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Enantioselective Coupling of Dienes and Phosphine Oxides

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Supporting Information

ABSTRACT: We report a Pd-catalyzed intermolecular hydrophosphinylation of 1,3-dienes to afford chiral allylic phosphine oxides. Commodity dienes and air stable phosphine oxides couple to generate organophosphorus building blocks with high enantio- and regiocontrol. This method constitutes the first asymmetric hydrophosphinylation of dienes.

Conjugated dienes are versatile motifs for constructing molecules that range from natural products to synthetic polymers.[1,2] In recent years, hydrofunctionalization has emerged as an attractive and atom-economical[3] method to transform dienes into valuable building blocks.[4] In comparison to other hydrofunctionalizations (e.g., hydroboration or hydroformylation), hydrophosphinylation remains in its infancy (Figure 1). Hirao first coupled isoprene and diethyl phosphonate to furnish an allylic phosphonate, albeit with low efficiency (10% yield) and at an elevated temperature (150 °C).[5] Tanaka later improved the hydrophosphorylation of 1,3-dienes by using a more reactive pinacol-derived phosphonate to synthesize allylphosphonates.[6] While promising, this strategy has been restricted to producing achiral regioisomers or racemic mixtures.[7] Given the potential for chiral phosphines in catalysis,[8] as well as the need for novel phosphine motifs in medicine[9] and agrochemical space,[10] we sought to develop an enantioselective hydrophosphinylation.[11] Herein, we report the transformation of several petroleum feedstocks and readily available dienes into chiral phosphine oxide building blocks, with high regio- and enantiocontrol.

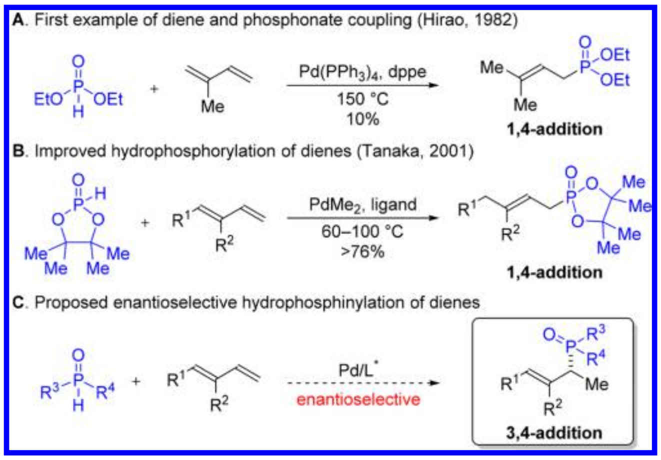
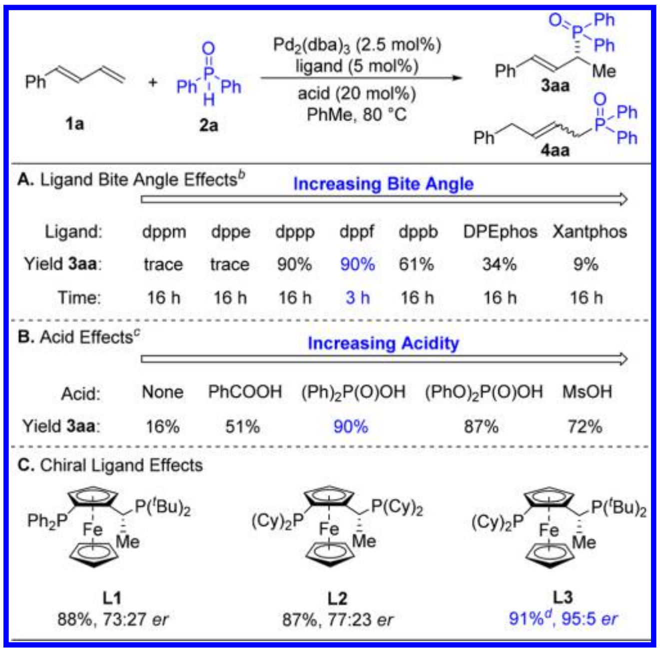


Figure 1. Inspiration for asymmetric hydrophosphinylation of 1,3-dienes.

Table 1. Ligand and Acid Effects on Asymmetric Hydrophosphinylation of 1a[a]



A. Ligand Bite Angle Effects[b]

Ligand:	dppm	dppe	dppp	dppf	dppb	DPEphos	Xantphos
Yield **3aa**:	trace	trace	90%	90%	61%	34%	9%
Time:	16 h	16 h	16 h	3 h	16 h	16 h	16 h

B. Acid Effects[c]

Acid:	None	PhCOOH	$(Ph)_2P(O)OH$	$(PhO)_2P(O)OH$	MsOH
Yield **3aa**:	16%	51%	90%	87%	72%

C. Chiral Ligand Effects

L1	**L2**	**L3**
88%, 73:27 *er*	87%, 77:23 *er*	91%[d], 95:5 *er*

[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), $Pd_2(dba)_3$ (2.5 mol %), ligand (5.0 mol %), acid (20 mol %), toluene (0.40 mL), 3 h (unless otherwise noted). Yield determined by GC-FID analysis of the reaction mixture, which was referenced to 1,3,5-trimethoxybenzene. Regioselectivity ratio (*rr*) is the ratio of **3aa** to **4aa**, which is determined by ^{31}P NMR analysis of reaction mixture. Enantioselectivity ratio (*er*) determined by chiral SFC. See Supporting Information (SI) for full structure of abbreviations used. Unless otherwise noted, *rr* is >20:1. [b]Standard conditions with $(Ph)_2P(O)OH$ as acid. [c]Standard conditions with dppf as ligand. [d]Isolated yield of **3aa**, 3.47 mmol scale, using $Pd_2(dba)_3$ (0.50 mol %) and **L3** (1.0 mol %) with standard conditions, 18 h.

Given previously reported asymmetric hydroamination[12] and hydrothiolation[13] of 1,3-dienes, we chose to focus on a phosphorus nucleophile that would possess intermediate nucleophilicity compared to amines and thiols. As part of our reaction design, we imagined using phosphine oxides (**2**) as P-based nucleophiles because they are air stable, commercially available, and readily reduced to the correspond-

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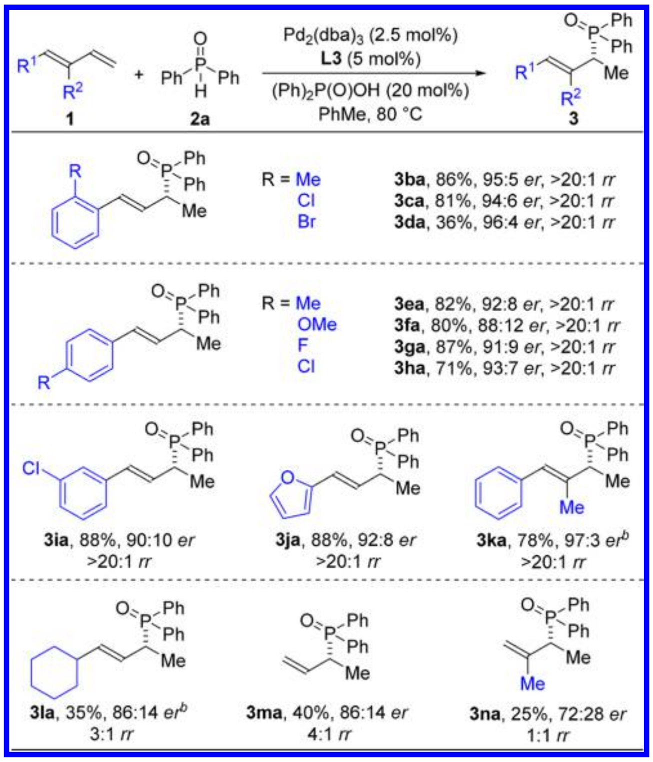
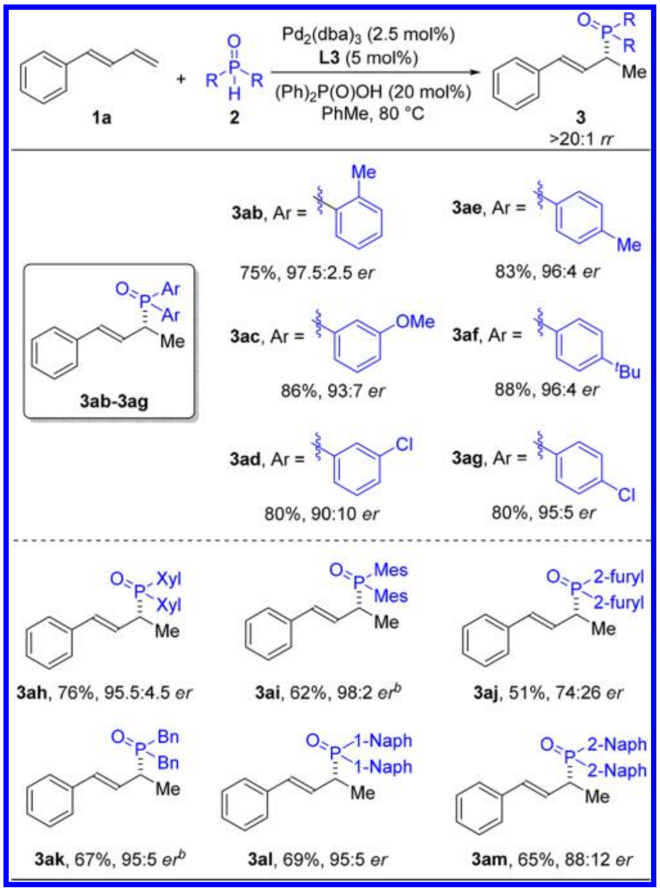
Table 2. Hydrophosphinylation of Various 1,3-Dienes[a]



[a]Reaction conditions: **1** (0.12 mmol), **2a** (0.10 mmol), $Pd_2(dba)_3$ (2.5 mol %), ligand (5.0 mol %), $(Ph)_2P(O)OH$ (20 mol %), toluene (0.40 mL), 6 h. Isolated yield of **3**. Regioselectivity ratio (*rr*) is the ratio of **3** to **4**, which is determined by ^{31}P NMR analysis of reaction mixture. Enantioselectivity determined by chiral SFC. [b](*S*)-DTBM-SegPhos (5.0 mol %) instead of **L3**, see SI for structure, 24 h.

Table 3. Hydrophosphinylation of 1a with Various Phosphine Oxides[a]



[a]Reaction conditions: **1a** (0.12 mmol), **2** (0.10 mmol), $Pd_2(dba)_3$ (2.5 mol %), ligand (5.0 mol %), $(Ph)_2P(O)OH$ (20 mol %), toluene (0.40 mL), 6 h. Isolated yield of **3**. Regioselectivity ratio (*rr*) is the ratio of **3** to **4**, which is determined by ^{31}P NMR analysis of reaction mixture. Enantioselectivity determined by chiral SFC. See SI for full structure of abbreviations used. [b]Reaction time is 24 h.

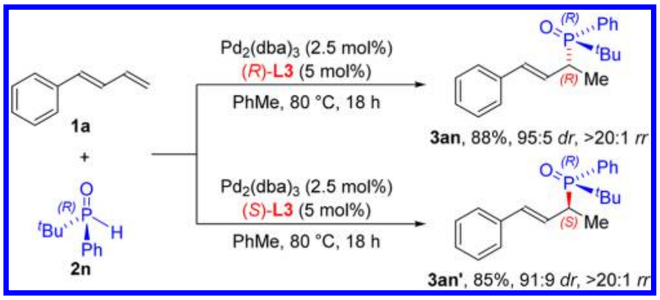


Figure 2. Diastereodivergent hydrophosphinylation of **1a**.

ing phosphine.[14] In addition, the pK_a of **2** (*ca.* 25)[15] is between that of amines and thiols. Although the phosphine oxide reagent and its corresponding product could inhibit catalysis, hydrophosphinylation of alkenes[16] and alkynes[17] using transition-metal catalysis and photocatalysis has been reported. Encouraged by these examples, we set out to identify a catalyst that would overcome the established 1,4-addition pathway to furnish the desired chiral isomer.

We began our investigations with the coupling of 1-phenylbutadiene (**1a**) and commercially available **2a** (Table 1). We examined a range of achiral bisphosphine ligands, with both Rh and Pd precatalysts. While Rh showed no reactivity, Pd was promising for the hydrophosphinylation of **1a**. As highlighted in Table 1A, we observed that the ligand bite angle affected the efficiency of the hydrophosphinylation.[18] Combining $Pd_2(dba)_3$ and ferrocene-based dppf offered optimal results (90%, >20:1 *rr*). Catalytic amounts of acid provided an increase in the reaction rate; P(V)-based Brønsted acids proved to be the most effective for hydrophosphinylation (Table 1B). In the absence of an acid cocatalyst, we observe 16% of product **3aa** after 3 h and an 87% yield after 24 h. Based on these results, we focused on the Josiphos ligand family with diphenylphosphinic acid as a cocatalyst.[19] As seen in Table 1C, with Pd(**L3**) we could lower the catalyst loading to 0.50 mol % and synthesize **3aa** on gram scale while retaining high reactivity (1.05 g, 91%) and selectivity (>20:1 *rr*, 95:5 *er*). The *er* in the presence of different acids shows little variation and ranges from 95:5 to 96:4.

With these conditions in hand, we investigated the hydrophosphinylation of various 1,3-dienes with phosphine oxide **2a** (Table 2). We found that a variety of 1-aryl substituted dienes could be transformed to chiral products **3ba**−**3ja** with moderate to high reactivity (36−88%) and selectivity (>20:1 *rr*, 88:12−96:4 *er*). Dienes containing aryl chlorides (**3ca**, **3ha**, **3ia**) offer higher reactivity than aryl bromides (**3da**), potentially due to the mitigation of side pathways initiated by oxidative addition into the C−X bond. The petroleum feedstocks butadiene (**1m**) and isoprene (**1n**) can be coupled with **2a** to furnish chiral building blocks **3ma**

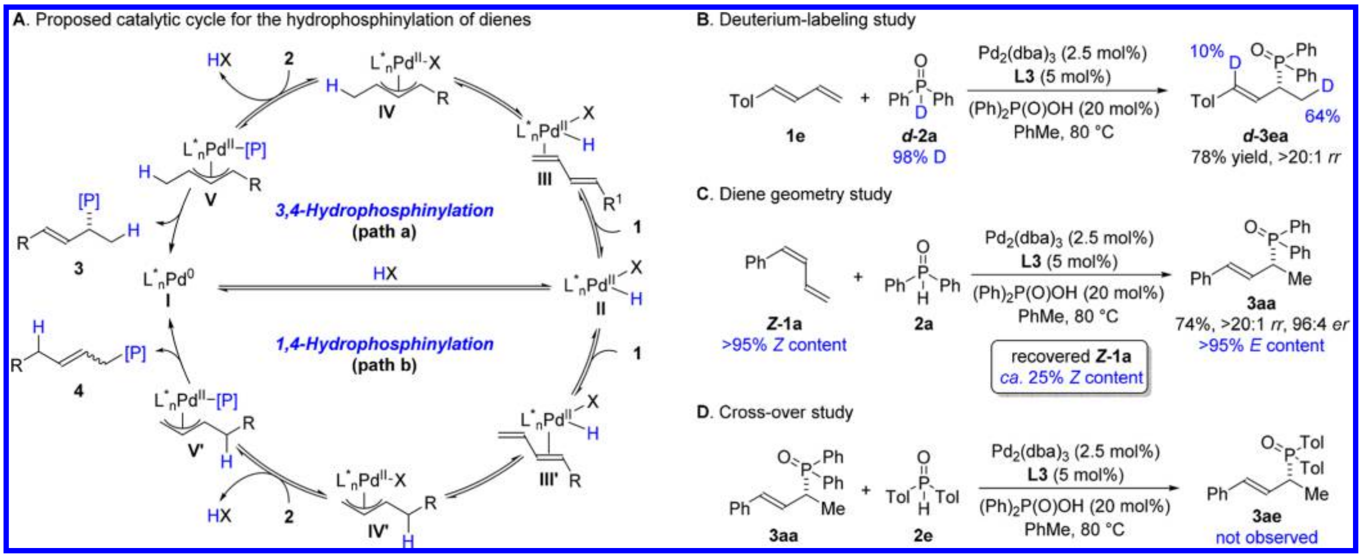


Figure 3. Proposed mechanism and initial investigations of the Pd-catalyzed hydrophosphinylation of 1,3-dienes.

and **3na**, respectively. We observed product mixtures of **3ma** and **3na** that equally, or moderately, favor 3,4-addition over the established 1,4-addition previously reported for the hydrophosphorylation of butadiene[6] (**1m**) and isoprene[5,6] (**1n**). To examine if the allylic phosphine oxide products (**3ma** and **3na**) could racemize by a sigmatropic rearrangement,[20] we resubjected **3ma** to the standard reaction conditions. After 12 h, we observed no change in the enantiomeric excess. The 1,2-disubstituted diene (**1k**) and 1-alkyl substituted diene (**1l**) transform to products **3ka** and **3la**, respectively, in the presence of (*S*)-DTBM-SegPhos. This result suggests that the diene substitution pattern must be matched with the appropriate ligand family, an observation in agreement with our previous studies on Rh-catalyzed hydrothiolation of 1,3-dienes.[13]

Next, we investigated the hydrophosphinylation of **1a** with structurally and electronically different phosphine oxides (Table 3). We observed high reactivity (**3ab**−**3am**, 51−88%), regioselectivity (>20:1 *rr*), and enantioselectivity (74:26−98:2 *er*). This coupling tolerates aryl (**3ab**−**3ai**), heterocyclic (**3aj**), and alkyl (**3ak**) phosphine oxides. Mono- (**2a**−**2g**), di- (**2h**), and trisubstituted (**2i**) aryl groups on the phosphine oxide partner can be coupled with **1a** to afford enantioenriched products (**3aa**−**3ai**). Fused ring motifs, which are the basis of a large class of ligand scaffolds, can also be incorporated in the phosphine oxide partner to generate products **3al** and **3am**.

Catalyst-controlled C−P bond formation would enable selective access to diastereomers. To test this idea, we prepared enantiopure phosphine oxide **2n** bearing a *tert*-butyl and phenyl group, a popular motif in chiral ligand design (Figure 2).[21] Depending on the enantiomer of the ligand **L3** used, the (*R*,*R*)-diastereomer **3an**[22] or (*R*,*S*)-diastereomer **3an′** can be obtained with high diastereocontrol (95:5 and 91:9 *dr*, respectively). This result represents a diastereodivergent strategy for making phosphine oxides.

Based on literature precedence and our own observations, we propose the mechanism depicted in Figure 3A. The Pd(0) precatalyst undergoes ligand substitution with the bisphosphine ligand to form a chiral monomeric species **I**, and subsequent oxidative addition to diphenylphosphinic acid (HX) forms Pd−H species **II**. A related oxidative addition has been implicated as a key step in the hydrophosphinylation of terminal alkynes.[17e] In the absence of acid additives, we observe a significant induction period.[23] We reason that the addition of an acid cocatalyst (i.e., diphenylphosphinic acid) shortens the induction period and favors the Pd−H catalyst (e.g., **II**). At this point, two different modes of diene **1** coordination lead to the major product **3** (**path a**) and the minor product **4** (**path b**). In **path a**, species **III** undergoes hydropalladation to provide the key Pd-π-allyl intermediate **IV**. Species **IV** then undergoes a ligand exchange with phosphine oxide **2** to form species **V**. Subsequent reductive elimination of **V** furnishes the allylic phosphine oxide **3** and regenerates the Pd-catalyst **I**.

To probe the mechanism, we conducted the following experiments (Figure 3B−D). First, down deuterium-labeled phosphine oxide ***d*-2a** was subjected to the standard reaction conditions. In this experiment, we see deuterium incorporation at the C1 (10% D) and C4 (64% D) positions of ***d*-3ea**. If hydropalladation was irreversible, we should observe about a 6:1 mixture of regioisomers. In contrast, we observe >20:1 *rr* and thus conclude that hydropalladation is reversible. Second, (*Z*)-1-phenylbutadiene (**Z-1a**) was subjected to the hydrophosphinylation. We observed only the (*E*)-product **3aa** (>95% *E* content) in similar yield (74%) and regioselectivity (>20:1 *rr*) compared to the model substrate (Table 1, **3aa**, 90% yield, >20:1 *rr*). This result suggests that isomerization occurs faster than C−P bond formation. Furthermore, excess diene **Z-1a** is recovered with *ca.* 25% *Z* content, which is consistent with a reversible hydropalladation and reversible diene coordination. By subjecting toluoyl phosphine oxide **2e** to product **3aa** under otherwise standard conditions, we confirm that the allylic phosphine oxide **3aa** cannot undergo further substitution to form **3ae**. Our proposal is in line with a study on alkyne hydrophosphinylation, where Pd−P bond cleavage requires elevated temperatures, and reductive elimination is the turnover-limiting step.[17e] We observe that alkyl-substituted dienes (**1l**−**1n**) form products (**3la**−**3na**) with lower regioselectivity compared to the aryl-substituted dienes (**3ba**−**3ka**). Thus, reductive elimination to form the conjugated product appears to be favorable.

The direct construction of chiral phosphines and phosphine oxides has previously been achieved *via* additions to Michael acceptors or transition-metal catalyzed substitutions.[24,25] Herein, we report a complementary way to access chiral phosphine oxides. This study features the first enantioselective hydrophosphinylation of dienes. Phosphine oxides and 1,3-dienes can be coupled to furnish chiral allylic products in high yields, regioselectivities, and enantioselectivities. Mechanistic studies suggest that the coupling proceeds through a reversible hydropalladation of the 1,3-diene partner, followed by irreversible reductive elimination to afford chiral phosphine oxide building blocks.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11150.

Experimental procedures and spectral data for all new compounds (PDF)

Crystallographic data for **3an** (CIF)

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Notes

The authors declare no competing financial interest.

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