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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).[1,2] 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.[3–5] On the other hand, skeletal functionalization, especially skeletal editing has emerged as an appealing approach to accessing new chemical space.[6–12] 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).[13,14] 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.[15] Enantioselective functionalization of performed four-membered ring substrates has become an efficient strategy to synthesize enantioenriched cyclobutane derivatives.[16–24] Cyclobutenones have been utilized as dienophiles in the enantioselective Diels–Alder reaction and natural product synthesis (Scheme 1c).[25,26] 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.[27,28] 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,[29,30] and cyclobutanes could be subsequently obtained employing the nitrogen deletion method.[31] 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-methoxycabonylcyclobutenone **1** and methyl (*E*)-2-(benzylideneamino)acetate **2a** (Table 1). Inspired by the work of Carretero,[32] 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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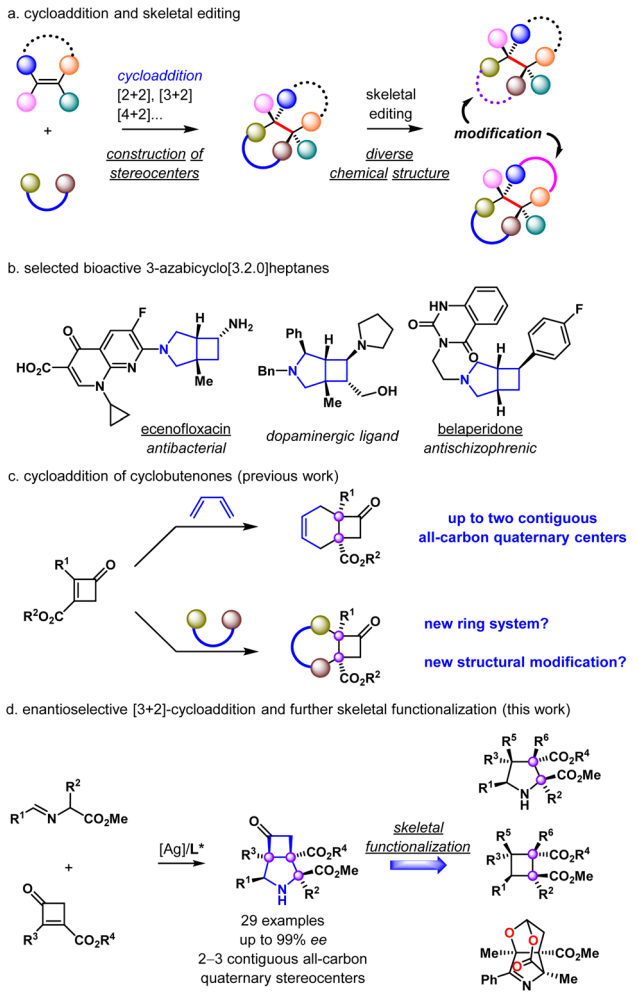
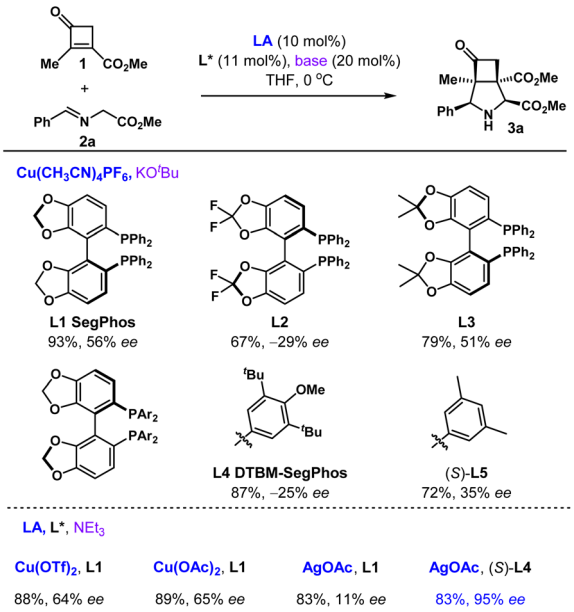


Scheme 1 Cycloaddition and sequential skeletal functionalization.

NEt_3, 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[a]



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

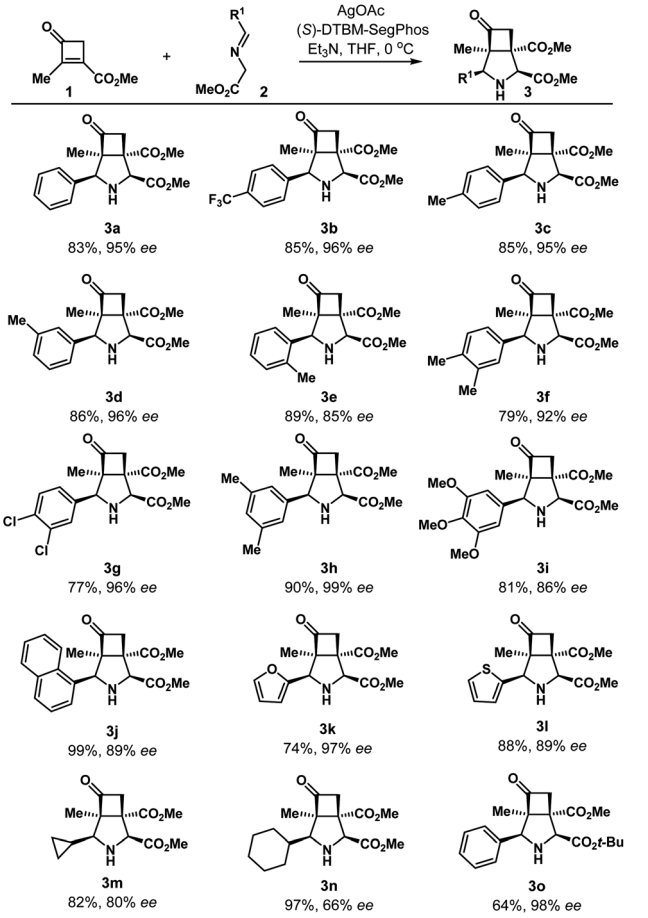
The substrate scope of cyclobutenones **4**, which could be easily prepared from [2+2]-cycloaddition of enol ethers and keteniminiums, was then investigated (Table 3). A group of 2-alkyl and aryl substituted cyclobutenones **4** was tolerated well under the current conditions. Ethyl (**5a**), benzyl (**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_3 to afford the reproducible results (Table S6†), 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_3 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.

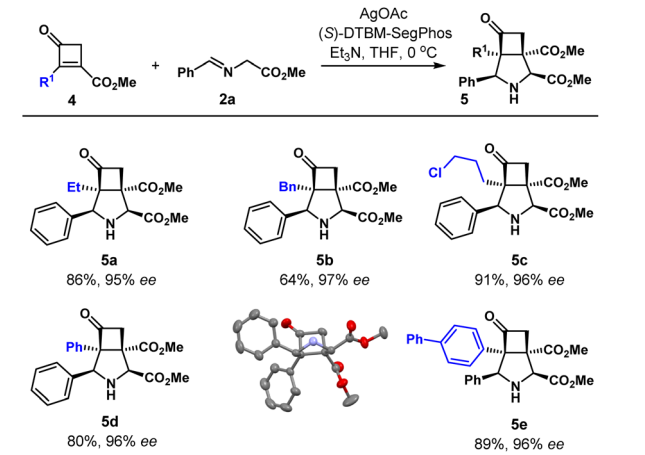
Control experiments were conducted to investigate the effect of chirality of iminoesters **6** (Scheme 2). To our surprise, an obvious difference of enantioselectivity was observed when in the reaction of **1** with iminoester **6a**. The product **7a** was isolated in 50% yield and only 73% ee when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

Table 2 The substrate scope of azomethine ylide precursors 2[a]



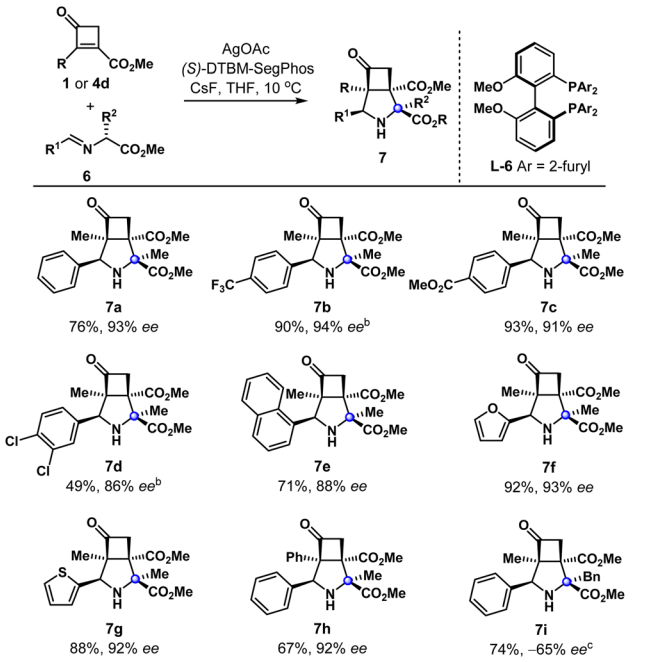
[a] Conditions: **1** (0.2 mmol), **2** (0.4 mmol), AgOAc (10 mol%), **L-4** (11 mol%), NEt_3 (20 mol%), THF, 0 °C, 9–12 h.

Table 3 The substrate scope of cyclobutenones 4[a]



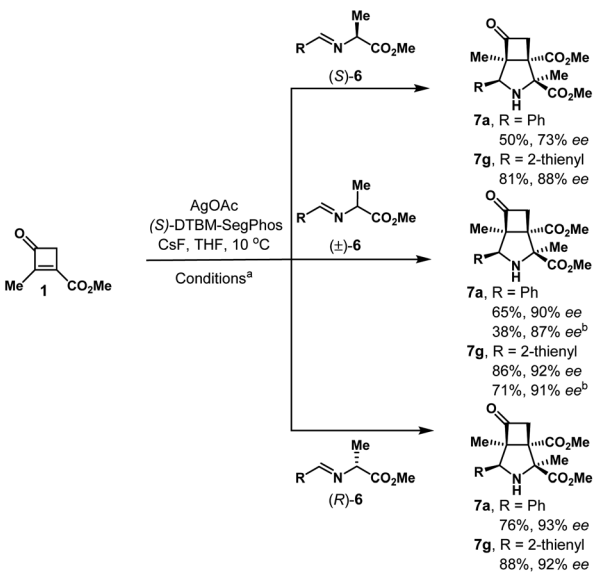
[a] Conditions: **4** (0.2 mmol), **2a** (0.4 mmol), AgOAc (10 mol%), **L-4** (11 mol%), NEt_3 (20 mol%), THF, 0 °C, 9–11 h.

Table 4 The substrate scope of azomethine ylide precursors 6 in the synthesis of 7[a]



[a] 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. [b] NEt_3 (20 mol%) and 10 °C were used. [c] **L-6** (11 mol%) and *N*-methylpiperidine (1.0 equiv.), and −20 °C were used.

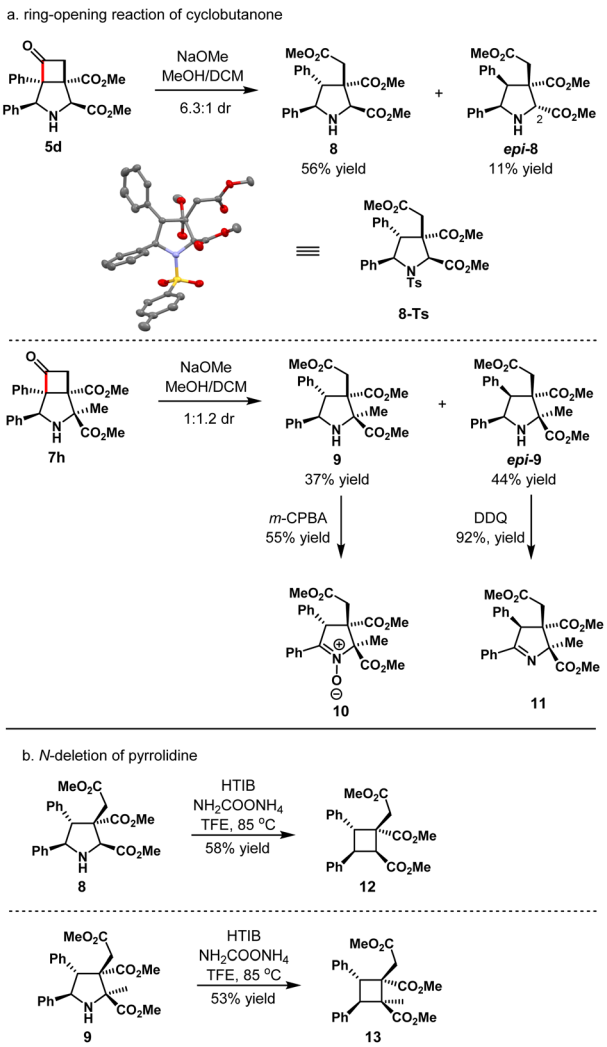
used. Instead, both racemic or (*R*)-**6a** gave the product **7a** in 65–76% yield and 90–93% ee. A subtle difference of enantioselectivity was also observed in the case of iminoester **6g**. We assumed these results may be attributed to memory of chirality (MOC) effect.[33,34]



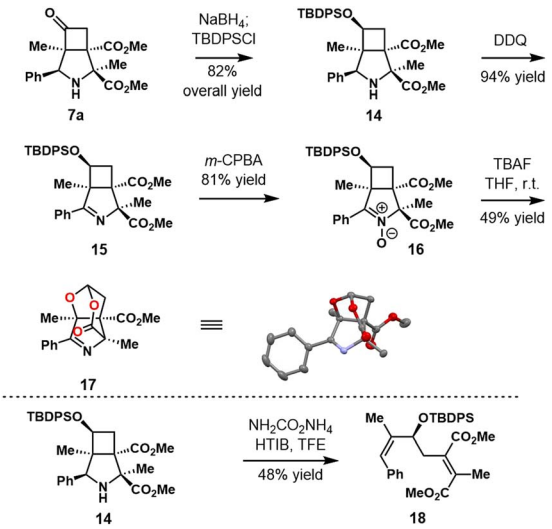
Scheme 2 The reaction of **1** with enantioenriched or racemic iminoesters **6**. [a]Conditions: **1** (0.2 mmol), **6** (0.4 mmol), AgOAc (10 mol%), **L-4** (11 mol%), CsF (40 mol%), THF, 10 °C, 21–22 h. [b]**6** (0.2 mmol).

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



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



Scheme 4 Further transformation of cycloadducts.

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.[35] 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.

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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.†