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Communication

P-Stereogenic N-Phosphinyl Compounds

Stereoselective Synthesis of *P*-Stereogenic *N*-Phosphinyl Compounds

Ahmed Chelouan,[a] Rocío Recio,[a] Eleuterio Álvarez,[b] Noureddine Khiar,*[b] and Inmaculada Fernández*[a]

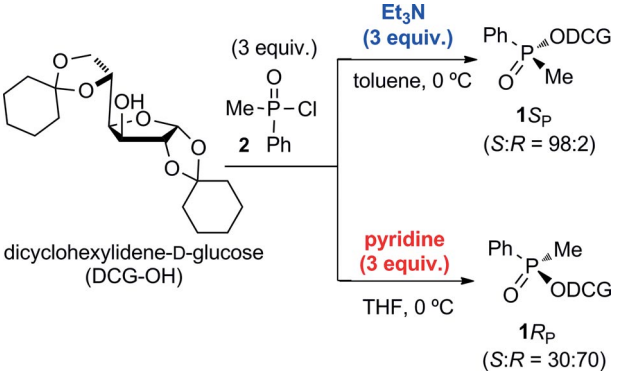
Abstract: A number of *P*-stereogenic *N*-phosphinyl compounds were stereoselectively prepared in good yields by a straightforward approach, thanks to the diversified and, up until now, unexplored reactivity of (*R*)- and (*S*)-dicyclohexylidene-D-glucose methyl phenyl phosphinates toward metal amides. Under adequate conditions, structurally different phosphinamides with one or two *P*-chiral centers were obtained.

Introduction

Since the Horner[1] and Knowles[2] groups reported the first asymmetric hydrogenation of olefins by using a *P*-chiral phosphine, a large number of structurally diverse organophosphorus derivatives have been used as chiral ligands in asymmetric catalysis.[3] The interest in *P*-stereogenic ligands has declined significantly over the past three decades, mainly because of the success of ligands for which the chirality resides in the "backbone" and not in the phosphorus atom, associated with the difficulty of stereoselectively synthesizing *P*-chirogenic derivatives. However, the outstanding performance of these ligands in asymmetric homogeneous transition-metal catalysis[4] and their excellent results as chiral Lewis bases in asymmetric organocatalysis[5] have triggered a resurgence in the appeal of the stereoselective synthesis of *P*-chirogenic compounds in general and of phosphinamides in particular.[6]

The synthesis of compounds with two stereogenic phosphorus atoms is more challenging and has generally been achieved by the dimerization of enantiopure lithiomethyl-phosphine oxide or by the enantioselective deprotonation of phosphine–boranes and phosphine–sulfides.[7] However, as far as we know, there is no method for the synthesis of 1,3-bis(*P*-chirogenic) compounds. Moreover within the family of *P*-stereogenic compounds, the synthesis of phosphinamides, which hold great promise as Brønsted acid and Lewis base organocatalysts, has scarcely been addressed, and until quite recently, the few *P*-stereogenic phosphinamides that are known were prepared by chiral separation.[8] However, in the course of this work, Han et al. reported the first stereoselective synthesis of *P*-chirogenic phosphinamides by using cyclic 1,3,2-benzoxazaphosphinine 2-oxides as chiral starting substrates.[9] Herein, we report our results in the synthesis of structurally relevant enantiopure phosphinamides, *N*-(phosphinyl)imines, a β-(phosphinyl)phosphinate, and a β-(phosphinyl)phosphinamide by using dicyclohexylidene-D-glucose methyl phenyl phosphinates as chiral *N*-phosphinylating agents.

Within a research program directed toward the synthesis of chiral sulfoxides and phosphine oxides from renewable biomass and their application in organic and organometallic catalysis, we reported an enantiodivergent approach for the synthesis of different phosphine oxides.[10] For this purpose, we applied modified Mislow methodology[11] by using a secondary carbinol derived from D-glucose as the chiral alcohol instead of (–)-menthol. This method facilitates the stereodivergent synthesis of both diastereomeric methyl phenyl phosphinates, **1**R_P and **1**S_P, by treatment of dicyclohexylidene-D-glucose (DCG-OH) with phosphinyl chloride **2** in the presence of triethylamine or pyridine as the base (Scheme 1). These phosphinates proved to be good C-phosphinylating agents and yielded the correspond-



Scheme 1. Diastereodivergent synthesis of (*S*)- and (*R*)-dicyclohexylidene-D-glucose methyl phenylphosphinates **1**S_P and **1**R_P

[a] *Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Profesor García González, 12, 41012 Seville, Spain E-mail: inmaff@us.es*

[b] *Asymmetric Synthesis and Functional Nanosystems Group, Instituto de Investigaciones Químicas (IIQ), CSIC – Universidad de Sevilla,, C/ Américo Vespucio 49, 41092 Seville, Spain E-mail: khiar@iiq.csic.es*

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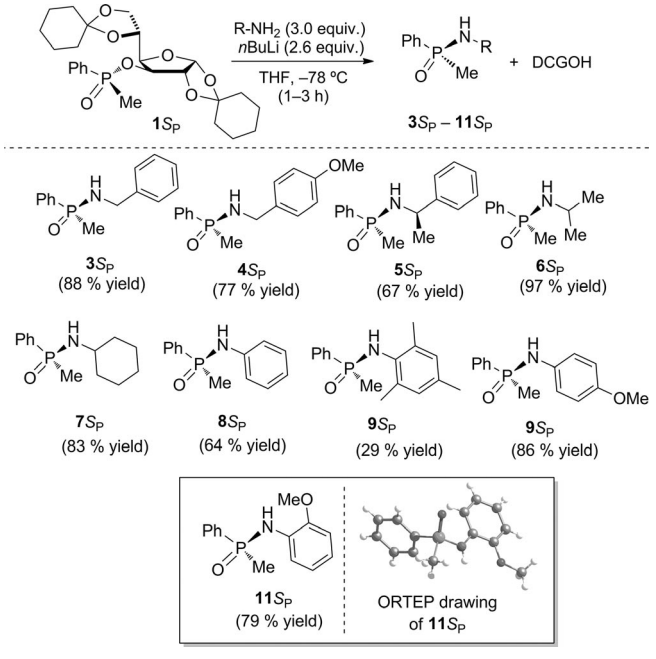
ing phosphine oxides by reaction with organometallic reagents with inversion of configuration at the stereogenic phosphorus atom.[10]

Results and Discussion

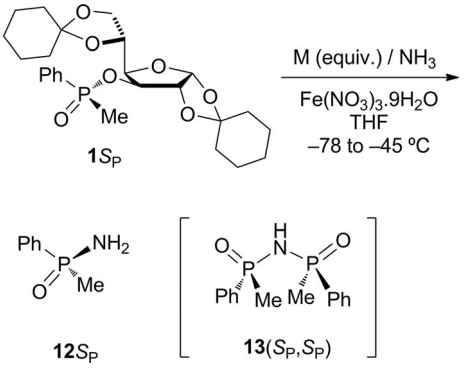
To study their capacity as *N*-phosphinylating agents, in the present study we used diastereomer **1**S_P, easily prepared on multigram scale, as the reference phosphinate (Scheme 1). Treatment of phosphinate **1**S_P with lithium alkyl or arylamides, prepared by treatment of the corresponding amine with *n*BuLi at –78 °C, yielded the *N*-phosphinylated products, the enantiomeric purities of which were determined by HPLC on a chiral stationary phase (Scheme 2). The reactions proceeded stereoselectively in all cases, as shown by HPLC, and enantiopure phosphinamides **3**S_P–**11**S_P were obtained in moderate to high yields. The reaction occurred with inversion of configuration at phosphorus, as demonstrated by X-ray study of *N*-(*o*-methoxyphenyl) derivative **11**S_P, and a similar behavior was assumed for the rest of the phosphinamides.[12] In this way, differently substituted *N*-alkyl-phosphinamides (see compounds **3**S_P–**7**S_P, Scheme 2) and *N*-aryl-phosphinamides (see compounds **8**S_P–**11**S_P, Scheme 2), with large structural diversity, were stereoselectively prepared.



Scheme 2. Asymmetric synthesis of *N*-alkyl- and *N*-aryl-phosphinamides from phosphinate **1**S_P.

Taking into account the synthetic interest in methyl-phenyl-phosphamides and the limited number of methods described for their stereoselective synthesis in good yields,[8,9] we decided to address their preparation by breaking the P–ODCG bond with different "NH_2" equivalents used as nucleophiles. Our initial studies were conducted by applying a standard method consisting of the condensation of metal amides MNH_2 (M = Na, Li) as nucleophiles. This required, first, fine-tuning the reaction conditions, as factors such as temperature, reaction time, number of equivalents of the amide used, and the nature of the counterion (Na or Li) determine the enantiomeric excess of the final product and its structure, as shown in Table 1. For the reaction to take place, the amide was generated by adding metal (sodium or lithium) to liquid ammonia at –78 °C, which was then added to a solution of phosphinate **1**S_P in THF at –40 °C. The reaction of **1**S_P with sodium amide yielded desired phosphinamide **12**S_P, and the reaction took place instantaneously. An excess amount of sodium amide (3 equiv.) and an increased reaction time (up to 10 min) favored epimerization of the final product, and aqueous workup of the reaction reduced the yield of the isolated product (Table 1, entry 1). Reducing the reaction time to 1 min led to higher enantioselectivities (Table 1, entries 2 and 3). Lowering the number of equivalents of sodium amide (up to 1.2 equiv.) caused a significant increase in the enantiomeric excess (*ee*) of the product but significantly reduced the chemical yield (Table 1, entry 4). The best result was obtained with 2.1 equiv. of sodium amide, subsequent workup with solid ammonium chloride, and purification with neutral silica gel (Table 1, entry 6); this resulted in phosphinamide **12**S_P in 69 % yield with 96 % *ee*. Simple crystallization from toluene/dichloromethane (3:1) yielded the enantiopure (*S*)-methyl-phenyl-phosphinamide in 50 % yield. Interestingly, by using lithium amide instead of sodium amide as the nucleophile under the same reaction conditions yielded quantitatively bis-phosphinamide **13**(S_PS_P) as the unique product.

Table 1. Reactivity of phosphinate **1**S_P with amides.



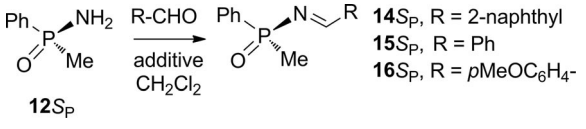
Entry	M (equiv.)	Time [min]	Workup	Product	Yield[a] [%]	*ee*[b] [%]
1	Na (3.0)	10	H_2O	**12**S_P	16	76
2	Na (3.0)	1	NH_4Cl[c]/CC[d]	**12**S_P	29	81
3	Na (3.0)	1	NH_4Cl/THF aq.	**12**S_P	30	80
4	Na (1.2)	1	NH_4Cl	**12**S_P	10	99
5	Na (2.1)	1	acid resin/CC[d]	**12**S_P	51	92
6	Na (2.1)	1	NH_4Cl/CC[d]	**12**S_P	69	96[e]
7	Li (2.1)	1	NH_4Cl/CC[d]	**13**(S_PS_P)	quant.	≥98[f]

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase: AD (2-propanol/hexane, 22:78, 0.5 mL min^{-1}). [c] Solid ammonium chloride was added. [d] The crude reaction product was directly purified by short column chromatography (CC) on silica gel. [e] 100 % *ee* after crystallization from CH_2Cl_2/toluene (1:3); 50 % yield. [f] Only one product was observed by analysis of the crude mixture by NMR spectroscopy.

Having delineated a suitable method for the enantioselective synthesis of phosphinamide **12**S_P, we decided to investigate its transformation into some other derivatives of interest in asym-

metric synthesis. Given the excellent results provided by chiral *N*-(sulfinyl)imines as electrophilic substrates in the synthesis of chiral amines, which have resulted in many applications,[13,14] in addition to our own interest in this field,[15] the analogous *N*-(phosphinyl)imines caught our attention as chiral substrates. Clearly, the phosphinyl group, like the sulfinyl group, can act as an electron-withdrawing group to activate the C=N bond for the addition of nucleophiles. Moreover, unlike the sulfinyl group, the possibility of oxidation or racemization of phosphorus in *N*-(phosphinyl)imines is excluded, which facilitates recovery of the chiral auxiliary once the process has finished. In this sense, *N*-(*P*,*P*-diaryl-phosphinoyl)imines behave as good electrophiles in reactions with different nucleophiles.[16] However, there are only a few examples that describe *N*-(phosphinyl)imines that are chiral at phosphorus. Royer et al. recently published their work on the stereoselective dimetalaluminum alkynylation of *N*-(phosphinyl)imines that were prepared from menthyl methyl phenyl phosphinate as a chiral starting substrate.[17] Colobert et al. described the addition of Grignard reagents to various chiral *N*-(*tert*-butyl-phenyl-phosphinyl)imines, obtained by a process based on racemate resolution of *tert*-butyl-phenyl-phosphine oxide as the precursor.[8a,8b] More recently, Riera et al. described the role of borane as a directing group in the stereoselective addition of organometallic reagents to borane *P*-stereogenic *N*-phosphanylimines.[8f] In our case, we addressed the stereoselective synthesis of different *N*-(methyl-phenyl-phosphinyl)aldimines by using enantiopure (*S*)-methyl-phenyl-phosphinamide **12**S_P as the starting chiral material by condensation with various aldehydes, and the results are shown in Table 2.

Table 2. Synthesis of *N*-(methyl-phenyl-phosphinyl)imines **14**S_P–**16**S_P from phosphinamide **12**S_P.

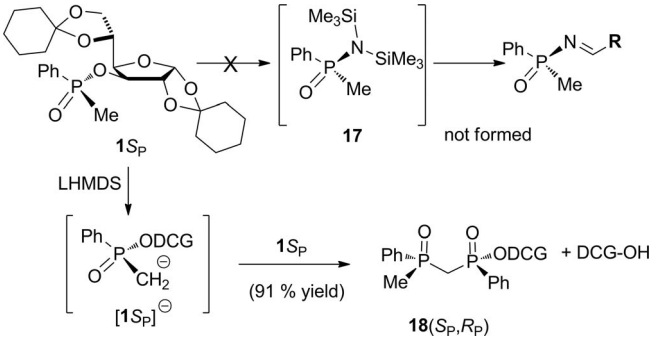


Entry	R	*T* [°C]	Additive (equiv.)	Product	Yield[a] [%]
1	2-naphthyl	r.t.	$CuSO_4$ (2.0)	**14**S_P	16
2	2-naphthyl	r.t.	Cs_2CO_3 (2.2)	**14**S_P	29
3	2-naphthyl	0	$TiCl_4$/Et_3N (1.5:3.0)	**14**S_P	30
4	Ph	r.t.	$CuSO_4$ (2.2)	**15**S_P	10
5	Ph	r.t.	Cs_2CO_3 (2.2)	**15**S_P	51
6	*p*MeOC_6H_4	r.t.	Cs_2CO_3 (2.2)	**16**S_P	69

[a] Yield of isolated product after chromatographic purification.

As can be seen from Table 2, in the case of arylaldimines **14**S_P–**16**S_P the best results were obtained by using dichloromethane as the solvent in the presence of cesium carbonate (2.2 equiv.) at room temperature; the products were obtained in low to moderate yields (up to 69 % in the case of *p*-methoxyphenyl derivative **16**S_P; Table 2, entry 6) in enantiopure form. Currently, these chiral *N*-(phosphinyl)imines are being evaluated as chiral electrophilic substrates in different processes. As in the case of the *N*-(sulfinyl)imine analogues, this is very rich and diversified chemistry, and the results will be published in due course.

Next, and in clear analogy to the methodology developed by Davis' group for the synthesis of *N*-(*p*-tolylsulfinyl)imines,[18] we envisaged the one-pot synthesis of *N*-(phosphinyl)imines by condensation with lithium hexamethyldisilazane (LHMDS), followed by in situ imination of *N*-bis(trimethylsilyl)-(*S*)-methyl-phenyl-phosphinamide intermediate **17** (Scheme 3). However, in this case intermediate **17** was not formed; instead, a single product was obtained in high yield. This new compound has still the sugar moiety, as shown by ^{1}H NMR spectroscopy, whereas ^{31}P NMR spectroscopy shows the presence of two phosphorus(V) atoms that appear as doublets (J_{PP} = 9 Hz) at δ = 37.2 and 29.6 ppm (Scheme 3).

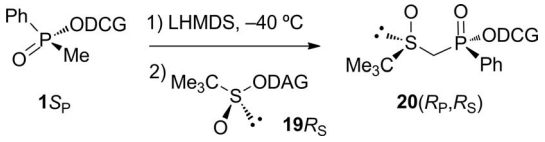


Scheme 3. Nucleophilic versus basic behavior of LHMDS in the reaction with DCG methyl phosphinate **1**S_P.

Taken all together, these data indicate that the product formed is the β-(phosphinyl)phosphinate. This result can be rationalized by recognizing that bulky LHMDS acts as a base leading to the intermediate formation of methyl carbanion [**1**S_P]$^-$ by abstraction of a proton from the methyl group. Subsequently, coupling of anion [**1**S_P]$^-$ with phosphinic ester precursor **1**S_P affords β-(phosphinyl)phosphinate derivative **18**(S_PR_P) almost quantitatively (91 % yield) as a single diastereomer (Scheme 3). Upon subjecting diastereomeric phosphinate **1**R_P to identical conditions, corresponding diastereomer **18**(R_PS_P) was obtained in high yield (73 %). It should be recalled that taking into account that in both cases one chiral fragment of DCG remains in the final products, the obtained compounds are diastereomers, which greatly simplifies analysis of the stereochemical outcome of the process. The reaction was also conducted with an equimolar mixture of diastereomeric phosphinates **1**S_P and **1**R_P and no chiral discrimination was observed in the nucleophilic substitution process.

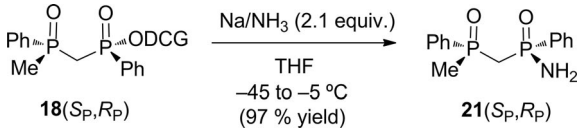
The described procedure is not limited to the preparation of β-(phosphinyl)phosphinates but can lead to other interesting *P*-stereogenic compounds by trapping the intermediate anion with other electrophiles. In this sense, addition of anion [**1**S_P]$^-$, generated at –40 °C in 2 h, over a solution of diastereopure (*R*)-DAG *tert*-butanesulfinate **19**R_S afforded corresponding β-(sulfinyl)phosphinate **20**(R_PR_S), which is a precursor of mixed S,P ligands, in good yield with good diastereoselectivity (Scheme 4).

Moreover, obtained β-(phosphinyl)phosphinates **18**, with an electrophilic phosphorus atom, can be used as intermediates for the synthesis of other compounds with two *P*-stereogenic



Scheme 4. Asymmetric synthesis of β-(sulfinyl)phosphinate **20**($R_P R_S$).

centers. The reaction of sodium amide with β-(phosphinyl)phosphinate derivative **18**($S_P R_P$) afforded almost quantitatively β-(phosphinyl)phosphinamide **21**($S_P R_P$), the configuration of which was assigned by assuming that the reaction proceeded by displacement of the sugar moiety with inversion of configuration at the phosphorus center, as in **1**S_P (Scheme 5).



Scheme 5. Asymmetric synthesis of β-(phosphinyl)phosphinamide **21**($S_P R_P$).

Conclusions

We reported an efficient approach for the preparation of structurally diverse *P*-chirogenic compounds with one or two *P*-chiral phosphorus atoms. The method is based on the interesting reactivity of dicyclohexylidene-D-glucose methyl phenyl phosphinates, **1**R_P and **1**S_P, easily accessible on multigram scale from a sugar carbinol, toward metal amides. Using nonhindered amides, such as $NaNH_2$, $LiNH_2$, and RNHLi, nucleophilic substitution at the phosphorus atom takes place to give the corresponding phosphinamides with inversion of configuration. By contrast, bulky lithium hexamethyldisilazane acts as base instead of a nucleophile, which results in the formation of the methyl-phosphinyl carbanion intermediate. This carbanion can then act as a nucleophile towards the same phosphinate to yield a β-(phosphinyl)phosphinate or can be trapped by other nucleophiles to afford other *P*-chirogenic compounds of interest. The obtained compounds, with an electrophilic phosphinic ester moiety, can further be used as starting materials for the synthesis of different *P*-chirogenic compounds of interest, which widens the scope of this approach. The application of this approach for the synthesis of highly efficient organocatalysts will be reported in due course.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all key intermediates and final products.

Acknowledgments

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Keywords: Asymmetric synthesis · Nucleophilic substitution · Phosphorus · Chirality

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