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Enantioselective Desymmetrization of Diphenylphosphinamides via (−)-Sparteine-Mediated *Ortho*-Lithiation. Synthesis of *P*-Chiral Ligands

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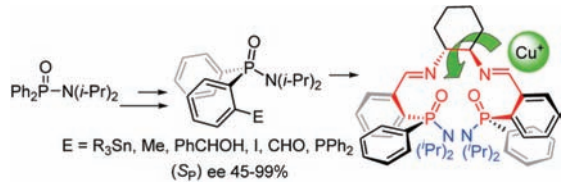
ABSTRACT



Asymmetric *ortho*-lithiation of *N*-dialkyl-*P*,*P*-diphenylphosphinamides using [*n*-BuLi·(−)-sparteine] is described as an efficient method for the synthesis of *P*-chiral *ortho*-functionalized derivatives in high yields and ee's from 45 to >99%. The method allows access to new enantiomerically pure *P*-chiral phosphine and diimine ligands.

Ortho-directed metalation has become one of the most employed strategies in organic synthesis for derivatizing arenes.[1] Although a broad range of functional groups promote *ortho*-deprotonation, *P*-containing derivatives have been less exploited.[2] P═X-Directed (X = O, S) *ortho*-dilithiation strategies have been also described.[3] To the best of our knowledge, there are no precedents on asymmetric *ortho*-deprotonation of aryl systems using chiral reagents (third-generation method).[4,5] Recently, we have achieved the diastereoselective desymmetrization of the $P(O)Ph_2$ (Pop) group of chiral diphenylphosphinamides.[6] As part of our ongoing project on selective phosphinamide-directed lithiations[7] we report herein (1) an efficient method for the enantioselective lithiation of diisopropylphosphinamide **1a** using (−)-sparteine as source of chirality, (2) the extension of the procedure to other Pop derivatives such as **1b**-**1f**, (3)

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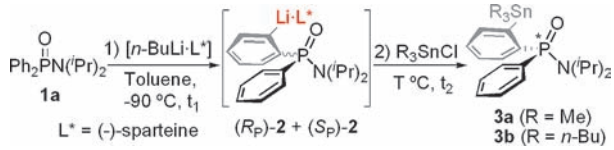
the application of the method to the synthesis of enantiomerically pure phosphine bidentate ligands, and (4) salen-type ligands containing *P*-chiral phosphinamide chelating arms including preliminary coordination chemistry with standard copper salts.

First, optimized reaction conditions were established for the prototypal asymmetric deprotonation−stannylation of phosphinamide **1a** (Table 1).

Table 1. Asymmetric *Ortho*-Lithiation−Stannylation of **1a**[a,b]



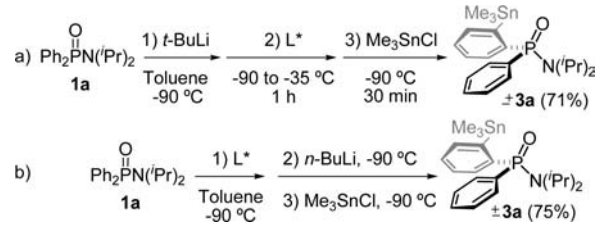
entry	temp (°C)	t_1 (h)	R	t_2 (h)	convn[c] (%)	ee[d] (%)
1	−90	1	Me	0.5	86 (35)[e]	58 (>99)[e]
2	−90	12	Me	0.5	75 (30)[e]	60 (>99)[e]
3[f]	−90	1	Me	0.5	83 (33)[e]	59 (>99)[e]
4[g]	−90	1	Me	0.5	81	50
5	−35	1	Me	1	75	50
6	−90	1	*n*-Bu	0.5	82	50

[a] [*n*-BuLi·L*] (L* = (−)-sparteine) preformed during 30 min. [b] A ratio of **1a**/[*n*-BuLi·L*] 1:1.5 was used. [c] Established on the basis of $^{31}P\{^1H\}$ NMR spectra. [d] Determined by chiral HPLC. [e] After recrystallization. [f] 1.1 equiv of [*n*-BuLi·L*] and Me_3SnCl were used. [g] 1.1 equiv of *n*-BuLi, 1.5 equiv of L*.

The best results were obtained by treating **1a** with [*n*-BuLi·L*] (L* = (−)-sparteine) in toluene for 1 h at −90 °C followed by addition of Me_3SnCl at the same temperature. After reaction during 30 min, stannane **3a** was obtained in 86% conversion and with an ee of 58% (Table 1, entry 1). Increasing the metalation time up to 12 h led to similar results, which indicates that the degree of enantioselection is established in the first hour of lithiation and that the complexes (*R*)-**2** and (*S*)-**2** formed do not interconvert with each other (entry 2). This hypothesis is supported by the observation that carrying out the electrophilic quench at −35 °C during 1 h caused only a slight decrease of the ee (entry 5) and that stannylation with *n*-Bu_3SnCl afforded **3b** in a yield and ee similar to **3a** (entry 6). An excess of (−)-sparteine does not affect the performance of the reaction (entries 3 and 4). Fortunately, recrystallization from cold hexane provided enantiomerically pure **3a** in 30−35% yield. We have previously prepared racemic **3a** through tin−lithium transmetalation of *ortho*-lithiated **1a** in THF.[6] The process described here represents the first example of asymmetric desymmetrization of the Pop group.

Preformation of complex [*n*-BuLi·L*] proved to be determinant for the asymmetric induction observed. Stepwise lithiation of **1a** with *t*-BuLi[8] followed by addition of (−)-sparteine and subsequent reaction with Me_3SnCl afforded racemic **3a** in 71% yield (Scheme 1a). Most importantly, reversing the order of addition of chiral reagent and base, in this case *n*-BuLi, gave **3a** in high yield but also without enantiodiscrimination (Scheme 1b).

Scheme 1. Stepwise Lithiation, Addition of (−)-Sparteine (L*), and Stannylation of **1a**



To extend the scope of our asymmetric method, the *ortho*-lithiated substrate was treated with a variety of electrophiles providing products **4**−**8** in good conversions and ee's in the range of 45−63% (Table 2). The stannilation process was complemented with the introduction of the Ph_3Sn moiety which required reaction times up to 18 h to obtain **3c** in acceptable yields (entry 3).

The synthesis of *o*-iodo derivative **4** was attempted using iodine and 1,2-diiodoethane as I^+ synthetic equivalents[9] (entries 4 and 5). The latter proceeded with higher conversion in shorter reaction time probably due to the higher solubility of the electrophile. Importantly, product **4** could be isolated optically pure after recrystallization (isolated yield of 22%). This compound is a valuable precursor for metal-mediated cross-coupling reactions,[10] a methodology successfully applied to the synthesis of chiral biphenyl derivatives bearing achiral phosphorus substituents.[11]

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(5) For enantioselective PC_α deprotonations, see: (a) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (b) Genet, C.; Canipa, S. J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc.* **2006**, *128*, 9336. (c) Gammon, J. J.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750.

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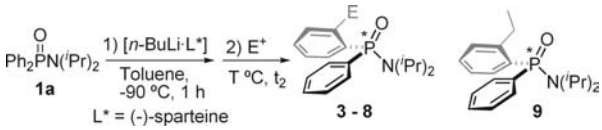
Table 2. Asymmetric *Ortho*-Lithiation−Substitution of **1a**[a]



entry	E^+	E	t_2 (h)	temp (°C)	convn[b] (%)	ee[c] (%)
1	Me_3SnCl	Me_3Sn	0.5	−90	86 (**3a**)	58 (>99)[d]
2	Bu_3SnCl	Bu_3Sn	0.5	−90	82 (**3b**)	50
3	Ph_3SnCl	Ph_3Sn	18	−90	51(**3c**)	45
4	I_2	I	14	−90	53 (**4**)	60 (>99)[d]
5	$(CH_2I)_2$	I	1	−90	86 (**4**)	63 (>99)[d]
6	MeI[e]	Me	2	−90	83 (**5**)	59
7	PhCHO	PhCHOH	1	−35	85[f] (**6/6′**)	47/63
8	DMF[e]	CHO	2	−90	80 (**7**)	52 (>99)[d]
9	Ph_2PCl[g]	Ph_2P	1	−35	75 (**8**)	55

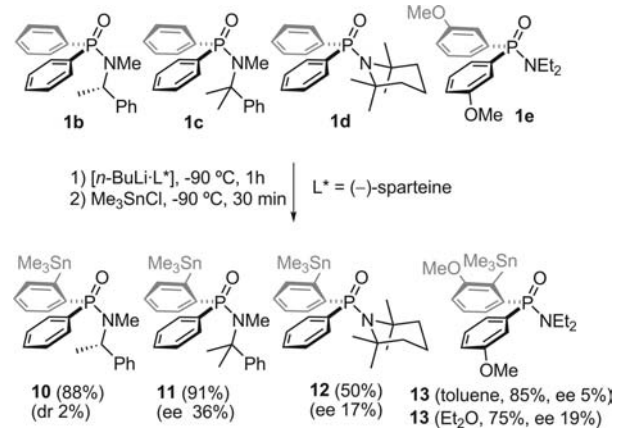
[a] A ratio of **1a**/[*n*-BuLi·L*] 1:1.5 was used. [b] Established on the basis of $^{31}P\{^1H\}$ NMR spectra. [c] Determined by chiral HPLC. [d] After recrystallization. [e] 5 equiv of E^+ was used. [f] Diastereoisomers in the C−OH, dr 1:2. [g] 1.1 equiv of [*n*-BuLi·L*] was used.

Alkylation with MeI afforded the corresponding *o*-methyl derivative **5** (entry 6). Good results were found by using 5 equiv of electrophile. Under standard reaction conditions, small amounts of a new compound **9** (3−13%) were always formed. After isolation through flash chromatography, **9** was identified as the product of lateral lithiation[12] of **5** and subsequent methylation (Supporting Information). This side deprotonation might be effected by remaining [*n*-BuLi·L*] in solution or via *ortho*-lithiated phosphinamide **2**. Benzaldehyde reacted smoothly with anions **2** to give alkylated derivatives **6/6′** in high conversion although with low face selectivity (entry 7, Table 2). The major diastereoisomer was obtained in higher optical purity (ee of 63 vs 47%).

The use of DMF as quenching reagent furnished the *o*-formyl product **7** in high yield (entry 8). To our delight, three-time recrystallization from hexane returned **7** with ee >99% in an isolated yield of 30%. The X-ray structure allowed us to establish the absolute configuration as S_P (Supporting Information). Based on the lithiation process discussed above, we assigned the same configuration to the major stereoisomer of all *ortho*-substituted phosphinamides **3**−**8** synthesized. The CHO moiety present in (S_P)-**7** offers a good chance of further manipulations (see below). Finally, the treatment of enantiomerically enriched *ortho*-lithium phosphinamide **1a** with chlorodiphenylphosphine led to **8** in a yield of 75% and ee of 55%. The ^{31}P NMR spectrum measured in $CDCl_3$ shows a diagnostic pattern with two doublets of $^3J_{PP}$ = 6.1 Hz at δ −10.95 and 33.36 ppm corresponding to the P(III) and P(V) atoms, respectively.

Next, substrate scope was investigated by varying the substituents at the nitrogen, **1b**−**d**, and phosphorus atom, **1e** (Scheme 2). As can be deduced from Scheme 2, *ortho*-deprotonation of **1b**−**e** under the conditions optimized for **1a** followed by addition of Me_3SnCl gave the corresponding tin derivatives in moderate to high yield. However, the level of asymmetric induction achieved was very low in all cases. Changing the solvent to diethyl ether produced only a modest increase of the ee.

Scheme 2. Asymmetric *Ortho*-Stannylation of **1b**−**e**[a]



[a] All of the reactions were carried out using a ratio of **1**/[*n*-BuLi·L*] 1:1.5.

Hemilabile *P*,*X*-bidentate ligands (X = O, N) are of great interest due to their utility in coordination chemistry.[13] β-Phosphine phosphinamide (S_P)-**8** is a new member of this type of ligands containing a chiral P═O very close to a P(III) binding site. We are not aware of *P*,*O*-ligands featuring the characteristics of (S_P)-**8**.[13,14] For practical applications of (S_P)-**8** in asymmetric catalysis, a workable route to a product of high optical purity is needed. Attempts to improve the ee of 55% of (S_P)-**8** by recrystallization failed. We envisaged an alternative route based on tin−lithium transmetalation using enantiomerically pure (S_P)-**3a**. The reaction of (S_P)-**3a** (ee >99%) with [*n*-BuLi·TMEDA] in toluene at −50 °C and subsequent addition of Ph_2PCl allowed the synthesis of the potential new ligand (S_P)-**8** (yield of 75%, ee >99%) in a straightforward manner (Scheme 3a). The generality of this strategy is evidenced by the analogous preparation of optically pure (S_P)-**3b** (Scheme 3b). These results indicate that (S_P)-**3a** can be considered as a synthetic equivalent of the optically pure lithium derivative (S_P)-**2** (Table 1), thereby allowing the entry of a large variety of enantiomerically pure

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(13) Reviews: (a) Espinet, P.; Soulantica, K *Coord. Chem. Rev.* **1999**, *193*−*195*, 499. (b) Slone, C. S.; Weinberger, D. A.; Mirkin, C. A. *Prog. Inorg. Chem.* **1999**, *48*, 233. (c) Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680. (d) Angell, S. E.; Rogers, C. W.; Zhang, Y.; Wolf, M. O.; Jones, W. E. *Coord. Chem. Rev.* **2006**, *250*, 1829.

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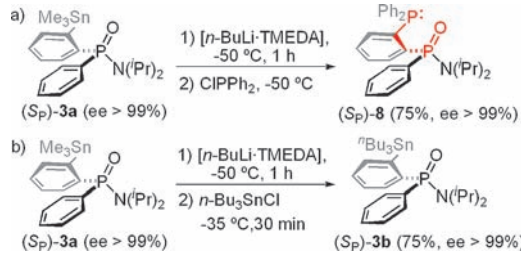
Scheme 3. Synthesis of Enantiopure (S_P)-**3b** and (S_P)-**8** by Tin−Lithium Exchange Reactions



P-chiral phosphinamide derivatives via Sn−Li exchange followed by electrophilic addition reactions. Moreover, the lack of partial racemization in these transformations provides definitive proof of the configurational stability of the *ortho*-lithiated phosphinamide (S_P)-**2** (Table 1).

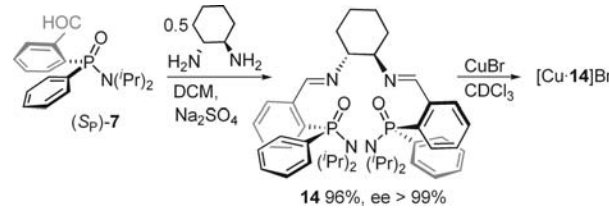
A further application of the asymmetric Pop-desymmetrization method described above consists of the synthesis of an optically pure diimine "salen"-type ligand[15] incorporating chiral phosphinamide chelating groups. C_2-Symmetric (1*R*,2*R*,S_P,$S_{P'}$)-**14** was prepared through condensation of (S_P)-**7** with (1*R*,2*R*)-1,2-diaminocyclohexane in DCM (Scheme 4).

NMR monitoring of the reaction showed the initial formation of the monocondensation adduct (δ_P 34.04 ppm), which transformed quantitatively into **14** (δ_P 33.83 ppm) as evidenced by the appearance of a singlet at δ 9.23 ppm in the ^{1}H NMR spectrum and the absence of the aldehyde CHO resonance. The structure of **14** was confirmed through X-ray analysis (Supporting Information).

Inspired by the catalytic capabilities of other bifunctionally hemilabile phosphorus ligands,[14] we decided to explore the metal-binding abilities of **14** against copper(I) bromide. NMR

(15) Wezenberg, S. J.; Kleij, A. W. *Angew. Chem., Int Ed.* **2008**, *47*, 2354.

Scheme 4. Synthesis of (1*R*,2*R*,S_P,$S_{P'}$)-**14** and Its Cu(I) Complex



spectra of an equimolecular mixture of (1*R*,2*R*,S_P,$S_{P'}$)-**14** and CuBr in in $CDCl_3$ evidenced the quantitative formation of a new Cu(I) complex, [Cu·**14**]Br (Scheme 4, Supporting Information).

In summary, asymmetric *ortho*-deprotonation of the Pop group of phosphinamides using [*n*-BuLi·(−)-sparteine] has been described for the first time. Electrophilic quench of the configurationally stable *ortho* anions provides an efficient method for synthesizing *P*-chiral *ortho*-functionalized derivatives. Enantiomerically pure products can be obtained in a straightforward manner by simple recrystallization and tin−lithium exchange reactions. A new family of compounds capable of participating in cross-coupling reactions and complex formation with transition metals have been prepared. Applications of the new chiral ligands in catalysis are currently under investigation.

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Supporting Information Available: Experimental details, characterization data, and crystallographic data for (*S*)-**7** and (1*R*, 2*R*, S_P, $S_{P'}$)-**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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