Synthetic Methods

International Edition: DOI: 10.1002/anie.201500350
German Edition: DOI: 10.1002/ange.201500350

Efficient Asymmetric Synthesis of Structurally Diverse P-Stereogenic Phosphinamides for Catalyst Design**

Zhengxu S. Han, Li Zhang, Yibo Xu, Joshua D. Sieber, Maurice A. Marsini, Zhibin Li, Jonathan T. Reeves, Keith R. Fandrick, Nitinchandra D. Patel, Jean-Nicolas Desrosiers, Bo Qu, Anji Chen, DiAndra M. Rudzinski, Lalith P. Samankumara, Shengli Ma, Nelu Grinberg, Frank Roschangar, Nathan K. Yee, Guijun Wang, Jinhua J. Song, and Chris H. Senanayake*

Abstract: *The use of chiral phosphinamides is relatively unexplored because of the lack of a general method for the synthesis. Reported herein is the development of a general, efficient, and highly enantioselective method for the synthesis of structurally diverse P-stereogenic phosphinamides. The method relies on nucleophilic substitution of a chiral phosphinate derived from the versatile chiral phosphinyl transfer agent 1,3,2-benzoxazaphosphinine-2-oxide. These chiral phosphinamides were utilized for the first synthesis of readily tunable P-stereogenic Lewis base organocatalysts, which were used successfully for highly enantioselective catalysis.*

Organophosphorus compounds have a rich history[1] and their use as achiral or chiral ligands for transition metal catalyzed transformations has been rapidly growing in both laboratory synthesis and industrial production.[2] In spite of heavy activities in this area and the emergence of a few methods for the synthesis of alkyl- or aryl-containing P-stereogenic phosphorus compounds or aminophosphines,[3] the field of phosphinamide chemistry remains relatively unexplored, and very few phosphinamides (**1**; Figure 1), in particular chiral compounds, have been prepared.

In recent years, phosphoric acid derivatives, in particular the -P(=O)-N- motif, have drawn significant attention and have been incorporated into the design and synthesis of several Brønsted acid and Lewis base organocatalysts (e.g. **A**, **B**, and **C**; Figure 1) for asymmetric transformations.[4,5] In all these cases, non-P-stereogenic phosphoramide motifs were used, and to achieve high asymmetric induction, a sterically hindered or rigid carbon backbone is typically needed. We envisioned that chiral, P-stereogenic phosphinamides such as

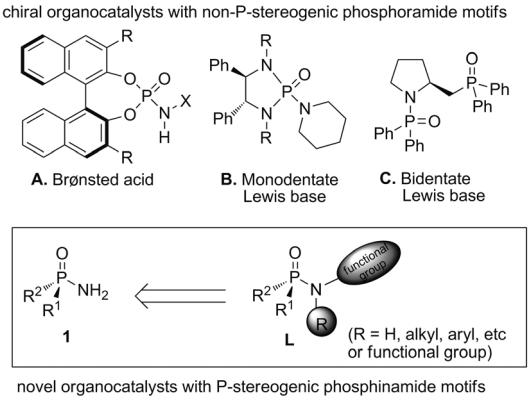


Figure 1. Design concept for P-stereogenic organocatalysts.

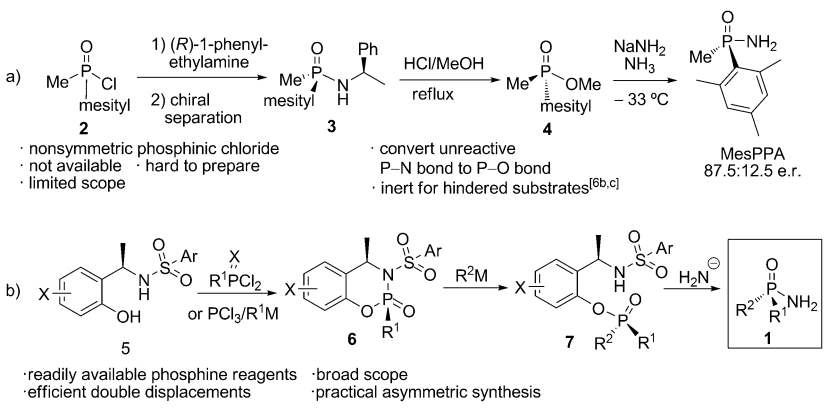
L (Figure 1) might serve either as an effective organocatalytic Brønsted acid (NH site) or a Lewis base (O site) depending on the nature of the substituent on N, and that the chiral environment could be induced by the P-stereogenicity. To the best of our knowledge, the use of P-stereogenic phosphinamides as catalysts for asymmetric transformations is heretofore unknown, most likely because of the lack of a general and efficient methodology for preparation of these valuable compounds in an enantioselective fashion.

A literature survey revealed that only three P-stereogenic phosphinamides, such as methylphenylphosphinamide (MPPA) and mesitylphenylphosphinamide (MesPPA; Scheme 1a), have been reported in enantiomerically pure/enriched form, and all were obtained by chiral separations.[6] In addition, their utility has only been examined for use as a chiral auxiliary.[6] It is apparent that these approaches have limited scope because of the use of difficult-to-prepare nonsymmetrical $R^1R^2P(O)Cl$ reagents.[6b,c] Therefore, to systematically explore the P-stereogenic phosphinamides as a new class of organocatalysts for asymmetric transformations, it is essential for us to first have an efficient method for accessing a range of structurally diverse P-stereogenic phosphinamides (**1**). Herein, we describe the development of the first general asymmetric synthesis of **1** and disclose our initial findings for their use as asymmetric organocatalysts.

Recently, we reported an efficient asymmetric method for the synthesis of P-stereogenic phosphine oxides with diverse steric and electronic properties using our novel template (**5**),

[*] Dr. Z. S. Han, L. Zhang, Y. Xu, Dr. J. D. Sieber, Dr. M. A. Marsini, Dr. Z. Li, Dr. J. T. Reeves, Dr. K. R. Fandrick, Dr. J.-N. Desrosiers, Dr. B. Qu, D. M. Rudzinski, Dr. L. P. Samankumara, Dr. S. Ma, Dr. N. Grinberg, Dr. F. Roschangar, Dr. N. K. Yee, Dr. J. J. Song, Dr. C. H. Senanayake
Department of Chemical Development
Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Road, Ridgefield, CT 06877 (USA)
E-mail: steve.han@boehringer-ingelheim.com
A. Chen, Dr. G. Wang
Department of Chemistry and Biochemistry
Old Dominion University, Norfolk, VA 23529 (USA)

[**] We thank Scott Pennino and Keith McKellop for HRMS analysis.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500350.



Scheme 1. Strategy for efficient asymmetric synthesis of P-stereogenic phosphinamides through a double displacement.

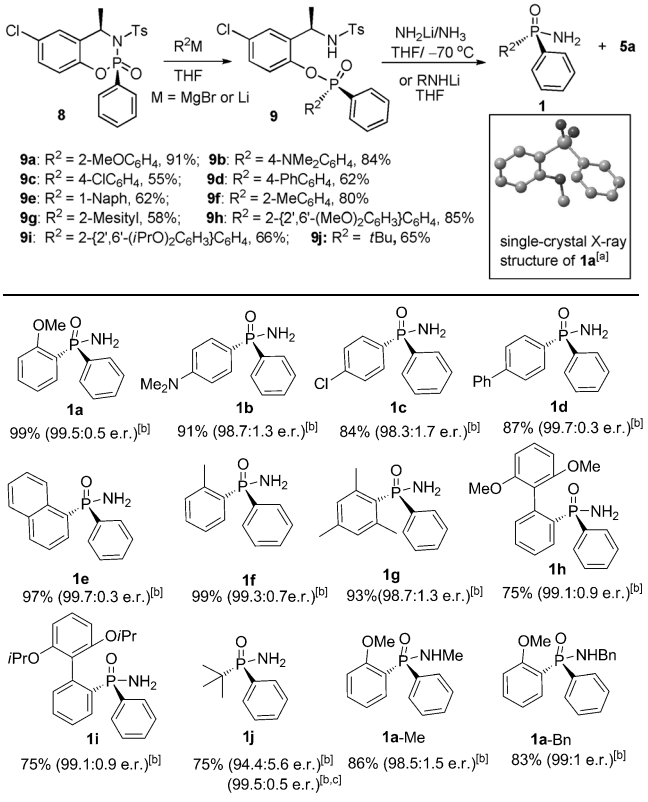
from which **6** is prepared with high stereoselectivity and good yields using readily available PCl_3, R^1PCl_2, or $R^1P(O)Cl_2$ reagents (Scheme 1b).[3h] Cleavage of the P–N bond by the first nucleophile provides the chiral intermediate **7**. Subsequent P–O bond cleavage of **7** with a second carbon nucleophile provided P-stereogenic phosphine oxides in high enantiomeric purity. We envisioned that use of an "NH_2" equivalent as the nucleophile for reaction with **7** should allow a general synthesis of the desired phosphinamide **1**.

Our initial studies geared toward probing reactivity of the P–O bond towards $LiNH_2$ revealed that phosphinates with a phenol functionality are more reactive than others,[6c,7,8] thus implying that **5** would have a more general use for the synthesis of **1** with a potentially wide scope. The stereoselectivity for the P–O bond cleavage of the chiral phosphinate **9a**[3h] was next examined by employing $LiNH_2$ as the nucleophile (Table 1). To our delight, when a THF solution of optically pure **9a** was added to a $LiNH_2/NH_3$ solution, prepared in situ at −70 °C, the reaction was completed in less than 30 minutes to provide the desired P-stereogenic phosphinamide **1a** in quantitative yield and 99.5:05 e.r. along with recycled (R)-**5a** (X = 4-Cl, Ar = p-tolyl).

Encouraged by this finding, the synthesis of diversely functionalized P-stereogenic diarylphosphinamides was investigated. A variety of chiral phosphinates (**9b–j**) were prepared from **8** in good yield on gram scale.[3h,9a] P-stereogenic phosphinamides with electron-donating (**1b**) and electron-withdrawing (**1c**) groups were readily prepared in excellent yields and enantioselectivities, as were the polyaromatic phosphinamides **1d** and **1e**. Furthermore, compounds with sterically hindered aromatic rings (**1f–i**) were also be produced in good yields and with excellent enantiomeric purity. These results compared favorably with the previously reported synthesis, for example, for compound **1g**, where low yield and low enantiomeric purity (87.5:12.5 e.r.) was obtained.[6b] The compound **1j**, containing a *tert*-butyl group, was also readily prepared by this method, and the initial enantiopurity of 95:5 e.r. was upgraded to greater than 99:1 e.r. following recrystallization from dichloromethane and hexanes. Additionally, reaction of either MeNHLi or BnNHLi with **9a** afforded the corresponding **1a**-Me and **1a**-Bn products in good yields and high enantiomeric purity.

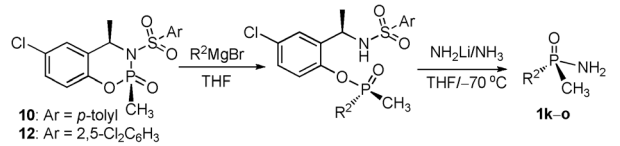
In light of these encouraging results, we turned our efforts to the preparation of P-stereogenic methyl-substituted arylphosphinamides analogous to MPPA (**1k**; Table 2). Initial attempts to synthesize the corresponding methylphosphinate by addition of MeMgCl to **8** afforded low yields (< 10 %). However, this issue was resolved by utilizing the methyl oxazaphosphinine 2-oxide derivative **10**. The addition of PhMgCl afforded **11a** in 66 % yield. The P-Stereogenic MPPA **1k** was then prepared from **11a** in excellent yield and high enantiomeric purity (Table 2).[6a] By using this methodology, **11b** and **11c** were prepared from **10** in good yields, and the synthesis of the corresponding **11l** and **1m** was accomplished as previously described. However, treatment of **10** with the more sterically hindered *o*-tolylMgCl and weakly nucleophilic 4-ClC_6H_4MgBr resulted in sluggish reactions and less than 30 % yields of the isolated, desired phosphinate products along with a large amount of double-addition side-products. We hypothesized that a system containing a more reactive P–N bond relative to the P–O

Table 1: Synthesis of P-stereogenic diaryl- or alkylarylphosphinamides.

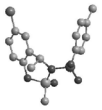


[a] Refer to CCDC 1037717 for crystal structure data.[13] [b] Yield is that of the isolated product. The e.r. value was determined by HPLC analysis using a chiral stationary phase. [c] After recrystallization from CH_2Cl_2/hexanes. THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

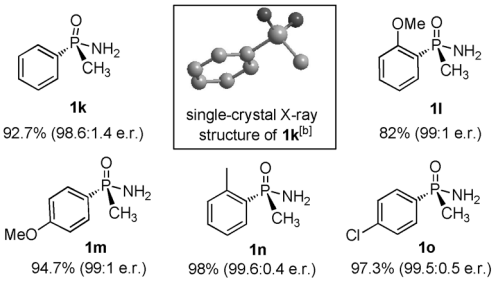
Table 2: Synthesis of methyl-containing P-stereogenic phosphinamides.



11a: Ar = *p*-tolyl, R^2 = Ph, 66.5%
11b: Ar = *p*-tolyl, R^2 = 2-$MeOC_6H_4$, 92%
11c: Ar = *p*-tolyl, R^2 = 4-$MeOC_6H_4$, 69%
13a: Ar = 2,5-$Cl_2C_6H_3$, R^2 = 2-MeC_6H_4, 85%
13b: Ar = 2,5-$Cl_2C_6H_3$, R^2 = 4 -ClC_6H_4, 80%



single-crystal X-ray structure of **10**[a]



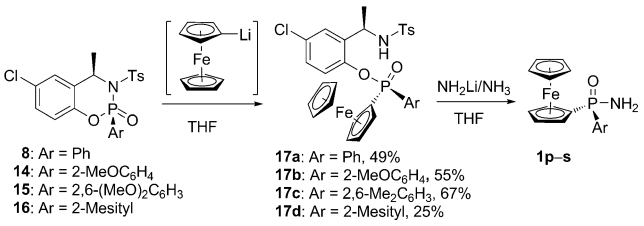
Yield is that of the isolated product. The e.r. value was determined by HPLC analysis using a chiral stationary phase. [a] Refer to CCDC 1037720 for crystal structure data.[13] [b] Refer to CCDC 1037718 for crystal structure data.

bond of **10** would be needed to allow a chemoselective ring-opening reaction. Therefore, we tested the cyclic template **12** which contains a stronger electron-withdrawing 2,5-dichlorobenzenesulfonyl moiety. Reaction of **12** with *o*-tolylMgBr and 4-ClC_6H_4MgBr now provided the desired products **13a** and **13b**, respectively, in excellent yields with only trace amounts of double addition side-products. Thus, methylarylphosphinamides **1n** and **1o** were prepared in excellent yields and enantiomeric purities.[9a]

P-stereogenic phosphinamides containing ferrocenyl substituents could also be prepared using this methodology. The required phosphinate intermediates **17a–d** were synthesized in moderate to good yields from the corresponding cyclic compounds **8** and **14**–**16** (Table 3).[9b] Subsequent aminolysis with $LiNH_2/NH_3$ afforded the ferrocenyl arylphosphinamides **1p–s** in excellent yields and enantiopurities. There were also no difficulties in the preparation of the sterically demanding phosphinamides **1r** and **1s**.

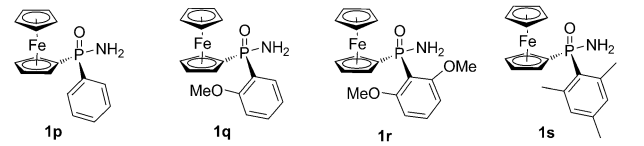
With these P-stereogenic phosphinamides in hand, we next investigated their utility in asymmetric catalysis. We have designed and synthesized the first simple and modular family of P-stereogenic phosphinamide-based bidentate phosphine oxide (P=O) Lewis base catalysts (**L1–L6**) from **1** by simply changing R^1 and R^2 only (see footnote of Table 4).[10] And their reactivities in the asymmetric reduction of chalcone derivatives were examined.[11] Our preliminary studies using these P-stereogenic Lewis base catalysts for promoting the challenging 1,4-reduction of the α,β-unsaturated ketone **19a** with trichlorosilane revealed a high potential for enantioselective catalysis (Table 4). All designed catalysts effected complete reaction within 24–40 hours at 0 °C to furnish the desired product **20a** in quantitative yield with significantly

Table 3: Synthesis of P-stereogenic ferrocenyl arylphosphinamides.



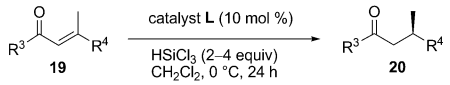
8: Ar = Ph
14: Ar = 2-$MeOC_6H_4$
15: Ar = 2,6-$(MeO)_2C_6H_3$
16: Ar = 2-Mesityl

17a: Ar = Ph, 49%
17b: Ar = 2-$MeOC_6H_4$, 55%
17c: Ar = 2,6-$Me_2C_6H_3$, 67%
17d: Ar = 2-Mesityl, 25%



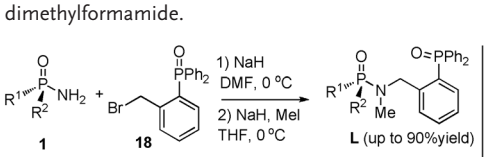
Yield is that of the isolated product. The e.r. value was determined by HPLC analysis using a chiral stationary phase.

Table 4: Enantioselective reduction catalyzed by P-stereogenic phosphinamide Lewis bases.

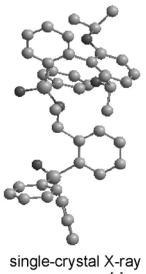


Entry	R^3	R^4	**19**	**L**	e.r.[b] (yield)[c]
1	Ph	Ph	**19a**	**L1**	66:34 (99%)
2	Ph	Ph	**19a**	**L2**	69:31 (99%)
3[d]	Ph	Ph	**19a**	**L3**	65:35 (74%) (*S*)[e]
4[d]	Ph	Ph	**19a**	**L4**	82:18 (94%) (*S*)[e]
5	Ph	Ph	**19a**	**L5**	92:8 (99%)
6	Ph	Ph	**19a**	**L6**	96:4 (99%)
7	Ph	4-$MeOC_6H_4$	**19b**	**L6**	96.3:3.7 (99%)
8	Ph	4-ClC_6H_4	**19c**	**L6**	96.2:3.8 (99%)
9	Ph	4-BrC_6H_4	**19d**	**L6**	97.5:2.5 (99%)

[a] Refer to CCDC 1037719 for crystal structure data.[13] [b] Determined by HPLC analysis using a chiral stationary phase. [c] Yield of isolated product. [d] Hünig's base (1 equiv) was added to prevent hydrolysis of catalyst. Base did not affect the reactivity and selectivity based on control experiments. [e] Confirmed by comparing with literature.[11] DMF = *N*,*N*-dimethylformamide.



L1: R^1 = 2-$MeOC_6H_4$, R^2 = Ph (97.7:2.3 e.r.)
L2: R^1 = *t*Bu, R^2 = Ph (99:1 e.r.)
L3: R^1 = Ph, R^2 = Me (98.2:1.8 e.r.)
L4: R^1 = 2-MeC_6H_4, R^2 = Me (99.6:0.4 e.r.)
L5: R^1 = 2-{2',6'-$(MeO)_2C_6H_3$}C_6H_4, R^2= Ph (99.8:0.2 e.r.)
L6: R^1 = 2-{2',6'-$(i$PrO$)_2C_6H_3$}C_6H_4, R^2 = Ph (99.9:0.1 e.r.)



single-crystal X-ray structure of **L6**[a]

high levels of enantioselectivity. This data verified that the chiral environment created by the P-stereogenic phosphinamide could be used to control asymmetric induction in catalytic asymmetric processes.[12] It is important to note that higher selectivity was obtained by the employing sterically congested catalysts **L5** and **L6** (entry 5 and 6). Furthermore, the viability of **L6** was demonstrated for the reduction of electronically differentiated chalcones **19b–d** with high selec-

tivities observed. These results illustrated that the potential of P-stereogenic phosphinamides as a synthetically accessible and easily tunable template for constructing useful chiral ligands and organocatalysts.

In conclusion, we have developed the first general method for the asymmetric synthesis of P-stereogenic phosphinamides with diverse substituents and functionalities in enantiomerically pure form. The methodology relies on the efficient synthesis of chiral phosphinates from cyclic 1,3,2-benzoxazaphosphinine 2-oxide intermediates which contain active P–O bonds, thus allowing facile displacement by a nitrogen nucleophile. Furthermore the use of these P-stereogenic phosphinamides in asymmetric catalysis has been demonstrated for the first time. Our results reveal the potential for the design of more selective catalysts through strategic tuning of the chiral phosphinamides. Further application of this chemistry to the synthesis of new catalysts and their utilization in asymmetric transformations is currently under investigation and will be reported in due course.

Keywords: asymmetric catalysis · chirality · nucleophilic substitution · organocatalyst · phosphinamides

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 5474–5477
Angew. Chem. **2015**, *127*, 5564–5567

[1] a) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050; b) M. Köhn, R. Breinbauer, *Angew. Chem. Int. Ed.* **2004**, *43*, 3106–3116; *Angew. Chem.* **2004**, *116*, 3168–3178.

[2] a) V. V. Grushin, *Chem. Rev.* **2004**, *104*, 1629–1662; b) A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, *251*, 25–90.

[3] a) C. Bauduin, D. Moulin, E. B. Kaloun, C. Darcel, S. Juge, *J. Org. Chem.* **2003**, *68*, 4293–4301; b) V. S. Chan, M. Chiu, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6021–6032; c) J. J. Gammon, V. H. Gessner, G. R. Barker, J. Granander, A. C. Whitwood, C. Strohmann, P. O'Brien, B. Kelly, *J. Am. Chem. Soc.* **2010**, *132*, 13922–13927; d) K. V. Rajendran, L. Kennedy, D. G. Gilheany, *Eur. J. Org. Chem.* **2010**, 5642–5649; e) M. Revés, C. Ferrer, T. Leon, S. Doran, P. Etayo, A. Vidal-Ferran, A. Riera, V. Verdaguer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9452–9455; *Angew. Chem.* **2010**, *122*, 9642–9645; f) T. Leon, A. Riera, X. Verdaguer, *J. Am. Chem. Soc.* **2011**, *133*, 5740–5743; g) D. Gatineau, L. Giordano, G. Buono, *J. Am. Chem. Soc.* **2011**, *133*, 10728–10731; h) 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; i) O. Berger, J.-L. Montchamp, *Angew. Chem. Int. Ed.* **2013**, *52*, 11377–11380; *Angew. Chem.* **2013**, *125*, 11587–11590.

[4] a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2793; b) C. Ogawa, M. Sugiura, S. Kobayashi, *Angew. Chem. Int. Ed.* **2004**, *43*, 6491–6493; *Angew. Chem.* **2004**, *116*, 6653–6655; c) B. List, *Chem. Rev.* **2007**, *107*, 5413–5415; d) I. Ćorić, B. List, *Nature* **2012**, *483*, 315–319; e) S. Kotani, M. Sugiura, M. Nakajima, *Chem. Rec.* **2013**, *13*, 362–370; f) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153.

[5] a) S. E. Denmark, S. K. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 4759–4762; *Angew. Chem.* **2001**, *113*, 4895–4898; b) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed.* **2008**, *47*, 593–596; *Angew. Chem.* **2008**, *120*, 603–606; c) S. Vellalath, I. Ćorić, B. List, *Angew. Chem. Int. Ed.* **2010**, *49*, 9749–9752; *Angew. Chem.* **2010**, *122*, 9943–9946; d) M. Bonsignore, M. Benaglia, F. Cozzi, A. Genoni, S. Rossi, L. Raimondi, *Tetrahedron* **2012**, *68*, 8251–8255; e) J. H. Kim, I. Ćorić, S. Vellalath, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 4474–4477; *Angew. Chem.* **2013**, *125*, 4570–4573.

[6] a) M. J. P. Harger, *J. Chem. Soc. Perkin Trans. 1* **1977**, 2057–2063; b) T. A. Hamor, W. B. Jennings, C. J. Lovely, K. A. Reeves, *J. Chem. Soc. Perkin Trans. 2* **1992**, 843–849; c) I. N. Francesco, A. Wagner, F. Colobert, *Chem. Commun.* **2010**, *46*, 2139–2141; d) M. Benamer, S. Turcaud, J. Royer, *Tetrahedron Lett.* **2010**, *51*, 645–648; e) I. Notar Francesco, C. Egloff, A. Wagner, F. Colobert, *Eur. J. Org. Chem.* **2011**, 4037–4045.

[7] O. Korpiun, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784–4786.

[8] a) See the Supporting Information for the synthesis of achiral phosphinates and the results on P–O bond reactivity study. b) No reaction was observed when LHMDS was used as a nucleophile.

[9] a) See the Supporting Information for detailed experimental procedure. b) The Supporting Information shows the synthesis of **14**–**16** using a non-optimized procedure started from PCl_3.

[10] See the Supporting Information for the synthesis of **L1**–**L6**.

[11] a) M. Sugiura, N. Sato, S. Kotani, M. Nakajima, *Chem. Commun.* **2008**, 4309–4311; b) S. Guizzetti, M. Benaglia, *Eur. J. Org. Chem.* **2010**, 5529–5541.

[12] Refer the Supporting Information for the computational details and results.

[13] CCDC 1037717, CCDC 1037718, CCDC 1037720, and CCDC 1037719 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: January 14, 2015
Revised: February 10, 2015
Published online: March 10, 2015

