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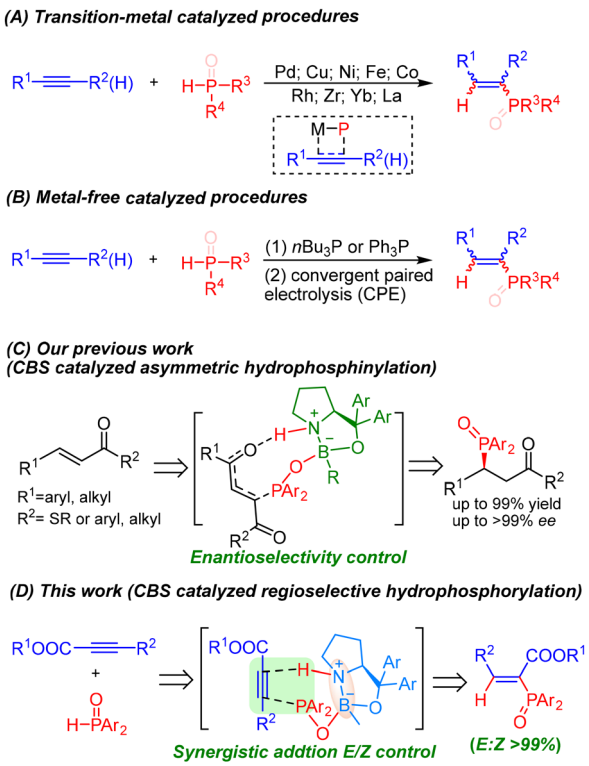
Metal-free regioselective hydrophosphorylation of electron-deficient alkynes catalyzed by oxazaborolidines†

Liangrui Xiao, Yu Chen, Liuyang Ding, Jiuling Li,* Yafei Guo * and Baomin Fan *

Here, we describe a metal-free strategy for the hydrophosphorylation of electron-deficient alkynyl to access various P-containing olefins catalyzed by commercial oxazaborolidines with high regioselectivity (*E* : *Z* up to 99%). Interestingly, the possible mechanism suggests that the catalytic path proceeds through a synergistic addition process which leads to single *E*-structure products. Moreover, the chiral oxazaborolidine catalyst probably works as a Lewis pair which can accelerate the cleavage of the O–H bond in diarylphosphine oxides and provide appropriate steric hindrance to control the regioselectivity.

Owing to the significant roles of phosphorus compounds in the chemical, pharmaceutical, agricultural, and materials industries, numerous methodologies have been developed for constructing P–C bonds.[1–6] Among these, the catalytic hydrophosphination strategy stands out as one of the most atom-economical routes to achieve this goal.[7–9] This approach is typically categorized into transition-metal catalysis and metal-free catalysis. The catalytic hydrophosphination of alkynes to the corresponding alkenes usually leads to regioselectivity in the form of Markovnikov and anti-Markovnikov products or *E*/*Z* selectivity.[10,11] For example, transition-metal catalyzed procedures initially generate metal–P(III/V) intermediates which also can activate the triple bonds and then four or five membered ring intermediates are formed (Scheme 1A).[12] Hence, the *E*/*Z* structures of the products are determined through the intermediates in synergistic addition forms. In the last decade, various metals, such as Pd, Cu, Ni, Fe, Co, Rh, Zr, Yb and La, were used in the catalytic regioselective hydrophosphorylation of alkynes, leading to numerous valuable phosphorus compounds (Scheme 1A).[13–18] Furthermore, recent advancements have seen successful development of metal-free strategies for electron-deficient alkynes (Scheme 1B).[19] For example, Ph_3P and nBu_3P were effectively utilized as catalysts in bis-addition reactions involving dialkyl phosphites and diaryl phosphine oxides with alkynoates.[20] Additionally, a convergent paired electrolysis method was disclosed for hydrophosphorylation of electron-deficient alkynes aimed at accessing γ-ketophosphine oxides. Interestingly, in that work, diarylphosphane oxide was converted into a phosphorus radical along with a hydrogen donor to yield the desired products.[21]



Scheme 1 (A) Transition-metal-catalyzed hydrophosphorylation of alkynes; (B) metal-free catalytic hydrophosphorylation of alkynes; (C) our previous work; (D) this work.

Yunnan Key Laboratory of Chiral Functional Substance Research and Application, Yunnan Minzu University, 2929 Yuehua road, Kunming 650500, China.
E-mail: gyfwin@sina.com, fanbaomin1979@163.com, lijiuling1990@163.com

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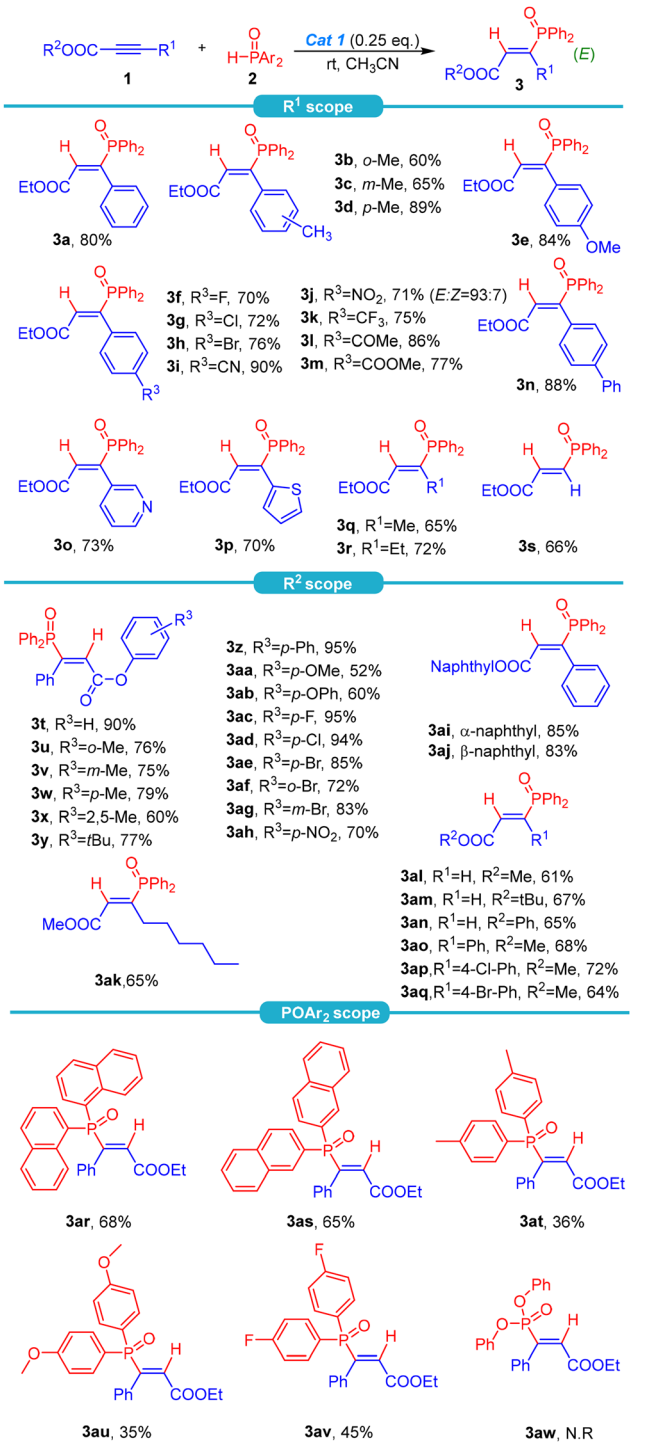
In our previous work, we identified novel applications of commercial oxazaborolidines (CBS) as chiral organocatalysts for the asymmetric hydrophosphorylation of various α,β-substrates, including ketones, thioesters, and esters (Scheme 1C).[22–25] Notably, the proposed mechanism indicated that the CBS catalyst could function as a frustrated Lewis pair to cleave the O–H bond and interact with the substrate to regulate enantioselectivity through a synergistic addition process. Building on these findings, we further incorporated electron-deficient alkynes into this catalytic system to validate the synergistic addition mechanism. As anticipated, regioselective hydrophosphorylation of alkynyl esters facilitated by diarylphosphine oxides occurred rapidly under CBS catalysis, achieving olefins with over 99% regioselectivity ($E:Z$ > 99%) (Scheme 1D). Moreover, alkynyl ketones and aldehydes are not discussed in this work due to the failure to control the regioselectivity.

We started off our investigations using ethyl 3-phenylpropiolate (**1a**) and diphenylphosphine oxide (**2a**) as model substrates to explore the optimal reaction conditions. Initially, the model reaction was carried out in the absence of a catalyst at room temperature. However, no product **3a** was detected (entry 1). Hence, the chiral CBS catalyst **Cat 1** was introduced in the model reaction. To our delight, the product **3a** was observed in 77% isolated yield, possessing a single *E*-structure (entry 2). Subsequently, **Cat 2–4** were further employed to explore their catalytic abilities. The results showed that less than 10% **3a** was obtained using these catalysts (entries 3–5). In order to further increase the yield, reactions at higher temperatures from 40 to 80 °C were performed. Outside of our expectation, the yields were not improved (entries 6–8).

Then, various solvents were examined using the model reaction. Chlorinated solvents, such as DCM and DCE, only gave 34–55% yields (entries 9 and 10) and ether solvents, such as THF and 1,4-dioxane, also could not improve the yields (entries 11 and 12). The protic solvent EtOH furnished **3a** only in a trace amount (entry 13). Interestingly, the yield of **3a** increased to 80% in the CH_3CN solvent (entry 14). After that, experiments investigating the catalyst loading (ranging from 10 mol% to 30 mol%) indicated that 25 mol% **Cat 1** was the most effective amount for subsequent substrate scope studies (entries 15–17). Consequently, we adopted the following reaction conditions as the optimal ones for further studies: 25 mol% **Cat 1** at room temperature in CH_3CN for 24 hours.

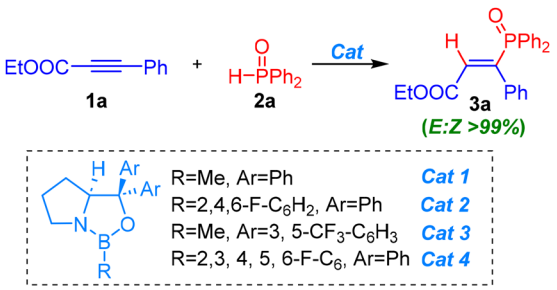
With the optimal reaction conditions established, a wide range of alkynes and diarylphosphine oxides were investigated (Scheme 2). As we mentioned in Table 1, the model product **3a** was obtained in 80% yield. In order to further explore the influence of the substituents on the phenyl group (β-position), substrates bearing *ortho*-, *meta*- and *para*-methyl groups were introduced to test this methodology. Interestingly, the product bearing the *para*-methyl group (**3d**) was obtained in a higher yield (89%) than **3b** (60%) and **3c** (65%). Then, the methoxyl group substituted product **3e** was obtained in 84% yield. Subsequently, various electron-withdrawing groups, such as –F, –Cl, –Br, –CN, $–NO_2$, $–CF_3$, –Ph, –C(O)Me and –COOMe,



Scheme 2 Substrate scope.

were all tolerated in this method, furnishing products **3f–3n** in 70–90% yields. Among them, the regioselectivity of **3j** was obtained with E/Z = 93 : 7. Moreover, substrates bearing pyridyl and thienyl groups were also applicable, leading to **3o** and **3p** in 73% and 70% yields. Notably, when the R^1 group was substituted with aliphatic groups, such as methyl and ethyl groups, the reactions still can work well, giving **3q** and **3r** in

Table 1 Optimization of reaction conditions[a]



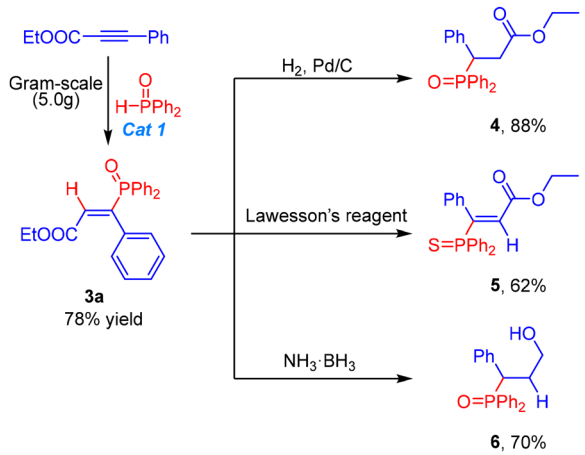
Entry	Cat. (mol%)	Solvent	T (°C)	Yield[b] (%)
1	—	Toluene	rt	ND
2	**Cat 1** (25)	Toluene	rt	77
3	**Cat 2** (25)	Toluene	rt	10
4	**Cat 3** (25)	Toluene	rt	Trace
5	**Cat 4** (25)	Toluene	rt	Trace
6	**Cat 1** (25)	Toluene	40	75
7	**Cat 1** (25)	Toluene	60	78
8	**Cat 1** (25)	Toluene	80	75
9	**Cat 1** (25)	DCM	rt	34
10	**Cat 1** (25)	DCE	rt	55
11	**Cat 1** (25)	THF	rt	45
12	**Cat 1** (25)	1,4-Dioxane	rt	48
13	**Cat 1** (25)	EtOH	rt	Trace
14	**Cat 1** (25)	CH_3CN	rt	80
15	**Cat 1** (10)	CH_3CN	rt	10
16	**Cat 1** (20)	CH_3CN	rt	67
17	**Cat 1** (30)	CH_3CN	rt	78

[a] Reactions performed with **1a** (0.2 mmol), **2a** (0.2 mmol), and a catalyst in solvent (2 mL) for 12 h. [b] Isolated yields.

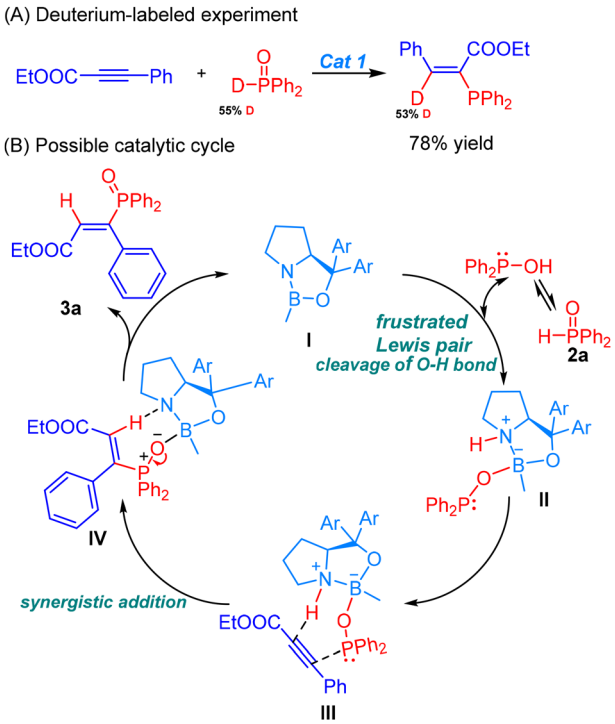
65% and 72% yields. Further investigation revealed that the terminal alkynyl substrate **1s** was also suitable for this methodology and generated **3s** in 66% yield. After that, a wide range of ester groups were examined, including various electron-withdrawing and electron-donating aromatic esters, furnishing the corresponding substrates **3t–3aj** in up to 95% yield. In addition, the aliphatic and terminal substrates were scoped and **3ak–3aq** were achieved in 61–72% yields. Afterwards, several commercial diarylphosphine oxides, including α- and β-naphthyl, Me-, MeO- and F-substituted phenyls, were selected and **3ar–3av** were obtained in 35–68% yields. However, it didn't work for diphenyl phosphite.

In order to evaluate the practicality of this method, a gram-scale model reaction (5.0 g) was conducted, yielding product **3a** with a yield of 78% (Scheme 3). Furthermore, synthetic transformations of **3a** were performed. Initially, the double bond in **3a** was reduced using hydrogen, resulting in product **4** with an impressive yield of 88%. Subsequently, compound **3a** underwent sulfuration with Lawesson's reagent to afford product **5** with a yield of 62%. Additionally, reduction of compound **3a** by boron hydride led to the formation of alcohol **6** with a yield of 70%.

With the substrate scope and synthetic transformation established, a possible mechanism is proposed in Scheme 4.



Scheme 3 Gram-scale reaction and synthetic transformations.



Scheme 4 Possible catalytic cycle.

First, a deuterium-labeled experiment was conducted using deuterated diphenylphosphine oxide (55% D). As anticipated, 53% of hydrogen atoms were replaced by deuterium atoms, indicating the source of α-H (Scheme 4A). The proposed mechanism begins with CBS acting as a frustrated Lewis pair. It is known that diphenylphosphine oxide P(v) can be converted to nucleophilic P(iii), which can then be cleaved by CBS to yield intermediate **II**. Subsequently, this intermediate can react with **1a** to form key intermediate **III**, providing an opportunity to determine regioselectivity through a synergistic addition process. Finally, a new P–C bond is formed and CBS proceeds to the next catalytic cycle.

Conclusions

In conclusion, we have developed a novel metal-free and regioselective methodology for the hydrophosphorylation of electron-deficient alkynes, utilizing cost-effective and commercially available oxazaborolidines as catalysts. This method demonstrates compatibility with a diverse array of alkynes and diarylphosphine oxides. Furthermore, the gram-scale reactions and subsequent synthetic transformations underscore its practicality. Most importantly, our investigation into the possible mechanism unveiled two intriguing processes: (1) the CBS catalyst functions as a frustrated Lewis pair that facilitates the cleavage of the O–H bond and (2) the products are generated in a single *E*-configuration through a synergistic addition process. These findings provide valuable insights into an efficient and practical approach for synthesizing valuable P-olefin products.

Author contributions

Y. G. and B. F. conceptualized and developed the project. L. X. and Y. C. performed experiments and data analysis. J. L. wrote and edited the manuscript. All authors contributed and agreed on the final version of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no conflicts of interest.

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