Palladium-catalyzed asymmetric hydrophosphorylation of alkynes: facile access to P-stereogenic phosphinates†‡

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Despite the importance of P-chiral organophosphorus compounds in asymmetric catalysis, transition metal-catalyzed methods for accessing P-chiral phosphine derivatives are still limited. Herein, a catalytic enantioselective method for the synthesis of P-stereogenic alkenylphosphinates is developed through asymmetric hydrophosphorylation of alkynes. This process is demonstrated for a wide range of racemic phosphinates and leads to diverse P-stereogenic alkenylphosphinates directly.

Introduction

P-Chiral organophosphorus compounds are broadly utilized as synthetic building blocks of bioactive molecules and have served as an important class of chiral ligands that have significantly contributed to metal-catalyzed and organocatalytic transformations. P-stereogenic phosphinates are important molecules in medicinal and synthetic chemistry. For example, arylphosphinosugars have received continuous attention and demonstrated powerful activities on human cancer cell line panels. However, P-chiral organophosphorus compounds are less studied due to their synthetic challenges, compared with chiral phosphine ligands where planar or point chirality is presented in the carbon framework.

Despite the importance of P-stereogenic phosphinates, general and efficient methods for their preparation are rather rare. Traditionally, enantioenriched P-chiral phosphorus compounds are achieved through the use of chiral reagents or auxiliary-assisted transformations, using menthol or chiral amino alcohol, for example. Recently, a variety of examples involving metal-catalyzed asymmetric processes through desymmetrization of prochiral phosphorus compounds have emerged. Dialkynylphosphine oxides are the typical examples for constructing P-stereogenic phosphate oxides, and the first desymmetrization of dialkynylphosphine oxides was reported by using Rh(Ⅰ)-catalyzed cycloaddition. Desymmetrization of divinylphosphine oxides and phospholene oxides was also well-developed to construct P-stereogenic centers. Several elegant examples of inter- or intramolecular Pd-catalyzed enantioselective C–H arylation of phosphinamides, phosphonates and phosphine oxides were disclosed independently by Duan, Tang, Ma, Xu and Han. Soon after, Cramer reported Rh-catalyzed desymmetric alkylation of phosphinamides with alkynes and Ir-catalyzed arylation and amination of phosphate oxides. Very recently, Zhang presented an asymmetric P-C cross-coupling for the efficient synthesis of P-stereogenic phosphate oxides catalyzed by Pd and their Xiao-phos. Nevertheless, there have been only two desymmetrization examples reported for the enantioselective synthesis of P-stereogenic phosphinates. In 2009, Hoveyda and Gouverneur reported a molybdenum-catalyzed asymmetric ring-closing

**Scheme 1** Enantioselective synthesis of P-stereogenic phosphinates.
metathesis to obtain $P$-stereogenic phosphinates (Scheme 1, eqn (2a)). In 2019, Trost showed the desymmetrization of phosphinic acids by stereoselectively alkyllating one of the enantiotopic oxygens through Pd-catalyzed asymmetric allylic alkylation to give $P$-stereogenic phosphinates with diversified substituents (Scheme 1, eqn (2b)). Therefore, it is desirable to develop other new methods for the synthesis of multifunctional $P$-stereogenic phosphinates.

Pd-catalyzed addition of an H–P(O)R$_1$R$_2$ to alkynes is one of the most straightforward and atom-efficient approaches for the construction of a C–P bond. The first Pd-catalyzed addition of (RO)$_2$P(O)H to alkynes was reported by Tanaka and Han to give the corresponding alkynylphosphonates. Later, they developed a similar oxidative addition using (R$_2$)-methyl-phenylphosphinophosphate to give enantiomerically pure $P$-chiral alkynylphosphinates with retention of configuration at phosphorus. Though Han and co-workers reported a comprehensive study on the generality, scope, limitations, and mechanism of the palladium-catalyzed hydrophosphorylation of alkynes recently, the catalytic enantioselective hydrophosphorylation of alkynes with phosphinates is still not reported, given more than 22 years have passed since the first Pd-catalyzed hydrophosphorylation was reported. In 2006, Gaumont reported the Pd-catalyzed asymmetric hydrophosphonation of alkynes with phosphine–boranes, only 70% conversion and 42% enantio-meric excess were obtained. In 2018, Dong reported the hydrophosphinylation of 1,3-dienes to a meric excess were obtained. Recently, we disclose the first catalytic enantioselective hydrophosphorylation reaction of alkynes with phosphinates, which provides a highly efficient approach to prepare chiral alkynylphosphinates with $P$-chirality.

**Results and discussion**

To begin the investigation, phenylacetylene 1a and ethyl phenylphosphinophosphate 2a were chosen as the model substrates. Various types of ligands were initially evaluated, and most bidentate bisphosphine ligands with $P$ chirality worked well in this transformation. When Duaphos L1 was used as the ligand, the reaction proceeded smoothly to afford alkynylphosphinate 3aa in 70% yield with 70% ee (Table 1, entry 1). (R,R)-Ph-BPE exhibited poor reactivity and enantioselectivity (Table 1, entry 2). (S,S,S,S)-BIBOP L3 showed good reactivity, yet no product enantioselectivity was observed (Table 1, entry 3). To our delight, (R,R)-QuinoxP$_*$ L4 afforded 3aa in 70% yield with 83% ee (Table 1, entry 4). A similar ligand (R,R)-benzP$_*$ L5 gave 86% ee but with poor yield (Table 1, entry 5). A higher reaction temperature was required to allow the reaction to reach completion when Pd(dba)$_2$ was used (Table 1, entry 6). A brief survey of solvents revealed that THF, 1,4-dioxane and DCE resulted in inferior yields and enantioselectivities (Table 1, entries 7–9). Unlike phosphinic acid and secondary phosphine oxide, phosphinate 2a was not able to be easily racemized by base or transition metals. Thus, it is difficult for phosphinate to realize the dynamic kinetic resolution. Then, a kinetic resolution process was desired (for details, see the ESI†). However, when 1 equiv. of phosphinate was used, the product 3aa was obtained in 50% yield with 55% ee and the (R)-2a was recovered in 40% yield with 61% ee at 60 °C (the S factor is only 6) (Table 1, entry 10). Optimization of the ratio of 1a/2a was performed to enhance enantioselectivity of 3aa. When 4 equiv. 2a was used, the best yield and ee were obtained (Table 1, entry 4 vs. entries 10–13). When the amount of ethyl phenylphosphinophosphate 2a was increased to 6 equiv., the yield was reduced which might due to the coordinative saturation of the palladium center by the excess amount of 2a, and hence resulted in catalyst deactivation (Table 1, entries 12 and 13). Omitting Ph$_2$P(O)OH resulted in a reduced yield, but a little enhanced product enantioselectivity (Table 1, entry 14 vs. 4). Thus, the optimal reaction conditions were toluene at 60 °C with 1 mol% Pd$_2$(dba)$_3$, 2 mol% (R,R)-QuinoxP$*$, and 4 mol% phosphinic acid.

With these optimized conditions in hand, the reaction scope was next examined (Table 2). It was found that a large range of

### Table 1 Optimization of the reaction conditions$^a$

| Entry | Ligand | Solvent | Temp (°C) | Yield (%) | ee (%) |
|-------|--------|---------|-----------|-----------|-------|
| 1     | L1     | Toluene | 60        | 70        | 70    |
| 2     | L2     | Toluene | 60        | Trace     | —     |
| 3     | L3     | Toluene | 60        | 85        | 7     |
| 4     | L4     | Toluene | 60        | 70        | 83    |
| 5     | L5     | Toluene | 60        | 11        | 86    |
| 6     | L6     | Toluene | 80        | 85        | 76    |
| 7     | L7     | THF     | 60        | 68        | 75    |
| 8     | L8     | Dioxane | 60        | 54        | 81    |
| 9     | L9     | DCE     | 60        | Trace     | —     |
| 10    | L10    | Toluene | 60        | 50        | 55    |
| 11    | L11    | Toluene | 60        | 59        | 78    |
| 12    | L12    | Toluene | 60        | 34        | 85    |
| 13    | L13    | Toluene | 60        | 44        | 86    |
| 14    | L14    | Toluene | 60        | 60        | 84    |

$^a$ Reaction conditions: 1 mol% Pd$_2$(dba)$_3$, 2 mol% ligand, and 4 mol% Ph$_2$P(O)OH in 1 mL toluene were stirred for 10 min in an argon atmosphere. 0.25 mmol alkynes and 1.0 mmol ethyl phenylphosphinate were added, and the mixture was stirred at the indicated temperature. Isolated yields. Determined by HPLC analysis. $^b$ 2 mol% Pd(dba)$_3$ was used instead of 1 mol% Pd$_2$(dba)$_3$. $^c$ 1 equiv. ethyl phenylphosphinate was used. $^d$ 3 equiv. ethyl phenylphosphinate was used. $^e$ 6 equiv. ethyl phenylphosphinate was used. $^f$ 2 mL toluene was used. $^g$ Without Ph$_2$P(O)OH.
Substrates with methyl ester or propyl ester were also subjected to hydrophosphorylation and the corresponding alkenylphosphonates (3ab and 3ac) were formed in moderate yields and enantioselectivities. A substrate with isopropyl ester gave decreased yield (3ad), only 32% yield, and slightly decreased enantioselectivity, 73% ee. The phenylphosphininate with Me on the arene ring only gave the product 3ae in 47% yield and 37% ee at a higher temperature. Compound 3fa with the t-Bu group was obtained in decreased yield compared to 3fa. When secondary phosphine oxides were tested under similar reaction conditions, the hydrophosphorylation product 3af was formed with 28% yield in 54% ee.

To evaluate the synthetic potential of the current catalytic system, a gram-scale reaction between phenylacetylene and ethyl phenylphosphinate was performed, and the product 3aa was furnished in 68% yield and 82% ee (Scheme 2a). Further synthetic transformations of the hydrophosphorylation products were also illustrated. Compounds 4 and 5 were prepared through a Suzuki–Miyaura coupling without loss of enantiopurity (Scheme 2b). The absolute configuration of the phosphinate product 3ja was confirmed as R-configuration by X-ray crystallography of its derivative 5a. The Heck-type reaction of aryl diazonium salts with alkenylphosphinate 3aa led to cis stilbenes 3qa with excellent stereoselectivity without loss of chirality (Scheme 2c, 99% yield and 82% ee) which could make up for the moderate yield and ee of 3qa obtained by direct hydrophosphorylation of diphenylacetylene (Table 2). To construct 1,2-biphosphine derivative, the addition of HPh2 to product 3aa was achieved by copper-catalyzed conjugate hydrophosphination to give biphosphine derivative 6 in 92% yield and 1.5 : 1 dr without loss of enantiopurity (Scheme 2d, 79% ee for both diastereomers).

A deuterium-labelling experiment has been conducted by using D-P(O)(OMe)Ph as the starting material, giving the

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**Table 2** Substrate scope of alkynes

| Ar– | R– | Ph–P(O)(OH) | Product |
|-----|-----|-------------|---------|
| MeO | Me | 2a | 3aa (91%, 30% ee) |
| MeO | Et | 2b | 3ab (91%, 30% ee) |
| MeO | n-pent | 2c | 3ac (91%, 30% ee) |
| MeO | t-Bu | 2d | 3ad (91%, 30% ee) |

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**Table 3** Substrate scope of phenylphosphinates and phenylphosphine oxide

| Ar– | R– | Ph–P(O)(OH) | Product |
|-----|-----|-------------|---------|
| MeO | Me | 2a | 3aa (91%, 30% ee) |
| MeO | Et | 2b | 3ab (91%, 30% ee) |
| MeO | n-pent | 2c | 3ac (91%, 30% ee) |
| MeO | t-Bu | 2d | 3ad (91%, 30% ee) |

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*a* Conditions: 1 mol% Pd2(dba)3, 2 mol% ligand L4, and 4 mol% Ph3P(O)OH in 1 mL toluene were stirred for 10 min in an argon atmosphere. 0.25 mmol alkynes 1a–1f and 1.0 mmol phenylphosphinate 2a–2d or phenylphosphine oxide 2e were added, and the mixture was stirred at 60 °C for 20 h. Isolated yields. Determined by HPLC analysis. b 80 °C was used instead.
triggers the reaction to produce the internal palladium intermediate B. The hydropalladation of allylaldehyde takes place first to give an internal alkylpalladium C by Markovnikov addition. Subsequent ligand exchange of this complex C with phosphinite 2a gives the internal phosphorylaluminium intermediate D. A reduced yield was observed in the absence of Ph₂P(O)OH. Thus, an alternative pathway is also possible in which the intermediate E is generated directly by the oxidative addition of the P-H bond of 2a to palladium. Then hydropalladation of alkynes takes place to give the same intermediate D. Finally, reductive elimination gives the desired alkenylphosphinite product 3aa and regenerates the active chiral palladium complex A.

Conclusions

In summary, we have developed an efficient method to synthesize alkenylphosphinates with P-chirality through the first Pd-catalyzed enantioselective hydrophosphorylation of alkynes, showing that this hydrophosphorylation reaction is a powerful and practical approach for the preparation of these valuable P-stereogenic organophosphorus compounds. Studies on further application of these chiral organophosphorus compounds are underway.

Conflicts of interest

There are no conflicts to declare.

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