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Phosphane-Catalyzed [3+3] Annulation of C,N-Cyclic Azomethine Imines with Ynones: A Practical Method for Tricyclic Dinitrogen-Fused Heterocycles

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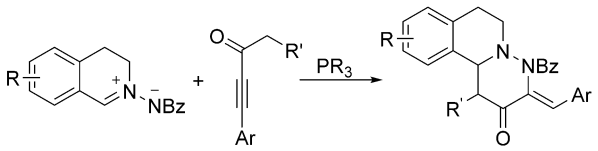
Abstract: A phosphane-catalyzed [3+3] annulation of azomethine imines with ynones has been developed. Under mild reaction conditions, the reaction proceeds smoothly to afford tricyclic dinitrogen-fused heterocyclic compounds in moderate to excellent yields with moderate to excellent stereoselectivies. Using a chiral phosphine as the catalyst, the reaction could work to give the cycloadduct in moderate yield with moderate enantioselectivity.

Keywords: annulation; azomethine imines; heterocycles; phosphanes; ynones

In the past two decades, nucleophilic phosphane-catalyzed annulation reactions have intensely been explored and have become a powerful tool for the synthesis of synthetically useful or biologically important carbocyclic and heterocyclic compounds,[1] and total syntheses of natural products.[2] These reactions generally proceed *via* zwitterionic intermediates formed *in situ* from the addition of the Lewis basic phosphane to phosphane acceptors such as activated allenes, alkynes, MBH carbonates and acetates. Therefore, the search for new phosphane acceptors and the exploration of their reaction activities are among the key tasks in the research on nucleophilic phosphane catalysis. In recent years, a new acceptor of phosphanes, the ynone unit, has attracted attention. Under phosphane catalysis conditions, ynone acts as a C_2 or C_3 synthon to furnish various annulation reactions. In 2012, the Shi group and the Huang group explored the phosphane-catalyzed [3+2] annulation of ynones with isatins, affording spiro[furan-2,3′-indoline]-2′,4(5*H*)-diones.[3,4] The Huang group presented a phosphane-catalyzed [3+2] annulation reaction of ynones and 2-arylideneindane-1,3-diones for the construction of spirocyclopentanone skeletons.[5] In 2013, Ramachary and co-workers achieved a phosphane-catalyzed Tomiat–Zipper cyclization of methyleneoxindoles with 4-phenylbut-3-yn-2-one, providing functionalized five-membered spirooxindoles.[6] Most recently, Du developed phosphane-promoted [4+2] annulation reactions of unsaturated pyrazolones with but-3-yn-2-one and [3+2] annulation reactions of unsaturated pyrazolones with 4-phenylbut-3-yn-2-one, providing pyrano[2,3-c]pyrazoles and spirocyclopentanonepyrazolones.[7] All these annulations have been focused on the [3+2] or [4+2] annulation of the ynone with electron-deficient alkenes or ketones; to the best of our knowledge, the [3+3] annulation reaction with the use of ynones as the phosphane acceptor has never been reported.

In the past five years, it has been demonstrated that 1,3-dipoles formed *in situ* from the addition of a phosphane to a phosphane acceptor, could react with a stable 1,3-dipole to furnish a stepwise [3+X] annulation reaction.[8] On the basis of this principle, when a stable 1,3-dipole meets with an ynone under phosphane catalysis conditions, a [3+3] annulation might be achieved. Among the various stable 1,3-dipoles, azomethine imines are highly valuable substrates and have often served as three-membered synthons in [3+2], [3+3] and [4+3] cycloaddition reactions for the synthesis of diverse biologically important dinitrogen-fused heterocyclic compounds,[9] which have displayed a wide range of bioactivities such as analgesic, antipyretic, anti-inflammatory, anorectic, antibacterial, antitumor, anti-Alzheimer, herbicidal and pesticidal activities.[10] In consideration of these characteristics, we chose an azomethine imine as the 1,3-dipole substrate and explored its annulation reaction with ynones under phosphane catalysis conditions. Herein we present the first example of a phosphane-catalyzed [3+3] annulation of azomethine imines with ynones to deliver dinitrogen-fused heterocycles (Scheme 1).

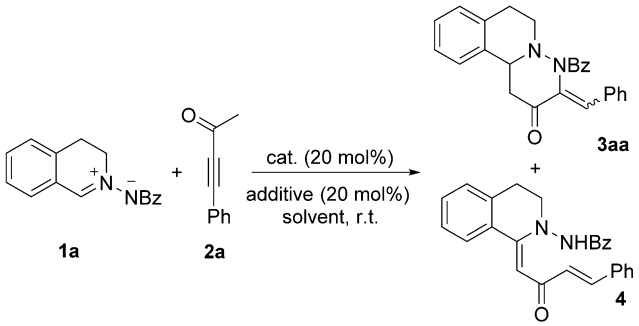


Scheme 1. Phosphane-catalyzed [3+3] annulation of ynones with azomethine imines.

In our initial study, the reaction of azomethine imine **1a** with but-3-yn-2-one **2a** was carried out in the presence of 20 mol% PPh_3 in CH_2Cl_2 at room temperature (Table 1, entry 1). The desired [3+3] annulation product **3aa** was obtained in 69% yield with >20:1 *Z*/*E* ratio. Unfortunately, the mixture of (*Z*)- and (*E*)-isomers could not be separated by flash column. Furthermore, a trace amount of addition product **4** was observed. Using more nucleophilic phosphanes such as $EtPPh_2$ and Me_2PPh as the catalyst, the yields deteriorated (entries 2 and 3). Next, with PPh_3 as the catalyst, a concise solvent screening was performed. In several solvents such as $CHCl_3$, toluene, THF and CH_3CN, no better results were obtained (entries 4–7). In order to improve both yield and selectivity of the reaction, we turned our attention to the use of different Brønsted acids as the additive, expecting that it would favour the reaction (entries 8–12). To our delight, this strategy was found to be effective in increasing the yield. In the presence of 20 mol% of benzoic acid, phenol, pivalic acid or acetic acid, the yields were remarkably increased to 86–92%. Particularly, when 20 mol% phenol was used, the [3+3] annulation product **3aa** was obtained in 91% yield, moreover the side-product **4** was not observed (entry 9). In contrast, with the use of 2-naphthol as the additive, the product was produced in a relatively low yield (entry 12). Finally, the optimal reaction conditions were determined as 20 mol% of Ph_3P as the catalyst and 20 mol% phenol as the additive in dichloromethane at room temperature.

Having established the optimal reaction conditions, the scope of C,N-cyclic azomethine imines was first explored. As shown in Table 2, various azomethine imines with different substituents including electron-neutral, electron-donating and electron-withdrawing group were well tolerated, providing the desired products in high yields and good to excellent *Z*/*E* ratios (entries 1–7). The substrates with electron-donating groups on the phenyl ring gave better yields than those bearing electron-withdrawing groups (entries 2–4 *vs.* 5–7). The substrates with electron-withdrawing groups seemed more active and were fully converted in shorter times than those substrates with electron-

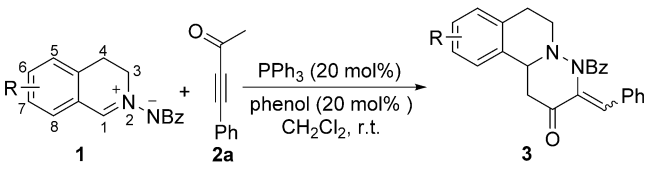
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Yield [%][b]
1	PPh_3	–[c]	CH_2Cl_2	69
2	$EtPPh_2$	–	CH_2Cl_2	48
3	Me_2PPh	–	CH_2Cl_2	39
4	PPh_3	–	$CHCl_3$	65
5	PPh_3	–	toluene	43
6	PPh_3	–	THF	48
7	PPh_3	–	CH_3CN	64
8	PPh_3	$PhCO_2H$	CH_2Cl_2	92
9	PPh_3	phenol	CH_2Cl_2	91[d]
10	PPh_3	PivOH	CH_2Cl_2	90
11	PPh_3	CH_3CO_2H	CH_2Cl_2	86
12	PPh_3	2-naphthol	CH_2Cl_2	58[d]

[a] Unless noted otherwise, reactions were carried out in 2 mL of solvent using 0.1 mmol of **1a**, 0.2 mmol of **2a** and 20 mol% of phosphane.
[b] Isolated yields, the *Z*/*E* ratio is >20:1, determined by ^{1}H NMR analysis of the crude product. Unless noted otherwise, a trace of the by-product **4**, which could not be separated out by flash column chromatography, was observed.
[c] No additive.
[d] No side product **4** was observed.

Table 2. Scope of the C,N-cyclic azomethine imines.[a]



Entry	R in **1**	Time [h]	**3**	Yield [%][b]
1	H (**1a**)	24	**3aa**	91
2	5-Me (**1b**)	23	**3ba**	79
3	7-Me (**1c**)	21	**3ca**	88
4	8-Me (**1d**)	24	**3da**	84[c]
5	7-Cl (**1e**)	15	**3ea**	67
6	5-Br (**1f**)	15	**3fa**	70
7	7-Br (**1g**)	14	**3ga**	71

[a] Unless noted otherwise, reactions were carried out in 2 mL of CH_2Cl_2 using 0.1 mmol of **1**, 0.2 mmol of **2a**, 0.02 mmol of phenol in the presence of 20 mol% of Ph_3P.
[b] Isolated yields. Unless noted otherwise, the *Z*/*E* ratio is >20:1, determined by ^{1}H NMR analysis of the crude product.
[c] The *Z*/*E* ratio is 8:1.

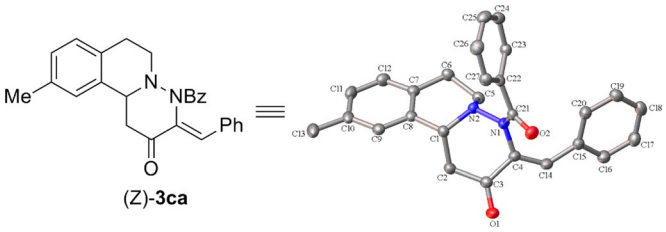
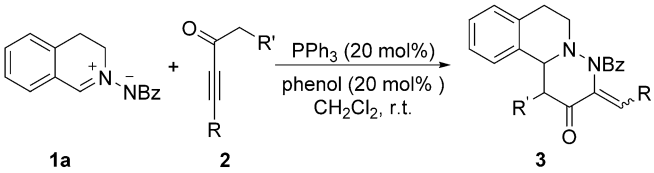


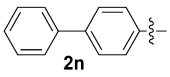
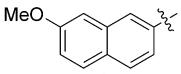
Figure 1. The X-ray crystallographic structure of (*Z*)-**3ca**.

donating groups, but a part of these substrates converted into side products, leading to relatively lower yields (entries 5–7). The major isomer of product **3** was unambiguously assigned to be *Z*-isomer according to X-ray crystallographic data of the product **3ca** (Figure 1).[11] It is worth noting that using 1.25 g (5 mmol) of azomethine imine **1a**, the Ph_3P-catalyzed [3+3] annulation reaction of **1a** with **2a** still proceeded smoothly in CH_2Cl_2 at room temperature for 24 h to afford the product **3aa** in 78% yield with >20:1 *Z*/*E*. Compared with the yield of the reaction on the milligram scale (Table 2, entry 1), the yield somewhat dropped, but is acceptable. Thus this reaction could be a practical method for the synthesis of dinitrogen-fused heterocycles.

Next, a variety of ynones was synthesized and investigated in the [3+3] annulation reaction. As shown in Table 3, the electronic properties of the substituents on the phenyl rings of the ynones **2** have a remarkable influence on the activity of the reaction (Table 3, entries 1–12). Compared with the substrates (**2b**–**2g**) with electron-donating groups, the substrates (**2h**–**2m**) bearing electron-withdrawing groups underwent the [3+3] annulation to afford the products **3** in higher yields (84–94% *vs.* 70–80% yields, entries 7–12 *vs.* 1–6). The substrates bearing electron-donating groups or electron-withdrawing groups showed moderate to good *Z*/*E* selectivity (entries 1–12). The protocol could also be applied to 4-biphenylyl and 2-naphthyl ynones, providing [3+3] annulation products in high yields with good to excellent *Z*/*E* selectivities (entries 13 and 14). The thienyl-substituted ynone (**2p**) smoothly underwent the annulation reaction as well, but the *Z*/*E* selectivity was very poor, moreover the (*E*)-isomer was produced as a major isomer (entry 15). Especially, the mixture of (*Z*)- and (*E*)-**3ap** could be separated by flash column. Both 1-phenylpent-1-yn-3-one (**2q**) and 1-phenylhex-1-yn-3-one (**2r**) also worked under the standard reaction conditions to give the cycloadducts in high yields, albeit requiring prolonged reaction time (entries 16 and 17). The relative configurations of the compounds **3aq** and **3ar** had not been determined because attempts to get their single crystals and the analysis through 2D NMR data failed. Disappointedly, with trimethylsilylalkynyl ketone (**2s**) and cyclohexylalkynyl ketone (**2t**) as substrates, the desired [3+3] annulation products could not be obtained and only starting materials were recovered (entries 18 and 19).

Table 3. Scope of the ynones.[a]

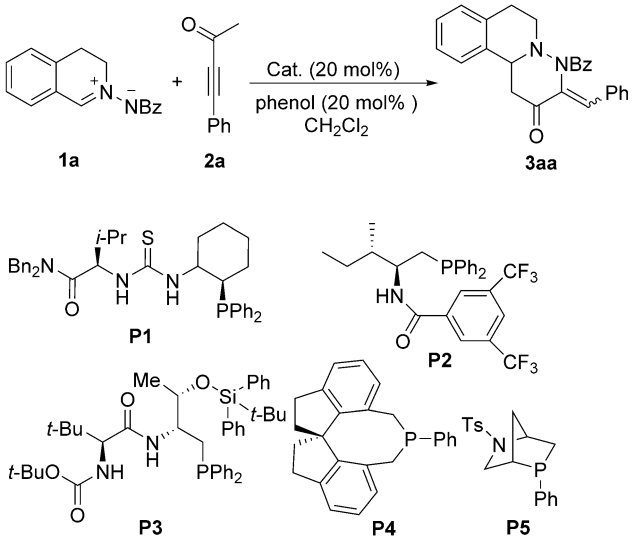


Entry	R in **2**	R′	Time [h]	**3**	Yield [%][b]	*Z*:*E*[b]
1	3-MeC_6H_4 (**2b**)	H	22	**3ab**	78	20:1
2	4-MeC_6H_4 (**2c**)	H	36	**3ac**	80	15:1
3	4-EtC_6H_4 (**2d**)	H	22	**3ad**	73	3:1
4	4-*n*-PrC_6H_4 (**2e**)	H	22	**3ae**	71	>20:1
5	4-*n*BuC_6H_4 (**2f**)	H	22	**3af**	70	>20:1
6	4-$OMeC_6H_4$ (**2g**)	H	20	**3ag**	72	>20:1
7	3-FC_6H_4 (**2h**)	H	11	**3ah**	91	5:1
8	4-FC_6H_4 (**2i**)	H	18	**3ai**	84	6:1
9	3-ClC_6H_4 (**2j**)	H	11	**3aj**	87	3:1
10	4-ClC_6H_4 (**2k**)	H	14	**3ak**	94	12:1
11	4-BrC_6H_4 (**2l**)	H	10	**3al**	88	4:1
12	4-CNC_6H_4 (**2m**)	H	14	**3am**	90	3:1
13	 **2n**	H	22	**3an**	82	>20:1
14	 **2o**	H	17	**3ao**	76	5:1
15	2-thienyl (**2p**)	H	22	**3ap**	71	3:4[c]
16	Ph (**2q**)	Me	72	**3aq**	75	1:1
17	Ph (**2r**)	Et	72	**3ar**	77	>20:1
18	TMS (**2s**)	H	72	–	–	–[d]
19	cyclohexyl (**2t**)	H	72	–	–	–[d]

[a] Reactions were performed in 2 mL of CH_2Cl_2 at room temperature using 0.1 mmol of **1a**, 0.2 mmol of **2**, 0.02 mmol of phenol and 20 mol% of Ph_3P.
[b] Isolated yields. The *Z*/*E* ratio was determined by ^1H NMR analysis of the crude product.
[c] (*Z*)- and (*E*)-**3ap** were separated by flash column.
[d] No reaction.

An asymmetric variant of this phosphane-catalyzed [3+3] annulation of C,N-cyclic azomethine imines with ynones was also investigated by employing several chiral phosphanes (**P1**–**P5**) (Table 4). The [3+3] annulation of the C,N-cyclic azomethine imine **1a** and but-3-yn-2-one **2a** was selected as a model reaction (Table 4). The thiourea and amino acid-based bifunctional chiral phosphanes (**P1**–**P3**) demonstrated moderate enantioselective catalytic capability, producing the desired product in 34–51% yield and 15–30% *ee* (Table 4, entries 1–4). In particular, the commercially available amino acid-based phosphane **P3** gave an encouraging result (51% yield and 30% *ee*) (entry 3)

Table 4. Screening of the reaction conditions for an asymmetric variant.[a]

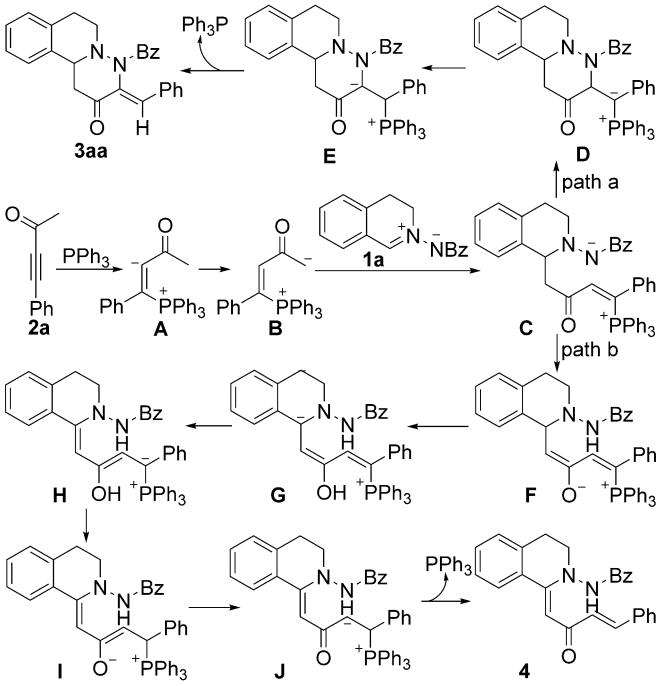


Entry	Cat.	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**P1**	25	36	34	−15
2	**P2**	25	36	48	−20
3	**P3**	25	24	51	30
4	**P3**	0	72	39	20

[a] Unless noted otherwise, reactions were carried out in 2 mL of CH_2Cl_2 using 0.1 mmol of **1a**, 0.2 mmol of **2a**, 0.02 mmol of phenol and 20 mol% of phosphane.
[b] Isolated yields. The *Z*/*E* ratio is >20:1, determined by ^{1}H NMR analysis of the crude product.
[c] Determined by chiral HPLC analysis.

(the absolute configuration of the product **3aa** has not been determined). However, with **P3** as chiral catalyst, the attempt to improve the enantioselectivity by decreasing the reaction temperature to 0°C failed, only affording the cycloadditon product in 39% yield and 20% *ee* (entry 4). Unfortunately, the catalytic activity of cyclic chiral phosphanes **P4** and **P5** was very weak, providing the cycloadduct in very low yield with accompanying formation of side product **4**.

A plausible mechanism to account for the formation of the product **3** and side product **4** is proposed in Scheme 2. Ph_3P acts as a nucleophilic promoter to initiate the reaction and undergoes an addition to ynone **2a** to produce zwitterionic intermediate **A**, followed by proton transfer to give intermediate **B**, which then undergoes conjugate addition to **1a** to afford intermediate **C**. In path a, the intermediate **C** performs intramolecular addition to give the intermediate **D**. Subsequent proton transfer led to intermediate **E**, which carries out elimination of Ph_3P to form the final product **3aa**. Isotopic labeling experiments and computation results had proved that water or other protic sources can promote [1,2]- and [1,3]-



Scheme 2. A proposed mechanism of phosphane-catalyzed [3+3] annulation.

proton shifts in phosphine-catalyzed annulations of allenoates,[12] thus assisting the [1,2]- or [1,3]-hydrogen shift. In this reaction, phenol might favor formation of **B** from **A** and formation of **E** from **D** through assisting [1,2]- and [1,3]-hydrogen shifts. In path b, the intermediate **C** undergoes intramolecular proton transfer and isomerization to give the intermediate **J**. Subsequent elimination of phosphane produces Mannich-type by-product **4**.

In conclusion, the phosphane-catalyzed [3+3] annulation of azomethine imines with ynones has been achieved under mild reaction conditions, providing tricyclic heterocyclic compounds in high yields with moderate to excellent stereoselectivies. Using a commercially available amino acid-based phosphane as chiral catalyst, the reaction could work to give the cycloadduct in moderate yield with moderate enantioselectivity. The present protocol provides a rapid, efficient and practical method to construct valuable dinitrogen-fused heterocycles with potential biological activity.

Experimental Section

General Procedure for Phosphane-Catalyzed [3+3] Annulation Reactions of Azomethine Imines with Ynones

To a stirred solution of C,N-cyclic azomethine imine (0.1 mmol) in 2 mL of CH_2Cl_2 was added but-3-yn-2-one

(0.2 mmol) at room temperature. Phosphane (0.02 mmol) was then added into the above solution. The resulting mixture was stirred at room temperature for the specified time, and was then concentrated. The residue was purified by flash column (ethyl acetate/petroleum ether) to afford the corresponding product.

Acknowledgements

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