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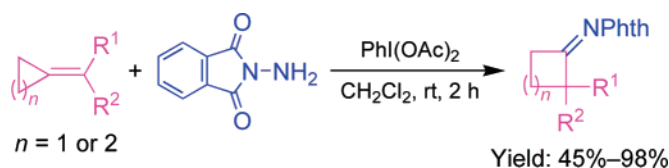
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## ABSTRACT



The ring expansion of small-ring compounds provides a powerful method for the construction of various cyclic compounds. Herein, nitrene equivalent mediated metal-free ring expansions of alkylidenecyclopropanes (ACPs) and an alkylidenecyclobutane (ACB) were described. In this synthesis, a series of aryl-substituted cyclobutylidene and cyclopentylidene hydrazine derivatives were obtained under mild conditions in moderate to good yields.

Metal-promoted ring expansions of three- and four-membered ring substrates as powerful methods for the construction of various cyclic compounds have been attracting extensive attention.<sup>1</sup> For example, transition-metal complexes can catalyze ring expansions of 1-alkenyl, 1-alkynyl, and 1-allenyl cyclopropanols and cyclobutanols to give four- and five-membered ring products.<sup>2</sup> Metal catalysts were also efficient in promoting the transformations of alkylidenecyclopropanes (ACPs) and alkylidenecyclobutanes (ACBs) to cyclobutanones and cyclopentanones.<sup>3</sup> Recently, Pt- or Pd-catalyzed ring expansion rearrangements of ACPs to cyclobutenes have also been reported.<sup>4</sup> These ring expansion

reactions not only provide new approaches for the synthesis of complex cyclic molecules but also enrich the chemistry of small-ring compounds.

Although many different reactions involving ACPs are already known,<sup>5,6</sup> only a few examples of ring expansions of ACPs without participation of a metal complex were reported.<sup>7</sup> Therefore, it will be significant to design new metal-free ring expansion reactions. It was reported that substituted 1-aza-spiro[2.2]pentanes generated from 1,3-

(1) (a) *Small Ring Compounds in Organic Synthesis V, Topics in Current Chemistry*; de Meijere, A., Ed.; Springer-Verlag: Berlin, 1996; Vol. 178. (b) *Small Ring Compounds in Organic Synthesis VI, Topics in Current Chemistry*; de Meijere, A., Ed.; Springer-Verlag: Berlin, 2000; Vol. 207.

(2) Selected recent papers: (a) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162–7163. (b) Yoshida, M.; Sugimoto, K.; Ihara, M. *Org. Lett.* **2004**, *6*, 1979–1982. (c) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708–9709. (d) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044–6045.

(3) (a) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707–1712. (b) Shao, L. X.; Shi, M. *Eur. J. Org. Chem.* **2004**, 426–430. (c) Kurahashi, T.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881–7884. (d) Shen, Y. M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429–1432.

(4) (a) Fürstner, A.; Aissa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306–6307. (b) Shi, M.; Liu, L. P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430–7431.

(5) For reviews, see: (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–635. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867–877. (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1269.

dipolar cycloadditions of ACPs and azides could undergo facile rearrangement to form cyclobutanamine derivatives.<sup>8</sup> We envisioned that, if a substituted 1-aza-spiro[2.2]pentane derivative was generated from the reaction of ACP and a nitrene,<sup>9</sup> a tandem ring expansion would take place to give rise to a cyclobutylideneamine derivative. To our best knowledge, the reactions of substituted ACPs with nitrenes have not been investigated so far.<sup>10</sup> In this paper, we disclose a new metal-free ring expansion reaction involving ACPs and nitrenes.

In recent years, Yudin and co-workers developed a new and elegant nitrene equivalent for aziridination of olefins, where *N*-aminophthalimide was used as the nitrogen source.<sup>11</sup> This method possesses several advantages: (a) the reaction conditions are very mild, (b) various olefins work well in the reactions, and (c) most importantly, this method does not require any metal additives. Thus, we chose a combination of *N*-aminophthalimide and diacetoxyiodobenzene (DIB) as the nitrene equivalent<sup>11,12</sup> to investigate its reactions with ACPs.

Initially, diphenylmethylenecyclopropane (**1**) was treated with nitrenoid species generated from *N*-aminophthalimide and DIB in dichloromethane at room temperature for 2 h. To our delight, the ring expansion product, cyclobutylidene hydrazine **2**, was obtained in 80% yield (Table 1, entry 1), and no aziridine product was observed by checking the <sup>1</sup>H NMR of the crude reaction mixture. Acetic acid was generated during the reaction, and to see whether this in situ generated acid catalyzed the ring expansion, we tested the same reaction in the presence of excess potassium carbonate (10 equiv). Similar results were obtained under this new condition, suggesting that participation of acid in the ring expansion can be ruled out.

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(7) For a representative reference on nonmetal-mediated ring expansions of ACPs, see: (a) Hanack, M.; Bäessler, T.; Eymann, W.; Heyd, W. E.; Kopp, R. *J. Am. Chem. Soc.* **1974**, 96, 6686–6691. (b) Crandall, J. K.; Conover, W. W. *J. Org. Chem.* **1978**, 43, 3533–3535. (c) de Meijere, A.; Erden, I.; Weber, W.; Kaufmann, D. *J. Org. Chem.* **1988**, 53, 152–161. (d) Nötzel, M. W.; Rauch, K.; Labahn, T.; de Meijere, A. *Org. Lett.* **2002**, 4, 839–841. (e) Liu, L. P.; Shi, M. *J. Org. Chem.* **2004**, 69, 2805–2808.

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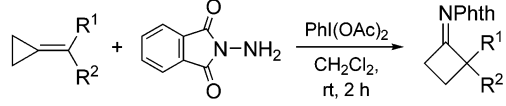
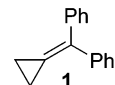
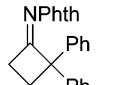
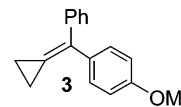
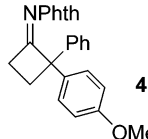
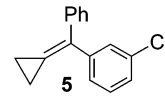
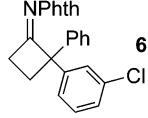
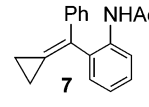
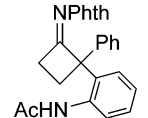
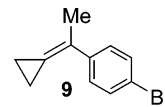
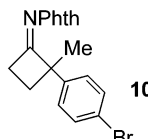
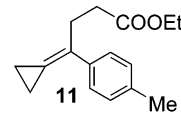
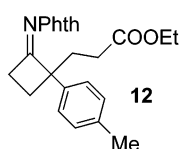
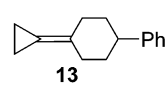
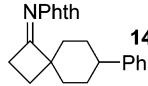
(9) Reviews on nitrenes: (a) Platz, M. S. In *Reactive Intermediate Chemistry*; Moss, R. A.; Platz, M. S.; Jones, M., Jr., Eds.; Wiley-Interscience: New Jersey, 2004; pp 501–559. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, 103, 2905–2919.

(10) In the reaction of methylenecyclopropane with methoxycarbonyl nitrene generated from photolysis of methyl azidoformate, only 1-methoxycarbonyl-1-aza-spiro[2.2]pentane was formed without rearrangement. See: Aue, D. H.; Lorens, R. B.; Helwig, G. S. *J. Org. Chem.* **1979**, 44, 1202–1207.

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**Table 1.** Metal-Free Ring Expansions of ACPs<sup>a</sup>

			
entry	substrate	product	yield <sup>b</sup> (%)
1			80 <sup>c</sup>
2			98 <sup>c</sup>
3			88 <sup>c</sup>
4			72 <sup>d</sup>
5			45 <sup>d</sup>
6			52 <sup>d</sup>
7			trace <sup>e</sup>

<sup>a</sup> Reaction conditions: ACP (1 mmol), *N*-aminophthalimide (1.5 mmol), DIB (1.5 mmol), CH<sub>2</sub>Cl<sub>2</sub> (20 mL). <sup>b</sup> Isolated yield after column chromatography. <sup>c</sup> Total yield of separable *Z*- and *E*-isomers. See Supporting Information for details. <sup>d</sup> Only one isomer was separated. <sup>e</sup> Most ACPs became messy.

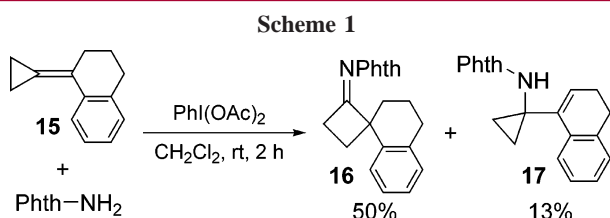
We next examined reactions of various types of disubstituted ACPs with the nitrene equivalent, and the results are summarized in Table 1. Diaryl-substituted ACPs possessing electron-donating or electron-withdrawing substituents gave good yields (Table 1, entries 1–4), and alkylaryl-substituted ACPs gave moderate yields (Table 1, entries 5 and 6). The metal-free ring expansion reactions were found to tolerate functional groups such as amide and ester (Table 1, entries 4 and 6). However, dialkyl-substituted ACP **13** could only give rise to a trace amount of the desired product **14** (Table 1, entry 7), indicating that aryl substituents play an important role in the ring expansion reactions. The proposed framework of the ring expansion products was further confirmed through the X-ray crystallographic structure of *E*-**6** (Figure 1).

When ACP **15** derived from  $\alpha$ -tetralone was used as a substrate, the desired spiro cyclobutylidene hydrazine **16** was



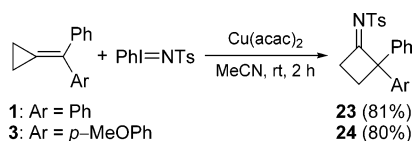
**Figure 1.** X-ray structure of *E*-6.

obtained in 50% yield, accompanied by **17** in 13% yield as a byproduct (Scheme 1).



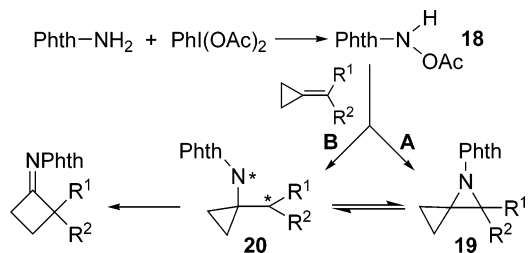
On the basis of the above results,<sup>13</sup> we proposed two plausible mechanisms for these ring expansion reactions (Scheme 2). At first, *N*-aminophthalimide reacts with DIB to generate the active nitrene equivalent **18**.<sup>11</sup> Intermediate **18** is then assumed to react with ACP in two paths. In path A, the reaction of ACP with **18** generates the corresponding aziridine **19**, which undergoes a facile rearrangement to form the final 2,2-disubstituted cyclobutylidene hydrazine product via an ionic or diradical<sup>14</sup> intermediate **20**. Alternatively, in path B, reaction of ACP with **18** directly generates inter-

(13) The traditional method for the generation of a metal nitrene complex was also attempted. The reactions of ACPs **1** and **3** (1 equiv) with PhI=NTs (1.5 equiv) in the presence of Cu(acac)<sub>2</sub> (10% mol to ACP) were conducted. It was found that the ring expansion products, cyclobutanimine derivatives **23** and **24**, were obtained in good yields, respectively. This suggests that various nitrene equivalents are applicable to the ring expansion reactions of ACPs.



(14) The aziridinations of olefins with metal nitrene complexes are considered to be a radical process. See: (a) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425–426. (b) Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P. *J. Am. Chem. Soc.* **2000**, *122*, 8013–8020.

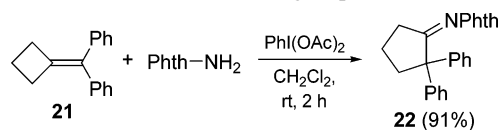
## Scheme 2. Proposed Mechanism



mediate **20**, which then undergoes a cation- or radical-induced ring expansion rearrangement to furnish the final product. At present, we cannot distinguish intermediate **20** as an ionic or diradical species.

The reaction of diphenylmethylenecyclobutane (**21**) with the nitrene equivalent was also attempted (Scheme 3). It was

## Scheme 3. Metal-Free Ring Expansion of ACB



found that a similar ring expansion reaction occurred to generate cyclopentylidene hydrazine derivative **22** in good yield. This suggests that the nitrene equivalent promoted ring expansion reaction is also suitable for ACBs.

In conclusion, we have found a novel reaction involving alkylidenecyclopropanes/alkylidenecyclobutane and nitrenes, where the metal-free ring expansions of three- and four-membered ring compounds were achieved. In this manner, a series of aryl-substituted cyclobutylidene and cyclopentylidene hydrazine derivatives were obtained under mild conditions in moderate to good yields. Further investigations on this and related types of nitrene-promoted reactions are ongoing.

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**Supporting Information Available:** Experimental details, spectroscopic data, <sup>1</sup>H and <sup>13</sup>C NMR spectra of all products, and crystal structure of (*E*)-6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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