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Directed *Ortho*-Lithiation of Aminophosphazenes: An Efficient Route to the Stereoselective Synthesis of *P*-Chiral Compounds

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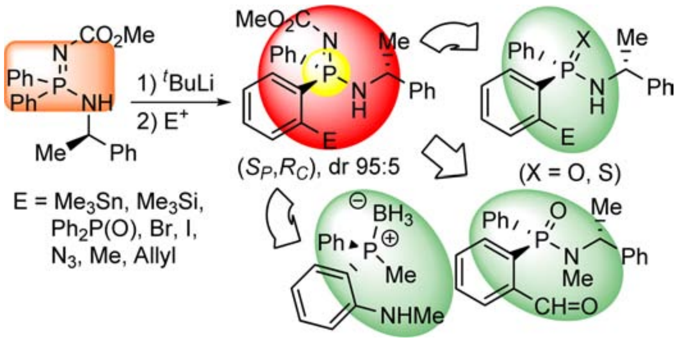
ABSTRACT



***Ortho*-directed lithiation of *P*,*P*-diphenylaminophosphazenes followed by electrophilic quench is described as an efficient process for synthesizing *P*-chiral *ortho*-functionalized derivatives in high yields and diastereoselectivities. The method allows the tunable preparation of structurally diverse enantiopure *P*-chiral compounds including phosphinic and phosphinothioic amides, phosphinic esters, phosphine oxides, and *o*-aminophosphines.**

The enantioselective deprotonations of prochiral PMe_2 moieties of phosphine-boranes and sulfides are well-established methods to synthesize *P*-chiral compounds.[1] Both enantiomers can be prepared by using alkyllithiums in the presence of stoichiometric[2] or catalytic[3] amounts of (−)-sparteine and (+)-sparteine surrogates as bases. In contrast, the stereoselective deprotonation of enantiotopic PPh_2 groups has been much less studied. Recently, we reported the desymmetrization of diphenylphosphinic amides via directed *ortho*-lithiation (D*o*Li)-electrophilic trapping reactions.[4] Although diverse functionalities could be introduced, the stereoselectivities obtained were low (dr[4a] $\leq$ 5:1; ee[4b] of 60%). Furthermore, *ortho*-lithiation of

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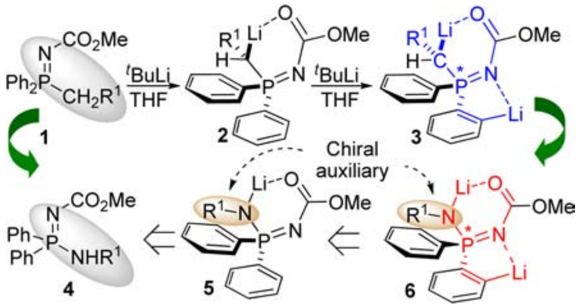
chiral phosphinothioic amides proceeded without chiral induction.[5]

We have shown that C_α-lithiated phosphazenes **2** are effective directors of *ortho*-lithiations leading to *like* C_α, C_{ortho} dianions **3** in which the Ph_2P moiety has been desymmetrized (Scheme 1).[6] Although **3** is configurationally stable, the very low barrier of racemization of the precursor C_α-anion **2** renders this route inefficient for the synthesis of enantiopure products. We reasoned that aminophosphazenes **4** may behave similarly to phosphazenes **1** in D*o*Li reactions[7] providing access to a new family of N, C_{ortho} dilithiated species **6** in which chirality could be easily introduced via the amino fragment.

Scheme 1. Rational for D*o*Li of Aminophosphazenes

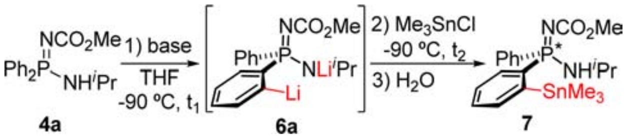


Herein, we report an efficient procedure for the N, C_{ortho} double deprotonation of aminophosphazenes **4** and the *ortho*-functionalization of the dianion through carbon–carbon and carbon–heteroatom bond-forming reactions with a series of electrophiles, the extension of the method to *C*-chiral aminophosphazenes, and its application to the highly stereoselective synthesis of structurally diverse *P*-chiral organophosphorus compounds.

The aminophosphazenes used in this study were prepared through one-pot reactions of Ph_2PCl with the corresponding amine and subsequent addition of N_3CO_2Me. Precipitation from Et_2O furnished compounds **4** in high yield (≥85%, Supporting Information (SI)).

At the start of our investigation, we studied the *ortho*-lithiation of aminophosphazene **4a** using Me_3SnCl as the electrophile for establishing the degree of C_{ortho}-lithiation achieved (Table 1). We have found that dilithiation of **4a** is efficiently accomplished by the reaction with 3 equiv of ^{t}BuLi in THF at −90 °C for 15 h. The reaction of the dianion **6a** formed with Me_3SnCl afforded stannane **7** in 95% conversion (Table 1, entry 7; 90% isolated yield). The conversion decreased notably by reducing the time of metalation (entry 6) and/or the amount of base added (entries 3, 4). Lithiation with a larger excess of base (4 equiv) during 9 h at −70 °C also resulted in lower conversion (entry 5). The use of ^{n}BuLi in the presence of TMEDA as base at either −90 or −70 °C failed to produce *ortho*-lithiation (entries 1, 2).

Table 1. *Ortho*-Lithiation–Stannilation of Aminophosphazene **4a**



entry	base	equivalents[a]	t_1 (h)	t_2 (h)	conversion (%)[b]
1	^{n}BuLi/TMEDA	2.2	9	12	0
2[c]	^{n}BuLi/TMEDA	2.2	9	12	0
3	^{t}BuLi	2.2	2	12	34
4	^{t}BuLi	2.2	9	12	44
5[c]	^{t}BuLi	4	9	1.5	80
6	^{t}BuLi	3	9	12	77
7	^{t}BuLi	3	15	1.5	95

[a] Equimolar amounts of base and electrophile were used. [b] Determined based on $^{31}P\{^1H\}$ NMR spectra. [c] Reaction performed at −70 °C.

Once optimized reaction conditions for the C_{ortho}-lithiation–stannilation of **4a** were available, we examined the reactivity of dianion **6a** toward a variety of electrophiles (Table 2). These include heteroatom- and carbon-based halides (Me_3SiCl, $Ph_2P(O)Cl$, MeI, allylBr), 1,2-diiodoethane as an I^+ synthetic equivalent, and $Ph_2C{=}O$. In all cases the reaction proceeded smoothly to give *ortho*-functionalized products **7**–**14** in high yield. In the reaction with benzophenone a mixture of adduct **13** (15%) and the heterocycle **14** (72%) formed via cyclocondensation of **13** with elimination of isopropyl amide was obtained. Purification through flash column chormatography (ethyl acetate/hexane 2:1) afforded **14** in 50% yield.

The products in Table 2 indicate that the D*o*Li methodology is a valuable method for synthesizing new *ortho*-functionalized aminophosphazenes showing wide structural diversity. Furthermore, products **7**, **8**, and **10** can be considered as precursors for additional manipulations via metal-mediated cross-coupling reactions.[8] Compound **9** containing two different P=X groups may be envisaged

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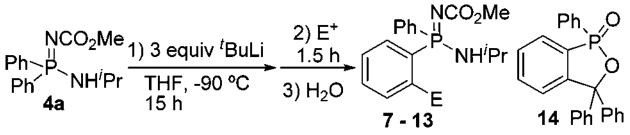
Table 2. *Ortho*-Lithiation−Substitution of **4a**



entry	E$^+$	E	product	conversion (%)[a]	yield (%)
1	Me_3SnCl	Me_3Sn	**7**	95	90
2	Me_3SiCl	Me_3Si	**8**	90	75
3	$Ph_2P(O)Cl$	$Ph_2P(O)$	**9**	88	60
4	ICH_2CH_2I	I	**10**	84	75
5	MeI	Me	**11**	88	75
6	AllylBr	Allyl	**12**	95	90
7	$Ph_2C{=}O$	$Ph_2C{-}OH$	**13** + **14**	15(**13**)/72(**14**)	50(**14**)

[a] Established based on $^{31}P\{^1H\}$ NMR spectra.

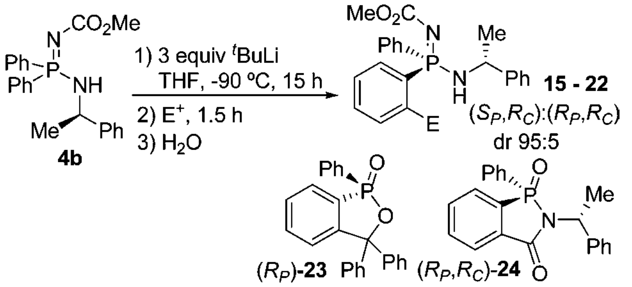
as a new chelating hemilabile ligand with potential applications in coordination chemistry.[9]

Next, we sought to extend the scope of the process to chiral aminophosphazene **4b** containing the readily accessible (*R*)-α-methylbenzylamine as a chiral auxiliary. We were pleased to find that the *ortho*-lithiation of **4b** under the conditions optimized for **4a** followed by the addition of Me_3SnCl gave the *ortho*-stannyl derivative **15** in very high yield (94%) and diastereoselectivity (dr of 95:5) (Table 3, entry 1). The major stereoisomer could be readily isolated through flash column chromatography. The synthesis of **15** represents the most efficient desymmetrization of a Ph_2P moiety reported to date.

The high diastereoselectivity observed in the formation of **15** implies that the *ortho*-deprotonation of one of the diastereotopic *P*-phenyl rings of **4b** is largely favored and that the *ortho*-anion generated is configurationally stable during the 15 h needed to complete the lithiation step. These features allow the preparation of new chiral derivatives through anion trapping with electrophiles. The results are shown in Table 3. In all cases, the ^{31}P NMR spectra of the crude reaction mixtures showed that the diastereoselectivity attained in the *ortho*-lithiation was preserved in the final products. The reaction with Me_3SiCl and $Ph_2P(O)Cl$ lead to the silyl and phosphoryl products **16** and **17**, respectively, in high yield (entries 2, 3). Bromination and iodination of the *ortho*-anion of **4b** by quenching with BrCN and $(CH_2)_2I_2$, respectively, provided the appropriate halogenated aminophosphazenes **18** and **19** (entries 4, 5)

Crystals of **19** suitable for X-ray diffraction were grown from a diethyl ether solution at ambient temperature. The X-ray structure allowed the absolute configuration as (S_P,R_C) to be established (Table 3, SI). Based on the lithiation procedure used we assigned the same configuration to the major stereoisomer of all *ortho*-substituted aminophosphazenes synthesized. The treatment of the *ortho*-anion with tosyl azide afforded the valuable *o*-azido derivative **20** in high yield (entry 6). C−C bond-forming reactions also proceeded efficiently. Alkylation with MeI and allylBr furnished the respective *ortho*-methylated, **21**, and allylated, **22**, products (entries 7, 8). The reactivity toward carbonyl reagents was assayed using benzophenone and methyl chloroformate as electrophiles. The products obtained were the heterocyclic phosphinic ester **23** and amide **24**, respectively (entries 9, 10). A reasonable mechanism explaining the formation of these compounds is given in the SI. We assume that nucleophilic attack to the PN linkage involved in the synthesis of **23** proceeds with inversion of configuration at phosphorus.

Table 3. Diastereoselective *ortho*-Lithiation−Substitution of **4b**



entry	E$^+$	E	product	yield (%)
1	Me_3SnCl	Me_3Sn	**15**	94
2	Me_3SiCl	Me_3Si	**16**	93
3	$Ph_2P(O)Cl$	$Ph_2P(O)$	**17**	70
4	BrCN	Br	**18**	75
5	ICH_2CH_2I	I	**19**	89
6	$TosN_3$	N_3	**20**	85
7	MeI	Me	**21**	78
8	AllylBr	Allyl	**22**	85
9	$Ph_2C{=}O$		**23**	50
10	MeO_2CCl		**24**	50

Phosphazenes can be easily converted into other phosphorus-containing functional groups. We envisaged that D*o*Li reactions of chiral aminophosphazenes combined with functional group transformations may be a useful synthetic strategy for accessing the structurally diverse enantiopure *P*-chiral compounds. These are important ligands[1b,c,3a,3b,10] and organocatalysts[11] in asymmetric synthesis. The aza-Wittig[12] reaction of **19** and **21** with phenylisothiocyanate is assumed to take place with retention of the *P*-configuration to give the enantiopure phosphinothioic amides **25** and **26**, respectively, in good yield (Scheme 2).[13]

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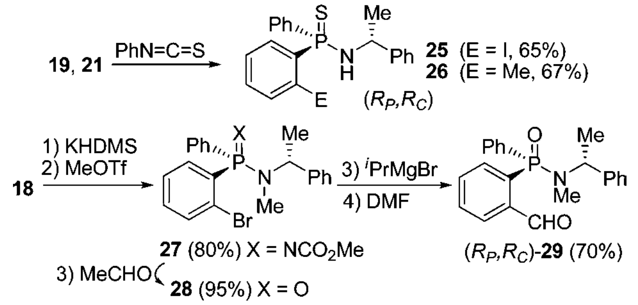
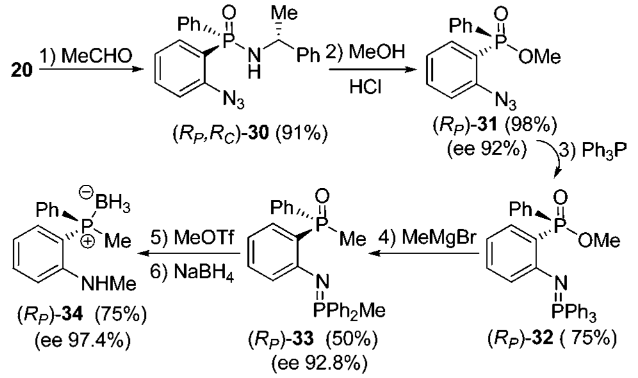
More elaborated difunctional products such as *o*-formylphosphinic amide **29** can be easily prepared starting from aminophosphazene **18**. Deprotonation with KHMDS and subsequent addition of methyl triflate produced the *N*-methylated derivative **27**. The latter undergoes P=N to P=O conversion by reaction with acetaldehyde,[12d] and the phosphinic amide **28** obtained is transformed into (R_P,R_C)-**29** through Grignard formation with ^{i}PrMgBr followed by quench with DMF.[13] The syntheses of **25**–**27** represent the most efficient route to *P*-chiral *o*-functionalized phosphinic[4] and phosphinothioic[5] amides described to date. Furthermore, the formyl group of **29** opens the way to additional straightforward derivatization, e.g., via imine formation reactions.[14]

Scheme 2. Synthesis of *P*-Chiral Compounds via *o*-Desymmetrized Aminophosphazenes



P-Chiral (*ortho*-amino)phosphines are ligands of great interest commonly prepared by resolution of racemates.[15] The stereoselective synthesis of these species remains a challenge. The synthesis of enantiopure *P*-protected (*o*-amino)phosphine (S_P)-**34** nicely illustrate the potential of applications of directed *ortho*-lithiations of aminophosphazenes (Scheme 3). The sequence of transformations begins with the aza-Wittig reaction of **20** with acetaldehyde to yield (R_P,R_C)-**30**.[13] HCl catalyzed methanolysis of this *o*-azidophosphinic amide furnished methyl phosphinate (R_P)-**31** (ee 92%).[16] The Staudinger reaction of this azidoester with Ph$_3$P gave phosphazene **32**, which upon treatment with MeMgBr afforded the phosphine oxide (R_P)-**33** (ee 92.8%) through substitution of a *P*-phenyl ring of the phosphazenyl moiety[17] and the methoxy group by a methyl group.[13,18] Finally, methylation of **33** with MeOTf and subsequent reduction with NaBH$_4$ provided phosphine-borane (R_P)-**34** with excellent optical purity (ee 97.4%).[13,19]

Scheme 3. Stereoseletive Synthesis of *P*-Chiral *o*-Aminophosphine-borane (S_P)-**34**



In conclusion, directed *ortho*-lithiation–electrophilic quench of aminophosphazenes is introduced as a very efficient procedure for desymmetrization of the prochiral Ph$_2$P=N moiety. The usefulness of the method was shown with the preparation under mild reaction conditions of a variety of functionalized *P*-chiral compounds in high yield and excellent stereoselectivity, including phosphinic esters, amides and thioamides, and phosphine oxides, and the first stereoselective synthesis of (2-aminophenyl)phosphine-boranes. The availability of both enantiomers of the chiral auxiliary ensures access to both product antipodes. Further work expanding the applications of this methodology in asymmetric synthesis and in coordination chemistry is in progress.

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Supporting Information Available. Experimental details, suggested mechanism of formation of **23** and **24**, characterization data, and crystallographic data for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.