

Iron(II) Phthalocyanine-Catalyzed Olefination of Aldehydes with Diazoacetoneitrile: A Novel Approach to Construct Alkenyl Nitriles

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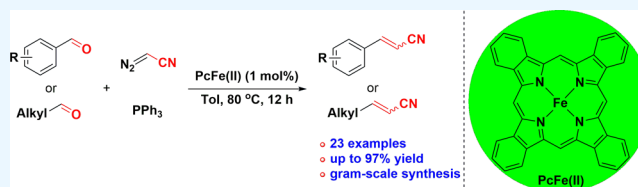


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Supporting Information

ABSTRACT: A novel synthetic approach to preparing alkenyl nitriles via the olefination of aldehydes with diazoacetoneitrile catalyzed by iron(II) phthalocyanine in the presence of PPh₃ has been developed. A broad variety of aldehydes are efficiently transformed into the corresponding products with the high yields of 75%–97%. And it is also suitable for its gram-scale preparation. The suggested mechanism involves the transformation of the phosphazine to ylide by iron(II) phthalocyanine.



INTRODUCTION

Alkenyl nitriles are valuable building blocks in organic synthesis and key structural motifs in many natural products and pharmaceutical molecules. Accordingly, some effective protocols about the construction of alkenyl nitrile units have been reported.¹ The traditional and effective method is Knoevenagel condensation, while some side-reactions, including aldol, Cannizzaro, and self-condensation of nitriles, are accompanied. Recently, a variety of metal-catalyzed methods have been developed to prepare alkenyl nitriles, and they involve the dehydrogenative coupling of alcohols with nitriles catalyzed by Ru, Rh, Co, or Mn (Scheme 1a),² vinylic C–H or C–X bond cyanation of alkenes or alkenyl halides with nitriles catalyzed by Pd or Cu (Scheme 1b),³ oxidative cyanation of alkynes or *gem*-difluoroalkenes with nitriles or azidotrimethylsilane (TMSN₃) catalyzed by Pd, Ni, or Cu (Scheme 1c),⁴ aryl-, bromo-, silyl-, or hydrocyanation of alkynes with K₄Fe(CN)₆, BrCN, or aryl/alkyl nitriles catalyzed by Rh, Pd, Ni, or GaCl₃ (Scheme 1d),⁵ and formal group-exchange reaction between α,β -unsaturated ketone and nitriles catalyzed by Pd (Scheme 1e),⁶ as well as aza-Meyer-Schuster rearrangement of propargylic alcohols with *para*-tolylsulfonohydrazide catalyzed by FeCl₃ (Scheme 1f).⁷ Undoubtedly, these methods provide alternative and very useful strategies for alkenyl nitriles, while most of them need expensive transition-metal catalysts, higher temperature, long reaction time, or even a highly toxic reagent; thus, it is necessary to develop new synthetic strategies to meet these challenges.

Olefination of carbonyl compounds with diazo reagents catalyzed by metals has been proved to be a powerful tool to construct the C=C double bond bearing functional groups on the vinylic carbon atom, and the groups mainly focused on ester groups,⁸ CF₃,⁹ and aromatic ring.¹⁰ Herein, we report a novel approach to construct the alkenyl nitriles via the olefination of aldehydes with diazoacetoneitrile (N₂CHCN) catalyzed by the commercially available iron(II) phthalocya-

nine (PcFe(II)), and the current method can afford the corresponding alkenyl nitriles in high yields. Then the potential of this reaction in gram-scale synthesis was also investigated. Subsequently, the mechanism research demonstrated that the transformation of phosphazine to ylide by PcFe(II) is involved.

RESULTS AND DISCUSSION

We carried out the olefination reaction between benzaldehyde (1 equiv) with diazoacetoneitrile (2 equiv) catalyzed by PcFe(II) (1 mol %) in toluene at 80 °C for 12 h in the presence of triphenylphosphine (PPh₃, 1.1 equiv; Table 1) and could get the olefination product in the yield of 80% (entry 1). When PcFe(II) was replaced by PcFe(III)Cl or PcCo(II), respectively, their corresponding yields were 77% and even trace (entries 2 & 3). Tetraphenylporphyrin iron(III) chloride and cobalt(II) complexes, (TPP)Fe(III)Cl and (TPP)Co(II), also gave the same product with the yields of 15% and 46% (entries 4 & 5). Obviously, PcFe(II) exhibited the highest catalytic activity under the above condition. Then, PcFe(II) was selected as catalyst for this reaction which was done at lower temperatures (entries 6–8), and their yields were lower than that at 80 °C, while some of their *trans*-selectivities were higher, indicating the lower temperature favored the *trans*-product. Compared with 80 °C, the higher reflux temperature only gave the same yield and lower *trans*-selectivity (entry 9). Accordingly, 80 °C was the optimal reaction temperature. Subsequently, different solvents were tested for the reaction (entries 10–12), but the results indicated that all of them

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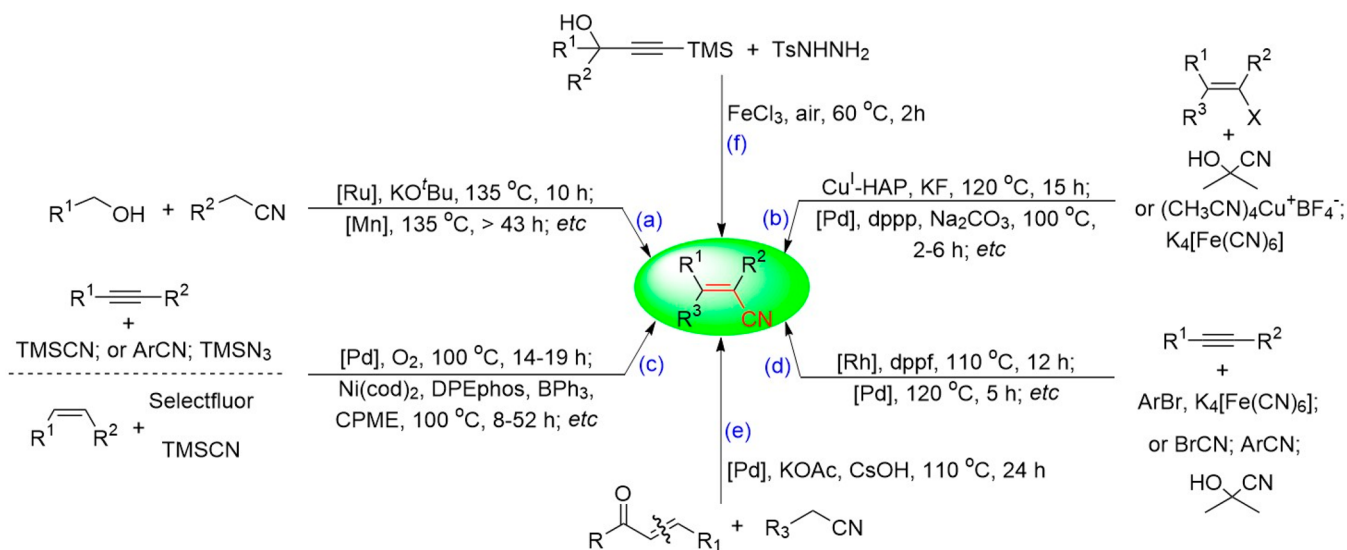
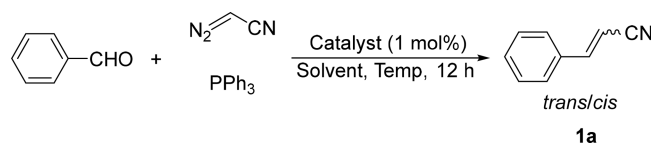
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Scheme 1. Summary of the Metal-Catalyzed Methods for the Preparation of Alkenyl Nitriles

Table 1. Optimization of Reaction Conditions for the Olefination of Benzaldehyde with N₂CHCN^a

Entry	Catalyst	Solvent	PPh ₃ (equiv)	Temperature (°C)	Yield of 1a (%) ^b	<i>trans</i> / <i>cis</i> ratio ^c
1	PcFe(II)	Toluene	1.1	80	80	3.6:1
2	PcFe(III)Cl	Toluene	1.1	80	77	4.5:1
3	PcCo(II)	Toluene	1.1	80	trace	1:1
4	(TPP)Fe(III)Cl	Toluene	1.1	80	15	3.8:1
5	(TPP)Co(II)	Toluene	1.1	80	46	3:1
6	PcFe(II)	Toluene	1.1	25	21	5.9:1
7	PcFe(II)	Toluene	1.1	40	33	5.3:1
8	PcFe(II)	Toluene	1.1	60	67	4.3:1
9	PcFe(II)	Toluene	1.1	reflux	81	2.8:1
10	PcFe(II)	DCM ^d	1.1	reflux	39	5.5:1
11	PcFe(II)	THF ^d	1.1	reflux	71	5.2:1
12	PcFe(II)	CH ₃ CN	1.1	reflux	36	5.2:1
13	PcFe(II)	Toluene	1.5	80	90	5.1:1
14	PcFe(II)	Toluene	2	80	96	5:1
15	PcFe(II)	Toluene	3	80	96	5:1
16 ^e		Toluene	2	80	N.D. ^f	N.D.
17 ^g	PcFe(II)	Toluene	2	80	N.R. ^f	N.D.
18	FeCl ₂	Toluene	2	80	N.D.	N.D.
19	FeSO ₄	Toluene	2	80	N.D.	N.D.
20	Fe(OAc) ₂	Toluene	2	80	N.D.	N.D.
21	Mn(OAc) ₂	Toluene	2	80	N.D.	N.D.
22	Co(OAc) ₂	Toluene	2	80	N.D.	N.D.
23	CoCl ₂	Toluene	2	80	N.D.	N.D.

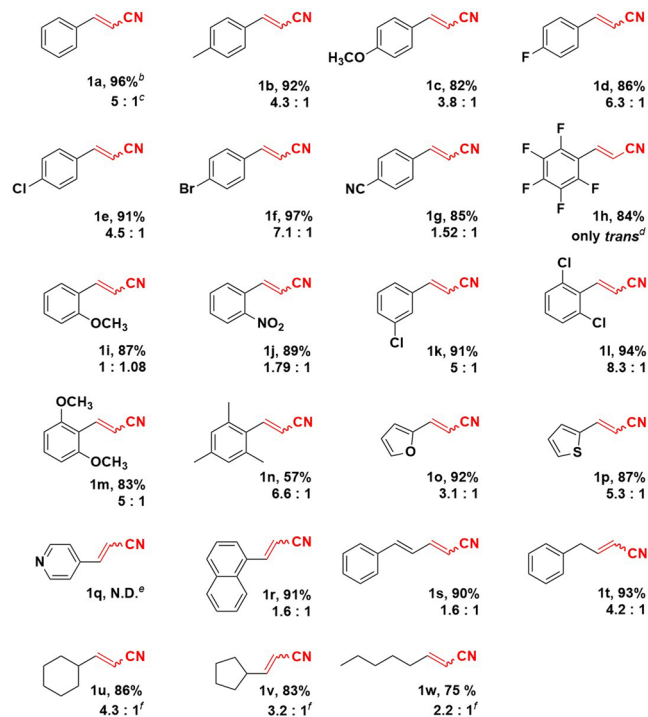
^aReactions were run with benzaldehyde (0.5 mmol, 1.0 equiv), N₂CHCN (2.0 equiv), PPh₃, and the catalyst (1 mol %) in solvent (5 mL) under N₂ for 12 h. ^bIsolated yield. ^cThe ratio of *trans*/*cis* isomers was determined by GC or ¹H NMR. ^dDCM: dichloromethane, THF: tetrahydrofuran. ^eWithout catalysts. ^fN.D. = not determined, N.R. = not reaction. ^gWithout PPh₃.

disfavored the reaction and toluene was most suitable for it. Additionally, the effect of the amount of PPh₃ versus benzaldehyde on the reaction was investigated (entries 13–15), and the results showed that 2 equiv of PPh₃ could significantly promote the transformation, giving the yield of up to 96%. It should be noted that the control reaction gave no olefination product (entry 16), and no benzaldehyde

consumption was observed in the absence of PPh₃ (entry 17), indicating that PPh₃ was necessary for the reaction. Other inexpensive and commercially available metal catalysts, such as FeCl₂, FeSO₄, and Fe(OAc)₂, etc., were also investigated (entries 18–23), but they could not work for this conversion. Based on these results, we obtained the optimization condition which was listed in entry 14, Table 1.

With the optimal reaction conditions in hand, the substrate scope of this olefination reaction was then examined. A variety of aldehydes underwent this transformation smoothly to give the alkenyl nitriles in high yields, as shown in Scheme 2. Most

Scheme 2. Substrate Scope of Aldehydes with N_2CHCN for the Olefination^a



^aReactions were run with aldehydes (0.5 mmol, 1.0 equiv), N_2CHCN (2.0 equiv), PPh_3 , and $PcFe(II)$ (1 mol %) in toluene (5 mL) under N_2 for 12 h. ^bIsolated yield. ^cThe ratio of *trans/cis* isomers was determined by 1H NMR. ^dOnly *trans*-isomer was isolated. ^eN.D. = not determined. ^fThe ratio of *trans/cis* isomers in reaction mixture was determined by GC.

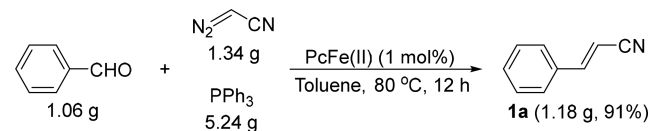
of the aryl aldehydes bearing electron-donating and -withdrawing groups performed very well, giving the corresponding products in high yields of 82%–97% (**1a**–**1n**). Among them, the extremely electron-deficient pentafluorobenzaldehyde obviously favored this reaction and provided a high yield (84%, **1h**). The steric hindrance at the 2-position of aryl aldehyde could not lower the yields (**1i** and **1j**); even the larger spatial hindrance at both 2,6-positions on the benzene ring is still beneficial for the reaction (**1l** and **1m**) with the exception of mesitaldehyde affording its product in relatively low yield of 57% (**1n**). Aromatic heterocyclic furfural and formylthiophene were compatible with the current catalytic system and gave the high yields of 92% and 87% (**1o** and **1p**), while the reaction of 2-formylpyridine did not work (**1q**), which may be due to the axial coordination of pyridyl nitrogen atom and central iron atom of $PcFe(II)$ and then totally deactivating its activity of the catalyst. Polycyclic 1-naphthalenecarboxaldehyde also generated the olefination product in excellent yield (91%, **1r**). α,β -Unsaturated cinnamaldehyde was smoothly converted to the corresponding product (90% yield, **1s**). Aliphatic aldehydes were also good substrates; for example, phenylacetaldehyde obtained the desired product with the yield of up to 93% (**1t**), cyclohexanecarbaldehyde and cyclopentanecarbaldehyde provided the high yields (86%, **1u**; 83%, **1v**), and

hexanal was converted into its alkenyl nitrile with 75% yield (**1w**). Unfortunately, ketones were proved to be unsuitable for this transformation.

Additionally, two other diazoacetone nitriles, 2-diazo-3-oxo-3-(*p*-tolyl)propanenitrile¹¹ (CAS No. 126893-71-8) and 2-diazo-2-phenylacetone nitrile¹² (CAS No. 61766-63-0), were tested for the current reaction with benzaldehyde, but no olefination products were found.

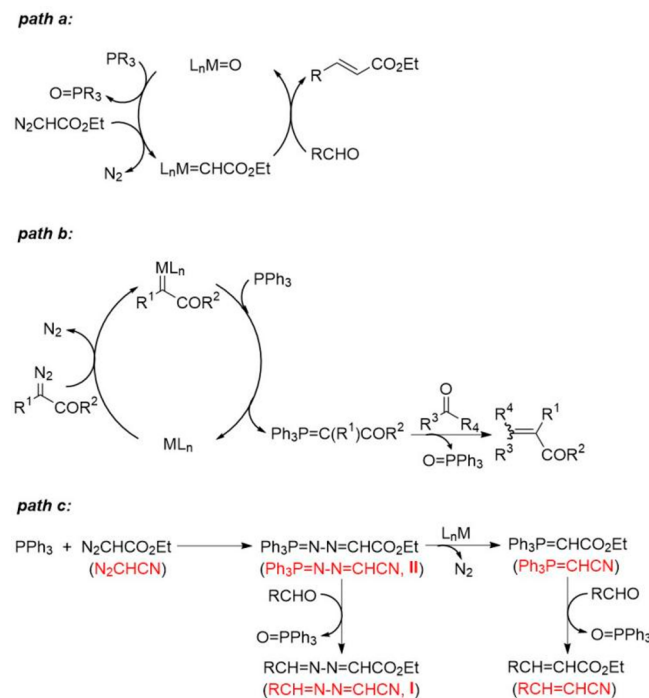
Furthermore, the potential of this reaction in large-scale synthesis was further investigated. The template reaction can be easily performed on a gram-scale to give 1.18 g of **1a** with a high yield of 91% (Scheme 3), which showed the synthetic application of this method.

Scheme 3. Gram-Scale Synthesis of **1a**



There are three possible mechanisms for the olefination of aldehydes with diazo reagents catalyzed by transition-metal complexes (Scheme 4).^{13,14} Most of these olefination reactions

Scheme 4. Three Possible Reaction Pathways for the Olefination of Aldehydes with Diazo Compounds Catalyzed by Transition-Metal Complexes



undergo path a or path b; only two examples via path c were reported by Lu¹⁴ and our group,¹⁵ respectively. In the current catalytic system, we observed that their 1H NMR spectrum of $PcFe(II)$ was exactly the same when diazoacetone nitrile exists and does not. This indicates that $PcFe(II)$ could not react with diazoacetone nitrile to form iron-carbene species or the generated carbene species is too reactive to be detected by 1H NMR.

In the absence of $PcFe(II)$ (Table 1, entry 16), no olefin product could be detected, but the reaction could still proceed

to produce azine $\text{PhCH}=\text{N}-\text{N}=\text{CHCN}$ (I) and $\text{O}=\text{PPh}_3$, which were observed by gas chromatography-mass spectrometry (GC-MS) (Figure S1, Supporting Information). We then prepared azine I (for its characterization, see the Supporting Information) and found it did not react with PcFe(II) to generate olefin detected by GC-MS. This implies that azine I is not the intermediate of the current olefination reaction. On the other hand, PPh_3 can react with N_2CHCN to form phosphazine $\text{Ph}_3\text{P}=\text{N}-\text{N}=\text{CHCN}$ II, which can be detected by high-performance liquid chromatography-mass spectrometry (HPLC-MS) (Figure S2, Supporting Information). Then the direct reaction of prepared phosphazine II (for its characterization, see Supporting Information) and PcFe(II) (1 mol % relative to II) in CDCl_3 was performed, and its ^{31}P NMR changes of the reaction were shown in Figure 1. A small

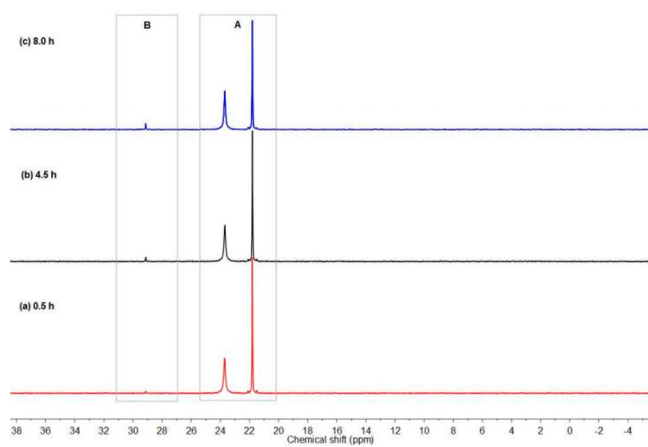


Figure 1. ^{31}P NMR changes of the reaction mixture of phosphazine II and PcFe(II) in CDCl_3 at room temperature: (A) phosphazine II ($\delta = 23.70$ ppm, 21.80 ppm); (B) phosphorus ylide ($\delta = 29.12$ ppm).

amount of phosphorus ylide $\text{Ph}_3\text{P}=\text{CHCN}$ at $\delta = 29.12$ ppm (Figure 1, signal B) could be monitored after 0.5 h. After some time, the amount of phosphazine II (signal A) decreased gradually, and the ylide concentration increased. This demonstrates that PcFe(II) can catalyze the transformation of phosphazine II to a phosphorus ylide. The chemical shift and peak shape of signal B are consistent with those of the commercial ylide sample (Figure S3, Supporting Information), and it herein should be noted that the peak at $\delta = 23.15$ ppm for the phosphorus ylide in Figure 1 disappeared due to the overlap of it and the peak at $\delta = 23.70$ ppm for the phosphazine II. Then the ylide reacts with aldehydes to produce olefins via Wittig reaction.¹⁶ Subsequently, the reaction of prepared phosphazine II (1 equiv) and benzaldehyde (1 equiv) in the presence of PcFe(II) (1 mol % relative to benzaldehyde) in toluene at 80 °C for 12 h obtains the isolated yield of 95% and *trans/cis* ratio of 5/1 as entry 14 of Table 1 (Figure S4, Supporting Information). The prepared phosphazine II reacts with benzaldehyde to generate the azine I detected by GC-MS. Therefore, the current transformation is proposed to take place via a phosphazine II to ylide route, similar to the mechanism suggested by Lu¹⁴ and our group.¹⁵

Based on the above results, a possible pathway for the current catalytic system is that diazoacetonitrile first reacts with PPh_3 to produce the phosphazine II, which is then decomposed into phosphorus ylide and dinitrogen released

in the presence of PcFe(II) . Finally the ylide reacts with aldehydes to form olefins (see the red marks in path c, Scheme 4).

For the Wittig reaction, higher temperatures usually tend to yield a *trans* isomer. Nevertheless, the current reactions at 25 and 40 °C (Table 1, entries 6 & 7) give higher *trans*-selectivities than those at 60, 80, and 110 °C (Table 1, entries 1, 8, & 9). This phenomenon seems abnormal. The reported calculations reveal that *trans*-oxaphosphetane derived from the stabilized ylide ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{CH}_3$) and benzaldehyde is more stable than *cis*-oxaphosphetane.¹⁷ In our current reactions, $\text{Ph}_3\text{P}=\text{CHCN}$ is also a stabilized ylide, which reacts with benzaldehyde to give the *trans*-product as the major product at low and high temperature. Furthermore, the formation of *cis*-product may be largely affected by temperature, resulting in higher *trans/cis* ratio at low temperatures, while at higher temperature, the *trans/cis* ratio decreases relatively.

CONCLUSION

In summary, we have developed a novel and efficient method for the construction of alkenyl nitriles by the olefination of aldehydes with diazoacetonitrile catalyzed by iron(II) phthalocyanine, and this approach can give their corresponding products with high yields and is also suitable for gram-scale synthesis. The transformation of phosphazine to ylide by PcFe(II) is involved in its mechanism.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all solvents and chemicals were reagent grade. Column chromatography was performed by using 200–300 mesh silica gel. Yields are based on the pure products isolated. The diazoacetonitrile was prepared according to the reported method.¹⁸ All ^1H , ^{13}C , and ^{31}P NMR spectra were recorded on a Bruker Avance III 400 MHz NMR spectrometer with tetramethylsilane (TMS) as internal reference in δ scale downfield from TMS. Coupling constants (*J*) were reported in hertz (Hz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; dt, double triplet; and m = multiplet. High-resolution mass spectrometry (HR-MS) electrospray ionization (ESI) mass spectra were recorded on an Agilent 1290/6545 UPLC-TOF/MS spectrometer. GC-MS and HPLC-MS analyses were conducted on an Agilent 8890–7000 and an Agilent 1290/6545 UPLC-TOF/MS apparatus, respectively.

General Procedure for the Olefination of Aldehydes with Diazoacetonitrile Catalyzed by Iron(II) Phthalocyanine PcFe(II) . A 0.5 mmol amount of aldehyde, 262 mg (1.0 mmol) of PPh_3 , and 2.84 mg (1 mol %) of PcFe(II) were placed into a reaction flask and dissolved in 5 mL of toluene at 80 °C under N_2 . A solution of 67 mg (1 mmol) of diazoacetonitrile in 1 mL of toluene was added dropwise over approximately 2 min to the reaction mixture with vigorous stirring. After 12 h, the solvent was removed *in vacuo*. The residue was separated through column chromatography using EtOAc/n -hexane as eluent, and then the desired target product was obtained upon evaporation of the solvent.

Procedure for the Preparation of Diazoacetonitrile.¹⁸ 2-Aminoacetonitrile hydrochloride (4.63 g, 50 mmol) was dissolved in water (10 mL) in a 100 mL round-bottomed flask immersed in an ice–water bath, and then CH_2Cl_2 (20 mL) was

added. The mixture was stirred vigorously, and NaNO₂ (3.45 g, 50 mmol) was added over 10 min. After being stirred for another 1 h, the mixture was extracted with CH₂Cl₂ (50 mL), and the organic layer was washed with brine and dried over Na₂SO₄. Removing the solvent at 0 °C under vacuum gave N₂CHCN as a yellow liquid (1.98 g, 59% yield), and then it is formulated into a 1.0 M toluene solution for storage and use.

Procedure for the Preparation of 2-Diazo-3-oxo-(*p*-tolyl)propanenitrile.¹¹ Ten millimoles of *p*-toluoyl chloride was added to the solution of 0.67 g (10 mmol) of diazoacetonitrile and 1.4 mL (10 mmol) of Et₃N in 50 mL of CH₂Cl₂ at −10 to 0 °C. After stirring at this temperature for 2 h, the reaction mixture was washed by 3 × 50 mL of water. The organic layer was dried by Na₂SO₄ and concentrated under reduced pressure at 20 °C. The product was purified by column chromatography using CH₂Cl₂/petroleum (9:1, v/v) to yield a yellow liquid (1.11 g, 60% yield).

Procedure for the Preparation of 2-Diazo-2-phenylacetoneitrile.¹² The aqueous solution of 2-amino-2-phenylacetoneitrile hydrochloride (1.68 g, 10 mmol) and diethyl ether (10 mL) was cooled to 0 °C, and this solution was treated with an aqueous solution (2.5 mL) of NaNO₂ (0.83 g, 12 mmol). To this mixture was added concentrated HCl (50 μL), and the reaction mixture was stirred for an additional 15 min. The solution was extracted with diethyl ether (5 mL), and the ether extracts were washed with 10% aqueous Na₂CO₃. The extract was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using CH₂Cl₂/*n*-pentane (3:17, v/v) to afford 2-diazo-2-phenylacetoneitrile as a red viscous oil (227 mg, 16% yield).

Procedure for the Preparation of Azine.¹⁴ A mixture of benzaldehyde (53 mg, 0.5 mmol), diazoacetonitrile (67 mg, 1 mmol), and PPh₃ (262 mg, 1 mmol) in toluene (5 mL) was refluxed for 5 h. After removal of the solvent, the residue was separated by column chromatography using EtOAc/*n*-hexane (1:20, v/v), giving a yellow oil (49 mg, 62% yield).

Procedure of the Preparation of Phosphazene.¹⁹ PPh₃ (1311 mg, 5.0 mmol) was dissolved in 20 mL of *n*-pentane. Diazoacetonitrile (335 mg, 5 mmol) was added to the clear mixture, and then, the solution was stirred for 8 h. The resulting solid was filtered and washed three times with cold *n*-pentane, giving a white powder (1205 mg, 73% yield).

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c06029>.

Characterization data and copies of ¹H, ¹³C, ¹⁹F, and ³¹P NMR as well as GC-MS, HPLC-MS spectrum (PDF)

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Notes

The authors declare no competing financial interest.

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