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Stereocontrol in Radical Cyclization: Change in Rate-Determining Step

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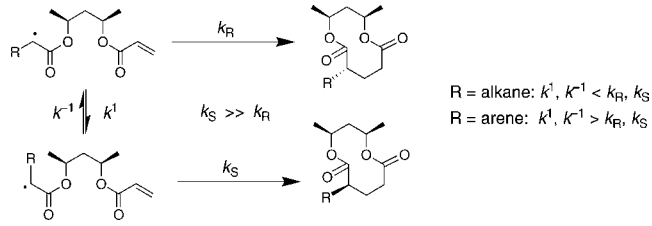
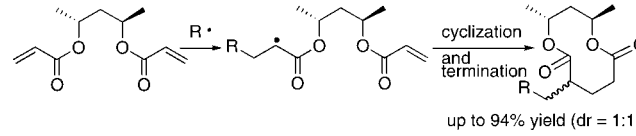
ABSTRACT



Intramolecular cyclization of an α-carbon radical of ester carrying a chiral 2,4-pentanediol tether shows low stereoselectivity when the radical carbon has an alkyl substituent, while the selectivity becomes high to give a single stereoisomer (>99% pure) when the substituent is an aryl group. The difference in the selectivity is attributable to the change in the rate-determining step from the conformational process to the cyclization.

The radical is synthetically useful because of its reactive nature, allowing expected reactions involving an unpaired electron irrespective of coexisting functional groups that can react with polar reagents.[1] For the same reason, the reaction control by a polar interaction is not usually workable for a neutral radical species. To realize a stereocontrolled radical reaction, many reaction systems have been developed by incorporating a proper steric fence,[2] although sufficiently stereocontrolled reactions for asymmetric synthesis are limited.[3,4] We have reported an efficient tandem reaction including radical cyclization using a detachable chiral auxiliary (Scheme 1).[5]

Scheme 1. Tandem Reaction via Radical Cyclization Using a 2,4-Pentanediol Tether



The product yield was very high (up to 94%), but the stereoselectivity at the cyclization step was very poor (dr = ca. 1:1).[6] We found a reason for the low selectivity, and a solution to address it will be reported herein.

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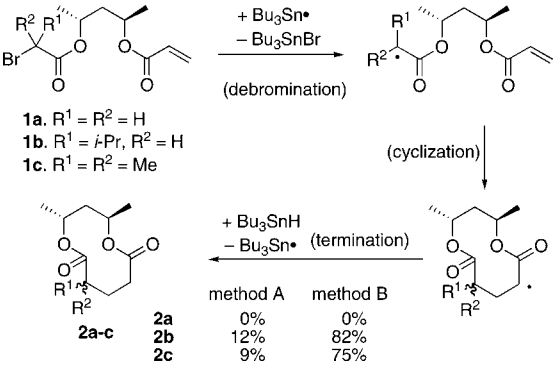
To investigate the stereoselectivity of the cyclization step, the radical intermediate was generated by reductive debromination of α-bromoester **1**. As preliminary studies, efficiency of the reaction, a debromination−cyclization−termination sequence (Scheme 2), was examined with **1a**−**c**

Scheme 2. Product Yields in Tethered Radical Cyclization[a]



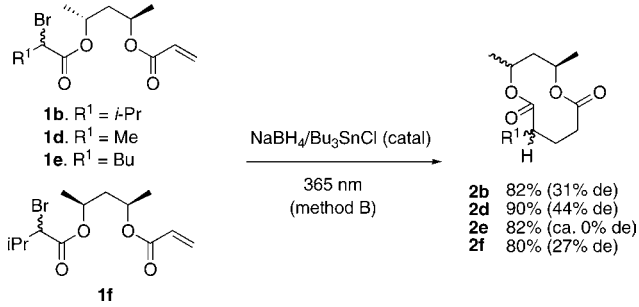
[a] Conditions. Method A: Bu_3SnH/AIBN/80 °C. Method B: $NaBH_4$/Bu_3SnCl/365 nm.

under two reaction conditions, use of a stoichiometric amount of Bu_3SnH with AIBN in benzene under reflux (method A) and a catalytic amount of Bu_3SnCl with $NaBH_4$ in ethanol under photolysis (method B).[7]

By method A, a considerable amount of the Michael-type tin-adducts of the acrylate were formed, and expected **2a**−**c** were obtained only in 0−12% yields. In contrast, method B using a limited amount of tin reagent resulted in good yields of **2b** and **2c**, although the primary bromide **1a** did not give **2a**, leading predominantly to the simple substitution of hydrogen for bromine.

Secondary bromides **1d**,**e** were converted to **2d**,**e** by method B in very high yields of 80−92% (Scheme 3). The

Scheme 3. Stereoselectivity with Secondary Substrates



stereoselectivities were very poor to give 0−44% de, irrespective of the size of R^1. These poor stereoselectivities are exceptional for the 2,4-pentanediol tethered reactions.[8]

The diastereomeric tethered substrates **1b** and **1f** showed similar selectivity, which is totally unexpected because the two methyl groups on the tether should work cooperatively or competitively depending on the relative configurations. It is also unusual that the lower reaction temperature did not give any higher stereoselectivity; e.g., the reaction of **1b** at −50 °C gave **2b** of 31% de (20% yield). Here, we have reached a working hypothesis that activation energy for the cyclization step to generate the new chiral center does not govern the product selectivity.

Stereoselectivity can be rationalized by slow change of the conformations of the generated radical intermediate.[9] Figure 1 shows a general case of the secondary α-carbon

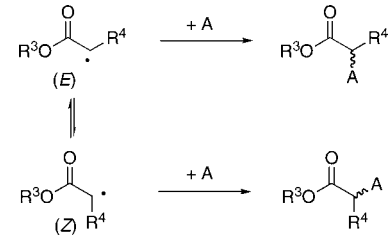


Figure 1. Pre-equilibration for cyclization of the α-radical of ester.

radical of ester. Since steric repulsions between R^4 and the different oxygens are similar, the equilibration is not shifted to one side, in contrast to the α-carbon radicals of amide.[10] In a diastereoselective reaction of chiral substrates, both the conformers are directed to give the same stereoisomer if the reaction is stereocontrolled by the chiral R^4 group, but the stereodirection between the conformers becomes opposite if the chiral R^3 group controls.[11] Activation energy for the conformational change of a typical secondary α-carbon radical of ester was reported to be 11−12 kcal/mol,[12] which could be larger than those for the cyclization with **1b** and **1d**−**f**, which correspond to the R^3-controlled reaction.

The reaction rate for the cyclization through the 2,4-pentanediol tether was experimentally evaluated using a radical clock (Scheme 4).[13] When **1g** or **1h** was treated under the reductive debromination conditions of method B, gener-

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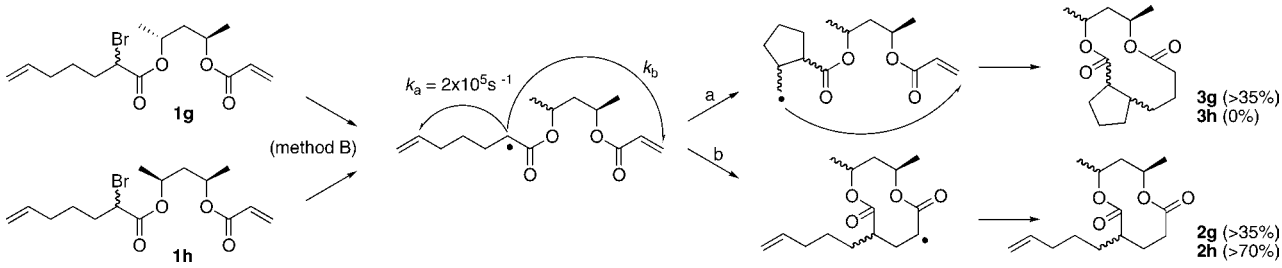
Scheme 4. Competitive Intermolecular Cyclization Reaction with the Radical Clock Reaction



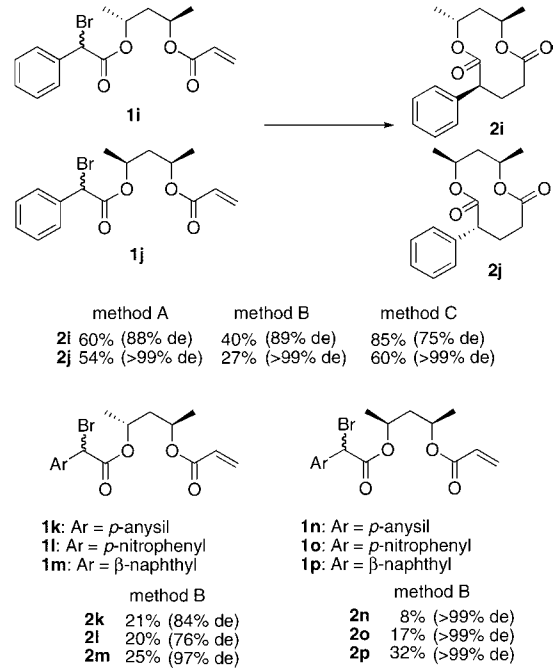
ated radicals underwent a quick formation of the five-membered ring at the rate of 2×10^5 s^{-1}.[13] From the reaction of **1g** carrying (2*R*,4*R*)-tether, two products **2g** and **3g** were obtained at a ratio of 1:1 in more than 70% total yield. Thus, the two competitive intramolecular reactions should occur at a similar rate. In the case of **1h** carrying (2*S*,4*R*)-tether, only **2h** was obtained in more than 70% yield, but **3h** or its derivative was undetected (<5% deduced from ^{1}H NMR). From these observations, the radical cyclization rates via the tether are concluded to be 2×10^5 s^{-1} for **1g** and $>4 \times 10^6$ s^{-1} for **1h**. The rates can be converted to the activation Gibbs energies of 10 kcal mol^{-1} and <8 kcal mol^{-1}, respectively, which are comparable to or lower than the activation energies expected for the conformational change of the radical intermediates.[12] Thus, the stereoselectivity is governed by the conformer ratio of the radical intermediate, in contrast to the implication from the Curtin−Hammett principle.[14,15]

Rotation of the radical intermediate about the CO−C$^{\bullet}$ R^1 bond in Scheme 2 becomes faster when the radical is delocalized to the R^1 group and conjugation with the carbonyl becomes weak. The delocalization also affects the reactivity of the radical to reduce the cyclization rate. Both the effects could work, in crossing the Curtin−Hammett borderline, to control the selectivity by the activation energy at the cyclization step. To attain the radical delocalization, the aromatic group was introduced (R^1 = Ar). By the treatment of phenyl-substituted **1i** and **1j** by method B, 89% de of **2i** and >99% de of **2j** were obtained in moderate yields (Scheme 5). Configuration of the newly generated chiral centers was assigned to be *S* for **2i** and *R* for **2j** by chemical correlation with (+)-(*S*)-2-phenylglutaric acid.[16] The moderately high selectivity with the (2*R*,4*R*)-tether (**1k**−**1m**) and very high selectivity with the (2*S*,4*R*)-tether (**1n**−**1p**) were also observed for the production of **2k**−**p**.

The low yields with the aryl-substituted substrates should be due to the low reactivity of the radicals generated. The yields were improved by using a stoichiometric amount of Bu_3SnH. That is, the reactions of **1i** and **1j** with AIBN at 80 °C (method A) resulted in higher yields than those by method B. Further improvement in the yields was achieved using a stoichiometric amount of Bu_3SnH under the photolysis conditions at rt to give 85% of **2i** and 60% of **2j** (method C).

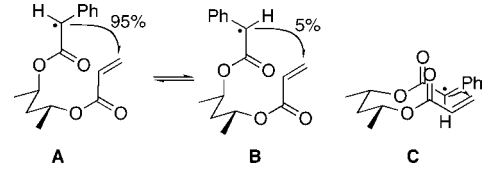
Expected geometries for the radical cyclization reactions are shown in Scheme 6. They seem to cause minimum strains both at the tether part and the addition sites.

Scheme 5. Stereoselectivity with Arene-Substituted Substrates[a]



[a] Conditions. Method A: Bu_3SnH/AIBN/80 °C. Method B: $NaBH_4$/Bu_3SnCl/365 nm. Method C: Bu_3SnH/365 nm.

Scheme 6. Expected Conformations for the Cyclization Reactions[a]



[a] Conformation **A** is for the major isomer of **2i**, **B** is for the minor of **2i**, and **C** is for the predominant isomer of **2j**.

(14) Conformation of the radical intermediate generated from **1b** is confirmed to be independent of the configuration at the bromide carbon. That is, the reaction with stereochemically pure **1b** prepared from (*S*)-α-bromoisovaleric acid gave the same diastereomer ratio of 31% de (54% yield) as those with the diastereomeric mixture, and thus, chirality in **1b** is not transferred to **2b**.

In the present report, the intramolecular radical reaction using the 2,4-pentanediol tether was shown to be stereouncontrolled if the cyclization is quicker than the conformational isomerization, but this problem was dissolved by a proper substitution at the radical center. The essential stereocontrollability of the 2,4-pentanediol tether for intramolecular reactions was confirmed to be very high even for the quick reaction, and sufficiently strong stereocontrol is attained when the conformational change is still fast.

Acknowledgment. We thank Professor Emeritus Tadashi Okuyama of University of Hyogo for his helpful discussions.

Supporting Information Available: Experimental procedure and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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