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Rhenium-Catalyzed Synthesis of 2*H*-1,2-Oxaphosphorin 2-Oxides via the Regio- and Stereoselective Addition Reaction of β-Keto Phosphonates with Alkynes

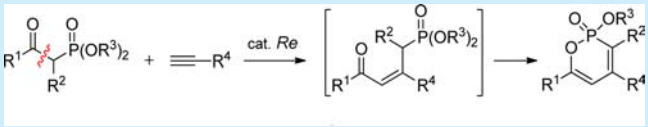
Masahito Murai,*[,†] Masahiro Nakamura,[†] and Kazuhiko Takai*[,†,‡]

[†]Division of Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

[‡]Research Center of New Functional Materials for Energy Production, Storage and Transport, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

Supporting Information

ABSTRACT: Treatment of β-keto phosphonates (Horner–Wadsworth–Emmons reagents) with terminal alkynes in the presence of a rhenium catalyst gave 2*H*-1,2-oxaphosphorin 2-oxides with various substitution patterns. The reaction proceeds via two consecutive processes: cleavage of a carbon–carbon σ-bond of the β-keto phosphonate with insertion of the alkyne in a regio- and stereoselective manner, followed by cyclization of the resulting δ-phosphonyl α,β-unsaturated ketone yielding the 2*H*-1,2-oxaphosphorin 2-oxide. Horner–Wadsworth–Emmons reagents were found to add to nonpolar unsaturated compounds under neutral conditions.



Phosphorus-containing heterocycles have received much attention due to their widespread applications in photoelectric materials, their use as ligands for homogeneous catalysis, and as key building blocks in organic synthesis.[1] Moreover, they can serve as phosphonic acid analogues of naturally occurring carboxylic acid esters and thus are useful in medicinal chemistry because of their similar biochemical activities. They may also serve as pharmaceuticals.[2] As an example, the 2*H*-1,2-oxaphosphorin 2-oxides are phosphorus analogues of 2-pyranones, which are known to exhibit a broad range of biological activities, including anti-HIV, anti-Alzheimer's, and antibacterial effects.[3] Considering their potential usefulness, the efficient synthesis of 2*H*-1,2-oxaphosphorin 2-oxides is an interesting subject of study.[4,5] Recently, several approaches to their synthesis were reported employing transition metal catalysts, including the intramolecular cross-coupling reaction of haloolefin-tethered hydrophosphines,[5a] the ring-closing metathesis of phosphorus-containing dienes and enynes,[5b,c,e] and the cycloisomerization of (*Z*)-2-alken-4-ynylphosphonic acid monoethylesters.[5c] Although these methods are highly attractive, they require multistep sequences to prepare the cyclization precursors and are limited in the possible substitution patterns of the products, all of which hampers their application in the syntheses of complex target molecules.[5] To enrich the field of phosphorus chemistry, the development of facile and efficient routes for the construction of functionalized 2*H*-1,2-oxaphosphorin 2-oxides with various substitution patterns directly from readily available materials in fewer steps still remains an important challenge.

Recently, we studied the rhenium-catalyzed carbon–carbon bond cleavage of various ketones having electron-withdrawing groups at their α-positions, such as β-keto esters, β-keto sulfones, and β-enamino ketones, followed by regio- and stereoselective addition reactions with alkynes.[6,7] To further advance this protocol, we postulated that employing β-keto phosphonates as substrates could allow efficient access to the synthetically useful 2*H*-1,2-oxaphosphorin 2-oxides. The work described herein represents our newest approach to creating functionalized 2*H*-1,2-oxaphosphorin 2-oxides via the insertion of alkynes into the carbon–carbon bonds of β-keto phosphonates, catalyzed by a rhenium complex. The present reaction offers a useful means of obtaining various substituted 2*H*-1,2-oxaphosphorin-2-oxides from readily available β-keto phosphonates and alkynes with reduced waste under neutral conditions.

The treatment of the β-keto phosphonate **1a** with 2 equiv of *p*-tolylacetylene **2a** in the presence of a catalytic amount of a rhenium complex, $[ReBr(CO)_3(thf)]_2$,[7d,f] in toluene at 120 °C afforded the expected 2*H*-1,2-oxaphosphorin 2-oxide **4a** in 14% yield, along with the δ-phosphonyl α,β-unsaturated ketone **3a** and its olefinic isomer **3a′** in 8% and 2% yields, respectively (Scheme 1). Based on our previous study, the 2*H*-1,2-oxaphosphorin 2-oxide **4a** is likely generated via the cyclization of the δ-phosphonyl ketones **3a** and **3a′** followed by the elimination of methanol.[7d,f] It is worth noting that although β-keto phosphonates, which are well-known as Horner–Wadsworth–Emmons reagents, usually prefer to react with polar unsaturated compounds such as aldehydes and ketones under basic conditions,[8] they react with nonpolar alkynes to give adducts **3a**, **3a′**, and **4a** in the current reaction under neutral conditions with the aid of the rhenium catalyst.[9] The complete conversion of **3a** and **3a′** to **4a** was achieved when the reaction mixture was heated to 160 °C in the presence of [ReBr-

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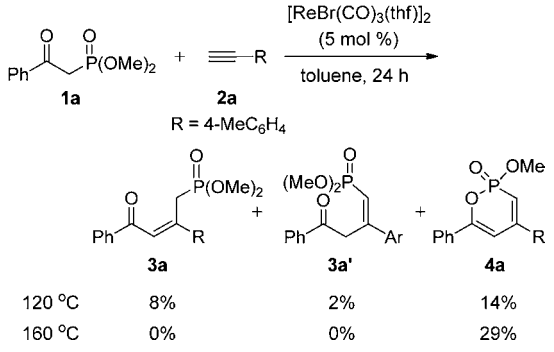
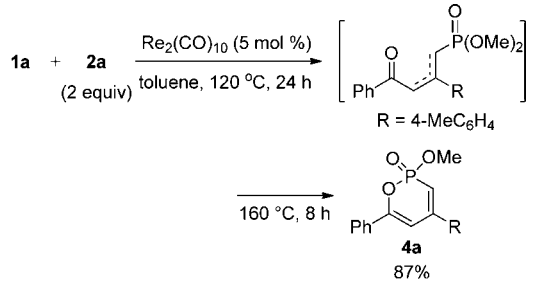
Scheme 1. Re-Catalyzed Reaction of β-Keto Phosphonate 1a with 4-Tolylacetylene 2a



$(CO)_3(thf)]_2$. In contrast to our previous study of the formation of the 2-pyranones, tetrabutylammonium (TBAF) or MS4A, which were found to promote the intermolecular cyclization and elimination of methanol, were not found to be effective in the present reaction.[7d,f]

After extensive screening, the yield of the 2*H*-1,2-oxaphosphorin 2-oxide **4a** was improved to 87% by using 5 mol % of $Re_2(CO)_{10}$ at 120 °C for 24 h followed by additional heating at 160 °C for 8 h (Scheme 2).[10,11] Rhenium complexes such as

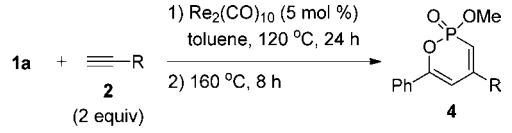
Scheme 2. Re-Catalyzed Synthesis of 2*H*-1,2-Oxaphosphorin 2-Oxide 4a



$[HRe(CO)]_n$ and $ReBr(CO)_5$ also exhibited catalytic activity, although none were superior to $Re_2(CO)_{10}$.[11] Other transition metal catalysts, including $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, $Mn_2(CO)_{10}$, $MnBr(CO)_5$, $Ru_3(CO)_{12}$, $RhCl(PPh_3)_3$, $Ir_4(CO)_{12}$, AuCl, $AuCl_3$, and $In(OTf)_3$, were completely ineffective and most of **1a** was recovered when employing these compounds. Due to the competitive oligomerization, the use of 2 equiv of **2a** was required to obtain the sufficient amount of 2*H*-1,2-oxaphosphorin 2-oxide **4a**.

With the optimized reaction conditions in hand, the alkyne substrate scope was examined. The series of alkynes shown in Table 1 were reacted with the β-keto phosphonate **1a** in the presence of the $Re_2(CO)_{10}$ catalyst giving moderate-to-good yields. For example, the reaction with phenylacetylene **2b** produced the corresponding 2*H*-1,2-oxaphosphorin 2-oxide **4b** in 64% yield (entry 1). The yields were slightly affected by adding an electron-donating methoxy group and an electron-withdrawing chloride group on the arylacetylenes **2c** and **2d** (entries 2 and 3). The heterocyclic acetylene **2e**, with an electron-donating thienyl group, reacted smoothly to give the desired 2*H*-1,2-oxaphosphorin 2-oxide **4e** in moderate yield (entry 4). The current reaction system was also viable when employing aliphatic alkynes, including 1-dodecyne **2f**, affording the corresponding phosphorus-containing heterocycle **4f**, albeit in low yield (entry

Table 1. Re-Catalyzed Reactions of β-Keto Phosphonate 1a with Alkynes 2

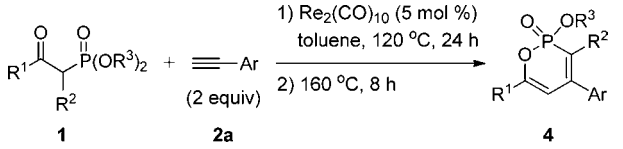


entry	R		product	yield/%
1	Ph	**2b**	**4b**	64
2	4-$MeOC_6H_4$	**2c**	**4c**	76
3	4-ClC_6H_4	**2d**	**4d**	66
4	2-thienyl	**2e**	**4e**	49
5	$^nC_{10}H_{21}$	**2f**	**4f**	34

5). Internal alkynes such as diphenylacetylene, 1-phenyl-1-propyne, and 4-octyne did not give the corresponding 2*H*-1,2-oxaphosphorin 2-oxides to any extent, even when heated to 200 °C. In these reactions, both β-keto phosphonate **1a** and internal alkynes were recovered intact.

Next, the scope and limitations of the β-keto phosphonate **1** were examined (Table 2). The reaction was found to be

Table 2. Re-Catalyzed Reactions of β-Keto Phosphonates 1 with 4-Tolylacetylene 2a[a]



entry	R	R^2	R^3		product	yield/%
1	4-$MeOC_6H_4$	H	Me	**1b**	**4g**	65
2	4-BrC_6H_4	H	Me	**1c**	**4h**	77
3	Me	H	Me	**1d**	**4i**	54
4	$^cC_6H_{11}$	H	Me	**1e**	**4j**	58
5	Ph	Me	Me	**1f**	**4k**	42[b]
6	Ph	H	Et	**1g**	**4l**	85
7	Ph	H	Ph	**1h**	—	0

[a]Ar = 4-$MeOC_6H_4$. [b]δ-Phosphonyl-α,β-unsaturated ketone **3k′** was obtained as a byproduct in 23% yield.

unaffected by the electronic feature of the aryl group of **1**. The β-keto phosphonates **1b** and **1c**, having electron-donating methoxy and electron-withdrawing bromide groups at the *para* position of their phenyl groups, reacted with 4-tolylacetylene **2a** to give the corresponding 2*H*-1,2-oxaphosphorin 2-oxides **4g** and **4h** in moderate-to-good yields, respectively (entries 1 and 2). In contrast, treatment of **1d** and **1e**, bearing aliphatic moieties on the carbonyl group, gave rise to the corresponding 2*H*-1,2-oxaphosphorin 2-oxides **4i** and **4j** in slightly lower yields (entries 3 and 4). The reaction also proceeded with **1f**, having a methyl group on the active methylene carbon, to give the variously substituted 2*H*-1,2-oxaphosphorin 2-oxide **4k** in 42% yield (entry 5). In this case, the intermediate δ-phosphonyl ketone **3k′** was also obtained in 23% yield. The β-keto phosphonate **1g**, incorporating an ethoxy group on the phosphorus atom, also underwent the reaction, whereas the corresponding phenoxy-group substituted **1h** did not react with **2a** at all (entries 6 and 7). These results indicate that the effects of both the electron density and steric crowding of the phosphorus atom might be important factors in promoting the reaction.

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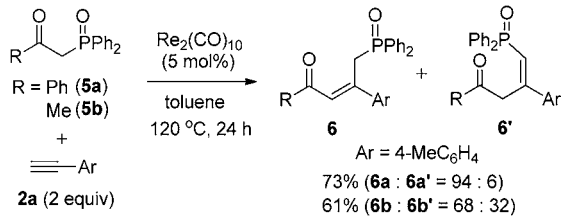
To further confirm the influence on the structure of the phosphine oxide moieties, the reaction of the α-phosphonyl ketone **5a**, having a phenyl group on the phosphorus atom, with 4-tolylacetylene **2a** was carried out (Scheme 3). In this reaction, a

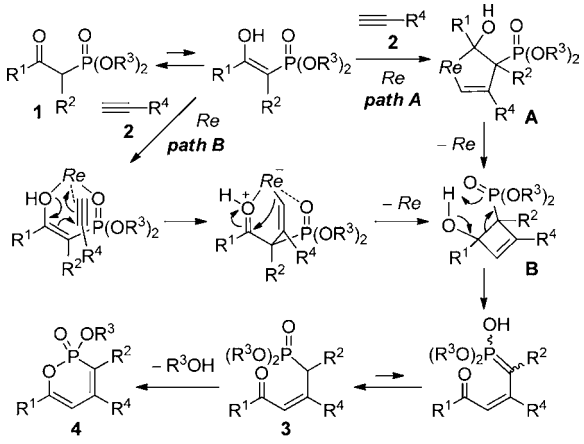
Scheme 3. Re-Catalyzed Reactions of α-Phosphonyl Ketones 5 with 4-Tolylacetylene 2a



mixture of the δ-phosphonyl α,β-unsaturated ketone **6a** and its olefinic isomer **6a′** was obtained in 73% total yield (**6a**:**6a′** = 94:6) with high regio- and stereoselectivity. Interestingly, the ratio of olefinic isomers **6** and **6′** was affected by the electronic features of the keto carbonyl moieties; the reaction of the α-phosphonyl ketone **5b**, with a methyl group on the carbonyl moiety, afforded a mixture of **6b** and **6b′** in the ratio of 68:32 under the current catalyst system.[12] These results can be explained by considering the improved thermodynamic stability of **6a**, in which the π-conjugation is more effectively delocalized over the aroylvinyl group compared to its isomer **6a′**. Since this effect is not significant for R = Me, the selectivity for the formation of isomer **6b** was thought to be decreased.

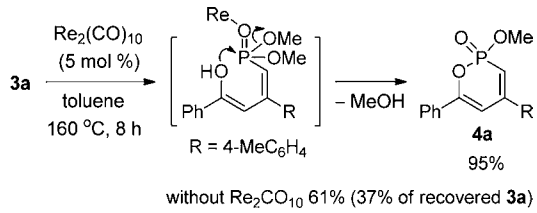
On the basis of the above results and our previous reports, the mechanism for the present reaction was proposed as follows (Scheme 4).[7] The transformation is initiated by regioselective

Scheme 4. Proposed Reaction Mechanism for the Formation of 2*H*-1,2-Oxaphosphorin 2-Oxides 4 via δ-Phosphonyl α,β-Unsaturated Ketones 3



oxidative cycloaddition of the β-keto phosphonate **1**, the alkyne **2**, and the rhenium catalyst to generate the rhenacyclopentene intermediate **A**. Reductive elimination of the rhenium complex from **A** affords the cyclobutene intermediate **B** (path A). Subsequent carbon−carbon bond cleavage via the retro-aldol reaction followed by protonation gives the δ-phosphonyl-α,β-unsaturated ketone **3**. An alternative pathway for the formation of the cyclobutene intermediate **B** consists of regioselective nucleophilic addition of the β-keto phosphonate **1** to the terminal alkyne **2** followed by intramolecular cyclization (path B). The resulting δ-phosphonyl-α,β-unsaturated ketone **3** is further converted to the 2*H*-1,2-oxaphosphorin 2-oxide **4** via cyclization followed by the elimination of an alcohol. Interestingly, this cyclization step was found to be promoted by a catalytic amount of the rhenium complex (Scheme 5). In the

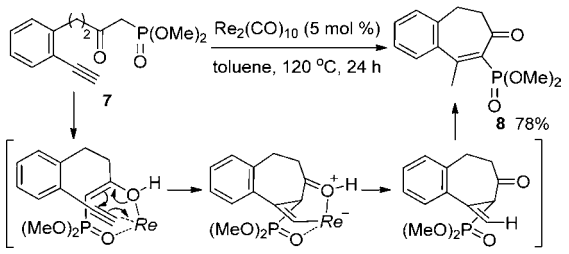
Scheme 5. Cyclization of δ-Phosphonyl α,β-Unsaturated Ketone 3a Leading to 2*H*-1,2-Oxaphosphorin 2-Oxide 4a



absence of $Re_2(CO)_{10}$, the yield of 2*H*-1,2-oxaphosphorin 2-oxide **4a** was decreased to 61% yield and some of the original **3a** was recovered.[13] It should be noted that the rhenium complex serves as both a π- and σ-acid catalyst in this sequence.

The intramolecular insertion of an acetylenic triple bond into a β-keto phosphonate having an ethynyl group, **7**, was examined under the current reaction conditions, and benzocyclohepten-7-one **8** was obtained in 78% yield (Scheme 6). The reaction

Scheme 6. Re-Catalyzed 7-*exo-dig* Cyclization of ω-Alkynyl-β-Keto Phosphonate 7 Leading to Benzocyclohepten-7-one 8



proceeded via a 7-*exo-dig* cyclization followed by protonation of the resulting alkenyl-rhenium species and isomerization of the double bond.[14] The alkenylrhenium species in this reaction could not attack the carbonyl carbon to form the cyclobutene intermediate **B** shown in Scheme 4 due to the ring strain (according to the Bredt's rule).[15] This result demonstrates the utility of the current catalytic transformation of Horner−Wadsworth−Emmons reagents for the formation of other phosphonated cyclic compounds.

In conclusion, we have developed a novel rhenium-catalyzed synthesis of 2*H*-1,2-oxaphosphorin 2-oxides with various substitution patterns from β-keto phosphonates and terminal alkynes in good yields under neutral conditions. The reaction proceeds via the cleavage of carbon−carbon σ-bonds of β-keto phosphonates followed by regio- and stereoselective addition reactions with alkynes. It is worth noting that β-keto phosphonates (known as Horner−Wadsworth−Emmons reagents) react with nonpolar carbon−carbon triple bonds under rhenium catalysis.[8,9] Compared with previous approaches, the present new method of producing 2*H*-1,2-oxaphosphorin 2-oxides has many unique advantages, including atom and step efficiency as well as reduced environmental impact. We hope that the present finding will serve as a useful tool for the synthesis of phosphorus-containing heterocycles that may have potential bioactivities.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: masahito.murai@cc.okayama-u.ac.jp.
*E-mail: ktakai@cc.okayama-u.ac.jp.

Notes

The authors declare no competing financial interest.

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(10) Investigation of solvents: toluene 87%, *n*-octane 72%, chlorobenzene 73%, 1,4-dioxane 46%, DMF 0%.

(11) Investigation of several transition-metal catalysts: $[ReBr(CO)_3(thf)]_2$ 29%, $ReBr(CO)_5$ 11%, $[HRe(CO)_4]_n$ 23%.

(12) The regio- and stereochemistry of each product was determined by nuclear Overhauser effect (NOE) studies. See Supporting Information for details.

(13) Although the catalytic activities of other transition metal complexes, including $[HRe(CO)_4]_n$, $FeCl_3$, $Cu(OTf)_2$, $AuCl_3$, and $Dy(OTf)_3$, were investigated, none were superior to $Re_2(CO)_{10}$ for the conversion of **3** to **4a**.

(14) For the indium-catalyzed 7-*exo*-*dig* cyclization of *ω*-alkynyl-*β*-ketoesters, see: (a) Tsuji, H.; Yamagata, K.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8060. (b) Itoh, Y.; Tsuji, H.; Yamagata, K.-I.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161.

(15) Path B in Scheme 4 might be more plausible than path A for the mechanism of the intermolecular reaction of **1** and **2**, because benzocyclohepten-7-one **8** obtained from the corresponding intramolecular reaction cannot be formed from the rhenacyclopentene intermediate **A**.