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Kazuya Sasazawa, Seijiro Takada, Toshihide Yubune, Naoya Takaki,
Ryotaro Ota, and Yoshinori Nishii*

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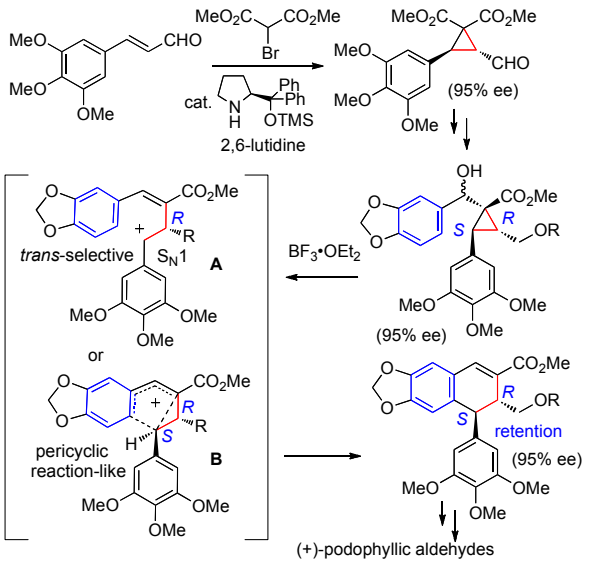
Stereochemical courses and mechanisms of ring-opening cyclization of donor-acceptor cyclopropylcarbinols and cyclization of 7-benzyloxy dibenzyl lignan lactones

Kazuya Sasazawa, Seijiro Takada, Toshihide Yubune, Naoya Takaki, Ryotaro Ota, and Yoshinori Nishii*
Department of Chemistry, Faculty of Textile Science and Technology, Shinshu University, Ueda, Nagano 386-8567, Japan.

(E-mail: nishii@shinshu-u.ac.jp)

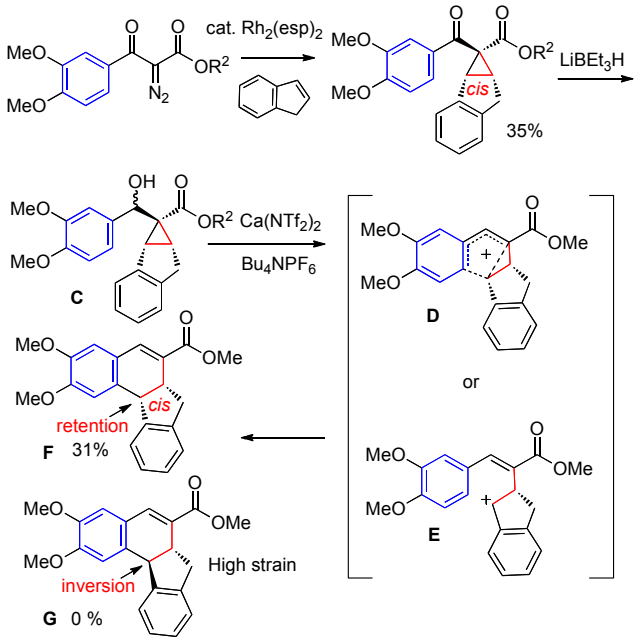
Lewis acid-mediated ring-opening cyclization of *trans*- and *cis*-cyclopropanes **1a** and **1b** afforded the same *trans*-dihydronaphthalene **2a**. Moreover, Lewis acid-mediated cyclization of 7*R*- and 7*S*-benzyloxy dibenzyl lignan lactones **5a** and **5b** also furnished the *trans*-tetralin **6a** with high diastereomeric and enantiomeric excess. Based on these results, we rationalized the mechanisms of the cyclizations via *trans*-selective intramolecular Friedel-Crafts alkylation/cyclization via the S_N1 pathway.

Cyclization reactions of donor-acceptor (D–A) cyclopropanes are recognized as versatile protocols for syntheses of carbocyclic and heterocyclic scaffolds.[1,2] As part of a program of synthetic studies using cyclopropropane moieties,[3,4] we achieved the first asymmetric total synthesis of (+)-podophillic aldehydes using highly stereoselective Lewis acid-mediated ring-opening cyclization of D–A cyclopropylcarbinols to afford 1-aryl-1,2-dihydronaphthalene with retention of stereochemistry and high enantiomeric excess (Scheme 1).[4f]



Scheme 1. Our previously reported asymmetric total synthesis of (+)-podophillic aldehydes.

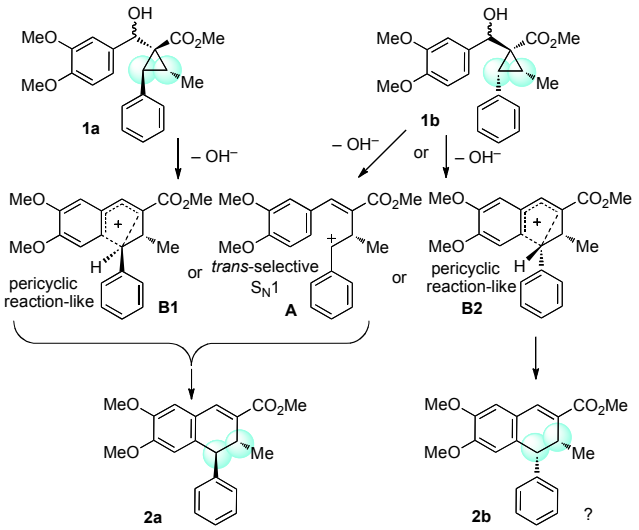
Recentry, France and co-workers improved our method by using catalytic amount of $Ca(NTf_2)_2$ instead of stoichiometric amount of $BF_3{\cdot}OEt_2$ or $Sc(OTf)_3$.[5] Although the modified method can provide variety of cyclic compounds, their method deals with racemic substrates. Meanwhile, the mechanism of the reaction has not been revealed and two plausible mechanisms can be proposed. One is Friedel-Crafts type attack of aromatic ring to the benzyl cation to furnish the trans-product based on the neighboring chiral center (trans-selective S_N1 pathway via cation A). The other one is the peri-cyclic reaction-like[6] mechanism via transition state B with retention of the stereochemistry of cyclopropane. In France's report, a substrate bearing cyclic cis-2,3-disubstituents was employed to investigate the diastereoselectivity and afforded the *cis*-substituted tetracyclic product (Scheme 2). This result seems to support the pericyclic reaction-like mechanism. However, cyclic cation can prevent the construction of the tetracyclic trans-cyclopentene product due to the high strain (On the basis of our calculation using Spartan 09 using B3LYP/6-31G(d), the energy of *cis*-product is 6.6 kcal/mol lower than that of *trans*-product). Here, we report the diastereoselectivities of the ring-opening cyclization of *trans*- and *cis*-cyclopropanes **1a** and **1b** along with similar cyclizations of 7-benzyloxy dibenzyl lignan lactones **4a** and **4b**. Based on those results, we elucidate the reaction mechanism.



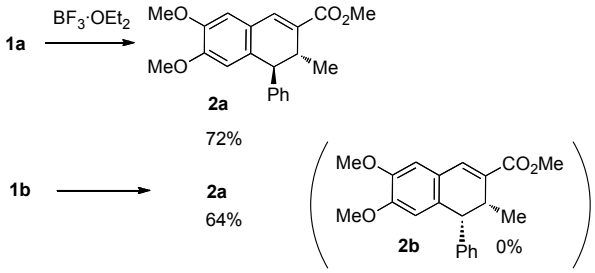
Scheme 2. An example of diastereoselective ring-opening cyclization in France's report.

Investigation of the diastereoselectivities of the ring-opening cyclizations of **1a** and **1b** is key to reveal the reaction mechanism (Scheme 3). Following our previously reported transformation[4a] of dichlorocyclopropane, the desired

substrates **1a** and **1b** were obtained in good yields. However, cyclopropanations of (*E*)- and (*Z*)-1-phenyl-1-propenes using α,α-diazo-β-ketoester in the presence of the $Rh_2(esp)_2$ catalyst used in France's report[5], or other catalysts such as $Rh_2(OAc)_2$, $Cu(acac)_2$, and $Cu(OTf)_2$, all failed to afford desired cyclopropanes due to the stereocongestions.[7,8]



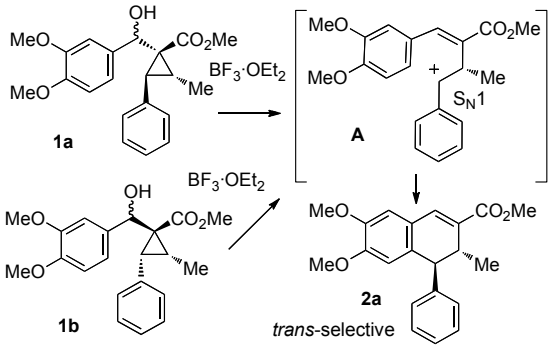
Scheme 3. Speculated mechanisms for the ring-opening cyclizations of substrates **1a** and **1b**



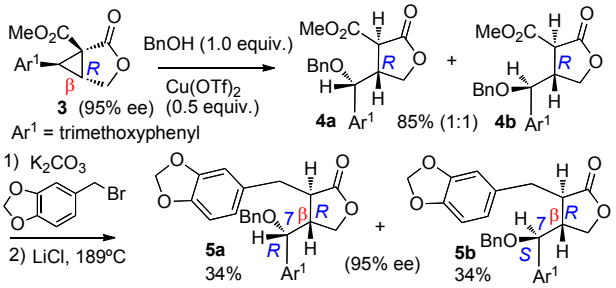
Scheme 4. Ring-opening cyclizations of **1a** and **1b**.

Treatment of **1a** with $BF_3{\cdot}OEt_2$ produced **2a** in 72 % yield as a single isomer (Scheme 4). During the reaction with retention, the *trans*-conformation of cyclopropane **1a** was preserved in the *trans*-conformation of **2a**. Remarkably, the same reaction of **1b** also afforded **2a** in 64% yield as a single isomer, resulting in an inversion at the donor site; this result is the first example of a formal homo-Nazarov-type ring-opening cyclization with complete inversion. Thus, the same *trans*-product **2a** was obtained from the reactions of both diastereomers. These results undoubtedly support the stepwise mechanism including the F-C type attack to the cation A to furnish the *trans*-product **2a** based on the neighboring chiral centre (Scheme 5). Thus, we verified the proposed mechanism in our previous report.[4f] The mechanism distinguishes the ring-opening cyclization of D–A cyclopropylcarbinols (formal homo-Nazarov cyclization[11]-type reaction) from concerted reactions or pericyclic reactions such as the original Nazarov cyclization.[12]

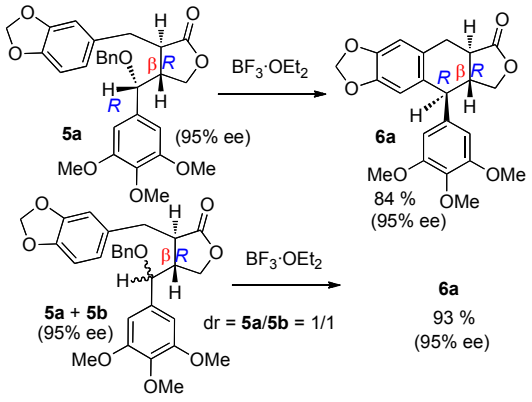
As a similar cyclization, we investigated the Lewis acid-mediated cyclization of **5a** and **5b**. The synthesis of these substrates was as follows (Scheme 6): i)[4h] the $Cu(OTf)_2$-mediated oxy-homo-Michael reaction of bicyclic donor-acceptor cyclopropanes **3**, which was prepared via asymmetric cyclopropanation[9] using Hayashi-Jørgensen catalyst,[10] with 1.0 equiv. of BnOH gave a 1:1 mixture of lactones **4a** and **4b** (If 2.0 equiv. of BnOH is used, lactone **4a** can be obtained with a high stereoselectivity.), ii)[13] benzylation of the resulting 1:1 mixture of lactones **4a** and **4b** using K_2CO_3 and benzylbromide afforded the corresponding benzylated lactones, and iii) finally, decarboxylation of the lactones with LiCl at 189˚C yielded a 1:1-mixture of **5a** and **5b**. Lactones **5a** and **5b** were each isolated by silica gel column chromatography.[14]



Scheme 5. Mechanisms for the ring-opening cyclizations of donor-acceptor cyclopropyldarbinols **1a** and **1b**.

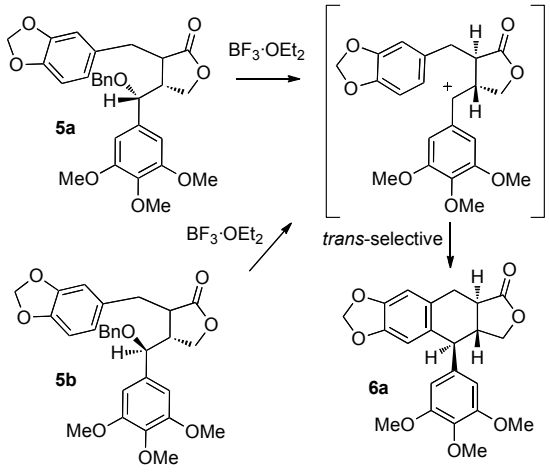


Scheme 6. Preparations of 7*R* and 7*S*-benzyloxy dibenzyl lignan lactones **5a** and **5b**.



Scheme 7. $BF_3{\cdot}OEt_2$-mediated cyclizations of 7-benzyloxy dibenzyl lignan lactones **5a** and a 1:1 mixture of (**5a** and **5b**).

Treatment of **5a** with $BF_3{\cdot}OEt_2$ afforded *trans*-tetralin **6a** as a single isomer in 84% yield (Scheme 7).[15] Notably, the same reaction of a 1:1 mixture of **5a** and the other diastereomer **5b** also furnished the same isomer **6a** in 93% yield as a sole product. Hence, both diasteremers **5a** and **5b** provide the same cation **A** and highly *trans*-selective F-C cyclization proceed through the S_N1 pathway utilizing the neighboring chiral centre (Scheme 8). Thus, optically active tetralin **6a** (95% ee) was obtained from enantioenriched dibenzyl lignan lactones **5a** and **5b** (95% ee).



Scheme 8. Mechanisms for the cyclizations of benzyloxy dibenzyl lignan lactones **5a** and **5b**.

In conclusion, Lewis acid-mediated ring-opening cyclization of cyclopropylcarbinol and simple cyclization of 7-benzyloxy dibenziy lignan lactones respectively provided *trans*-isomers. Based on the results, we verified the mechanism of those cyclizations via *trans*-selective F-C reaction on S_N1 pathway.

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