Cross-Coupling

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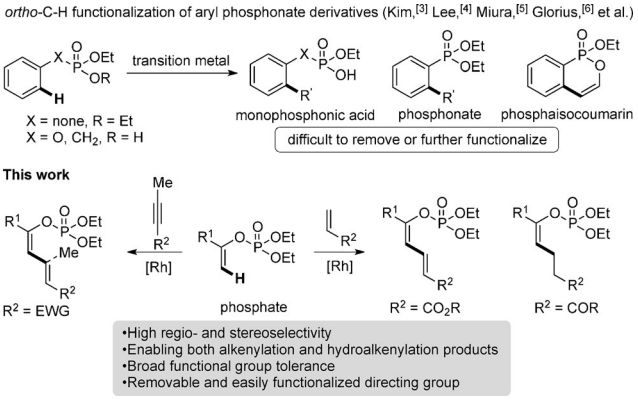
Selective Alkenylation and Hydroalkenylation of Enol Phosphates through Direct C–H Functionalization

*Xu-Hong Hu, Xiao-Fei Yang, and Teck-Peng Loh**

Abstract: *An efficient and selective Rh-catalyzed direct C–H functionalization reaction of enol phosphates was developed. The method is applicable to a variety of coupling partners, including activated alkenes, alkynes, and allenes, and leads to the formation of various valuable alkenylated and hydroalkenylated enol phosphates through the action of the phosphate directing group. The versatility and utility of the coupling products were demonstrated through further transformations into synthetically useful building blocks.*

Phosphates are key structural motifs of many bioactive natural products and pharmaceuticals. Of particular synthetic relevance are enol phosphates, which have proven to be versatile intermediates in metal-catalyzed cross-coupling reactions. They serve as an attractive alternative to the corresponding halide and triflate because of their stability and low cost.[1] Given their widespread utility, the development of convenient synthetic methods to prepare such phosphates with structural diversity and functionality is thus of great importance.[2] As an atom-economically tool, direct C–H functionalization of simple enol phosphates is among the most efficient strategies for forming C–C bonds to furnish a myriad of privileged phosphate scaffolds. As reported by the groups of Kim,[3] Lee,[4] Miura,[5] and Glorius,[6] the phosphorus-containing groups have been identified as useful directing groups analogous to their carboxylic counterparts.[7] Despite these remarkable achievements, activation of the intrinsically unreactive vinyl C–H bond of enol phosphate still remains undeveloped. Furthermore, auxiliary phosphorus-containing directing groups, such as the monophosphonic acid and phosphonate employed in the majority of these reported methods, are often difficult to remove or further functionalize,[8] thus largely limiting the synthetic applications of the products. In line with our ongoing interest in the direct C–H functionalization of alkenes,[9] we herein disclose Rh-catalyzed regio- and stereoselective cross-couplings of the vinyl C–H bond of enol phosphates with a variety of coupling partners (Scheme 1). This unprecedented catalytic method provides a facile and atom-economical route to both alkenylated and hydroalkenylated enol phosphates, which represent



Scheme 1. Selective C–H functionalization of enol phosphate.

significant versatile synthetic intermediates in organic and medicinal chemistry.

Our optimization study commenced with examining the reaction of phenylvinyl phosphate **1a**, which was easily assembled from acetophenone, with *n*-butyl acrylate **2a**. Evaluation of various reaction parameters including oxidants and solvents revealed that the cross-coupling product 1,3-diene[10] **3a** could be obtained in 83% yield and with a *Z*,*E*/*Z*,*Z* ratio of 91:9 in the presence of $[\{Cp^*RhCl_2\}_2]$ (2.5 mol%), $AgSbF_6$ (10 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (1.1 equiv) in THF at 80°C for 17 h (Conditions A).[11] Control experiments indicated that all of the catalyst components are indispensable in this reaction (see the Table S1 in the Supporting Information).

With the optimal reaction conditions in hand, we next investigated the effect of diverse substituents on the oxygen atoms of both substrates (Table 1). A wide variety of commercially available acrylates were initially utilized and all were found to be viable coupling partners, allowing access to the corresponding 2,4-dienoates with yields and selectivities that were generally little influenced by the substituent on the oxygen atom. A gram-scale synthesis of **3aa** demonstrated the robustness of this methodology. After screening a series of enol phosphate analogues bearing other directing groups, we found that the electronic properties of the substituents dominated the reaction efficiency (**3ba–fa**). Likewise, enol phosphamide reacted readily to afford the desired product **3ga** in 88% yield. A range of electrophilic alkenes were also tested, and sulfone, styrene, and acrylonitrile proved to be

[*] Prof. Dr. T.-P. Loh
Department of Chemistry
University of Science and Technology of China
Hefei, Anhui 230026 (China)
Dr. X.-H. Hu,[+] Dr. X.-F. Yang,[+] Prof. Dr. T.-P. Loh
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
Singapore 637371 (Singapore)
E-mail: teckpeng@ntu.edu.sg
[+] These authors contributed equally to this work.

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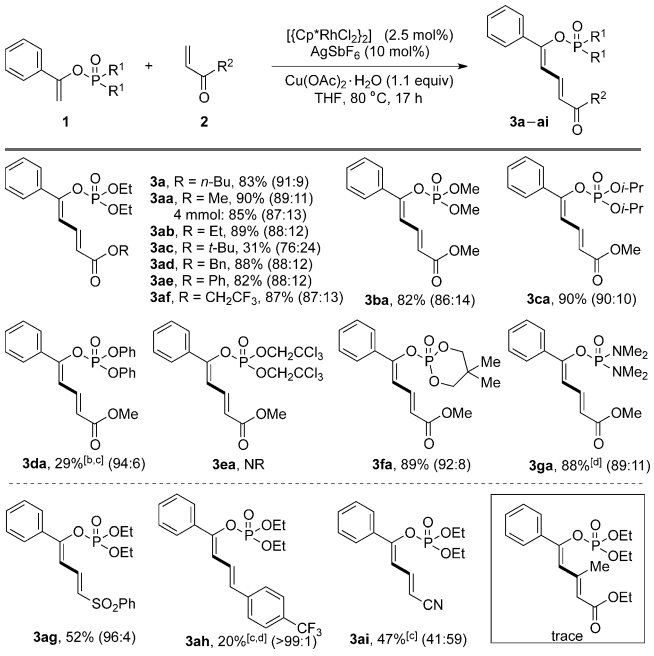
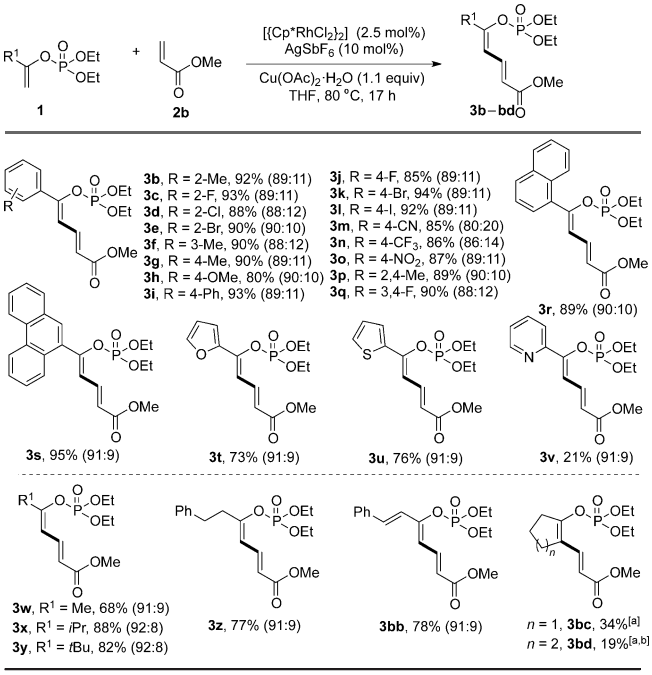
Table 1: Investigation of diverse enol phosphates and alkenes.[a]



[a] Reaction conditions A: **1** (0.15 mmol), **2** (2.0 equiv), [{Cp*RhCl$_2$}$_2$] (2.5 mol%), $AgSbF_6$ (10 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (1.1 equiv) in tetrahydrofuran (THF; 0.8 mL) at 80°C for 17 h. Yields of isolated product are given; *Z*,*E*/*Z*,*Z* ratios of the isomers given in parentheses were determined by ^{1}H NMR analysis. [b] 65% of **1** was recovered. [c] At 100°C. [d] 5 mol% Rh and 20 mol% $AgSbF_6$ were used. NR = no reaction.

Table 2: Scope of alkenylation with respect to enol phosphates.



[a] 1,2-dichloroethane as solvent. [b] At 110°C.

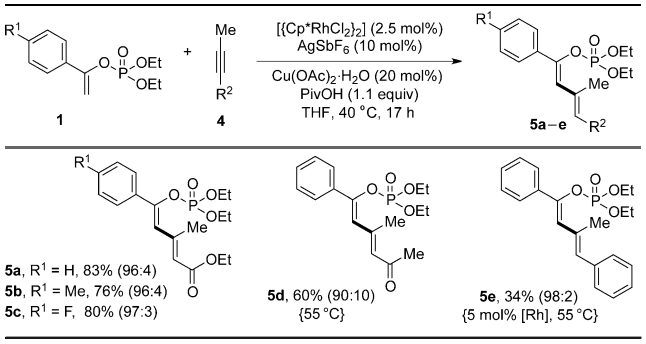
suitable coupling partners (**3ag**–**ai**). Ethyl crotonate, not surprisingly, failed to give the coupling product.[12]

In light of these encouraging results, the scope and limitation with respect to the enol phosphates was subsequently explored with methyl acrylate **2b** as the coupling partner (Table 2). The reaction is insensitive to the steric effect of substitutions on phenyl vinyl phosphates, since comparable results were observed when an *ortho*-, *meta*-, or *para*-methyl group was present in the phenyl ring (**3b**,**f**,**g**,**p**). Arenes bearing either an electron-withdrawing or electron-donating substituent participated well under the current conditions to afford the corresponding targets in 80–93% yields (**3c**–**q**), where the former substitution had a beneficial impact on the reactivity. Importantly, several valuable functional groups such as iodo (**3l**), nitrile (**3m**), and nitro (**3o**) groups are readily tolerated, delivering the alkenylation products in excellent combined yields. The structure of a major isomer **3o** was unambiguously confirmed by an X-ray crystallography. We were pleased to find that the scope could be extended from the phenyl to naphthyl and phenanthryl systems (**3r**,**s**). In addition, heteroaryl enol phosphates bearing furyl and thienyl moiety smoothly furnished the corresponding products **3t** and **3u** with good selectivity, while the pyridinyl group (**3v**) did not undergo the reaction, presumably owing to strong coordination to the Rh catalyst. Furthermore, the transformation is not restricted to aromatic enol phosphates but is also applicable to enol phosphates with aliphatic substituents (**3w**–**z**). Subjection of dienol phosphate to coupling with **2b** gave the desired product with the internal double bond intact (**3bb**), thus suggesting that substitution at the α-position was essential to facilitate the cleavage of vinyl C–H bond. Nevertheless, in the case of cyclic enol phosphates, only low yields of the coupling products were observed (**3bc**,**bd**).

The unsuccessful result previously experienced with the cross-coupling of **1a** and ethyl crotonate prompted us to seek a feasible C–H activation pathway toward highly functionalized 1,3-dienoates by using the present catalyst system. To this end, we conducted the conjugate addition of a vinyl C–H bond to electron-deficient alkynes as the Michael acceptors. Gratifyingly, a series of multisubstituted 1,3-dienes (**5a**–**e**) could be obtained with 34–83% yields and high selectivity under mild reaction conditions (Table 3). It is worth noting that this method offers a regioisomeric alternative to the existing reductive couplings of alkenes with alkynes for the synthesis of 1,3-dienes, which rely on coordination of the alkene and alkyne to the metal catalyst.[13]

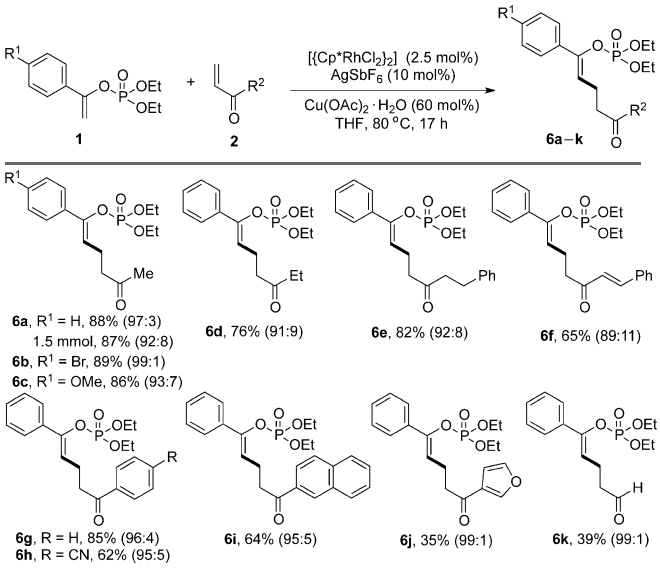
In view of that fact that enones are well-established as superior electrophiles in catalytic conjugate addition reactions,[14] we speculated that the direct addition of a *Z*-selective vinyl C–H bond to enone could be realized by using an appropriate directing group, which will open new horizons for the generation of γ,δ-unsaturated carbonyls in a complementary stereoselective manner by other mechanistically different strategies.[15] In fact, compared to the impressive advancements in the catalytic addition of aryl C(sp^2)-M intermediates, generated in situ upon C–H activation, to polarized C–X (X = N, O, C) unsaturated bonds,[16] chelation-assisted vinyl C–H bond addition to C–X bonds has received much less attention and is still a challenging subject.[17] To our satisfac-

Table 3: Cross-couplings of enol phosphates with alkynes.



tion, the conjugate addition adduct **6a** could be obtained by employing methyl vinyl ketone as the coupling partner under a slightly modified catalytic system (Conditions B; Table 4).[18] When altering other terminal enones, including

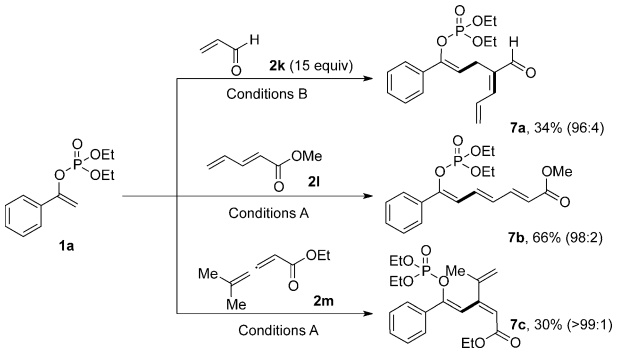
Table 4: Scope of hydroalkenylation with respect to enol phosphates and enones.[a]



[a] Reaction conditions B: **1** (0.15 mmol), **2** (2.0 equiv), [{Cp*RhCl$_2$}$_2$] (2.5 mol%), $AgSbF_6$ (10 mol%) and $Cu(OAc)_2 \cdot H_2O$ (60 mol%) in THF (0.8 mL) at 80 °C for 17 h. Yields of isolated product are shown; numbers in parentheses indicate the ratio between the *Z* isomer and the corresponding diene product, as determined by ^{1}H NMR analysis.

both alkyl and aryl vinyl ketones, the reaction gave the hydroalkenylation products in 62–89% yields (**6b–i**), along with a trace amount of alkenylation products, which are produced by the competitive β-hydride elimination. A heteroaryl vinyl ketone embedded with a furyl moiety (**6j**) was also compatible with this method, albeit with low yield. Notably, when using acrolein as the Michael acceptor, the expected adduct **6k** could be obtained in reasonable yield.

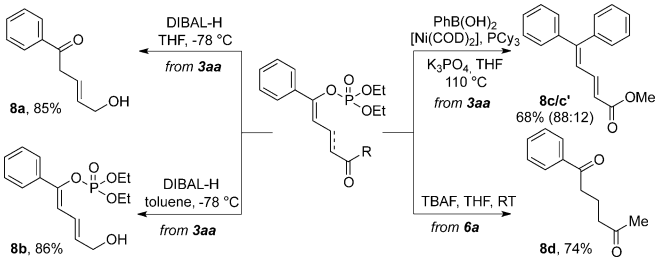
It is interesting to note that the reaction of model substrate **1a** with a large excess of acrolein **2k** delivered the unexpected adduct **7a** (Scheme 2). The result might be



Scheme 2. Synthetic applicability of enol phosphate.

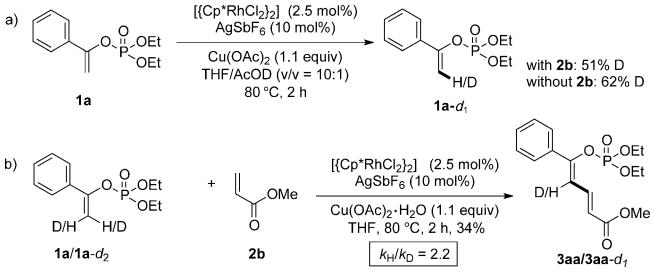
attributed to conjugate addition followed by an intermolecular aldol condensation.[19] To further improve the synthetic applicability of enol phosphates in this C–H activation, we performed the alkenylation reaction by using other structurally related coupling partners containing a dienyl[20] or allenyl[21] subunit under standard but unoptimized reaction conditions, which resulted in the formation of trienes **7b** and **7c** in 66 and 30% yield, respectively. The unconsumed starting material could be recovered completely.

As an additional dimension, the phosphate directing group can be easily removed by using DIBAL-H or TBAF in THF to give β,γ-unsaturated ketone **8a** and 1,5-diketone **8d**, respectively (Scheme 3). Treatment of **3aa** with DIBAL-H in toluene cleanly provided the corresponding alcohol **8b** in 86% yield without over-reduction of the phosphate moiety. Under the Ni-catalyzed reaction system developed by Skrydstrup,[1f–h] Suzuki–Miyaura cross-coupling with enol phosphate and phenyl boronic acid enables the installation of increased diversity in the form of an dienoate to afford product, **8c** along with its 1,2-migration analogue.



Scheme 3. Synthetic application of the coupling adducts. Dibal-H = diisobutylaluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, COD = 1,5-cyclooctadiene.

Having demonstrated the application of the coupling products, we finally pursued some preliminary mechanistic studies of the process. Exposure of enol phosphate **1a** to conditions A in the presence or absence of **2b** with the addition of deuterated acetic acid led to an exclusively *Z*-selective vinyl H/D exchange, thus suggesting reversible cyclometalation modes (Scheme 4a). An intermolecular kinetic isotope effect (KIE) for the alkenylation was determined with **1a** and **1a**-d_2 to probe the relevance of C–H



Scheme 4. Isotopic labeling experiments for KIE studies.

activation. A KIE value of 2.2 reveals that the C(sp^2)–H bond cleavage might be involved in the rate-determining step (Scheme 4b).[22]

In summary, we have accomplished the first Rh-catalyzed cross-couplings of enol phosphates with a diverse array of activated coupling partners. The directing ability of the phosphate group enables the substrate to undergo synthetically tunable transformations through alkenylation with acrylates and hydroalkenylation with enones. The latter process involves a challenging conjugate addition of a vinylrhodium species to enones through chelation-assisted C–H activation, which can be expanded to other Michael acceptors such as electron-deficient alkynes. The versatility of the catalyst system has been further demonstrated through a series of cross-coupling reactions with other congeners, which gave a facile access to highly functionalized conjugated alkenes. Noteworthy features of this method include high regio- and stereoselectivity, good functional-group compatibility, and versatile utility of the coupling products. Considering the practicability of the method for gram-scale synthesis and the usefulness of such functionalized enol phosphates, we anticipate their implementation as building blocks in complex syntheses.

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