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Phosphine-catalyzed [4 + 3] Cycloaddition Reaction of Aromatic Azomethine Imines with Allenoates

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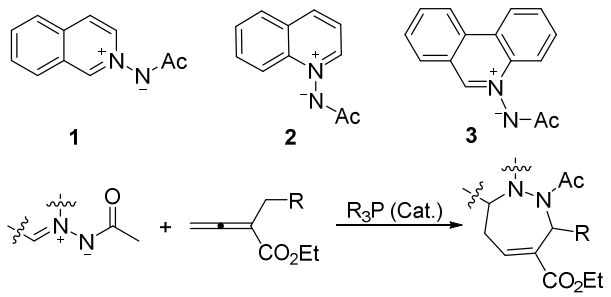
An efficient phosphine-catalyzed [4 + 3] cycloaddition of aromatic azomethine imines with allenoates has been developed, providing dinitrogen-fused heterocyclic compounds in moderate to excellent yields. The reaction proceeds smoothly under mild conditions, providing an expedient access to highly valuable heterocyclic compounds with isoquinoline, quinoline and phenanthridine skeleton.

The 1, 3-dipolar cycloadditions are one of the most powerful methods for the convergent synthesis of various heterocycles. Among 1, 3-dipoles for 1, 3 -dipolar cycloadditions, azomethine imines have attracted much attention due to its stability and high accessibility. A variety of thermal, metal-catalyzed and organocatalytic cycloadditions including [3 + 2], [3 + 3] and [4 + 3] cycloadditions have been developed to construct dinitrogen-fused heterocyclic derivatives.[1-3] Of these reactions, [4 + 3] cycloaddition reactions of azomethine imines provide a concise and efficient approach for the synthesis of dinitrogen-fused seven-membered heterocycles. However, the successful examples on metal-catalyzed and organocatalytic [4 + 3] cycloaddition of azomethine imines are quite limited. In 2007, Hayashi reported Pd-catalyzed [4 + 3] cycloadditions of azomethine imines with *γ*-methylidene-*δ*-valerolactones for the synthesis of hexahydropyrazolodiazepinone.[4] Most recently, Chi disclosed the first *N*-heterocyclic carbene (NHC)-catalyzed [4 + 3] cycloaddition of azomethine imines and enals for the synthesis of tetrahydropyrazolodiazepinedione.[5] In addition to above efforts, our group developed phosphine-catalyzed [4 + 3] cycloaddition reactions of *N*, *N'*-cyclic azomethine imines and *C*,*N*-cyclic azomethine imines with allenoates, affording biologically important dinitrogen-fused seven-membered heterocyclic compounds.[6] As a continuation of our research interest in developing novel 1, 3-dipolar cycloaddition reactions,[7] we set out to investigate the phosphine-catalyzed [4 + 3] cycloaddition of *C*, *N*-cyclic aromatic azomethine imines including *N*-acetyliminoisoquinolinium betaine (**1**), *N*-acetyliminoquinolinium betaine (**2**), *N*-acetyliminophenanthridinium betaine (**3**) with allenoates (Scheme 1).[8–9] The phosphine-catalyzed [4 + 3] cycloaddition reaction will provides efficient synthetic methods for the heterocyclic compounds with isoquinoline, quinoline and phenanthridine skeleton, which display a broad range of uses and work as key units in of many pharmaceuticals, agrochemicals, and other useful chemicals.[10] Herein, we report our results on this phosphine-catalyzed [4 + 3] cycloaddition reaction of aromatic azomethine imines with allenoates.

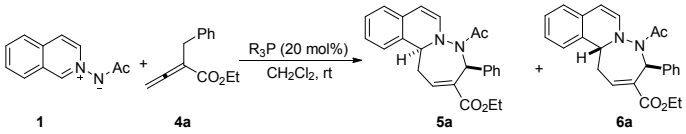


Scheme 1 Phosphine-catalyzed [4 + 3] cycloaddition of *C*, *N*-cyclic aromatic azomethine imines with allenoates.

The investigation was initiated by evaluating the reaction of *N*-acyliminoisoquinolinium betaine **1** with allenoate **4a**[11] at room temperature. A control experiment indicated that no [4 + 3] cycloadduct was observed in the absence of phosphine and only the thermal [3 + 2] cycloaddition product was obtained (Table 1, entry 1).[7d] Using 20 mol% of Ph_3P as the catalyst, a very small amount of [4 + 3] cycloadduct could be observed, and thermal cycloadduct was isolated as the major product (entry 2). When more nucleophilic $MePPh_2$ was used, 15% yield of [4 + 3] cycloaddition product was obtained, although the competitive thermal cycloaddition reaction still dominated the reaction process (entry 3). To our delight, when strong nucleophilic Bu_3P was used as the catalyst, the competitive thermal cycloaddition was effectively suppressed, and the [4 + 3]

cycloaddition reaction of azomethine imine **1** with allenoate **4a** proceeded efficiently to provide a seven-membered cycloadduct in 88% yield with 9:1 dr (entry 4). Unfortunately, the product is a mixture of two diastereoisomers which could not be separated by flash column chromatography. Lowering the reaction temperature to 0 °C led to lower 64%yield (entry 5). The solvent screening revealed that dichloromethane is the optimal solvent (entries 6−7).

Table 1 Screening of reaction conditions for the cycloaddition of azomethine imine **1** with allenoate **4a**.[a]



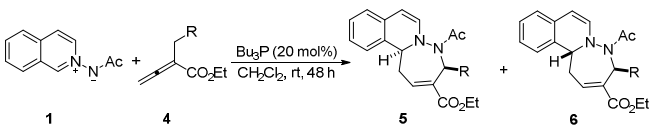
1 4a 5a 6a

Entry	PR_3	Solvent	time (h)	Yield (%)[b]	*dr* (**5a**:**6a**)[c]
1	-[d]	CH_2Cl_2	48	0	-
2	Ph_3P	CH_2Cl_2	48	<5	-
3	$MePPh_2$	CH_2Cl_2	48	15	8:1
4	Bu_3P	CH_2Cl_2	40	88	9:1
5[e]	Bu_3P	CH_2Cl_2	48	64	9:1
6	Bu_3P	toluene	48	62	7:1
7	Bu_3P	THF	48	73	7:1

[a] Reactions of azomethine imine **1** (0.125 mmol) and the allenoate **4a** (0.15 mmol) were carried out in 3 mL of dichloromethane . [b] Isolated yields of two products. [c] Based on ^{1}HNMR analysis. [d] Without phosphine catalyst. [e] The reaction was performed at 0 °C.

With the optimal reaction conditions in hand, we investigated the [4 + 3] cycloaddition reactions of azomethine imine **1** with various α-substituted allenoates **4**.[11] As shown in the Table 2, various *α*-benzyl allenoates bearing electron-withdrawing and electron-donatinging substituents at the different aromatic position underwent the reaction to give the desired cycloadducts in excellent yields and moderate diastereoselectivities (entries 1−11). The relative configuration was determined by the NMR spectroscopy and the single *X*-ray crystallographic analysis.[12] The *α*-(2-naphthylmethyl) allenoate (**4k**) was also tolerated, thus producing the desired [4 + 3] cycloadduct in 69% yield with 7:1 *dr* (entry 11). Disappointingly, the mixture of two diastereomers could not be separated by the flash column. The *α*-ethylallenoate (**4l**) and *α*-*n*-propylallenoate (**4m**) underwent the reaction to give the desired product as a single diastereomer in 81% and 78% yield respectively (entries 12−13). α-Ethoxycarbonylallenoate (**4n**) was also a compatible substrate to provide the corresponding product in 79% yield with 5:1 *dr* (entry 14).

Table 2 Bu_3P-catalyzed cycloaddition of *N*-acetyliminoisoquinolinium betaine **1** with α-substituted allenoates **4**.[a]



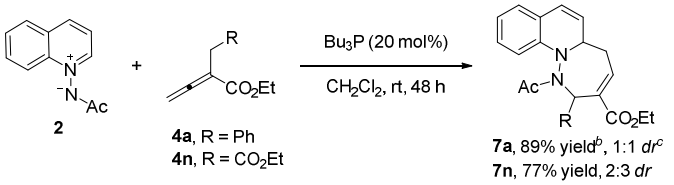
1 4 5 6

Entry	R	Product	Yield (%)[b]	*dr* (**5**:**6**)[c]
1	Ph (**4a**)	**5a** + **6a**	88	9:1
2	2-MeC_6H_4 (**4b**)	**5b** + **6b**	80	9:1
3	3-MeC_6H_4 (**4c**)	**5c** + **6c**	70	6:1
4	4-MeC_6H_4 (**4d**)	**5d** + **6d**	85	10:1
5	2-FC_6H_4 (**4e**)	**5e** + **6e**	90	>20:1
6	4-FC_6H_4 (**4f**)	**5f** + **6f**	87	14:1
7	3-ClC_6H_4 (**4g**)	**5g** + **6g**	78	8:1
8	4-ClC_6H_4 (**4h**)	**5h** + **6h**	89	7:1
9	3-BrC_6H_4 (**4i**)	**5i** + **6i**	83	4:1
10	4-BrC_6H_4 (**4j**)	**5j** + **6j**	90	7:1
11	2-Nap (**4k**)	**5k** + **6k**	69	7:1
12	CH_3 (**4l**)	**5l** + **6l**	81	>20:1
13	CH_2CH_3 (**4m**)	**5m** + **6m**	78	>20:1
14	CO_2Et (**4n**)	**5n** + **6n**	79	5:1

[a] Reactions of azomethine imine **1** (0.125 mmol) and the allenoates **4** (0.15 mmol) were carried out in 3 mL of dichloromethane at rt for 48 h. [b] Isolated yields of two products. [c] Based on ^{1}H NMR analysis.

As indicated in Table 3, in the presence of 20 mol% of Bu_3P, *N*-acetyliminoquinolinium betaine (**2**) could also undergo the [4 + 3] cycloaddition reaction with allenoates (**4**), affording the corresponding cycloadduct as a diastereoisomeric mixture in high yield, albeilt with moderate diastereoselectivity. Pitifully, the relative configuration had not been determined because the single crystal of the product could not be obtained. We next investigated the [4 + 3] cycloaddition of *N*-acetyliminophenanthridinium betaine (**3**) with a variety of allenoates **4** (Table 4). Under the optimal reaction conditions, various allenoates could be tolerated to give the desired cycloadducts in high yields. In general, *α*-aryl-CH_2-substituted allenoates afford the corresponding products in excellent yields, albeit in moderate diastereoselectivities. Fortunately, compared with the products from azomethine imine **1** or **2**, the mixture of two diastereomers from **3** could be separated by using flash column, except for the product from the reaction **3** with **4l**. The α-alkyl-substituted allenoates including α-ethyl allenoate (**4l**) and α-n-propyl allenoate (**4m**) gave the corresponding product in 81% yield and 94% yield, respectively (entry 5 and 6). Additionally, allenoate with an ester group on *β'*-position (**4n**) gave a high yield of the cycloadduct with poor diastereoselectivity (entry 7). The relative configuration of the products **8a** and **9a** was unambiguously confirmed by X-ray diffraction analysis.[12]

Table 3 Bu_3P-catalyzed cycloaddition of *N*-acetyliminoquinolinium betaine **2** with allenoates **4**[a]



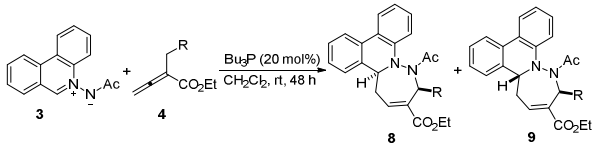
2

4a, R = Ph
4n, R = CO_2Et

7a, 89% yield[b], 1:1 *dr*[c]
7n, 77% yield, 2:3 *dr*

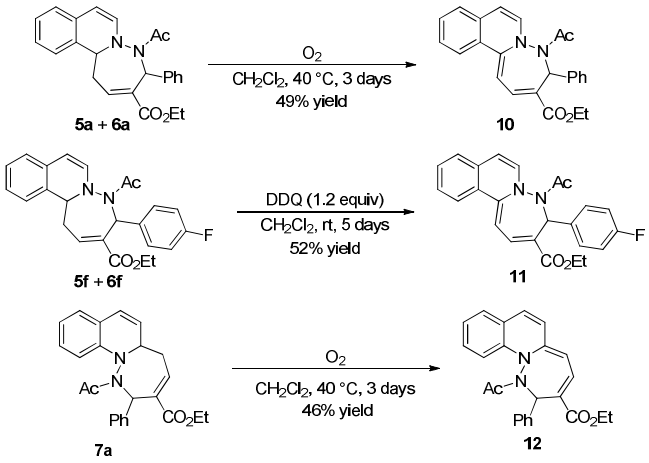
[a] Reactions of azomethine imine **2** (0.125 mmol) and the allenoates **4** (0.15 mmol) were carried out in 3 mL of dichloromethane at rt. [b] Isolated yields. [c] Based on integration of signals in the ^{1}H NMR analysis.

Table 4 Bu_3P-catalyzed cycloaddition of *N*-acetyliminophenanthridinium betaine **3** with allenoates **4**.[a]



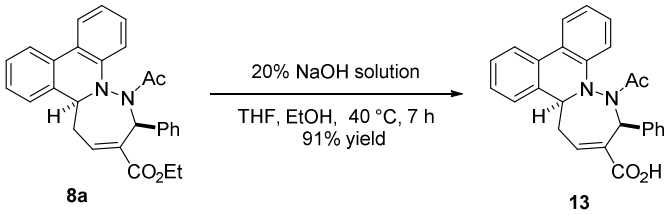
Entry	R	**8**, Yield (%)[b]	**9**, Yield (%)[b]
1	Ph (**4a**)	**8a**, 57	**9a**, 29
2	2-FC_6H_4 (**4e**)	**8e**,76	**9e**, 15
3	4-ClC_6H_4 (**4h**)	**8h**, 71	**9h**, 26
4	2-naphthyl (**4k**)	**8k**, 61	**9k**, 19
5	Me (**4l**)	**8l** + **9l**, 81[c]	
6	Et (**4m**)	**8m**, 71	**9m**, 23
7	CO_2Et (**4n**)	**8n**, 49	**9n**, 40

[a]Reactions of azomethine imine **3** (0.125 mmol) and the allenoates 4 (0.15 mmol) were carried out in 5 mL of dichloromethane. [b] Isolated yields. [c] total yield of two diastereomers, **8l** : **9l** = 10 : 1.



Scheme 2 Oxidation of the cycloadducts .

During the purification process of the cycloadducts, we observed an interesting oxidation phenomenon. In the air, the [4 + 3] cycloadducts could slowly be oxidized, but the full conversion required 10 days. Although full conversation could be accomplished, the yield was not high due to decomposition of the [4 + 3] cycloadduct in the process of oxidation. Gratefully, under oxygen atmosphere, the cycloadducts **5a** and **6a** were stirred in dichloromethane at 40 °C for 3 days to give the oxidation product **10** in 49% yield. With the use of 1.2 equiv of DDQ, the cycloadduct **5f** and **6f** could be oxidized to the corresponding derivative **11** in 52% yield (Scheme 2). Under oxygen atmosphere, the cycloadduct **7a** from *N*-acetyliminoquinolinium betaine **2** was oxidized in 46% yield. Treatment of the cycloadduct **8a** with 20% NaOH solution resulted in the hydroxylation of ester group, giving the carboxylic acid derivative **13** in 91% yield (Scheme 3).



Scheme 3 The synthetic transformations of the cycloadduct **8a**

EXPERIMENTAL

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Reactions were monitored through thin-layer chromatography (TLC). Chromatograms were visualized by fluorescence quenching under UV light at 254 nm. Flash column chromatography was performed using Qingdao Haiyang flash silica gel (200-300 mesh). Infrared spectra were recorded using a Bruker Optics TENSOR 27 instrument. 1H and 13C NMR spectra were recorded using a Bruker-300 spectrometer. Accurate mass measurements were performed using an Agilent instrument with the ESI-MS technique.

General procedure for the phosphine-catalyzed [4 + 3] cycloaddition reaction: An oven-dried 15 mL of Schlenk tube was charged with azomethine imine (0.125 mmol), 3 mL or 5 mL of CH_2Cl_2 and the allenoate (0.15 mmol) at room temperature, then catalyst (0.025 mmol) was added to the above solution. The reaction mixture was stirred at room temperature for 48 h, and then was concentrated. The residue was purified by flash column (ethyl acetate/ petroleum ether) to afford the corresponding product.

Conclusions

In summary, we have developed an efficient phosphine-catalyzed [4 + 3] cycloaddition of aromatic azomethine imines with allenoates, providing dinitrogen-fused heterocyclic compounds in moderate to excellent yields. The catalytic [4 + 3] cycloaddition reaction provided a practical synthetic method for biologically important heterocycles.

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Notes and references

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† Electronic Supplementary Information (ESI) available: characterization data spectra of all products. See DOI: 10.1039/b000000x/

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12 Crystallographic data for **5j**, **8a**, **9a**, **11**, and **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 1049475–1049479. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

