Direct stereoselective construction of cyclopropane $\alpha$-amino acid with contiguous quaternary centers via $[4 + 2]$ annulation reaction†

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A direct diastereoselective synthetic approach to useful cyclopropane $\alpha$-amino acid was established via base-promoted $[4 + 2]$ annulations between o-aminobenzaldehydes and alkyl 2-aroyl-1-chlorocyclopropanecarboxylates. The annulation reaction proceeded quickly under mildly basic conditions, affording $\alpha$-aminocyclopropane carboxylic acid derivatives in moderate to excellent yields with high diastereoselectivities (up to 19 : 1).

Since $\alpha$-aminocyclopropanecarboxylic acid (ACC) was first isolated from cowberries by Vähätalo and Virtanen in 1955, ACC motifs and their derivatives have attracted considerable attention. ACC not only exists in many natural products, bioactive compounds and pharmaceuticals, but also serves as a valuable tool for the mechanistic study and characterization of enzymes. Some representative bioactive examples bearing this skeleton are given in Fig. 1. Great interest has been shown in the efficient construction of ACC frameworks, especially those with tertiary-quaternary carbon centers. In addition, recent medicinal research revealed that compound I and its derivatives as a combination of 1-aminocyclopropane-1-carboxylic acid and 1,2,3,4-tetrahydroquinoline-2-carboxylic acid moieties have strong affinities with the glycine binding site of the NMDA receptor, and also play an important role in neuronal cell death during ischaemic or hypoxic conditions such as stroke or epilepsy. Unfortunately, however, a multiple-step synthesis is essential to construct two contiguous quaternary centers. Therefore, the development of more efficient and general methods for the synthesis of ACC derivatives containing contiguous quaternary centers is highly desirable.

The previously reported synthetic methods of ACC framework, such as insertion reaction of transition-metal-mediated $\alpha$-nitroacacetate carbene with disubstituted alkenes (Scheme 1A), [3 + 2] cycloaddition (Scheme 1B) and multi-step synthesis (Scheme 1C), are outlined in Scheme 1. The main disadvantages for these routes include low functional group tolerance and the expensive precursors prepared through multiple steps. Thus, it still remains a challenge to develop a more practical method for this core structure.

Over the last decade, the field of transition-metal-catalyzed aromatic C–H bond functionalization has gained significant development, and these strategies to form carbon–carbon and carbon–heteroatom bond have become increasingly commonplace. Recently, Yu et al. reported the use of glycine as a transient directing group for functionalization of C(sp³)–H bond of aldehyde. Then, Yu and our group have collectively demonstrated an ortho-C(sp³)–H functionalization of benzaldehyde using transient directing groups. As part of our ongoing work, we found that the products 3 derived from ortho-amidation of aldehydes were donor–acceptor species substantially which can be further transformed into useful core architectures. In addition, Gong et al. developed a convenient way to prepare a new type of electron-deficient cyclopropene intermediate II (marked in Scheme 1) in situ by carrying out a simple 1,2-elimination of

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Fig. 1 Typical bioactive molecules containing ACC motifs.

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alkyl 2-aroyl-1-chlorocyclopropanecarboxylates under basic conditions. This reagent has been successfully applied to construct strained ring-fused bioactive molecules through its base-promoted annulation reactions. The above progress encouraged us to assess the possibility of constructing the important ACC subunit directly through the designed \([4 + 2]\) annulation reaction between donor–acceptor reagents and alkyl 2-aroyl-1-chlorocyclopropanecarboxylates. To our delight, the expected products were obtained in moderate to high yields under mildly basic conditions. The details about the Ir-catalyzed amidation of benzaldehydes with sulfonyl azides and subsequent \([4 + 2]\) annulation reaction with alkyl 2-aroyl-1-chlorocyclopropanecarboxylates are described herein.

Firstly, the preparation of donor–acceptor reagents followed our previous work. Under the same conditions, the yield of \(3a\) was obtained only in 50%. Therefore, we preliminarily screened the influence of various amines, and found that amine \(L1\) gave the desired product \(3a\) in 75% yield (Table S1†).

Under the optimal reaction conditions, we obtained various \(\text{ortho-aminobenzaldehyde products} \, 3\), which are summarized in Table 1, in good (57%) to excellent (97%) yields.

With \(\text{ortho-aminobenzaldehyde products} \, 3\), the reaction of \(3a\) with \(4a\) was first carried out in the presence of \(\text{Cs}_2\text{CO}_3\) as model. In THF, the reaction readily proceeded at room temperature, and \(4a\) was almost completely consumed after 12 h. The product, isolated through silica gel column chromatography in 15% yield with 9 : 1 dr value, was identified to be the fused ACC ester \(5aa\) by spectroscopic means (Table 2, entry 1). The diastereomeric ratio of \(5aa\) was determined by \(^1\text{H}\) NMR spectroscopy. The stereochemistry for this process was confirmed by single crystal X-ray diffraction analysis. To optimize the reaction conditions, various solvents were taken into account. As shown in Table 2, in aprotic polar solvents such as \(\text{N,N-dimethylformamide (DMF)}\) and \(\text{dimethyl sulfoxide (DMSO)}\), this reaction proceeded smoothly to produce \(5aa\) with high dr value (Table 2, entries 2 and 3), and a satisfactory yield (84%) was

| Entry | Solvent | Base     | \(T\) (h) | Yield\(^b\) (%) | dr\(^c\) |
|-------|---------|----------|-----------|----------------|--------|
| 1     | THF     | \(\text{Cs}_2\text{CO}_3\) | 12         | 15             | 9 : 1  |
| 2     | DMSO    | \(\text{Cs}_2\text{CO}_3\) | 2          | 84             | 13 : 1 |
| 3     | DMSO    | \(\text{Cs}_2\text{CO}_3\) | 2          | 86             | 14 : 1 |
| 4     | CH_3CN  | \(\text{Cs}_2\text{CO}_3\) | 12         | 70             | 14 : 1 |
| 5     | 1,4-\(\text{Dioxane}\) | \(\text{Cs}_2\text{CO}_3\) | 12         | <5             | —      |
| 6     | DMF     | \(\text{NaOH}\)  | 1          | 23             | 10 : 1 |
| 7     | DMF     | \(\text{K}_2\text{PO}_4\) | 12         | 56             | 9 : 1  |
| 8     | DMF     | \(\text{K}_2\text{CO}_3\) | 12         | <5             | —      |
| 9     | DMF     | \(\text{TEA}\)   | 12         | —              | —      |
| 10    | DMF     | \(\text{DBU}\)   | 12         | —              | —      |

\(^{a}\) Reactions carried out using 0.10 mmol of \(3a\), 0.11 mmol of \(4a\) and 0.20 mmol of \(\text{Cs}_2\text{CO}_3\) in 1.0 mL of solvent at room temperature. \(^{b}\) Isolated yields given. \(^{c}\) Diastereomeric ratio (\(\text{cis} : \text{trans}\)) of the crude product determined by \(^1\text{H}\) NMR.
observed in DMF. In acetonitrile, the reaction proceeded slowly, and the yield of 5aa was relatively lower than the observed in DMF (Table 2, entry 4). In weakly polar solvent 1,4-dioxane, almost none of the desired product was detected (Table 2, entry 5).

In view of the yields observed above, we chose DMF as the most promising solvent to optimize the various bases. As shown in Table 2, the yield of 5aa was remarkably dependent on the properties of the bases used. Strong inorganic base like NaOH could greatly promote this reaction, giving 5aa only in 23% yield (Table 2, entry 6). In contrast, a satisfactory result was achieved when K3PO4 was employed (Table 2, entry 7). On the other hand, the common inorganic base K2CO3, the organic base Et3N and strong organic base DBU (Table 2, entries 8, 9 and 10) were hardly able to promote this process.

With the optimized conditions of annulation reaction in hand, we subsequently examined the substrate scope of this reaction. First, the range of substrates 3 was investigated and the observed results are summarized in Table 3. Under the optimal reaction conditions, substrates 3a–3e with electron-donating groups at the benzene ring afforded the products 5aa–5ea in good yields and good dr values, respectively. Among the substrates 3f–3k with electron-withdrawing groups, the substrate 3f with 2-fluoro group afforded the highest yield and high dr value of the annulation product 5fa, whereas the substrate 3g with 2-chloro group furnished a high yield of the product 5ga with an excellent dr value (19:1) and the substrate 5i with 2,4-dichloro group gave the lowest yield of 5ia. Besides, substrate 3l with phenyl group was well tolerated in this reaction, producing the product 5la in a high yield with a good dr value.

Next, we further investigated the structure effect of 2-aryl-1-chlorocyclopropanecarboxylates 4 on the reaction. As shown in Table 3, the electronic nature of the Ar group couldn’t obviously influence the product yields and the diastereomeric ratios, affording the products 5ab–5ae in high yields with good dr values, respectively. When the R1 group was replaced with a small methyl group, the corresponding product 5af could be obtained in the highest yield and good dr value.

As known to all, stereoselective construction of ACC subunits is a challenging but demanding target. Encouraged by above results, we chose substrates 4 containing chiral auxiliary to expand this protocol to the synthesis of chiral ACC subunits. To our delight, the substrates 4g–4i underwent a smooth transformation to afford products 5ag–5ai in high yields and good dr values, respectively (Table 4).

Based on the above observations, we proposed a possible reaction mechanism as shown in Scheme 2. The reaction could
proceed through a highly regioselective aza-Michael addition to the strained C–C bond of the highly reactive cyclopropene intermediate II, generated in situ in the presence of base. We realize that the diastereoselectivity of the reaction may be dominated by the coordination state of the intermediate 6. Owing to the apparent steric hindrance, the coordination state 6 was converted into fused polycyclic intermediate 7 with high dr value. Then 7 was subsequently protonated into the final product 5.

In summary, we have developed an efficient and practical [4 + 2] annulation reaction between alkyl 2-aroyl-1-chlorocyclopropanecarboxylates and donor–acceptor reagents derived from ortho-amidation of aldehydes in the presence of an inorganic base. This protocol is suitable for directly constructing the biologically and pharmaceutically useful cyclopropane derived from the strained C–C bond of the highly reactive cyclopropene aldehyde in situ.

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