Diastereoselective [Cu(MeCN)₄BF₄/BF₃·Et₂O]-Catalyzed Cyclopropenation of Alkynes: Asymmetric Synthesis of β-Amino-α-cyclopropenyl Phosphonates

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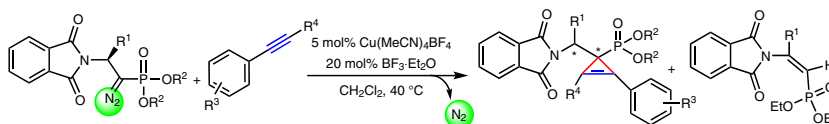
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Abstract The diastereospecific formation of β-amino-α-cyclopropenyl phosphonates has been achieved in moderate yields from the cyclopropenation of 1-alkynes with dialkyl α-diazophosphonates. The reaction was performed by using a combined catalyst consisting of Cu(MeCN)₄BF₄ and BF₃·Et₂O as additive in dichloromethane at 40 °C. A possible mechanism for the reaction has been proposed to explain the origin of the activation and the asymmetric induction. This method provides a versatile approach to β-amino-α-cyclopropenylphosphonates containing a quaternary stereogenic center with good efficiency and diastereoselectivity.

**Key words** cyclopropenation, α-diazophosphonates, asymmetric synthesis, cyclopropenylphosphonates, Cu(MeCN)₄BF₄/BF₃·Et₂O

Cyclopropenes are a unique class of the smallest ring compound with a double bond, and the combination of high strain and unsaturation renders cyclopropenes as versatile synthons in a wide variety of organic synthesis.[1] To enhance the synthetic potential of cyclopropenes further, the development of expeditious methods for their synthesis is highly desirable.[2] One of the most efficient catalytic asymmetric methods for their preparation involves the reaction of alkynes with diazo compounds using chiral copper(I),[3] iridium(II),[4] cobalt(II),[5] or rhodium(II)[6] catalysts. Diazo compounds are commonly used in formation of metallocarbenoids, which can subsequently undergo diverse chemical transformations.[7] In 1992, Doyle, Müller and co-workers reported the first cyclopropenation reactions of diazoacetates with terminal alkynes using [Rh₂(5S-mepy)₄] as a chiral catalyst.[8] Corey and co-workers also reported a sig-

nificantly improved enantioselective cyclopropenation of ethyl diazoacetate with 1-alkynes using a new rhodium complex, Rh₂(OAc)(DPTI)₃, as a catalyst.[9] Although high levels of enantioselectivity (up to 99% *ee*) in cyclopropenations of terminal alkynes with aryldiazoacetates under catalysis by [Rh₂(S-dosp)₄] have been reported by Davies and co-workers,[10] stereoselective syntheses of the corresponding cyclopropenylphosphonates using such a strategy remain scarce.[11]

α-Diazophosphonates are phosphorus analogues of α-diazoacetates, and therefore could undergo a range of chemical transformations and the synthesis of varieties of functionalized phosphorous compounds.[12] In 2013, Charette and co-workers reported the first catalytic asymmetric synthesis of bis-acceptor cyclopropylphosphonates through the reaction of α-cyano diazophosphonates with allenes catalyzed by Rh₂(S-IBAZ)₄ under mild reaction conditions.[13] Cyclopropylphosphonates demonstrate a range of biological and biochemical properties.[14] By analogy with cyclopropylphosphonates,[15] the development of efficient methods for the preparation of cyclopropenephosphonates is attracting increasing attention. In particular, the presence of a quaternary stereocenter in a highly substituted cyclopropenephosphonate can lead to interaction with certain proteases and a resistance to proteolytic degradation.[14]

Recently, we reported novel α-diazophosphonyl compounds prepared from natural amino acids that be used to could perform combined C–H functionalization and O–H insertion to form tertiary β-alkoxy-substituted β-aminophosphonates (Scheme 1, Eq. 1).[16] As a natural extension of the combined C–H functionalization/O–H insertion reaction, we have developed a regioselective boron trifluoride-catalyzed C–H functionalization/S–H insertion reaction for

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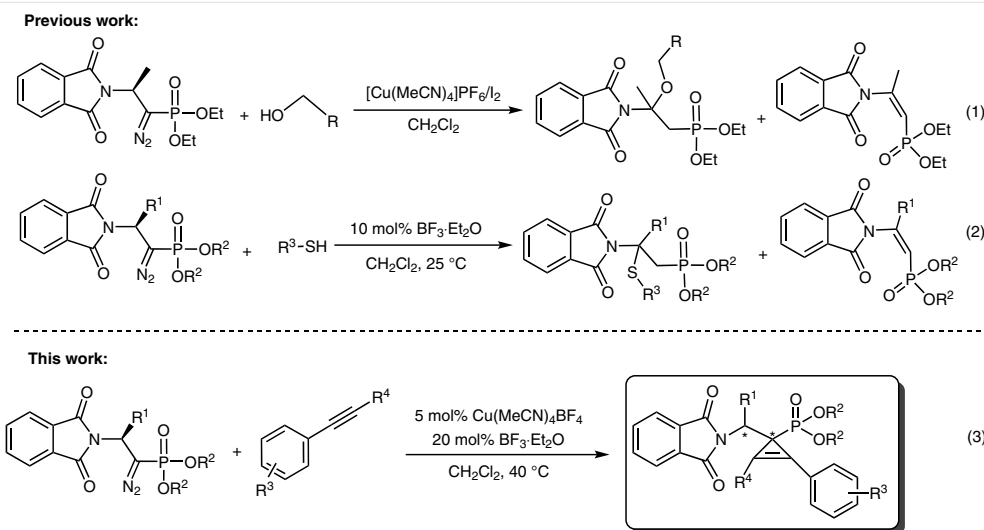
Scheme 1 Previous and proposed work

the synthesis of *N,S*-acetals containing quaternary centers (Scheme 1, Eq. 2).[17] In a continuation of our interest in the chemistry of aminophosphorus derivatives,[18] we herein report the first example of the conversion of dialkyl α-diazophosphonates into cyclopropenylphosphonate derivatives catalyzed by tetrakis (acetonitrile)copper(I) tetrafluoroborate/boron trifluoride [Cu(MeCN)$_4$BF$_4$/BF$_3$·Et$_2$O] in a highly diastereoselective manner (Scheme 1, Eq. 3).

We began our investigations by studying the reaction of diethyl α-diazophosphonate **1a**[16] with phenylacetylene **2a** in the presence of catalyst in dichloromethane at 25 °C (Table 1). The results revealed that transition-metal catalysts such as Rh$_2$(OAc)$_4$ and Hg(OTf)$_2$ did not decompose **1a** in the presence of **2a** (entries 1 and 2). The other catalysts tested (e.g., CuOTf, AgOTf, and Cu(MeCN)$_4$PF$_6$) could be used to promote the reaction, resulting in low yields of product with moderate diastereoselectivities (entries 3–5). To our delight Cu(MeCN)$_4$BF$_4$ catalyzed the decomposition of **1a**, and diethyl(2-(phenyl-cycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)phosphonate (**3a**) was obtained with good diastereoselectivity (*dr* = 12:1) in 29% yield (entry 6). In addition, a 1,2-hydrogen migration by-product (*Z*)-diethyl(2-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl) phosphonate (**4a**) was obtained in 9% yield. The molecular structure of **3a** was determined based on ¹H, ³¹P, ¹³C NMR, and 2D NMR spectroscopy and mass spectrometry.[19] This result encouraged us to choose Cu(MeCN)$_4$BF$_4$ as the catalyst for further optimization of the reaction conditions. To improve the reactivity and diastereoselectivity, the effects of different additives and solvents were investigated.

Initially, additives were evaluated to study the diastereoselectivity of this transformation. As shown in Table 1, both the diastereoselectivity and the ratio of the two products **3a** and **4a** was affected dramatically by the additive. In the presence of Cu(MeCN)$_4$BF$_4$ as the catalyst (5 mol%) and

BF$_3$·Et$_2$O (20 mol%) as the additive in dichloromethane, the reaction proceeded with an increased combined yield and good diastereoselectivity (*dr* = 12:1) (entry 7). Furthermore, we found that high temperatures favored this reaction. When the reaction was carried out at 40 °C, the desired product **3a** could be obtained in 66% yield (entry 8). After screening BF$_3$·Et$_2$O, it was found that acetone, CH$_3$CN, DMF, and iodine did not give superior results in terms of either reactivity or stereoselectivity (entries 9–12).

With the optimum combination of Cu(MeCN)$_4$BF$_4$ catalyst and BF$_3$·Et$_2$O additive, we next carried out the reaction in different solvents to determine the best solvent for this reaction. Toluene, THF, DME, and 1,2-dichloroethane all provided lower yields of the desired products **3a** and **4a** with moderate diastereoselectivities (Table 1, entries 13–16). This screening therefore identified CH$_2$Cl$_2$ as the optimal solvent for this reaction. Furthermore, a decrease in the catalyst loading to 2 mol% Cu(MeCN)$_4$BF$_4$ and 10 mol% BF$_3$·Et$_2$O led to a decrease in both yield and diastereoselectivity (entry 17). A similar result was obtained when the reaction was performed in CH$_2$Cl$_2$ with increased catalyst loading to 10 mol% Cu(MeCN)$_4$BF$_4$ and 30 mol% BF$_3$·Et$_2$O (entry 18). Thus, the optimal reaction conditions for this transformation were determined to be 0.28 mmol α-diazo phosphonate **1a**, 5.0 equivalents of phenylacetylene **2a**, 5 mol% Cu(MeCN)$_4$BF$_4$ and 20 mol% BF$_3$·Et$_2$O as co-catalyst in 6 mL CH$_2$Cl$_2$ as solvent at 40 °C.

Under the optimal reaction conditions, the substrate scope of this reaction was investigated (Table 2). The impact of different groups on the β-position of dialkyl α-diazophosphonates **1** was evaluated. α-Diazophosphonates **1a–e** with different substituents in the β-position, such as methyl, benzyl, isobutyl, ethyl, and 4-acetoxybenzyl groups, afforded moderate yields of the β-amino-α-cyclopropenylphosphonates **3a–e** and the 1,2-hydride migration products

Table 1 Optimization of the Reaction Conditions[a]
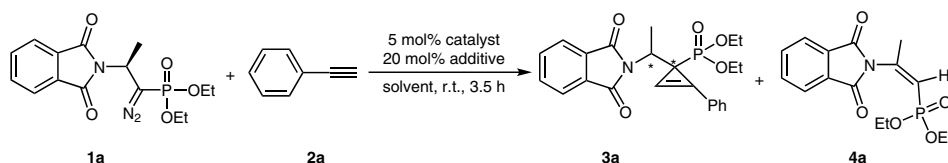
Entry	Catalysts	Additive	Solvent	(3a:4a) ratio[b]	Overall yield (%)[c]	Yield 3a (%)[d]	dr[e]
1	Rh$_2$(OAc)$_4$	–	CH$_2$Cl$_2$	–	N.R.	N.R.	–
2	Hg(OTf)$_2$	–	CH$_2$Cl$_2$	–	N.R.	N.R.	–
3	CuOTf	–	CH$_2$Cl$_2$	63:37	<10	<10	8:1
4	AgOTf	–	CH$_2$Cl$_2$	57:43	<10	<10	10:1
5	Cu(MeCN)$_4$PF$_6$	–	CH$_2$Cl$_2$	60:40	23	14	12:1
6	Cu(MeCN)$_4$BF$_4$	–	CH$_2$Cl$_2$	77:23	38	29	12:1
7	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	CH$_2$Cl$_2$	78:22	42	33	12:1
8[f]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	CH$_2$Cl$_2$	82:18	81	66	12:1
9	Cu(MeCN)$_4$BF$_4$	CH$_3$COCH$_3$	CH$_2$Cl$_2$	75:25	28	21	10:1
10	Cu(MeCN)$_4$BF$_4$	CH$_3$CN	CH$_2$Cl$_2$	70:30	33	23	>25:1
11	Cu(MeCN)$_4$BF$_4$	DMF	CH$_2$Cl$_2$	78:22	25	20	15:1
12	Cu(MeCN)$_4$BF$_4$	iodine	CH$_2$Cl$_2$	64:36	40	26	13:1
13[f]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	toluene	76:24	38	29	16:1
14[f]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	THF	80:20	47	38	15:1
15[f]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	DME[g]	78:22	42	33	10:1
16[f]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	1,2-dichloroethane	82:18	42	34	12:1
17[f,h]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	CH$_2$Cl$_2$	68:32	44	30	8:1
18[f,i]	Cu(MeCN)$_4$BF$_4$	BF$_3$·Et$_2$O	CH$_2$Cl$_2$	66:34	51	34	10:1

[a] Unless otherwise specified, all reactions were carried out using α-diazophosphonate **1a** (0.28 mmol, 1 equiv) and phenylacetylene **2a** (1.40 mmol, 5 equiv) in the specified solvent (6 mL) with 5 mol% catalyst and 20 mol% additive at 25 °C for 3.5 h (addition over 1.5 h, then a further 2 h).
[b] The product ratio was determined by ^{31}P NMR spectroscopic analysis of the crude product.
[c] Overall yield of the mixture of **3a** and **4a** after silica gel chromatograph.
[d] Yield of isolated product.
[e] Diastereomeric ratio (dr) based on ^{31}P NMR spectroscopic analysis of the isolated product **3a**.
[f] Reaction temperature 40 °C.
[g] DME = dimethoxyethane.
[h] 2 mol% Cu(MeCN)$_4$BF$_4$ and 10 mol% BF$_3$·Et$_2$O were used.
[i] 10 mol% Cu(MeCN)$_4$BF$_4$ and 30 mol% BF$_3$·Et$_2$O were used.

4a–e (entries 1–5). It is worth noting that diethyl α-diazophosphonate **1f**, derived from methionine, did not undergo reaction to give the desired products, probably due to the fact that the sulfur atom coordinates with the copper(I) and hinders the reaction (entry 6). Instead, the starting material **1f** decomposed under the reaction conditions. In addition to phenylacetylene, 3-methylphenyl acetylene and 4-methylphenylacetylene were also examined in the cyclopropenation reaction with carbenoids derived from dialkyl α-diazophosphonates **1b** and **1g**. Electron-rich phenylacetylene derivatives, substituted either at the *meta*-, or *para*-position, all provided good yields and diastereoselectivities of the corresponding β-amino-α-cyclopropenylphosphonates (entries 7 and 8). Chiral cyclopropene derivatives **3i** and **3j** from reactions of aromatic alkynes containing both electron-withdrawing and -donating groups at the *para*-posi-

tion could also be obtained in poor yields but with good diastereoselectivities (entries 9 and 10). The cyclopropenation could also be conducted on the internal alkyne prop-1-ynyl-benzene **2f** with excellent diastereoselectivity (>30:1), albeit in diminished yield (11%), presumably due to the steric effect (entry 11).

To assess the effects of the substrate on product selectivity, we set out to study the reactions of a series of dialkyl α-diazophosphonates **1h–l** under Cu(MeCN)$_4$BF$_4$/BF$_3$·Et$_2$O catalysis. When the steric bulk of the R^2 group was increased from methyl to isopropyl or *n*-butyl, similar yields were obtained. These results showed that the size of the R^2 group on the α-diazophosphonates **1** has almost no influence on reactivity in this cyclopropenation reaction (Table 2, entries 12–16). The method was successful for alkynes that are conjugated to an arene. However, cyclopropene

Table 2 Scope of the Reaction[a]
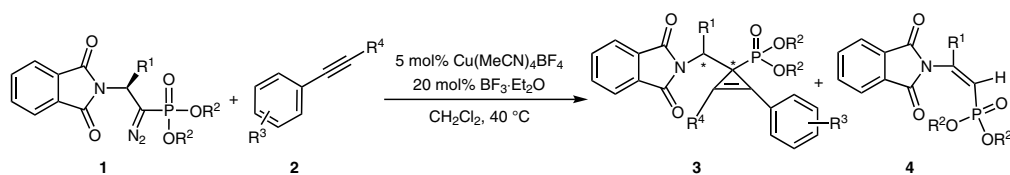
Entry	Product	R¹	R²	R³	R⁴	3/4 Ratio[b]	Overall yield (%)[c]	Yield 3 (%)[d]	dr[e]
1	**3a**	CH_3 (**1a**)	CH_2CH_3	H (**2a**)	H	82:18	81	66	12:1
2	**3b**	$CH_2C_6H_5$ (**1b**)	CH_2CH_3	H (**2a**)	H	78:22	74	58	>30:1
3	**3c**	$CH_2CH(CH_3)_2$ (**1c**)	CH_2CH_3	H (**2a**)	H	83:17	67	56	16:1
4	**3d**	CH_2CH_3 (**1d**)	CH_2CH_3	H (**2a**)	H	81:19	74	60	8:1
5	**3e**	p-$AcOC_6H_4$ (**1e**)	CH_2CH_3	H (**2a**)	H	84:16	64	54	>30:1
6	**3f**	$CH_2CH_2SCH_3$ (**1f**)	CH_2CH_3	H (**2a**)	H	–	N.R.	–	–
7	**3g**	$CH_2C_6H_5$ (**1b**)	CH_2CH_3	3-CH_3 (**2b**)	H	81:19	76	62	12:1
8	**3h**	$CH_2C_6H_5$ (**1g**)	n-Bu	4-CH_3 (**2c**)	H	82:18	78	64	12:1
9	**3i**	CH_3 (**1a**)	CH_2CH_3	4-F (**2d**)	H	61:39	31	19	30:1
10	**3j**	$CH_2C_6H_5$ (**1b**)	CH_2CH_3	4-OMe (**2e**)	H	45:55	55	25	31:1
11	**3k**	CH_3 (**1a**)	CH_2CH_3	H (**2f**)	CH_3	33:67	33	11	>30:1
12	**3l**	CH_3 (**1h**)	CH_3	H (**2a**)	H	86:14	64	55	15:1
13	**3m**	$CH_2C_6H_5$ (**1i**)	CH_3	H (**2a**)	H	88:12	75	66	>30:1
14	**3n**	$CH_2C_6H_5$ (**1j**)	i-Pr	H (**2a**)	H	82:18	73	60	12:1
15	**3o**	CH_3 (**1k**)	n-Bu	H (**2a**)	H	87:13	77	67	21:1
16	**3p**	$CH_2C_6H_5$ (**1l**)	n-Bu	H (**2a**)	H	82:18	73	60	>30:1

[a] Reaction conditions: α-diazophosphonate **1** (0.28 mmol) and **2** (1.40 mmol, 5 equiv) in CH_2Cl_2 (6 mL) at 40 °C in the presence of 5 mol% $Cu(MeCN)_4BF_4$ and 20 mol% $BF_3 \cdot Et_2O$ for 3.5 h (addition over 1.5 h, then a further 2 h).
[b] The product ratio was based on ^{31}P NMR spectroscopic analysis of the crude product.
[c] Overall yield of the mixture of **3** and **4** after silica gel chromatography.
[d] Yield of isolated product.
[e] Diastereomeric ratio (dr) based on ^{31}P NMR spectroscopic analysis of the isolated product **3a**.

products were not obtained when diethyl α-diazophosphonate **1a** was reacted with (triisopropyl)silylacetylene or 1-hexyne.

A stepwise mechanism for the formation of the cyclopropenylphosphonates is outlined in Scheme 2. Firstly, α-diazophosphonate **1** releases N_2 under the influence of the Cu catalyst on heating, affording Cu-carbenoid **A**.[20] The role of the strong Lewis acids ($BF_3 \cdot Et_2O$) could be to coordinate to the copper to give metallocarbenoid **B** in order to make the α-diazo position more electron deficient. Carbenoid **B** is then trapped by the triple bond of ethynylbenzene to give vinyl cation **C**. Subsequent cleavage of the C–Cu bond of intermediate **C** with delivery of the electrons to the vinyl cation leads to cyclopropenyl phosphonate **3** with simultaneous regeneration of the Cu(I) catalyst and $BF_3 \cdot Et_2O$. Intermediate **B** may also be transformed into by-product **4** through loss of $Cu(MeCN)_4BF_4$ and $BF_3 \cdot Et_2O$ before the attack of phenylacetylene **2a**.

The diastereoselectivity observed in generating the cyclopropenyl phosphonates implies that conformational factors may play a role in the cyclopropenation process. In fact, the stereoselectivity can be attributed to steric hindrance between the phosphonate group and the R¹ group, with attack occurring on the back face of the carbenoid preferentially. In forming intermediate **C**, the terminal alkyne carbon is involved in C–C bond formation with the carbenoid carbon, while positive charge build-up occurs at the internal sp-carbon. Furthermore, the second C–C bond forms with inversion of the carbenoid center. This model is partly consistent with the observed sense of asymmetric induction, but there are a few anomalies. For instance, isopropyl phosphonate **1j** leads to lower dr than methyl phosphonate **1i** (Table 2, entries 13 and 14).

In conclusion, we have developed a $Cu(MeCN)_4BF_4/BF_3 \cdot Et_2O$-catalyzed cyclopropenation of 1-alkynes with dialkyl α-diazophosphonates to synthesize β-amino-α-cyclopropenyl phosphonates in moderate yields with good to excellent diastereoselectivities. The observed sense of asymmetric induction is rationalized by invoking steric hindrance between the phosphonate group and the R¹ group of the α-diazophosphonate. The present catalytic protocol provides attractive and easy access to β-amino-α-

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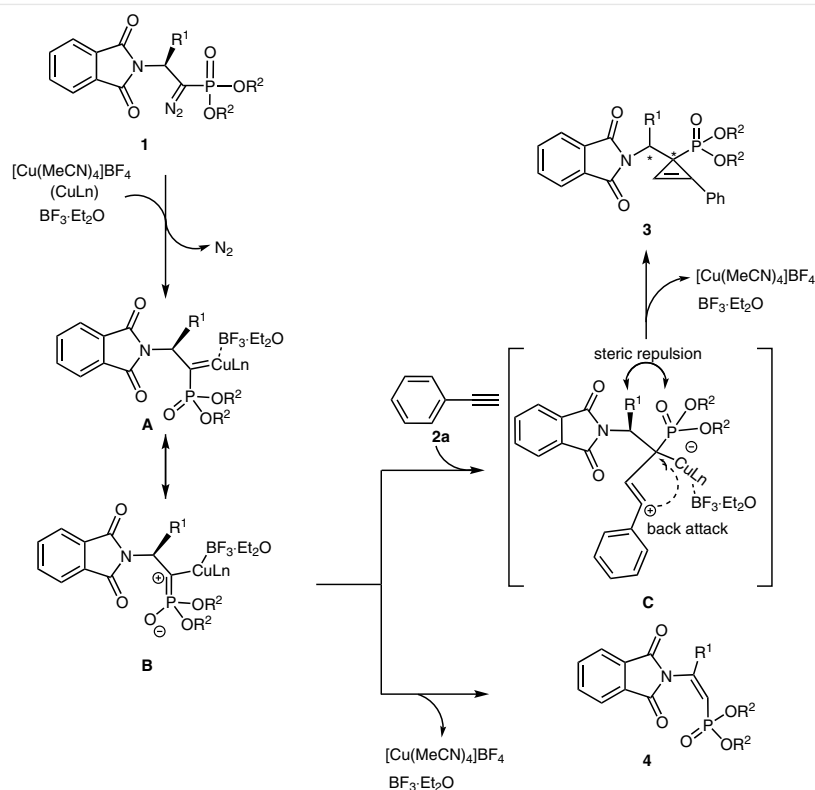
Scheme 2 Proposed reaction mechanism

cyclopropenyl phosphonates containing a quaternary stereogenic center. Further studies to explore the enantioselective synthesis of cyclopropenyl phosphonates are in progress in our laboratory.

All reactions and manipulations were performed using standard Schlenk techniques. Solvents were dried and distilled prior to use according to standard methods. Unless otherwise indicated, all materials were obtained from commercial sources, and used as purchased without dehydration. Flash column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, China). Nitrogen gas (99.999%) was purchased from Boc Gas Inc. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded in CDCl$_3$ with Bruker 400 MHz spectrometers, TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR and ^{13}C NMR, H$_3$PO$_4$ served as internal standard (δ = 0 ppm) for ^{31}P NMR. Mass spectra were recorded with a LCQ advantage spectrometer with ESI resource. HRMS were recorded with a PEXII and ZAB-HS spectrometer.

Preparation of 3 and 4; General Procedure

In an oven-dried Schlenk tube, [Cu(MeCN)$_4$]BF$_4$ (0.014 mmol) and BF$_3$·Et$_2$O (0.056 mmol) were dissolved in freshly distilled CH$_2$Cl$_2$ (4 mL) under nitrogen, the requisite phenylacetylene **2** (1.4 mmol) was added and the solution was stirred for 30 min at 25 °C. α-Diazophosphonate **1** (0.28 mmol) dissolved in CH$_2$Cl$_2$ (2 mL) was then added to the reaction mixture dropwise over a period of 1.5 h by using a syringe pump. When the addition was complete, the reaction mixture

was stirred for a further 2 h at 40 °C. The solvent was then removed under reduced pressure and the crude residue was purified by silica gel chromatography, eluting with CH$_2$Cl$_2$/EtOAc (15:1) to afford the corresponding products **3** and **4**.

Diethyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)phosphonate (3a)

Yield: 0.085 g (66%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.61 (dd, J = 5.2, 3.2 Hz, 2 H), 7.56 (dd, J = 5.3, 3.1 Hz, 2 H), 7.49 (d, J = 7.1 Hz, 2 H), 7.16–7.25 (m, 3 H), 7.01 (d, J = 4.1 Hz, 1 H), 5.17–5.27 (m, 1 H, CH), 4.11 (dd, J = 12.8, 5.7 Hz, 4 H), 1.70 (d, J = 7.2 Hz, 3 H), 1.30 (td, J = 7.0, 4.2 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.35, 133.57, 131.51, 129.77, 129.59, 128.30, 125.48, 122.71, 116.00, 97.61, 62.02, 61.88, 47.44 (d, J = 36.5 Hz), 30.15, 28.17, 16.16.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.86.

HRMS (ESI): m/z [M + H]$^{+}$ calcd for C$_{23}$H$_{24}$NO$_5$P: 426.1426; found: 426.1470.

Diethyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)phosphonate (3b)

Yield: 0.086 g (58%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, J = 6.5 Hz, 5 H), 7.11–7.28 (m, 7 H), 7.09 (d, J = 4.0 Hz, 2 H), 5.43 (d, J = 11.0 Hz, 1 H), 4.17 (dd, J = 15.5, 7.7 Hz, 4 H), 3.06–3.83 (m, 2 H), 3.51 (dd, J = 14.2, 4.0 Hz), 1.32–1.38 (m, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 137.33, 133.40, 132.40, 128.71, 128.58, 127.66, 127.30, 125.21, 124.36, 122.66, 121.58, 114.55, 96.66, 61.04, 52.60 (d, *J* = 45.4 Hz), 33.87, 28.68, 15.44.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.57.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{29}$H$_{28}$NO$_5$P: 502.1739; found: 502.1783.

Diethyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-3-methylbutyl)phosphonate (3c)

Yield: 0.078 g (56%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.50–7.60 (m, 4 H), 7.43 (d, *J* = 6.7 Hz, 2 H), 7.08–7.23 (m, 3 H), 6.97 (d, *J* = 4.2 Hz, 1 H), 5.17 (d, *J* = 12.2 Hz, 1 H), 4.31 (t, *J* = 6.7 Hz, 1 H), 4.04–4.15 (m, 4 H), 2.50 (t, *J* = 13.3 Hz, 1 H), 2.34 (t, *J* = 7.4 Hz, 1 H), 1.73 (dd, *J* = 13.2, 9.3 Hz, 3 H), 1.44 (dd, *J* = 15.4, 7.6 Hz, 3 H), 0.88–0.93 (m, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.65, 133.52, 129.68, 129.47, 128.85, 128.26, 125.45, 122.68, 115.62, 97.48, 65.58, 61.97, 50.16 (d, *J* = 36.2 Hz), 37.45, 29.71, 25.44, 23.59, 22.70, 21.11, 16.48, 14.13, 13.74.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.80.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{26}$H$_{30}$NO$_5$P: 468.1895; found: 468.1924.

Diethyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)propyl)phosphonate (3d)

Yield: 0.079 g (60%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54–7.64 (m, 4 H), 7.47 (d, *J* = 6.7 Hz, 2 H), 7.15–7.24 (m, 3 H), 6.99 (d, *J* = 4.2 Hz, 1 H), 4.92–5.03 (m, 1 H), 4.10 (ddd, *J* = 14.5, 11.7, 7.1 Hz, 4 H), 2.35–2.42 (m, 1 H), 2.06–2.14 (m, 1 H), 1.34–1.49 (m, 3 H), 0.87 (dd, *J* = 15.3, 7.9 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.66, 133.56, 131.39, 129.72, 129.52, 128.29, 125.55, 122.71, 115.64, 97.64, 61.97, 53.99 (d, *J* = 36.1 Hz), 22.71, 22.11, 14.14, 11.20.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.94.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{24}$H$_{26}$NO$_5$P: 440.1582; found: 440.1619.

(2-(Diethoxyphosphoryl)-1-(1,3-dioxoisoindolin-2-yl)-2-(phenyl-cycloprop-2-enyl)ethyl)phenyl Acetate (3e)

Yield: 0.087 g (54%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.42–7.49 (m, 5 H), 7.14–7.21 (m, 4 H), 6.96–7.11 (m, 2 H), 6.82–6.86 (m, 2 H), 5.35–5.42 (m, 1 H), 4.13 (dt, *J* = 7.1, 4.7 Hz, 4 H), 3.07–3.94 (m, 1 H), 3.69 (dd, *J* = 14.2, 12.6 Hz, 1 H), 3.47 (dd, *J* = 14.4, 4.2 Hz, 1 H), 2.20 (s, 3 H), 1.32 (dd, *J* = 7.0, 3.5 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 169.37, 149.05, 135.95, 133.67, 133.50, 130.69, 129.75, 129.64, 128.95, 128.33, 125.27, 122.68, 121.36, 115.53, 97.54, 62.07, 53.44 (d, *J* = 36.9 Hz), 34.38, 29.72, 21.10, 16.54.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.52.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{31}$H$_{30}$NO$_7$P: 560.1793; found: 560.1838.

Diethyl(1-(2-*m*-tolylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)phosphonate (3g)

Yield: 0.095 g (62%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.47 (s, 4 H), 7.24 (s, 2 H), 7.11–7.20 (m, 4 H), 7.02–7.09 (m, 3 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 5.35–5.45 (m, 1 H), 4.09–4.19 (m, 4 H), 3.61–3.70 (m, 1 H), 3.47 (dd, *J* = 14.2, 4.2 Hz, 1 H), 2.18 (s, 3 H), 1.33 (td, *J* = 7.0, 3.5 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 138.36, 137.91, 133.38, 130.41, 130.35, 128.70, 128.32, 128.26, 126.90, 126.23, 125.20, 123.70, 122.55, 115.48, 97.31, 62.03, 53.54 (d, *J* = 37.3 Hz), 34.96, 29.71, 21.05, 16.52.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.79.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{30}$H$_{30}$NO$_5$P: 516.1895; found: 516.1912.

Dibutyl(1-(2-*p*-tolylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)phosphonate (3h)

Yield: 0.108 g (64%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (s, 4 H), 7.13–7.27 (m, 5 H), 7.07 (dt, *J* = 10.2, 5.8 Hz, 3 H), 6.96 (d, *J* = 7.4 Hz, 1 H), 5.43 (d, *J* = 12.3 Hz, 1 H), 4.00–4.18 (m, 4 H), 3.64–3.74 (m, 1 H), 3.51 (dd, *J* = 14.3, 4.1 Hz, 1 H), 2.37 (t, *J* = 7.4 Hz, 1 H), 2.21 (s, 3 H), 1.35–1.52 (m, 8 H), 0.94 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 171.20, 138.37, 137.87, 133.36, 130.93, 130.36, 128.85, 128.68, 128.31, 128.21, 126.90, 126.21, 122.54, 97.22, 65.80, 60.42, 53.53 (d, *J* = 37.2 Hz), 34.97, 32.66, 31.93, 29.70, 22.70, 21.07, 18.79, 14.20, 13.65.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.74.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{34}$H$_{38}$NO$_5$P: 572.2521; found: 572.2569.

Diethyl(1-(4-fluorophenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)phosphonate (3i)

Yield: 0.019 g (19%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.50–7.56 (m, 4 H), 7.41 (dd, *J*, 7.41 (dd Hz, 2 H), 6.82–6.89 (m, 3 H), 5.11 (d, *J* = 7.1 Hz, 1 H), 3.97–4.05 (m, 4 H), 1.60 (d, *J*, 1.6 Hz, 3 H), 1.18–1.24 (m, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.30, 133.67, 131.86, 131.78, 131.51, 122.74, 115.57 (d, *J* 168.30 Hz), 97.17, 61.96 (dd, *J* = 18.1, 6.9 Hz), 47.39 (d, *J* z), 47 Hz), 30.20, 28.23, 16.42.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.56.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{23}$H$_{24}$FNO$_5$P: 444.1371; found: 444.1378.

Diethyl(1-(4-methoxyphenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)phosphonate (3j)

Yield: 0.030 g (25%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.40–7.48 (m, 5 H), 7.13–7.19 (m, 4 H), 7.09–7.10 (m, 1 H) 7.05 (t, *J* (t, Hz, 1 H), 6.89 (d, *J* (d, Hz, 1 H), 6.71–6.79 (m, 2 H), 5.38 (d, *J* (d, (Hz, 1 H), 4.12 (dd, *J* (dd, (400 M Hz, 4 H), 3.72 (s, 3 H), 3.62–3.69 (m, 1 H), 3.44–3.53 (m, 1 H), 1.29–1.34 (m, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 160.63, 138.46, 133.38, 131.44, 128.70, 128.29, 126.19, 122.61, 118.09, 115.03, 113.88, 94.80, 61.97, 55.23, 53.68 (d, *J* J60.63 Hz), 34.99, 29.39, 27.40, 16.52, 16.45.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.93.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for C$_{30}$H$_{31}$NO$_6$P: 532.1884; found: 532.1882.

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Diethyl(1-(2-methyl-3-phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)phosphonate (3k)

Yield: 0.011 g (11%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.85–7.87 (m, 2 H), 7.72–7.74 (m, 2 H), 7.58–7.60 (m, 1 H), 7.52–7.54 (m, 1 H), 7.36 (d, J J 7.3 Hz, 1 H), 7.05–7.16 (m, 2 H), 4.98–5.20 (m, 1 H), 4.05–4.15 (m, 4 H), 2.05 (s, 3 H), 1.70 (dd, J , 1.70 (dd, Hz, 3 H), 1.24–1.29 (m, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 167.37, 134.11, 133.43, 131.67, 129.14, 128.25, 128.15, 123.49, 122.63, 108.45, 108.05 61.41, 47.60 (d, J J 47.60 Hz), 29.69, 21.03, 16.58, 15.16, 14.19.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 27.73.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{24}$H$_{26}$NO$_5$P: 440.1621; found: 440.1613.

Dimethyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)phosphonate (3l)

Yield: 0.066 g (55%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54–7.65 (m, 4 H), 7.48 (d, J = 6.7 Hz, 2 H), 7.17–7.26 (m, 3 H), 7.03 (d, J = 4.2 Hz, 1 H), 5.16–5.25 (m, 1 H), 3.77 (dd, J = 10.6, 5.5 Hz, 6 H), 1.72 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.34, 133.58, 131.46, 129.76, 129.69, 128.38, 125.26, 122.73, 115.73, 97.37, 52.84, 52.70, 47.40 (d, J = 37.1 Hz), 16.07.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 29.30.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{21}$H$_{20}$NO$_5$P: 398.1113; found: 398.1148.

Dimethyl(1-(phenyl-cycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenyl-ethyl)phosphonate (3m)

Yield: 0.093 g (66%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.45–7.51 (m, 5 H), 7.13–7.24 (m, 7 H), 7.08 (dd, J = 12.8, 5.7 Hz, 2 H), 5.39 (ddd, J = 12.4, 4.3, 2.6 Hz, 1 H), 3.79–3.84 (m, 6 H), 3.61–3.74 (m, 2 H), 3.46–3.50 (m, 1 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 138.16, 133.49, 129.76, 129.73, 129.63, 128.70, 128.42, 128.35, 126.29, 125.10, 123.48, 122.66, 115.33, 97.46, 53.44 (d, J = 37.0 Hz), 34.94.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 29.11.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{27}$H$_{24}$NO$_5$P: 474.1426; found: 474.1468.

Diisopropyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)phosphonate (3n)

Yield: 0.094 g (60%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.70 (dd, J = 26.3, 19.1 Hz, 6 H), 7.37–7.51 (m, 3 H), 7.21 (d, J = 4.3 Hz, 1 H), 7.00–7.09 (m, 4 H), 5.44 (d, J = 8.9 Hz, 1 H), 4.52 (ddd, J = 13.4, 11.0, 6.2 Hz, 2 H), 2.74–3.25(m, 2 H), 2.55 (dd, J = 14.0, 4.2 Hz, 1 H), 1.19 (d, J = 6.2 Hz, 6 H), 1.03 (dd, J = 16.5, 6.2 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 153.59, 140.51, 137.65, 133.50, 129.97, 128.85, 128.09.127.98, 127.57, 126.44, 126.29, 123.42, 116.36, 100.21, 70.03 (d, J = 7.4 Hz), 52.71 (d, J = 25.3 Hz), 35.70, 29.71, 23.78.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 24.92.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{31}$H$_{32}$NO$_5$P: 530.2052; found: 530.2091.

Dibutyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)ethyl)phosphonate (3o)

Yield: 0.096 g (67%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.57–7.62 (m, 2 H), 7.52–7.56 (m, 2 H), 7.45 (d, J = 6.8 Hz, 2 H), 7.14–7.23 (m, 3 H), 6.98 (d, J = 4.1 Hz, 1 H), 5.21 (dt, J = 6.9, 5.1 Hz, 1 H), 3.98–4.05 (m, 4 H), 1.70 (d, J = 7.2 Hz, 3 H), 1.56–1.64 (m, 4 H), 1.36 (dd, J = 7.3, 4.6 Hz, 4 H), 0.87–0.92 (m, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.30, 133.51, 131.50, 129.76, 129.52, 128.23, 125.49, 122.67, 116.09, 97.56, 65.58, 47.49 (d, J = 36.9 Hz), 32.70, 32.41, 18.71, 16.17, 13.58.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.73.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{27}$H$_{32}$NO$_5$P: 482.2052; found: 482.2094.

Dibutyl(1-(phenylcycloprop-2-enyl)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)phosphonate (3p)

Yield: 0.099 g (60%); pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.45 (d, J = 8.2 Hz, 5 H), 7.11–7.21 (m, 7 H), 7.05 (d, J = 4.0 Hz, 2 H), 5.36–5.46 (m, 1 H), 4.07 (tt, J = 13.4, 6.7 Hz, 4 H), 3.80 (ddd, J = 31.7, 18.3, 9.8 Hz, 2 H), 3.50 (dd, J = 14.3, 4.1 Hz, 1 H), 1.61–1.68 (m, 4 H), 1.39 (dd, J = 11.2, 4.0 Hz, 4 H), 0.91 (td, J = 7.3, 1.4 Hz, 6 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 138.38, 133.43, 129.75, 129.59, 128.68, 128.33, 128.30, 126.23, 125.36, 123.68, 122.62, 115.62, 97.59, 65.74, 53.60 (d, J = 37.3 Hz), 35.02, 32.66, 29.68, 18.78, 13.66.

^{31}P NMR (162 MHz, CDCl$_3$): δ = 26.53.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{33}$H$_{36}$NO$_5$P: 558.2365; found: 558.2412.

(Z)-Diethyl(2-(1,3-dioxoisoindolin-2-yl)prop-1-en-1-yl)phosphonate (4a)

Yield: 0.014 g (15%); white solid; mp 140–143 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.87–7.94 (m, 2 H, Ph), 7.69–7.80 (m, 2 H, Ph), 5.96 (dd, J = 10.4, 1.2 Hz, 1 H, CH), 3.98–4.13 (m, 4 H, 2 °CH$_2$), 2.25 (s, 3 H, CH$_3$), 1.28 (t, J = 7.1 Hz, 6 H, 2CH$_3$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 166.63 (C=O), 146.83 (CN), 134.11, 132.28, 123.71 (Ph), 118.32 (d, J = 186.2 Hz, CP), 62.08 (d, J = 5.3 Hz, OCH$_2$), 24.56 (d, J = 17 Hz, CH$_3$), 16.27 (d, J = 6.6 Hz, CH$_3$).

^{31}P NMR (162 MHz, CDCl$_3$): δ = 11.34 (s).

HRMS (ESI): m/z [M + Na]$^+$ calcd for C$_{15}$H$_{18}$NO$_5$PNa: 346.0815; found: 346.0815.

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Supporting Information

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