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Phosphine-Catalyzed [3 + 3]-Domino Cycloaddition of Ynones and Azomethine Imines To Construct Functionalized Hydropyridazine Derivatives

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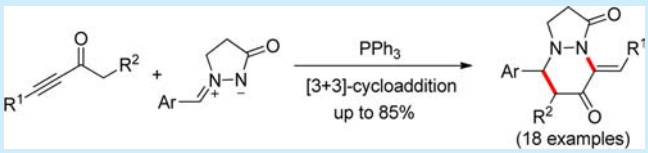
Supporting Information

ABSTRACT: The first phosphine-catalyzed [3 + 3]-domino annulation reaction of ynones and azomethine imines has been developed. With this simple and efficient method, the functionalized hydropyridazine derivatives were obtained in good to excellent yields with highly stereoselectivities.



1,2-Dinitrogen-containing heterocycles, especially hydropyridazine derivatives, occur widely in agrochemicals, pharmaceuticals, and biologically active compounds (Figure 1).[1−3]

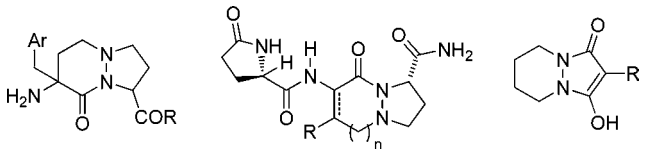


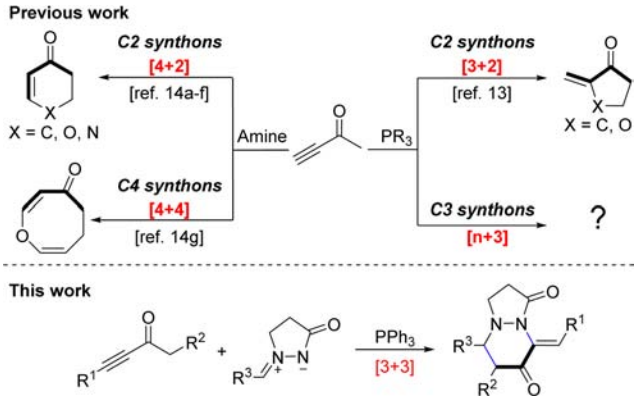
Figure 1. Biologically active molecules containing the diazobicycle scaffold.

Consequently, considerable attention has been paid to discover approaches for the construction of such a skeleton.[4] It is known that the cycloaddition reaction has become one of the most powerful methods for the construction of (fused-)cyclic compounds from readily available materials since the Diels−Alder reaction became prevalent. The traditional strategy for the synthesis of hydropyridazine was realized via a Diels−Alder reaction of azo compounds and dienes.[5] However, most of the existing methods suffered from low efficiency or multiple steps, which could not match the need for atom economy. Recently, new protocols for the construction of hydropyridazines via an unusual [3 + 3]-process have emerged.

Azomethine imines have attracted considerable attention in dipolar [3 + 2]-cycloaddition[6] reactions and become one of the most efficient strategies for the construction of dinitrogen-fused heterocyclic derivatives. However, few examples have been reported on the study of their [3 + 3]-cycloadditions[7] for the convenient synthesis of hydropyridazine derivatives, and most of the existing methods employ a transition metal as catalyst.

In the past decade, phosphine-catalyzed domino reactions have become a powerful tool in the construction of carbo- and heterocycles.[8] The catalytic transformation of a set of electrodeficient alkenes[9] and alkynes[10] has been extensively investigated, while little attention has been paid to ynones[11] in organocatalytic cascade reactions (Scheme 1). In 2003,

Scheme 1. Lewis Base Promoted Intermolecular Cycloaddition Reaction of Ynones



Tomita et al. reported a phosphine-catalyzed intramolecular cycloaddition reaction of certain yne−diones.[12a] In 2010, Fu et al. reported a phosphine-catalyzed intramolecular cycloaddition reaction of ynones and unsaturated C−C bonds.[12b] Later, the intermolecular versions of these reactions were realized by Shi et al., Huang et al., and Ramachary et al. separately.[13] Generally, ynones acted as three-carbon synthons (C3) in phosphine-catalyzed systems but as four-carbon synthons (C4) when amines were employed instead of phosphine.[14] Based on this knowledge, we envisioned that when ynones react with three-membered synthons in the presence of phosphine catalyst the [3 + 3]-annulation reactions might occur. Following our ongoing efforts in the exploration of the reactivity of ynones, we herein report that the phosphine-catalyzed intermolecular [3 + 3]-cycloaddition of ynones and azomethine imines deliver multifunctionalized hydropyridazine derivatives under simple and mild conditions.

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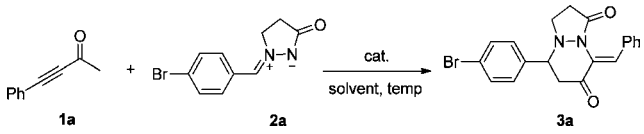
To test our hypothesis, 4-phenylbut-3-yn-2-one **1a** and *N*,*N*′-cyclic azomethine imine **2a** were chosen as model substrates in the presence of a catalytic amount of PPh_3 at 50 °C in methanol (Table 1), and we were pleased to find that bicyclic

Table 1. Optimization of Reaction Conditions for the Formal [3 + 3]-Cycloaddition[a]



1a 2a 3a

entry	cat.	solvent	temp (°C)	time (h)	yield[b] (%)
1	PPh_3	CH_3OH	50	4	24
2	PPh_3	C_2H_5OH	50	4	41
3	PPh_3	*n*-PrOH	50	4	40
4	PPh_3	*i*-PrOH	50	4	45
5	PPh_3	*n*-BuOH	50	4	60
6	PPh_3	*i*-BuOH	50	4	56
7	PPh_3	*t*-BuOH	50	4	23
8	PPh_3	$CHCl_3$	50	24	27
9	PPh_3	THF	50	24	NR
10	PPh_3	toluene	50	24	NR
11	PPh_3	CH_3CN	50	24	25
12	PPh_3	$C_2H_5OH/CHCl_3$ 1:1	50	4	70
13	PPh_3	*n*-BuOH/$CHCl_3$ 1:1	50	4	77
14	PPh_3	*n*-BuOH/CH_3CN 1:1	50	4	53
15	PBu_3	*n*-BuOH/$CHCl_3$ 1:1	50	24	27
16	$P(4\text{-}OMeC_6H_4)_3$	*n*-BuOH/$CHCl_3$ 1:1	50	3	67
17	$P(4\text{-}FC_6H_4)_3$	*n*-BuOH/$CHCl_3$ 1:1	50	4	75
18[c]	PPh_3	*n*-BuOH/$CHCl_3$ 1:1	50	4	78
19[d]	PPh_3	*n*-BuOH/$CHCl_3$ 1:1	50	4	71
20	0	*n*-BuOH/$CHCl_3$ 1:1	50	24	NR
21	PPh_3	*n*-BuOH/$CHCl_3$ 1:1	30	4	82

[a]Reactions were performed using **1a** (0.45 mmol), **2a** (0.3 mmol), and 30 mol % of catalyst in 5.0 mL of solvent. [b]Isolated yields based on **2a**. [c]With 50 mol % of PPh_3. [d]With 10 mol % of PPh_3.

[3 + 3]-cycloadduct **3a** was formed in 24% yield (Table 1, entry 1). Our initial investigation was focused on screening different protonic solvents, such as C_2H_5OH, *n*-PrOH, *i*-PrOH, *n*-BuOH, *i*-BuOH, and *t*-BuOH. We found that *n*-BuOH was the best for this reaction in terms of yield (Table 1, entries 2−7). Other solvents ($CHCl_3$, THF, toluene, and CH_3CN) were also tested, and no better results were obtained (Table 1, entries 8−11). To further improve the yield, cosolvents were surveyed, and the yield could be increased to 77% with *n*-BuOH/$CHCl_3$ (1:1) as solvent (Table 1, entries 12−14). Next, other catalysts with electron-withdrawing and -donating groups on the aromatic ring were tested but with no positive results (Table 1, entries 15−17). Increasing the catalytic loading to 50 mol % gave the same yield as before, while a decreased yield was obtained when 10 mol % of PPh_3 was employed (Table 1, entries 18 and 19). To our great delight, **3a** could be isolated with 82% yield when the reaction was conducted at 30 °C (Table 1, entry 21). In addition, the structure and stereochemistry of **3a** were unambiguously determined by single-crystal X-ray diffraction analysis (Figure 2).[15]

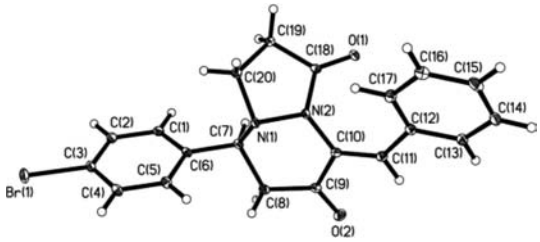
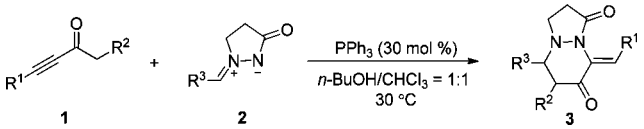


Figure 2. X-ray crystal structure of **3a**.

With the optimized conditions in hand, we further tested the substrate scope, and the results are listed in Table 2. Generally,

Table 2. Substrate Scope[a]



1 2 3

entry	R^1	R^2	R^3	time (h)	3, yield[b] (%)
1	Ph	H	$4\text{-}BrC_6H_4$	4	**3a**, 82
2	Ph	H	$4\text{-}ClC_6H_4$	4	**3b**, 81
3	Ph	H	$3\text{-}ClC_6H_4$	4	**3c**, 76
4	Ph	H	$2\text{-}ClC_6H_4$	4	**3d**, 81
5	Ph	H	$4\text{-}FC_6H_4$	4	**3e**, 68
6	Ph	H	C_6H_5	4	**3f**, 65
7	Ph	H	$4\text{-}MeC_6H_4$	6	**3g**, 60
8	Ph	H	$4\text{-}OMeC_6H_4$	24	**3h**, 38
9	Ph	H	$4\text{-}NO_2C_6H_4$	4	**3i**, 48
10	Ph	H	$4\text{-}CNC_6H_4$	4	**3j**, 54
11	Ph	H	$4\text{-}CF_3C_6H_4$	4	**3k**, 84
12	Ph	H	$2,4\text{-}Cl_2C_6H_3$	4	**3l**, 85
13	Ph	H	2- furyl	24	
14	Ph	H	2-thienyl	24	
15	Ph	H	2-naphthyl	4	**3m**, 66
16	Ph	Me	$4\text{-}BrC_6H_4$	4	**3n**, 82
17	$4\text{-}MeC_6H_4$	H	$4\text{-}BrC_6H_4$	4	**3o**, 66
18	$4\text{-}FC_6H_4$	H	$4\text{-}BrC_6H_4$	4	**3p**, 64
19	Ph	H	$4\text{-}BrC_6H_4$	4	**3a**, 80[c]

[a]Reactions were performed using **1a** (0.45 mmol), **2a** (0.3 mmol), and 30 mol % of PPh_3 in 5.0 mL of solvent (*n*-BuOH/$CHCl_3$ = 1:1) at 30 °C. [b]Isolated yields based on **2**. [c]The reaction was carried out with 3.0 mmol of **2a**.

various ynones and azomethine imines could participate in the reaction furnishing the desired products with moderate to good yields (38−85%). Furthermore, diverse functional groups such as halide (F, Cl, Br), methyl, methoxyl, cyano, nitro and trifluoromethyl were tolerated in the present protocol (Table 2, entries 1−11). It should be noted the azomethine imine **2l** with an ortho-substituted on the aromatic ring could also be converted into the expected diazabicycle **3l** with good yield (85%). The naphthyl group was compatible with the reaction conditions (66%), while a 2-furyl- or 2-thienyl-substituted azomethine imine was not a good candidate for this transformation (Table 2, entries 13−15). When 1-phenylpent-1-yn-3-one was used, **3n** was obtained as a single *trans*-

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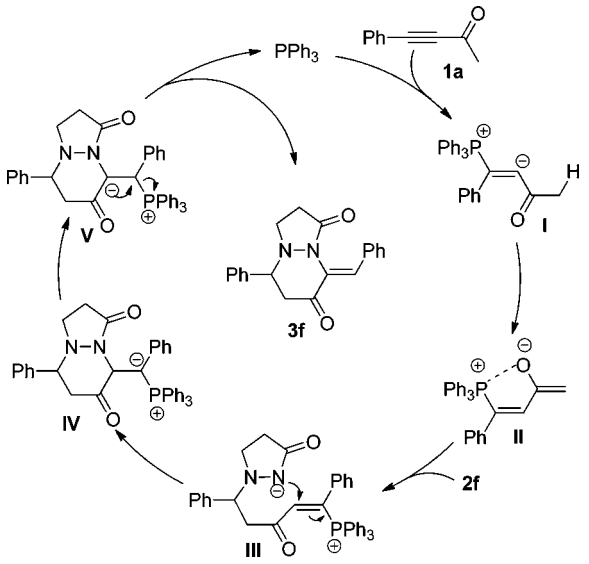
isomer in 82% yield (Table 2, entry 16). Substituted phenyls on R^1 were accommodated in this transformation and gave the cycloaddition products in good yields (Table 2, entries 17 and 18). For one representative example, we showed that the reaction could be performed in a 3.0 mmol scale to afford the product **3a** without loss of reactivity (entry 19).

On the basis of our experimental results and previous studies, a tentative catalytic cycle was proposed for the current domino reaction (Scheme 2). The reaction was initiated by the

Scheme 2. Proposed Catalytic Cycle for the [3 + 3]-Cycloaddition Reaction



conjugate addition of PPh_3 to the ynone **1a** providing the zwitterionic intermediate **I**, which subsequently underwent a proton transfer (mediated by *n*-BuOH) and produced the enolate **II**. Then enolate **II** nucleophilically added to azomethine imine **2f** furnishing intermediate **III**. The latter then underwent intramolecular umpolung addition to generate intermediate **IV**. Finally, further proton transfer (assisted by *n*-BuOH) and elimination of the phosphine catalyst afforded the annulation product **3f**.

In summary, we have developed an efficient method to prepare *N*,*N*-bicyclic hydropyridazine derivatives by phosphine-catalyzed [3 + 3]-annulation reaction with ynones and azomethine imines. To our knowledge, this reaction is the first example of [3 + 3]-annulation reaction of ynones. This transformation constructed two new bonds and one ring with 100% atom economy and good yields in a single step. Readily available starting materials, mild reaction conditions, inexpensive catalyst, and practical processes make this reaction valuable in synthetic chemistry. We expect that this new process could be potentially applied to the synthesis of diazabicycle containing natural products and biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00988.

X-ray crystallographic data for **3a** (CIF)
Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) CCDC 1456641 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/services/structure_deposit/cif.

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