldimethylphosphine-boranes. (+)-Sparteine surrogate **43a** gave the best results in all cases except for phenyldimethylphosphine-borane for which slightly higher enantioselectivity was obtained with the N-ethyl analogue **43b** (Scheme 24) [48, 49].



1a,e,i **2a,e,i**

		(-)-sparteine			(+)-**43a**		
	R	yield (%)	ee (%)	R/S	yield (%)	ee (%)	R/S
2a	Ph	87	78	(*S*)	89	67	(*R*)
2e	*t*-Bu	83	76	(*S*)	78	92	(*R*)
2i	*c*-Hex	67	70	(*S*)	77	73	(*R*)

Scheme 24.



1e **2e**

entry	ligand	solvent[a]	yield (%)	er (*S*:*R*)
1	(-)-sparteine	Et_2O	88	95:5
2	(-)-sparteine	THF	30	50:50
3	(+)-**35a**	Et_2O	89	5:95
4	(+)-**35a**	THF	44	12:88
5	(+)-**35a**	THF[b]	78	9:91

[a] c = 0,1 M

[b] c = 0,3 M

Scheme 25.

O'Brien et al. compared *s*-BuLi/(–)-sparteine and *s*-BuLi/(+)-sparteine surrogate complexes in asymmetric deprotonation of *tert*-butyldimethylphosphine-borane **1e** using diethyl ether and THF as solvents (Scheme 25). Surprisingly, the reaction with the (+)-sparteine surrogate could be stereoselectively carried out in THF which is not the case for (–)-sparteine. [50]

A similar result was obtained in asymmetric lithiation of N-Boc-pyrrolidine and phenylpropyl carbamate which prompted the authors to elucidate the structures of *s*-BuLi complexes with (–)-sparteine and (+)-sparteine surrogate in both solvents. *i*-PrLi was used as the model for *s*-BuLi. The analysis of ^{6}Li NMR and ^{13}C NMR spectra revealed that in diethyl ether *i*-PrLi forms a heterodimer with (–)-sparteine (Fig. 3, structure A) and homodimer with (+)-sparteine surrogate (Fig. 4, structure B).

A much greater difference in the coordinating properties of sparteine and its surrogate was found in THF. A weak signal from complexed *i*-PrLi appeared on the ^{6}Li NMR spectrum only after the addition of 3 eq. of (–)-sparteine, thus the complexing properties of sparteine in this solvent are much weaker. However, with (+)-sparteine surrogate the signal from monomeric complex with *i*-PrLi (Fig. 3, structure C) appeared on the ^{6}Li NMR spectrum even with 0.5 eq. of the ligand and with 1.0 eq. this was the only signal present on the spectrum.

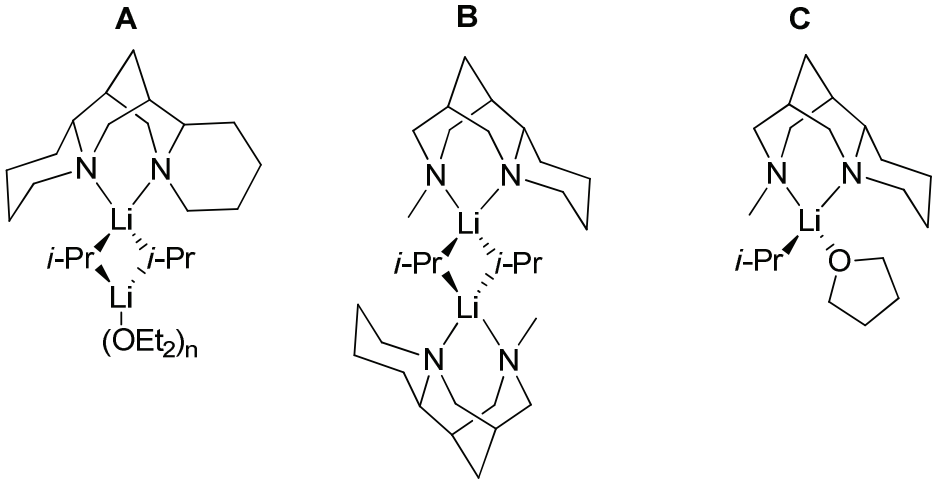
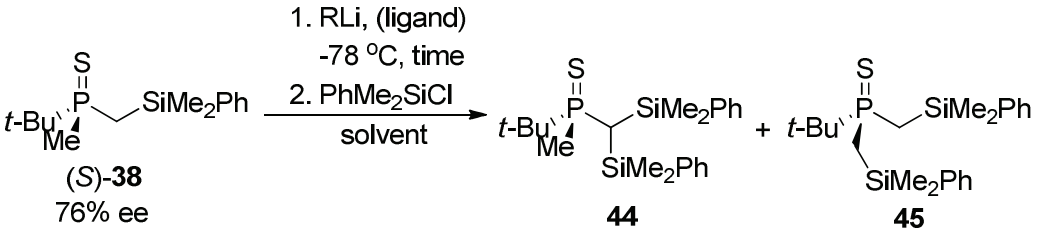


Fig. 4. Structures of *i*-PrLi complexes with (–)-sparteine and (+)-sparteine surrogate found in ethereal solutions

2.2. Regioselective lithiation of silylated dimethylphosphine derivatives

As shown in the previous section the utility of butyllithium/sparteine-mediated asymmetric deprotonation as a technique to obtain chiral phosphine ligands is limited by the lack of natural source of (+)-sparteine which means accessing chiral phosphine ligand precursors with opposite configuration requires the synthesis of (+)-sparteine or its surrogates. O'Brien proposed an alternative solution to this problem relying on regioselective lithiation of α-silylated dimethylphosphine derivatives obtained through enantioselective deprotonation using butyllithium/(-)-sparteine as the chiral base (Scheme 26) [51].

Enantioenriched phosphine sulfide **38** subjected to deprotonation with *n*-BuLi followed by the addition of $PhMe_2SiCl$ affords α,α-disilylmethylphosphine sulfide **44** as a result of selective lithiation at the more acidic methylene group. However, under the same reaction conditions switching to more hindered *s*-BuLi as the base led to a 50:50 mixture of **44** and **45**. The authors were able to considerably increase the selectivity of deprotonation towards less sterically hindered methyl group to a 85:15 ratio through the addition of *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) as a ligand for *s*-BuLi increasing steric bulk of the base, shortening the lithiation time to 1.5 h and using THF as the solvent.



RLi	time	solvent	**44**:**45**[a]	**44** yield[b]	**45** yield[b]
n-BuLi (1.1)	3 h	Et_2O	100:0	68%	0%
s-BuLi (1.1)	3 h	Et_2O	50:50	32%	50%
s-BuLi (1.5), PMDETA (1.5)	1.5 h	THF	15:85	14%	72%

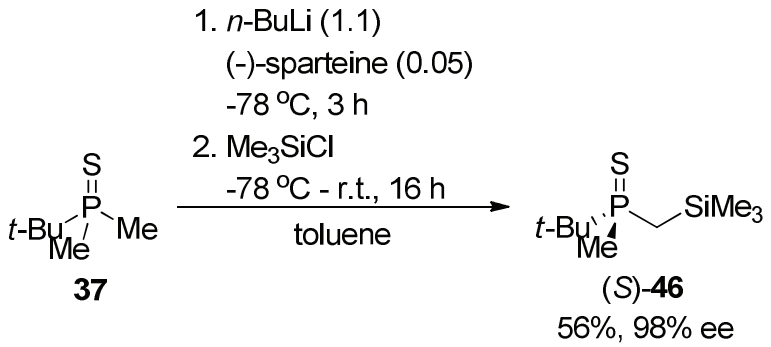
[a] ratio determined based on ^1H NMR spectrum of the crude mixture

[b] isolated yields

Scheme 26.

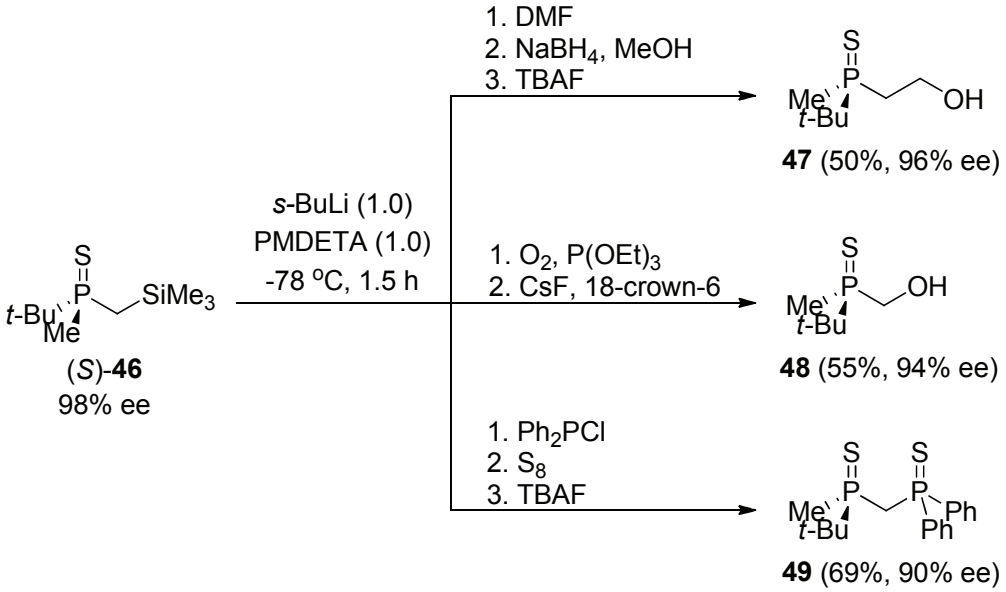
Although the method was proved to be viable, silylated phosphine sulfide **38** was not suitable as a starting point for the synthesis of chiral phosphine ligands as it could not be recrystallized

to obtain an enantiopure sample. This problem was solved by using TMSCl as the silylating agent for lithiated *tert*-butyldimethylphosphine sulfide **37** which led to the formation of α-(trimethylsilyl)methylphosphine sulfide **46** that was easily recrystallized affording the compound with very high enantiopurity (Scheme 27).



Scheme 27.

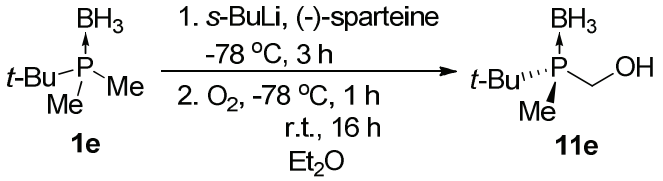
Using the regioselective lithiation of (*S*)-**46** with *s*-BuLi/PMDETA followed by electrophilic quench and subsequent desilylation the authors prepared phosphine derivatives **47**-**49** with opposite configuration at the phosphorus atom compared to direct transformations of *tert*-butyldimethylphosphine sulfide **37** using *n*-BuLi/(-)-sparteine as the base (Scheme 28).



Scheme 28.

2.3. Asymmetric deprotonation with catalytic sparteine

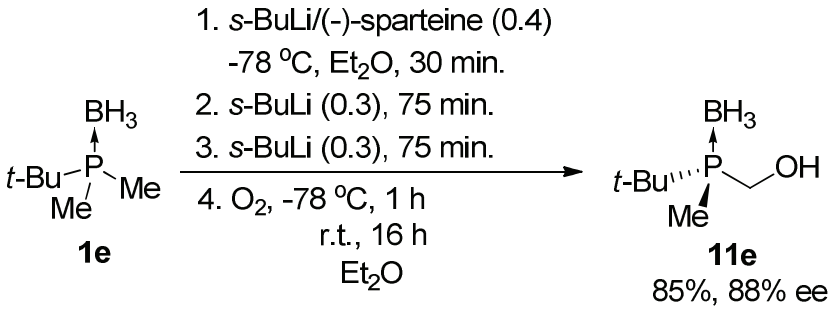
The first attempts to carry out asymmetric deprotonation with catalytic sparteine date back to 1994 and the publication of Beak et al. on the lithiation of N-Boc-pyrrolidine and trapping the intermediate with TMSCl. However, decreasing the amount of sparteine to substoichiometric quantity caused considerable drop in enantioselectivity [52].



(-)-sp (eq.)	yield (%)	ee (%)
1.2	65	84
0.5	61	74
0.2	57	54

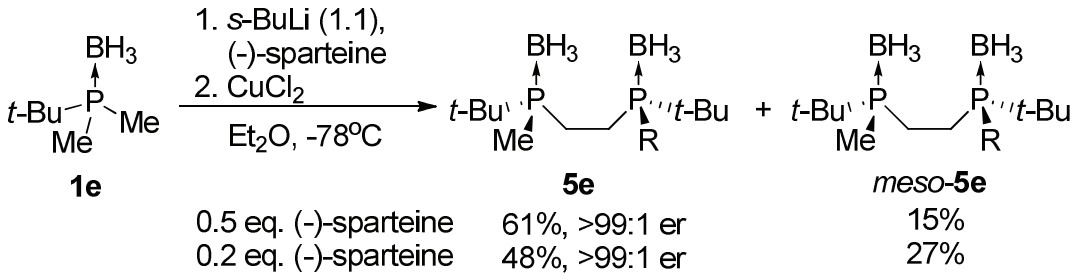
Scheme 29.

A similar outcome was obtained by O'Brien et al. who attempted asymmetric lithiation/hydroxylation of phosphine-borane **1e** with catalytic sparteine (Scheme 29). [53] However, they managed to achieve considerable increase in enantioselectivity with sequential addition of *s*-BuLi in three portions in order to prevent deprotonation of the substrate with uncomplexed base (Scheme 30). [55]

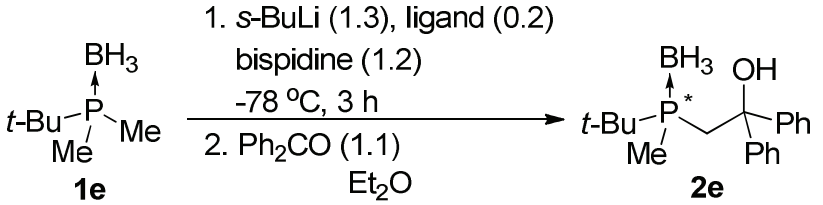


Scheme 30.

On the other hand Cu-mediated homocoupling was successfully carried out in the presence of 0.5 and 0.2 eq. of sparteine and enantiopure product was obtained in both cases (Scheme 31). As the authors point out, the most likely explanation for high stereoselectivity is chiral amplification. [53]



Scheme 31.



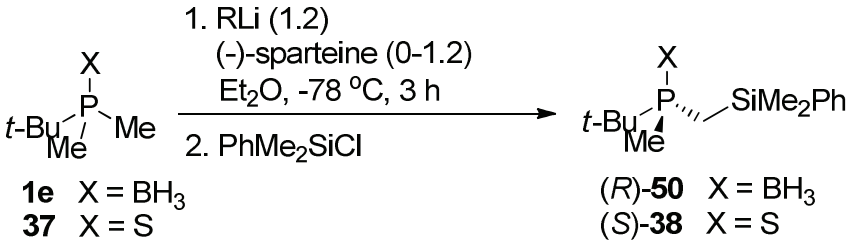
ligand	yield (%)	er (*S*:*R*)
(-)-sparteine	67	83:17
(+)-**35a**	68	11:89

Scheme 32.

Another approach proposed by O'Brien to reduce the amount of sparteine is the use of bispidine, a more sterically hindered achiral diamine which forms a complex with *s*-BuLi that does not deprotonate the substrate but can undergo ligand exchange with the α-lithiated intermediate complexed with sparteine or sparteine surrogate (Scheme 32). This approach was also used with success for *N*-Boc-pyrrolidine and *O*-phenylpropyl-carbamate [56].

O'Brien et al. also showed that the choice of organolithium base is crucial to obtain optimally stereoselective reaction depending on the phosphine derivative used. Comparison of asymmetric lithiation/silylation of *tert*-butyldimethylphosphine-borane and sulfide with stoichiometric and substoichiometric sparteine revealed a major difference in the behavior of the two phosphine derivatives (Scheme 33, Table 4). [54] The results with stoichiometric sparteine confirmed the findings of Evans that the complex of *s*-BuLi gives the product with higher ee for phosphine-boranes and for phosphine sulfides the complex of *n*-BuLi is more suitable (Table 4, Entries 1 & 4). With 0.2 eq. of sparteine the use of *s*-BuLi caused a drastic

drop in ee both for the borane and sulfide, but the yield stayed at the same level (Table 4, Entry 2). With *n*-BuLi decrease in ee was around 10% for both derivatives, however, in case of phosphine-borane the yield of the product was only 21% (Table 4, Entry 5). Moreover, when *n*-BuLi was used without sparteine no reaction took place for the phosphine-borane and the yield was reduced for the phosphine sulfide (Table 4, Entry 6), this is in sharp contrast to reactions with *s*-BuLi alone (Table 4, Entry 3) which gave comparable yields to the reactions with *s*-BuLi/sparteine complex.



Scheme 33.

Table 4.

			X = BH_3		X = S	
no.	RLi	(-)-sparteine (eq.)	yield (%)	ee (%)	yield (%)	ee (%)
1	*s*-BuLi	1.2	74	84	74	68
2		0.2	76	48	75	20
3		0	70	0	83	0
4	*n*-BuLi	1.2	76	78	88	76
5		0.2	21	68	82	66
6		0	0	0	45	0

In case of the phosphine sulfide with *s*-BuLi non-stereoselective deprotonation by uncomplexed organolithium competes with stereoselective deprotonation by the *s*-BuLi/sparteine complex and enantioselectivity is very low, with *n*-BuLi deprotonation with uncomplexed organolithium is much slower and the catalytic process predominates. In case of the phosphine-borane the catalytic process does operate with *s*-BuLi, but competing deprotonation by uncomplexed organolithium lowers the ee considerably. With *n*-BuLi it is not possible to have a catalytic reaction as *n*-BuLi is most likely not capable of freeing sparteine from the complex with α-lithiated

substrate and the second step of the cycle does not take place (Table 4, Entry 5).

These results suggest that the α-position in dimethylphosphine-boranes is less acidic than in the corresponding phosphine sulfides, also, coordination of the thiophosphoryl group to the lithium atom likely aids in lithiation as well as the transfer of sparteine from α-lithiated intermediate to uncomplexed base.

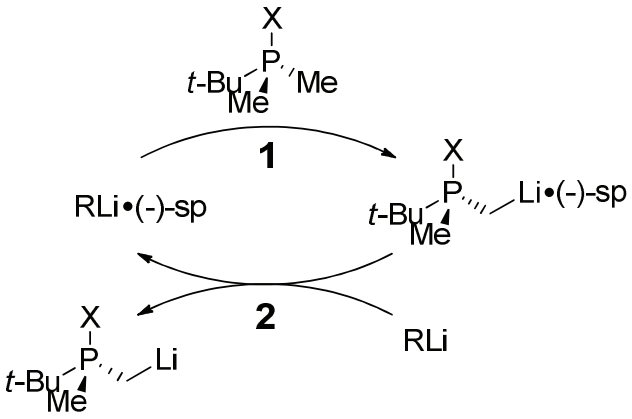


Fig. 5. Catalytic cycle of sparteine-mediated asymmetric deprotonation.

3. CONCLUSIONS

As disclosed in this review, the asymmetric desymmetrization of heteroleptic phosphine derivatives using butyllithium/sparteine or sparteine surrogate complexes as chiral bases combined with the reactions of enantioenriched α-lithiated intermediates with a wide spectrum of electrophiles and oxidative homocoupling is a powerful tool that has been used to prepare both known and new chiral phosphine ligands with the application in stereoselective transition metal catalysis. This approach complements the more traditional methods for obtaining enantiopure organophosphorus compounds based on the resolution of molecular complexes of phosphine oxides and phosphonium salts or installing chiral auxiliary groups at the phosphorus atom. Recently published research shows that the method still has great potential which has not been fully realized.

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