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ARTICLE

Metal-free C(aryl)–P bond cleavage: Experimental and computational studies of the Michael addition/aryl migration of triarylphosphines to alkenyl esters

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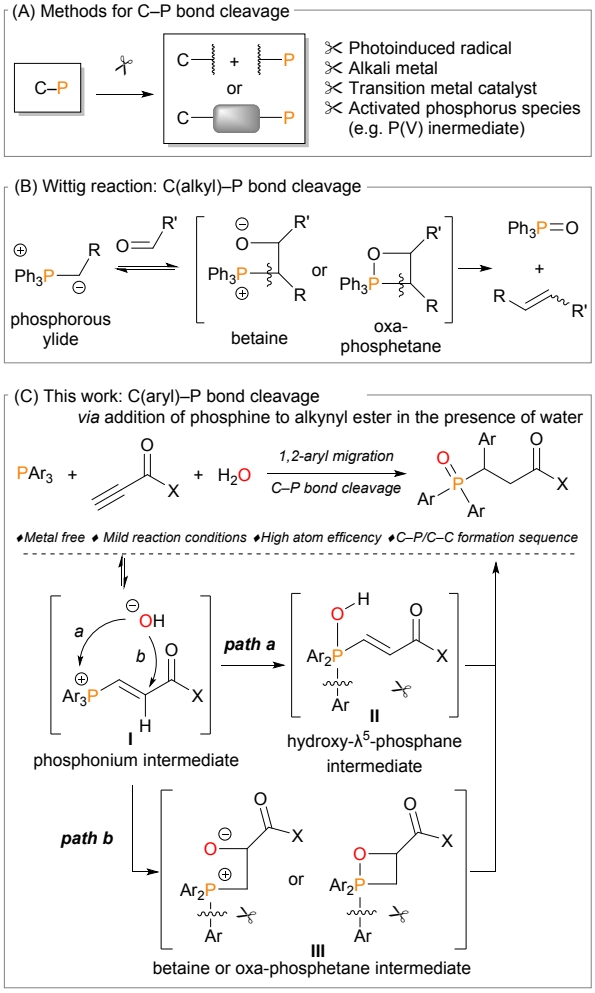
The nucleophilic addition and aryl migration of triarylphosphines to alkynyl esters in the presence of water results in the formation of 3-(diarylphosphoryl)-3-aryl propanoic acid derivatives through a metal-free C(aryl)–P bond cleavage process. Experimental and computational investigations of the mechanism indicate that the rapid formation of hydroxy-λ^5-phosphane as a key intermediate plays a crucial role in smooth C(aryl)–P bond cleavage.

Introduction

Bond cleavage reactions have attracted much attention from chemists interested in modern organic synthesis because of their potential applications in chemoselective molecular transformations.[1,†] Among the reported examples of carbon–carbon (C–C)[2–4] and carbon–heteroatom (C–X)[1,5–7] bond cleavage reactions, carbon–phosphorus (C–P) bond cleavage reactions[8–15,‡] are one of the most important transformations because organophosphorus compounds are widely utilized as pharmaceuticals,[16] phosphine ligands,[17,18] organocatalysts,[19] and functional materials.[20] Therefore, C–P bond cleavage reactions have been developed using various approaches such as radicals produced using photolysis[8] or peroxides,[9] reduction using transition metal catalysts[10] and alkali metals,[11] and *via* P(V) intermediates[12–15] (Scheme 1A). However, these synthetic methodologies require relatively harsh conditions, leading to low functional group tolerance. In addition, they require the use of precious transition metals and the formation of highly polarized C–P bonds in activated species.

The Wittig reaction, which provides an alkene from a phosphorus ylide and an aldehyde or ketone, proceeds *via* a highly reactive intermediate such as a betaine or oxaphosphetane (Scheme 1B).[21] The driving force for C–P bond cleavage in the Wittig reaction is the structural strain in the zwitterionic species. In this reaction, tertiary phosphines are often utilized as Lewis bases, causing nucleophilic addition to activated alkenes, allenes, and alkynes *via* Michael addition to generate phosphonium intermediate **I** (Scheme 1C).

Scheme 1. Methods of C(aryl)–P bond cleavage.



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Here, an alkynyl ester is employed, and the resulting zwitterionic species can react with nucleophiles or electrophiles to afford structurally diverse products.[19] As part of our continuous effort to develop Lewis-base-mediated reactions,[22,23] we envisioned that by using water as both a nucleophile and an electrophile, phosphonium intermediate **I** and a hydroxide ion would be generated *in situ* (Scheme 1C). Owing to the high oxophilicity of the phosphonium and neighboring α,β-unsaturated carbonyl moiety (a Michael acceptor) in intermediate **I**, the hydroxide ion could attack the phosphonium, and, thus, C(aryl)–P bond cleavage would be enhanced and induce the 1,2-rearrangement of the aryl group to the Michael acceptor *via* a hydroxyl-5λ-phosphane[24] intermediate **II** (Scheme 1C, *path a*), thus providing 3-(diarylphosphoryl)-3-aryl propanoic acid derivatives.[25-27] As an alternative pathway, the high electron demand of the phosphonium moiety[28] could promote the umpolung-type Michael addition[29–34] of the hydroxide ion, leading to C(aryl)–P bond cleavage *via* Wittig-type intermediate **III** (Scheme 1C, *path b*). In this context, we investigated the metal-free cleavage of C(aryl)–P bonds in the Michael addition/aryl migration of triarylphosphines to alkenyl ester derivatives in the presence of water. In addition, we carried out computational studies on the reaction mechanism, and this combined experimental and computational study provides insights into key questions about the rearrangement reaction mechanism and reveals the exact reaction pathways of intermediates **II** or **III** *via* cascade reactions.[35,§]

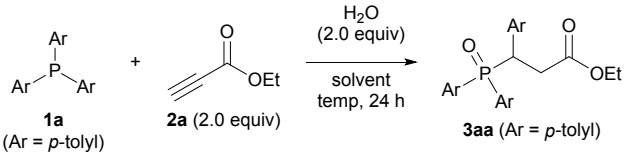
Results and discussion

Optimization of reaction conditions and substrate scope

In our work directed toward the development of metal-free C(aryl)–P bond cleavage, the reaction of tri(*p*-tolyl)phosphine (**1a**) and ethyl propiolate (**2a**, 2.0 equiv), an electron-deficient alkyne, was initially attempted in the presence of H_2O (2.0 equiv) (Table 1). The reaction in toluene at 10 °C afforded the desired adduct **3aa** in 88% yield (entry 1). After screening the reaction solvents (CH_2Cl_2, *N*,*N*-dimethylformamide (DMF), Et_2O, tetrahydrofuran (THF), cyclopentyl methyl ether (CPME), and *tert*-butyl methyl ether (TBME)), **3aa** was isolated in 94% yield using TBME (entry 7). When the reaction was performed at 0 and 20 °C instead of 10 °C, **3aa** was obtained in 87% and 86% yields, respectively (entries 8 and 9). The use of lower quantities of **2a** (1.5 equiv) or H_2O (1.5 equiv) decreased the yield of **3aa** to 91% (entry 10).

Next, we investigated the scope of the phosphine reagents under the optimal conditions (Scheme 2). Reactions using triphenylphosphine (**1b**) afforded the desired product **3ba** in 95% yield. Triarylphosphines bearing methoxy, fluoro, and chloro groups at the *para*-positions also furnished the corresponding rearrangement products **3ca–ea** in good yields (71–95%), whereas tris(*p*-(trifluoromethyl)phenyl)phosphane (**1f**) with highly electron-withdrawing group was converted to **3fa** in only 31% yield, probably because of the lower nucleophilicity of **1f** to **2a**.[36,37]

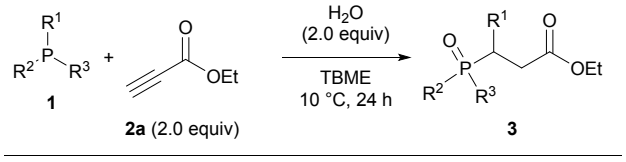
Table 1. Optimization of reaction conditions[a].

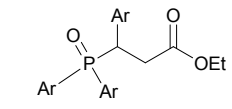


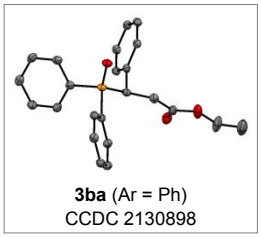
Entry	Solvent	Temp (°C)	Yield (%)[b]
1	Toluene	10	88
2	DCM	10	84
3	DMF	10	26
4	diethyl ether	10	94
5	THF	10	90
6	CPME	10	91
7	TBME	10	98 (94)[c]
8	TBME	0	87
9	TBME	20	86
10[d]	TBME	10	91

[a]The reaction of **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv), and H_2O (0.2 mmol, 2.0 equiv) was conducted in 0.5 mL of solvent. [b]Yields were determined by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]**2a** (0.15 mmol, 1.5 equiv) or H_2O (0.15 mmol, 1.5 equiv) were used. DCM: dichloromethane. DMF: *N*,*N*-dimethylformamide. THF: tetrahydrofuran. CPME: cyclopentyl methyl ether. TBME: *tert*-butyl methyl ether

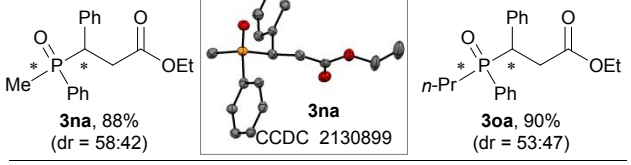
Scheme 2. Substrate scope for phosphines **1**. In the ORTEP plot of compounds **3ba** and **3na**, the ellipsoids are plotted at 50% probability (H atoms have been omitted for clarity). dr = diastereomeric ratio.







3	Ar	yield (%)
3ba	Ph	95
3aa	*p*-tolyl	94
3ca	*p*-MeO-C_6H_4	71
3da	*p*-F-C_6H_4	93
3ea	*p*-Cl-C_6H_4	85
3fa	*p*-CF_3-C_6H_4	31
3ga	*m*-tolyl	84
3ha	*m*-MeO-C_6H_4	82
3ia	*m*-F-C_6H_4	93
3ja	*m*-Cl-C_6H_4	59
3ka	*o*-tolyl	28
3la	*o*-F-C_6H_4	7
3ma	2-naphthyl	36

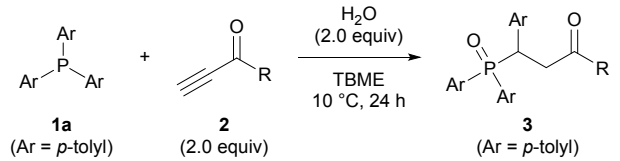


When *meta*-substituted triarylphosphines **1g–j** were employed, the products **3ga–ja** were obtained in moderate-to-good yields (59–93%). The reactions using tri(*o*-tolyl)phosphine (**1k**), tris(o-

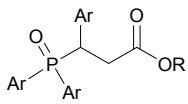
fluorophenyl)phosphine (**1l**), and tri(2-naphthyl)phosphine (**1m**) afforded products **3ka**, **3la**, and **3ma**, respectively, in only 28%, 7%, and 36% yields, respectively. These results suggest the nucleophilic attack of water on the phosphonium moiety in intermediate **I** or steric repulsion between the *o*-position and the β-position during the migration process in intermediate **II** or **III**. We also attempted to use alkyl-substituted phosphines under the present reaction conditions. When monoalkyldiphenylphosphines such as $MePPh_2$ (**1n**) and *n*-$PrPPh_2$ (**1o**) were employed under the optimal conditions, the aryl group was preferentially rearranged to afford the corresponding products **3na** and **3oa**, which have two chiral centers on the phosphorus and carbon atoms, in 88% and 90% yields, respectively, as mixtures of diastereomers. These results differ from those of the Wittig reaction product *via* cleavage of the C(alkyl)–P bond. The structures of products **3ba** and **3na** were identified by X-ray crystallographic analysis.

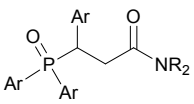
Next, we examined the use of various activated alkynes (Scheme 3). Thus, reactions involving a series of propiolate esters **2b–f** having methyl, benzyl, bromoethyl-, allyl-, and phenyl groups were conducted in the rearrangement reaction to form the corresponding products **3ab–af** in good yields (76–97%). Instead of propiolate esters, propiolamides can also be utilized as activated alkynes. In particular, amides **2g** and **2h** afforded the corresponding products **3ag** and **3ah** in 60% and 90% yields, respectively. Further, when chiral propiolate ester **2i** bearing a menthyl group was used, the reaction proceeded to give **3ai** in 95% yield as a mixture of diastereomers (53:47 diastereomeric ratio (dr)). Finally, under these reaction conditions, internal alkynes such as ethyl 3-phenylpropiolate and dimethyl but-2-ynedioate were unsuitable for the creation of a chiral quaternary carbon center under our optimized reaction conditions.

Scheme 3. Substrate scope for alkynes **2**. dr = diastereomeric ratio.

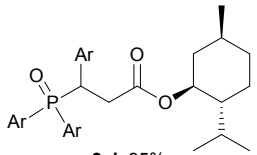


3	R	Yield	3	R	Yield
3aa	Et	94%	**3ad**	CH_2CH_2Br	76%
3ab	Me	97%	**3ae**	CH_2CHCH_2	80%
3ac	Bn	82%	**3af**	Ph	76%





3	NR_2	Yield
3ag	NMe_2	60%
3ah	4-morpholinyl	90%

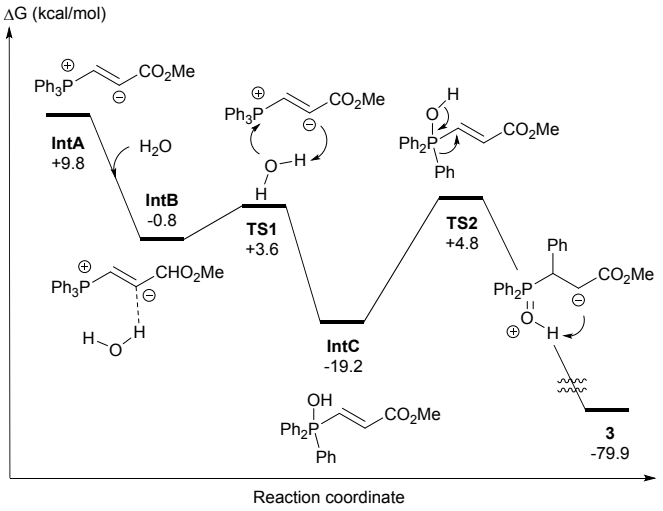


3ai, 95%
(dr = 53:47)

Computational studies of the reaction mechanism

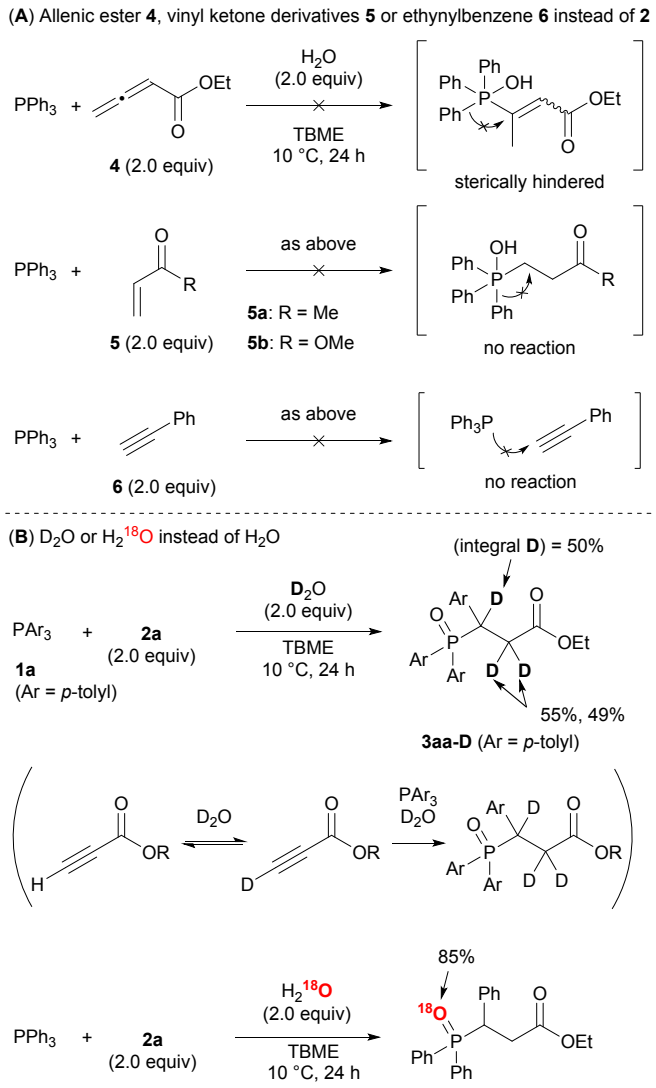
To verify the reaction pathway in our Michael addition/aryl migration reaction, density functional theory (DFT) calculations were performed using model structures, namely methyl propiolate and triphenylphosphine (Scheme 4). After conjugate addition of the phosphine to the propiolate ester to form **IntA**, complexation with a water molecule forms **IntB**. Subsequently, the protonation of the α-carbon *via* **TS1** is immediately followed by the addition of a hydroxy group to the phosphonium moiety to form **IntC**. Finally, 1,2-rearrangement of the phenyl group through C(aryl)-P bond cleavage *via* **TS2** and subsequent intramolecular proton migration from the phosphorous oxygen to the α-carbon would provide product **3**. Therefore, the present reaction took place through reaction *path a* shown in Scheme 1C.[38]

Scheme 4. Calculated energy diagram. The Gibbs free energies (kcal/mol) of intermediates and transition states are shown relative to the sum of the free energies of the starting materials (**1**, **2**, and H_2O). All calculations were performed at B3LYP/6-31G(d) level of theory in the gas phase.



As control experiments, allenic ester **4** and vinyl ketone derivatives **5**, which are also activated Michael acceptors, were employed instead of propiolate esters **2** (Scheme 5A). In both cases, the corresponding rearrangement products were not obtained, probably owing to the difficulty of rearrangement of the phenyl group in each intermediate. Thus, the intermediate derived from PPh_3 and allenic ester **4** suffers from the steric hindrance of the methyl group at the β-position of the carbonyl, and the intermediate derived from PPh_3 and vinyl ketone derivatives **5** do not include a Michael acceptor moiety. The reaction of ethynylbenzene (**6**) as a non-activated alkene under the optimized conditions afford no desired product at all. When deuterium oxide or O-isotopic labelling water was used instead of water, the scrambling of hydrogen and deuterium at the α- and β-positions and the scrambling ^{16}O and ^{18}O on the phosphine atom were observed (Scheme 5B). This result indicates that the exchange of hydrogen from the terminal alkyne with deuterium occurs rapidly during the reaction.

Scheme 5. (A) Control and (B) D_2O or $H_2{}^{18}O$ experiments.



Conclusions

In conclusion, we investigated the scope and mechanism of the C(aryl)–P bond cleavage reaction of arylphosphines with activated alkynes in the presence of water. The C(aryl)–P bond cleavage proceeded under metal-free and mild reaction conditions with high functional group tolerance. The computational study supported the rapid formation of a hydroxy-λ^5-phosphane intermediate, enabling 1,2-aryl migration through smooth C(aryl)–P bond cleavage. The investigation of these catalytic and enantioselective rearrangements is ongoing in our laboratory.

Author Contributions

M. S., S. T., and H. S. designed the study and managed manuscript preparation. M. S., M. S. H. S., and T. F. performed the experiments. K. K. investigated the reaction mechanism using DFT calculations and assisted with manuscript preparation.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

†For selected reviews, see references 1–7.
‡For selected reports, see references 8–15.
§Tebby and Richards found a similar C–P bond cleavage reaction, but the scope and mechanism of the reaction had remained unclear until now. For further information, see reference 32.

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38 During our DFT study, any key intermediate through *path b* (the umpolung-type Michael addition of water to the phosphonium intermediate, Scheme 1c) could not be found.