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Palladium-Catalyzed Regio- and Enantioselective Hydrophosphination of *gem*-Difluoroallenes

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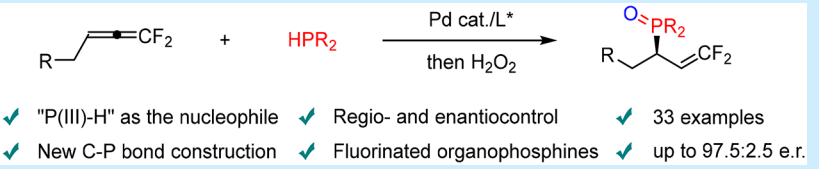
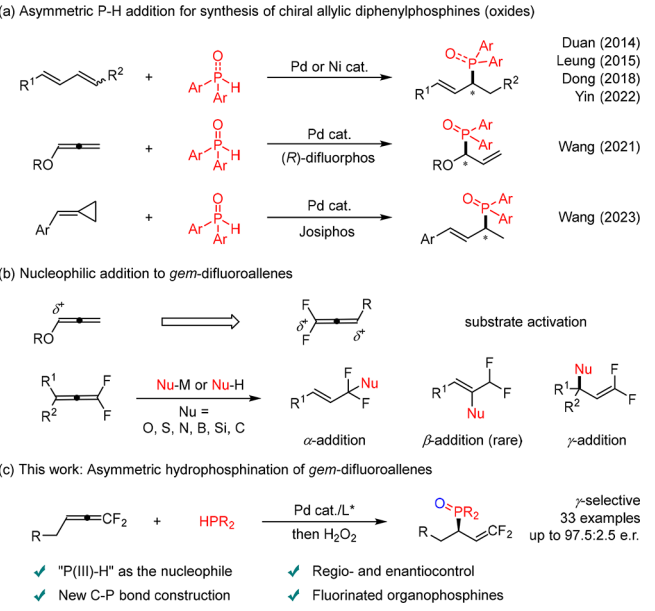


ABSTRACT: Chiral allylic phosphines and *gem*-difluoroalkenes are both important structural motifs in various bioactive molecules, chiral ligands, and natural products. These two motifs are now integrated, and we herein report a straightforward and atom-economical enantioselective hydrophosphination of *gem*-difluoroallenes using disubstituted phosphines. A wide array of enantioenriched fluorinated allylic phosphines has been accessed with excellent regio- and enantioselectivity and high efficiency. Synthetic and catalytic applications of phosphine products have been demonstrated.

Enantioenriched organophosphorus compounds have been widely employed in asymmetric catalysis,[1] material science,[2] and biological studies.[3] Thus, the selective construction of chiral organophosphorus compounds has attracted increasing attention. In particular, allylic phosphines are useful chiral ligands as well as versatile synthetic building blocks for downstream conversions.[4] Therefore, various asymmetric catalytic methods have been developed to synthesize chiral allylic phosphine (oxides), including asymmetric allylation of secondary phosphine oxides,[5] conjugate addition to electron-deficient dienes,[6] and hydrofunctionalization of diphenylphosphinylallenes.[7] Among them, asymmetric hydrophosphination of unsaturated molecules has emerged as a straightforward and atom-economical strategy. In this respect, the Duan group and the Leung group independently reported palladium-catalyzed asymmetric addition of diarylphosphines to electronically activated 1,3-dienes, affording chiral allylic phosphine derivatives.[6] In 2018, the Dong group reported Pd-catalyzed enantioselective hydrophosphinylation of unactivated dienes with excellent enantio- and regiocontrol (Scheme 1a).[8] In 2022, Yin realized a related hydrophosphinylation system by employing nickel/Brønsted acid catalysis.[9] Very recently, other unsaturated reagents started to be employed in this line.[10−12] A highly enantioselective hydrophosphinylation of alkyl- and aryl-functionalized oxyallenes was achieved by the Wang group in 2021 (Scheme 1a).[11] The same group further reported palladium-catalyzed hydrophosphinylation of methylenecyclopropanes (MCPs) via a regioselective ring-opening process.[12]

Despite these impressive reports, a P(V)−H reagent remains predominantly used as in hydrophosphinylation reactions. This is likely ascribed to the strong inhibitive effect of the P(III)−H counterpart that may readily cause catalyst poisoning. Thus, asymmetric access to chiral allyl phosphine via hydro-

Scheme 1. Synthesis of Allylphosphine (Oxide) via Addition of P−H Bonds



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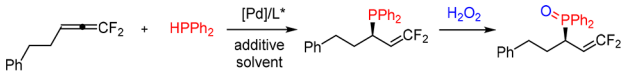
phosphination of unsaturated molecules has remained largely underdeveloped. Our initiative was to adopt substrate activation by employing an allene that is activated by an electron-withdrawing group (EWG) instead of by an electron-donating group (EDG) as in Wang's recent report (Scheme 1b).[11]

Indeed, the introduction of a *gem*-difluoro group significantly enhances the reactivity of the allene reagent, and partial positive charge is distributed at the α-carbon (CF_2) of *gem*-difluoroalkenes. Meanwhile, the non-fluorinated double bond is also activated with a lower HOMO energy.[13] Consequently, nucleophilic addition to *gem*-difluoroalkenes may follow complex regioselectivity. In 2006, Hammond and co-workers reported the α-selective nucleophilic addition−vinylic substitution (S_NV reaction) of the *gem*-difluoroallenes to deliver trisubstituted monofluoroallenes.[14] γ-Selective addition seems more common in the reaction with various nucleophiles. Ichikawa found that 1,1-difluoroallenes underwent γ-selective nucleophilic addition with an organometallic species (Nu−M), and the resulting difluorovinylcopper intermediates were then trapped by an electrophile to generate a 2,2-disubstituted 1,1-difluoroalkene.[15,16] Subsequently, the Xu group and the Feng group independently demonstrated copper-catalyzed γ-selective boryl- and silyl-addition to *gem*-difluoroallenes.[17] Impressively, Shi reported regiodivergent additions of thiol S−H bonds to *gem*-difluoroallenes at the β- and γ-positions under ligand control in 2022. Shi also extended the nucleophile to amines.[18] Later, the Feng group presented Rh-catalyzed γ-selective hydroarylation of disubstituted *gem*-difluoroallenes to create benzylic quaternary centers.[19] Very recently, the Gao group reported, in one example, rhodium-catalyzed γ-hydroamination of *gem*-difluoroallenes with NH sulfoximines. However, only poor enantioselectivity and reactivity were realized.[20] Thus, only very limited examples of asymmetric catalytic additions of *gem*-difluoroallenes have been reported so far, among which secondary phosphines have not been included as a nucleophile.

We reasoned that moving from oxyallenes to the oppositely activated *gem*-difluoroallenes should render significant substrate activation (Scheme 1b). In addition, the high activity of the *gem*-difluoroallenes may also accommodate less reactive secondary phosphine nucleophiles. Building on our interest in asymmetric hydrophosphination of unsaturated molecules,[21] we now report palladium-catalyzed asymmetric hydrophosphination of *gem*-difluoroallenes with secondary phosphines, which offers an atom-economic method to access *gem*-difluoroallylphosphines in good reactivity and excellent regio- and enantioselectivity (Scheme 1c).

We initiated our studies by employing *gem*-difluoroallene **1a** and diphenylphosphine **2a** as model substrates under palladium catalysis (Table 1). Our screening of ligands indicated that electron-rich bidentate phosphine ligands **L1**−**L5** with three different chiral backbones all enabled formation of the γ-selective product in good yield when palladium acetate was used as the catalyst (entries 1−5). The initial trivalent phosphine product was slightly unstable in air, and it was treated with H_2O_2 to facilitate subsequent isolation and analysis. Ligand **L4** was identified as a superior one, affording **3aa** in 67% yield and 84:16 er (entry 4). Further optimization of the palladium source showed that the use of (η^3-allyl)(η^5-Cp)Pd (**Pd1**) led to improved enantioselectivity (88:12 er, entry 7). The enantioselectivity was further improved when a 1-phenyl group was introduced to the allyl ligand (**Pd2**

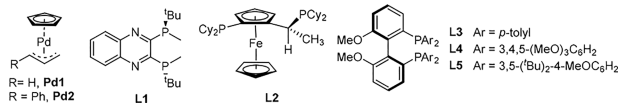
Table 1. Optimization of Reaction Conditions[a,b]



1a 2a 3aa' 3aa

entry	Pd	L*	additive	solvent	yield (%)	e.r.
1	$Pd(OAc)_2$	**L1**		PhMe	64	30:70
2	$Pd(OAc)_2$	**L2**		PhMe	59	66:34
3	$Pd(OAc)_2$	**L3**		PhMe	55	70.5:29.5
4	$Pd(OAc)_2$	**L4**		PhMe	67	84:16
5	$Pd(OAc)_2$	**L5**		PhMe	46	52.5:47.5
6	$Pd(dba)_2$	**L4**		PhMe	58	87:13
7	**Pd1**	**L4**		PhMe	75	88:12
8	**Pd2**	**L4**		PhMe	73	89:11
9	**Pd2**	**L4**		DCM	76	90.5:9.5
10	**Pd2**	**L4**		THF	60	88:12
11	**Pd2**	**L4**	$PhCO_2H$	DCM	61	89.5:10.5
12	**Pd2**	**L4**	KOPiv	DCM	78	93:7
13	**Pd2**	**L4**	KOPiv	DCM	83	95:5[c]

[a]



[b]Reaction conditions: *gem*-difluoroallenes (0.12 mmol), $HPPh_2$ (0.1 mmol), [Pd] (5 mol %), chiral ligand (6 mol %), additives (50 mol %) in a solvent (2.0 mL) at 25 °C for 48 h, then H_2O_2 was added and stirred for 20 min at 0 °C. Isolated yield. The e.r. was determined by HPLC analysis using a chiral stationary phase. [c]The reaction was conducted at −20 °C for 60 h.

catalyst, entry 8). DCM turned out to be an optimal solvent (entry 9). To further improve the enantioselectivity, a base additive was introduced.[21] It was found that the addition of KOPiv noticeably enhanced the enantioselectivity (entry 12), while other acids or bases appeared to give inferior results (entry 11). Finally, the reaction was subjected to −20 °C for a prolonged reaction time, delivering the target product **3aa** in 83% isolated yield and 95:5 e.r. (entry 13). In all cases, only the γ-selective product was detected.

With the optimized conditions in hand, we then examined the scope of *gem*-difluoroallenes with Ph_2PH as the coupling reagent (Scheme 2). *gem*-Difluoroallenes with a distal benzene ring functionalized with an electron-donating (**3ab**), halogen (**3ac**), electron-withdrawing (**3ad** and **3ae**), and electron-neutral substituent (**3af**) at the *para* position were well tolerated. Besides, the *ortho*- and *meta*-substituted phenyl ring also showed excellent stereoselectivity and efficiency (**3ag**−**3ai**, 94:6 to 95.5:4.5 e.r.). Moreover, various substituents such as a long aliphatic chain (**3aj**), a chloro substituent (**3am**), a benzyloxy (**3an**), and an OTBS group (**3ao**) at the distal end were well compatible with the standard conditions. It is worth mentioning that allene substrates containing terminal alkene and alkyne motifs were all applicable (**3ak** and **3al**, 97:3 and 96:4 e.r., respectively). Extension of the arene ring to heterocycles such as thiophene, furan, and indole also turned out to be successful (**3ap**−**3ar**, 95:5 to 96.5:3.5 e.r.). Significantly, the substrate bearing a stereogenic center also underwent smooth reaction with high diastereoselectivity (**3as**, 94:6 d.r.). Substrate **1t** with a pendent tertiary group reacted to furnish the corresponding product **3at** with moderate yield and lower enantioselectivity at a higher temperature (90:10 er), probably due to the steric effect. The tetrasubstituted *gem*-

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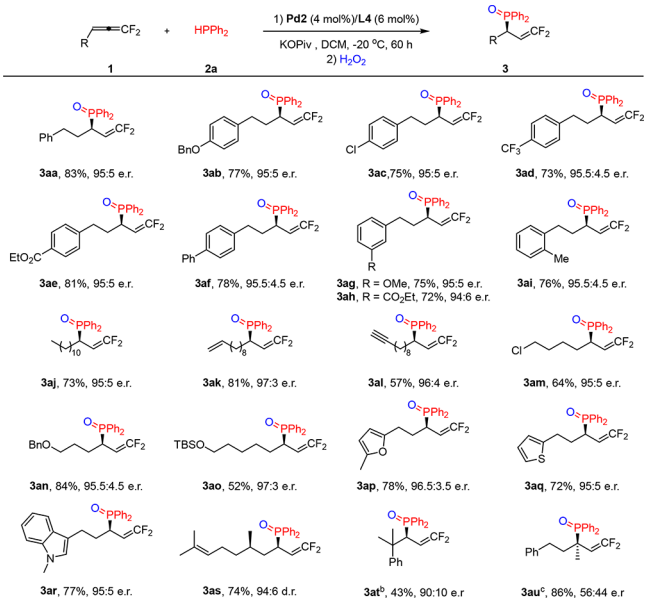
Scheme 2. Scope of Substrates in Enantioselective Hydrophosphination with *gem*-Difluoroallenes[a−c]

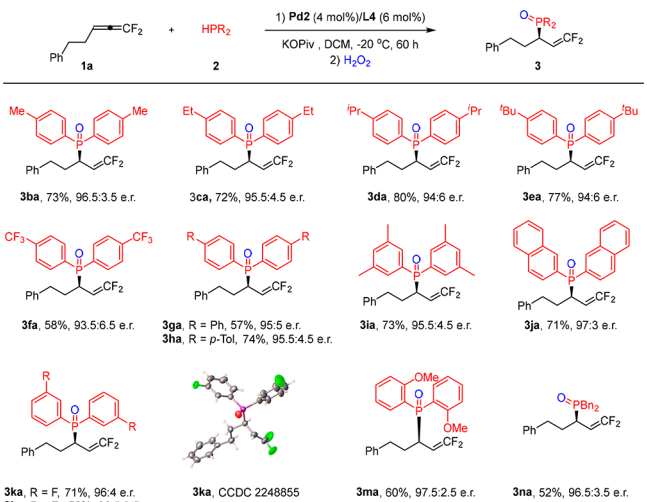


[a]Reaction conditions: *gem*-difluoroallenes (0.12 mmol), $HPPh_2$ (0.1 mmol), **Pd2** (5 mol %), **L4** (6 mol %), KOPiv (50 mol %) in DCM (2.0 mL) at −20 °C, 60 h, then H_2O_2 at −20 °C for 20 min. Isolated yield. The e.r. was determined by HPLC analysis using a chiral stationary phase. [b]The reaction was conducted at 0 °C for 60 h. [c]The reaction was conducted at 30 °C for 24 h.

difluoroallenes **1u** gave the target product **3au** in 86% yield with poor enantioselectivity.

We next explored the scope of symmetric diarylphosphines in coupling with *gem*-difluoroallene **1a**. As given in Scheme 3, diarylphosphines bearing different electron-donating and -withdrawing groups at the *para* position all reacted smoothly

Scheme 3. Scope of Symmetric Secondary Phosphines in Enantioselective Hydrophosphination[a]

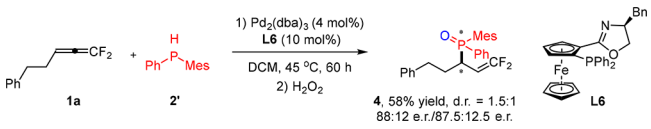


[a]Reaction conditions: *gem*-difluoroallenes (0.12 mmol), HPR_2 (0.1 mmol), **Pd2** (5 mol %), **L4** (6 mol %), KOPiv (50 mol %) in DCM (2.0 mL) at −20 °C, 60 h, then H_2O_2 at −20 °C for 20 min. Isolated yield. The e.r. was determined by HPLC analysis using a chiral stationary phase.

to give the corresponding products with excellent enantioselectivity (**3ba**−**3ha**). A 1,3-disubstituted diarylphopshine also performed well in terms of reactivity and enantioselectivity (**3ia**, 95.5:4.5 e.r.). Other diarylphosphines with different *meta* substituents also coupled smoothly to yield the products in comparable enantioselectivity and yields (**3ka** and **3la**). The absolute configuration of product **3ka** was determined to be (*R*) by X-ray crystallographic analysis (CCDC 2248855), and those of other products were assigned by analogy. In addition, di(2-naphthyl)phosphine also reacted efficiently to deliver the desired product **3ja** in 97:3 er and 71% yield. Significantly, an *ortho*-methoxy-substituted diarylphosphine was also tolerated regardless of its steric effect (**3ma**, 97.5:2.5 e.r.). The phosphine substrate is not restricted to diaryl substitution, and dibenzylphosphine participated with high enantioselectivity and good yield (**3na**, 96.5:3.5 e.r.). In contrast, no reactivity was observed for dialkylphsophines such as Cy_2PH and $^tBu_2PH$ under various reaction conditions, possibly due to substrate inhibition.

Encouraged by the success of symmetric phosphines, we next evaluated a non-symmetric secondary phosphine **2′** (Scheme 4). The coupling with allene **1a** was extensively

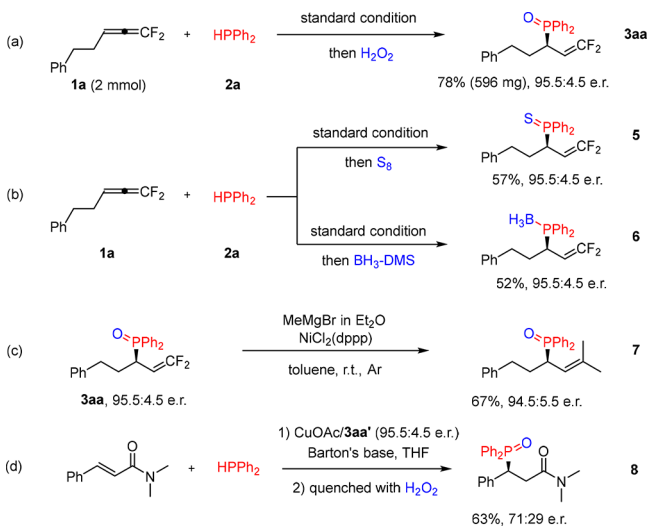
Scheme 4. Unsymmetric Secondary Phosphines in Enantioselective Hydrophosphination



attempted under various catalytic conditions, eventually furnishing product **4** in 58% yield as a mixture of diastereomers (dr = 1.5:1) with 88:12 e.r. for the major diastereomer and 87.5:12.5 e.r. for the minor one.

To demonstrate the synthetic utility of this methodology (Scheme 5), *gem*-difluoroallylphosphine **3aa** was synthesized in high yield on a 2.0 mmol scale without a loss of enantioselectivity (Scheme 5a). The direct hydrophosphinated product (**3aa′**) could be protected by sulfur and borane, affording phosphine sulfide **5** and borane−phosphine adduct **6**, respectively (Scheme 5b). Treatment of **3aa** with Grignard

Scheme 5. Derivatization Reactions



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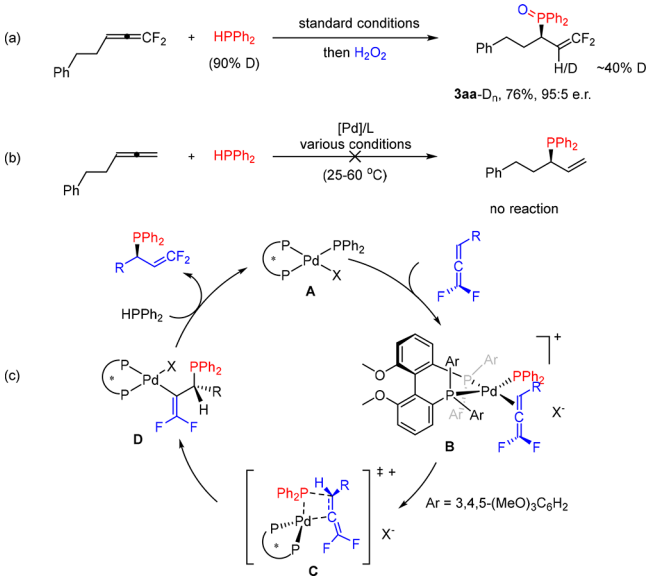
reagent in the presence of a nickel catalyst afforded the methylated product **7** in 67% yield with erosion of the enantiopurity (Scheme 5c). Phosphine **3aa′** was then utilized as a chiral ligand in copper(I)-catalyzed asymmetric 1,4-conjugate hydrophosphination of α,β-unsaturated amides,[22] delivering product **8** with promising enantioselectivity (71:29 e.r., Scheme 5d).

Preliminary studies were conducted to investigate the mechanism (Scheme 6). A deuterium labeling experiment

Scheme 6. Mechanism Studies and the Proposed Mechanism for Hydrophosphination



was conducted using D-PPh_2 (90% D) and *gem*-difluoroallene **1a** under the standard conditions, producing the partially deuterated **3aa-d_n** with approximately 29% D at the β-position. After rigorously drying all substrates and the solvent, we found that the deuterium incorporation of **3aa-d_n** was increased to 40% (Scheme 6a). This observation may imply the plausibility of a palladium vinyl species in this coupling system, which is followed by a process of protonolysis or sigma-bond metathesis. The high acidity of the PH and adventitious water may account for the reduced level of deuteration in the product. In a control experiment using a non-fluorinated terminal allene, no desired coupling was observed, which further substantiated the critical role of the *gem*-difluoro group to ensure reactivity (Scheme 6b). A plausible reaction mechanism is then proposed (Scheme 6c). Initially, $HPPh_2$ and L*PdX_2 reacted to afford a Pd(II)−PPh_2 species (**A**) through ligand exchange. Given the strong ligating ability of the non-fluorinated double bond and the electron-richness of the allene middle carbon,[16,23] olefin-bound intermediate **B** was proposed, where the R group in the allene is pointed away from the chiral ligand and the metal center for minimized steric repulsions. Then, enantiodetermining and regioselective migratory insertion of the PPh_2 occurs into the γ-carbon of *gem*-difluoroallenes via transition state **C** to give intermediate **D**. Finally, protonolysis of the Pd−vinyl bond or σ bond metathesis furnishes the direct product **3aa′** with regeneration of the Pd(II) catalyst.

In summary, we have developed an asymmetric hydrophosphination of *gem*-difluoroallenes by integrating organofluorine and organophosphine chemistry. With substrate activation enabled by the *gem*-difluoro group, the palladium-catalyzed system tolerated a broad scope of secondary phosphines with excellent regio- and enantioselectivity. The reaction exhibits good compatibility of functional groups, and the *gem*-difluoroallylphosphine products could be further engaged in asymmetric catalysis as a potential chiral ligand. The asymmetric hydrophosphination reaction may open a new avenue to access chiral fluorinated allylic phosphine derivatives. The reactivity of *gem*-difluoroallenes warrants further investigation, and other potential applications are actively explored in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02031.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 2248855 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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