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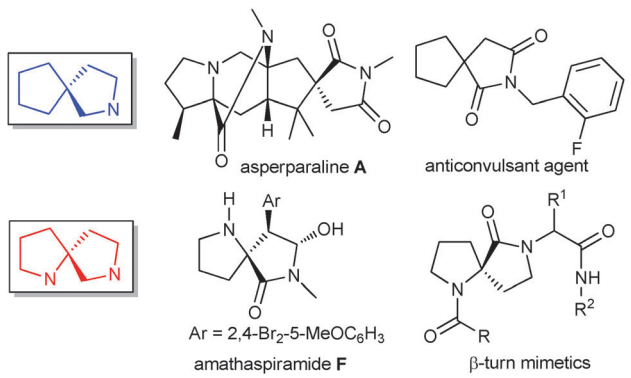
Phosphine-catalyzed [4+1] annulation of 1,3-(aza)dienes with maleimides: highly efficient construction of azaspiro[4.4]nonenes†

Mei Yang, Tianyi Wang, Shixuan Cao and Zhengjie He*

Phosphine-catalyzed [4+1] annulation of electron-deficient 1,3-dienes or 1,3-azadienes with maleimides has been successfully developed under very mild conditions, providing a convenient and highly efficient method for constructing 2-azaspiro[4.4]nonenes and 1,7-diazaspiro[4.4]nonenes. This reaction represents the first example of [4+1] cyclization between electron-deficient 4π-conjugated systems and non-allylic phosphorus ylides.

Azaspiro[4.4]nonane cores like 2-azaspiro[4.4]nonane and 1,7-diazaspiro[4.4]nonane have been recognized as uniform substructures in many biologically active natural and artificial compounds (Scheme 1).[1] For example, the 2-azaspiro[4.4]nonane skeleton as a structural characteristic has been found in indolizine alkaloid asperparaline A[1a] and a series of spirosuccinimides with anticonvulsant activity.[1b–d] The 1,7-diazaspiro[4.4]nonane framework also features the molecular structures of a group of marine alkaloids amathaspiramides possessing antiviral, cytotoxicity, and antimicrobial activities.[1f] Due to its structural rigidity, the 1,7-diazaspiro[4.4]nonane core has been proven to be a key structural factor in an array of spirolactams as promising β-turn mimetics.[1g–i] Given their structural uniqueness and biological importance, syntheses of the azaspiro[4.4]nonane skeletons have therefore attracted considerable interest from chemists.[2] In the reported effective syntheses, the azaspirocyclic structures were generally constructed through multi-step synthetic strategies.[2a–e] Encouragingly, a couple of novel synthetic protocols have also been realized to construct the spirocyclic core and the quaternary carbon centre in a one-step operation.[2f–i] Meanwhile, developing a new and efficient synthetic strategy for azaspiro[4.4]nonane skeletons remains highly desirable.



Scheme 1 Representative examples of biologically active natural and artificial compounds containing azaspiro[4.4]nonane skeletons.

Common ylides of nitrogen, sulfur, and phosphorus can be considered as masked carbanion nucleophiles with different leaving groups. The ylide-initiated [4+1] annulation reaction of electron-deficient 4π-conjugate systems provides a straightforward and feasible protocol to construct five-membered cycles.[3] *N*- and *S*-ylides initiated [4+1] annulation reactions of α,β-unsaturated carbonyls, imines, and nitroalkenes have been well documented by Tang, Xiao and other research groups,[4] providing chemo- and stereoselective access to dihydrofurans, pyrrolines, and isoxazoline *N*-oxides. Mechanistically, these reactions are generally proposed to proceed through a Michael addition-intramolecular substitution mode.[3] Contrary to *N*- and *S*-ylides, structurally analogous *P*-ylides have achieved little success in similar [4+1] annulation reactions owing to the poor leaving group ability of the phosphonium moiety.[5] Recently, a series of phosphine-catalyzed [4+1] annulations have been successfully developed by Zhang, Shi and other groups[6] from Morita–Baylis–Hillman (MBH) derivatives and α,β-unsaturated ketones, imines, or polar 1,3-dienes, leading to efficient syntheses of dihydrofurans, pyrrolines, and cyclopentenes. In these reactions, the *in situ* generated allylic *P*-ylides from MBH derivatives and phosphines presumably effect the [4+1] annulation by a tandem

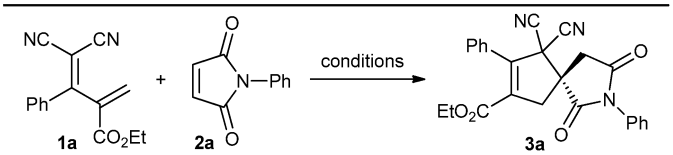
The State Key Laboratory of Elemento-Organic Chemistry and Department of Chemistry, Nankai University and Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, P. R. China.
E-mail: zhengjiehe@nankai.edu.cn

† Electronic supplementary information (ESI) available: General procedures; characterization data and NMR spectra of all new compounds; ORTEP drawings of compounds **3a** and **5a**. CCDC 1013074 and 1012903. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc05624h

sequence of Michael addition-intramolecualr S_N2' substitution.[6b] By the S_N2' substitution mode (also called the addition–elimination mode), the ring-closure step can circumvent the problem arising from the poor leaving group ability of the phosphonium moiety.[7] However, to the best of our knowledge, the non-allylic *P*-ylide-initiated [4+1] annulation of electron-deficient conjugated systems has not been reported before. Herein, we wish to communicate the phosphine-catalyzed [4+1] annulation of 1,3-(aza)dienes and maleimides, which represents the first example of non-allylic *P*-ylide-initiated [4+1] cyclization of a 4π-conjugated system. This annulation reaction also provides a novel and efficient method to construct azaspiro[4.4]nonane skeletons.

In our recent investigations on tertiary phosphine-mediated annulation reactions, we found that tuning the leaving group ability and nucleophilicity of phosphines could significantly change the chemoselectivity of the reactions.[8] Considering the fact that triarylphosphines have a relatively better leaving group ability while compared with trialkylphosphines,[8b] we suspected that the non-allylic *P*-ylide of triarylphosphine might be able to effect the [4+1] annulation of an electron-deficient 4π-conjugated system. Keeping this idea in mind, we started to investigate the model reaction of 4,4-dicyano-2-methylenebut-3-enoates **1a** and *N*-phenyl maleimide **2a** (Table 1).[9,10] Gratifyingly, under the co-catalysis of PPh_3 (20 mol%, relative to **1a**) and benzoic acid (20 mol%), a mixture of **1a** (0.2 mmol) and **2a** (0.24 mmol) in CH_2Cl_2 (2.0 mL) was stirred at rt for 24 h to give an expected spirocyclic product **3a** in 94% isolated yield (entry 1). A brief survey of the reaction conditions was then conducted (Table 1). Acetic acid was also a good acid additive (entry 2). Without the acid additive, the annulation reaction could not occur at all (entry 3). A screening of the phosphine catalysts unveiled that relatively electron-deficient triarylphosphines were all good for the reaction but electron-richer $(4\text{-MeOC}_6H_4)_3P$ and alkylphosphines were much less effective (entries 4–9). With Ph_3P employed as the catalyst, a couple of common solvents including toluene, THF, acetonitrile and ethanol were also examined, giving product **3a** in modest to good yields (entries 10–13).

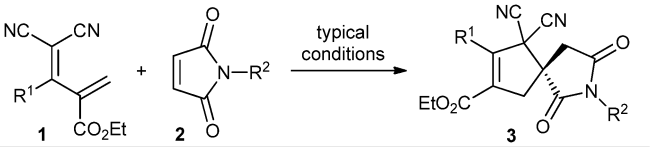
Table 1 A brief survey of the model reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Ph_3P	CH_2Cl_2	24	94
2[c]	Ph_3P	CH_2Cl_2	24	88
3[d]	Ph_3P	CH_2Cl_2	48	0
4	$(4\text{-FC}_6H_4)_3P$	CH_2Cl_2	24	93
5	$(4\text{-ClC}_6H_4)_3P$	CH_2Cl_2	24	89
6	$(4\text{-CF}_3C_6H_4)_3P$	CH_2Cl_2	24	87
7	$(4\text{-MeOC}_6H_4)_3P$	CH_2Cl_2	48	19
8	$MePh_2P$	CH_2Cl_2	48	14
9	$n\text{-Bu}_3P$	CH_2Cl_2	48	Trace
10	Ph_3P	Toluene	72	85
11	Ph_3P	THF	72	52
12	Ph_3P	CH_3CN	72	46
13	Ph_3P	Ethanol	72	53

[a] Typical conditions: under a N_2 atmosphere, a mixture of **1a** (0.2 mmol), **2a** (0.24 mmol), benzoic acid (0.04 mmol) and a phosphine catalyst (0.04 mmol) in solvent (2.0 mL) was stirred at rt. [b] Isolated yield based on **1a**. [c] Acetic acid (0.04 mmol) was used instead of benzoic acid. [d] Without the acid additive.

Table 2 Phosphine-catalyzed [4+1] annulation of 1,3-dienes **1** and maleimides **2**[a]

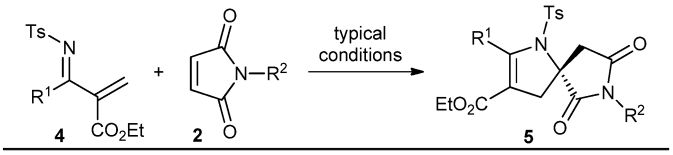


Entry	R^1 in **1**	R^2 in **2**	Time (h)	**3**, Yield[b] (%)
1	Ph (**1a**)	Ph (**2a**)	24	**3a**, 94
2	Ph	4-MeC_6H_4 (**2b**)	36	**3b**, 99
3	Ph	$4\text{-NO}_2C_6H_4$ (**2c**)	12	**3c**, 88
4	Ph	Bn (**2d**)	48	**3d**, 89
5	Ph	*n*-Bu (**2e**)	48	**3e**, 81
6	Ph	Boc (**2f**)	24	**3f**, 59
7	4-ClC_6H_4 (**1b**)	Ph	48	**3g**, 80
8	4-FC_6H_4 (**1c**)	Ph	48	**3h**, 88
9	4-MeOC_6H_4 (**1d**)	Ph	48	**3i**, 76
10	4-MeC_6H_4 (**1e**)	Ph	48	**3j**, 99
11	$4\text{-CF}_3C_6H_4$ (**1f**)	Ph	48	**3k**, 73
12[c]	2-MeC_6H_4 (**1g**)	Ph	48	**3l**, 99
13	2-MeOC_6H_4 (**1h**)	Ph	48	**3m**, 58
14[d]	2-BrC_6H_4 (**1i**)	Ph	48	**3n**, 62
15	3-BrC_6H_4 (**1j**)	Ph	48	**3o**, 48
16	3-MeOC_6H_4 (**1k**)	Ph	48	**3p**, 99
17	3-FC_6H_4 (**1l**)	Ph	48	**3q**, 87
18	3-MeC_6H_4 (**1m**)	Ph	24	**3r**, 99
19	$3,4,5\text{-(MeO)}_3C_6H_2$ (**1n**)	Ph	48	**3s**, 99
20	2-Naphthyl (**1o**)	Ph	48	**3t**, 99
21	2-Furyl (**1p**)	Ph	24	**3u**, 99
22	2-Thienyl (**1q**)	Ph	48	**3v**, 94

[a] Typical conditions: under a N_2 atmosphere, a mixture of diene **1** (0.2 mmol), maleimide **2** (0.24 mmol), benzoic acid (0.04 mmol) and Ph_3P (0.04 mmol) in CH_2Cl_2 (2.0 mL) was stirred at rt for a specified time. [b] Isolated yield. [c] Product **3l** was obtained as a diastereomeric mixture of dr 2 : 1. [d] Product **3n** was obtained as a diastereomeric mixture with dr 3 : 1.

With the optimized conditions in hand, we then examined the substrate scope of this [4+1] annulation reaction, and the results are summarized in Table 2. With dicyano-2-methylenebut-3-enoate **1a** used as a representative partner, a series of *N*-substituted maleimides **2** were firstly surveyed. Both *N*-aryl and *N*-alkyl maleimides **2** all worked well, giving the corresponding annulation products **3** in high yields (entries 1–5). *N*-(*tert*-Butoxycarbonyl) maleimide **2f** also readily delivered its annulation product in a moderate yield (entry 6). With *N*-phenyl maleimide **2a** chosen as one reactant, a series of different aryl-substituted dienes **1** was proven to be effective, giving the corresponding products **3** in moderate to excellent yields (Table 2, entries 7–22). Apart from products **3l** and **3n**, all of the annulation products **3** were obtained as single racemates. Products **3l** and **3n** were isolated as diastereomeric mixtures since the steric hindrance of the *ortho*-substituents at the benzene rings results in axis chirality in their structures (entries 12 and 14). Thus, the results in Table 2 indicate that the phosphine-catalyzed [4+1] annulation reaction of electron-deficient 1,3-dienes **1** and maleimides **2** has a wide substrate scope and accordingly provides a convenient and efficient method to construct highly functionalized 2-azaspiro[4.4]nonane skeletons.

Table 3 Phosphine-catalyzed [4+1] annulation of 1,3-azadienes **4** and maleimides **2**[a]



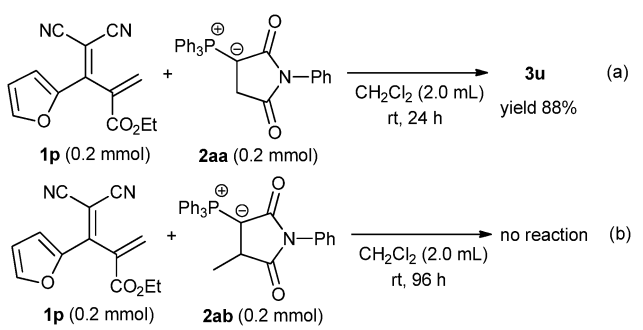
Entry	R^1 in **4**	R^2 in **2**	Time (h)	**5**, Yield[b] (%)
1	Ph (**4a**)	Ph (**2a**)	48	**5a**, 82
2	Ph	4-MeC_6H_4 (**2b**)	72	**5b**, 69
3	Ph	4-$NO_2C_6H_4$ (**2c**)	48	**5c**, 87
4	Ph	Bn (**2d**)	96	**5d**, 49
5	Ph	*n*-Bu (**2e**)	96	Trace
6	Ph	Boc (**2f**)	48	**5e**, 32
7	4-$MeOC_6H_4$ (**4b**)	Ph	48	**5f**, 76
8	4-ClC_6H_4 (**4c**)	Ph	48	**5g**, 45

[a] Typical conditions: under a N_2 atmosphere, a mixture of azadiene **4** (0.2 mmol), maleimide **2** (0.24 mmol), benzoic acid (0.04 mmol) and Ph_3P (0.04 mmol) in CH_2Cl_2 (2.0 mL) was stirred at rt for a specified time. [b] Isolated yield.

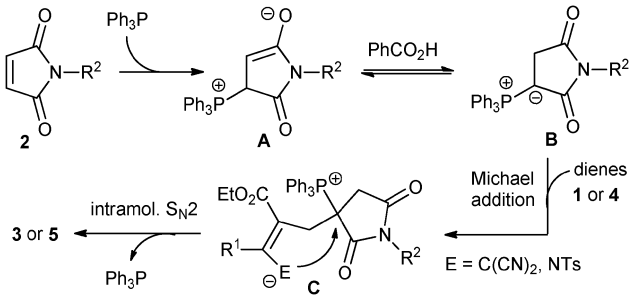
Structurally similar α,β-unsaturated imines **4** as electron-deficient 1,3-azadienes were also explored under the standard conditions (Table 3). With phenyl-substituted azadiene **4a** used as a reactant, a series of *N*-substituted maleimides **2** were examined (entries 1–6). Except *N*-butyl maleimide **2e**, *N*-aryl, *N*-benzyl, and *N*-(*tert*-butoxycarbonyl) maleimides **2** were good substrates in the [4+1] annulations with **4a**, readily affording the corresponding products **5** in modest to good yields. Representative aryl-substituted 1,3-azadienes **4b** and **4c** were also examined in the reactions with maleimide **2a**, smoothly giving the expected azaspirocyclic products **5** in moderate yields (entries 7 and 8). Therefore, 1,3-azadienes **4** were proven to be effective candidates in the phosphine-catalyzed [4+1] annulation reaction with maleimides **2**, which provided efficient access to highly functionalized 1,7-diazaspiro[4.4]nonane skeletons.

The structures of products **3** and **5** were well identified by NMR (^1H, ^{13}C) and HRMS. Representative compounds **3a** (CCDC 1013074) and **5a** (CCDC 1012903) were further confirmed by X-ray crystallographic analyses. For detailed spectroscopic data, see ESI.†

To glean some mechanistic insights into the annulation reaction, the following experiments were deliberately conducted (Scheme 2). In the absence of benzoic acid, a phosphorus ylide **2aa**, prepared by a known procedure,[10] was treated with equimolar diene **1p** in CH_2Cl_2 at rt for 24 h to smoothly give the spirocyclic product **3u** in 88% yield (Scheme 2, a). However, a methylated analogous ylide **2ab** failed to bring about a similar product (Scheme 2, b).



Scheme 2 Mechanistic investigation.



Scheme 3 A proposed mechanism for formation of **3** and **5**.

Based on the above experimental results and closely related reports,[3,8c] a plausible mechanism is depicted in Scheme 3 to account for the formation of **3** or **5**. A phosphorus ylide **B** is *in situ* generated *via* the nucleophilic attack of phosphine at maleimide **2** followed by benzoic acid-aided proton transfer.[8c] The ylide **B** then undergoes a Michael addition to electron-deficient diene **1** or azadiene **4** to generate intermediate **C**, which subsequently cyclizes by an intramolecular S_N2 mode to furnish spirocyclic product **3** or **5** and regenerate the phosphine catalyst.

In conclusion, we have successfully developed a novel phosphine-catalyzed [4+1] annulation reaction of electron-deficient 1,3-dienes or 1,3-azadienes with maleimides, which provides a convenient and highly efficient method to construct important azaspiro[4.4]nonane skeletons. This reaction also represents the first example of the [4+1] annulation between electron-deficient 4π-conjugated systems and non-allylic phosphorus ylides by the Michael addition-intramolecular substitution mode. Further expanding its scope and developing its asymmetric version are currently under investigation in our laboratory.

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