ChemPubSoc Europe

DOI: 10.1002/chem.201501324

CHEMISTRY A European Journal Communication

Phosphine Oxides

Experimental and Theoretical Investigations of the Stereoselective Synthesis of P-Stereogenic Phosphine Oxides

Laurent Copey,[a] Ludivine Jean-Gérard,[a] Eric Framery,[a] Guillaume Pilet,[b] Vincent Robert,[c] and Bruno Andrioletti*[a]

Abstract: An efficient enantioselective strategy for the synthesis of variously substituted phosphine oxides has been developed, incorporating the use of (1*S*,2*S*)-2-aminocyclohexanol as the chiral auxiliary. The method relies on three key steps: 1) Highly diastereoselective formation of P^V oxazaphospholidine, rationalized by a theoretical study; 2) highly diastereoselective ring-opening of the oxazaphospholidine oxide with organometallic reagents that takes place with inversion of configuration at the P atom; 3) enantioselective synthesis of phosphine oxides by cleavage of the remaining P–O bond. Interestingly, the use of a P^{III} phosphine precursor afforded a P-epimer oxazaphospholidine. Hence, the two enantiomeric phosphine oxides can be synthesized starting from either a P^V or a P^{III} phosphine precursor, which constitutes a clear advantage for the stereoselective synthesis of sterically hindered phosphine oxides.

Access to P^{III}- or P^V-stereogenic molecules is currently a subject of intense research, owing to of their promising use in enantioselective metallo- or organocatalysis.[1–3] However, P-stereogenic ligands used in enantioselective catalysis remain scarce due to the limited enantiostability of chiral arylphosphines and the difficulty in accessing enantiopure phosphorus compounds.

However, several very elegant methods giving access to enantioenriched P-stereogenic phosphines or phosphine oxides have been developed. Among them, the resolution of racemic mixtures was proposed,[4] as well as the enantioselective deprotonation of phosphine–boranes and phosphine oxides.[5–9] An alternative strategy involves the use of chiral auxiliaries[10–12] and the use of ephedrine represents a breakthrough in this field.[13] The so-called Jugé–Stephan method involves the stereoselective ring-opening of an oxazaphospholidine incorporating (+)- or (−)-ephedrine by using organometallic reagents. This very reliable method allowed the preparation of a large range of borane-protected phosphines in good to excellent yields and enantiomeric excesses. However, as ephedrine is an acknowledged precursor for methamphetamine and Methcathinone,[14] its commercial availability has become troublesome.

Additional efforts are currently dedicated to developing new chiral scaffolds and the recent reports by the groups of Verdaguer[15] and Han[16] undoubtedly constitute key contributions in this area. Inspired by the oxazaphospholidine method,[13] Verdaguer and co-workers carefully studied the ring opening of bulky oxazaphospholidines based on the *cis*-1-amino-2-indanol.[15] Conversely, Han et al. chose the tosylamide derived from (*R*)-2-(1-aminoethyl)-4-chlorophenol that affords a 6-membered-ring oxazaphospholidine upon reaction with phenylphosphonic dichloride. The latter strategy has proven fruitful as a large range of sterically crowded phosphine oxides was prepared in good yields and excellent enantioselectivities.

Simultaneously with Han's work, we investigated the possibility of using a new chiral auxiliary that would allow easy access to sophisticated P-stereogenic systems. We chose the readily available (1*S*,2*S*)-2-aminocyclohexanol, a chiral scaffold found in a large number of catalytic systems.[17] It was expected that the relatively rigid and bulky cyclohexyl backbone would lead to highly diastereoselective transformations, even in the case of sterically crowded phosphines.[18] Moreover, the four stereoisomers of 2-aminocyclohexanol are either commercially available or can be readily prepared.[17a] Within the frame of our study, we decided to use the *trans* stereoisomer, which was seldom used in related studies and would afford a fairly reactive 5-membered oxazaphospholidine ring. During our investigations, only the (*S*,*S*) enantiomer was used when enantioselective reactions were carried out. Tolylsulfonamide afforded good results in the case of Han's (*R*)-2-(1-aminoethyl)-4-chlorophenol strategy. Hence, we decided to first investigate the effect of the tolylsulfonamide substituent on the outcomes of the reaction.

The reaction of tosyl-protected (+/-)-*trans*-1,2-aminocyclohexanol (±)-**1** with phenylphosphonic dichloride in the presence of *N*-methylimidazole (*N*-MeIm) in dichloromethane at 25 °C afforded the expected oxazaphospholidine oxide **4** with

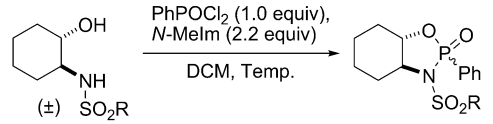
[a] *L. Copey, Dr. L. Jean-Gérard, Dr. E. Framery, Prof. B. Andrioletti*
Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS-UMR CNRS 5246), Université Claude Bernard Lyon 1, Bâtiment Curien (CPE)
43, Bd du 11 Novembre 1918, 69622 Villeurbanne cedex (France)
Fax: (+33) 472-44-6264
E-mail: bruno.andrioletti@univ-lyon1.fr
Homepage: http://www.icbms.fr/casyen/45-casyen-andrioletti/23-andrioletti

[b] *Dr. G. Pilet*
Laboratoire des Multimatériaux et Interfaces (UMR 5615)
Université Claude Bernard Lyon 1
43, Bd du 11 Novembre 1918, 69622 Villeurbanne cedex (France)

[c] *Prof. V. Robert*
Laboratoire de Chimie Quantique—UMR 7177, Institut de Chimie 1
rue Blaise Pascal 67081 Strasbourg (France)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201501324.

Table 1. Diastereoselective formation of oxazaphospholidine.



Entry	R	Amino alcohol	T [°C]	d.r. of the crude (yield [%])[a]	Oxazaphospholidine
1	Tol	(±)-**1**	25	91:9	**4**
2	Me	(±)-**2**	25	80:20	**5**
3	Mes	(±)-**3**	25	87:13	**6**
4	Tol	(±)-**1**	−20	94:6 (100)	**4**
5	Tol	(±)-**1**	−78	99:1 (100)	**4**

[a] Determined by ^{31}P NMR spectroscopy (see the Supporting Information).

a diastereoisomeric ratio (d.r.) of 91:9 (Table 1, entry 1). Switching from a tolyl to a methyl or mesityl sulfonamide (Table 1, entries 2 and 3) afforded a lower d.r. of 80/20 and 87/13, respectively. Hence, we decided to optimize the reaction conditions with the tosyl amide and screened various bases, solvents, and reaction temperatures (see the Supporting Information). The study revealed that the d.r. increased when the temperature decreased and the highest d.r. (99:1) was obtained at −78 °C, without altering the chemical yield (100%; Table 1, entry 5). It is also important to note that the concentration of the starting *N*-tosylamido alcohol (±)-**1** must be kept below 0.5 M to avoid the formation of a dimeric species.[19,23]

The configuration at the phosphorus atom of the major diastereoisomer was assigned unambiguously by using NMR spectroscopy. For example, structural determination of oxazaphospholidine **4** was determined by NOESY experiments (see the Supporting Information). As ^{1}H NMR spectroscopy indicated that the bicyclic structure of oxazaphospholidine **4** is rigid, it was anticipated that the phenyl group would display NOE signals with either H1 or H2, depending on the absolute configuration of the phosphorus atom. The NOESY spectrum exhibited only one NOE signal between H2 and Ph. No cross-peak with H1 was observed, and the *cis* position of H2 and the phenyl group was unequivocally established (Figure 1). X-Ray crystal structure analysis of single crystals obtained from vapor diffusion of pentane into a solution of oxazaphospholidine **4** in chloroform confirmed the assignment unambiguously (Figure 1, right).[23] Computational studies were also performed to rationalize the high diastereoselectivity observed (see below).

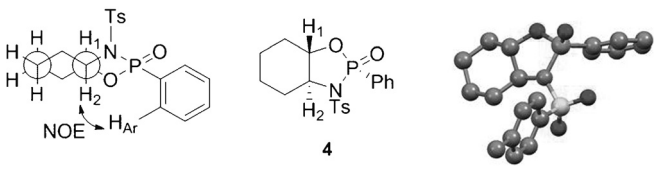
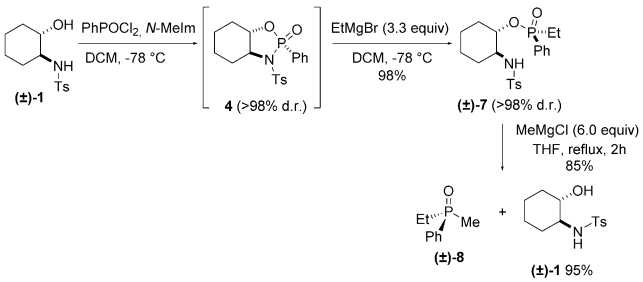


Figure 1. P configuration of oxazaphospholidine **4** determined by using NOESY (^{1}H–^{1}H) experiment and X-Ray crystal structure determination.

As oxazaphospholidine **4** appeared rather unstable during purifications, the activated P–N bond was next selectively cleaved[15] upon treatment of the crude oxazaphospholidine with 3.3 equivalents of ethylmagnesium bromide at −78 °C in dichloromethane (Scheme 1). At this temperature, only one diastereoisomer (±)-**7** was detected and was isolated by silica gel flash chromatography in 98% yield over two steps.



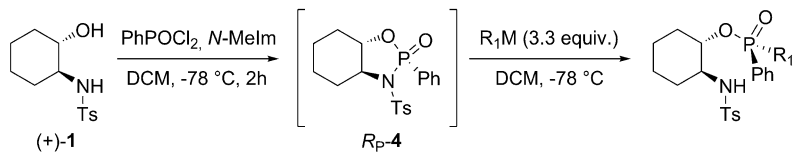
Scheme 1. Synthesis of phosphine oxide (±)-**8** by sequential cleavage of P–N and P–O bonds.

Cleavage of the P–O bond appeared more difficult and harsh conditions were needed. Indeed, addition of 6 equivalents of Grignard reagents and heating of the reaction mixture at reflux for 2 h were required to ensure the conversion of phosphinate (±)-**7** to phosphine oxide (±)-**8** in 85% yield. It should also be noted that the chiral auxiliary (±)-**1** could be recovered in 95% yield. When 4 equivalents of Grignard were used under reflux, the desired phosphine oxide (±)-**8** was formed in 58% yield. Switching to organolithium reagents resulted in the degradation of the phosphinate at elevated temperature, and did not afford (±)-**8** in more than 15% yield at 25 °C. X-Ray diffraction analysis of the obtained single crystals of (±)-**7** proved that, as expected,[16] ring opening occurred with inversion of configuration at the P atom.[20,23]

The method was then applied to the enantiomerically pure tosylamido-protected *trans*-1,2-aminocyclohexanol (+)-**1**.[21] By using the previously optimized conditions, oxazaphospholidine R_P-**4** was formed by treatment of (+)-**1** with *N*-MeIm and phenylphosphonic dichloride in dichloromethane at −78 °C. After 2 h of reaction at this temperature and 1 hour at 25 °C, ^{31}P NMR spectroscopy confirmed the quantitative and highly diastereoselective conversion of the starting amino alcohol to the oxazaphospholidine (see the Supporting Information). Next, we turned our attention to the in situ ring opening of oxazaphospholidine R_P-**4** with various Grignard reagents. To this end, the reaction mixture was cooled to −78 °C and 3.3 equivalents of Grignard reagent were added (Table 2).

Different alkyl and aryl Grignard reagents were investigated. Primary alkylmagnesium reagents afforded the corresponding phosphinates (+)-R_P-**7** and (+)-R_P-**9** in very good yields and excellent diastereoselectivities (Table 2, entries 1 and 2). Secondary alkylmagnesium reagents could also be employed as nucleophiles, albeit with diminished diastereoselectivity (Table 2, entries 3 and 4). The reactions of sterically hindered Grignard reagents, such as *t*BuMgBr and FcMgBr, were more challeng-

Table 2. Diastereoselective ring opening of oxazaphospholidine.



Entry	R_1–M	d.r. of the crude[a]	Yield [%] (d.r.)[a]	Phosphinate
1	EtMgBr	99:1	98 (>99:1)	(+)-R_P-**7**
2	MeMgCl	95:5	81 (>99:1)	(+)-R_P-**9**
3	*i*PrMgCl	90:10	60 (96:4)	(+)-R_P-**10**
4	CyMgBr	76:24	50 (>99:1)	(−)-R_P-**11**
5	*t*BuLi[b]	82:18	31 (97:3)	(+)-R_P-**12**
6	FcLi[b]	99:1	60 (>99:1)	(−)-S_P-**13**
7	vinylMgBr	99:1	67 (>99:1)	(−)-R_P-**14**
8	*o*AnMgBr	99:1	97 (>99:1)	(−)-S_P-**15**
9	*o*BiPhMgBr	99:1	65 (>99:1)	(−)-S_P-**16**
10	MesMgBr	80:20	35 (>99:1)	(−)-S_P-**17**

[a] Yield of isolated product; d.r. determined by ^{31}P NMR spectroscopy; [b] the corresponding Grignard reagent did not afford any desired phosphinate. Dichloromethane was thus removed by evaporation and replaced with anhydrous THF.

ing. The use of the less basic but more nucleophilic organolithium reagents was required to afford the expected phosphinates, although in a lower yield (Table 2, entries 5 and 6). The addition of arylmagnesium reagents (*o*-anisyle and 2-biphenyl) resulted in the formation of the corresponding phosphinates (−)-S_P-**15** and (−)-S_P-**16** in good to excellent yields (97% and 65% respectively) and excellent diastereoselectivities (99/1) (Table 2, entries 8 and 9). In contrast, the addition of a bulky mesitylmagnesium reagent took place with a moderate selectivity of 60% (Table 2, entry 10).

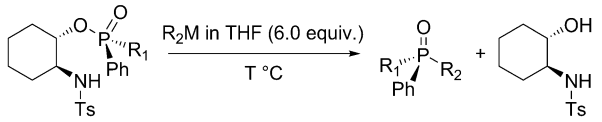
X-Ray crystal structure analysis of (−)-S_P-**15** confirmed the inversion of stereochemistry previously observed (Scheme 1; see the Supporting Information).[23] Interestingly, the reaction could be easily scaled up to allow the preparation of phosphinates (+)-R_P-**9**, (−)-S_P-**15**, and (−)-S_P-**16** on a gram scale (81, 54, and 64% yield, respectively) with excellent diastereoselectivities (d.r. > 99:1).

Cleavage of the P–O bond to afford the desired phosphine oxides was next assayed. The previously developed conditions were applied to phosphinate (−)-S_P-**15**, but the enantioselectivity was moderate (e.r. = 86:14; Table 3, entry 1). Higher *ee* values were obtained when the temperature was decreased to 40 °C and the Grignard reagent reacted with the neat phosphinate. These precautions led to a significant increase in the enantioselectivity (e.r. = 97:3) after 10 h of reaction without altering the reaction yield (Table 3, entry 2). As expected,[16] the P–O bond cleavage occurred with inversion of configuration at the phosphorus atom (see the Supporting Information). The scope of this P–O bond cleavage was next evaluated using various Grignard reagents.[22]

Methylmagnesium chloride reacted successfully with phosphinate (−)-S_P-**15** with a satisfying enantioselectivity (Table 3, entry 3). Unfortunately, bulkier Grignard reagents such as *i*PrMgCl failed to provide the desired phosphine oxide (Table 3, entry 4). Similar results were obtained when bulky phosphinates and small nucleophiles were used (Table 3, entries 6 and 7). Interestingly, a biphenyl-based phosphine oxide ligand (−)-S_P-**20** could be synthesized in 78% yield and good enantioselectivity (e.r. = 96:4; Table 3, entry 5). By using a less sterically hindered phosphinate, such as methylphenyl phosphinate (+)-R_P-**9**, a larger range of nucleophiles could be introduced, affording the desired phosphine oxides (+)-R_P-**19**, (−)-S_P-**8**, and (−)-S_P-**21** with excellent enantioselectivities, albeit with limited yields when the steric hindrance of the Grignard nucleophiles increased.

The first cyclization step to form oxazaphospholidine was critical because of the *trans* disposition of the two nucleophilic groups. As far as we know, such rigid *trans* oxazaphospholidine species have not been reported to date and, contrary to the P–N and P–O bond cleavage, the formation of the major diastereoisomer was thus not predictable. To gain insights into the high stereoselectivity obtained and the underlying mechanism of the reaction, we carried out complementary density functional theory (DFT) calculations (see the Supporting Information). Preliminary investigations revealed that the reaction proceeds under kinetic control (see the Supporting Information). Accordingly, different reaction paths were considered to clarify the *R* kinetic preference in the cyclization reaction. Assuming that the reaction is a two-step process, first involving the P–O bond formation between the alcohol and $PhPOCl_2$ followed by the P–N bond formation, activation energies calculations favor a base-assisted S_N2 mechanism for the initial P–O bond forma-

Table 3. Synthesis of P-stereogenic phosphine oxides.



Entry	R_1	R_2–M	*T* [°C]	Yield [%] (e.r.)[a]	Phosphine oxide
1[b]	*o*An	EtMgBr	66	61 (86:14)	(−)-S_P-**18**
2	*o*An	EtMgBr	40	60 (97:3)	(−)-S_P-**18**
3[c]	*o*An	MeMgCl	40	95 (90:10)	(−)-S_P-**19**
4	*o*An	*i*PrMgCl	40[d]	No reaction	–
5	*o*BiPh	MeMgCl	40	78 (96:4)	(−)-S_P-**20**
6	*t*Bu	MeMgCl	40	No reaction	–
7	Fc	MeMgCl	40	No reaction	–
8	Me	*o*AnMgBr	40	60 (93:7)	(+)-R_P-**19**
9	Me	EtMgBr	40	82 (>99:1)	(−)-S_P-**8**
10	Me	*i*PrMgCl	40	50 (>99:1)	(−)-S_P-**21**
11	Me	CyMgCl	40[d]	No reaction	–

[a] Yield of isolated product; e.r. determined by HPLC; [b] EtMgBr (3 M in Et_2O) was added to a solution of phosphinate (−)-R_P-**14** in THF (1 M); [c] the optically pure chiral auxiliary was recovered in 81% yield; [d] heating the reaction mixture under reflux only led to decomposition of the starting phosphinate.

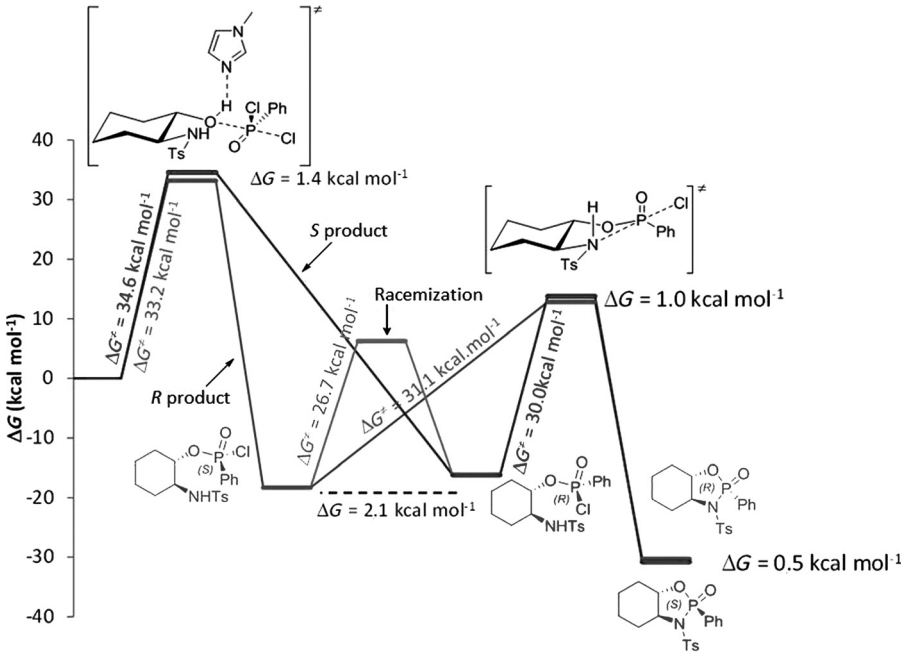
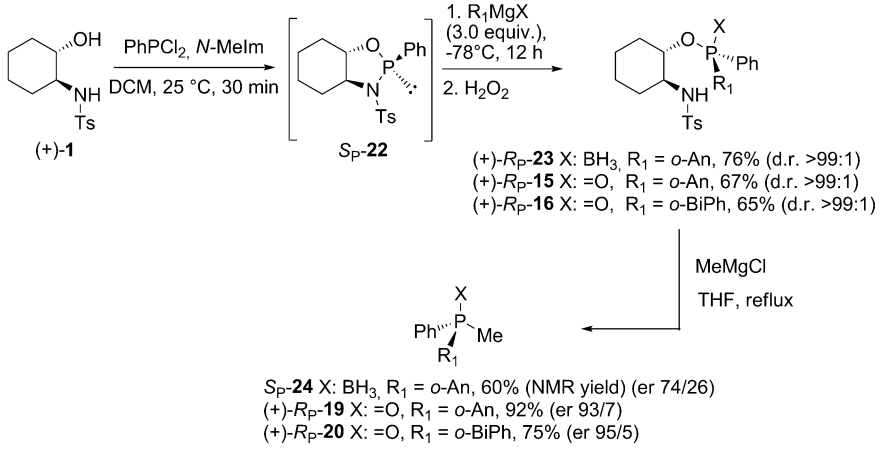


Figure 2. Free energy profile with corresponding activation energies (kcal mol^{-1}). The energy difference between the second-step transition states $\Delta G = 1.0$ kcal mol^{-1}.

tion, ruling out the addition–elimination pathway. In light of this model inspection, the activation barriers to forming the *R* and *S* compounds were evaluated in dichloromethane as solvent and using a chlorine anion (Figure 2). From our calculations, the *S* adduct is kinetically favored over the *R* adduct, the energy barriers being 33.8 and 34.5 kcal mol^{-1}, respectively. Let us stress that the *R* intermediate is less stable than the *S* (2.1 kcal mol^{-1}) and the interconversion energy barrier is 26.4 kcal mol^{-1}, a much smaller value than previously calculated energy barriers. Starting from the identified intermediates, the second reaction step leading to the cyclic adduct was then considered. Two different sets of transition states were identified. They differ by the relative orientations of the P=O and N–H bonds. For the sake of simplicity, these will be referred to as parallel and antiparallel transition states. The calculated energy barriers are very similar (ca. 30 kcal mol^{-1}). Nevertheless, the antiparallel transition state generated from the preferred *S* intermediate is the lowest in energy and leads to the *R* cyclic adduct. The competing route that produces the *S* stereoisomer goes through a transition state lying $\Delta G = 1.0$ kcal mol^{-1} higher in energy. At this stage, one should remember that the interconversion barrier between the *R* and *S* reaction intermediates is 26.7 kcal mol^{-1}. Therefore, this particular reaction is not rate-limiting and suggests that the second step discriminates between the *R* and *S* products. Interestingly, the ΔG value is compatible with our experimental findings. The overall reaction is diastereoselective at room temperature with a 10:1 ratio in favor of the least thermodynamically stable adduct.

Given the different reactivity of P^V and P^{III} derivatives, it was appealing to apply the methodology previously developed to the synthesis of chiral phosphines. Accordingly, dichlorophenylphosphine was treated with *N*-tosyl-protected *trans*-1,2-aminocyclohexanol (+)-**1**. After 30 min at room temperature, the formation of the desired oxazaphospholidine **22** could be detected with the apparition of a single peak at $\delta = 137.6$ ppm on the ^{31}P NMR spectrum. Due to its low stability, the product could not be isolated, but NOESY experiments measured on the crude mixture evidenced the formation of only one diastereoisomer S_P-**22**, epimer at the P atom of oxazaphospholidine oxide R_P-**4** (see the Supporting Information).

Similarly to the strategy developed for the phosphine oxide synthesis, the reaction of Grignard reagents with the crude oxazaphospholidine **22** at low temperature afforded the ring-opened phosphinate, which was trapped as a borane adduct (+)-R_P-**23**. Purification issues only permitted the isolation of the *o*-anisylphenylphosphinite–borane complex, albeit in a good 76% yield and with a diastereoselectivity over 99/1 (Scheme 2). Unfortunately, the desired chiral phosphine–borane S_P-**24** was not obtained with satisfying yield or enantioselectivity when



Scheme 2. P^{III} strategy.

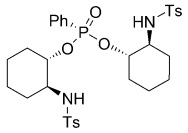
phosphinite (+)-R_P-**23** was treated with 6.0 equivalents of methylmagnesium chloride. Further optimization, such as the use of the more nucleophilic methyllithium, failed to provide the desired phosphine S_P-**24**. Nevertheless, the phosphinites could be oxidized in situ to the corresponding phosphinates upon treatment with hydrogen peroxide (Scheme 2) and reacted with the appropriate Grignard reagents to afford the final phosphine oxides (+)-R_P-**19** and (+)-R_P-**20**, respectively, in very good yields and enantioselectivities.

In conclusion, we have reported the efficient synthesis of a large range of enantioenriched phosphine oxides using the readily available chiral 2-aminocyclohexanol scaffold. We have also demonstrated that the P^V and P^{III} strategies afford the P-epimeric oxazaphospholidines. Hence, if the order of addition of the 2 Grignard reagents is maintained, the two enantiomeric phosphine oxides are obtained. This constitutes a clear advantage for the synthesis of sterically hindered phosphine oxides, knowing the difficulty to introduce a bulky substituent at the last step. Thorough theoretical investigations revealed the *R* kinetic preference for the cyclization step and a preference for the *S* enantiomer with a $\Delta G = 1.0$ kcal mol^{-1} in agreement with the experimental observations.

Acknowledgements

This work was supported by the French Ministry of Higher Education (MESR), Université Claude Bernard, Lyon 1, and the CNRS.

Keywords: asymmetric synthesis · chiral auxiliaries · computational studies · phosphanes · stereochemistry

[1] *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis* (Eds.: P. C. J. Kamer, P. W. N. M. van Leeuwen), John Wiley & Sons, New York, **2012**.
[2] A. Grabulosa, *P-Stereogenic Ligands in Enantioselective Catalysis, RSC Catalysis Series No. 7*, Royal Society of Chemistry, London, UK, **2011**.
[3] S. Takizawa, E. Rémond, F. A. Arteaga, Y. Yoshida, V. Sridharan, J. Bayardon, S. Jugé, H. Sasai, *Chem. Commun.* **2013**, *49*, 8392 – 8394.
[4] A. Grabulosa, *P-Stereogenic Ligands in Enantioselective Catalysis, RSC Catalysis Series No. 7*, Royal Society of Chemistry, London, UK, **2011**, pp. 21 – 113.
[5] T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamagushi, *J. Am. Chem. Soc.* **1998**, *120*, 1635 – 1636.
[6] Y. Yamanoi, T. Imamoto, *J. Org. Chem.* **1999**, *64*, 2988 – 2989.
[7] A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075 – 976.
[8] B. Wolfe, T. Livinghouse, *J. Am. Chem. Soc.* **1998**, *120*, 5116 – 5117.
[9] C. Popovici, P. Oña-Burgos, I. Fernández, L. Roces, S. García-Granda, M. J. Iglesias, F. L. Ortiz, *Org. Lett.* **2010**, *12*, 428 – 431.
[10] a) O. Korpiun, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784 – 4786; b) O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4842 – 4846.
[11] U. Schmidt, B. Riedl, H. Griesser, C. Fitz, *Synthesis* **1991**, 655 – 657.
[12] A. Benabra, A. Alcudia, N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron: Asymmetry* **1996**, *7*, 3353 – 3356.
[13] a) S. Juge, M. Stephan, J. A. Laffite, J. P. Genet, *Tetrahedron Lett.* **1990**, *31*, 6357 – 6360; b) F. Chaux, S. Frynas, H. Laureano, C. Salomon, G. Morata, M.-L. Auclair, M. (M.) Stephan, R. Merdès, P. Richard, M.-J. Ondel-Eymin, J.-C. Henry, J. Bayardon, C. Darcel, S. Jugé, *C. R. Chim.* **2010**, *13*, 1213 – 1226.
[14] J. P. Morgan in *Substance Abuse A Comprehensive Textbook, 4th ed.* (Eds.: J. H. Lowinson, P. Ruiz, R. B. Millman, J. G. Langrod), Lippincott, Williams & Wilkins, Philadelphia, USA, **2005**, pp. 367 – 373.
[15] a) T. León, A. Riera, X. Verdaguer, *J. Am. Chem. Soc.* **2011**, *133*, 5740 – 5743; b) H. Zijlstra, T. León, A. de Cózar, C. Fonseca Guerra, D. Byrom, A Riera, X. Verdaguer, F. M. Bickelhaupt, *J. Am. Chem. Soc.* **2013**, *135*, 4483 – 4491.
[16] Z. S. Han, N. Goyal, M. A. Herbage, J. D. Sieber, B. Qu, Y. Xu, Z. Li, J. T. Reeves, J.-N. Desrosiers, S. Ma, N. Grinberg, H. Lee, H. P. R. Mangunuru, Y. Zhang, D. Krishnamurthy, B. Z. Lu, J. J. Song, G. Wang, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 2474 – 2477.
[17] See for instance a) I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2320 – 2331; b) K. Glegoła, C. Midrier, E. Framery, K. M. Pietrusiewicz, *Phosphorus Sulfur Silicon Relat. Elem.* **2009**, *184*, 1065 – 1075.
[18] Using 1-amino-2-indanol (ref. [15]), Verdaguer et al. demonstrated that bulky P-stereogenic amino phosphines could be efficiently prepared. Hence a phenol motif is a not a pre-requisite for the preparation of bulky phosphines.
[19] When the concentration of the reaction mixture exceeds 0.5 M, the dimer was formed in variable amounts. Its structure was elucidated thanks to X-Ray analysis and NOESY experiments (see the Supporting Information).


[20] Oxazaphospholidine oxide R_P-**4** and phosphinate (±)-R_P-**7** possess the same R_P configuration descriptor but the spatial arrangement around the phosphorus atom differs.
[21] J. Huang, P. O'Brien, *Synthesis* **2006**, 425 – 434.
[22] The optical purities and the inversion of configuration at the P atom were confirmed by comparing the specific rotation measured for the obtained phosphine oxides with the known values reported in the literature (see the Supporting Information).
[23] CCDC 1052841, 1052842, 1052843 and 1052844 contain the supplementary crystallographic data for complexes R_P-**4**, (±)-R_P-**7**, (−)-S_P-**15**, and dimeric phosphonate, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: April 3, 2015
Published online on May 15, 2015