



## Digest Paper

# 1,4-Zwitterionic intermediates formed by cleavage of a cyclobutane ring and their cycloaddition reactions



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## ABSTRACT

Cycloaddition reaction is an efficient organic reaction because all of the substrate components are introduced into a product skeleton. Recently, more than six-membered rings have been synthesized by Lewis acid-promoted ring cleavage of a cyclobutane ring followed by addition to an unsaturated bond. Typical examples in the literature of these types of reactions using 1-donor–2-acceptor cyclobutanes and 3-donor cyclobutanones with Lewis acids are presented in this Letter.

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Six-membered ring compounds are frequently seen in pharmaceuticals and natural products. Efficient construction of a multifunctionalized six-membered ring has been studied extensively, especially in the chemistry of the Diels–Alder reaction.<sup>1</sup> However, the Diels–Alder reaction requires a suitable combination of a diene and a dienophile. This requirement sometimes makes construction of a six-membered ring by the Diels–Alder reaction difficult.

Cyclobutanes and cyclobutanones are useful synthetic blocks in organic synthesis, and there have been many excellent reviews.<sup>2</sup> This digest focuses on generation of 1,4-zwitterionic intermediates from cyclobutanes or cyclobutanones and their addition reaction to unsaturated bonds by using a Lewis acid. In this Letter, this cleavage and addition reaction to an unsaturated bond is called formal cycloaddition. The addition of a zwitterionic intermediate is ex-

pected to be quite different from the Diels–Alder reaction in the aspects of reactivity, regioselectivity, chemoselectivity, and stereoselectivity. The different natures of zwitterionic intermediates make this formal cycloaddition a powerful method for construction of a six-membered ring.

## 1-Donor–2-acceptor cyclobutane

Formal cycloaddition of donor–acceptor (D–A) cyclopropanes **1** has been extensively studied,<sup>3</sup> but only a small number of synthetic methodologies for D–A cyclobutanes **2**, a homolog of D–A cyclopropane **1**, were studied until 2008 (Fig. 1).

Typical D–A cyclobutanes **3** have an alkoxy group as a donor substituent and two geminally substituted electron-withdrawing groups on the cyclobutane ring. Other typical D–A cyclobutanes **4** have an amino group as the donor substituent and one electron-withdrawing group (Fig. 2).

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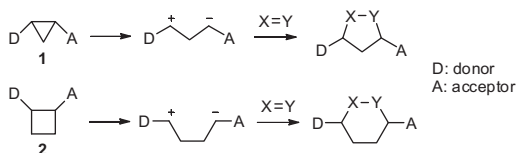


Figure 1. Formal cycloaddition of a D–A cyclopropane and a D–A cyclobutane.

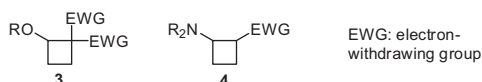


Figure 2. Typical D–A cyclobutanes.

First, the historical background of ring cleavage of 1-amino-2-ketocyclobutane **4** is introduced here. Wilson and co-workers attempted to prepare cyclobutylmethanol **7** by addition of phenylmagnesium bromide to cyclobutylcarboxy ester **5** (Fig. 3) However, they found that ring-opened  $\gamma$ -amino ketone **6** was formed by adding two equivalents of Grignard reagent without forming alcohol **7**.<sup>4</sup> They proposed a mechanism in which one equivalent of phenylmagnesium bromide reacted with **5** to give amino ketone **8** and facile ring cleavage of D–A cyclobutane **8** with magnesium salt gave iminium ion **9**, which reacted with another equivalent of phenylmagnesium bromide to form **6**. This is not a formal cycloaddition, but it showed very facile ring-opening of  $\beta$ -dialkylamino cyclobutyl ketone **8**.

Saigo and co-workers studied Lewis acid-promoted reactions of D–A cyclopropanes with aldehydes. They extended this research to D–A cyclobutane and used Wilson's cyclobutane **5** in ring-opening and addition to aldehyde.<sup>5</sup> Activation of cyclobutane **5** with  $\text{TiCl}_4$  and reaction with aldehyde gave cyclic product **10** and its hydrolysis gave **11** (Scheme 1). This is the first example of formal [4+2] cycloaddition of D–A cyclobutanes.

D–A cyclobutane **12** bearing a carboxylic ester group as an acceptor group and geminally substituted methoxy and trimethylsilyloxy groups as donor groups reacted with aldehydes in the presence of a Lewis acid to give linear aldol products **13** (Scheme 2) Though cyclized product **14** was not obtained directly, cyclization by catalysis with *p*-toluenesulfonic acid gave *cis*-4,5-substituted  $\delta$ -lactones **14** with good diastereoselectivity.<sup>6</sup> This type of cyclobutane **12** reacted more smoothly than did 2-(dimethylamino)cyclobutanecarboxylic esters **5**.

Yokozawa and co-workers reported that highly activated D–A cyclobutane **15** reacted with 2-oxazoline at room temperature without any Lewis acid to give a cycloadduct **16** in 45% yield (Scheme 3).<sup>7</sup>

Extensive study of the chemistry of D–A cyclobutanes began in 2009. Christie and co-workers reported ring cleavage of a D–A cyclobutane and cycloaddition to aldehyde (Scheme 4).<sup>8</sup> They set up a D–A cyclobutane **17** by employing an alkyne–cobalt complex as a donor substituent and geminally substituted diester as an acceptor group. Ring-opening of **17** proceeded with a catalytic amount of  $\text{Sc}(\text{OTf})_3$  and cycloaddition to aldehyde gave a tetrahydropyran derivative **18** in 92% yield. The carbocation part of a zwitterionic intermediate **19** was stabilized by the neighboring cobalt complex.

At nearly the same time, Johnson et al. reported malonate-derived cyclobutanes **20** bearing an aryl group as a donor group (cation-stabilizing group).<sup>9</sup> They showed a sequenced alkene/alkene [2+2]-cyclobutane/aldehyde [4+2] cycloaddition (Scheme 5). A low degree of chirality transfer was observed by using enantio-enriched cyclobutane **21**, although ring fission of D–A cyclopropane occurred via an  $\text{S}_{\text{N}}2$ -type mechanism (Eq. 1).<sup>10</sup>

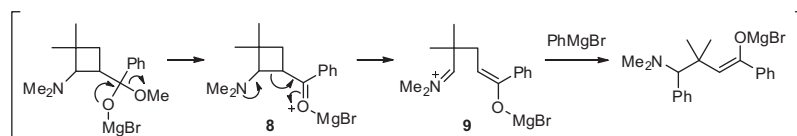
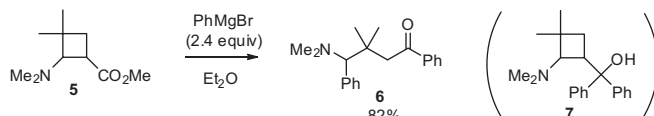
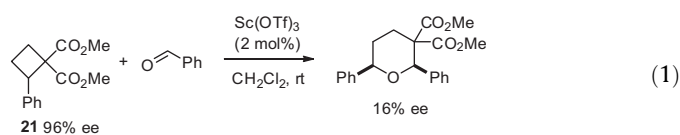
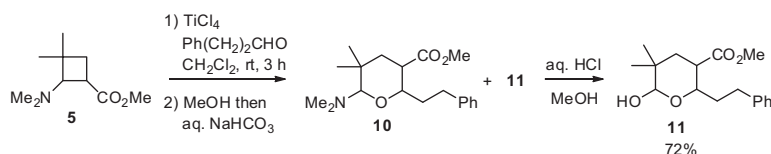
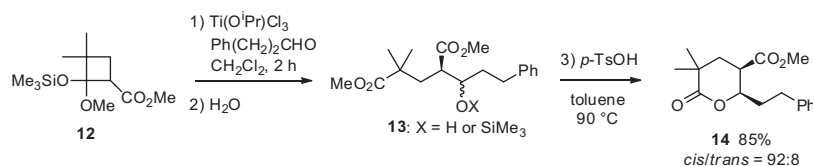


Figure 3. A reaction of cyclobutane **5** and  $\text{PhMgBr}$  to form **6**.



Scheme 1. Formal [4+2] cycloaddition of **5** with an aldehyde.



Scheme 2. Reaction of D–A cyclobutane **12** with an aldehyde.

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