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Pd(0)-Catalyzed Intramolecular "Ylide-Ullmann-Type" Cyclization of Carbonyl-Stabilized Phosphonium Ylides and Access to Phosphachromones by Exocyclic P−C Cleavage

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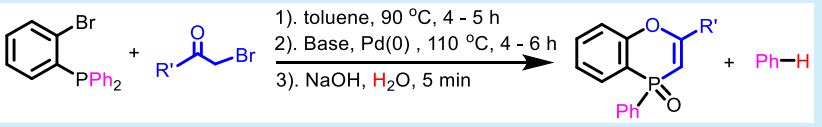
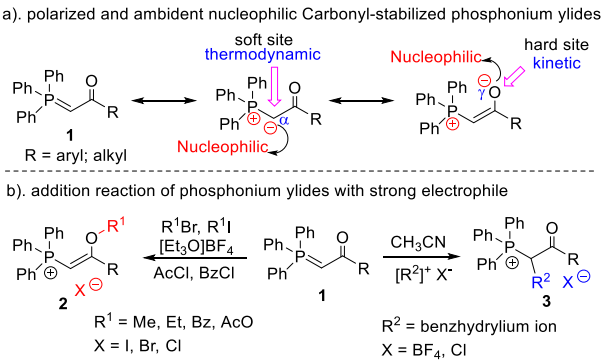
Supporting Information



ABSTRACT: An unprecedented palladium-catalyzed intramolecular Ullmann-type cyclization of carbonyl-stabilized phosphonium ylides with aryl bromides was successfully developed. Furthermore, a base-promoted chemoselective hydrolysis of exocyclic P−C bond of the corresponding phosphonium salts delivered various phosphachromones. Excellent selectivity and high efficiency and good functional group tolerance were observed.

The catalyzed Ullmann-type coupling reactions of aryl bromides/iodides with alcohols/phenols are widely used to afford various aryl ethers.[1] However, a strong nucleophilic group (O^-) seems essential for the success of reported *O*-arylation reactions.[2] Classical phosphonium ylides as mild nucleophiles have been widely applied in modern Wittig chemistry.[3] Particularly, milder nucleophilic carbonyl-stabilized phosphonium ylides **1**, which have been proven to be a new type of phosphonium ylide, have been investigated and applied in very recent synthetic chemistry.[4] (see Scheme 1a). It is important to note that this type of new ylide is an ambident nucleophile,[4c] and there exists a tautomeric equilibrium. Kinetically controlled γ-oxygen could act as a "hard" site, and, in contrast, thermodynamically controlled α-carbon became a "soft" site. Both α-carbon atom and γ-oxygen atom could couple with electron-deficient centers, for instance, benzhydrylium ions,[4a,c] alkyl iodides or bromides,[5] acyl chloride,[6] $[Et_3O]BF_4$[7] and MeOTf[4c] etc., to provide the corresponding products **2** and **3**, respectively (see Scheme 1b).

Scheme 1. Carbonyl-Stabilized Phosphonium Ylides as Nucleophiles



The reactions of carbonyl-stabilized phosphonium ylides with highly reactive alkyl iodides/bromides to phosphoniums **2** have been widely reported.[4−7] However, none of them concerned reaction with unactivated aryl halides—that is, Ullmann-type reaction of phosphonium ylides as nucleophiles. Therefore, it is of interest to develop a new catalytic methodology that could efficiently couple carbonyl phosphonium ylides with unactivated aryl halides. In view of catalyzed Ullmann-type *O*-arylations, we reasoned that using transition metals as a catalyst might facilitate the nucleophilic reaction, although our initial trials for the intermolecular cross couplings of carbonyl-stabilized phosphonium ylides with aryl halides failed to provide the desired product under various conditions (see Table s1 in the Supporting Information). We then continued to investigate the intramolecular variants, which successfully furnished heterocyclic phosphonium salts **7** (Scheme 2). Moreover, several interesting phosphachromones could be readily constructed via highly chemoselective hydrolysis of exocyclic C−P bond of **7** under mild conditions.

Initially, phosphonium ylide **6a** was chosen as a model substrate to optimize the reaction conditions. A series of palladium catalysts, such as $Pd(Ph_3P)_4$, $(Ph_3P)_2PdCl_2$, $PdCl_2$, and $Pd(OAc)_2$, etc. were first investigated. Control experiments revealed that $Pd(Ph_3P)_4$ turned out to be a highly effective catalyst for catalyzing the cyclization; however, bivalent palladium had little effect (Table 1, entries 1−4). Reaction solvents, temperatures, and time evaluation then indicated that toluene as a solvent at 110 °C for 4 h was optimal for giving the expected product (Table 1, entries 4−9).

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Scheme 2. Ullmann-Type Cyclization of Carbonyl Phosphonium Ylides

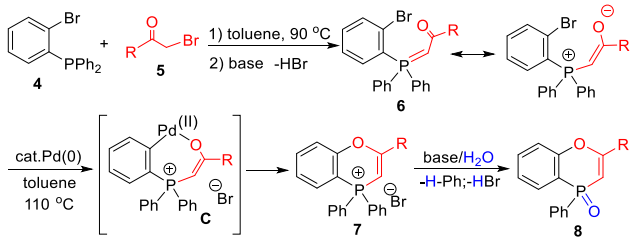
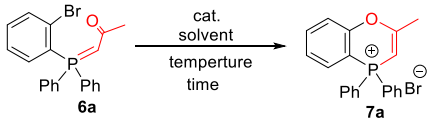


Table 1. Optimization of Pd-Catalyzed Cyclization Reaction of Carbonyl-Stabilized Phosphonium Ylide[a]



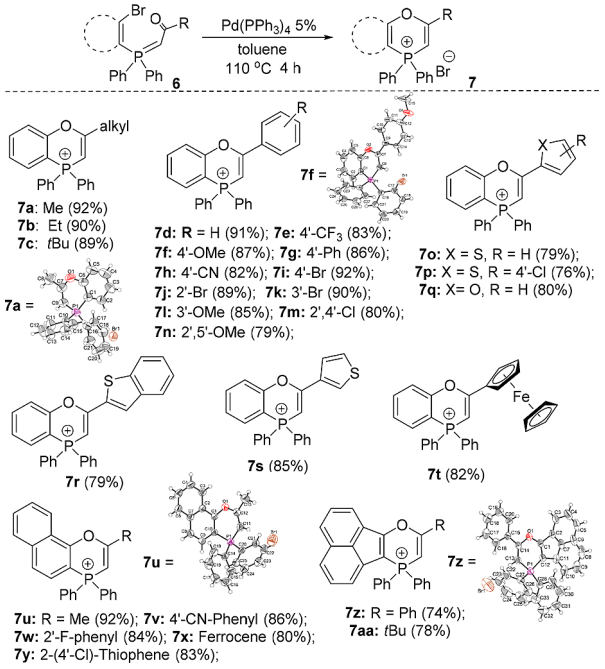
entry	catalyst	solvent	temperature (°C)	time (h)	yield[b] (%)
1	$Pd(OAc)_2$ (8%)	toluene	120	12	trace
2	$PdCl_2$ (8%)	toluene	120	12	trace
3	$(Ph_3P)_2PdCl_2$ (8%)	toluene	120	12	trace
4	$Pd(Ph_3P)_4$ (8%)	toluene	120	12	78
5	$Pd(Ph_3P)_4$ (8%)	toluene	110	4	92
6	$Pd(Ph_3P)_4$ (8%)	toluene	120	4	90
7	$Pd(Ph_3P)_4$ (8%)	DMF	110	4	34
8	$Pd(Ph_3P)_4$ (8%)	THF	110	4	45
9	$Pd(Ph_3P)_4$ (8%)	dioxane	110	4	67
10	none	toluene	120	24	trace
11	$Pd(Ph_3P)_4$ (3%)	toluene	110	4	87
12	$Pd(Ph_3P)_4$ (5%)	toluene	110	4	91

[a]Unless otherwise noted, all reactions were performed using 1 mmol of **6a**, 5−8 mol % of catalyst, and 5 mL of solvent. [b]Isolated yield of **7a**.

Further investigation on the amount of the catalysts shows that 5 mol % seems to be the minimum amount required by cyclization (Table 1, entries 10−12).

Under the optimized reaction conditions, the generality and limitation of the intramolecular cyclization of carbonyl phosphonium ylides was investigated, and the results are illustrated in Scheme 3. Generally, all of the tested substrates could react smoothly to deliver the desired cyclic products in high efficiency and yields. Moreover, all the products can be easily isolated by simple filtration without time and energy-consuming chromatography purification manipulation. Several alkyl carbonyl phosphonium ylides **6a**−**6c** were first evaluated, the cyclization proceeded smoothly, even with the large steric-hindrance tertiary butyl group (**7c**). We then moved to aryl carbonyl phosphonium ylides. It was found that both electron-rich and electron-poor phenyl substitutes could be well-tolerated (**7d**−**7h**). Furthermore, a series of halide atoms, including F, Cl, and Br, were also compatible for the process. Different positions on the phenyl ring were also tested and no evident steric influence was noticed (**7i**−**7n**). Eventually, several heteroaryl substitutions, such as furan, thiophene, and benzothiophene were also examined, and the corresponding six-members phosphoniums **7o**−**7s** were obtained in good yields. Note that the ferrocene group could also be tolerated for the transformation (**7t** and **7x**). Meanwhile, naphthalene and acenaphthylene skeleton were also appropriate substrates

Scheme 3. Substrate Scope for 1,4-Addition of Carbonyl Phosphonium Ylides with Aryl Bromide[a]

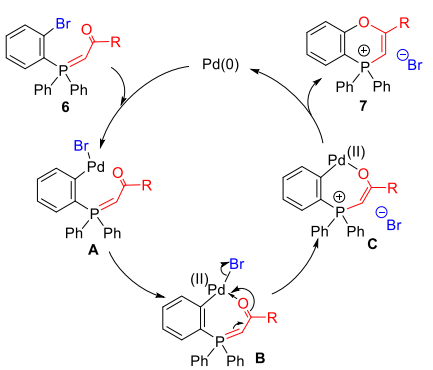


[a]Reaction conditions: phosphonium ylides **6a**−**6n**, **6v**−**6ab**, **6t**, **6u** (1 mmol) in toluene (5 mL) at 110 °C in an argon atmosphere for 4 h; **6o**−**6r**, **6y** (1 mmol) in toluene (5 mL) at 120 °C in an argon atmosphere for 8 h.

for the reaction with good reactivity (**7u**−**7aa**). More importantly, to demonstrate the practical synthetic utility of this newly developed method, gram-scale reaction of **6i** (2 g) was performed under the identical conditions, and 1.85 g of **7i** was obtained in 92% yield without any erosion in the efficiency. Unfortunately, the substrates cannot be extended to bromo-ketones bearing an ortho-substituted group, such as phenyl or alkyl group. The absolute structures of **7a**, **7f**, **7u**, and **7z** were unambiguously confirmed by X-ray crystallography (see the Supporting Information).

In light of the experimental results and previous reports,[8] a plausible reaction mechanism is proposed in Scheme 4. First, oxidation addition of palladium(0) to the C−Br bond generates Pd(II) intermediate A, and then intramolecular ligand displacement of one of Ph_3P ligands by the carbonyl group gives rise to intermediate B. Subsequently, enolate displaces bromide, resulting in palladacycle C. Finally,

Scheme 4. Proposed Mechanism



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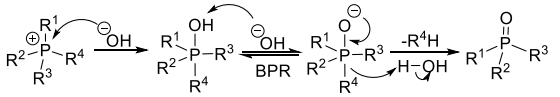
reductive elimination provided the heterocyclic phosphonium salt **7**, while regenerating active Pd(0) catalyst for the next catalytic cycle. The cyclization reaction process follows the traditional Ullmann-type reaction mechanism.[1]

It is well-known that phosphonium salts not only constitute one of the important functional materials that possess special physicochemical properties,[9] but also stand for the main reactants of phosphoxides.[10] Especially, heterocyclic phosphoxides are represented as important organic *n*-type material[11] and pharmaceuticals,[12] because of their unique optical, electrochemical, and biological properties. Hydrolysis of phosphoniums and phosphonium ylides is one of the most direct synthetic approaches for phosphoxides by forming intermediate of the trigonal bipyramidal (TBP) hydroxytetraorganophosphorane.[13] Recently, the mechanism study of TBP oxaphosphoranes has attracted special attention, including the theoretical computation,[14] observation of intermediates,[15] and mechanisms of stereomutuation,[16] etc. Until now, the mechanism for hydrolysis process has been well-established, which can be summarized by the following three steps:

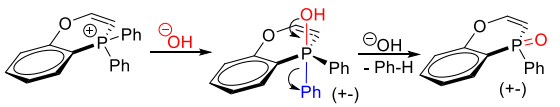
(a) nucleophilic attack of hydroxide to electron-deficient phosphorus center to afford a P(V) intermediate hydroxytetraorganophosphorane with apical oxygen;
(b) deprotonation by hydroxide to form an oxyanionic phosphorane (berry pseudorotation (BPR)[17] or turnstile rotation[18] may occur in this process); and
(c) cleavage of apical P−C bond and electron transfer provide phosphine oxide product (see Scheme 5a).

Scheme 5. Hydrolysis of Phosphonium Salt

a) The mechanism of alkaline hydrolysis of phosphonium salt.



b) The procese of alkaline hydrolysis of compounds **7**.



Because of weak aromaticity caused by the negative hyperconjugation, ring opening via the hydrolysis reaction of phophacycles seems easier.[11a,15b,20d,e,19] Careful analysis of the single crystals of **7a**, **7f**, **7u**, and **7z** (see the Supporting Information) showed that the bond length of exocyclic P−C bonds (1.78−1.80 Å) are longer than internal bonds (1.73−1.77 Å), and, meanwhile, the internal angle (102°) is larger than that of the corresponding phosphindolium species (~95°).[15b,20] Besides, note that pentacoordinate phosphoric intermediates can self-adjust the position of their substituents with stronger electronegativity or longer bonds located at apical sites and bigger bond angles at equatorial sites.[16,21] Based on these features, we envisioned that intra-annular P−C bonds are both self-adjusted to equatorial ligands by stereomutation of pseudorotation of the trigonal bipyramid intermediate; on the other hand, one of the phenyl groups would locate on apical sites, which could act as the leaving group (Scheme 5b). Thus, it is reasonable to speculate that chemoselective cleavage of exocyclic P−C bond should be realized under suitable conditions.

To test our hypothesis, aqueous sodium hydroxide was added to dichloromethane or toluene solution of phosphonium **7a** at 0−25 °C. As expected, the experimental results showed that the new signal of **8a** arose and the signal of **7a** faded away within 5 min. Besides, the high chemoselectivity was also clearly demonstrated by ^{31}P NMR tracing of hydrolysis process of **7a** (Figure 1). Although a trace amount of product **9a** of

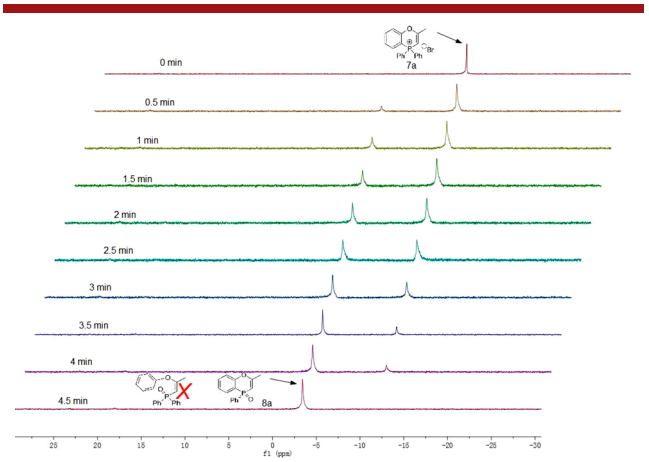


Figure 1. ^{31}P NMR tracing of hydrolysis reaction of **7a** with NaOH aqueous at 0 °C in CH_2Cl_2.

internal P−C bond cleavage can be detected when the hydrolysis reaction is performed at room temperature (see Figure s1 in the Supporting Information), almost quantitative exocyclic C−P bond cleavage is observed to give the expected phosphachromone skeleton in a ice bath. The improved selectivity of exocyclic P−C cleavage at lower temperature proved that the hydrolysis reaction is a kinetically controlled process. Further optimization of other inorganic and organic bases, as well as solvents, did not generate better outcomes (see Table s3 in the Supporting Information).

Under mild conditions, the first phosphachromone **8a** was obtained rapidly in excellent yield, which may possess extensive potential biological activities, because of its similar skeleton to chromones **I** (see Figure 2).[22] However, compared with the

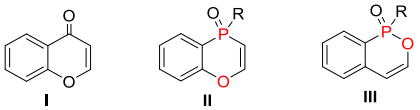


Figure 2. Skeletons of chromones (**I**), phosphachromones (**II**), and phosphaisocoumarins (**III**).

many literature reports concerning synthetic and applied research about cognate phosphaisocoumarins **III**,[23] there is limited synthetic protocols for phosphachromones **II**.[24] Therefore, it is important to develop a general and practical useful synthetic method toward the direct construction of phosphachromone frameworks with high efficiency.

Consequently, we set out to investigate the scope of the hydrolysis reaction using preceding heterocyclic phosphonium salt products **7** as starting materials (Scheme 6). It is delight to find that all of the heterocyclic phosphonium salts **7** proved to be suitable substrates for hydrolysis in the presence of aqueous sodium hydroxide, either using dichloromethane or toluene as a solvent. High yields along with excellent chemoselectivity were obtained under mild conditions to complete the

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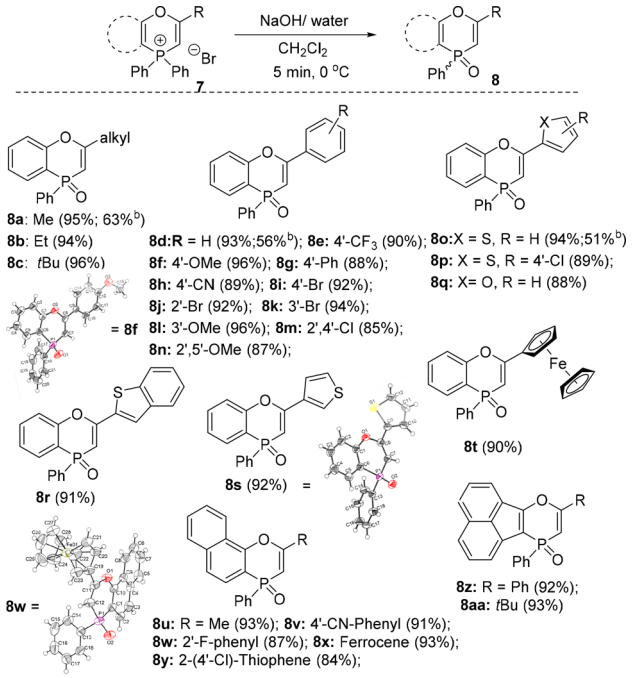
Scheme 6. Substrate Scope for Hydrolysis Reaction of Six-Member Phosphoniums[a]



[a]Reaction conditions: phosphonium salts **7a**–**7ab** (0.5 mmol) and saturated NaOH aqueous (0.5 mL) in CH_2Cl_2 (5 mL) at 0 °C for 5 min. [b]Isolated yields by the "one-pot" four-step syntheses.

transformation rapidly (the reaction time is only 5 min in CH_2Cl_2). No evident electronic and steric effects were noticed during the hydrolysis reaction. Furthermore, the "one-pot" four-step syntheses of phosphachromones, through sequential phosphonium formation, HBr elimination, Ullmann-type cyclization, and hydrolysis, has been proved to be completely feasible. The absolute structures of **8f**, **8s**, and **8w** were also unambiguously confirmed by X-ray crystallography (see the Supporting Information).

In conclusion, a general, efficient, and sustainable synthesis of novel phosphachromone derivatives was successfully developed through Pd-catalyzed intramolecular "Ylide-Ullmann-type" cyclization of carbonyl-stabilized phosphonium ylides and tandem highly chemoselective hydrolysis of exocyclic C–P bond. High yields and excellent selectivity, along with good functional group compatibility, were achieved under mild conditions. A possible mechanism was proposed to clarify the selectivity. This newly developed methodology would open up a new avenue for practical synthesis of novel phosphorus heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03948.

Experimental procedures; copies of ^1H, ^{13}C, and ^{31}P spectra of the products (PDF)

Accession Codes

CCDC 1920938–1920944 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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