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Asymmetric Deprotonation−Substitution of *N*-Pop-benzylamines Using [RLi/(−)-Sparteine]. Enantioselective Sequential Reactions and Synthesis of N-Heterocycles

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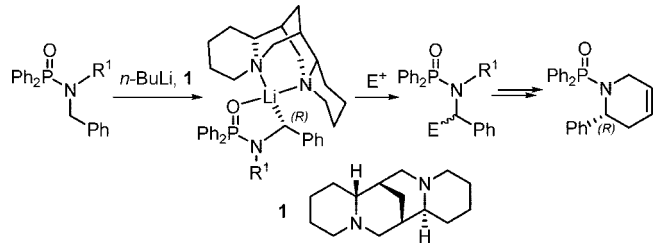
ABSTRACT



Pop-directed asymmetric deprotonation of benzylic amines using [*n*-BuLi/(−)-sparteine] provides an efficient method for the synthesis of chiral NC_α and $NC_{\alpha,\alpha'}$ derivatives with total selectivity with respect to competing allylic and ortho lithiation. The method described herein offers a straightforward route of accessing chiral *N*-Pop-protected nitrogen heterocycles.

Benzylic lithiation of carbamates mediated by (−)-sparteine has become a well established method for the enantiocontrolled generation of OC_α and NC_α stereogenic carbon centers.[1] The carbamate moiety contributes to directing the deprotonation and stabilizing the carbanion formed. After electrophilic quench, α-substituted oxy[2] and amino[3] derivatives are obtained with excellent enantioselectivities. This asymmetric deprotonation−substitution sequence can be successfully applied to a number of Csp^3-heteroatom systems.[4,5]

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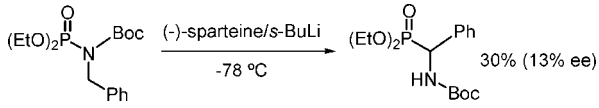
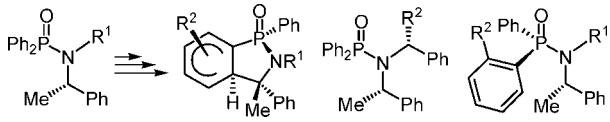
P=O-assisted benzylic lithiation has been much less studied, and its usefulness in organic synthesis remains almost unexploited.[6] We are aware of only one example of asymmetric NC_α metalation of an organophosphorus compound. The deprotonation of *N*-benzylphosphoramidates with [*s*-BuLi/L*] (L* = (−)-sparteine) or chiral lithium amides affords rearranged α-aminophosphonates in moderate yield and low enantiomeric excess (Scheme 1).[7]

Scheme 1. Enantioselective Phosphoramidate−Aminophosphonate Rearrangement



We have developed Pop-directed [Pop = $Ph_2P(O)$] lithiation of phosphinamides into a versatile method for obtaining dearomatized compounds[8] and NC_α-[9] and ortho-substituted[10] products (Scheme 2). In all cases, asymmetry was introduced

Scheme 2



by using chiral starting materials. We report herein the first examples of the efficient asymmetric deprotonation−substitution reaction of *N*-benzyl-*N*-alkylphosphinamides using the complex [*n*-BuLi/(−)-sparteine] as a base.

The scope of the methodology is demonstrated through the application to one-pot double-$NC_{\alpha,\alpha'}$ dibenzylic enantioselective substitution and to the synthesis of a chiral tetrahydropyridine.

First, optimized reaction conditions were established for the prototypal asymmetric deprotonation−methylation of phosphinamide **1a** (Table 1).[11] The best results are obtained

Table 1. Asymmetric NC_α Lithiation−methylation Optimization of **1a** in Toluene Using MeI as Eletrophile[a,b]

entry	RLi	*T* (°C): RLi	*T* (°C): MeI	**2**, convn (%)[c]	er[d]
1	*n*-Bu	90	90	90 (85)	80:20
2	*n*-Bu	90	50	91	62:38
3	*n*-Bu	50	90[e]	90	60:40
4	*n*-Bu	90[f]	90[e]	92	60:40
5	*n*-Bu	90[g]	90	92	80:20
6	*t*-Bu	90	90	56	56:44
7[h]	*n*-Bu	90	90	0[i]	

[a] Lithiation during 60 min, reaction with the electrophile 5 min. In all cases, 1.31 mmol of [*n*-BuLi/L*] and 0.93 mmol of **1a** were used. [b] In THF, racemic product is formed. In Et_2O, very low conversion is observed due to poor substrate solubility. Phosphinamide **1a** is completely insoluble in hexanes. [c] Established based on $^{31}P\{^1H\}$ NMR spectra. Yield in parentheses. [d] Determined by chiral HPLC. [e] The temperature was stabilized for 60 min before quench. [f] The temperature was allowed to increase to −50 °C. [g] 240 min of lithiation time. [h] Absence of (−)-sparteine. [i] Ca. 6% of products derived from *n*-BuP(O)Ph_2 were observed.

by treating **1a** with [*n*-BuLi/L*] in toluene for 1 h at −90 °C followed by addition of MeI at the same temperature. After reaction for 5 min, phosphinamide **2a**[8b] is obtained in 90% conversion and with an er of 80:20 (Table 1, entry 1). Increasing the temperature of either deprotonation or methylation to −50 °C caused a significant decrease in the er (entries 2−4 and Table S1, Supporting Information).

This implies that at −90 °C the deprotonation of **1a** takes place enantioselectively leading to a benzylic carbanion configurationally stable in the time scale of electrophilic quench. Prolonged lithiation of **1a** for 4 h produced a marginal improvement of the conversion without affecting the er (entry 5). Significantly, products of ortho deprotonation were not observed. The use of [*t*-BuLi/L*] affords almost racemic **2a** in low yield (entry 6). In the absence of (−)-sparteine, **1a** is recovered almost unaffected (entry 7 and Table S1, Supporting Information). Next, we extended the (−)-sparteine-assisted deprotonation−substitution process to other phosphinamides and electrophiles (Table 2). The anion of **1a** (R^1 = Me) reacts with alkyl, acyl, and tin halides to give compounds **2**−**6** in high yield and with er ranging from 80:20 to 88:12 (entries 1−5).[12] Electrophilic quench with aldehydes proceeds with very high conversion although with low face selectivity (entries 6 and 7). Interestingly, acrolein undergoes [1,2] addition exclusively.[13] The diastereoisomers were separated through column chromatography. *N*-Pop-1,2-amino alcohols of *unlike* configuration are formed predominantly with high er.

(6) Phosphoramides: (a) Savignac, P.; Dreux, M. *Tetrahedron Lett.* **1976**, *17*, 2025, and references therein. (b) Seebach, D.; Yoshifuji, M. *Helv. Chim. Acta* **1981**, *64*, 643. (c) Seebach, D.; Lohmann, J. J.; Syfrig, M. A.; Yoshifuji, M. *Tetrahedron* **1983**, *39*, 1963. (d) Müller, J. F. K.; Zehnder, M.; Barbosa, F.; Spingler, B. *Helv. Chim. Acta* **1999**, *82*, 1486, and references therein. Phosphonamides: (e) Afarinkia, K.; Jones, C. L.; Yu, H.-W. *Synlett* **2003**, 509. (f) Pedrosa, R.; Maestro, A.; Pérez-Encabo, A.; Raliegos, R. *Synlett* **2004**, 1300. (g) López, B.; Maestro, A.; Pedrosa, R. *Synthesis* **2006**, 817.

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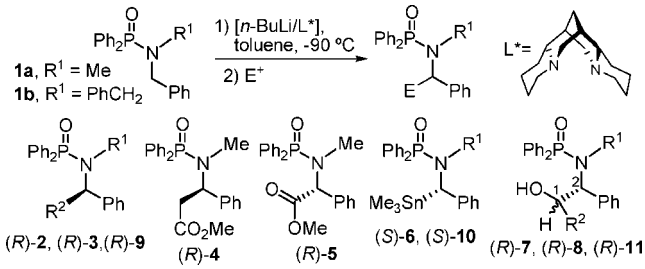
(12) For analogue NC_α-methylations of *N*-Boc-*N*-methylbenzylamine, see: (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (b) Park, Y. S.; Beak, P. *Bull. Kor. Chem. Soc.* **1998**, *19*, 1253.

(13) α-Lithiated *N*-Boc-*N*-arylbenzylamine exclusively attacks the CO group of acrolein: (a) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.

Table 2. Asymmetric Deprotonation−Electrophilic Trapping of *N*-Benzylphosphinamide **1a** and **1b**[a]



entry	R^1	E^+	product	convn[b] (%)	er[c]
1	Me	MeI	(*R*)-**2**	90 (85)	80:20
2	Me	$PhCH_2Br$	(*R*)-**3**	89 (83)	85:15
3	Me	MeO_2CCH_2Br	(*R*)-**4**	69 (61)	84:16
4	Me	MeO_2CCl	(*R*)-**5**	95 (83)	82:18
5	Me	Me_3SnCl	(*S*)-**6**	96 (91)	88:12
6	Me	CH_2=CHCHO	(*R*)-**7**[d]	84 (76)	92:8;[e] 88:12
7	Me	PhCHO	(*R*)-**8**[d]	88 (80)	93:7;[e] 87:13
8	Bn	MeI	(*R*)-**9**	91 (83)	87:13
9	Bn	MeOTf	(*R*)-**9**	94 (85)	90:10
10	Bn	Me_3SnCl	(*S*)-**10**	94 (84)	>99
11	Bn	PhCHO	(*R*)-**11**[f]	94 (87)	98:2;[e] 95:5

[a] 60 min of lithiation, 5 min of electrophilic quench. In all cases, 1.31 mmol of [*n*-BuLi/L*] and 0.93 mmol of **1** were used. [b] Established based on $^{31}P\{^1H\}$ NMR spectra. Yield in parentheses. [c] Determined by HPLC using Chiralcel OD-H. [d] Diastereoisomers in the COH, dr 66:34. [e] (1*S*,2*R*). [f] Diastereoisomers in the COH, dr 78:22; er established trough Mosher ester derivatives.

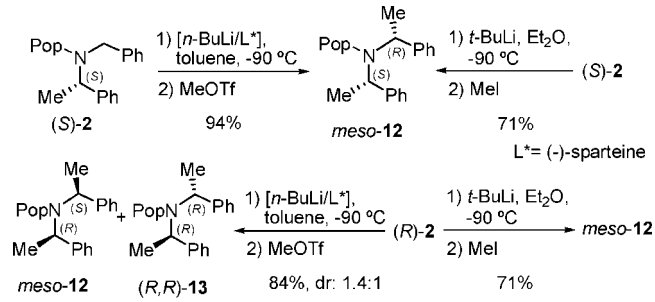
The performance of the electrophilic quench step improved notably by increasing the size of the R^1 substituent linked to the nitrogen. Thus, from phophinamide **1b** (R^1 = CH_2Ph) NC_α-substituted derivatives **9**−**11** are obtained in excellent yields and very high enantioselectivities (entries 8−11). It is worth mentioning that the stannylation reaction leads almost quantitatively to (*S*)-**10**, which may be used for further transformations without purification.

The absolute configuration of (*R*)-**2** and (*R*)-**9** was assigned by comparison of retention times (Chiralcel OD-H) with enantiomerically pure compounds. The sense of electrophile substitution leading to (*R*)-**3** and (*R*)-**4** is assumed to be the same. The structure of (*R*)-**5** was correlated with the corresponding *N*-deprotected α-amino ester (Supporting Information). The configuration of (1*S*,2*R*)-**8**, (1*S*,2*R*)-**11** (Mosher ester derivative), and (*S*)-**10** was established on the basis of their X-ray crystal structures (Figure 1, Supporting Information). Indirectly, this allows assigning the absolute configuration of (*S*)-**6** and (1*S*,2*R*)-**7**.

The stereochemical course of the synthesis of **2**−**11** could be ascertained by applying the method to phosphinamides of known behavior toward lithiation−electrophilic quench (Scheme 3).

Deprotonation of (*S*)-**2** with *t*-BuLi in Et_2O followed by addition of MeI affords *meso*-**12** via diastereoespecific abstraction of the *pro-R* proton and iodide displacement with retention of the configuration.[9c] As expected, under the same conditions (*R*)-**2** also affords *meso*-**12**. When (*S*)-**2** is allowed

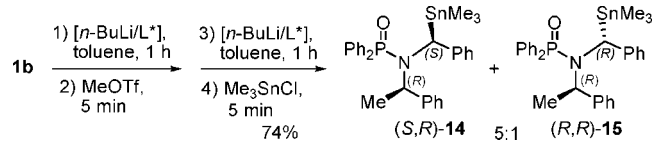
Scheme 3. Diastereospecific Lithiation of Phosphinamide (*S*)-**2** and (*R*)-**2**



to react with [*n*-BuLi/(−)-sparteine] for 1 h and the resulting anion is quenched with MeOTf, *meso*-**12** is formed as the only product (Scheme 2). In contrast, the analogous reaction of (*R*)-**2** leads to a mixture of *meso*-**12** and (*R*,*R*)-**13** in a ratio of 1.4:1 (Scheme 3). The above results suggest that [*n*-BuLi/(−)-sparteine] removes the *pro-R* proton of phosphinamides **1** enantioselectively and that the configurationally stable carbanion generated is alkylated with retention with MeI, MeOTf, $PhCH_2Br$, and MeO_2CCH_2Br, whereas MeO_2CCl, Me_3SnCl, and R^2CHO react with inversion.[14]

Successive application of the asymmetric deprotonation−substitution method to **1b** allowed installation of a different electrophile in each benzylic arm (Scheme 4). Treating **1b**

Scheme 4. $NC_{\alpha,\alpha'}$ Sequential Asymmetric Deprotonation−Substitution Method



with [*n*-BuLi/L*] at −90 °C in toluene for 1 h followed by addition of MeOTf and then repeating the procedure by using Me_3SnCl as electrophile provides a mixture of diasteroisomers (*S*,*R*)-**14** and (*R*,*R*)-**15** (dr 5:1) in a yield of 74% and er of 94:6 and 79:21, respectively. Interestingly, the direct stannylation of (*R*)-**4** via deprotonation with *t*-BuLi proceeds without stereoselectivity.[9c] To the best of our knowledge, this is the first time that double-asymmetric induction mediated by (−)-sparteine on two different methylene groups of an acyclic amine is achieved.[15]

Pop-directed enantioselective lithiation−substitution can be readily applied to the asymmetric synthesis of *N*-heterocycles, an area of current interest.[16]

Using phosphinamide **1c** as scaffold (Supporting Information), lithiation with [*n*-BuLi/L*] and subsequent allylation

(14) These features are in some cases different to those found in the analogue reactions of *N*-Boc-benzylamines: (a) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. See also ref 13.

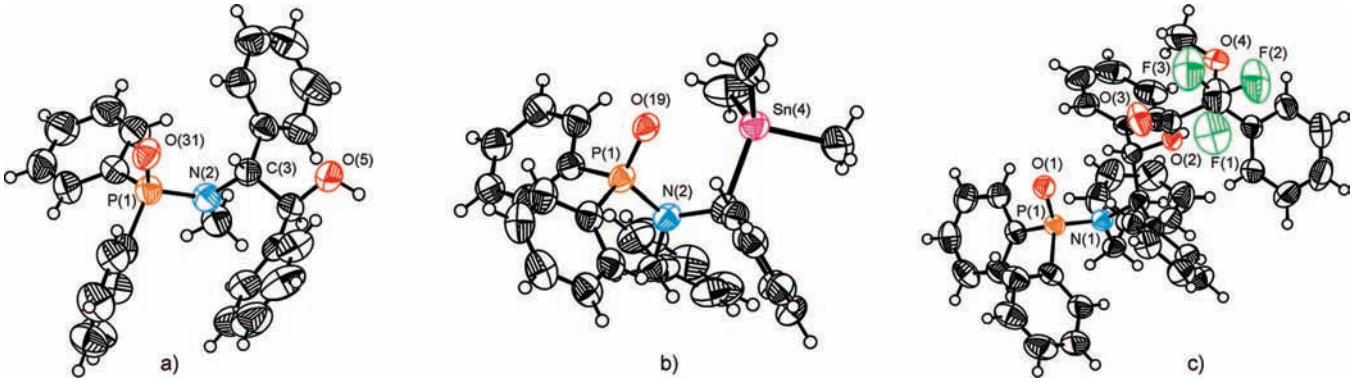
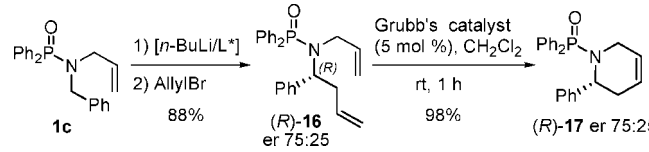


Figure 1. X-ray crystal structures of compounds (a) (1*S*,2*R*)-**8**, (b) (*S*)-**10**, and (c) Mosher ester of (1*S*,2*R*)-**11**.

with allylBr gives the product of benzylic substitution (*R*)-**16** with total regioselectivity in 88% isolated yield and er of 75:25 (Scheme 5).[17] Exposure of (*R*)-**16** to Grubb's catalyst (second generation) in dichloromethane at room temperature for 1 h furnishes tetrahydropyridine (*R*)-**17** quantitatively. The absolute configuration of (*R*)-**16** is assigned by analogy with compounds (*R*)-**2** to (*R*)-**4** (Table 1, entries 1−3).

In summary, Pop-directed asymmetric deprotonation of benzylic amines using [*n*-BuLi/(−)-sparteine] is an efficient method for the synthesis of chiral NC_{α} and $NC_{\alpha,\alpha'}$ derivatives with total selectivity with respect to competing allylic and ortho lithiation and provides a straightforward route of accessing to chiral *N*-Pop protected nitrogen heterocycles. Contrary to *N*-benzylphosphoramidates, products of [1,2] rearrangement of the benzylic carbanion are not observed. Moreover, Pop removal can be readily achieved in a variety of ways.[9c]

Scheme 5. Enantioselective Lithiation−Allylation of **1c** and Subsequent Ring-Closing Metathesis



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Supporting Information Available: Experimental details, characterization data, and crystallographic data for (1*S*,2*R*)-**8**, Mosher ester of (1*S*,2*R*)-**11**, and (*S*)-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For a sequential deprotonation−electrophilic trapping of Boc-pyrrolidine, see: (a) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

(16) (a) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H.; Reider, P. J. *Org. Lett.* **2001**, *3*, 671. (b) Weihofen, R.; Dahnz, A.; Tverskoy, O.; Helmchen, G. *Chem. Commun.* **2005**, 3541.

(17) Formation of **16** via competing [1,2] or [2,3] anion rearrangement reactions has been discarded by trapping the anion formed by treatment of **1c** with *t*-BuLi at −90 °C in Et_2O with MeI. Methylation happened exclusively at the benzylic position.