An asymmetric approach to bicyclo[2.2.1]heptane-1-carboxylates via a formal [4 + 2] cycloaddition reaction enabled by organocatalysis†

Jian-Guo Fu,‡ Yi-Fan Shan,‡ Wang-Bin Sun, Guo-Qiang Lin and Bing-Feng Sun*

An organocatalytic formal [4 + 2] cycloaddition reaction has been realized that permits rapid access to a wide range of bicyclo[2.2.1]heptane-1-carboxylates in a highly enantioselective manner from simple starting materials under mild and operationally simple conditions.

A bicyclo[2.2.1]heptane scaffold is a privileged molecular structure embedded in numerous compounds with various functions (Fig. 1). Camphor, sordarins, α-santalol and β-santalol are bioactive natural products that contain this structural moiety. In addition, bicyclo[2.2.1]heptane is featured by drug candidates such as LMV-601 and AMG 221. Moreover, the bicyclo[2.2.1]heptane scaffold provides the basis for asymmetric synthesis and catalysis. Bornanesultam is a well-known chiral auxiliary, while dibenzylidene and diphonane are effective chiral ligands for transition-metal catalysis. The development of enantioselective approaches to functionalized bicyclo[2.2.1]heptanes is critical for target-oriented and diversity-oriented syntheses of related biologically significant molecules, and therefore it is highly desirable for relevant drug discovery.

From the perspective of molecular architecture, the molecules depicted in Fig. 1 may be classified into two main groups contingent on whether or not a bridgehead carbon is present. In this regard, camphor, sordarins, and bornanesultam belong to the same group. We are interested in the development of a synthetic approach that would allow direct access to bicyclo[2.2.1]heptanes with a functionalized bridgehead, particularly in view of the absence of such a method so far. We envisaged an enantioselective approach to bicyclo[2.2.1]heptane-1-carboxylates via a formal [4 + 2] cycloaddition reaction, with an understanding of the carboxylate group being a versatile function amenable to various transformations (Scheme 1). Mechanistically distinct from the preceding methods, which involve enamine catalysis or Brønsted acid catalysis, this reaction would be effected through a hydrogen bond catalysis. To this end, a chiral tertiary amine would be employed as the catalyst. Herein, we present the asymmetric approach to bicyclo[2.2.1]heptane-1-carboxylates by the reaction of α′-ethoxycarbonyl cyclopentenones with nitroolefins (Scheme 1).

Our research commenced with investigating the reaction between 1a and 2a. When 10 mol% A was employed as the catalyst, a stepwise incomplete reaction was observed that produced a mixture containing both the Diels–Alder product and the Michael addition product. This problem was solved successfully by the addition of DBU after consumption of 1a to promote the second Michael addition reaction. Various reaction parameters were evaluated and selected results are listed in Table 1. The reaction of 1a and 2a catalyzed by 10 mol% A at room temperature produced a 2.3/1 diastereomeric ratio of the Diels–Alder product and the Michael addition product.
mixture in 82% yield, with the major diastereomer 3a bearing an enantiopurity of 88% ee (entry 1). Lower temperatures of 0 °C and −20 °C appeared to give slightly higher diastereoselectivities and enantioselctivities (entries 2 and 3). The same reaction with catalyst B gave the best result at −40 °C, with 82% yield, 7.1/1 dr and 87% ee being achieved, however, further decreasing the temperature to −60 °C resulted in eroded selectivities (entries 4–7). The same was observed for catalyst C, which achieved the highest selectivities at −40 °C with the product being obtained in 84% yield with 3.2/1 dr and 94% ee (entries 8 and 9). Therefore, reactions with other catalysts were further tested at −40 °C. At this temperature, while the reaction with catalyst D was considerably less stereoselective, the enantioselectivity obtained with catalyst E was similar to that with C (entries 10 and 11). In light of these results, C was determined as the catalyst of choice and the solvent effect was then evaluated with this catalyst. The reactions in toluene, CH3CN, and THF, respectively, were similarly eroded selectivities (entries 10 and 11). An aromatic ring at the distal end of the chain was tolerable (entries 4 and 5 vs. entry 6). For nitroolefins 2k and 2l bearing other aromatic substituents, the diastereoselectivity as well as the enantioselectivity dropped considerably (entries 11 and 12).

Based on these results, it may be concluded for β-arylnitroalkene substrates that more electron-deficient nitroolefins are better substrates. Considering that more electron-deficient nitroolefins are more reactive electrophiles, it became a logical deduction for us that more reactive nitroolefins are better substrates for this reaction.

Accordingly, we then studied the reaction of 1a with β-alkyl-nitroalkenes. As summarized in Table 3, the various sterically undemanding β-alkyl-nitroalkenes are excellent substrates for this formal cycloaddition reaction. Nitroolefins with a saturated hydrocarbon chain provided the [2.2.1] bicyclic products in excellent yield with ca. 20/1 dr and extremely high ee (entries 1–3). An aromatic ring at the distal end of the chain was tolerable (entries 4–6). Importantly, nitroolefins with functional groups were excellent substrates for this reaction, providing the [2.2.1] products amenable for further elaborations (entries 7–10). Interestingly, 2w bearing a cyclopropyl group was also an effective substrate (entry 11). As the bulkiness of the substituent increased, the reactivity as well as the enantioselectivity dropped considerably (entry 12).

We further examined the reaction between 1b and various 2-alkyl-1-nitroethenes (Table 4). With 1b being employed as the nucleophile, products with the [2.2.1] bicyclic core decorated with two all-carbon quaternary stereocenters were expected to be garnered. To our delight, the reactions between 1b and 2 underwent smoothly and furnished the formal cyclo-
addition products in good yields with satisfactory selectivities (entries 1–7).

The structure as well as the absolute configuration of 3rb was established unambiguously through X-ray crystallographic analysis (Fig. 2).14

Based on the preceding results and in the light of our previous proposal,13 the stereochemical outcome of the tandem reaction could be rationalized, as exemplified by the reaction of 1b with 2r (Scheme 2). In the first step, 1b may form a complex with C via hydrogen-bonding interactions, thereby discriminating between the two faces of the enol. Directed by the hydrogen bonding interactions developing between the nitro and the quinolinol groups, the nitroolefin approaches the enol selectively from the α-face with the substituents of the two bond-forming carbons positioned in a staggered arrangement (4), leading to the formation of the intermediate compound 5. In the second step where DBU is used as the base, the open transition state 6 should be operative to minimize the steric repulsion between the nitro and the alkyl groups, delivering 3rb as the major product.

Eventually, to demonstrate the efficiency and synthetic utility of this newly developed formal [4 + 2] cycloaddition reaction, a gram-scale reaction was performed with 1a and 2p.
In summary, an organocatalytic formal [4 + 2] cycloaddition reaction has been realized that permits rapid access to a wide range of functionalized [2.2.1] bicyclic heptanes in a highly enantioselective manner from simple starting materials. The reaction features metal free, mild, and operationally simple conditions, providing synthetically useful bicyclo[2.2.1] heptane-1-carboxylates in good yields with excellent enantioselectivity. Importantly, this method is amenable to large scale preparation, thus facilitating relevant drug discovery and pharmaceutical activities. Efforts aiming at the application of this newly developed method are pursued in our laboratory and will be reported in due course.

Acknowledgements

We acknowledge the financial support from the National Natural Science Foundation of China (21172246, 21290180, 21472210), and the Youth Innovation Promotion Association CAS.

Notes and references

14 CCDC 1474474 (3rb) contains the supplementary crystallographic data for this paper.