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Phosphinamide-Directed Benzylic Lithiation. Application to the Synthesis of Peptide Building Blocks

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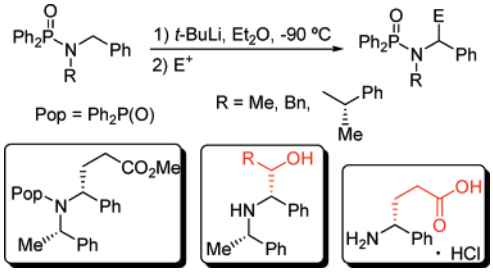
ABSTRACT



***N*-Benzyldiphenylphosphinamides are deprotonated at the NC$_\alpha$ position diastereospecifically upon treatment with *t*-BuLi in diethyl ether at low temperature. The reaction of the anions with alkyl, acyl, and tin halides, aliphatic and aromatic aldehydes, and Michael acceptors allowed installation of a variety of functional groups into the benzylic arm in excellent yields. Cleavage of the P–N linkage affords 1,2-amino alcohols and α-, *β*-, and *γ*-amino acids.**

Dipole-stabilized carbanions adjacent to the nitrogen atom of amides and carbamates have been studied in great detail due to the utility of these synthons in organic synthesis.[1] For instance, they have been used for the stereoselective synthesis of N/C-protected α-, *β*-, and *γ*-amino acids.[2] In contrast, α-aminoalkyl organolithiums stabilized by phosphorus-based functional groups have received much less attention. Savignac et al. described the first *N*-benzylic deprotonation assisted by a P═O group on *N*-benzylphosphoramides and subsequent electrophilic trapping.[3] Although some additional examples have been reported,[4] the scope of this synthetic methodology remains largely unexplored. Further, the attempted NC$_\alpha$ lithiation of *N*-benzyl-*N*-methyldiphenylthiophosphinamide with *s*-BuLi or *t*-BuLi led after electrophilic quench to products of ortho attack exclusively.[5]

We have shown that *N*-benzyldiphenylphosphinamides can be deprotonated in THF at either the benzylic[6] or ortho[7] position (Scheme 1) with excellent regiocontrol. The NC$_\alpha$

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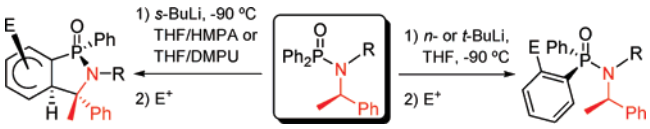
Scheme 1

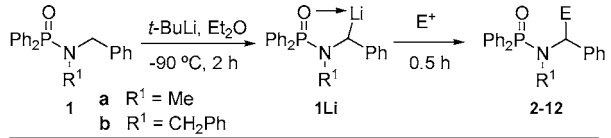


anions undergo dearomatization through anionic cyclization quantitatively.[8] The benzylic anions proved to be stable in diethyl ether and were characterized through NMR.[9]

These results indicate that the deprotonation of *N*-benzylphosphinamides can be tuned by selecting the appropriate reaction conditions. Here we wish to report on the regio- and stereocontrolled NC_α lithiation of *N*-benzyldiphenylphosphinamides and their reactivity toward a broad selection of electrophiles. Dephosphorylation of the new functionalized phosphinamides provides access to important building blocks for organic synthesis such as 1,2-amino alcohols and α-, *β*-, and *γ*-amino acids.

Phosphinamides **1** are smoothly deprotonated by the action of *t*-BuLi in Et_2O at −90 °C to give the NC_α lithiated species **1Li**. Electrophilic quench of the anions affords products **2**−**12** in good to excellent yields (Table 1). Wide structural diversity is achieved through reaction with alkyl halides, aliphatic and aromatic aldehydes, acyl halides, and Michael acceptors (Figure 1). The reaction with aldehydes takes place with moderate to excellent face selectivity (entries 3−6). In all cases the major compound corresponded to the *u* configuration. The diastereoselectivity is sterically controlled since the ratio of epimers increases notably when the alkyl group attached to the nitrogen is the more sterically demanding benzyl group. The formation of a single stereosiomer **6b** in the reaction of lithiated **1b** with pivalaldehyde supports this conclusion (entry 5, Table 1).

Table 1. NC_α Lithiation of **1** and Electrophilic Quench of **1Li**



E+ = MeI, BnBr, PhCHO, Ph(CH2)2CHO, t-BuCHO, CH2=CHCHO, CH2=CHCOMe, CH2=CHCO2Me, ClCO2Me, BrCH2CO2Me, Me3SnCl

entry	E	product	**1a**, yield [%][a,b]	**1b**, yield [%][a,b]
1	Me	**2**	71	63
2	Bn	**3**	82	60
3	PhCHOH	**4**	96 (3:1)	89 (8:1)
4	$Ph(CH_2)_2CHOH$	**5**	95 (2.6:1)	97 (3.8:1)
5	*t*-BuCHOH	**6**	83 (1.8:1)	76 (>99)
6	CH_2=CHCHOH	**7**	90 (5:1)	98 (6.5:1)
7	CH_2CH_2COMe	**8**	70	68
8	$CH_2CH_2CO_2Me$	**9**	78	84
9	CO_2CH_3	**10**	72	76
10	$CH_2CO_2CH_3$	**11**	63	25
11	$SnMe_3$	**12**	70	86

[a] Isolated yields. [b] The diastereomeric ratio *u*:*l* is shown in parentheses.

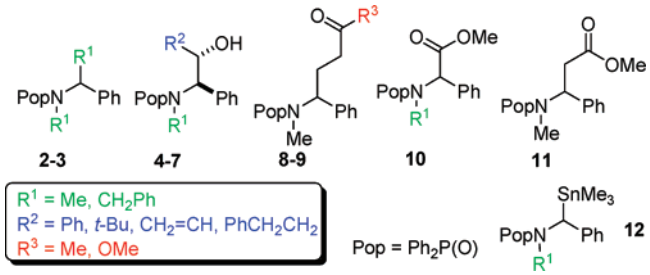


Figure 1. Structural diversity achieved for *N*-Pop derivatives.

Acroleine undergoes [1,2] addition exclusively furnishing **7**, whereas methyl vinyl ketone and methyl acrylate react in a [1,4] manner with total chemoselectivity leading to **8** and **9**, respectively (entries 7 and 8).

The conjugate addition to methyl acrylate represents a facile entry to N- and C-protected γ^4-amino acids (Figure 1).[10] The α and β[10] homologues **10** and **11** also can be prepared in good yields by the respective addition of methyl chloroformiate and methyl bromoacetate to **1Li** (entries 9 and 10, Table 1).[11] In addition, tin may be readily installed at the benzylic position by treating **1Li** with Me_3SnCl (entry 11, Table 1). The stannanes **12a**,**b** thus obtained are interesting reagents for transmetalation and/or cross coupling reactions.[12] The structure of **2**−**12** was assigned based on their spectroscopic data (see the Supporting Information). The relative configuration of **4**−**7** is supported by the magnitude of $^3J_{XY}$ (X = ^{31}P, ^{1}H; Y = ^{13}C, ^{1}H) for the amino alcohol moiety. Compounds **4** were identified previously as byproducts in the dearoamatizing anionic cyclization of **1a** and the same structural motif is present in two ortho-substituted derivatives of *u*-**4** characterized through X-ray diffraction.[8b] Additionally, the X-ray crystal structure of

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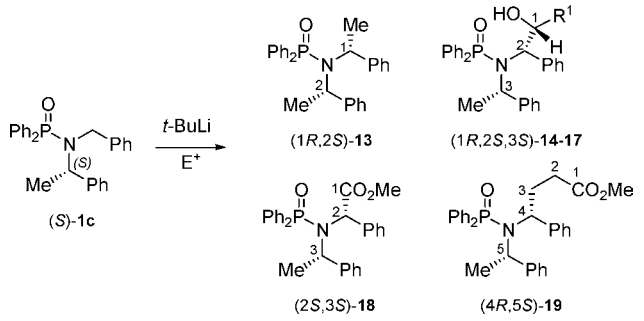
amino alcohol **6b** (Supporting Information) confirmed the assignments of relative configuration made.

Once the synthesis of α-functionalized phosphinamides **2**−**12** was available, we envisaged to enhance the scope of the process by introducing asymmetry. For that purpose we employed the (*S*)-α-methylbenzylphosphinamide, (*S*)-**1c**, which contains a readily accessible chiral auxiliary. We have previously shown that the lithiation of the *N*-methyl analogue of (*S*)-**1c** by *t*-BuLi in THF occurs selectively at the chiral carbon.[13] The benzylic anion formed undergoes anionic cyclization to give enantiomerically pure dearomatized products (Scheme 1, route a). To our delight, treatment of (*S*)-**1c** with *t*-BuLi in Et_2O at −90 °C followed by quenching with the electrophiles shown in Table 2 provides enantio-

Table 2. Reactions of Lithiated (*S*)-**1c** with Electrophiles[a]



entry	electrophile (E^+)	product	yield [%][a]	ratio *u*:*l*
1	MeI	(1*R*,2*S*)-**13**	71	
2	PhCHO	(1*R*,2*S*,3*S*)-**14**[b]	76 (88)	91:9[c]
3	*t*-BuCHO	(1*R*,2*S*,3*S*)-**15**[b]	95 (96)	>99[c]
4	$Ph(CH_2)_2CHO$	(1*R*,2*S*,3*S*)-**16**[b]	81 (97)	88:12[c]
5	CH_2=$CHCHO$	(1*R*,2*S*,3*S*)-**17**[b]	78 (89)	92:8[c]
6	$ClCO_2Me$	(2*S*,3*S*)-**18**	60	
7	CH_2=CH_2CO_2Me	(4*R*,5*S*)-**19**	74	

[a] Isolated yields, numbers in parentheses indicate conversion. [b] Absolute configuration of the major compound **14a**−**17a** isolated. [c] Diastereomeric ratio calculated from ^{31}P NMR data.

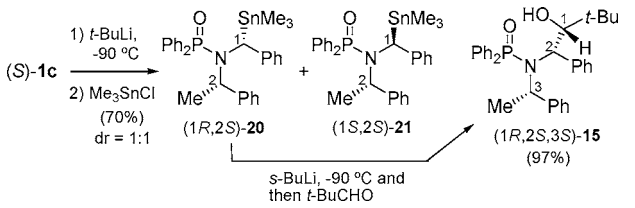
merically pure compounds **13**−**19**, substituted exclusively at the secondary NC_α-center. Product ratios and isolated yields are given in Table 2.

Alkylation with MeI affords the *meso* phosphinamide (1*R*,2*S*)-**13** (Table 2, entry 1).[14] The benzylic anion attacks the CO group of aliphatic and aromatic aldehydes with high preference for the *re* face (entries 2−5). In the case of pivalaldehyde, the reaction proceeds diastereospecifically to give (1*R*,2*S*,3*S*)-**15** (entry 3). The use of methyl chloroformiate and methyl acrylate leads to the respective *N*-phosphoryl α- and γ-amino esters (2*S*,3*S*)-**18** and (4*R*,5*S*)-**19** (entries 6 and 7).

Similar to the achiral series, the magnitude of $^3J_{XY}$ (X = ^{31}P, ^1H; Y = ^{13}C, ^1H) allowed for establishing the absolute configuration of **14**−**17**. Slow evaporation at room temperature of a saturated solution of **15** in ethyl acetate provided X-ray quality crystals. The X-ray structure of **15** confirms the assignment made (Supporting Information). The absolute configuration of γ-amino ester **19** has been established through correlation with the corresponding amino acid (see bellow). We assume that the reaction yielding **18** follows the same stereochemical sense.[2b,15]

The origin of the stereoselectivity in the deprotonation−electrophilic quench sequence could be unraveled by synthesizing **15** through an indirect route involving lithium−tin exchange steps. The reaction of the benzylic anion of (*S*)-**1c** with Me_3SnCl (Scheme 2) furnished a 1:1 mixture of

Scheme 2. Diastereospecific Lithiation of Phosphinamide (*S*)-**1c**



the two possible diasteroisomeric stannanes **20** and **21**. After chromatographic separation, successive treatment of compound **20** with *s*-BuLi and pivalaldehyde gave (1*R*,2*S*,3*S*)-**15** as a single stereoisomer (Scheme 2).

The formation of epimers **20** and **21** may be explained through two conflicting pathways: stannilation of a configurationally unstable carbanion or a benzylic anion configurationally stable which undergo addition to Me_3SnCl both with inversion and retention of configuration. The stereospecific transformation of (*S*)-**1c** into **15** via **20** supports the second assertion.[13] Moreover, assuming that tin−lithium exchange proceeds with retention of configuration,[15] these results also reveal that both the deprotonation and electrophilic quench proceed diastereospecifically, the *pro-R* proton is exclusively removed, and the reactions with carbon-centered electrophiles shown in Table 2 take place with retention of configuration.[16] The diastereospecificity of the lithiation−alkylation of (*S*)-**1c** is a distinguishing feature with respect to the carboxamide analogues.[2c]

The products of benzylic alkylation and acylation of phosphinamides **1** shown so far can be viewed as functionalized amino compounds protected at the nitrogen by a Pop group.[17] Although a number of methods may be used for cleavage of the P−N linkage of tertiary phosphinamides,[18] the efficiency of the deprotection depends on the structure

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(14) Structure confirmed through alternative synthesis via phosphorylation of the appropriate amine.

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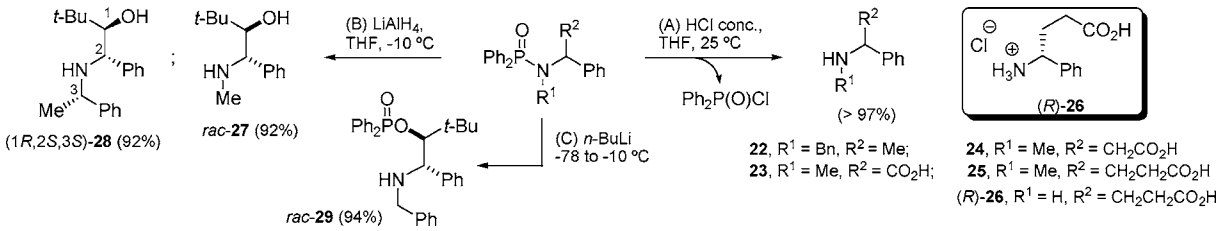
(16) *N*-Boc anilino benzylic anions react with Me_3SnCl with inversion, while tin−lithium exchange occurs with retention of configuration. Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. See also ref 15.

(17) We suggest the use of Pop as an abbreviation for **P(O)Ph**$_2$ by similarity with Boc stabilized benzyllithium anions.

Scheme 3. Synthesis of 1,2-Amino Alcohols and α-, *β*-, and *γ*-Amino Acids through Ephosphinylation of NC_α-Functionalized Phosphinamides[a]



[a] The enantiomeric purity of **25** and **27** was >99, determined by chiral HPLC.

of the substrate. After some experimentation we found that the Ph_2PO group of **2b**, **10a**, **11a**, and (4*R*,5*S*)-**19** can be successfully removed with concentrated HCl in THF at room temperature (Scheme 3, route A). Neutralization with diluted NaOH furnishes the respective secondary amine **22**, and amino acids **23** (α), **24** (*β*), and **25** (*γ*). Under these reaction conditions the phosphorus-containing byproduct formed is recovered as $Ph_2P(O)Cl$, which can be recycled for the synthesis of the starting phosphinamide. Surprisingly, dephosphorylation of (4*R*,5*S*)-**19** affords unprotected (*R*)-**26** directly.[19] Very few stereoselective syntheses of the N/C-protected biologically relevant[10] γ^4-amino acid **26** are available.[2a,20] Moreover, attemps to generate the free amino acid led to the formation of the corresponding *γ*-lactone.[21] The two-step route that converts (*S*)-**1c** into (*R*)-**26** exemplifies nicely the synthetic utility of the methodology described here.

N-Deprotection of **6b** and **15** to give 1,2-amino alcohols **27** and **28**, respectively, is best achieved by $LiAlH_4$ in THF at low temperature (Scheme 3, route B). Interestingly, the treatment of **6b** with *n*-BuLi in THF at −78 °C and subsequent warming to −10 °C promoted the quantitative nitrogen-to-oxygen rearrangement of the $Ph_2P(O)$ group to give **29** (Scheme 3, route C).[22] This lithiation procedure offers the possibility of accessing enantiomerically pure 1,2-amino alcohols selectively protected at the O or N, which are important synthons in organic chemistry.

In summary, we have shown that diphenylphosphinamides are very convenient starting materials for the synthesis of functionalized amines via amino-substituted benzyllithiums. Compared with carboxamides the Pop group provides excellent control of the absolute configuration along the deprotonation−substitution pathway. Lithiation of chiral phosphinamides leads to configurationally stable *N*-benzylic carbanions diastereospecifically, which react with a series of electrophiles to give NC_α-functionalized phosphorus-based compounds diastereospecifically in high yields. Excellent [1,2] vs [1,4] additions have been observed for Michael acceptors. The Pop group can be efficiently removed under a variety of reaction conditions. The potential of N-Pop based chemistry has been demonstrated by the synthesis of 1,2-amino alcohols and α-, *β*-, or *γ*-amino acids. Additional work on enantioselective deprotonations directed by the Pop group is in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and tables of crystallographic data for **6b** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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