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Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b07340 • Publication Date (Web): 23 Aug 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Desymmetrization of Phosphinic Acids via Pd-Catalyzed Asymmetric Allylic Alkylation – Rapid Access to *P*-Chiral Phosphinates

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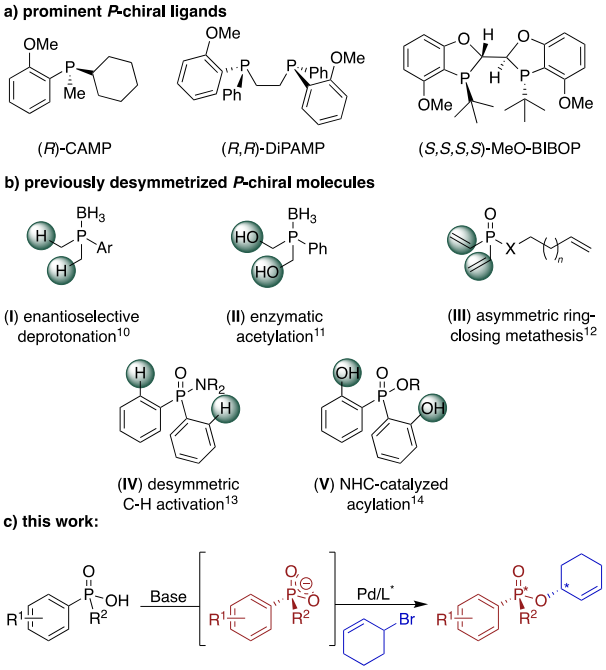
Supporting Information Placeholder

ABSTRACT: The synthesis of *P*-chiral compounds is challenging, especially since useful catalytic methods for preparing such molecules are scarce. Herein we disclose a desymmetrization that employs phosphinic acids as prochiral nucleophiles in a Pd-catalyzed asymmetric allylic alkylation reaction, furnishing phosphinates with high enantio- and diastereoselectivity. This new method has broad scope and is applied to the synthesis of an enantioenriched tertiary phosphine oxide.

Since the 1970s, *P*-chiral molecules such as phosphines have seen widespread use in transition metal catalysis[1] and organocatalysis[2]. The introduction of the highly active *P*-chiral DiPAMP ligand (Scheme 1a) by Knowles and coworkers[3] boosted the demand for synthetic methods for accessing *P*-chiral molecules. The development of such methods has been challenging, however, and remains an active field of research today. Menthol-based resolution strategies have been explored extensively[4] and paved the way for the development of other chiral-auxiliary based methods[5]. Several catalytic asymmetric strategies have also been developed using secondary phosphines or phosphine oxides as starting materials. A seminal contribution from Toste and Bergman demonstrated that chiral ruthenium complexes promoted the asymmetric alkylation of secondary phosphines with moderate enantioselectivity.[6] Later, Glueck developed a platinum catalyst for the same transformation and achieved similar levels of enantioinduction.[7] More recently, Hayashi and Leung disclosed a highly enantioselective oxidation of secondary phosphines to *P*-chiral phosphinites[8] and Gaunt achieved excellent results in his Cu-catalyzed resolution of secondary phosphine oxides.[9]

A variety of methods for desymmetrizing prochiral phosphorus compounds have also been developed (Scheme 1b). Good enantioselectivity is generally achieved with sparteine-promoted lithiation followed by trapping with electrophiles, but these processes are limited to phosphorus compounds with enantiotopic methyl groups (Scheme 1b, **I**).[10] In addition, while bis(hydroxymethyl) phosphines can be desymmetrized enzymatically, this method has only been demonstrated on a single substrate (Scheme 1b, **II**).[11] Asymmetric ring-closing metathesis can differentiate enantiotopic alkenyl sidechains (Scheme 1b, **III**), but the yields and enantioselectivities are highly substrate-dependent.[12] Finally, phosphorus compounds bearing two identical aryl groups have been desymmetrized using both asymmetric C-H activation[13] and enantioselective acylation[14] (Scheme 1b, **IV** and **V**).

Scheme 1. Synthetic Methods for *P*-Chiral Molecules

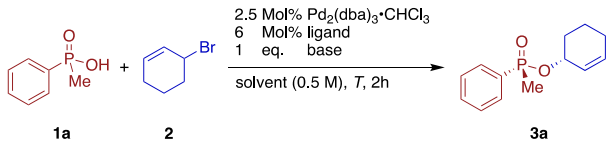


Because all of the aforementioned desymmetrizations involve selective functionalization of two identical carbon sidechains, the amount of structural diversity these methods can generate is inherently limited since the substituents in the products are necessarily related to each other. To address this

key limitation, we envisioned a process in which we could preinstall two completely different carbon substituents on a phosphinic acid, then desymmetrize it by stereoselectively alkylating one of the enantiotopic oxygens (Scheme 1c). To the best of our knowledge, this type of transformation has never been explored.

In light of our group's success using Pd-catalyzed asymmetric allylic alkylation to desymmetrize both nucleophiles and electrophiles, we elected to evaluate this methodology in the present context. We initiated our studies with 3-bromocyclohexene (**2**) as the electrophile for two reasons. First, 3-bromocyclohexene is a highly reactive electrophile that can outcompete the allyl phosphinate products **3** for ionization. Second, cyclic systems are exceptionally well-matched substrates for our ligands **L1**-**L4**.[15]

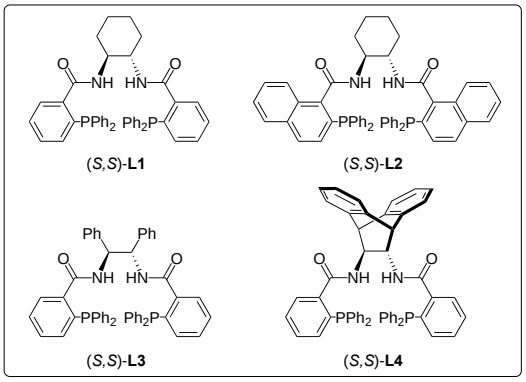
Table 1. Optimization of Reaction Conditions[a]



1a **2** **3a**

entry	ligand	solvent	base	*T*	yield	d.r.	ee%
1	**L1**	THF	Cs_2CO_3	r.t.	83%	1:1	96/93
2	**L2**	THF	Cs_2CO_3	r.t.	97%	2:1	80
3	**L3**	THF	Cs_2CO_3	r.t.	70%	1:1	91/92
4	**L4**	THF	Cs_2CO_3	r.t.	70%	6:1	97
5	**L4**	2-Me-THF	Cs_2CO_3	r.t.	77%	5:1	94
6	**L4**	Dioxane	Cs_2CO_3	r.t.	89%	5:1	95
7	**L4**	DME	Cs_2CO_3	r.t.	77%	4:1	91
8	**L4**	DCE	Cs_2CO_3	r.t.	86%	4:1	95
9	**L4**	Toluene	Cs_2CO_3	r.t.	92%	4:1	94
10	**L4**	THF	Li_2CO_3	r.t.		no reaction	
11	**L4**	THF	K_2CO_3	r.t.	67%	4:1	–
12	**L4**	THF	NEt_3	r.t.	77%	5:1	90
13	**L4**	THF	Cs_2CO_3	0 °C	76%	5.5:1	93
14	**L4**	THF	Cs_2CO_3	40 °C	79%	4.5:1	93
15[b]	**L4**	**THF**	**Cs_2CO_3**	**r.t.**	**96%**	**7:1**	**97**

[a] All reactions performed on 0.1 mmol scale. Yields are isolated yields; d.r. determined by crude ^{31}P-NMR, ee determined by chiral HPLC. In diastereoselective cases, only the ee of the major diastereomer is reported. [b] Reaction concentration of 0.1 M, based on phosphinic acid.

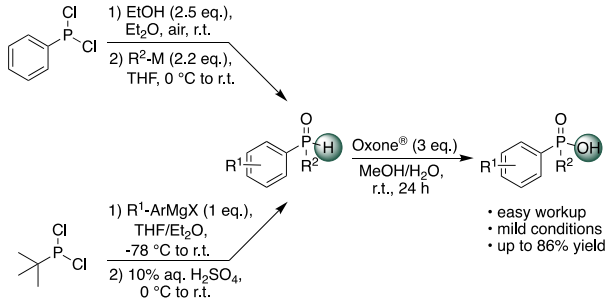


Optimization commenced with a ligand screen (Table 1). Although enantioinduction was excellent with standard Trost ligand (*S,S*)-**L1** (entry 1), no diastereoselectivity was observed, presumably due to ineffective desymmetrization of the phosphorus center. Naphthyl ligand (*S,S*)-**L2** showed slightly increased diastereoselectivity but reduced enantioselectivity (entry 2), whereas stilbenyl ligand (*S,S*)-**L3** (entry 3) offered no improvement over **L1**. Fortunately, anthracenyl ligand (*S,S*)-**L4** (entry 4) was highly differential and generated good stereoinduction at both the electrophile and the nucleophile, furnishing phosphinate **3a** in excellent ee (97%) and d.r. (6:1).

With the optimal ligand in hand, we directed our attention to the solvent. Other ethereal solvents like 2-MeTHF, 1,4-dioxane, and 1,2-dimethoxyethane offered slightly better yields than THF, but inferior diastereoselectivities (entries 5-7). Similarly, while the yields and enantioselectivities were satisfactory in non-coordinating solvents like 1,2-dichloroethane and toluene, the diastereoselectivity dropped to 4:1 (entries 8 and 9). Screening bases revealed that Cs_2CO_3 was optimal; no reaction occurred with Li_2CO_3 (entry 10), whereas reduced selectivities were observed with K_2CO_3 (entry 11) and triethylamine (entry 12). Lastly, the effects of temperature and concentration were investigated. Performing the reaction at 0 °C had a minimal impact on diastereoselectivity, whereas heating the reaction to 40 °C decreased the d.r. slightly. Since ligands **L1**-**L4** are known to form oligomeric species[16] in solution, decreasing reaction concentration can sometimes increase selectivity. This effect appears to be operative here, and we were delighted to find that at 0.1 M, the combination of **L4** and Cs_2CO_3 in THF afforded **3a** in an improved 7:1 d.r. (entry 15). It should be mentioned that short reaction times are beneficial since erosion of diastereoselectivity was observed with longer reaction times, potentially due to reionization of the phosphinate products. The absolute configuration of the cyclohexene stereocenter was assigned as (*R*) by analogy to the literature, but is inconsequential.[16,17] As we demonstrate later, the cyclohexene moiety is disposable and simply provides a convenient means for imparting stereochemistry to the phosphorus center.

At this stage, we were ready to evaluate the scope of this reaction, but were underwhelmed by the methods available for synthesizing the requisite phosphinic acid nucleophiles. Although secondary phosphine oxides seemed like attractive intermediates because of their stability and easy accessibility, methods for oxidizing phosphine oxides to phosphinic acids are scarce and involve harsh conditions[13d] or expensive reagents.[18] Given our previous success using Oxone to chemoselectively oxidize sulfides to sulfones,[19] we hypothesized that we could use this mild, inexpensive oxidant to convert phos

Scheme 2. Synthesis of Phosphinic Acids



phine oxides into phosphinic acids as well. Indeed, this transformation works well and provides phosphinic acids in good yields after simple acid-base extraction (Scheme 2).

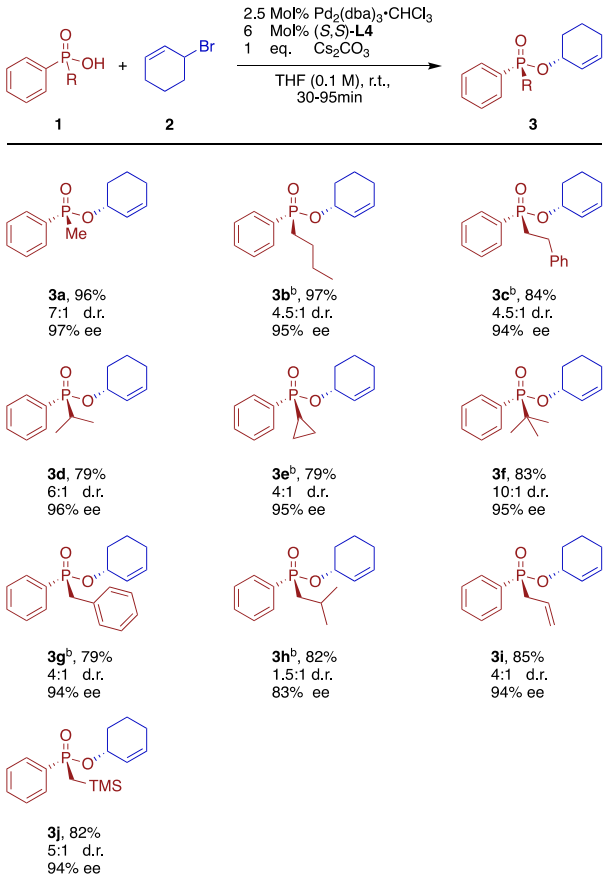
With optimized conditions (Table 1, entry 15) and a robust nucleophile synthesis in hand, we set out to explore the scope of the desymmetrization by varying the alkyl substituent on the phosphorus center (Table 2). Replacing the methyl group in **1a** with either *n*-butyl (**1b**) or phenethyl (**1c**) substituents was well-tolerated and the corresponding phosphinate esters **3** formed in 4:1 d.r. with excellent yield and enantioselectivity. Notably, branching adjacent to the phosphorus center was not problematic. Isopropyl- (**1d**) and cyclopropyl-substituted (**1e**) phosphinic acids gave similar results to those obtained with the standard methyl substrate (**1a**), whereas replacing the methyl group with a *t*-butyl substituent (**1f**) significantly increased the d.r. to 10:1 without impacting yield or enantioselectivity.

While steric bulk adjacent to the phosphorus center is beneficial, branching *β*- to the heteroatom is not. With a benzyl substituent (**1g**), 4:1 d.r. is observed and with an isobutyl group (**1h**), the diastereoselectivity curiously drops to 1.5:1. Notably, phosphinic acids with functionalized alkyl groups – including allyl (**1i**) and (trimethylsilyl)methyl (**1j**) substituents – were well-tolerated, giving phosphinates **3i** and **3j** with high enantio- and diastereoselectivity.

Next, we further evaluated the scope of the desymmetrization by varying the aryl group (Table 3). First, we investigated electronic effects by changing the *para*- substituents. Electron-rich *p*-anisyl (**1k**) and *p*-tolyl (**1l**) groups afford slightly increased enantioselectivities and slightly decreased diastereoselectivities relative to a simple phenyl substituent (**1f**). With electron-deficient aromatics such as **1m** and **1n**, diastereoselectivity drops to around 4:1, though yield and enantioselectivity are not significantly impacted. Additionally, unlike most other products, the major and minor diastereomers of **3n** are separable by preparatory thin-layer chromatography.

We were delighted to find that shifting the steric bulk closer to the phosphorus center increased diastereoselectivity; with *m*-tolyl phosphinate **1o**, the d.r. improved to 10.5:1 and with the corresponding *o*-tolyl substrate (**1p**), near-perfect diastereo- and enantioselectivity was achieved. Similarly, the

Table 2. Scope of Phenyl-Substituted Phosphinic Acids[a]

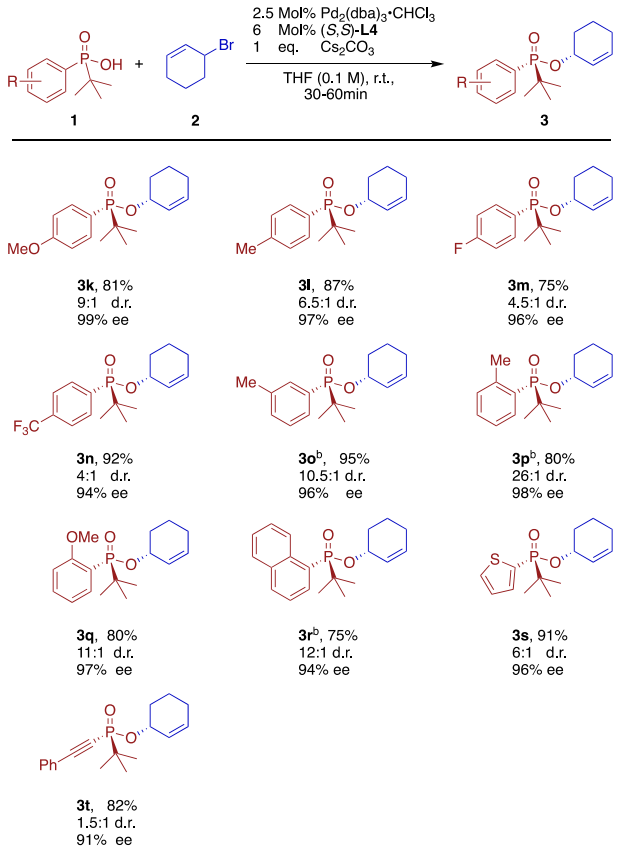


[a] All reactions performed on 0.1 mmol scale at room temperature. Yields are isolated yields; d.r. determined by crude ^{31}P-NMR, ee is reported for the major diastereomer and was determined by chiral HPLC. [b] ee may be slightly lower than reported due to lack of baseline separation; see SI for details.

diastereoselectivities for both *o*-anisyl- (**1q**) and 1-naphthyl-substituted (**1r**) phosphinic acids were superior to the 10:1 d.r. observed with an unsubstituted phenyl group (**1f**). Conversely, lower diastereoselectivities were obtained with less sterically demanding groups. Replacing the phenyl group in **1f** with a 2-thienyl substituent gave rise to **3s** in 6:1 d.r. and while acetylene-substituted phosphinate **3t** was obtained in 91% ee, the diastereoselectivity was modest.

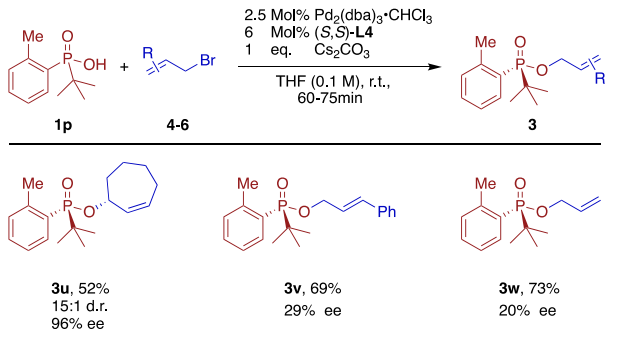
Since the electrophile in our desymmetrization is effectively a resolving agent, 3-bromocyclohexene **2** is an optimal coupling partner since it is commercially available, inexpensive, and low molecular weight. We were curious to see whether this process would extend to other electrophiles, however, and evaluated several other allylic bromides (Table 4) using the best nucleophile from Table 3 (**1p**). With 3-bromocycloheptene **4**, phosphinate **3u** was obtained in 52% yield and 96% ee, but slightly lower d.r. (15:1) than the 3-bromocyclohexene adduct (**3p**). This may be due to the greater conformational flexibility of 7-membered rings relative to 6-membered rings. With acyclic electrophiles, good reactivity was retained, but stereoselectivity was poor. Cinnamyl bromide (**5**) furnished **3v** in 69% yield and 29% ee;

Table 3. Scope of *t*-Butyl-Substituted Phosphinic Acids[a]



[a] All reactions performed on 0.1 mmol scale at room temperature. Yields are isolated yields; d.r. determined by crude ^{31}P-NMR, ee is reported for the major diastereomer and was determined by chiral HPLC. [b] ee may be slightly lower than reported due to lack of baseline separation; see SI for details.

Table 4. Exploring Other Electrophiles[a]

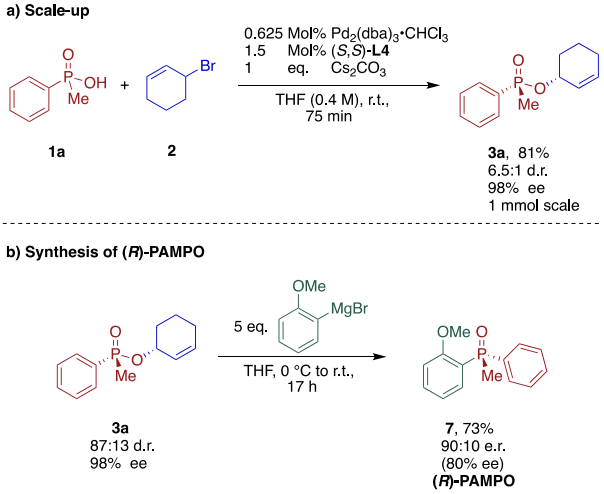


[a] All reactions performed on 0.1 mmol scale at room temperature. Yields are isolated yields; d.r. determined by crude ^{31}P-NMR, ee is reported for the major diastereomer and was determined by chiral HPLC.

allyl bromide (**6**) performed similarly, giving **3w** in 73% yield and 20% ee. Thus, in addition to being an excellent electrophile from a practicality standpoint, 3-bromocyclohexene (**2**) is also highly differential in terms of selectivity.

After demonstrating the utility of our method for the enantioselective synthesis of phosphinates, we set out to highlight its practicality as a general method for synthesizing other *P*-chiral compounds. Importantly, our process is scalable, as **3a** could be prepared on 1 mmol scale at reduced catalyst loading (1.25 mol % Pd) with no appreciable reduction in yield or selectivity (Scheme 3a). To ensure similar rates, the reduction in catalyst was accompanied by an increase in reaction concentration. Notably, treatment with excess *o*-anisyl Grignard converted phosphinate **3a** into (*R*)-PAMPO **7** – which is a precursor to both (*R*)-CAMP and (*R*)-DiPAMP – in 73% yield (Scheme 3b). This transformation is stereospecific, and all of the chiral information present at the phosphorus center in **3a** was transferred to **7**. Additionally, this catalytic asymmetric synthesis of **7** – which proceeds in two steps from commercially available starting materials – compares favorably with the literature route,[20] which involves four steps and requires a stoichiometric amount of enantiomerically pure menthol as an auxiliary.

Scheme 3. Scale-Up and Synthesis of (*R*)-PAMPO



Comparing the optical rotation of our synthetic **7** ($[\alpha]_D^{24}$=+17.8, c=1.0 in MeOH) to the literature value for (*R*)-PAMPO ($[\alpha]_D^{20}$=+25.9, c=1.0 in MeOH)[21] enabled us to unambiguously assign the phosphorus stereocenter in **3a** as (*R*), after taking into account the well-known inversion of configuration that occurs when phosphinates react with Grignard reagents.[5b] Although the relative sizes of the substituents on the phosphinic acids may impact the stereochemistry of the phosphorus center, we tentatively assign all of the phosphinate esters **3** in this work an absolute configuration of (R_P, *R*) by analogy to **3a**.

In conclusion, we developed a novel desymmetrization of phosphinic acids that proceeds via a Pd-catalyzed asymmetric allylic alkylation. Unlike all previous approaches for desymmetrizing symmetrical phosphorus compounds, which differentiate between two enantiotopic carbon substituents, our method discriminates between two enantiotopic oxygens. This allows us to access *P*-chiral phosphinates bearing two structurally diverse side chains in excellent yield and enantioselectivity and good to excellent diastereoselectivity. Furthermore, these enantioenriched phosphinates can easily be converted to tertiary phosphine oxides, which are conven-

ient precursors for *P*-chiral phosphine ligands, in stereospecific fashion. This method represents a general and practical approach for synthesizing chiral phosphines and phosphine oxides, and should enable the development of new ligands and organocatalysts.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and $^{1}H/^{13}C/^{31}P$ NMR spectra for **1**, **3** and **7** (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the Tamaki Foundation and Chugai Pharmaceuticals for their generous partial financial support of our programs. S.M.S. is grateful for the ISAP program funded by the DAAD. A.B.R. is grateful to the Elitenetzwerk Bayern for a SynCat fellowship. We also thank Jacob S. Tracy (Stanford University) for experimental assistance.

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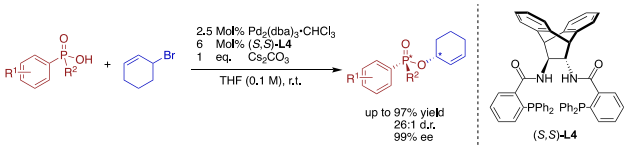
2.5 Mol% Pd2(dba)3•CHCl3
6 Mol% (S,S)-L4
1 eq. Cs2CO3
THF (0.1 M), r.t.
up to 97% yield
26:1 d.r.
99% ee
(S,S)-L4