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Bisphosphine catalyzed sequential [3 + 2] cycloaddition and Michael addition of ynones with benzylidenepyrazolones *via* dual α′,α′-C(sp^3)–H bifunctionalization to construct cyclopentanone-fused spiro-pyrazolones†‡

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A bisphosphine-catalyzed sequential [3 + 2] cycloaddition and Michael addition reaction of ynones with benzylidenepyrazolones has been developed. Under the catalysis of DPPB [1,4-bis(diphenylphosphino) butane], the reaction proceeded smoothly to give spiro-[cyclopentanone] pyrazolone derivatives in moderate to good yields with good diastereoselectivities *via* sequential dual α′,α′-C(sp^3)–H bifunctionalization annulation. This strategy provides a novel route toward the synthesis of spiro-[cyclopentanone] pyrazolones containing three contiguous stereocenters which possess potential pharmaceutical activities.

Introduction

Pyrazolones are of considerable interest in both synthetic and medicinal chemistry and are used as versatile intermediates for further transformation in the synthesis of drugs and natural products.[1] Particularly intriguing is the spirocarbocyclic pyrazolone scaffold with a five-membered ring, which features in a large number of natural and unnatural compounds with important biological activities.[2] For example, phenylbutazone has anti-inflammatory activity.[3] BW357U shows anorexic activity.[4] 4-Spiro-5-pyrazolones have been shown to possess valuable biological properties, and have been identified as effective clinical pharmaceutical agents for use as PPAR α antagonists and inhibitors of type-4 phosphodiesterases (Fig. 1).[5] Therefore, the development of novel catalytic synthetic methods for accessing functionalized 4-spiro-5-pyrazolones with a five-membered ring has attracted attention from synthetic chemists.[6]

Functionalization of sp^3 C–H bonds for the construction of carbon–carbon and carbon–heteroatom bonds has emerged as a powerful tool for assembling highly complex structures of chemical and biomedical importance.[7] This strategy provides a practical and atom-economical way for substantially intriguing syntheses. An extensive literature survey revealed that mono C–H bond functionalization on an sp^3 carbon atom has been widely studied.[8] However, the dual α′,α′-C(sp^3)–H bifunctionalization on the same carbon center has been much less explored so far and still remains a great challenge.

In the past few years, new progress has been made in dual α′,α′-C(sp^3)–H bifunctionalizations of alkanes for C–C bond formation.[9] The dual α′,α′-C(sp^3)–H bifunctionalization has attracted increasing and continuous interest because aliphatic C–H bonds are ubiquitous in organic compounds and are among the least reactive bonds. Undoubtedly, the α′,α′-C(sp^3)–H bifunctionalization along with dual C–C bond formation provides attractive access to the diversity and complexity of the final product.

Nucleophilic phosphine organocatalysis has been demonstrated to be a versatile tool in the construction of carbo- and heterocycles.[10] Organophosphine-catalyzed [C(sp^3)–H]-functionalization has been the subject of intense research. In

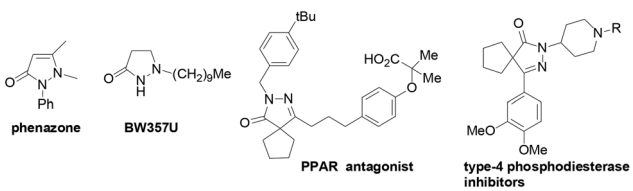

Fig. 1 Examples of spiro-[cyclopentanone]pyrazolone skeletons possessing biological activities.

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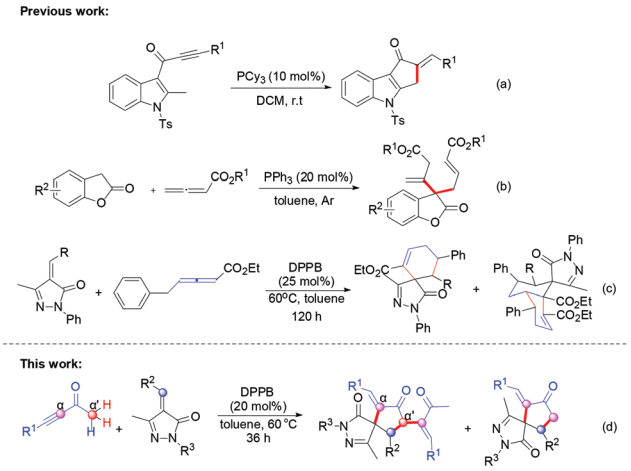


Scheme 1 Previous and proposed work.

2016, Ramasastry and co-workers reported organophosphine-catalyzed γ′[C(sp^3)–H]-functionalization/intramolecular hydroalkylation of ynones for cyclopenta[*b*] annulated heteroarene formation (Scheme 1a).[11] In 2017, Zhou and co-workers developed a phosphine-catalyzed sp^3 C–H bond dual-alkylation protocol for the synthesis of highly functionalized unsymmetrical 3,3-disubstituted benzofuranones from benzofuranones and allenoates (Scheme 1b).[12] In this aspect, our group has successfully developed a one-pot sequential [4 + 2]/[4 + 2] annulation for the construction of highly substituted 2*H*-spiro[naphthalene-pyrazole] skeletons. In this transformation, a series of tandem C(sp^3)–H/C(sp^2)–H bond functionalizations is achieved by intramolecular annulation catalyzed by bisphosphine to construct this polycyclic system (Scheme 1c).[13] However, to the best of our knowledge, bisphosphine catalyzed direct conversion of dual C(sp^3)–H bonds on the same carbon atom to double C–C functionalities has not been documented yet.

Inspired by these studies, and in continuation of our interest on bioactive fused polycyclic structure synthesis,[13,14] we here describe an unusually efficient bisphosphine-catalyzed one-pot sequential [3 + 2] cycloaddition and Michael addition reaction of ynones with benzylidenepyrazolones to deliver spiro[cyclopentanone] pyrazolone skeletons in moderate to good yields (Scheme 1d). The notable feature of this strategy is the sequential formation of three new C–C bonds *via* dual α′,α′-C(sp^3)–H bifunctionalization of ynones on the same carbon atom by using a single catalyst in one pot without the need for isolation of the intermediates.

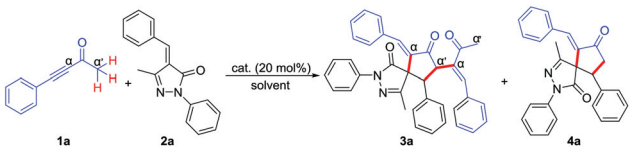
Results and discussion

The studies were initiated by evaluating the reaction between 4-phenylbut-3-yn-2-one **1a**[15] and 4-benzylidene-5-methyl-2-phenylpyrazolone **2a**[13] using triphenylphosphine (PPh_3) (20 mol%) as the catalyst in toluene at room temperature. We were surprised to find that the desired sequential [3 + 2] cycloaddition and Michael addition annulation product **3a** was not obtained; however a single [3 + 2] cycloadduct **4a** was obtained in 11% yield (Table 1, entry 1).

Triphenylphosphine (PPh_3) was replaced by more strongly nucleophilic phosphines, including ethyldiphenyl phosphine (Ph_2PEt), dimethyl(phenyl)phosphine ($PhPMe_2$), methyl(diphenyl)phosphane (Ph_2PMe), and tributylphosphine (PBu_3), and these more nucleophilic phosphines all gave similar results to each other (Table 1, entries 2–5). According to Ma's report, the sequential annulation reaction may involve two molecules of ynone **1a**. We hypothesized that the use of bisphosphines could facilitate the formation of the biszwitterionic intermediate and enable the second annulation to proceed well in an intramolecular-like fashion.[16]

Next, we tested the sequential annulation reaction using a number of bisphosphines as nucleophilic catalysts that have previously been used in reactions involving ynones.[17] To our delight, when the bisphosphines 1,3-bis(diphenylphosphanyl) propane (DPPP), 1,2-bis(diphenylphosphanyl)ethane (DPPE), and 1,4-bis(diphenylphosphanyl)butane (DPPB) were used as nucleophilic catalysts, we isolated the sequential cycloadduct (*i.e.*, **3a**) and the single [3 + 2] cycloadduct (*i.e.*, **4a**) in low yield with moderate to good diastereoselectivities (Table 1, entries 6–8). This implied that the nature of the phosphine catalyst had a significant effect on the outcome of chemoselectivity.

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	*T* (°C)/time (h)	Yield **3a**[b] (%)	Yield **4a**[b] (%)	dr[c] (**3a**)
1	PPh_3	Toluene	25/24	—	11	—
2	Ph_2PEt	Toluene	25/24	—	15	—
3	$PhPMe_2$	Toluene	25/24	—	26	—
4	Ph_2PMe	Toluene	25/24	—	21	—
5	PBu_3	Toluene	25/24	—	28	—
6	DPPP[d]	Toluene	25/24	34	16	10 : 1
7	DPPE[e]	Toluene	25/24	21	12	15 : 1
8	DPPB[f]	Toluene	25/24	42	13	>20 : 1
9	DPPB	Toluene	25/36	61	22	>20 : 1
10	DPPB	Toluene	40/36	72	5	>20 : 1
11	**DPPB**	**Toluene**	**60/36**	**88**	7	**>20 : 1**
12	DPPB	DCM[g]	25/36	32	10	>20 : 1
13	DPPB	THF	60/36	25	9	>20 : 1
14	DPPB	DCE[h]	60/36	42	17	>20 : 1
15	DPPB	MeCN	60/36	32	15	>20 : 1
16[i]	DPPB	Toluene	60/36	38	8	>20 : 1
17[j]	DPPB	Toluene	25/48	55	23	>20 : 1

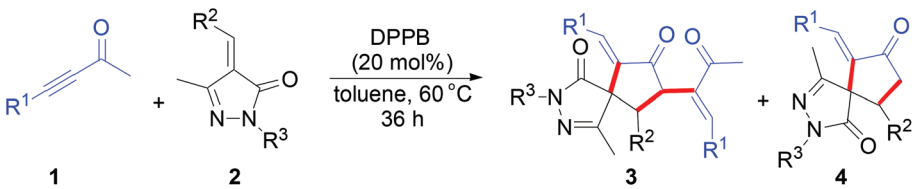
[a] Unless otherwise specified, all reactions were carried out using ethyl 4-phenylbut-3-yn-2-one **1a** (0.22 mmol) and 4-benzylidene-5-methyl-2-phenylpyrazolone **2a** (0.10 mmol) in 1 mL solvent with 20 mol% of catalyst. [b] Yield of isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis. [d] DPPP = 1,3-bis(diphenylphosphino)propane. [e] DPPE = 1,2-bis(diphenylphosphino)ethane. [f] DPPB = 1,4-bis(diphenylphosphino)butane. [g] DCM = dichloromethane. [h] DCE = 1,2-dichloroethane. [i] 10 mol% DPPB was used. [j] 3.0 equiv. of **1a** was used.

The yield of **3a** could be improved from 42 to 61% by extending the reaction time to 36 h (Table 1, entry 9). The subsequent change in the reaction temperature had a significant effect on the overall yield and ratio of **3a** to **4a** (Table 1, entries 10 and 11). Since DPPB gave a higher yield and good chemoselectivity and diastereoselectivity of **3a** (61%) than the other catalysts, it was used in further investigation at 60 °C.

We then examined the effect of the solvent on the yield. Compared with CH_2Cl_2, THF, DCE, and MeCN, the use of toluene as a solvent gave a better yield (Table 1, entries 12–15). The loading of catalysts has some influence on the yield. Lower yield was observed when the catalyst loading was decreased to 10 mol% (Table 1, entry 16). It is noteworthy that under the catalysis of DPPB, the use of excess 4-phenylbut-3-yn-2-one **1a** did not significantly increase the sequential annulation yield (Table 1, entry 17). Thus, the optimal reaction conditions for this transformation were determined to be 4-phenylbut-3-yn-2-one (**1a**, 0.22 mmol), 4-benzylidene-5-methyl-2-phenylpyrazolone (**2a**, 0.10 mmol), and DPPB (20 mol%) as a catalyst in toluene (1 mL) as a solvent at 60 °C.

Using these optimized reaction conditions, we then examined the scope and limitation of the DPPB-catalyzed sequential [3 + 2] cycloaddition and Michael addition annulation between different ynones **1** and benzylidenepyrazolone **2**, and the results are shown in Table 2. In the cases of benzylidenepyrazolone **2**, either bearing a neutral, electron-withdrawing, or electron-donating group at the *ortho*, *meta* or *para* position of the benzene ring, the reactions proceeded smoothly to give cyclopentanone 4-spiro-pyrazolones **3a–e** in moderate to good yields and diastereoselectivities, along with small amounts of cycloadducts **4a–e** (Table 2, entries 1–5). All of the major products (*i.e.*, **3**) could be cleanly isolated from the reaction mixtures. The substrate bearing two methyl groups on the aromatic ring participated in the slower transformation, delivering the sequential product **3e** in 79% yield after 48 h, together with a small amount of the cycloadduct **4e** (Table 2, entry 5). We were delighted to find that pyrazolone derivatives **2f**, **2g** and **2h**, bearing furanyl, thienyl, and naphthyl groups, respectively, underwent smooth sequential annulations with **1a**, to give the corresponding products (*i.e.*, **3f**, **3g** and **3h**) in high yields with excellent diastereoselectivities (dr > 20 : 1) (Table 2, entries 6–8). The structures of products **3a** and **4h** were assigned on the basis of spectroscopic analyses and unambiguously confirmed by X-ray diffraction of single crystals

Table 2 Substrate scope of the reaction[a]



1 **2** **3** **4**

Entry	R^1	R^2	R^3	Yield 3[b] (%)	Yield 4[b] (%)	dr[c] (3)
1	C_6H_5 (**1a**)	C_6H_5	C_6H_5 (**2a**)	88 (**3a**)	7 (**4a**)	>20 : 1
2	C_6H_5 (**1a**)	3-MeC_6H_4	C_6H_5 (**2b**)	85 (**3b**)	5 (**4b**)	>20 : 1
3	C_6H_5 (**1a**)	4-$iPrC_6H_4$	C_6H_5 (**2c**)	76 (**3c**)	11 (**4c**)	10 : 1
4	C_6H_5 (**1a**)	4-ClC_6H_4	C_6H_5 (**2d**)	84 (**3d**)	9 (**4d**)	10 : 1
5[d]	C_6H_5 (**1a**)	2,4-$(Me)_2C_6H_3$	C_6H_5 (**2e**)	79 (**3e**)	8 (**4e**)	10 : 1
6	C_6H_5 (**1a**)	2-Furanyl	C_6H_5 (**2f**)	89 (**3f**)	6 (**4f**)	>20 : 1
7	C_6H_5 (**1a**)	2-Thienyl	C_6H_5 (**2g**)	82 (**3g**)	10 (**4g**)	>20 : 1
8	C_6H_5 (**1a**)	1-Naphthyl	C_6H_5 (**2h**)	75 (**3h**)	11 (**4h**)	>20 : 1
9	3-MeC_6H_4 (**1b**)	4-$OEtC_6H_4$	C_6H_5 (**2i**)	89 (**3i**)	9 (**4i**)	>20 : 1
10	3-MeC_6H_4 (**1b**)	3-MeC_6H_4	C_6H_5 (**2b**)	83 (**3j**)	8 (**4j**)	>20 : 1
11	4-EtC_6H_4 (**1c**)	C_6H_5	C_6H_5 (**2a**)	76 (**3k**)	14 (**4k**)	>20 : 1
12	4-EtC_6H_4 (**1c**)	2-$OMeC_6H_4$	C_6H_5 (**2j**)	64 (**3l**)	18 (**4l**)	10 : 1
13	4-EtC_6H_4 (**1c**)	4-$OEtC_6H_4$	C_6H_5 (**2i**)	79 (**3m**)	10 (**4m**)	10 : 1
14	4-MeC_6H_4 (**1d**)	C_6H_5	C_6H_5 (**2a**)	86 (**3n**)	8 (**4n**)	10 : 1
15	4-$OMeC_6H_4$ (**1e**)	C_6H_5	C_6H_5 (**2a**)	91 (**3o**)	5 (**4o**)	9 : 1
16	4-$OMeC_6H_4$ (**1e**)	3-MeC_6H_4	C_6H_5 (**2b**)	88 (**3p**)	7 (**4p**)	10 : 1
17	4-$OMeC_6H_4$ (**1e**)	3-FC_6H_4	C_6H_5 (**2k**)	85 (**3q**)	10 (**4q**)	4 : 1
18	4-FC_6H_4 (**1f**)	C_6H_5	C_6H_5 (**2a**)	63 (**3r**)	20 (**4r**)	5 : 1
19	3-ClC_6H_4 (**1g**)	4-$OEtC_6H_4$	C_6H_5 (**2i**)	57 (**3s**)	19 (**4s**)	10 : 1
20	3-ClC_6H_4 (**1g**)	3-FC_6H_4	C_6H_5 (**2k**)	49 (**3t**)	22 (**4t**)	4 : 1
21	4-FC_6H_4 (**1f**)	2-Furanyl	C_6H_5 (**2f**)	93 (**3u**)	4 (**4u**)	>20 : 1
22	2-thienyl (**1h**)	C_6H_5	C_6H_5 (**2a**)	87 (**3v**)	8 (**4v**)	>20 : 1
23	2-MeC_6H_4 (**1i**)	C_6H_5	C_6H_5 (**2a**)	0 (**3w**)	76 (**4w**)	—
24	2-BrC_6H_4 (**1j**)	C_6H_5	C_6H_5 (**2a**)	0 (**3x**)	72 (**4x**)	—
25	C_6H_5 (**1a**)	C_6H_5	4-$CH_3C_6H_4$ (**2l**)	78 (**3y**)	10 (**4y**)	>20 : 1
26	C_6H_5 (**1a**)	C_6H_5	CH_3 (**2m**)	0 (**3z**)	67 (**4z**)	—

[a] Reaction conditions: Ynone **1** (0.22 mmol), benzylidenepyrazolones **2** (0.10 mmol) in 1 mL of toluene at 60 °C in the presence of 20 mol% of DPPB. [b] Yield of the isolated product after column chromatography. [c] Determined by ^1H NMR analysis. [d] The reaction time was 48 h.

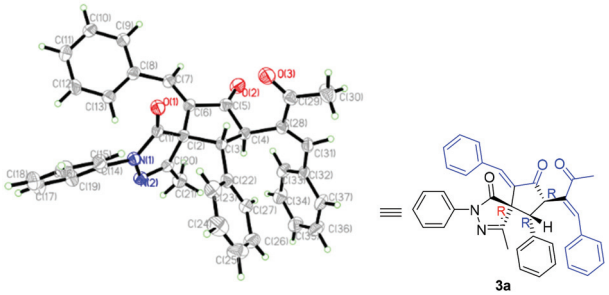


Fig. 2 The X-ray crystallographic structure of **3a**.

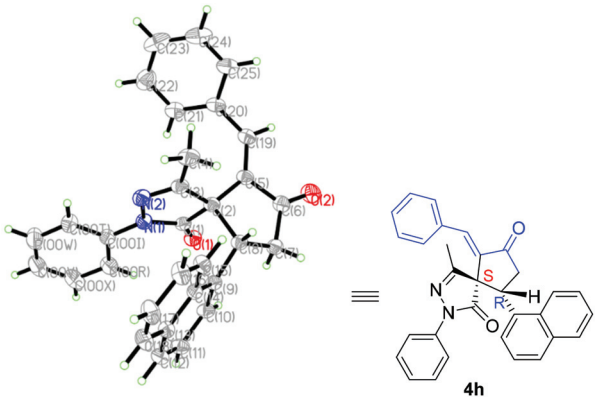


Fig. 3 The X-ray crystallographic structure of **4h**.

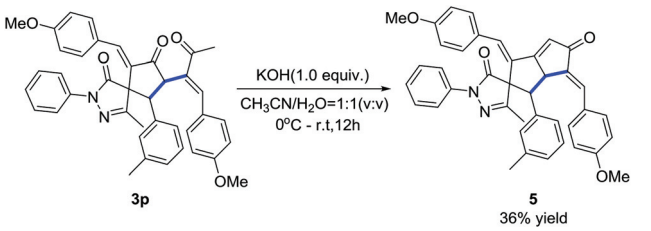
of **3a** and **4h**, thus allowing the determination of the relative configurations of three adjacent stereogenic centers of **3a** and two adjacent stereogenic centers of **4h** (Fig. 2 and 3).[18]

Finally, selected 4-aryl-but-3-yn-2-ones (**1**) were further examined in the sequential dual α′,α′-C(sp^3)–H bifunctionalization reaction with representative benzylidenepyrazolones **2**. The substituents in the ynone **1** were well tolerated, leading to the formation of the desired products **3** in moderate to high yields with moderate to good diastereoselectivities and a small amount of the [3 + 2] cycloaddition products **4** (Table 2, entries 9–22). When substrate **1** bearing an electron-donating group at the *meta* or *para* position of the benzene ring was used, the reaction proceeded much better compared to those bearing electron-withdrawing groups (Table 2, entries 18–20).

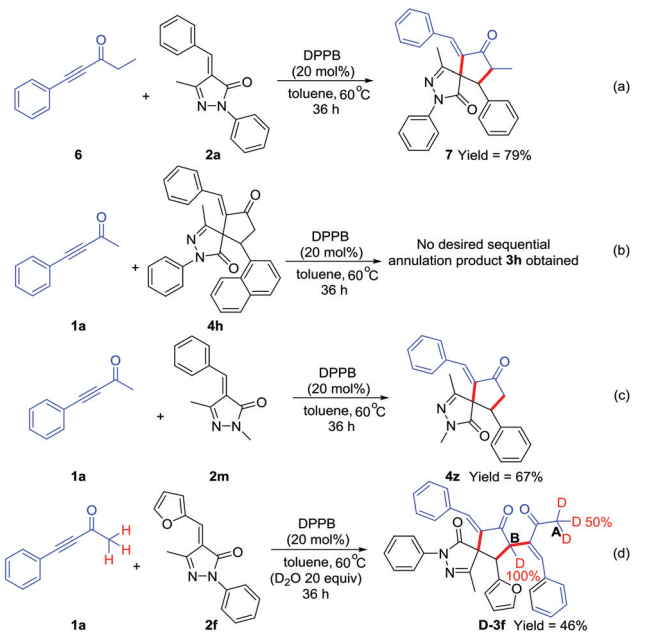
However, when 5-methyl-2-phenyl-4-(tetrahydro-furan-2-yl-methylene)-2,4-dihydro-pyrazolone **2f** and 4-(4-fluoro-phenyl)-but-3-yn-2-one **1f** were employed in this reaction, the sequential annulation product **3u** was obtained in 93% yield with dr > 20 : 1 (Table 2, entry 21). In a similar manner, when 4-thiophen-2-yl-but-3-yn-2-one **1h** was employed as the substrate, the desired product **3v** was obtained in 87% yield with good diastereoselectivity (Table 2, entry 22). It is noteworthy that steric hindrance significantly affected the efficiency of the dual α′,α′-C(sp^3)–H bifunctionalization reaction. When ynone **1** bearing an electron-withdrawing or -donating group at the *ortho* position of the benzene ring was employed, the desired sequential annulation products **3** were not obtained (Table 2, entries 23–24). It appears that the *N*-protecting group in the pyrazolone is critical for achieving the desired product **3**. Masking of the "*N*" (*e.g.*, 4-$CH_3C_6H_4$, entry 25) led to **3y** in 78% yield with good diastereoselectivity. However, the reaction of *N*-methyl protected pyrazolone **2m** with 4-phenylbut-3-yn-2-one **1a** under the catalysis of DPPB in toluene at 60 °C furnished the [3 + 2] cycloaddition product of **4z** in 67% yield without the detection of the dual functionalization product **3z** (Table 2, entry 26).

To demonstrate the synthetic utility of the sequential [3 + 2] cycloaddition and Michael addition adduct **3p**, we subjected it to the intramolecular aldol reaction. Treatment of **3p** with KOH delivered the corresponding spiro-pyrazolone fused hexahydro-pentalene **5** in 36% yield (Scheme 2). The structure of product **5** was assigned on the basis of ^{1}H NMR, ^{13}C NMR and HRMS analyses (see the ESI‡).

In order to gain insight into the mechanism, we carried out three control experiments (Scheme 3). Under the identified conditions, the treatment of 1-phenylpent-1-yn-3-one **6** with 4-benzylidene-5-methyl-2-phenylpyrazolone **2a** in the presence of 20 mol% of DPPB at 60 °C furnished the normal [3 + 2]



Scheme 2 Transformation of product **3p**.



Scheme 3 Control experiments and deuterium labelling experiment for mechanism study.

annulation product **7** in 79% yield (Scheme 3a). Further annulation of [3 + 2] cycloadduct product **4h** with 4-phenylbut-3-yn-2-one **1a** under the catalysis of DPPB did not obtain the sequential annulation product **3h** (Scheme 3b).

In addition, when 4-benzylidene-5-methyl-2-methylpyrazolone **2m** reacted with **1a**, the [3 + 2] cycloadduct product **4z** was produced in 67% yield, and no corresponding sequential annulation product was obtained (Scheme 3c). These results indicated that the methyl group in ynone **1** and phenyl as the *N*-protecting group at 4-alkenyl pyrazolin-3-one **2** were critical for the dual α′,α′-C(sp^3)–H bifunctionalization annulations to occur. To gain more mechanistic insights we performed an isotopic labeling experiment by adding 20 equiv. of D_2O to the reaction system; the reaction was carried out under the standard conditions (Scheme 3d). The deuterated product **D-3f** was obtained in a yield of 46%. ^{1}H NMR analysis showed 50% deuterium incorporation at the A position, and 100% deuterium incorporation at the B position, indicating the possibility of the involvement of a carbanion intermediate.

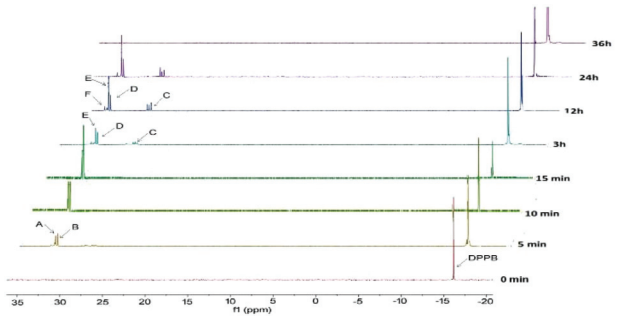
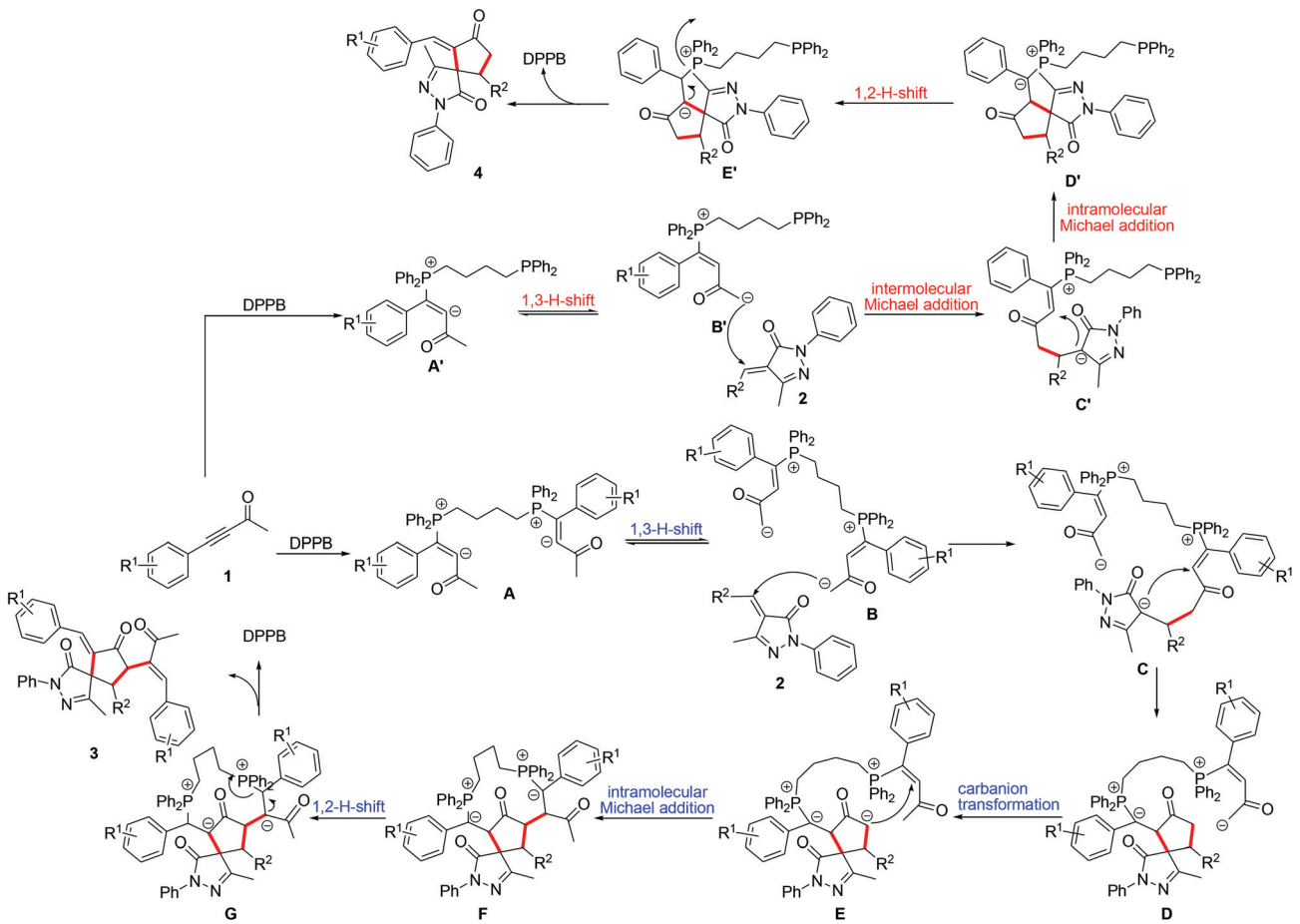


Fig. 4 Time-elapsed ^{31}P NMR spectra for the synthesis of **3a**.

To further investigate the mechanism, the formation of **3a** was monitored by ^{31}P NMR spectroscopy as shown in Fig. 4 (the reaction was monitored by the application of room temperature ^{31}P NMR spectroscopy). The DPPB in toluene-d8 showed a signal in the ^{31}P NMR spectrum at δ = −16.16 ppm. After 4-phenylbut-3-yn-2-one **1a** was added to the solution of DPPB, the peak shifted from δ = −16.16 to 32.08 and 31.87 ppm as intermediates **A** and **A′** are formed. When 4-benzylidene-5-methyl-2-phenylpyrazolone **2a** was added to the mixture, the expected Michael addition product intermediate **C** was produced (multi peaks at δ = 27.25, 27.29 and 27.53 ppm) in 3 hours. In the meantime, there are three intermediates that appeared during the synthesis of **3a**. The signals at δ_p = 32.01,



Scheme 4 Proposed reaction mechanism.

32.22 and 32.51 ppm may belong to intermediates **D**, **E** and **F**, respectively. The reaction was almost completed after 36 hours according to the ^{31}P NMR spectra (Fig. 4). The ^{31}P chemical shift of intermediates **A** and **A′** was assigned by comparing the similar chemical structure of biszwitterion and monozwitterion in the literature,[16,19,20] and the resulting intermediates **C**, **D**, **E** and **F** were tentatively assigned by analogy.

On the basis of the above experimental results and the previous literature,[16,19] the possible mechanism for this sequential [3 + 2] cycloaddition and Michael addition annulation reaction is outlined in Scheme 4. The first step involves the nucleophilic attack of the bisphosphine DPPB on ynone **1** to give biszwitterion **A** or monozwitterion **A′**. Biszwitterion **A** can isomerize to intermediate **B**. Intermediate **B** is assumed to undergo nucleophilic addition to the carbon–carbon double bond of benzylidenepyrazolone **2** to furnish intermediate **C**. A sequential intramolecular Michael addition reaction of **C** gives cycloadduct **D**. This is the initial methyl ketone group α′-C(sp^3)–H functionalization of ynone **1**. Subsequently, intermediate **D** undergoes a transformation of the carbanion to afford the biszwitterionic intermediate **E**. Finally, intermediate **E** effects intramolecular nucleophilic addition to give the cyclic adduct **F**. Then, 1,2-H shift of **F** leads to intermediate **G**. Expulsion of the bisphosphine catalyst DPPB from **G** then produces the dual α′,α′-C(sp^3)–H bifunctionalization annulation product **3**. In the second cycle, intermediate **A′** can isomerize to intermediate **B′**. An intermolecular Michael addition of intermediate **B′** to benzylidenepyrazolone **2** leads to the addition intermediate **C′**, which undergoes an intramolecular Michael addition to form **D′**. Intermediate **D′** can be converted to intermediate **E′** *via* an H-shift. Upon releasing the bisphosphine DPPB the products **4** are finally furnished.

Conclusions

In conclusion, we have developed a new and efficient bisphosphine-triggered sequential [3 + 2] cycloaddition and Michael addition reaction of 4-benzylidene-5-methyl-2-phenyl-2,4-dihydropyrazolones with β-aryl-substituted ynones through an unpresented dual α′,α′-C(sp^3)–H bifunctionalization annulation. This protocol provides a simple and practical strategy for the synthesis of cyclopentanone-fused spiro-pyrazolone derivatives with three contiguous stereocenters, which possess potential pharmaceutical activities. The bond-forming efficiency, accessibility of starting materials and functional group tolerance makes this reaction a promising approach with a great substrate scope. Further studies on the scope extension and asymmetric version of this reaction are currently underway in our laboratory and will be reported in due course.

Experimental section

General information

All reactions were performed under an N_2 atmosphere in oven-dried glassware with magnetic stirring. Solvents were dried and distilled prior to use according to the 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. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 400 MHz spectrometers, and TMS served as the internal standard (δ = 0 ppm) for ^1H NMR and ^{13}C NMR. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were obtained using an electrospray ionization (ESI-TOF) mass spectrometer. Melting points were determined on a T-4 melting point apparatus (uncorrected).

General procedure for the synthesis of products 3 and 4

Under a nitrogen atmosphere, to a mixture of benzylidenepyrazolone **2** (0.1 mmol, 1.0 equiv.) and DPPB (8.5 mg, 0.02 mmol, 20 mmol%) was added toluene (1 mL) *via* a syringe and allowed to stir for 5 min at 60 °C. Ynones **1** (0.22 mmol, 2.2 equiv.) were added and the reaction was allowed to stir for 36 h at 60 °C. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was directly purified by flash column chromatograph (eluted with 5 : 1 petroleum ether/EtOAc) to afford the corresponding cycloaddition products **3** and **4**.

6-((*E*)-Benzylidene)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2,9-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3a). Yellow solid, mp: 153–155 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.84 (s, 1H), 7.40 (d, J = 35.3 Hz, 6H), 7.27 (s, 1H), 7.18 (t, J = 4.0 Hz, 2H), 7.12–7.00 (m, 7H), 6.88 (d, J = 7.3 Hz, 2H), 6.45 (s, 2H), 4.53 (d, J = 11.8 Hz, 1H), 4.31 (d, J = 12.1 Hz, 1H), 2.32 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 197.08, 171.8, 158.58, 146.4, 139.8, 139.1, 137.4, 135.4, 133.8, 133.7, 132.7, 131.2, 129.9, 129.6, 129.5, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.1, 126.7, 125.4, 119.6, 66.7, 54.8, 48.7, 25.7, 16.5. HRMS (ESI): calcd for $C_{37}H_{31}N_2O_3$ $[M + H]^+$ m/z 551.2329, found 551.2331.

6-((*E*)-Benzylidene)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-9-(*m*-tolyl)-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3b). Yellow solid, mp: 162–165 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.52 (s, 3H), 7.46 (s, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.14 (ddd, J = 14.6, 14.0, 7.1 Hz, 6H), 6.91 (d, J = 7.4 Hz, 1H), 6.83 (t, J = 7.7 Hz, 1H), 6.32 (s, 2H), 4.62 (d, J = 12.6 Hz, 1H), 4.36 (d, J = 12.1 Hz, 1H), 2.40 (s, 3H), 1.92 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 170.8, 157.5, 145.1, 138.7, 138.2, 136.9, 136.3, 134.5, 132.8, 132.7, 131.6, 128.9, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 127.3, 127.1, 126.6, 124.2, 123.1, 118.5, 65.1, 53.8, 47.6, 24.6, 20.1, 15.3. HRMS (ESI): calcd for $C_{38}H_{33}N_2O_3$ $[M + H]^+$ m/z 565.2486, found 565.2495.

6-((*E*)-Benzylidene)-9-(4-isopropylphenyl)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-2,3-diaza-spiro[4.4]non-3-ene-1,7-dione (3c). Yellow solid, mp: 158–162 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.47 (d, J = 7.0 Hz, 3H), 7.34 (t, J = 7.4 Hz, 4H), 7.29 (d, J = 7.7 Hz, 2H), 7.19–7.14 (m, 3H),

7.08 (dd, J = 10.5, 4.6 Hz, 3H), 6.80 (d, J = 8.1 Hz, 2H), 6.55 (d, J = 8.1 Hz, 2H), 5.00 (d, J = 12.4 Hz, 1H), 4.09 (d, J = 12.4 Hz, 1H), 2.67 (dt, J = 13.8, 6.9 Hz, 1H), 2.42 (s, 3H), 1.79 (s, 3H), 1.03 (d, J = 2.1 Hz, 3H), 1.01 (d, J = 2.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 197.5, 170.9, 157.5, 147.8, 146.7, 137.4, 137.3, 135.8, 133.9, 132.5, 131.4, 129.1, 129.0, 128.4, 128.3, 127.9, 127.5, 127.4, 127.3, 126.9, 124.9, 124.7, 119.4, 65.3, 50.1, 47.2, 32.6, 28.7, 24.9, 22.8, 22.6, 12.6. HRMS (ESI): calcd for $C_{40}H_{37}N_2O_3$ $[M + H]^+$ m/z 593.2799, found 593.2799.

6-((*E*)-Benzylidene)-9-(4-chlorophenyl)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-2,3-diazaspiro-[4.4]non-3-ene-1,7-dione (3d). Yellow solid, mp: 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.93 (s, 1H), 7.53 (s, 3H), 7.45–7.33 (m, 5H), 7.30 (d, J = 7.4 Hz, 2H), 7.16 (ddd, J = 11.6, 9.1, 4.8 Hz, 5H), 6.92 (d, J = 8.3 Hz, 2H), 6.43 (s, 2H), 4.54 (d, J = 11.6 Hz, 1H), 4.35 (d, J = 12.1 Hz, 1H), 2.41 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 196.9, 171.6, 158.2, 146.4, 140.0, 138.9, 137.2, 135.3, 133.8, 133.7, 132.4, 131.2, 130.0, 129.7, 129.4, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 125.4, 119.8, 119.4, 118.9, 66.0, 54.2, 48.8, 25.7, 16.5. HRMS (ESI): calcd for $C_{37}H_{30}ClN_2O_3$ $[M + H]^+$ m/z 585.1939, found 585.1936.

6-((*E*)-Benzylidene)-9-(2,4-dimethylphenyl)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-2,3-diaza-spiro[4.4]non-3-ene-1,7-dione (3e). Yellow solid, mp: 155–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.53 (d, J = 6.0 Hz, 3H), 7.47 (s, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.32–7.26 (m, 2H), 7.25–7.04 (m, 6H), 6.70 (d, J = 7.6 Hz, 1H), 6.27 (d, J = 8.6 Hz, 2H), 4.61 (d, J = 12.2 Hz, 1H), 4.35 (d, J = 12.6 Hz, 1H), 2.39 (s, 3H), 2.08 (s, 3H), 1.86 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 195.8, 170.9, 157.6, 145.1, 138.7, 138.2, 136.4, 135.5, 135.4, 134.5, 132.8, 131.7, 130.1, 129.9, 128.9, 128.6, 128.5, 127.9, 127.8, 127.6, 127.4, 127.0, 124.2, 123.3, 118.5, 65.2, 53.5, 47.6, 24.6, 18.4, 18.3, 15.4. HRMS (ESI): calcd for $C_{39}H_{35}N_2O_3$ $[M + H]^+$ m/z 579.2642, found 579.2644.

6-((*E*)-Benzylidene)-9-(furan-2-yl)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-2,3-diaza-spiro[4.4]non-3-ene-1,7-dione (3f). Yellow solid, mp: 167–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 2H), 7.53–7.43 (m, 5H), 7.34–7.28 (m, 4H), 7.14 (ddt, J = 18.9, 11.9, 7.0 Hz, 6H), 6.99 (s, 1H), 6.07 (dd, J = 3.1, 1.9 Hz, 1H), 5.64 (s, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.32 (d, J = 12.5 Hz, 1H), 2.44 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 197.0, 171.4, 159.0, 148.9, 146.7, 142.4, 139.8, 139.0, 137.6, 135.1, 133.7, 132.5, 129.9, 129.4, 129.3, 128.8, 128.6, 128.5, 128.2, 125.2, 119.3, 110.2, 108.2, 64.6, 49.2, 48.9, 25.6, 16.1. HRMS (ESI): calcd for $C_{35}H_{29}N_2O_4$ $[M + H]^+$ m/z 541.2122, found 541.2125.

6-((*E*)-Benzylidene)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-9-(thiophen-2-yl)-2,3-diazaspiro-[4.4]non-3-ene-1,7-dione (3g). Yellow solid, mp: 178–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.53–7.42 (m, 7H), 7.30 (t, J = 7.9 Hz, 2H), 7.20–7.09 (m, 6H), 6.98 (d, J = 4.9 Hz, 1H), 6.72–6.62 (m, 1H), 6.24 (s, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.50 (d, J = 12.5 Hz, 1H), 2.42 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 197.0, 171.4, 158.4, 146.7, 140.0, 138.7, 137.5, 135.2, 133.7, 132.6, 129.9, 129.5, 129.4, 128.9, 128.6, 128.5, 128.4, 126.7, 125.3, 124.7, 119.4, 66.1, 51.3, 50.2, 25.6, 16.5. HRMS (ESI): calcd for $C_{35}H_{29}N_2O_3S$ $[M + H]^+$ m/z 557.1893, found 557.1895.

6-((*E*)-Benzylidene)-4-methyl-9-(naphthalen-1-yl)-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-2-phenyl-2,3-diaza-spiro[4.4]non-3-ene-1,7-dione (3h). Yellow solid, mp: 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.85 (s, 1H), 7.54 (s, 3H), 7.43–7.24 (m, 7H), 7.18 (dd, J = 8.8, 6.9 Hz, 3H), 7.12–6.99 (m, 7H), 6.71 (d, J = 8.1 Hz, 2H), 4.73 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 12.6 Hz, 1H), 2.31 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 197.0, 171.9, 158.6, 146.3, 140.0, 139.2, 137.4, 135.6, 133.8, 132.9, 132.8, 131.6, 129.9, 129.7, 129.5, 129.2, 128.7, 128.6, 128.2, 127.8, 127.5, 126.2, 126.1, 125.8, 125.4, 125.0, 119.5, 66.1, 54.7, 48.7, 25.6, 16.3. HRMS (ESI): calcd for $C_{41}H_{33}N_2O_3$ $[M + H]^+$ m/z 601.2486, found 601.2488.

9-(4-Ethoxyphenyl)-4-methyl-6-((*E*)-3-methylbenzylidene)-8-((*E*)-3-oxo-1-(*m*-tolyl)but-1-en-2-yl)-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3i). Yellow solid, mp: 173–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.25–7.19 (m, 3H), 7.17–7.07 (m, 5H), 6.98 (d, J = 7.5 Hz, 1H), 6.85 (s, 1H), 6.57 (d, J = 8.7 Hz, 2H), 6.47 (d, J = 8.6 Hz, 2H), 4.95 (d, J = 12.5 Hz, 1H), 4.05 (d, J = 12.4 Hz, 1H), 3.84–3.77 (m, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 2.12 (s, 3H), 1.76 (s, 3H), 1.27 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9, 197.5, 171.1, 157.5, 146.9, 137.5, 137.3, 137.0, 136.2, 133.9, 132.4, 131.4, 129.9, 129.1, 128.6, 128.4, 127.9, 127.8, 127.5, 127.3, 125.6, 124.4, 124.3, 123.8, 118.6, 112.9, 65.4, 62.3, 49.9, 47.7, 24.9, 20.5, 20.3, 13.6, 12.6. HRMS (ESI): calcd for $C_{41}H_{39}N_2O_4$ $[M + H]^+$ m/z 623.2904, found 623.2908.

4-Methyl-6-((*E*)-3-methylbenzylidene)-8-((*E*)-3-oxo-1-(*m*-tolyl)but-1-en-2-yl)-2-phenyl-9-(*m*-tolyl)-2,3-diaza-spiro[4.4]non-3-ene-1,7-dione (3j). Yellow solid, mp: 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.84 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.24–7.01 (m, 10H), 6.96 (d, J = 7.5 Hz, 1H), 6.83 (d, J = 7.0 Hz, 3H), 6.46 (d, J = 6.9 Hz, 1H), 6.40 (s, 1H), 5.03 (d, J = 12.5 Hz, 1H), 4.04 (d, J = 12.5 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 198.5, 171.9, 158.6, 148.0, 138.6, 138.3, 138.2, 138.1, 137.5, 137.1, 135.0, 133.4, 132.8, 132.4, 130.9, 130.2, 129.6, 128.9, 128.8, 128.3, 127.7, 126.7, 125.7, 125.4, 125.3, 119.5, 66.3, 51.5, 48.4, 25.9, 21.4, 21.3, 21.1, 13.7. HRMS (ESI): calcd for $C_{40}H_{37}N_2O_3$ $[M + H]^+$ m/z 593.2799, found 593.2802.

6-((*E*)-4-Ethylbenzylidene)-8-((*E*)-1-(4-ethylphenyl)-3-oxobut-1-en-2-yl)-4-methyl-2,9-diphenyl-2,3-diazaspiro-[4.4]non-3-ene-1,7-dione (3k). Yellow solid, mp: 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.87 (s, 1H), 7.35 (d, J = 8.0 Hz, 6H), 7.28 (d, J = 7.5 Hz, 2H), 7.15–7.08 (m, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.95 (dd, J = 11.7, 7.8 Hz, 4H), 6.54 (s, 2H), 4.64 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 12.7 Hz, 1H), 2.77 (q, J = 7.6 Hz, 2H), 2.51 (q, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.90 (s, 3H), 1.32 (t, J = 7.6 Hz, 3H), 1.07 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) 201.9, 198.6, 171.9, 158.9, 147.9, 146.8, 145.9, 144.9, 138.5, 137.9, 136.9, 133.1, 132.2, 131.5, 130.7, 129.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 125.6, 120.2, 66.2, 51.4, 48.4, 28.8, 26.9,

15.3, 15.1, 13.7. HRMS (ESI): calcd for $C_{41}H_{39}N_2O_3$ $[M + H]^+$ *m*/*z* 607.2955, found 607.2955.

6-((*E*)-4-Ethylbenzylidene)-8-((*E*)-1-(4-ethylphenyl)-3-oxobut-1-en-2-yl)-9-(2-methoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3l). Yellow solid, mp: 159–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.83 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 3H), 7.22 (d, *J* = 7.3 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 2H), 7.13–7.03 (m, 6H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 6.41 (t, *J* = 7.5 Hz, 1H), 4.99 (d, *J* = 12.6 Hz, 1H), 4.79 (d, *J* = 12.6 Hz, 1H), 3.61 (s, 3H), 2.74 (q, *J* = 7.6 Hz, 2H), 2.62 (dd, *J* = 15.2, 7.6 Hz, 2H), 2.40 (s, 3H), 1.79 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 197.3, 171.3, 159.6, 157.1, 146.7, 145.7, 144.7, 137.5, 137.2, 136.1, 130.8, 128.6, 127.6, 127.5, 127.4, 127.3, 126.9, 124.4, 120.8, 119.2, 118.9, 108.8, 65.1, 64.8, 53.8, 47.5, 42.6, 27.7, 24.9, 14.2, 14.1, 13.0. HRMS (ESI): calcd for $C_{42}H_{41}N_2O_4$ $[M + H]^+$ *m*/*z* 637.3061, found 637.3072.

9-(4-Ethoxyphenyl)-6-((*E*)-4-ethylbenzylidene)-8-((*E*)-1-(4-ethylphenyl)-3-oxobut-1-en-2-yl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3m). Yellow solid, mp: 174–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.87 (s, 1H), 7.40–7.32 (m, 6H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.44 (s, 4H), 4.58 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 3.87 (q, *J* = 7.0 Hz, 2H), 2.77 (q, *J* = 7.5 Hz, 2H), 2.49 (q, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 1.89 (s, 3H), 1.33 (t, *J* = 6.9 Hz, 6H), 1.07 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 197.2, 171.9, 158.9, 158.4, 146.6, 146.4, 146.1, 139.8, 138.7, 137.5, 132.8, 132.0, 131.3, 129.7, 128.6, 128.5, 128.3, 128.2, 128.1, 125.7, 125.2, 119.6, 114.0, 66.3, 63.2, 54.4, 49.1, 28.8, 28.7, 25.7, 16.4, 15.6, 15.1, 14.7. HRMS (ESI): calcd for $C_{43}H_{43}N_2O_4$ $[M + H]^+$ *m*/*z* 651.3217, found 651.3219.

4-Methyl-6-((*E*)-4-methylbenzylidene)-8-((*E*)-3-oxo-1-(*p*-tolyl)but-1-en-2-yl)-2,9-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3n). Yellow solid, mp: 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.86 (s, 1H), 7.76–7.43 (m, 2H), 7.30 (d, *J* = 20.7 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 3H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.09 (dd, *J* = 11.6, 7.7 Hz, 3H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.97 (t, *J* = 7.3 Hz, 2H), 6.69 (d, *J* = 7.4 Hz, 2H), 5.05 (d, *J* = 12.5 Hz, 1H), 4.14 (d, *J* = 12.5 Hz, 1H), 2.44 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1, 197.7, 170.9, 157.9, 147.1, 139.7, 138.6, 137.5, 136.7, 135.9, 132.0, 130.9, 130.4, 129.9, 129.5, 128.7, 128.5, 128.2, 127.6, 127.4, 127.2, 126.9, 124.6, 119.2, 65.2, 64.5, 50.3, 47.3, 24.9, 20.5, 12.7. HRMS (ESI): calcd for $C_{39}H_{35}N_2O_3$ $[M + H]^+$ *m*/*z* 579.2642, found 579.2645.

6-((*E*)-4-Methoxybenzylidene)-8-((*E*)-1-(4-methoxyphenyl)-3-oxobut-1-en-2-yl)-4-methyl-2,9-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3o). Yellow solid, mp: 151–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.83 (s, 1H), 7.72 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.53 (dd, *J* = 5.7, 3.3 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.21 (dt, *J* = 8.7, 7.7 Hz, 4H), 7.08 (t, *J* = 10.4 Hz, 3H), 7.00 (d, *J* = 8.4 Hz, 3H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 7.4 Hz, 2H), 5.08 (d, *J* = 12.4 Hz, 1H), 4.17 (d, *J* = 12.5 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 2.38 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 171.14, 160.3, 146.7, 137.3, 135.9, 132.1, 130.6, 129.9, 129.2, 129.1, 129.0, 127.8, 127.6, 127.2, 127.0, 126.9, 126.3, 125.9, 124.8, 124.6, 119.0, 113.4, 112.9, 64.6, 54.3, 29.5, 28.7, 24.9, 18.2, 12.7. HRMS (ESI): calcd for $C_{39}H_{35}N_2O_5$ $[M + H]^+$ *m*/*z* 611.2540, found 611.2544.

6-((*E*)-4-Methoxybenzylidene)-8-((*E*)-1-(4-methoxyphenyl)-3-oxobut-1-en-2-yl)-4-methyl-2-phenyl-9-(*m*-tolyl)-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3p). Yellow solid, mp: 162–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (d, *J* = 4.6 Hz, 1H), 7.48–7.39 (m, 4H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.06 (dd, *J* = 11.0, 8.6 Hz, 4H), 6.94–6.85 (m, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 6.39 (s, 2H), 4.65 (d, *J* = 12.8 Hz, 1H), 4.39 (d, *J* = 12.9 Hz, 1H), 3.91 (s, 3H), 3.66 (s, 3H), 2.37 (s, 3H), 1.93 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 196.2, 171.2, 160.1, 159.6, 157.9, 145.1, 138.7, 136.8, 136.5, 132.9, 130.9, 129.0, 127.8, 127.7, 127.6, 127.1, 126.8, 125.3, 124.3, 124.2, 123.0, 118.6, 113.4, 113.1, 112.4, 65.3, 54.5, 54.2, 47.6, 25.9, 24.6, 20.1, 15.4. HRMS (ESI): calcd for $C_{40}H_{37}N_2O_5$ $[M + H]^+$ *m*/*z* 625.2697, found 625.2699.

9-(3-Fluorophenyl)-6-((*E*)-4-methoxybenzylidene)-8-((*E*)-1-(4-methoxyphenyl)-3-oxobut-1-en-2-yl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3q). Yellow solid, mp: 171–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.49–7.42 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 3H), 6.95 (d, *J* = 6.4 Hz, 1H), 6.87–6.73 (m, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.45 (d, *J* = 6.2 Hz, 1H), 6.20 (s, 1H), 4.57 (d, *J* = 13.0 Hz, 1H), 4.41 (d, *J* = 12.5 Hz, 1H), 3.91 (s, 3H), 3.65 (s, 3H), 2.38 (s, 3H), 1.89 (d, *J* = 27.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 196.4, 170.9, 160.2, 159.7, 157.6, 145.5, 138.9, 136.8 (d, J_{C-F} = 7.0 Hz), 135.8, 135.7, 130.8, 130.6, 129.9 (d, J_{C-F} = 8.0 Hz), 128.8, 127.8, 127.7, 125.2, 124.4, 123.3 (d, J_{C-F} = 3.0 Hz), 122.3, 118.7, 118.5, 115.0 (d, J_{C-F} = 21.0 Hz), 114.3 (d, J_{C-F} = 34.0 Hz), 113.5, 113.1, 65.1, 54.4, 54.2, 24.6, 18.2, 15.5, 12.71. HRMS (ESI): calcd for $C_{39}H_{34}FN_2O_5$ $[M + H]^+$ *m*/*z* 629.2446, found 629.2450.

6-((*E*)-4-Fluorobenzylidene)-8-((*E*)-1-(4-fluorophenyl)-3-oxobut-1-en-2-yl)-4-methyl-2,9-diphenyl-2,3-diazaspiro-[4.4]non-3-ene-1,7-dione (3r). Yellow solid, mp: 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.85 (s, 1H), 7.38 (d, *J* = 7.9 Hz, 3H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 8.4 Hz, 2H), 7.18–7.13 (m, 2H), 7.12–7.06 (m, 3H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.83 (t, *J* = 8.6 Hz, 2H), 6.56 (s, 2H), 4.50 (d, *J* = 9.2 Hz, 1H), 4.37 (d, *J* = 12.5 Hz, 1H), 2.40 (d, *J* = 4.2 Hz, 3H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 170.6, 163.6 (d, J_{C-F} = 15.0 Hz), 161.2 (d, J_{C-F} = 13.0 Hz), 157.3, 144.0, 137.6, 136.2, 132.6, 131.5, 130.7 (d, J_{C-F} = 9.0 Hz), 129.3 (d, J_{C-F} = 8.0 Hz), 128.9 (d, J_{C-F} = 4.0 Hz), 127.8, 127.4, 127.2, 125.9, 124.5, 118.3, 115.2 (d, J_{C-F} = 22.0 Hz), 114.8 (d, J_{C-F} = 22.0 Hz), 65.1, 47.6, 28.7, 24.6, 15.5. HRMS (ESI): calcd for $C_{37}H_{29}F_2N_2O_3$ $[M + H]^+$ *m*/*z* 587.2141, 587.2143.

6-((*E*)-3-Chlorobenzylidene)-8-((*E*)-1-(3-chlorophenyl)-3-oxobut-1-en-2-yl)-9-(4-ethoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3s). Yellow solid, mp: 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.81 (s, 1H), 7.48–7.40 (m, 4H), 7.34–7.27 (m, 4H), 7.17–7.09 (m, 4H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 8.1 Hz,

2H), 6.45 (s, 1H), 4.41 (d, J = 7.2 Hz, 1H), 4.28 (d, J = 9.6 Hz, 1H), 3.88 (q, J = 7.0 Hz, 2H), 2.39 (s, 3H), 1.93 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 196.8, 171.5, 158.7, 158.3, 144.4, 140.2, 137.9, 137.2, 137.1, 135.5, 135.0, 134.7, 134.1, 130.2, 129.9, 129.8, 129.4, 129.3, 128.9, 128.6, 128.3, 128.1, 127.3, 126.3, 125.3, 124.9, 120.0, 119.4, 114.2, 66.2, 63.3, 54.4, 49.0, 25.6, 16.5, 14.7. HRMS (ESI): calcd for $C_{39}H_{33}Cl_2N_2O_4$ $[M + H]^+$ m/z 663.1812, found 663.1816.

6-((*E*)-3-Chlorobenzylidene)-8-((*E*)-1-(3-chlorophenyl)-3-oxobut-1-en-2-yl)-9-(3-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3t). Yellow solid, mp: 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.85 (s, 1H), 7.50 (ddd, J = 19.0, 7.0, 3.8 Hz, 3H), 7.41–7.28 (m, 5H), 7.16 (dd, J = 8.2, 2.8 Hz, 2H), 7.11–7.04 (m, 2H), 6.96 (dd, J = 15.7, 7.2 Hz, 2H), 6.84 (dd, J = 10.3, 8.1 Hz, 1H), 6.39 (s, 1H), 6.15 (s, 1H), 4.42 (s, 1H), 4.34 (s, 1H), 2.42 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.6, 170.2, 162.7, 156.9, 137.3, 136.0, 135.8, 135.0, 134.3 (d, J_{C-F} = 7.0 Hz), 133.7, 132.7, 129.9, 129.4, 129.1, 128.9, 128.7 (d, J_{C-F} = 12.0 Hz), 128.2, 127.6, 127.2, 126.2, 125.2, 124.5, 122.1 (d, J_{C-F} = 2.0 Hz), 118.3, 114.3 (d, J_{C-F} = 21.0 Hz), 112.7 (d, J_{C-F} = 22.0 Hz), 64.9, 53.5, 28.7, 24.6, 15.5. HRMS (ESI): calcd for $C_{37}H_{28}Cl_2FN_2O_3$ $[M + H]^+$ m/z 637.1456, found 637.1458.

6-((*E*)-4-Fluorobenzylidene)-8-((*E*)-1-(4-fluorophenyl)-3-oxobut-1-en-2-yl)-9-(furan-2-yl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3u). Yellow solid, mp: 198–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 1.8 Hz, 2H), 7.55–7.51 (m, 2H), 7.36–7.32 (m, 2H), 7.31–7.27 (m, 2H), 7.19–7.13 (m, 3H), 7.10–7.06 (m, 2H), 7.03 (d, J = 1.2 Hz, 1H), 6.85–6.79 (m, 2H), 6.10 (dd, J = 3.2, 1.9 Hz, 1H), 5.71 (d, J = 2.7 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 4.30 (d, J = 12.3 Hz, 1H), 2.43 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 195.9, 170.3, 163.5 (d, J_{C-F} = 27.0 Hz), 161.0 (d, J_{C-F} = 24.0 Hz), 158.0, 147.7, 144.5, 141.5, 138.2, 137.6, 136.5, 131.3, 130.7 (d, J_{C-F} = 9.0 Hz), 130.0 (d, J_{C-F} = 4.0 Hz), 129.2 (d, J_{C-F} = 9.0 Hz), 128.8 (d, J_{C-F} = 3.0 Hz), 127.8, 124.4, 118.1, 115.0 (d, J_{C-F} = 19.0 Hz), 114.9 (d, J_{C-F} = 19.0 Hz), 109.4, 107.5, 63.6, 48.0, 47.9, 24.6, 15.1. HRMS (ESI): calcd for $C_{35}H_{27}F_2N_2O_4$ $[M + H]^+$ m/z 577.1933, found 577.1936.

6-Methyl-8-((*E*)-3-oxo-1-(thiophen-2-yl)but-1-en-2-yl)-2,9-diphenyl-6-(thiophen-2-ylmethylene)-2,3-diazaspiro-[4.4]non-3-ene-1,7-dione (3v). Yellow solid, mp: 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.85 (s, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 5.0 Hz, 1H), 7.43 (d, J = 4.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 3H), 7.22–7.10 (m, 5H), 7.08–7.03 (m, 2H), 7.00 (s, 2H), 4.90 (d, J = 12.8 Hz, 1H), 4.64 (d, J = 13.1 Hz, 1H), 2.36 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 196.6, 172.0, 157.2, 138.1, 137.6, 137.0, 136.7, 135.9, 135.3, 133.9, 133.0, 132.8, 131.6, 129.5, 128.8, 128.4, 128.3, 128.0, 127.6, 127.4, 125.4, 119.5, 66.5, 56.0, 50.5, 25.8, 16.6. HRMS (ESI): calcd for $C_{33}H_{27}N_2O_3S_2$ $[M + H]^+$ m/z 563.1458, found 563.1454.

6-((*E*)-Benzylidene)-4-methyl-8-((*E*)-3-oxo-1-phenylbut-1-en-2-yl)-9-phenyl-2-(*p*-tolyl)-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (3y). Yellow solid, mp: 163–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.51 (s, 3H), 7.43 (s, 2H), 7.18 (ddd, J = 19.1, 9.3, 4.6 Hz, 5H), 7.12–7.06 (m, 5H), 6.95 (t, J = 7.3 Hz, 2H), 6.52 (s, 2H), 4.60 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 196.9, 171.5, 158.2, 146.3, 139.7, 139.2, 135.5, 135.0, 134.9, 133.8, 132.7, 129.9, 129.6, 129.5, 129.2, 128.9, 128.6, 128.3, 128.0, 127.1, 119.7, 66.1, 54.8, 48.7, 25.7, 21.0, 16.4. HRMS (ESI): calcd for $C_{38}H_{33}N_2O_3$ $[M + H]^+$ m/z 565.2486, found 565.2495.

6-((*E*)-Benzylidene)-4-methyl-2,9-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (4a). Yellow solid, mp: 105–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.31 (d, J = 7.0 Hz, 3H), 7.25 (dd, J = 12.6, 5.4 Hz, 6H), 7.20–7.09 (m, 3H), 7.05 (t, J = 7.2 Hz, 2H), 4.15–3.95 (m, 0.5H), 3.78–3.53 (m, 1H), 3.09 (ddd, J = 26.1, 18.0, 10.5 Hz, 1H), 2.77 (dd, J = 15.9, 5.4 Hz, 0.5H), 1.87 (s, 1H), 1.70 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.98, 172.59, 171.82, 159.21, 157.98, 140.22, 138.23, 137.34, 137.00, 135.18, 133.48, 133.16, 130.33, 129.37, 128.97, 127.82, 126.9, 125.68, 119.78, 66.92, 50.33, 48.17, 39.77, 39.28, 16.44, 13.85. HRMS (ESI): calcd for $C_{27}H_{23}N_2O_2$ $[M + H]^+$ m/z 407.1754, found 407.1752.

(*E*)-6-Benzylidene-4-methyl-9-(naphthalen-1-yl)-2-phenyl-2,3-diazaspiro[4.4]non-3-ene-1,7-dione (4h). Eluent: PE/EtOAc (5 : 1). Yield: 21% (9.6 mg). Mp: 135–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.91 (dd, J = 7.5, 3.4 Hz, 2H), 7.84–7.78 (m, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.60–7.50 (m, 1H), 7.47–7.29 (m, 6H), 7.25 (s, 2H), 7.15–7.06 (m, 3H), 6.94 (dd, J = 46.9, 4.2 Hz, 1H), 4.68 (dd, J = 13.6, 7.2 Hz, 1H), 3.78 (dd, J = 17.4, 13.6 Hz, 1H), 2.93 (dd, J = 17.4, 7.2 Hz, 1H), 1.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1, 171.1, 157.4, 137.6, 135.9, 132.7, 132.4, 132.2, 131.0, 129.4, 129.3, 128.4, 128.3, 128.0, 127.6, 127.5, 127.2, 125.1, 124.6, 124.5, 124.4, 124.0, 120.6, 118.6, 52.4, 40.7, 20.4, 13.7. HRMS (ESI): calcd for $C_{31}H_{25}N_2O_2$ $[M + H]^+$ m/z 457.1911, found 457.1915.

(*E*)-6-Benzylidene-2,4-dimethyl-9-phenyl-2,3-diazaspiro-[4.4]non-3-ene-1,7-dione (4z). Eluent: PE/EtOAc (5 : 1). Yield: 72% (24.8 mg). Yellow solid, mp: 108–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.27–7.21 (m, 5H), 7.16–7.10 (m, 2H), 6.97 (d, J = 7.2 Hz, 2H), 3.59 (dd, J = 16.6, 14.4 Hz, 1H), 3.45 (dd, J = 14.4, 6.4 Hz, 1H), 2.79 (s, 3H), 2.67 (dd, J = 16.7, 6.4 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 171.7, 156.1, 136.7, 132.8, 132.2, 132.1, 129.3, 128.4, 127.4, 127.3, 127.2, 126.8, 65.0, 46.9, 38.2, 29.8, 12.7. HRMS (ESI): calcd for $C_{22}H_{21}N_2O_2$ $[M + H]^+$ m/z 345.1598, found 345.1598.

4-((*E*)-4-Methoxybenzylidene)-1-((Z)-4-methoxybenzylidene)-3′-methyl-1′-phenyl-3-(*m*-tolyl)-3a,4-dihydro-1*H*-spiro[pentalene-2,4′-pyrazole]-5,5′(1′*H*,3*H*)-dione (5). Eluent: PE/EtOAc (3 : 1). Yield: 36% (21.8 mg). Yellow solid, mp: 136–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.79 (d, J = 7.7 Hz, 2H), 7.43 (t, J = 7.8 Hz, 3H), 7.29 (s, 4H), 7.18 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 4.43 (d, J = 3.3 Hz, 1H), 3.75 (s, 6H), 3.69 (d, J = 3.2 Hz, 1H), 2.50 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 160.6, 160.5, 152.4, 146.9, 146.8, 141.0, 139.2, 139.1, 136.9, 130.4, 130.3, 129.3, 129.1, 129.0, 128.2, 126.3, 125.6, 122.4, 114.2, 113.9,

56.1, 55.4, 55.3, 31.9, 25.8, 21.5, 14.1. HRMS (MALDI): calcd for $C_{40}H_{35}N_2O_4$ $[M + H]^+$ m/z 607.2591, found 607.2594.

(*E*)-6-Benzylidene-4,8-dimethyl-2,9-diphenyl-2,3-diaza-spiro[4.4] non-3-ene-1,7-dione (7). Eluent: PE/EtOAc (5 : 1). Yield: 79% (33.2 mg). Yellow solid, mp: 110–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.39–7.30 (m, 5H), 7.30–7.26 (m, 5H), 7.22–7.11 (m, 3H), 7.09 (d, J = 7.4 Hz, 2H), 3.76 (dq, J = 13.5, 6.7 Hz, 1H), 3.15 (d, J = 13.7 Hz, 1H), 1.71 (s, 3H), 1.20 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 170.8, 157.1, 137.1, 135.9, 132.2, 131.9, 131.8, 128.2, 127.7, 127.6, 127.5, 127.4, 127.0, 124.7, 118.9, 64.8, 54.7, 42.2, 12.8, 11.1. HRMS (ESI): calcd for $C_{28}H_{25}N_2O_2$ $[M + H]^+$ m/z 421.1911, found 421.1914.

Conflicts of interest

There are no conflicts to declare.

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