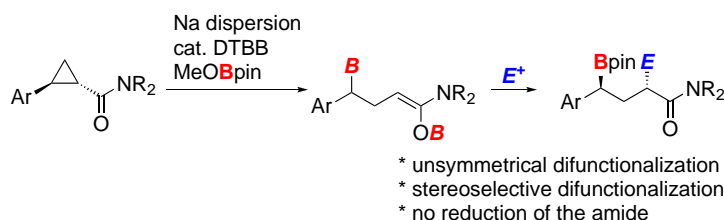# Reductive Ring-opening of Arylcyclopropanecarboxamides Accompanied by Borylation and Enolate Formation

Shuo Wang, Atsushi Kaga, Takashi Kurogi, and Hideki Yorimitsu*

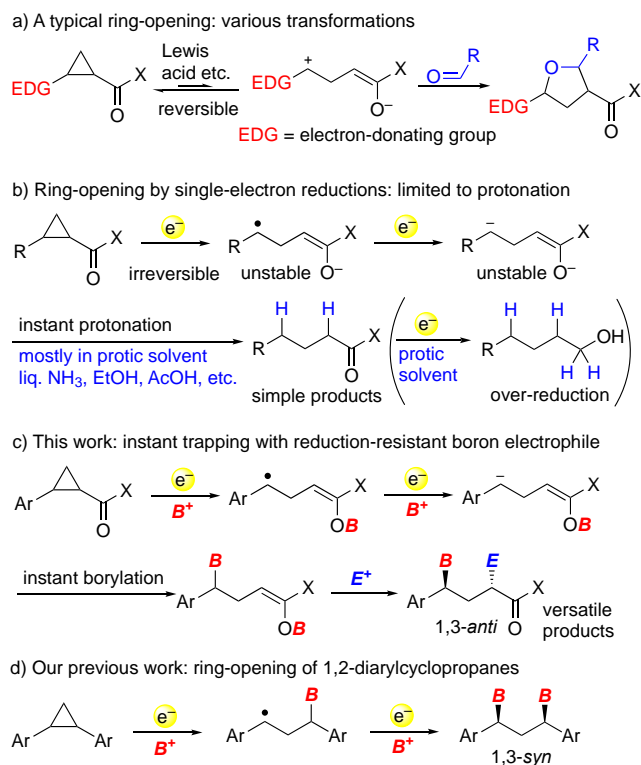Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

* unsymmetrical difunctionalization
* stereoselective difunctionalization
* no reduction of the amide

ABSTRACT: Treatment of arylcyclopropanecarboxamides with sodium dispersion in the presence of methoxypinacolborane as a reduction-resistant electrophile leads to reductive cleavage of the cyclopropane ring followed by instant trapping with the boron electrophile to yield the enolates of γ-aryl-γ-borylalkanamides. The enolates react further with a different electrophile to yield the corresponding α-substituted amides with *anti* selectivity.

Cyclopropyl carbonyl compounds do not only provide unique chemical space for biologically active compounds[1] but serve as useful building blocks in organic synthesis.[2] The cyclopropane rings are prone to release their ring strain to engage in unique ring-opening transformations that lead to a variety of 1,3-difunctionalizations. Most of previous research on the ring-opening of cyclopropyl carbonyls rely on the use of vicinal donor-acceptor-type cyclopropanes for Lewis-acid-mediated heterolytic cleavage (Scheme 1a).[2d–h] The heterolytic cleavage can be reversible, and the zwitterionic ring-opening intermediates can be efficiently trapped by polar compounds and eventually converted to a variety of products such as heterocycles. As a different mode, reductive ring-opening via radical anion intermediates generated by single-electron reductions would be a useful strategy (Scheme 1b) yet has been underdeveloped.[3–6] The immaturity would mainly originate from reaction conditions that require specially reactive substrates such as cyclopropyl dicarbonyls and/or strongly reducing agents such as alkali metals and SmI$_2$. Moreover, the peculiar reduction conditions irreversibly generate highly unstable anionic species, which are difficult to trap with suitable electrophiles[7] other than proton sources that can co-exist under the conditions. The protonation naturally limits the variety of products and the usefulness of the ring-opening reaction. Undesired over-reduction of the carbonyl moieties into alcohols is another issue of difficulty that one has to avoid contradictorily under strong reduction conditions in a protic medium.[3f–i,4j,k]

Scheme 1. Ring-opening Reactions of Cyclopropyl Carbonyls

a) A typical ring-opening: various transformations

b) Ring-opening by single-electron reductions: limited to protonation

c) This work: instant trapping with reduction-resistant boron electrophile

d) Our previous work: ring-opening of 1,2-diarylcyclopropanes

Recently, we have been interested in the combined use of alkali metals and reduction-resistant electrophiles to develop new reductive transformations for organic synthesis.[8] Reduction-resistant electrophiles other than proton sources have realized trapping of reductively generated unstable carbanion species to

synthesize versatile products. Here we report that our strategy is applicable to reductive ring-opening of arylcyclopropanecarboxamides (Scheme 1c). Sodium-mediated reduction in the presence of methoxypinacolborane as a reduction-resistant electrophile efficiently affords the enolates of γ-aryl-γ-borylalkanamides. The enolates show good reactivity toward a different electrophile to result in *anti*-selective α-functionalization. Although we previously developed reductive ring-opening diborylation of 1,2-diarylcyclopropanes (Scheme 1d),[8d] the scope with respect to substrates was limited and the yields of the products were moderate. More importantly, while the 1,2-diarylcyclopropanes were converted to 1,3-*syn* diborylated products, arylcyclopropanecarboxamides are converted to 1,3-*anti* difunctionalized products. The products, γ-borylalkanamides, are expected to represent a useful building block for organic synthesis.

Phenylcyclopropanecarboxamide **1a** was treated with sodium dispersion[9] (3.0 equiv) in THF at 0 °C for 30 min in the presence of methoxypinacolborane (3.0 equiv) as a reduction-resistant electrophile and 4,4'-di-*t*-butylbiphenyl (DTBB) as an electron-transfer catalyst (0.2 equiv) (Scheme 2).[10,11] The ring-opening reaction proceeded to afford γ-borylated alkanamide **2a**, after aqueous workup, in 77% isolated yield. Instead of the aqueous workup to terminate the reaction, an addition of methyl iodide (3.0 equiv) at –78 °C[10] led to α-methylation of the resulting enolate to afford **3a** with high *anti* selectivity of 89:11. It is worth noting that none of the reduction of the carbonyl group was detected.

Scheme 2. Ring-opening Reaction of Amide 1a
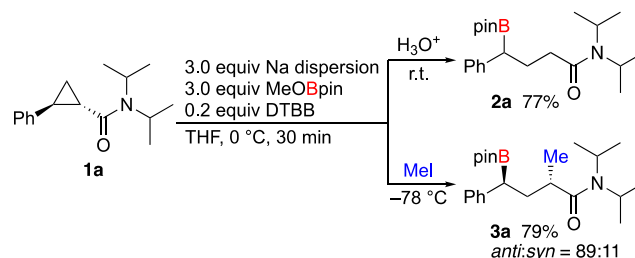
Scheme 3. Scope of Reductive Ring-opening of Amides 1 and Electrophilic Trapping of Resulting Enolates[a]
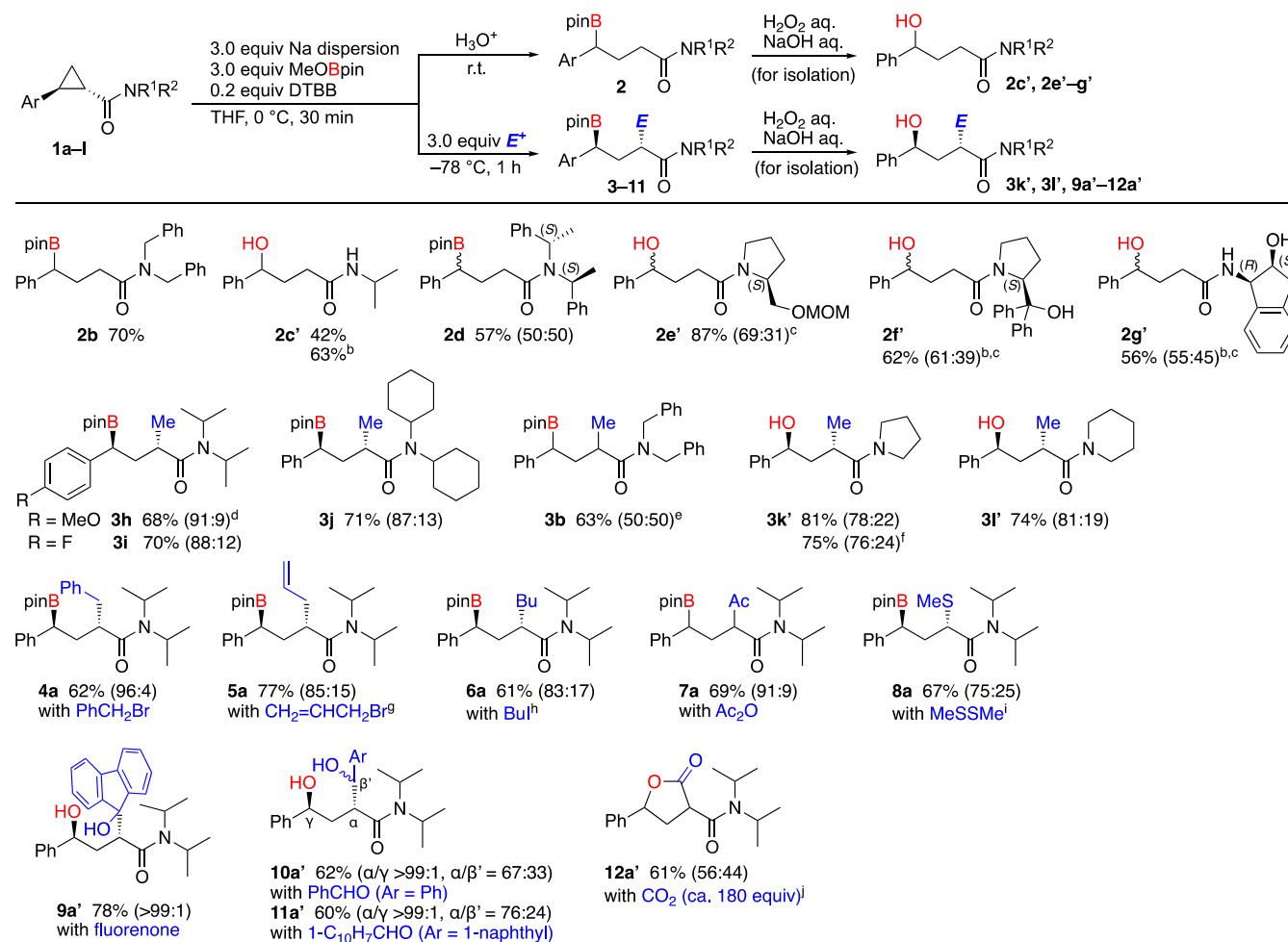
[a] *syn*:*anti* Ratios are in parentheses. [b] Butyllithium (1.0 or 2.0 equiv) was added for deprotonation prior to the reductive process and a boron electrophile (6.0 equiv) was then added. [c] B(OMe)₃ instead of MeOBpin. [d] DTBB (0.5 equiv). [e] 0 °C for the methylation. [f] Starting from 5.0 mmol of **1k**. [g] Allyl bromide (5.0 equiv). [h] –40 °C for 1 h then 0 °C for 1 h for the butylation. [i] 0 °C for the methylsulfanylation. [j] After oxidation, the crude product was treated with conc. HCl aq. in THF/EtOH = 1/1 at room temperature overnight.

The scope of the ring-opening γ-borylation reaction and the subsequent electrophilic α-functionalization is shown in Scheme 3. A variety of N-substituents were found to be compatible under the reaction conditions and to have little influence on the yields of the products. In the case of N-monosubstituted amide **1c**, deprotonation by butyllithium in advance improved the yield of **2c'** up to 63%. None of amides **1d**–**g** bearing a chiral auxiliary showed meaningful levels of asymmetric induction. The aryl group on the cyclopropane is essential, and ring-opening of simple N,N-diisopropylcyclopropanecarboxamide was not observed (not shown in Scheme 3).

Substituents on the nitrogen have influence clearly on the diastereoselectivity of the α-functionalization. While diisopropyl and dicyclohexyl endowed with controlling the diastereoselectivity to yield **3a,h**–**j** with high *anti* selectivities, dibenzylamide **1b** was converted to **3b** with no diastereoselectivity. The formation of piperidine derivative **3l'** with the larger ring size showed slightly higher diastereoselectivity than that of pyrrolidine derivative **3k'**.

Not only methylation but also other alkylations proceeded with high *anti* selectivity to yield **4a**–**6a**. Acetylation afforded **7a** with high selectivity although **7a** should undergo facile epimerization and the relative stereochemistry of the major isomer of **7a** has not been determined here. Methylsulfanylation proceeded to yield **8a** with marginal *anti* selectivity. The reaction with a ketone, fluorenone, proceeded with perfect *anti* selectivity to afford **9a'**. The reaction with aldehydes also provided the corresponding α,γ-*anti* products **10a'** and **11a'**, whereas the stereocontrol of the additional stereogenic center β' originating from the aldehyde carbonyl was moderate. The relative α,γ-*anti* stereochemistry of the products in Scheme 3 was deduced from the unambiguous X-ray crystallographic analysis of *syn*-**3k'** and **9a'**. Notably, carbon dioxide was proved to be a viable electrophile to successfully obtain the corresponding lactone **12a'**.

Scheme 4 illustrates our mechanistic hypothesis and rationale of the *anti* stereoselectivity shown in Scheme 3. The ring-opening of **1a** via one-electron reduction[3-6] would proceed to predominantly generate the more sterically favorable (Z)-**13** over (E)-**13**. The second one-electron reduction followed by the benzylic C–B bond formation would provide cyclic boron enolate **14**. An electrophile, methyl iodide, is likely to approach the cyclic enolate **14** preferably from the side displaying the phenyl substituent to yield *anti*-**3a** as the major isomer. Although our brief computational analysis of the reaction of **14** with an electrophile did not provide any clear explanation for the *anti* selectivity, steric environment controlled synergistically by the phenyl, spirocyclic pinacolatoboryl, and diisopropylamino groups would determine the diastereoface selectivity. Further investigation is necessary to understand the stereoselectivity of the reaction of such cyclic boron enolates.[12,13]

**Scheme 4. Mechanistic Hypothesis and Origin of *anti* Selectivity**
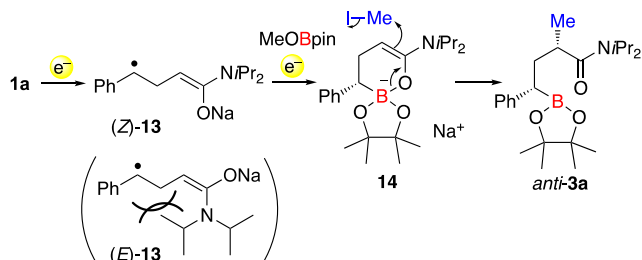
Thioamide **15** reacted similarly to yield **16** with the thiocarbonyl moiety intact at a temperature as low as –78 °C (Scheme 5). Carboxylic acid **17** also underwent the borylative ring-opening to eventually yield lactone **18** after the oxidation of the boryl group.

Scheme 5. Ring-opening Reaction of Other Carbonyls
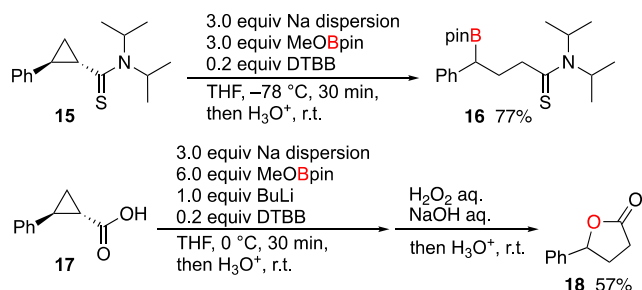
Isobutylene oxide and chlorotrimethylsilane served as coexisting electrophiles[8b,d] instead of MeOBpin although a larger amount of the electrophiles (6.0 equiv) and a lower temperature (–78 °C or –95 °C) were necessary (Scheme 6). Unfortunately, the diastereoselectivity in the formation of **20** was modest. The configuration of the minor isomer of **20** was determined to be *syn* by X-ray diffraction analysis (XRD).

Scheme 6. Ring-opening Reaction with Other Coexisting Electrophiles
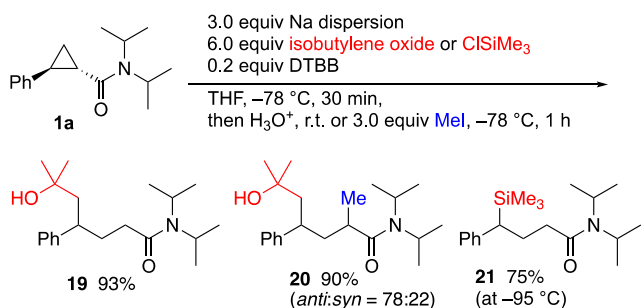
We then attempted ring-opening borylation of 2,3-diphenyl-cyclopropanecarboxamides 2,3-*cis*-**22** and 2,3-*trans*-**22** (Scheme 7). The reaction of 2,3-*cis*-**22** proceeded similarly regardless of the reaction temperature via the C–C bond cleavage at the α position of the carbonyl to yield γ-boryl-β,γ-diphenyl-butanamide **23** with moderate *anti* selectivity. The relative stereochemistry of *syn*-**23** was determined unambiguously by XRD. Interestingly, while the diastereomer, 2,3-*trans*-**22**, was similarly converted to *anti*-**23** at room temperature, the same reaction performed at –78 °C afforded a totally different product *anti*-**24** exclusively. The formation of *anti*-**24** should occur via the C–C bond cleavage at the β position of the carbonyl. Instead of the aqueous workup to obtain *anti*-**24**, an addition of methyl iodide yielded the methylated product **25** as a mixture

of diastereomers. The major isomer of **25** was found to have *anti,syn* configuration by XRD. The 1,3-*anti* configuration along the 1,3-diphenylpropane chain in terms of the boryl and methyl groups is opposite to the configuration previously observed in the ring-opening diborylation of 1,2-diphenylcyclopropanes.[8d] The reversal can be explained by the knowledge that methylation takes place with inversion of the stereochemistry of such a benzylic anion.[8b] The reason for the temperature-dependent change in the position of C–C bond cleavage in 2,3-*trans*-**22** is unclear at this stage. At such a low temperature, the *trans*-2,3-diphenylcyclopropyl unit may take a conformation that is favorable for the C–C bond cleavage between the phenylated carbons.[14]

Scheme 7. Ring-opening Borylation of 2,3-Diphenylcyclopropanecarboxamides
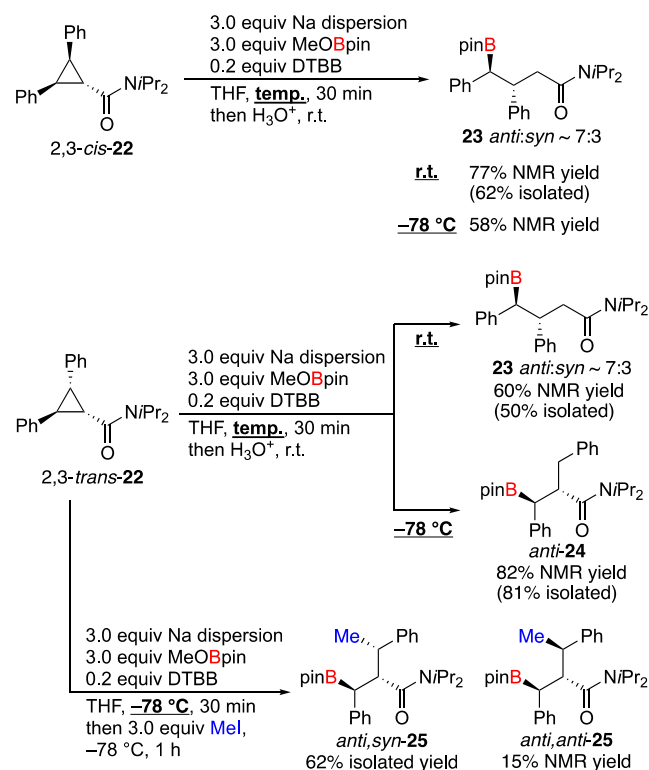
In summary, arylcyclopropanecarboxamides were found to undergo reductive ring-opening with sodium dispersion in the presence of methoxypinacolborane as a reduction-resistant electrophile to afford the enolates of γ-aryl-γ-borylalkanamides. The enolates react with another electrophile to yield the corresponding α-substituted γ-aryl-γ-borylalkanamides with *anti* selectivity. The overall transformation represents unsymmetrical and stereoselective ring-opening difunctionalization and provides potentially useful synthetic intermediates for organic synthesis. Further investigation on the use of alkali metals for C–C bond cleavage is underway in our laboratory.

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Supporting Information

Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Optimization of reaction conditions is shown in Supporting Information.

(11) DTBB is not essential yet was used to slightly improve yields. See the optimization section in Supporting Information.

(12) As we have no clear evidence of the formation of cyclic enolate **13**, there remains the possibility of forming acyclic γ-boryl boron enolate. For established discussion about stereochemistry of enolate alkylation, see: (a) Caine, D. Alkylation of Enols and Enolates in *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I. Eds., Pergamon Press, Oxford, 1991, Vol. 3, Chapter 1.1. (b) Stoltz, B. M.; Bennett, N. B.; Duquette, D. C.; Goldberg, A. F. G.; Liu, Y.; Loewinger, M. B.; Reeves, C. M. Alkylation of Enols and Enolates in *Comprehensive Organic Synthesis II*, Knochel, P. Molander, G. A. Eds., Elsevier, Amsterdam, 2014, Vol. 3, Chapter 3.1.

(13) To investigate difference in diastereoselectivity of **10a'** by decon-voluting the cyclic borate enolate **14**, **14** was treated with Cy_2BOTf at 0 °C and then with benzaldehyde. Interestingly, we observed reversal of the stereochemistry in **10a'** (α/β' = 14:86), although the yield of the desired **10a'** was low (28%) and the protonated by-product **2a'** was obtained in 42% yield. This result somewhat supports the formation of the cyclic enolate **14**.

(14) This unusual temperature effect is full of uncertainty. We found two more interesting observations: 1) The "kinetically generated ben-zylic anion" and the "thermodynamic enolate" are very likely to be in equilibrium, even though they are very different skeletal isomers. 2) When isobutylene oxide was used instead of MeOBpin, at –78 °C the "kinetic product" was obtained in 57% yield, and at 0 °C a complex mixture was obtained. Details of these discoveries are described in Supporting Information.