Strategies for the asymmetric synthesis of *H*-phosphinate esters†

Karla Bravo-Altamirano, Laëtitia Coudray, Eric L. Deal and Jean-Luc Montchamp*

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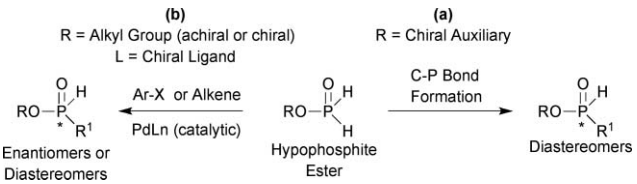
Access to *P*-chiral *H*-phosphinates *via* desymmetrization of hypophosphite esters was investigated. The use of chiral auxiliaries, chiral catalysts, and of a bulky prochiral group that could lead to kinetic resolution was explored. A chiral NMR assay for enantiomeric excess determination of *H*-phosphinates was developed. An asymmetric route to *C*-chiral *H*-phosphinates is also examined and an assay was developed.

Introduction

Among the most common methods to prepare *P*-stereogenic organophosphorus compounds are the classical resolution of racemates based on solubility differences of diastereomeric species,[1] the enantioselective syntheses reported by Juge,[2] Brown[3] and Corey[4] that rely on stereospecific displacements at the phosphorus stereocenter in cyclic, ephedrine- and camphor-based structures that allow the prediction and control of the streochemical outcome, as well as the highly substrate-specific enzymatic resolution processes with lipases and esterases.[5] Recently, moderate success has been reported in emerging methodologies for the preparation of *P*-chiral organophosphorus compounds,[6,7] such as the asymmetric catalytic synthesis of tertiary *P*-chiral phosphines and phosphine-boranes through alkylation,[8] arylation[9] and hydrophosphination reactions.[10] Besides these new catalytic approaches, two of the most effective synthetic routes to chiral tertiary phosphines are the Evans enantioselective deprotonation of prochiral dimethylphosphine boranes and sulfides with alkyllithium complexes of (–)-sparteine[11] or (+)-sparteine surrogates,[12] and the Livinghouse dynamic resolution of a lithiated secondary phosphine borane with (–)-sparteine.[13] However, no success has yet been observed in differentiating the two hydrogen atoms in primary phosphines.[14] Lebel and Imamoto reported failure in desymmetrizing primary phosphine boranes *via* deprotonation–alkylation under phase-transfer catalysis[15] or using an *n*-BuLi/(–)-sparteine complex,[16] respectively. Over the past several years, our group has established a series of methods for the preparation of *H*-phosphinates[17] and their hypophosphite esters precursors,[18] emphasizing in particular the versatility of *H*-phosphinates as intermediates in the preparation of a broad range of organophosphorus compounds. We therefore envisioned the development of new routes to access *P*-stereogenic *H*-phosphinates.

Since the classical resolution of menthyl *H*-phosphinates discovered by Mislow forty years ago,[19] only a few resolution processes for the synthesis of optically pure *H*-phosphinates have appeared in the literature, such as the optical resolution–esterification of an α-hydroxy-*H*-phosphinic acid with a chiral amine,[20] and the lipase-catalyzed hydrolysis of racemic α-acetoxy-*H*-phosphinates.[5g] Herein, we report a study of the impact of chiral auxiliaries and chiral catalysts in the desymmetrization of *tetrahedral* hypophosphite esters [ROP(O)H_2] *via* C–P bond-formation processes (Scheme 1). An example where a bulky prochiral group is used as a strategy toward kinetic resolution at the *P*-stereocenter is illustrated.[21] Finally, a catalytic asymmetric benzylation of H_3PO_2 is discussed as a representative approach to *C*-chiral organophosphorus compounds.[17m]



Scheme 1 Strategies for desymmetrizing hypophosphite esters.

Results and discussion

Chiral auxiliaries

Asymmetric induction *via* the use of chiral auxiliaries is a very useful strategy in enantioselective synthesis.[22] Our initial aim was to understand the basis for transferring asymmetric information from the remote alkoxy substituent in hypophosphite esters. Because of the tetrahedral nature of these compounds, and considering that most of the chiral auxiliaries in asymmetric synthesis have been specifically designed to differentiate between the two faces of a plane but not quadrants in a volume (or geometrically speaking, distinguishing the faces of at least two planes *simultaneously*), we anticipated facing a rather different and difficult scenario.

Hypophosphite esters **1** were prepared *via* three different esterification methods using enantiomerically pure or racemic chiral alcohols: (a) Method A: pivaloyl chloride-mediated esterification,[17c,18b,23] (b) Method B: transesterification with phenyl hypophosphite – itself prepared by *in situ* reaction of tetraphenyl orthosilicate with hypophosphorous acid,[17b–c] and (c) Method C: Dean–Stark esterification with hypophosphorous acid.[24] Once ^{31}P NMR analysis of the crude reaction mixture indicated the generation of the desired ester **1**, a C–P bond-forming reaction was performed *in situ* to afford the expected *H*-phosphinate ester **2** as a mixture of diastereomers. ^{31}P NMR analysis allows the direct determination of diastereomeric excesses (de's) regardless

Department of Chemistry, TCU Box 298860, Texas Christian University, Fort Worth, TX, 76129, USA. E-mail: j.montchamp@tcu.edu; Fax: +1 817 257 5851; Tel: +1 817 257 6201

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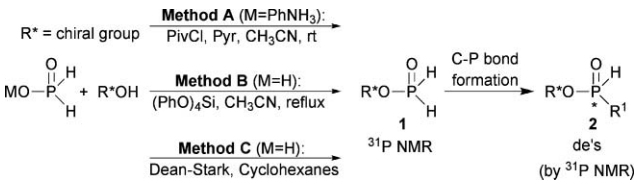
of whether racemic or enantioenriched chiral alcohols are used (Scheme 2). Certainly, for actual application to asymmetric synthesis, enantiopure auxiliaries are required (unless the separation of the diastereoisomeric products is straightforward). It is important to note that in addition to an efficient esterification, good yields of *H*-phosphinate products and high de's are *all required* to constitute a successful scalemic synthesis of the target molecules.



Scheme 2 *P*-Chiral *H*-phosphinates *via* chiral auxiliaries.

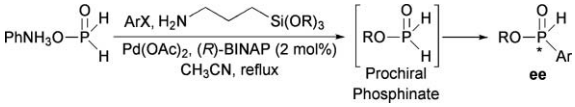
The notorious efficacy and broad tolerance of experimental conditions in the Pd-catalyzed hydrophosphinylation (addition of hypophosphite esters across unsaturated substrates)[17d] led us to initially choose this reaction as the model study to evaluate the effectiveness of a variety of chiral alcohols as auxiliaries. The alcohols were either commercially available or synthesized through known protocols, and used in stoichiometric amounts for the preparation of the corresponding hypophosphite esters, which in turn were reacted with an alkene using Pd/xantphos (2 mol%). Acetonitrile proved to be the best solvent. The results are summarized in Table 1. In general, esterification methods A and B were, not only the most effective, but also complementary for the preparation of hypophosphite intermediates. As observed in Table 1, only a few of the alcohols screened in this study could induce the desymmetrization of **1** with moderate de's. (–)-8-Phenylmenthol (entry 12)[25] led to products with the highest de's of 66% and 71% in the hydrophosphinylation reaction with 1-octene and the highly reactive 2-bromostyrene, respectively. Naphthyl analogs of (–)-8-phenylmenthol (entries 13 and 14)[26] did not provide satisfactory results. Other auxiliaries, such as 1,1,2-triphenyl-1,2-ethanediol 2-acetate,[27] quinic acid derivatives,[28] and ferrocenyl-based alcohols,[29] were screened but they did not lead to an effective formation of hypophosphite esters. Furthermore, hypophosphite esters derived from some alcohols simply did not undergo efficient hydrophosphinylation (*i.e.* ephedrine,[27] pseudoephedrine derivatives,[30] isoborneol-based sulfonamides[27] and phosphonate-based cyclohexanols[31]). Intrigued by the prospect of desymmetrizing hypophosphorous amides ($R_2NP(O)H_2$) which could offer conformational rigidity, we also attempted their synthesis, but were unable to reproduce the single literature report that describes the synthesis of such species using glycine.[32]

We therefore turned our attention to assess the effects of simplifying the structure of the costly (–)-8-phenylmenthol, in order to facilitate further screening and structural modification. This was done by preparing racemic 2-substituted cyclic alcohols in a single epoxide-opening step with benzylic anions (Table 2).[33] The 3,5-bis(isopropyl)phenyl-derived cyclohexanol (entry 2) was less successful than the one bearing a phenyl group (entry 1).[33a]

Next, the top two auxiliaries were evaluated in desymmetrizing hypophosphite esters through various other C–P bond-forming reactions (Table 3). Base-promoted alkylations[17n] and free radical-mediated reactions[17f–g] required the use of esterification Method C. Unfortunately, none of the other tested C–P bond forming reactions proved to be better than the Pd-catalyzed hydrophosphinylation, both in terms of chemical yields and de's.[17d] Although still modest (Table 1, entry 12b), a 71% de supports the feasibility of using chiral auxiliaries to promote the desymmetrization of tetrahedral hypophosphite esters. However, auxiliaries that have been traditionally used for enantiofacial differentiation do not appear to be appropriate for our purpose.

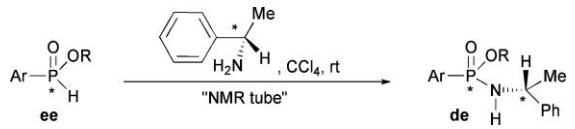
Chiral catalysts

In a different approach toward *P*-chiral *H*-phosphinate esters, we aimed to develop asymmetric variants of our Pd-catalyzed cross-coupling[17j] and hydrophosphinylation reactions.[17d] At this stage, HPLC conditions to measure directly the enantiomeric excesses (ee's) of *H*-phosphinates had to be identified since prior resolution attempts have been reported as unsuccessful by other groups.[34] With this in mind, and in order to facilitate the analysis, we focused initially on the synthesis and resolution of substrates bearing aryl groups that could favor π–π stacking interactions. Previous mechanistic studies of our Pd-catalyzed cross-coupling with aryl electrophiles suggested that aryl iodides might be the only substrates capable of undergoing a direct cross-coupling with hypophosphite esters, which is the minimum requirement for the development of an asymmetric version of this reaction.[17j] Nonetheless, we chose to evaluate (and compare) the reactions of aryl iodides and bromides with anilinium hypophosphite using an aminosilicate (which acts as both the esterifying agent and the base) in the presence of $PdCl_2$ or $Pd(OAc)_2$ and (*R*)-BINAP as a ligand (eqn (1)). Other ligands, such as Josiphos and Walphos-type led to sluggish reactions.



(1)

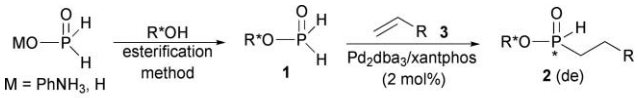
Various chiral stationary phases were screened for the resolution of racemic ethyl phenyl-*H*-phosphinate. It was found that WHELK-01 from Regis® Technologies worked effectively, contrary to various carbohydrate-based chiral columns. However, in order to alleviate the need for an aryl group within the molecule for a successful HPLC resolution, and to ease ee determination over a broad substrate scope, we opted to develop a ^{31}P-NMR assay instead. Toward this end, *H*-phosphinates were oxidized with carbon tetrachloride in the presence of a chiral secondary amine under Atherton–Todd conditions.[35] (*S*)-(–)-(α)-Methylbenzylamine provided the best results in terms of yields, reproducibility, and cost (eqn (2)).



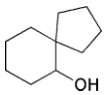
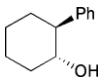
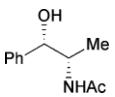
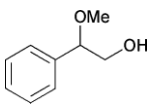
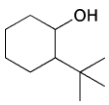
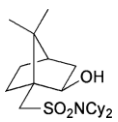
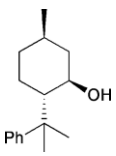
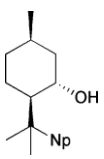
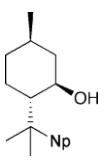
(2)

With the assay in hand, a substrate screening was performed in the Pd-catalyzed cross-coupling reaction. The best results were obtained with 1-bromo and 1-iodonaphthalene, as well as with 2-methyliodobenzene, which all furnished the product with 15% ee according to our NMR assay. However, we needed to establish the stereospecificity of the Atherton–Todd reaction, thus we developed an HPLC method for the resolution of ethyl (1-naphthyl)-*H*-phosphinate. The latter compound was prepared through the

Table 1 Screening of chiral auxiliaries for the desymmetrization of **1**

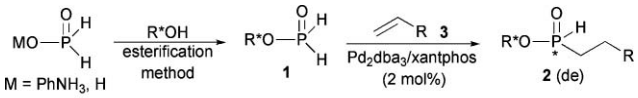


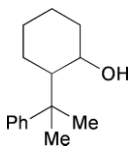
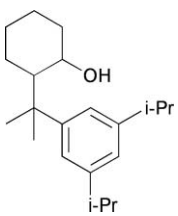
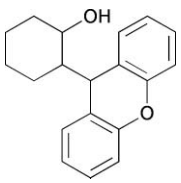
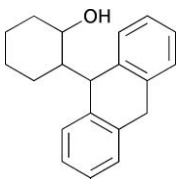
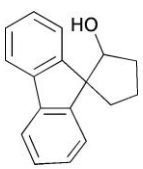
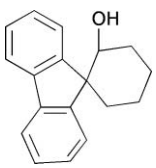
3a: R=hex; **3b:** R=oct; **3c:** R=2-BrPh; **3d:** R=*t*-Bu

		1			**2**	
Entry	R*OH	Method	Yield (%)[a]	Alkene[b]	Yields (%) NMR[a] (isolated)	de[c] (%)
1	Fenchyl alcohol	A	77	**3a**	100	20
2	(+)-Isopinocampheol	A	66	**3a**	100	34
3	Isoborneol	B	68	**3a**	18	5
4		A	100	**3a**	30	41
5		A B	93 95	**3a** **3c**	100 94	24 26
6		B	100	**3b**	100	0
7		A	92	**3a**	0	—[d]
8		A	100	**3a**	10	13
9		B	100	**3a**	100	36[e]
10		A	91	**3a**	0	—
11	(–)-Menthol	B	100	**3a**	100	18
12a 12b 12c		A B B	100 94 94	**3a** **3c** **3d**	100 (100) 67 (57) 88[f]	66 71 46
13[g]		B	60	**3a**	traces	—
14[g]		B	0	—	—	—

[a] By ^{31}P NMR. [b] Reactions with **3a**, **3b** and **3d** were conducted at reflux; reactions with **3c** were conducted at rt. [c] Based on the difference in heights and/or integrals in the ^{31}P NMR spectrum of the crude. [d] Ester hydrolysis takes place. [e] Mixture of *cis*/*trans* isomers (17/83), as in the alcohol precursor. [f] Mixture of linear/branched isomers. [g] Np = 2-naphthyl.

Table 2 Screening of racemic, 2-substituted cyclic alcohols as auxiliaries for the desymmetrization of **1**

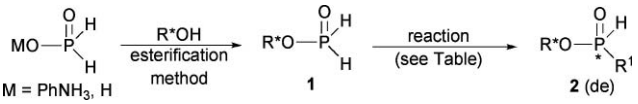


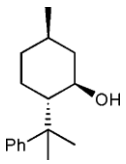
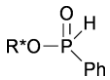
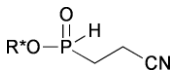
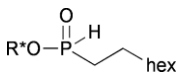
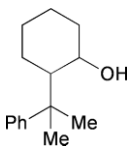
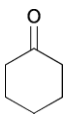
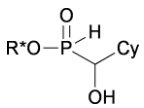
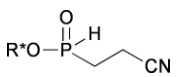
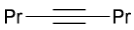
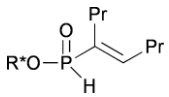
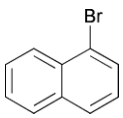
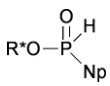
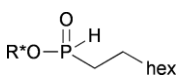
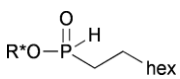
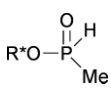
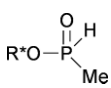
		1			2	
Entry	R*OH	Method	Yield (%)[a]	Alkene[b]	Yields (%) NMR[a] (isolated)	de[c] (%)
1a		B	100	**3a**	100 (93)	55
1b				**3c**	43	59
2		B	100	**3a**	100 (66)	48
3		B	64	**3a**	90	26
4		B	65	**3a**	76	5
5		A	67	**3a**	64	18
		B	59	**3a**	59	7
6		B	66	**3a**	66	11

[a] By ^{31}P NMR. [b] Reactions with **3a** were conducted at reflux; reactions with **3c** were conducted at rt. [c] Based on the difference in heights and/or integrals in the ^{31}P NMR spectrum of the crude mixture.

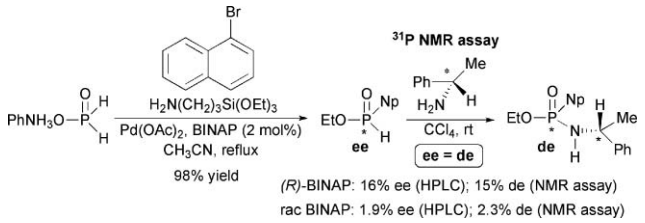
cross-coupling of 1-bromonaphthalene with a hypophosphorous acid derivative, using either racemic- or (*R*)-BINAP as ligand. A good match was obtained between both measurements (de = ee), thus validating our NMR assay (Scheme 3). This is also supported by studies from other groups that have demonstrated complete inversion of configuration at the phosphorus stereocenter in similar transformations.[36] The present finding was therefore a key step toward our ultimate goal of developing asymmetric catalytic synthesis of *H*-phosphinates since a simple and reliable assay was needed.

Table 3 Effect of chiral auxiliaries in the desymmetrization of hypophosphite esters *via* different C–P bond forming reactions



		1			2		
Entry	R*OH	Method (yield (%))[a]	Reaction[b]	Reagent	Product	Yields (%)[a] NMR (isol)[c]	de (%)[d]
1a		A (100)	a	PhI		71 (63)	11
1b		B (100)	b			20	30
1c		C (83)	c			38	—[e]
2a		B (100)	b			37	53
2b			b			74 (69)	38
2c			d			0	—
2d			a[f]			0	—
2e		C (90)	c			68	33
2f			e			49	42
2g			f	MeI		100 (53)	21
2h			g	MeI		72	11

[a] By ^{31}P NMR. [b] a: Et_3N, 2 mol% $Pd(OAc)_2$/dppp, CH_3CN, reflux; b: 1,1,3,3-Tetramethylguanidine (TMG) or iPr_2NEt, CH_3CN, rt; c: Et_3B, cyclohexane:CH_3CN (1 : 1), rt; d: 4 mol% $NiCl_2$, CH_3CN, reflux; e: AIBN, cyclohexane:CH_3CN (1 : 1), reflux; f: *n*-BuLi, cyclohexane:THF (1 : 1), −78 °C to rt; g: *n*-BuLi/(−)-sparteine, cyclohexane:THF (1 : 1), −78 °C to rt. [c] isol = isolated. [d] Based on the difference in heights and/or integrals in the ^{31}P NMR spectrum of the crude. [e] Inaccurate de determination. [f] Np = 1-naphthyl.



Scheme 3 Validation of the ^{31}P NMR assay.

It is worth noting that, in order to attain the desymmetrization of hypophosphite esters (P-V tautomer: (RO)P(O)H_2 and P-III tautomer: (RO)P(OH)(H)), the enantiodetermining step must involve the distinction between enantiotopic groups at the tetrahedral *P*-center, whereas most popular asymmetric transition metal-catalyzed reactions deal with planar systems.[37] This explains, at least in part, the very low enantioselectivities observed in our cross-coupling reactions.

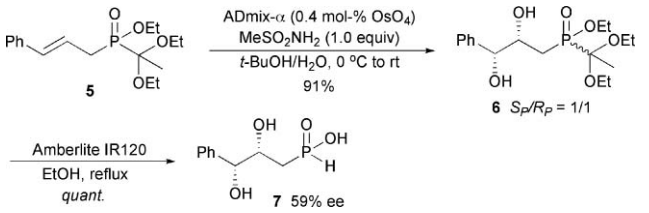
Finally, a brief chiral catalyst screening was performed in the hydrophosphinylation reaction using the NMR assay. The results (Table 4) are very preliminary. Jacobsen's ligand provided the best result in terms of yield and ee using toluene as solvent (entry 1), however the control experiment with an achiral phosphine catalyst furnished the product with a similarly low ee (entry 7), thereby indicating that an ee determination below 10% is inaccurate. Furthermore, even $PdCl_2$ *in the absence of added ligand* was found to still catalyze the reaction in 77% yield (entry 8a). This implies that in order to achieve an enantioselective process, this racemic pathway must be completely suppressed. Furthermore, the reactivity of the preformed Pd-Jacobsen chiral complex[38] varied from the presumably *in situ* formed complex (entry 1a *vs.* 1b), suggesting a role for an achiral palladium species.

Other approaches

(a) *P*-Chiral hypophosphite esters: kinetic resolution. In principle, combining a racemic *P*-chiral hypophosphite ester (through the use of a racemic auxiliary) with a chiral metal catalyst could lead to catalytic desymmetrization through kinetic resolution. However, since the results obtained with auxiliaries were, at best, modestly successful (Tables 1–3), and those obtained with ligands (Table 4) were poor, this approach was not pursued.

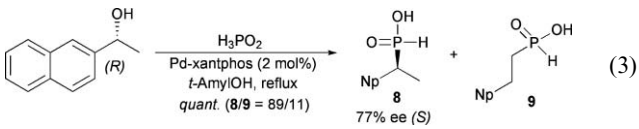
(b) *P*-Chiral *H*-phosphinate esters: kinetic resolution. Instead of resolving P-chiral *H*-phosphinate esters (such as menthyl phenyl-*H*-phosphinate), an alternative strategy toward *P*-chiral *H*-phosphinates could be the kinetic resolution of a protected *H*-phosphinate. For example, kinetic resolution of the bulky acetal **5**[21] was attempted *via* Sharpless' asymmetric dihydroxylation (Scheme 4).[39] Unfortunately, no resolution took place and **6** was isolated in a 1/1 diastereomeric ratio (dr), that after acid hydrolysis delivered diol **7** in 59% ee. The absolute configuration was assigned based on the Sharpless–Corey models[40] and the ee was determined *via* ^{31}P NMR analysis of a diastereomeric salt with quinine. This approach, even if it were successful, would be much less desirable than the desymmetrization of hypophosphorous esters.

An elegant solution was recently reported by Zhao and coworkers through the use of an organocatalytic asymmetric aldol reaction.[41] However, the resulting diastereoisomers still require separation.



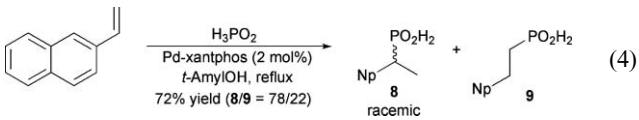
Scheme 4 Effect of a prochiral group in the Sharpless asymmetric dihydroxylation.

(c) *C*-Chiral *H*-phosphinic acids: asymmetric benzylation. One last approach toward chiral *H*-phosphinate derivatives could rely on the formation of a chiral carbon atom using more traditional methods. Access to enantioenriched *H*-phosphinic acids *via* Pd-catalyzed cross-coupling of H_3PO_2 with (*R*)-(+)-1-(2-naphthyl)ethanol (>97% ee)[27] was evaluated.[17m] The benzylation reaction afforded target product **8** in 77% ee, along with the byproduct **9** (eqn (3)). The result strongly suggests that a competing β-hydrogen elimination-hydrophosphinylation process is also involved.



(3)

A control reaction with 2-vinylnaphthalene was thus conducted leading to a mixture of racemic **8** and compound **9** (**8**/**9** = 78/22, eqn (4)), which clearly indicates that significant asymmetric induction is observed when starting from the alcohol, perhaps *via* the undissociated alkene.[42] Once again, a ^{31}P-NMR assay was employed to measure the enantiomeric excess. This time, treatment of the *H*-phosphinic acids with (*R*)-(+)-(α)-methylbenzylamine resulted in the formation of diastereomeric salts which could be quantified directly. Overall, this result is comparable or better to that reported in other asymmetric reactions with benzylic electrophiles.[43] The absolute configuration was assigned based on the catalytic oxidation[44] of **8** to the known phosphonic acid and comparison of optical rotations.

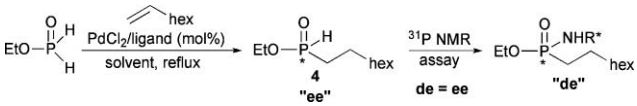


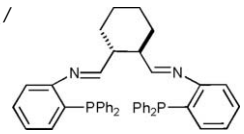
(4)

Conclusions

The desymmetrization of hypophosphorous esters was investigated using various strategies. With a few very rare exceptions,[37] the desymmetrization of comparable tetrahedral species has never been successful. Our best outcome was achieved through 8-phenylmenthol as a chiral auxiliary (~70% de). A general ^{31}P-NMR assay was developed to determine enantiomeric excesses on *H*-phosphinates, and this was validated through chiral HPLC. Much work remains to be done in order to achieve the desymmetrization of hypophosphorous esters, either through a chiral auxiliary, through reaction with a chiral catalyst, or a combination of both. A truly general and practical synthesis of *H*-phosphinate esters which does not rely on classical resolution of diastereoisomers, remains elusive but one of the most important goals of asymmetric organophosphorus chemistry. Since

Table 4 Screening of ligands for the Pd-catalyzed asymmetric hydrophosphinylation



Entry	$PdCl_2$/ligand or complex[a]	Catalyst, mol% Pd	Solvent	NMR yield (%)	**4** ee (%)[b]
1a	$PdCl_2$/(*R*,*R*)-Jacobsen	3	toluene	100	13[c]
1b	Pd.(*R*,*R*)-Jacobsen[d]	2	toluene	0	—
1c	Pd.(*R*,*R*)-Jacobsen[d]	2	CH_3CN	20	9
2a	$PdCl_2$/ 	2	toluene	13	4
2b			CH_3CN	24	17
3a	$PdCl_2$/SALEN	2	toluene	81	0
3b			CH_3CN	47	
4a	$PdCl_2$/Phthalocyanine	2	toluene	97	0
4b			CH_3CN	42	
5a	$PdCl_2$/*meso*-tetraphenylporphine	2	toluene	89	0
5b			CH_3CN	50	
6	$PdCl_2$/(*R*)-BINOL	2	toluene	89	9
7	$PdCl_2$(dppf).MeLi	2	toluene	100	7
8a	$PdCl_2$/no ligand	2	toluene	77	0
8b			CH_3CN	30	

[a] Unless otherwise specified, the chiral catalyst was prepared *in situ*: $PdCl_2$/ligand, 1/1. [b] Determined as "de" by ^{31}P NMR assay. [c] HPLC resolution with (*S*,*S*)-WHELK-01 column/UV detector was unsuccessful. [d] Complex was preformed according to ref. 38.

H-phosphinates are nearly ideal, synthetically flexible, functional groups in phosphorus chemistry, this objective is of paramount importance. One problem which was identified in the present studies is the conformational control in hypophosphorous esters. Since the C–O–P arrangement is conformationally flexible, some sort of restriction will be necessary. Perhaps the design of a conformationally rigid auxiliary will be the answer. A possibility which has not been investigated is to introduce a rationally-designed metal-binding ligand into the auxiliary itself. This, and other approaches will be investigated in the near future. Ours and other groups' efforts clearly demonstrate that the desymmetrization of compounds containing a PH_2 group remains a Holy Grail in organophosphorus chemistry.[45]

Experimental

General

All reactions were conducted in oven-dried glassware, under nitrogen. Reactions carried out at a temperature below 0 °C employed a CO_2/acetone bath. All reagents and solvents were used as received unless otherwise specified. Concentrated H_3PO_2 was obtained by rotary evaporation (0.5 mmHg) of the 50 wt% aq. solution at rt for 20–30 min before reaction. *Caution*: *overdrying H_3PO_2may result in the formation of a yellow solid of high phosphorus content that could be pyrophoric.* Anilinium hypophosphite and stock solutions of ethyl hypophosphite were prepared as previously described.[17e,18a] Unless otherwise specified, HPLC or reagent grade solvents were purchased from Aldrich and used as received. THF was distilled from sodium benzophenone ketyl. CH_3CN was distilled from CaH_2, and used immediately. Et_3N and iPr_2NEt were distilled from CaH_2 and stored over 4 Å molecular sieves. Catalysts and ligands were commonly purchased from Aldrich or Strem Chemicals. Analytical thin layer chromatography (TLC) was performed on SiO_2 60 F-254 plates. Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde or $KMnO_4$ solution. Flash column chromatography was performed using SiO_2 60 (particle size 0.040–0.055 mm, 230–400 mesh). Radial chromatography was carried out using 2 or 4 mm layers of silica gel 60 PF_{254} containing gypsum. Proton, carbon and phosphorus NMR spectra were recorded at 300 MHz/150 MHz/121 MHz (^1H NMR/^{13}C NMR/^{31}P NMR). Chemical shifts are reported as δ values in parts per million (ppm) as referenced to: (a) internal standard (^1H NMR, Me_4Si, $\delta = 0.00$ ppm), (b) residual solvent (^{13}C NMR, $CDCl_3$, $\delta = 77.0$ ppm), and (c) external standard (^{31}P NMR, 85% H_3PO_4, $\delta = 0.00$ ppm). ^1H NMR spectra are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, m = multiplet), number of protons, and coupling constant(s). NMR yields are determined by integration of all the resonances in the ^{31}P NMR spectra, an approach that is valid if no phosphorus-containing gas evolves, or if the precipitate in a heterogeneous mixture does not contain phosphorus. The yields determined by NMR are generally accurate within ~10% of the

value indicated, and are reproducible. The validity of the method has been carefully verified.[17c,17e] Isolated yields are sometimes significantly lower because *H*-phosphinate esters are highly polar compounds and hydrolytically labile. Chiral HPLC resolutions were performed with a (*S*,*S*)-Whelk-01 Column (250 × 4.6 mm, 5 μm) from Regis® Technologies, which was accompanied with a guard column (Agilent Zorbax® ODS, 4.6 × 12.5 mm, 5 μm), using hexanes/isopropanol mixtures as the mobile phase. Low resolution mass spectrometry was performed on a Bruker Esquire 6000, Bruker Daltonics, Inc., ± ESI. High resolution mass spectrometry was provided by the Mass Spectrometry Facility of the University of South Carolina.

Selected experimental procedures

Scheme 2. Esterification methods

Method A: Pivaloyl chloride-mediated esterification.[17c,18b,23]. To a suspension of anilinium hypophosphite (0.318 g, 2.0 mmol, 2.0 equiv) in reagent grade CH_3CN (12–15 mL), was added pyridine (0.20 mL, 0.198 g, 2.50 mmol, 2.50 equiv), the corresponding alcohol (3.0 mmol, 3.0 equiv) and pivaloyl chloride (0.27 mL, 0.265 g, 2.20 mmol, 2.20 equiv) at rt under N_2. The resulting solution was stirred at rt for 2 h. If successful, ^{31}P NMR monitoring of the reaction mixture shows the appearance of the expected hypophosphite ester product (with the appropriate coupling pattern) within the range of 7–20 ppm. The solution is used *in situ* for the following reaction.

Method B: Transesterification with phenyl hypophosphite.[17b–c]. To a solution of freshly concentrated H_3PO_2 (0.132 g, 2.0 mmol, 2.0 equiv) in CH_3CN (12–15 mL) was added $(PhO)_4Si$[46] (0.80 g, 2.0 mmol, 2.0 equiv) and the corresponding alcohol (4.0 mmol, 4.0 equiv). The resulting suspension is heated at reflux for 2 h under N_2. ^{31}P NMR analysis is used to monitor the progress of the reaction. The appearance of a peak within the range of 7–20 ppm, with the adequate multiplicity indicates a successful formation of the alkyl phosphinate product. The suspension is allowed to reach rt and used *in situ* for the next reaction. Alternatively, a stock solution can be prepared and used within a week.

Method C: Dean–Stark esterification.[24]. (Note: *Generally prepared as a stock solution and used immediately or within a week. It requires storing under N_2*). A mixture of aq. H_3PO_2 (1.0 equiv), the corresponding alcohol (1.50–2.0 equiv) and a drop of concentrated H_2SO_4 in reagent grade cyclohexane (0.40 M relative to the amount of H_3PO_2) is heated at reflux temperature using a Dean–Stark trap (prefilled with cyclohexane) for 12–20 h, according to the progress of the reaction (by ^{31}P NMR analysis).

Tables 1, 2 and 3. General procedures for the desymmetrization of hypophosphite esters *via* C–P bond forming reactions

Pd-Catalyzed hydrophosphinylation.[17d]. To a solution of hypophosphite ester (2.0 mmol, 2.0 equiv) in CH_3CN was added an alkene (1.0 mmol, 1.0 equiv), Pd_2dba_3 (9.20 mg, 0.010 mmol, 2.0 mol% Pd) and xantphos (127.0 mg, 0.0220 mmol) at rt. The solution was heated at reflux for 7–14 h, or stirred at room temperature for 30–60 h under N_2. After cooling to rt, ^{31}P NMR analysis was used to determine the diastereomeric excess (de). The workup of the reaction was performed as follows: the mixture was diluted with EtOAc and washed with 2 M aq. HCl (1 ×), followed by extraction of the aqueous phase with EtOAc (2 ×). The organic fractions were combined and washed with saturated aq. $NaHCO_3$ (1 ×) and brine (1 ×). Drying ($MgSO_4$) and concentration furnished the crude compound, which was purified by radial or flash chromatography using hexanes/EtOAc solvent mixtures.

Pd-Catalyzed cross-coupling.[17j]. To a solution of hypophosphite ester (2.0 mmol, 3.0 equiv) in CH_3CN was added an aryl halide (0.70 mmol, 1.0 equiv), Et_3N (0.28 mL, 0.2020 g, 2.0 mmol, 3.0 equiv), $Pd(OAc)_2$ (3.20 mg, 0.0140 mmol, 2.0 mol% Pd) and dppp (6.40 g, 0.0154 mmol) at rt. The solution was heated at reflux for 7 h under N_2. ^{31}P NMR analysis and workup were performed as indicated above for the hydrophosphinylation reaction.

Ni-Catalyzed hydrophosphinylation.[17e]. To a solution of hypophosphite ester (2.0 mmol, 2.0 equiv) in CH_3CN was added an alkyne (1.0 mmol, 1.0 equiv) and $NiCl_2$ (5.20 mg, 0.040 mmol) at rt. The solution was heated at reflux for 12 h under N_2. ^{31}P NMR analysis and workup were performed as indicated above for the hydrophosphinylation reaction.

Nucleophilic addition reactions.[18a]. To a solution of hypophosphite ester (2.0 mmol, 1.20 equiv) in CH_3CN was added a carbonyl-containing or an α,β-unsaturated substrate (1.70 mmol, 1.0 equiv) followed by the corresponding base, either *i*Pr_2NEt (0.24 mL, 0.220 g, 1.70 mmol, 1.0 equiv) or 1,1,3,3-tetramethylguanidine (TMG) (0.22 mL, 0.196 g, 1.70 mmol, 1.0 equiv). The reactions were stirred at rt for 2–4 h uner N_2. ^{31}P NMR analysis and workup were performed as indicated above for the hydrophosphinylation reaction.

Et_3B- and AIBN-mediated radical addition.[17f–g]. A 0.40 M solution of hypophosphite ester (5.0 mL, 2.0 mmol, 3.0 equiv) in cyclohexane (from Dean–Stark esterification) was diluted with CH_3CN (5.0 mL) followed by addition of an alkene (0.667 mmol, 1.0 equiv) and the corresponding radical initiator. Depending on the choice of initiator, either conditions (a) or (b) were used, as follows: (a) AIBN (0.20 equiv) followed by heating at reflux for 15 h before another addition of AIBN (0.30 equiv) and heating for another 15 h under N_2, or (b) Et_3B (0.667 mmol, 1.0 equiv) followed by stirring at rt for 18–24 h under air. ^{31}P NMR analysis and workup were performed as indicated above for hydrophosphinylation reaction.

Base-promoted alkylation.[17n]. A 0.40 M solution of hypophosphite ester (5.0 mL, 2.0 mmol, 1.50 equiv) in cyclohexane (from Dean–Stark esterification) was diluted with anhydrous THF (5.0 mL). An alkyl iodide (1.33 mmol, 1.0 equiv) was added, followed by dropwise addition of *n*-BuLi (1.60 M in hexanes, 1.10 mL, 1.73 mmol, 1.30 equiv) or a solution of *n*-BuLi/(–)-sparteine (1/1, previously stirred at −78 °C for 15 min) at −78 °C under N_2. The reaction was allowed to reach rt over a 1.5 h period followed by ^{31}P NMR analysis. The reaction was quenched with 20% aq. $NaHSO_4$ and extracted with EtOAc (3 x). The combined organic phase was washed with brine (1 x), dried ($MgSO_4$) and purified by radial or flash chromatography using hexanes/EtOAc solvent mixtures.

Tables 1 and 2. Representative procedure for the desymmetrization of hypophosphite esters *via* Pd-catalyzed hydrophosphinylation

Preparation of (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2-(2-bromo-phenyl)-ethyl) phosphinate (Table 1, entry 12b). To a solution of concentrated H_3PO_2 (0.132 g, 2.0 mmol, 2.0 equiv) in CH_3CN (15.0 mL) was added $(PhO)_4Si$[43] (0.800 g, 2 mmol, 2.0 equiv) and (–)-8-phenylmenthol[25] (0.930 g, 4.0 mmol, 4.0 equiv). The reaction was heated at reflux for 2 h under N_2 and then cooled down to rt. 2-Bromostyrene (0.13 mL, 0.183 g, 1.0 mmol, 1.0 equiv), Pd_2dba_3 (9.20 mg, 0.010 mmol) and xantphos (127.0 mg, 0.0220 mmol) were added and the reaction was stirred at rt for 50 h. The reaction was diluted with EtOAc and washed with 2 M aq. HCl (1 ×). The aqueous layer was extracted with EtOAc (2 x) and the combined organic phase was washed with saturated aq. $NaHCO_3$ (1 ×) and brine (1 ×), dried ($MgSO_4$), and concentrated to give the crude product. Purification by radial chromatography (2 mm thickness, hexanes/EtOAc, 5/1, v/v to EtOAc, 100%) furnished the title product as a clear oil (0.264 g, 57% yield) with a 71% de according to ^{31}P NMR analysis as a mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (ddd, J_{HP} = 527 Hz, J = 2, 1 Hz, 1 H), 7.02–7.56 (m, 18 H), 6.80 (dt, J_{HP} = 537 Hz, J = 2 Hz, 1 H), 4.38–4.53 (m, 1 H), 4.19–4.32 (m, 1 H), 3.45–3.61 (m, 2 H), 2.51–2.85 (m, 2 H), 2.0–2.15 (m, 4 H), 0.81–1.89 (m, 34 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.7, 139.6, 133.2, 130.4, 128.6 (d, J_{PCCC} = 14 Hz), 128.1 (2 C), 127.8, 126.0, 125.8 (2 C), 125.2, 77.4 (d, J_{POC} = 8 Hz), 51.8 (d, J_{POCC} = 7 Hz), 45.5, 41.9, 40.0, 34.6, 31.5, 28.0, 27.9 (d, J_{PC} = 95 Hz), 26.7, 25.0, 22.0; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 36.91 (dm, J_{PH} = 537 Hz), 31.09 (dm, J_{PH} = 527 Hz); HRMS (APCI) m/z calcd. for $C_{24}H_{32}BrO_2P$ (M + H)$^+$, 463.1401, found 463.1412.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl octylphosphinate (Table 1, entry 12a). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.41 (m, 8 H), 7.07–7.17 (m, 2 H), 7.02 (d, J_{HP} = 519 Hz, 1 H), 6.64 (d, J_{HP} = 528 Hz, 1 H), 4.35–4.5 (m, 1 H), 4.12–4.3 (m, 1 H), 1.97–2.3 (m, 4 H), 1.58–1.81 (m, 4 H), 1.0–1.57 (m, 44 H), 0.78–1.0 (m, 16 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.5, 151.9, 128.1, 128.0, 125.7, 125.5, 125.3, 125.1, 79.0 (d, J_{POC} = 7 Hz), 78.4 (d, J_{POC} = 7 Hz), 51.7 (d, J_{POCC} = 6 Hz), 51.6 (d, J_{POCC} = 6 Hz), 44.8, 41.8, 39.9, 39.8, 34.6, 31.9, 31.7 (d, J_{PCC} = 11 Hz), 31.5, 30.5 (d, J_{PCCC} = 16 Hz), 29.9, 30.2 (d, J_{PCCC} = 15 Hz), 29.3 (d, J_{PC} = 94 Hz), 29.2, 28.3, 28.2 (d, J_{PC} = 96 Hz), 26.6, 24.9, 24.6, 22.8, 22.0, 21.9, 21.0, 20.4, 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.36 (dm, J_{PH} = 528 Hz), 33.55 (dm, J_{PH} = 519 Hz); HRMS (CI) m/z calcd. for $C_{24}H_{41}O_2P$ (M + H)$^+$, 393.2922, found 393.2916.

2-(1-Methyl-1-phenylethyl)cyclohexyl octylphosphinate (Table 2, entry 1a). Mixture of isomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.43 (m, 8 H), 7.07–7.19 (m, 2 H), 7.0 (d, J_{HP} = 524 Hz, 1 H), 6.76 (d, J_{HP} = 530 Hz, 1 H), 4.30–4.47 (m, 1 H), 4.07–4.28 (m, 1 H), 1.99–2.19 (m, 4 H), 1.59–1.82 (m, 6 H), 0.98–1.50 (m, 48 H), 0.89 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 152.5, 151.9, 128.6, 128.1, 128.0, 126.0, 125.8, 125.5, 125.3, 125.1, 79.5, 77.8, 77.4 (d, J_{POC} = 9 Hz), 76.9, 54.8, 52.2 (d, J_{POCC} = 6 Hz), 40.1, 37.0, 36.3, 33.5, 32.1, 32.0 (d, J_{PCC} = 11 Hz), 30.5 (d, J_{PCCC} = 17 Hz), 29.9, 29.7 (d, J_{PCCC} = 16 Hz), 29.3, 29.2, 28.6, 28.4, 28.2 (d, J_{PC} = 96 Hz), 27.1, 26.5, 26.0, 25.9, 25.3, 24.8, 24.7, 24.5, 22.9, 21.0, 20.5, 14.3; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.23 (dm, J_{PH} = 530 Hz), 33.41 (dm, J_{PH} = 524 Hz).

2-(2-(3,5-diisopropylphenyl)propan-2-yl)cyclohexyl octylphosphinate (Table 2, entry 2). Mixture of isomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (s, 2 H), 7.05 (d, J_{HP} = 521 Hz, 1 H), 6.92 (s, 1 H), 4.15–4.25 (m, 1 H), 2.87 (dq, J = 7 Hz, 7 Hz, 2 H), 2.2–0.8 (m, 23 H), 1.44 (s, 3 H), 1.29 (s, 3 H), 1.24 (d, J = 7 Hz, 12 H), 0.88 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.22 (dm, J_{PH} = 525 Hz), 33.75 (dm, J_{PH} = 524 Hz).

Table 3. Representative examples

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl phenylphosphinate (Table 3, entry 1a). Mixture of isomers (R_P/S_P). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, J_{HP} = 551 Hz, 1 H), 7.26 (d, J_{HP} = 564 Hz, 1 H), 6.93–7.61 (m, 20 H), 4.44–4.62 (m, 2 H), 1.02–2.32 (m, 28 H), 0.78–0.96 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ 151.8, 151.6, 133.9 (d, J_{PC} = 119 Hz), 132.0 (d, J_{PC} = 119 Hz), 132.8 (m, 2 C), 130.9 (d, J_{PCC} = 12 Hz), 130.6 (d, J_{PCC} = 12 Hz), 129.2 (2 C), 128.7 (d, J_{PCCC} = 14 Hz, 2 C), 128.6 (d, J_{PCCC} = 14 Hz, 2 C), 128.2 (2 C), 127.9 (2 C), 125.7, 125.6, 125.4 (2 C), 124.4, 120.2, 78.9 (d, J_{POC} = 7 Hz), 78.3 (d, J_{POC} = 7 Hz), 52.3 (d, J_{POCC} = 6 Hz), 52.1 (d, J_{POCC} = 6 Hz), 44.8, 42.6, 40.3, 40.2, 34.6, 31.7, 28.3, 27.9 (2 C), 27.4, 27.1, 26.9, 26.1, 25.8, 22.0, 21.9; ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 24.17 (dm, J_{PH} = 564 Hz), 19.34 (dm, J_{PH} = 551 Hz); HRMS (CI) m/z calcd. for $C_{22}H_{29}O_2P$ (M + H)$^+$, 357.1983, found 357.1979.

2-(1-Methyl-1-phenylethyl)cyclohexyl (2-cyanoethyl) phosphinate (Table 3, entry 2b). Mixture of isomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.41 (m, 8 H), 7.14–7.24 (m, 2 H), 7.10 (ddd, J_{HP} = 539 Hz, J = 4, 1 Hz, 1 H), 6.83 (dd, J_{HP} = 553 Hz, J = 1 Hz, 1 H), 4.34–4.48 (m, 1 H), 4.13–4.29 (m, 1 H), 2.07–2.38 (m, 8 H), 1.69–2.02 (m, 6 H), 1.08–1.64 (m, 24 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 31.32 (dm, J_{PH} = 553 Hz), 25.0 (dm, J_{PH} = 539 Hz).

2-(1-Methyl-1-phenylethyl)cyclohexyl octylphosphinate (Table 3, entry 2e). Mixture of isomers. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 39.23 (dm, J_{PH} = 530 Hz), 33.41 (dd, J_{PH} = 524 Hz, J = 6 Hz). Two other unidentified products: δ 44.79 (dm, J_{PH} = 379 Hz, 16%), 32.13 (dm, J_{PH} = 556 Hz, 9%).

2-(1-Methyl-1-phenylethyl)cyclohexyl methylphosphinate (Table 3, entry 2 g). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.38 (m, 8 H), 7.16 (dq, J_{HP} = 532 Hz, J = 2 Hz, 1 H), 7.07–7.17 (m, 2 H), 6.89 (dq, J_{HP} = 537 Hz, J = 2 Hz, 1 H), 4.30–4.44 (m, 1 H), 4.07–4.23 (m, 1 H), 2.08–2.32 (m, 4 H), 1.62–1.87 (m, 6 H), 1.32–1.59 (m, 8 H), 1.18–1.30 (m, 10 H), 0.96–1.06 (m, 8 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 34.51 (ddd, J_{PH} = 537 Hz, J = 15, 10 Hz), 27.55 (ddd, J_{PH} = 532 Hz, J = 16, 7 Hz).

Scheme 3. Validation of the ^{31}P NMR assay

(a) Synthesis of ethyl (1-naphthyl) phosphinate. To a suspension of anilinium hypophosphite (0.382 g, 2.40 mmol, 1.20 equiv) and 3-aminopropyltriethoxysilane (0.531 g. 2.40 mmol, 1.20 equiv) in CH_3CN (12.0 ml) was added 1-bromonaphthalene (0.28 mL, 0.414 g, 2.0 mmol), $Pd(OAc)_2$ (9.0 mg, 0.040 mmol, 2 mol% Pd) and either racemic BINAP or (*R*)-BINAP (28.8 mg, 0.044 mmol). The reaction mixture was heated at reflux for 8 h under N_2. After cooling to rt, ^{31}P NMR analysis showed the product at

~28 ppm (100%, doublet). The mixture was diluted with EtOAc and washed with aq. HCl (2 M). The aqueous phase was extracted with EtOAc (3 ×) and the combined organic phase was washed with saturated aq. $NaHCO_3$ (1 ×) and brine (1 ×), dried ($MgSO_4$) and concentrated to afford the pure title product (0.431 g, 98% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (d, J = 8 Hz, 1 H), 8.09 (dd, J = 7, 1 Hz, 1 H), 8.07 (d, J = 7 Hz, 1 H), 7.94 (d, J_{HP} = 563 Hz, 1 H), 7.93 (d, J = 8 Hz, 1 H), 7.75–7.89 (m, 1 H), 7.48–7.69 (m, 2 H), 4.05–4.29 (m, 2 H), 1.37 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 26.76 (dm, J_{PH} = 563 Hz).

(b) ^{31}P NMR assay validation.

Derivatization with (S)-(−)-(α)-methylbenzylamine/CCl_4. To an NMR tube charged with a solution of ethyl (1-naphthyl) phosphinate (20 mg) in CCl_4 (1 mL) was added an excess of (*S*)-(−)-(α)-methylbenzylamine at rt. The solution was kept for 2-4 h at rt and then analyzed by ^{31}P NMR to determine the corresponding de (de = ee) by the difference in heights and integrals.

From (R)-BINAP. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 20.94 (s, 60.9%, height: 155.7); 20.53 (s, 39.1%, height: 114.8); $ee_{(heights)}$ = 15%. HPLC analysis: ee = 16%; Product1, t_R 37.919 min; Product2, t_R 46.663 min; conditions: (*S*,*S*)-Whelk-01 column (Regis® Technologies, 250 × 4.6 mm, 5 μm) with guard column (Agilent Zorbax® ODS, 4.6 × 12.5 mm, 5 μm), 1 mL min^{-1} (isocratic), rt, hexanes/*i*PrOH (7/3, v/v).

From racemic BINAP. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 21.507 (s, height: 104.5); 21.413 (s, height: 110.0); $ee_{(heights)}$ = 2.3%. HPLC analysis: ee = 1.9%; Product1, t_R 29.482 min; Product2, t_R 35.995 min; conditions: (*S*,*S*)-Whelk-01 Column (Regis® Technologies, 250 × 4.6 mm, 5 μm) with guard column (Agilent Zorbax® ODS, 4.6 × 12.5 mm, 5 μm), 1 mL min^{-1} (isocratic), rt, hexanes/*i*PrOH (7/3, v/v).

MS (ESI$^+$) for $C_{12}H_{13}O_2P$, $[M + H]^+$ m/z 221.1; $[NpP(O)(OH)(H) + H]^+$ m/z 193; $[NpP(O) + H]^+$ m/z 175; $[Np + H]^+$ m/z 129.1 (Np = 1-naphthyl).

Table 4. General procedure for the Pd-catalyzed asymmetric hydrophosphinylation

Preparation of non-racemic ethyl octyl-*H*-phosphinate. To a 0.50 M solution of $EtOP(O)H_2$[17e,18a] in CH_3CN or toluene (2.0 equiv) was added 1-octene (1.0 equiv) followed by the appropiate Pd-catalyst (2–3 mol%). In those cases where the Pd-complex was formed *in situ*, a 1/1 ratio of $PdCl_2$/ligand was used. The solution was heated at reflux for 8–12 h under N_2. The mixture was diluted with EtOAc and washed with 2 M aq. HCl (1 ×). The aqueous phase was extracted with EtOAc (2 ×) and the combined organic phase was washed with saturated aq. $NaHCO_3$ (1 ×) and brine (1 ×), dried ($MgSO_4$) and concentrated to yield the crude ethyl octyl-*H*-phosphinate product,[17d,17g] which was used without further purification in the ^{31}P NMR assay for enantiopurity determination. Note: the title product was isolated by column chromatography (hexanes/EtOAc, 3/1, v/v to EtOAc, 100%) as a colorless oil for identity confirmation.[17d,17g] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, J = 526 Hz, 1 H), 4.03–4.23 (m, 2 H), 1.21–1.82 (m, 14 H), 1.37 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H); ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 40.3 (d, J_{PH} = 526 Hz).

Table 4, entry 1a. Representative procedure for the hydrophosphinylation - enantiopurity determination

To a freshly prepared 0.50 M solution of $EtOP(O)H_2$[18a] in toluene (4.0 mL, 2.0 mmol) was added 1-octene (0.16 mL, 0.114 g, 1.016 mmol), $PdCl_2$ (5.32 mg, 0.030 mmol, 3 mol% Pd) and (*R*,*R*)-Jacobsen ligand (16.4 mg, 0.030 mmol) under N_2. The reaction mixture was heated at reflux for 12 h, diluted with EtOAc and worked up as described in the general procedure to yield the crude ethyl octyl-*H*-phosphinate.[17g] The identity and yield of the product were determined by ^{31}P NMR (δ 40.3 ppm, d, J_{PH} = 526 Hz, 100% yield). An NMR tube was charged with a solution of the crude product (20 mg) in CCl_4 (1 mL) followed by addition of an excess of (*S*)-(−)-(α)-methylbenzylamine at rt. The solution in the NMR tube was kept at rt for 4 h mixing it occasionally to yield a mixture of diastereomers in quantitative yield. ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 35.2 (s, height: 126.0); 34.5 (s, height: 97.8); de(= ee) = 13%.

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