

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

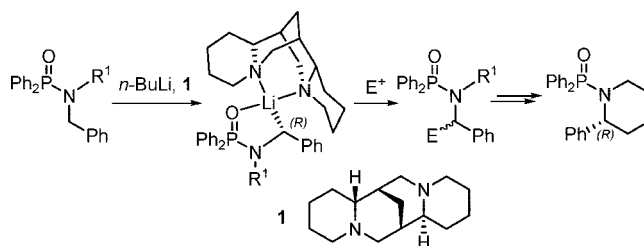
Pascual Oña-Burgos,[†] Ignacio Fernández,[†] Laura Rocas,[‡]
Laura Torre-Fernández,[‡] Santiago García-Granda,[‡] and Fernando López-Ortiz^{*,†}

Área de Química Orgánica, Universidad de Almería, Carretera de Sacramento s/n,
04120 Almería, Spain, and Departamento de Química Física y Analítica, Universidad
de Oviedo, C/ Julián Clavería 8, 33006 Oviedo, Spain

flortiz@ual.es

Received May 5, 2008

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_{α,α'} 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 oxy² and amino³ deriva-

tives are obtained with excellent enantioselectivities. This asymmetric deprotonation–substitution sequence can be successfully applied to a number of Csp³-heteroatom systems.^{4,5}

[†] Universidad de Almería.

[‡] Universidad de Oviedo.

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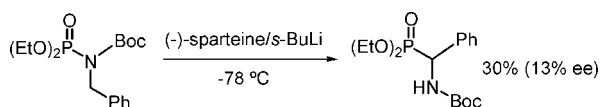
(3) (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

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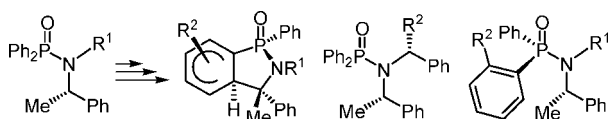
P=O-assisted benzylic lithiation has been much less studied, and its usefulness in organic synthesis remains almost unexploited.⁶ We are aware of only one example of asymmetric NC $_{\alpha}$ metalation of an organophosphorus compound. The deprotonation of *N*-benzylphosphoramidates with [*s*-BuLi/L*] (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 = Ph₂P(O)] lithiation of phosphinamides into a versatile method for obtaining dearomatized compounds⁸ and NC $_{\alpha}$ -⁹ and ortho-substituted¹⁰ 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.

(6) Phosphoramidates: (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.

(7) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, 65, 6121.

(8) Review: (a) López-Ortiz, F.; Iglesias, M. J.; Fernández, I.; Andújar-Sáñez, C. M.; Ruiz-Gómez, G. *Chem. Rev.* **2007**, 107, 1580. See also: (b) Fernández, I.; Ruiz-Gómez, G.; Alfonso, I.; Iglesias, M. J.; López-Ortiz, F. *Chem. Commun.* **2005**, 5408. (c) Morán-Ramallal, A.; Fernández, I.; López-Ortiz, F.; González, J. *Chem. Eur. J.* **2005**, 11, 3022. (d) Ruiz-Gómez, G.; Iglesias, M. J.; Serrano-Ruiz, M.; García-Granda, S.; Francesch, A.; López-Ortiz, F.; Cuevas, C. *J. Org. Chem.* **2007**, 72, 3790. (e) Ruiz-Gómez, G.; Iglesias, M. J.; Serrano-Ruiz, M.; López-Ortiz, F. *J. Org. Chem.* **2007**, 72, 9704.

(9) (a) Fernández, I.; González, J.; López-Ortiz, F. *J. Am. Chem. Soc.* **2004**, 126, 12551. (b) Fernández, I.; López-Ortiz, F. *Chem. Commun.* **2004**, 1142. (c) Oña-Burgos, P.; Fernández, I.; Iglesias, M. J.; García-Granda, S.; López-Ortiz, F. *Org. Lett.* **2008**, 10, 537.

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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 $_{\alpha}$ Lithiation–methylation Optimization of **1a** in Toluene Using MeI as Electrophile^{a,b}

entry	RLi	<i>T</i> (°C): RLi	<i>T</i> (°C): MeI	2 , convn (%) ^c	er ^d
1	<i>n</i> -Bu	90	90	90 (85)	80:20
2	<i>n</i> -Bu	90	50	91	62:38
3	<i>n</i> -Bu	50	90 ^e	90	60:40
4	<i>n</i> -Bu	90 ^f	90 ^e	92	60:40
5	<i>n</i> -Bu	90 ^g	90	92	80:20
6	<i>t</i> -Bu	90	90	56	56:44
7 ^h	<i>n</i> -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 Et₂O, very low conversion is observed due to poor substrate solubility. Phosphinamide **1a** is completely insoluble in hexanes. ^c Established based on ³¹P{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)Ph₂ 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).

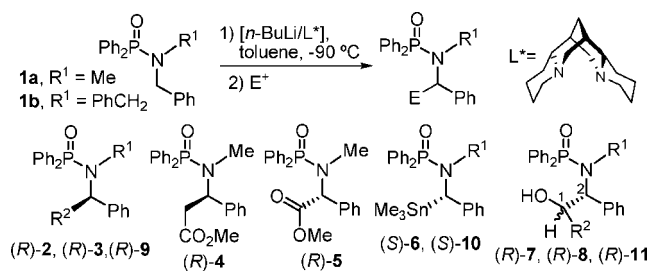
This implies that at –90 °C the deprotonation of **1a** takes place enantioselectively leading to a benzylic carbanion configurationally stable in the time scale of electrophilic quench. Prolonged lithiation of **1a** for 4 h produced a marginal improvement of the conversion without affecting the er (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** (R¹ = 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.

(11) Synthesis of **1a** and **1b**: (a) Fernández, I.; López-Ortiz, F.; Tejerina, B.; García-Granda, S. *Org. Lett.* **2001**, 3, 1339.

(12) For analogue NC $_{\alpha}$ -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	(<i>R</i>)- 2	90 (85)	80:20
2	Me	PhCH ₂ Br	(<i>R</i>)- 3	89 (83)	85:15
3	Me	MeO ₂ CCH ₂ Br	(<i>R</i>)- 4	69 (61)	84:16
4	Me	MeO ₂ CCl	(<i>R</i>)- 5	95 (83)	82:18
5	Me	Me ₃ SnCl	(<i>S</i>)- 6	96 (91)	88:12
6	Me	CH ₂ =CHCHO	(<i>R</i>)- 7 ^d	84 (76)	92:8; ^e 88:12
7	Me	PhCHO	(<i>R</i>)- 8 ^d	88 (80)	93:7; ^e 87:13
8	Bn	MeI	(<i>R</i>)- 9	91 (83)	87:13
9	Bn	MeOTf	(<i>R</i>)- 9	94 (85)	90:10
10	Bn	Me ₃ SnCl	(<i>S</i>)- 10	94 (84)	>99
11	Bn	PhCHO	(<i>R</i>)- 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 ³¹P{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 through Mosher ester derivatives.

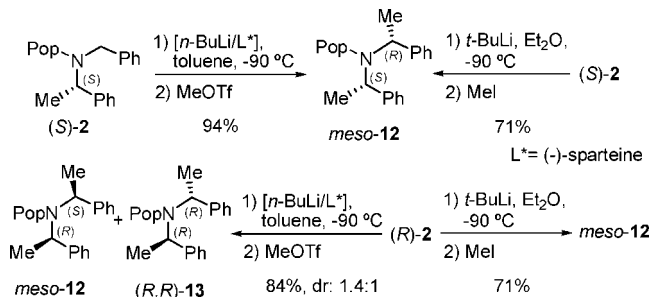
The performance of the electrophilic quench step improved notably by increasing the size of the R¹ substituent linked to the nitrogen. Thus, from phosphinamide **1b** (R¹ = CH₂Ph) NC_α-substituted derivatives **9–11** are obtained in excellent yields and very high enantioselectivities (entries 8–11). 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 Et₂O followed by addition of MeI affords *meso*-**12** via diastereospecific 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

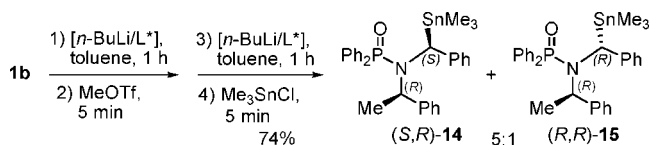
Scheme 3. Diastereospecific Lithiation of Phosphinamide (*S*)-**2** and (*R*)-**2**



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, PhCH₂Br, and MeO₂CCH₂Br, whereas MeO₂CCl, Me₃SnCl, and R²CHO 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_{α,α'} 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 Me₃SnCl as electrophile provides a mixture of diastereoisomers (*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.

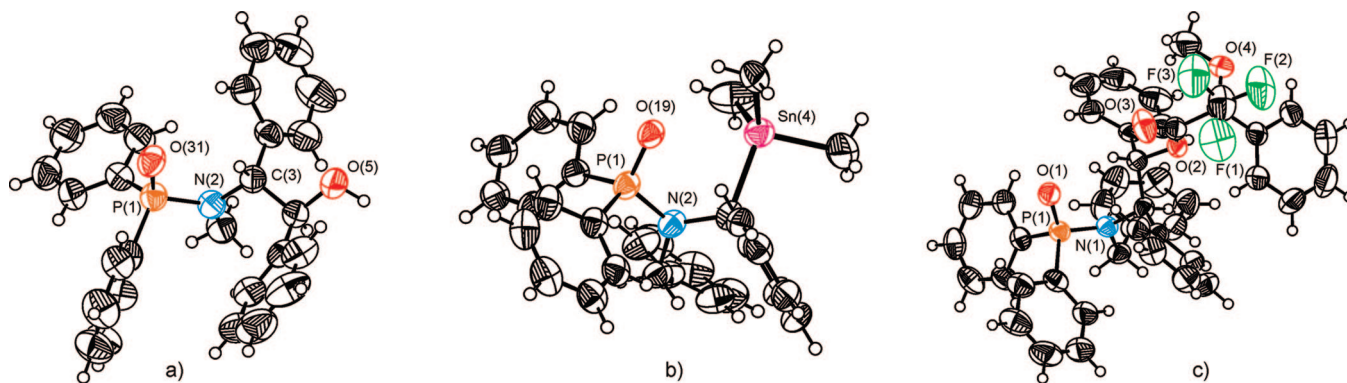
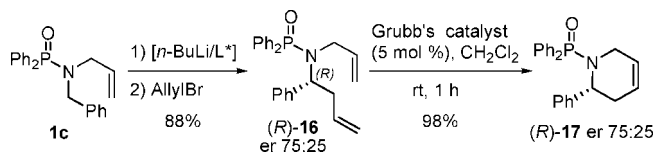


Figure 1. X-ray crystal structures of compounds (a) (1*S*,2*R*)-**8**, (b) (*S*)-**10**, and (c) Mosher ester of (1*S*,2*R*)-**11**.

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_{α,α'} 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]

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



rearrangement of the benzylic carbanion are not observed. Moreover, Pop removal can be readily achieved in a variety of ways.^{9c}

Acknowledgment. We thank the Ministerio de Educación y Ciencia (MEC) (project: CTQ2005-1792BQU) for funding. I.F. thanks the Ramón y Cajal program for financial support.

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 Et₂O with MeI. Methylation happened exclusively at the benzylic position.