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# Pd(II)-Catalyzed $Ph_2(O)P$-Directed C–H Olefination toward Phosphine–Alkene Ligands

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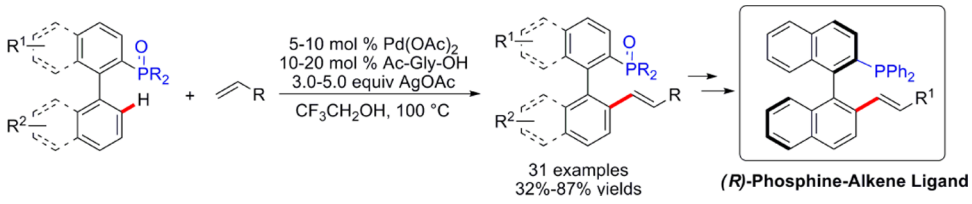
## ABSTRACT




**The Pd(II)-catalyzed $Ph_2(O)P$-directed C–H olefination to synthesize alkene–phosphine compounds is reported. In contrast to previous examples of various directing groups that guide selective C–H activation, the $Ph_2(O)P$ group not only acts as the directing group but also serves to construct the alkene–phosphine ligands. The monoprotected amino acid (MPAA) ligand Ac-Leu-OH is found to promote this reaction in a significant manner.**

Phosphine-based ligands have found widespread use in homogeneous catalysis and often have been applied to enhance the metal catalyst efficiency or control chiral induction.[1] In general, the choice of ligand is very crucial to the success of a reaction. In the past decades, many metal complexes using various phosphine ligands have been found to catalyze various reactions, especially the cross-coupling reactions and asymmetric catalysis.[2] However, despite impressive progress in this area, the design and synthesis of new ligands that possess novel electronic and steric properties and functional groups for a particular application remain a formidable task. Recently, one novel type of biaryl-based chiral alkene–phosphine hybrid ligands have received considerable attention and have proven to be highly effective for asymmetric conjugate additions and allylic substitutions.[3] At present, the strategy for the synthesis of biaryl-based alkene-phosphine hybrid ligands involves some traditional procedures such as bromination, lithiation, and so on, which lead to tedious workup procedures and complicated operations. Furthermore, tediously long synthetic steps also greatly increase

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(1) (a) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (b) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119. (c) Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Phosphorus (III) Ligands in Homogeneous Catalysis: Design and Synthesis*; Wiley-VCH: Chichester, 2012.

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(4) For selected reviews of C–H activation: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (e) Charles, S. Y.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (h) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (i) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (j) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (k) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Tetrahedron* **2012**, *68*, 5130.

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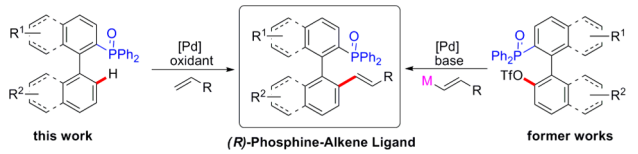
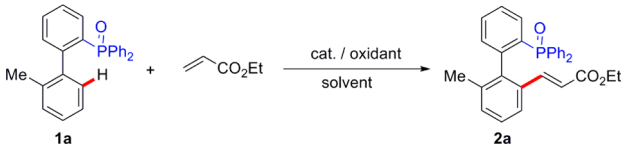
**Scheme 1.** Different Pathways for Synthesis of Phosphine−Alkene Ligand




preparation costs. Therefore, the development of concise and highly efficient methods is still extremely attractive and a significant challenge. Combining a directing group with transition-metal-catalyzed direct C−H olefination provides one straightforward and atom-efficient protocol for the construction of alkene−phosphine hybrid compounds.[4,5] Over the past several years, we have trained our focus on the development of new and efficient protocols for the transition metal-catalyzed C−P bond formation.[6] Herein, by using the $P(O)Ph_2$ as a new directing group, we first disclose a novel protocol of palladium-catalyzed C−H olefination to synthesize a series of alkene−phosphine hybrid compounds (Scheme 1). In contrast to the former reports that involve Pd(II)- and Rh(III)-catalyzed phosphorous acid or phosphate ester directed C−H functionalizations,[7] diphenylphosphine oxide ($P(O)Ph_2$) not only acts as the directing group to direct C−H activation to make a useful ligand but also incorporates broadly useful ligands in the reactions.

We began our exploration with 2-diphenylphosphino-2′-methylbiphenyl (**1a**) and ethyl acrylate as the model substrates with which to identify suitable reaction conditions (Table 1). First, we evaluated various oxidants in the presence of $Pd(OAc)_2$ (10 mol %) as a catalyst in

**Table 1.** Reaction Conditions Screening[a,b]




| entry | cat. (mol %) | oxidant (equiv) | ligand (mol %) | yield[c] (%) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2$ (3.0) | | 52 |
| 2 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | | 56 |
| 3 | $Pd(OAc)_2$ (10) | $AgNO_3$ (3.0) | | 44 |
| 4 | $Pd(OAc)_2$ (10) | $PhI(OAc)_2$ (3.0) | | 51 |
| 5 | $Pd(OAc)_2$ (10) | Selectfluor (3.0) | | 63 |
| 6 | $Pd(OAc)_2$ (10) | $K_2S_2O_8$ (3.0) | | 42 |
| 7 | $Pd(OAc)_2$ (10) | $O_2$ (1.0 atm) | | n. r. |
| 8 | $Pd(OAc)_2$ (10) | $Cu(OAc)_2$ (3.0) | L-Ac-Leu-OH (20) | 74 |
| 9 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | L-Ac-Leu-OH (20) | 83 |
| 10 | $Pd(OAc)_2$ (10) | $AgNO_3$ (3.0) | L-Ac-Leu-OH (20) | 61 |
| 11 | $Pd(OAc)_2$ (10) | $PhI(OAc)_2$ (3.0) | L-Ac-Leu-OH (20) | 53 |
| 12 | $Pd(OAc)_2$ (10) | Selectfluor (3.0) | L-Ac-Leu-OH (20) | 43 |
| 13 | $Pd(OAc)_2$ (10) | $K_2S_2O_8$ (3.0) | L-Ac-Leu-OH (20) | 44 |
| 14 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | Bipy (20) | nr |
| 15 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | 1,10-Phen (20) | nr |
| 16 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | L-Ac-Ala-OH (20) | 78 |
| 17 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | Ac-Gly-OH (20) | 85 |
| 18 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | L-Ac-Val-OH (20) | 76 |
| 19 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | L-Ac-lle-OH (20) | 70 |
| 20 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | $PPh_3$ (20) | 30 |
| 21 | $Pd(OAc)_2$ (10) | AgOAc (3.0) | dppe (20) | nr |
| 22 | $PdCl_2$ (10) | AgOAc (3.0) | Ac-Gly-OH (20) | 78 |
| 23 | $Pd(PPh_3)_4$ (10) | AgOAc (3.0) | Ac-Gly-OH (200 | 63 |
| 24 | $Pd(TFA)_2$ (10) | AgOAc (3.0) | Ac-Gly-OH (20) | 76 |
| 25 | $Pd(PhCN)_2Cl_2$ (10) | AgOAc (3.0) | Ac-Gly-OH (20) | 75 |
| 26 | $Pd(PPh_3)_2Cl_2$ (10) | AgOAc (3.0) | Ac-Gly-OH (20) | 78 |
| 27 | **$Pd(OAc)_2$ (5)** | **AgOAc (3.0)** | **Ac-Gly-OH (10)** | **87** |
| 28 | $Pd(OAc)_2$ (2.5) | AgOAc (3.0) | Ac-Gly-OH (5) | 77 |
| 29 | $Pd(OAc)_2$ (5) | AgOAc (2.0) | Ac-Gly-OH (10) | 71 |
| 30 | $Pd(OAc)_2$ (5) | AgOAc (3.0) | Ac-Gly-OH (10) | 76[d] |

[a] All reactions were carried out in the presence of 0.2 mmol of **1a** in 2.0 mL of different solvents at 100 °C under air atmosphere. [b] 1, 10-Phen = 1, 10-phenanthrline, Bipy = 2, 2′-bipyridine, dppe = 1, 2-bis(diphenylphosphino)ethane. [c] Yield of isolated product. [d] Reaction temperature: 110 °C.

$CF_3CH_2OH$ at 100 °C. To our delight, the use of $Cu(OAc)_2$, AgOAc, $AgNO_3$, $K_2S_2O_8$, $PhI(OAc)_2$, and Selectfluor as oxidants yielded the desired product of **2a**; AgOAc was most effective (entries 1−6, Table 1). Notably, the reaction failed with oxygen as the oxidant (entry 7, Table 1). Furthermore, the control experiment showed that the palladium as catalyst is necessary to the success of the transformation. Results of solvents screening indicated that $CF_3CH_2OH$ was still the best choice. Recently, in the field of Pd(II)-catalyzed carboxylate-directed C−H olefination reactions, Yu and co-workers reported a highly significant discovery: the addition of mono-*N*-protected

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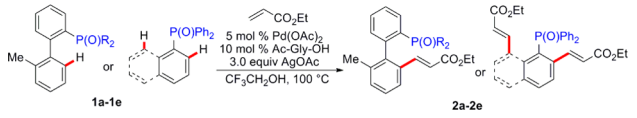
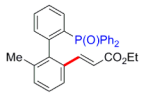
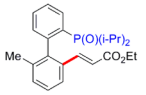
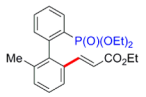
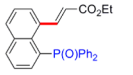
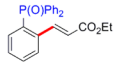
(7) (a) Meng, X.; Kim, S. *Org. Lett.* **2013**, *15*, 1910. (b) Chan, L. Y.; Kim, S.; Ryu, T.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 4682. (c) Chan, L.; Cheong, L.; Kim, S. *Org. Lett.* **2013**, *15*, 2186. (d) Seo, J.; Park, Y.; Jeon, I.; Ryu, T.; Park, S.; Lee, P. H. *Org. Lett.* **2013**, *15*, 3358. (e) Chary, B. C.; Kim, S.; Park, Y.; Kim, J.; Lee, P. H. *Org. Lett.* **2013**, *15*, 2692. (f) Unoh, Y.; Hashimoto, Y.; Takeda, D.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 3258. (g) Zhao, D.; Nimphius, C.; Lindale, M.; Glorius, F. *Org. Lett.* **2013**, *15*, 4504.

(8) (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169. (c) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967. (d) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183. (e) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (f) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245.

**Table 2.** Evaluation of Different Directing Groups[a,b]




| entry | product | yield (%)[b] | entry | product | yield (%)[b] |
|---|---|---|---|---|---|
| 2a |  | 87% | 2c |  | 67%[c] |
| 2b |  | 68%[c] | 2d |  | 0% |
| | | | 2e |  | 0% |

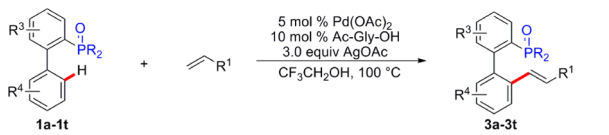
[a] All reactions were carried out under the optimal conditions reported in the text. [b] Isolated yields. [c] 10 mol % $Pd(OAc)_2$ was used.

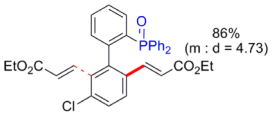
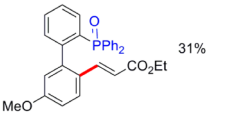
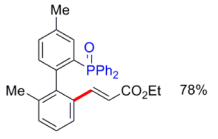
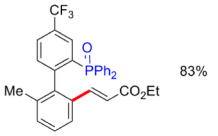
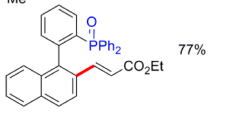
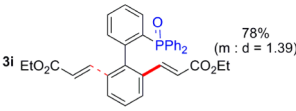
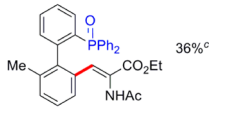
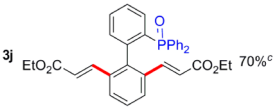
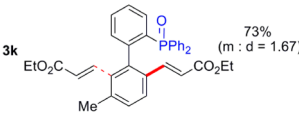
amino acids as ligand could enhance the reactivity of the catalytically active Pd(II) species.[8] With this research in mind, we selected the amino acid L-Ac-Leu-OH as the ligand and tested the reactions under different oxidant conditions (entries 8−13, Table 1). Use of L-Ac-Leu-OH as the ligand was very effective; indeed, the highest yield of **2a** was afforded in an 83% yield when AgOAc was used as the oxidant. Subsequently, we carried out evaluations of other amino acids and some phosphine or nitrogen ligands (e.g., Bipy, 1, 10-Phen, dppe and $PPh_3$) with encouraging results: the amino acids of Ac-Gly-OH were revealed as the best choice, and the yield of **2a** was improved to 85% (entries 14−21, Table 1). Other Pd catalysts, such as $PdCl_2$, $Pd(PPh_3)_4$, $Pd(TFA)_2$, and $Pd(PhCN)_2Cl_2$, could also prompt this reaction, but with relatively lower yields (entries 22−26, Table 1). Decreasing the load of $Pd(OAc)_2$ to 5 mol % was helpful: **2a** was obtained in 87% yield (entries 27−28, Table 1). The equivalent of the AgOAc evaluation demonstrated that 3.0 equiv was best (entry 29, Table 1). Moreover, reductions in temperature also decreased the yield (entry 30, Table 1).

Under optimized reaction conditions (entry 27, Table 1), we evaluated various phosphate directing groups. In addition to $P(O)Ph_2$, the $P(O)(OEt)_2$ and $P(O)(i\text{-}Pr)_2$ groups were also effective in this transformation with corresponding products afforded in good yields (Table 2, **2a**−**c**). However, use of other phosphates, including triphenylphosphine oxide and α-diethyl naphthalenyl phosphonate, failed to induce C−H olefination (Table 2, **2d**,**e**). Notably, these results demonstrate the significance of the seven-member cyclopalladium pretransition state as the key to this reaction.

We next examined the scope of different substituted diphenylphosphine oxide derivatives and various acrylates (Table 3). The structure of **3f** was confirmed by single X-ray diffractions analysis (see the Supporting Information). We focused first on various acrylates, using 2-diphenylphosphino-2′-methylbiphenyl as a substrate for

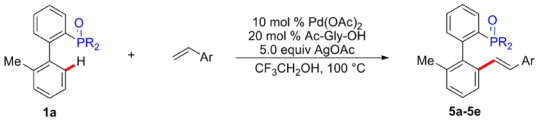
**Table 3.** Pd(II)-Catalyzed C−H Olefination with Different 2-Diphenylphosphino Oxide Derivatives and Various Acrylates[a,b]




| entry | product | yield (%)[b] | entry | product | yield (%)[b] |
|---|---|---|---|---|---|
| 3a | $R^1 = CO_2Me$ | 82% | 3l | $R^4$ = Cl | 62% |
| 3b | $R^1 = CO_2Bu$ | 81% | 3m | $R^4$ = OMe | 54% |
| 3c | $R^1 = CO_2Bn$ | 86% | 3n | $R^4$ = F | 67% |
| 3d | $R^1 = P(O)(OEt)_2$ | 75% | 3o |  | 86% (m : d = 4.73) |
| 3e | $R^1 = P(O)Ph_2$ | 76% | 3p |  | 31% |
| 3f | $R^1 = SO_2Ph$ | 32%[c] | 3q |  | 60% |
| 3g |  | 78% | 3r |  | 70% |
| 3h |  | 83% | 3s |  | 77% |
| 3i |  | 78% (m : d = 1.39) | 3t |  | 36%[c] |
| 3j |  | 70%[c] | | | |
| 3k |  | 73% (m : d = 1.67) | | | |

[a] All reactions were carried out in the presence of 0.2 mmol of **1a**−**t** in 2.0 mL of $CF_3CH_2OH$. [b] Isolated yield. [c] 10 mol % $Pd(OAc)_2$ was used.

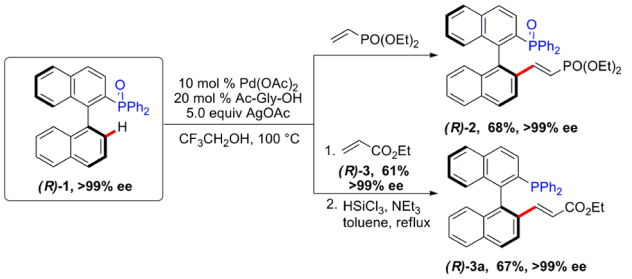
**Table 4.** Pd(II)-Catalyzed C−H Olefination with Different Styrenes[a,b]




| entry | R | Ar | yield[b] (%) | entry | R | Ar | yield[b] (%) |
|---|---|---|---|---|---|---|---|
| **5a** | Ph | Ph | 58 | **5e** | Ph | *p*-FPh | 52 |
| **5b** | *i*-Pr | Ph | 52 | **5d** | Ph | *m*-$NO_2$Ph | 56 |
| **5c** | Ph | *o*-ClPh | 45 | | | | |

[a] All reactions were carried out in the presence of 0.2 mmol of **1a**−**r** in 2.0 mL of $CF_3CH_2OH$. [b] Isolated yield.

**Scheme 2.** Synthesis of Different (*R*)-Phosphine−Alkenes

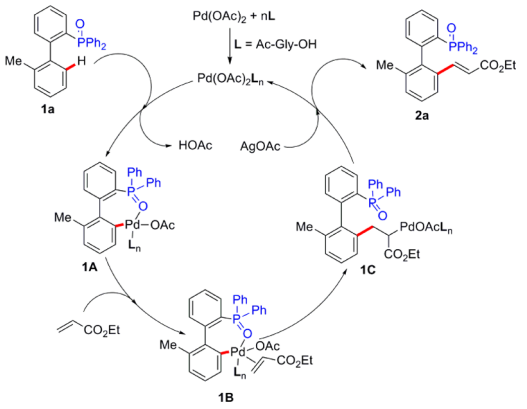



the investigation. We were pleased to find that electron-deficient olefins such as butyl and benzyl acrylates, alkenyl phosphite, and sulfone were compatible with the transformation and that the corresponding products were afforded in good yields (**3a**−**f**). Furthermore, a variety of diphenylphosphine oxide derivatives could be converted to the desired products using these olefins. For example, both the aromatic ring of 2-diphenylphosphino with an electron-donating substituent group (**1g**) and an electron-withdrawing group (**1h**) exhibited good reactivity to afford olefinated products (**3g** and **3h**) in 78% and 83% yields. If the substrate was altered to 2-diphenylphosphinobiphenyl, a mixture of mono- and diolefinated products (**3i**) was obtained. Interestingly, when the loading of the catalyst was increased to 10 mol %, only the diolefinated product (**3j**) was obtained in 70% yield. Other electron-donating substituent groups such as methoxyl and electron-withdrawing substituent groups such as F and Cl on the 2′-position were also well tolerated in this C−H olefination, but lower yields of products were observed (**3l**−**n**). On the other hand, when different substituent groups were situated on the 3′-position, the electronic effect was very distinct, and the electron-deficient substrates performed far better than electron-rich ones (**3o**−**q**). As expected, multisubstituted 2-diphenylphosphino-2′, 3′-dimethylbiphenyl can also be converted into the desired product of **3r** with 70% yield. In particular, when we selected naphthalene as a substrate, the reaction successfully provided the product of **3s** in a 77% yield. Finally, the ethyl 2-acetamidoacrylate also afforded the product of **3t** in 36% yield.

To our delight, we discovered that less electrophilic styrenes were also compatible with the C−H olefination reaction, albeit with a higher loading of catalyst. As expected, different phosphate directing groups such as P(O)-$Ph_2$ and P(O)(*i*-Pr)$_2$ proved suitable for this transformation (Table 4, **5a**,**b**). Furthermore, various substituted styrenes were also investigated with 2-diphenylphosphino-2′-methylbiphenyl as the reaction partner (Table 4, **5c**−**e**). We found that the electronic effect was very distinct and that the electron-deficient styrenes afforded higher yields than electron-rich styrenes.

Phosphorus-based ligands are key to many metal-catalyed organic transformations, including many asymmetric

**Scheme 3.** Proposed Mechanisms of $Pd(OAc)_2$-Catalyzed C−H Olefination




reactions.[1,2] Using commercial chiral binaphthyl-based diphenylphosphine oxide (*R*)-**1** as the substrate, we were able to synthesize different chiral alkene−phosphine hybrid oxide compounds easily without lowering the ee value via diphenylphosphine oxide directed C−H olefination reactions ((*R*)-**2** and **3**, Scheme 2). We selected the product (*R*)-**3** carried out the reduction with $HSiCl_3$ under basic conditions to obtain the pure binaphthyl-based chiral alkene−phosphine hybrid ligands (*R*)-**3a**.

On the basis of the observed experimental results and pioneering reports,[8] we propose a plausible mechanistic pathway outlined in Scheme 3. $Pd(OAc)_2$ first coordinates with the ligand of Ac-Gly-OH to form the activated palladium catalyst, which reacts with substrate **1a** to produce the cyclopalladium intermediate **1A**. This active species subsequently undergoes coordination with alkenes to form the complex **1B**, which then undergoes insertion to afford the intermediate **1C**. Finally, the product of **2a** is afforded by *β*-hydride elimination, and the active palladium catalyst was regenerated in the presence of AgOAc as the oxidant.

In conclusion, we have developed a $Ph_2(O)P$-directed Pd(II)-catalyzed C−H olefination to synthesize the highly important alkene-phosphine compounds. C−H olefination of biaryls is shown to be promoted by the MPAA ligand Ac-Gly-OH for the first time, providing a new approach for biaryl ligand synthesis.

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**Supporting Information Available.** Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.