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# Enantioselective [3+2]-cycloaddition of 2,3-disubstituted cyclobutenones: vicinal quaternary stereocenters construction and skeletal functionalization†

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Cycloaddition is a fundamental transformation, featuring the assembly of complex cyclic molecules with multiple stereocenters. We report here a silver-catalyzed [3+2]-cycloaddition of 2,3-disubstituted cyclobutenones with an array of azomethine ylide precursors iminoesters, furnishing azabicycles in good yields and enantioselectivities. Up to three contiguous all-carbon quaternary centers, including two angular stereocenters, could be constructed efficiently, due to high reactivity of strained cyclobutenones. Subsequent skeletal remodeling provided versatile molecules with distinct structural characters.

## Introduction

Stereoselective organic synthesis is a continuously evolving field in the organic community, and substantial progress has been achieved with the development of creative and elegant methodologies. As a fundamental organic reaction, cycloaddition features a powerful construction of complex cyclic molecules with multiple stereocenters (Scheme 1a).<sup>1,2</sup> However, the efficient enantioselective construction of the all-carbon quaternary stereocenters is still synthetically challenging due to inherent steric and conformational demands encountered in the preparation.<sup>3–5</sup> On the other hand, skeletal functionalization, especially skeletal editing has emerged as an appealing approach to accessing new chemical space.<sup>6–12</sup> In this context, 3-azabicyclo[3.2.0]heptane derivatives have garnered our interest. These derivatives have been used as bioisosteres of piperazine in the design of biologically active compounds (Scheme 1b).<sup>13,14</sup> We envisioned that an enantioselective construction of such a bicyclic ring system would create vicinal stereocenters and provide a potentially valuable platform for skeletal modification.

Cyclobutenones have been used as highly reactive dienophiles due to their inherent ring strain.<sup>15</sup> Enantioselective functionalization of performed four-membered ring substrates has become an efficient strategy to synthesize enantioenriched cyclobutane derivatives.<sup>16–24</sup> Cyclobutenones have been utilized

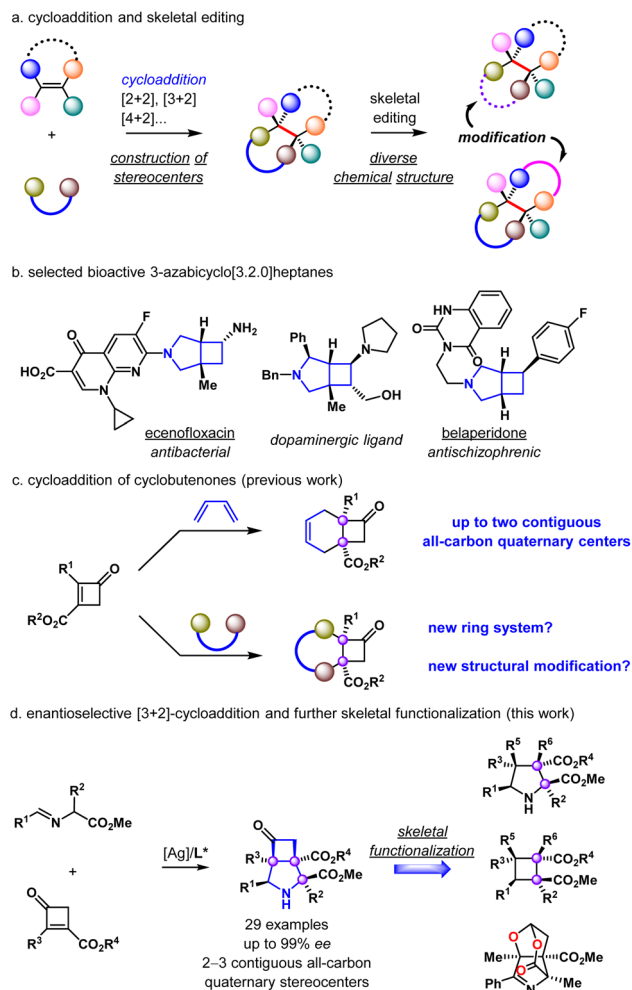
as dienophiles in the enantioselective Diels–Alder reaction and natural product synthesis (Scheme 1c).<sup>25,26</sup> We postulated that new ring systems could be prepared with versatile cycloaddition partners and the corresponding adducts would offer a new entry for structural modifications. 1,3-Dipolar cycloaddition has demonstrated its powerful utility in organic chemistry.<sup>27,28</sup> We envisioned that a [3+2]-cycloaddition of 2,3-disubstituted cyclobutenones with azomethine ylide precursors iminoesters would afford the 3-azabicyclo[3.2.0]heptane derivatives containing two angular quaternary centers in a stereocontrolled manner (Scheme 1d). The regioselective ring-opening reaction of cyclobutanones could provide densely substituted pyrrolidines,<sup>29,30</sup> and cyclobutanes could be subsequently obtained employing the nitrogen deletion method.<sup>31</sup> Similarly, the ring-opening reaction of 3-azabicyclo[3.2.0]heptanes would generate acyclic dienes *via* simultaneous openings of both pyrrolidine and cyclobutane rings. Herein, we report our work on these speculations, benefiting from the enhanced reactivity of strained cyclobutenones.

## Results and discussion

We started our studies with the reaction of 2-methyl-3-methoxycarbonylcyclobutenone **1** and methyl (*E*)-2-(benzylideneamino)acetate **2a** (Table 1). Inspired by the work of Carretero,<sup>32</sup> the copper catalytic system was investigated. After an initial evaluation of chiral ligands (see Table S1† for full details), the copper-catalysed cycloaddition afforded the desired 3-azabicyclo[3.2.0]heptane **3a** in 93% yield and 56% ee using (*S*)-Segphos (**L1**) as a ligand and *t*-BuOK as a base. Further optimization of Segphos-type ligands (**L2–L5**) gave no improvement. The enantioselectivity was slightly enhanced using mild base

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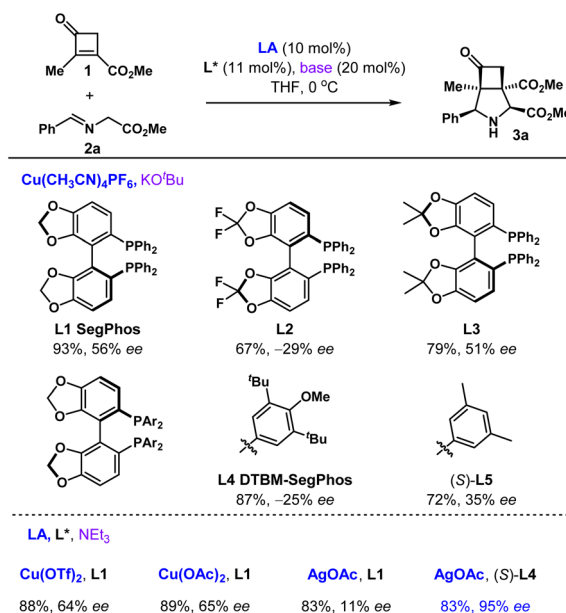
† Electronic supplementary information (ESI) available. CCDC 2263230–2263236. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc02485g>



Scheme 1 Cycloaddition and sequential skeletal functionalization.

NEt<sub>3</sub>, and cyclobutanone **3a** could be obtained in 89% yield and 65% ee. When switching from copper to silver catalytic system, satisfactory results could be achieved. In the presence of AgOAc/**L4**, the [3+2]-cycloaddition provided cyclobutanone **3a** in 83% yield and 95% ee. The absolute configuration of **3a** was unambiguously determined by single crystal X-ray diffraction analysis.

The substrate scope of iminoesters **2** investigated is summarized in Table 2. A variety of iminoesters derived from aryl aldehydes were applicable, affording the corresponding cycloadducts smoothly in good enantioselectivities. Both electron-rich and deficient substituents at the *para*-, *meta*-, *ortho*-, and multi-position on the aromatic ring provided azabicycles **3b–3i** as single diastereomers in 77–90% yields and 85–99% ee. In addition, 1-naphthyl, 2-furyl, and 2-thienyl derived iminoesters furnished the cycloadducts **3j–3l** in good yields and enantioselectivities (74–99% yields, 89–97% ee). Alkyl iminoesters with cyclopropyl (**2m**) and cyclohexyl (**2n**) substituents were also examined, and the enantioselectivity was in the range of 66–80% ee. Besides, the cycloaddition of **1a** with *t*-butyl iminoester **2o** provided the product **3o** in 64% yield and 98% ee.

Table 1 Optimization of cycloaddition<sup>a</sup>

<sup>a</sup> Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), LA (10 mol%), L\* (11 mol%), base (20 mol%), THF, 0 °C, 9–12 h.

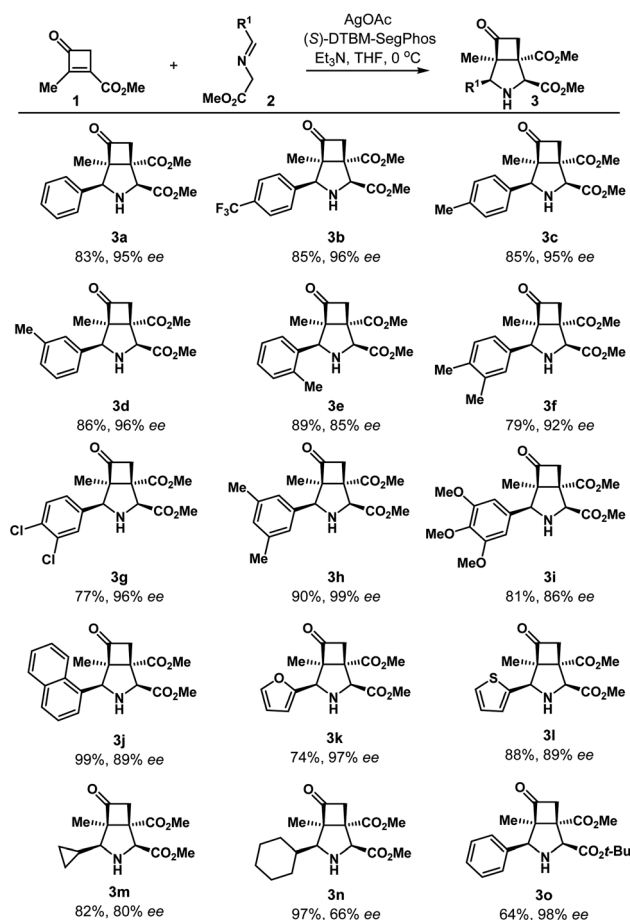
The substrate scope of cyclobutenones **4**, which could be easily prepared from [2+2]-cycloaddition of enol ethers and keteniminiums, was then investigated (Table 3). A group of 2-alkyl and aryl substituted cyclobutenones **4** was tolerated well under the current conditions. Ethyl (**5a**), benzyl (**5b**), 3-chloropropyl (**5c**), phenyl (**5d**), and (1,1'-biphenyl)-4-yl (**5e**) substituents were effectively installed in the angular position.

The enantioselectivity was in the range of 95–97%. The absolute configuration of **5d** was unambiguously determined by single crystal X-ray diffraction analysis.

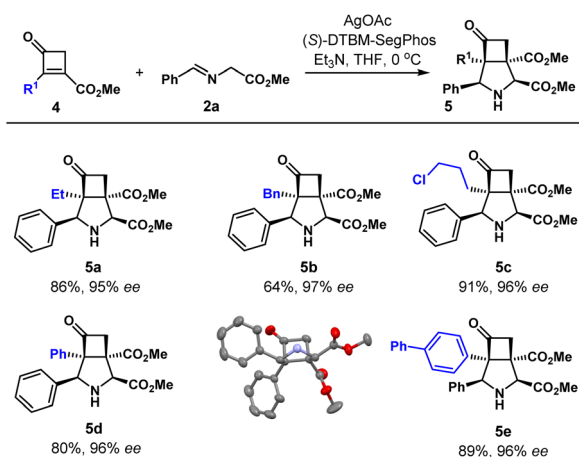
The reaction of (*R*)-iminoesters **6** and cyclobutenones **1** was then explored to synthesize bicyclic products **7** containing three contiguous quaternary stereocenters (Table 4). It has to mention that CsF was utilized as a base instead of NEt<sub>3</sub> to afford the reproducible results (Table S6<sup>†</sup>), and the reaction of **1** with **6a** provided the cycloadduct **7a** in 76% yield and 93% ee. The absolute configuration of **7a** was unambiguously determined by single crystal X-ray diffraction analysis. A range of iminoesters **6**, derived from (hetero)aryl aldehydes worked well under optimal conditions, providing the corresponding cycloadducts **7b–7g** in 49–93% yields and 86–94% ee. Of mention, in the case of electron-deficient phenyl-substituted iminoesters **6**, NEt<sub>3</sub> was used to provide slightly better results (**7b** and **7d**). In addition, the reaction of **4d** with **6a** provided the product **7h** in 67% yield and 92% ee. The reaction of **1a** with 2-benzyl iminoester **6h** worked as well, affording product **7i** in 74% yield and –65% ee.

Control experiments were conducted to investigate the effect of chirality of iminoesters **6** (Scheme 2). To our surprise, an obvious difference of enantioselectivity was observed when in the reaction of **1** with iminoester **6a**. The product **7a** was isolated in 50% yield and only 73% ee when iminoester (*S*)-**6a** was

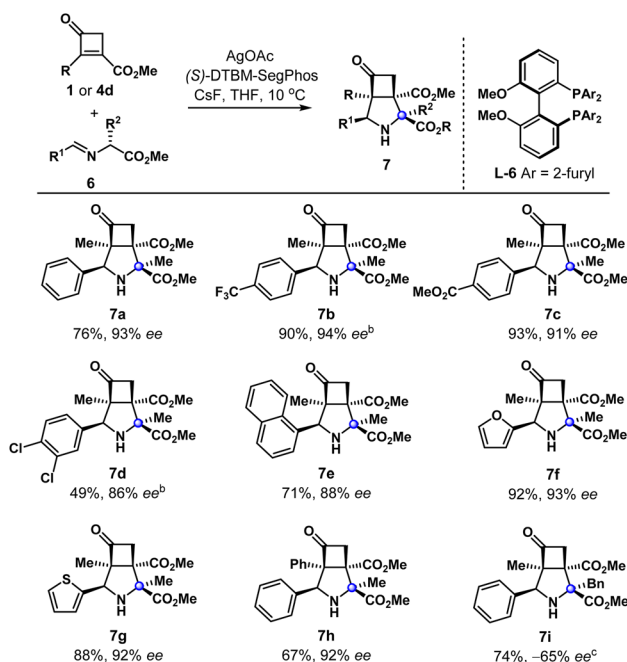


Table 2 The substrate scope of azomethine ylide precursors **2**<sup>a</sup>

<sup>a</sup> Conditions: **1** (0.2 mmol), **2** (0.4 mmol), AgOAc (10 mol%), L-4 (11 mol%), NEt<sub>3</sub> (20 mol%), THF, 0 °C, 9–12 h.

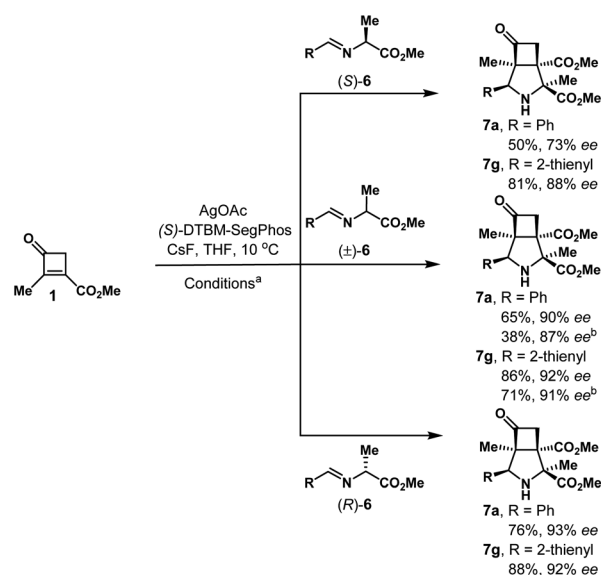
Table 3 The substrate scope of cyclobutenones **4**<sup>a</sup>

<sup>a</sup> Conditions: **4** (0.2 mmol), **2a** (0.4 mmol), AgOAc (10 mol%), L-4 (11 mol%), NEt<sub>3</sub> (20 mol%), THF, 0 °C, 9–11 h.

Table 4 The substrate scope of azomethine ylide precursors **6** in the synthesis of **7**<sup>a</sup>

<sup>a</sup> Conditions: **1** or **4d** (0.2 mmol), **6** (0.4 mmol), AgOAc (10 mol%), L-4 (11 mol%), CsF (40 mol%), THF, 10 °C, 21–33 h. <sup>b</sup> NEt<sub>3</sub> (20 mol%) and 10 °C were used. <sup>c</sup> L-6 (11 mol%) and *N*-methylpiperidine (1.0 equiv.), and –20 °C were used.

used. Instead, both racemic or (*R*)-**6a** gave the product **7a** in 65–76% yield and 90–93% ee. A subtle difference of enantioselectivity was also observed in the case of iminoester **6g**. We assumed these results may be attributed to memory of chirality (MOC) effect.<sup>33,34</sup>

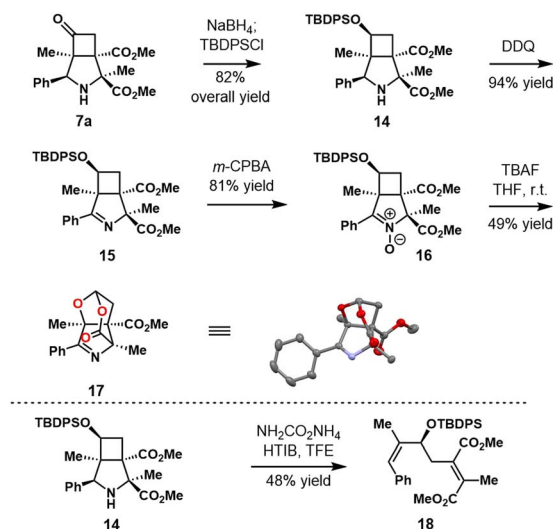


**Scheme 2** The reaction of **1** with enantioenriched or racemic iminoesters **6**. <sup>a</sup>Conditions: **1** (0.2 mmol), **6** (0.4 mmol), AgOAc (10 mol%), L-4 (11 mol%), CsF (40 mol%), THF, 10 °C, 21–22 h. <sup>b</sup> **6** (0.2 mmol).



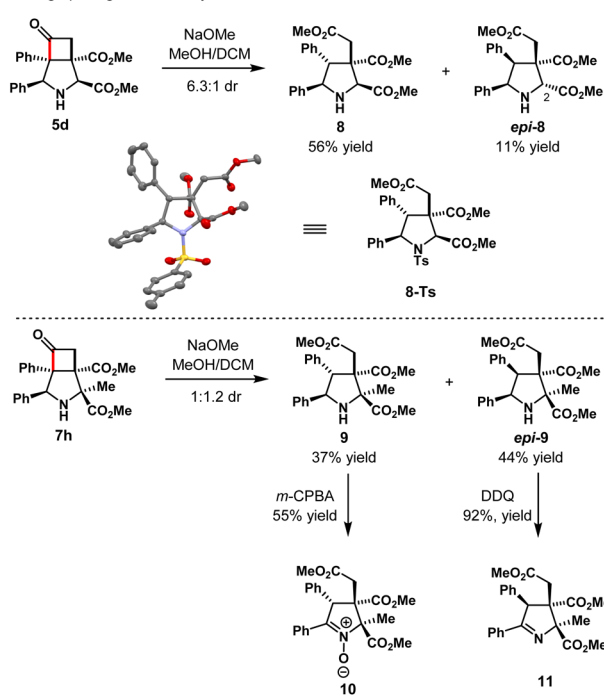
Skeletal functionalization has presented as an appealing strategy to build new chemical space. Selective ring-opening reactions of either cyclobutanone or pyrrolidine ring moiety could offer various densely functionalized molecules with structural diversities. Along with these lines, treatment of 3-azabicyclo[3.2.0]heptane **5d** with NaOMe led to the products **8** and epi-**8** in 67% yield and 6.3 : 1 dr (Scheme 3). The absolute configuration of **8** was unambiguously determined by single crystal X-ray diffraction analysis of its tosyl derivative. For minor diastereomers epi-**8**, epimerization at position 2 took place as well, and its structure was determined by single crystal X-ray diffraction analysis as well. Similarly, the ring-opening reaction of **7h** provided diastereomers **9** in 81% yield and 1 : 1.2 dr. Oxidation of **9** with *m*-CPBA gave the product **10** in 55% yield. In the same way, the product epi-**10** could be obtained in 89% yield by oxidation of epi-**9** with *m*-CPBA (not shown). Meanwhile, oxidation of epi-**9** with DDQ gave the product **11** in 92% yield.

Densely substituted cyclobutane **12** could be obtained in 58% yield as a single diastereomer *via* nitrogen deletion of

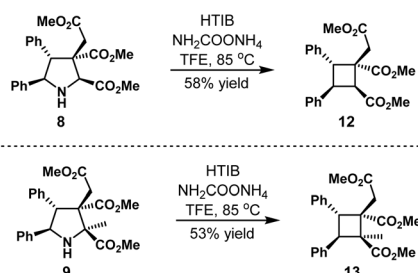


Scheme 4 Further transformation of cycloadducts.

#### a. ring-opening reaction of cyclobutanone



#### b. N-deletion of pyrrolidine



Scheme 3 The cleavages of cyclobutane ring and further ring contractions.

pyrrolidine **8** with the use of hydroxy(tosyloxy)iodobenzene (HTIB) and ammonium carbamate under Antonchick's conditions.<sup>31</sup> Similarly, the cyclobutane **13** with two vicinal quaternary stereocenters could be furnished in 53% yield smoothly.

In addition, the reduction of **7a** and sequential silylation gave the product **14** in 82% yield (Scheme 4). DDQ oxidation of **14** led to imine **15** smoothly, and further oxidation using *m*-CPBA provided product **16** in 81% yield. Interestingly, removal of silyl group using TBAF furnished an unexpected skeletal rearrangement product **17** in 49% yield.<sup>35</sup> The structure of **17** was unambiguously determined by single crystal X-ray diffraction analysis. Meanwhile, treatment of **14** with HTIB and ammonium carbamate gave diene **18** in 48% yield *via* a simultaneous cleavage of both the pyrrolidine and cyclobutane rings process.

## Conclusions

We developed here a silver-catalysed enantioselective [3+2]-cycloaddition of cyclobutenones and azomethine ylide precursors. Up to three contiguous all-carbon quaternary stereocenters could be efficiently constructed, owing to highly reactive cyclobutenones. Further transformations were investigated to access new chemical space.

## Data availability

General information, detailed experimental procedures, characterization data for all new compounds, and NMR spectra are in the ESI.†

## Author contributions

P. Lu conceptualized the project. L. Lu performed all the experimental work; both authors interpreted the data and co-wrote the manuscript.





## Conflicts of interest

The authors declare no conflict of interest.

## Acknowledgements

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- 34 One referee suggested that the chiral iminoester might act as a ligand, thus leading to these observations. For more details, see Table S7.†
- 35 For a proposed mechanism, see Scheme S1.†

