Thermal Decarboxylative Nazarov Cyclization of Cyclic Enol Carbonates Involving Chirality Transfer

Akane Kozuma, Keiichi Komatsuki, Kodai Saito, and Tohru Yamada^{*} Department of Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan

E-mail: yamada@chem.keio.ac.jp

Decarboxylative Nazarov cyclization of chiral cyclic enol carbonates proceeded to afford chiral 2-cyclopentenones with excellent chirality transfer under thermal conditions without any catalyst. Interestingly, the thermal decarboxylative Nazarov cyclization furnished the desired product with better chirality transfer than the Lewis acid-catalyzed reaction.

| Keywords: | Electrocyclization | | Decarboxylation | 1 |
|-----------|--------------------|--|-----------------|---|
| | Chirality transfer | | | |

Asymmetric construction of cyclopentenone units is highly desired due to their wide utility as building blocks for the synthesis of a variety of natural products and biologically-active compounds.¹ Nazarov cyclization, a conrotatory 4π electrocyclization reaction, is promoted by a Lewis acid to provide the stereoselective synthesis of cyclopentenones.² The consideration of torquoselectivity,³ i.e., the control of clockwise/counter-clockwise rotation in electrocyclization reactions, is essential for the production of chiral cyclopentenones based on the Nazarov cyclization, because it defines the newly generated stereochemistry. Some solutions for this issue, such as a substrate control strategy using a chiral auxiliary,³ etc.,⁴ have been reported.

We have recently developed an asymmetric synthesis of cyclopentenones based on chirality transfer through decarboxylative Nazarov cyclization of cyclic enol carbonates by using a Lewis acid catalyst.⁵ In a general Nazarov cyclization, the formation of the pentadienyl cation intermediate **1** involving the loss of chirality at C(2) (Scheme 1) is inevitable. However, in the decarboxylative Nazarov cyclization, cleavage of the C(2)-O(2) bond and subsequent bond formation between C(4) and C(5) occur before racemization, and therefore the stereochemistry at



(3) Chirality at C(2) transfers into C(4) and C(5)

Scheme 1. Decarboxylative Nazarov cyclization.

C(2) of the 5-membered enol carbonate is transferred to C(4)and C(5) of the product.⁶ The cyclic carbonates were prepared by silver-catalyzed incorporation of carbon dioxide into chiral propargyl alcohols. The efficiency of the chirality transfer is strongly affected by the reaction conditions, such as catalysts and solvents, which can contribute to the stabilization of the cationic intermediate 1. Additionally, the introduction of electrondonating groups on the substrates causes a decrease in chirality transfer. For example, the reaction of **2b** (R = 4-CH₃C₆H₄, 82% ct) showed lower chirality transfer compared with 2a (R = Ph, 95% ct) (Scheme 2). To examine the effect of the substituent R in more detail, we newly prepared 2c (R = 4-MeOC₆H₄) in this work and employed it in the reaction, which resulted in a drastic decrease of chirality transfer (21% ct). We hypothesized that good chirality transfer occurs when O(2) tightly coordinates to C(2) before the decarboxylation and C(4) and C(5) bond formation. However, in the case of 2c, by addition of a Lewis acid and the introduction of an electron-donating group on the substrate, the contribution of a zwitterionic structure, such as 5c, is not negligible compared with the suitable structure 4c (Scheme 3). To improve the chirality transfer, the development of a thermal decarboxylative Nazarov cyclization for the asymmetric synthesis of 2-cyclopentenones is described in the present report.⁷

Based on this hypothesis, we initially investigated whether the reaction proceeds under catalyst-free conditions. The reaction temperature and solvent were screened first (Table 1).







Scheme 3. Plausible intermediates.

Table 1. Examination of reaction conditions



| Entry | Solvent | Temp/°C | Time/h | Yield/% ^a | Ct/%b |
|-------|------------------------|---------|--------|----------------------|-------|
| 1° | <i>t</i> -butylbenzene | -40 | 12 | 72 | 21 |
| 2 | t-butylbenzene | 40 | 96 | n. r. | |
| 3 | t-butylbenzene | 60 | 72 | 80 | 79 |
| 4 | t-butylbenzene | 80 | 12 | 84 | 81 |
| 5 | benzene | 60 | 30 | 83 | 71 |
| 6 | C_6F_6 | 70 | 72 | 81 | 75 |
| 7 | mesitylene | 80 | 12 | 87 | 75 |
| 8 | toluene | 60 | 30 | 84 | 77 |
| 9 | trimethylphenylsilane | 80 | 12 | 74 | 81 |
| 10 | cyclohexane | 70 | 90 | 86 | 69 |

^aIsolated yields. ^bOptical purity was determined by HPLC on a chiral stationary phase. Chirality transfer was calculated using: Ct (%) = ee of **3c** (% ee)/ee of the corresponding propargyl alcohol **6c** (% ee). ^cB(C₆F₅)₃ (10 mol %) and MS 5Å was used. n. r. = no reaction.

Although the reaction of $2c^{8,9}$ did not proceed at 40 °C (Entry 2), it was fully converted into 3c at 60 °C in 80% yield with 79% ct (Entry 3).^{10,11} At higher temperatures, 2c was consumed faster and the selectivity was maintained (Entry 4). When the reaction was carried out in benzene or hexafluorobenzene, a decrease in ct was observed (Entries 5 and 6). Alkyl-substituted benzenes, such as mesitylene and toluene, were employed for this reaction to give 3c with 75% ct and 77% ct, respectively (Entries 7 and 8). The use of trimethylphenylsilane showed good chirality transfer (81% ct), but with a slight decrease in the yield of 3c (Entry 9). Hydrocarbon solvents, such as cyclohexane, did not have a favorable effect on the selectivity of this reaction (Entry 10). Based on the above results, it was found that benzene derivatives bearing a bulky substituent were suitable as solvents for this reaction in terms of the chirality transfer, with tert-butylbenzene being the optimal solvent.

With the optimized reaction conditions in hand, the scope of the thermal decarboxylative Nazarov cyclization was examined and compared with the results under Lewis acid-catalyzed conditions. The reactions of 2d and 2e bearing a 2,4,6-trimethoxy group and a 4-methylthiophenyl group at R², respectively, proceeded to provide 3d and 3e in good yields with a large improvement in the chirality transfer (Entries 2 and 3). Next, introduction of an electron-donating group on R¹ was attempted. Substrates 2f and 2g substituted with the PMP group and the MOM-protected phenolic group were tolerant to the conditions, and the corresponding cyclopentenones 3f and 3g were obtained in 85% and 93% yields with 98% ct and 79% ct, respectively (Entries 4 and 5). The reaction time was shortened and the yield of 3f was further improved to 87% by microwave irradiation. Substrates containing 3,4-dimethoxyphenyl (2h) and 4-methylthiophenyl (2i) groups at R^1 were also applicable and a significant improvement of chirality transfer was observed under thermal conditions (Entries 6 and 7). The thermal reaction of 2j

Table 2. Substrate scope

| F | R ¹ Optimized c | onditions | R^1 R^5 R^5 |
|-------|----------------------------|-------------------------|---|
| | $2^{\mathbf{R}^2}$ | | R ² R ⁴ 3 |
| Entry | Product | Conditions ^a | Yield/Ct (%) ^{b,c} |
| 1 | PhMe | 80°C, 12 h | 84%, 81% Ct |
| | PMP 3c | L. A. | 72%, 21% Ct |
| 2 | PhMe | 60 °C, 72 h | 80%, 73% Ct |
| | MeO | | |
| | MeO OMe 3d | L. A. | 88%, 32% Ct |
| 3 | Ph, Me | 80°C, 12h | 81%, 88% Ct |
| | MeS 3e | L. A. | 84%, 14% Ct |
| 4 | PMP | 80°C, 12h | 85%, 98% Ct 87%, 98% Ct ^d |
| | 3f | L. A. | 80%, 69% Ct |
| 5 | MOMO O Me | 80 °C, 24 h | 93%, 79% Ct |
| | 3g | L. A. | 83%, 66% Ct |
| 6 | MeO Me | 60 °C, 72 h | 83%, 90% Ct |
| | 3h | L. A. | 73%, 51% Ct |
| 7 | MeS Me | 80 °C, 24 h | 90%, 98% Ct |
| | 3i | L. A. | 86%, 65% Ct |
| 8 | Ph Me | 60 °C, 24 h | 83%, 99% Ct |
| | PMP ^{``} Me 3j | L. A. | 92%, 99% Ct |

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^aL. A.: B(C₆F₅)₃ (10 mol %), $-40 \,^{\circ}$ C, MS 5Å, 12 h. ^bIsolated yields. ^cOptical purity was determined by HPLC on a chiral stationary phase. ^dMicrowave (80 W) was irradiated for 9 h. ^eIsolated **2n** was used as the substrate. Chirality transfer was calculated using: Ct (%) = ee of **3** (% ee)/ee of **6** (% ee).

bearing a tri-substituted olefin with a PMP group at \mathbb{R}^2 proceeded as successfully as the reaction under Lewis-acid conditions (Entry 8). On the other hand, a large difference in chirality transfer was observed depending on the reaction conditions in the case of the synthesis of tetrasubstituted 2-cyclopentenone **3k** having a PMP group at \mathbb{R}^1 (Entry 9). The conversion of **2l** derived from a terminal alkyne showed lower reactivity and the corresponding **3l** was obtained with much better chirality transfer than under Lewis acid conditions (Entry 10). When substrates **2m–2o** were employed under the thermal conditions, the efficient construction of the corresponding cyclopentenones **3m–3o** was accomplished (Entries 11–13).¹²

In summary, the asymmetric synthesis of 2-cyclopentenone derivatives based on decarboxylative Nazarov cyclization involving chirality transfer under thermal conditions was achieved using chiral cyclic carbonates, which were prepared by silver-catalyzed incorporation of carbon dioxide into a chiral propargyl alcohol. The substrate scope was successfully extended by the development of catalyst-free conditions. Further investigation of the reaction mechanism and application of the reaction to the synthesis of more complex molecules are underway. Supporting Information is available on https://doi.org/ 10.1246/cl.190763.

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8 As previously reported in ref 5, 2c was prepared by the silver-catalyzed CO₂ incorporation reaction into opticallypure propargyl alcohol **6c**.

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and it was confirmed that the present reaction also proceeded through a clockwise rotation as well as the reaction of Lewis acid conditions.

- 11 Although the driving force of this reaction is unclear so far, the decarboxylation might be triggered by a polarization of C(2)-O(2) bond in the transition state under thermal conditions.
- 12 Among substrates employed for this reaction, some substrates showed a better chirality transfer in the Lewis acid conditions as follows.

Ph

$$R^2 = Ph; \frac{90\%, 95\% \text{ Ct (LA)}}{78\%, 79\% \text{ Ct (100 °C, 20 h)}}$$

 $R^2 = C_6H_4CO_2Me; \frac{83\%, 97\% \text{ Ct (LA)}}{80\%, 70\% \text{ Ct (100 °C, 72 h)}}$